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Male health: is prostate specific antigen alone useful?

João Henrique Godoy Rodrigues[1*], Murillo de Souza Tuckumantel[2], Luís Cesar Fava Spessoto[3], Fernando Facio Nestor Júnior[3]

Historically, men tend to neglect their health, especially with regard to seeking health care services which may be either due to incompatibility between working hours and the hours of health establishments or for cultural reasons.

The Blue November campaign emerges as an attempt to raise awareness among men regarding the need for prevention of examinations, vaccines when recommended, and the development of a healthy lifestyle with a balanced diet, reduction in alcohol intake and smoking, and the regular practice of physical exercise[1]. However, the Blue November became limited as the period of combating prostate cancer with the determination of PSA alone without considering other factors in the development of this disease that should be interpreted before and after this examination. The interpretation of the PSA level should be performed together with other data, such as sexual activity, the practice of sports, prostate infection, and benign prostate enlargement[2].

The PSA level can contribute to the diagnosis provided that risk factors, symptoms, and variations in the PSA over time are also analyzed. This examination and its interpretation could avoid unnecessary procedures, such as prostate biopsy in a patient with high PSA alone[2,3].

Limiting Blue November to the determination of PSA level alone could further contribute to the exclusion of men to access to integral health care[4]. We should use this campaign as a period to encourage the culture of care, regular medical appointments, disease prevention, and the promotion of healthy habits, with a consequent improvement in individual and social quality of life.

The culprit here is not the PSA examination, but its isolated use as a representative of male health. The clinical assessment, digital rectal examination, and PSA together can improve the quality of the diagnosis.

AUTHORS' CONTRIBUTIONS

JHGR: Conceptualization, Writing – original draft, Writing – review & editing. **MST**: Writing – original draft. **LCFS**: Supervision, Writing – review & editing. **FFNJ**: Supervision, Writing – review & editing.

REFERENCES

1. Espósito RC, Medeiros PJ, Dantas Júnior JH, Oliveira AG, Moreira SA, Sales VSF. Blue November campaign as an annual male self-care strategy for healthy aging. Aging Male. 2020;23(5):865-72. https://doi.org/10.1080/13685538.2019.1610731
2. Paschen U, Sturtz S, Fleer D, Lampert U, Skoetz N, Dahm P. Assessment of prostate-specific antigen screening: an evidence-based report by the German Institute for Quality and Efficiency in Health Care. BJU Int. 2022;129(3):280-9. https://doi.org/10.1111/bju.15444
3. Bennett A, Beck A, Shaver N, Grad R, LeBlanc A, Limburg H, et al. Screening for prostate cancer: protocol for updating multiple systematic reviews to inform a Canadian Task Force on Preventive Health Care guideline update. Syst Rev. 2022;11(1):230. https://doi.org/10.1186/s13643-022-02099-9
4. Pathirana T, Sequeira R, Del Mar C, Dickinson JA, Armstrong BK, Bell KJL, et al. Trends in prostate specific antigen (PSA) testing and prostate cancer incidence and mortality in Australia: a critical analysis. Cancer Epidemiol. 2022;77:102093. https://doi.org/10.1016/j.canep.2021.102093

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Cannabis products: medical use

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct, and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.
Guideline conclusion: 5 January 2023. Submission: 6 January 2023.

INTRODUCTION

The Board of the Brazilian Medical Association triggered the formation of a commission with the purpose of contributing to current scientific knowledge on the use of cannabis-derived products in patient health care.

This scientific committee met weekly and virtually for about 2 months, during which analyses and documents were discussed and developed on the therapeutic indications of products derived from cannabis, focusing on indications based on efficacy and safety, as well as compassionate use, in addition to aspects of a regulatory nature.

We know that there are limits of scientific knowledge in the timeline on all aspects involved in the health care of our patients, which have been overcome since the dawn of medicine through ethical aspect for the needs of patients combined with the constant generation of scientific evidence that guarantees the lowest level of uncertainty regarding the benefit and safety of all clinical situations faced on a daily basis by physicians.

This is not different with regard to products derived from cannabis, and therefore current scientific knowledge allows us to make inferences at the moment, which can be modified as new consistent evidence emerges, allowing this scientific document to be lively and permanently updated, incorporating this evidence.

This responsible and modern behavior protects the needs of patients by disseminating and implementing evidence-based recommendations with the health system, which guarantees medical decision-making with low uncertainty, high benefit, and safety, especially in compassionate indications that, despite the lack of efficacy, are applicable consistently and are conditioned to the use of informed consent signed between doctor and patient.

This document is made up of four different and complementary parts, expressed in a summary way that allows a quick understanding of its content and conclusions: (1) regulatory aspects of the use of products of cannabis; (2) cannabis use in pediatric patients with autism spectrum disorder (ASD); (3) medical use of cannabis-derived products: efficacy and safety; and (4) compassionate medical use of cannabis-derived products.

REGULATORY ASPECTS OF THE USE OF CANNABIS PRODUCTS[1,2]

Analysis carried out based on the rules published by ANVISA demonstrates the regulatory evolution of cannabis products in Brazil.

Collegiate Board Resolution No. 3 of January 26, 2015, as a framework, including a brief analysis of Technical Note No.

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01/2017/GMESP/GGMED/ANVISA – 01/09/2017, enabled the registration of Mevatyl (Nabiximols), which to date is the only cannabis-derived drug registered in Brazil.

The current regulatory context, composed of "RDC's" No. 327, 659, and 660 – all from ANVISA, was analyzed and demonstrated the regulatory challenges that are being faced by the agency, especially due to the characteristics of "cannabis products" (innumerable dilutions and regulation in the countries of origin).

RDC No. 327/2019 also disciplines the possibility that the final phase of the process of elaboration of the cannabis product is carried out in Brazil, provides the form of prescription (prescription A or B) based on the percentage of THC present in the product (up to 0.2% mg/mL), and describes the processes for dispensing, tracking, storage, and import.

The alternatives that the physician can use to prescribe cannabis products for their patient were also analyzed (products available at the pharmacy/RDC 327 and prescription of imported product for direct purchase by the patient with prior authorization from ANVISA/RDC 660), as well as the importance of formalizing the informed consent form (proposed treatment, desired effects, possible adverse reactions, chosen product, and effective consent of the patient or his/her legal representative).

We understand the need to analyze the concepts of "compassionate use" and "expanded access" in view of the expression used by ANVISA in the aforementioned resolutions that are in force: "other therapeutic options available in the Brazilian market have been exhausted."

This expression brings us to the concepts of "compassionate use" and "expanded access," which are subject to regulation by RDC 38/2013 of the same agency. This analysis is relevant and deserves special attention because, depending on the interpretation of these concepts, we will have a direct impact on the daily lives of physicians who consider this therapeutic possibility viable.

PEDIATRIC USE OF CANNABIS IN ASD[3]

The considerations and recommendations woven below, in relation to pediatric use in ASD, are derived from the position of the Brazilian Society of Pediatrics carried out through a document published and released recently[3].

Cannabidiol (CBD) is not without its adverse effects, the most commonly reported being drowsiness, increased appetite, and irritability. They published a case of a patient with a severe psychotic crisis that required interruption of treatment. In addition, in all published studies, however, the administration of CBD was performed concomitantly with other medications already used by patients; therefore, it is not possible to relate adverse effects to a specific drug, and it is also important to emphasize that it is not possible to evaluate the long-term safety of CBD, since the studies do not bring patient follow-up data for a period longer than 6 months.

To date, the literature that associates cannabinoids with the treatment of ASD symptoms is based on case reports or open, uncontrolled clinical trials with a limited number of participants. To date, only one randomized, double-blind clinical trial has been performed.

It is also important to note that the subjective reports of parents and caregivers of people with autism were used as a basis for determining the effectiveness of CBD in several of these studies. Based on this fact, it is possible that expectations regarding a new treatment may have influenced the responses provided.

The lack of methodologically adequate studies has contributed to the emergence of several anecdotal reports of exceptional, sometimes miraculous, improvements in autism, attributed to the use of CBD. Coupled with the frustration of many family members with the lack of a readily effective treatment, many have advocated the unrestricted use of CBD as a treatment for ASD.

In view of the quality scientific evidence currently available, the safe prescription of cannabinoids for the treatment of ASD symptoms should not be widely indicated. Well-designed studies are in progress and may pave the way to clarifying the potential role of these drugs in neurobehavioral diseases. So far, common sense and caution are recommended, which can be summarized as follows:

1. Every doctor who treats people with ASD must be informed and trained about CBD, as well as about the different treatments considered alternatives for autism. It is known that around 60% of family members of people within the autism spectrum have already tried one or more treatments that have yet to be proven to be effective, and it is up to physicians to know them and guide them in this regard.
2. It is necessary to create a doctor-patient relationship of mutual trust, without judgment by the clinician. Once the link is generated, evidence of efficacy and safety of the different treatments can be more easily discussed.
3. Evidence of safety and efficacy must be constantly reviewed, as new studies are frequently published.
4. Many physicians receive requests directly from family members to prescribe CBD, but the shared decision is obtained only through proper understanding of autism (about the clinical characteristics, available treatments, expected benefits, and potential risks).

5. Finally, the use of CBD in autism is still based on a small number of studies, individual medical experience, and the expectations of patients' relatives.

MEDICINAL USE OF CANNABIS-DERIVATIVE PRODUCTS: EFFECTIVENESS AND SAFETY[4-59]

As defined previously in the methodology, analyses were selected if they meet two requirements: significant differences between cannabis and placebo, and a quality of evidence assessed as moderate or high. Under these conditions, the only analysis and results that met these requirements are those related to the treatment with cannabis (CBD) in drug-resistant seizures such as the failure of ≥2 appropriate and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve sustained freedom from crises. Six RCTs were included to support this assessment, which evaluated the use of CBD plus usual therapy in the treatment of patients with Drave syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex, compared to placebo plus usual therapy. The CBD versus placebo comparison was evaluated for the outcome's reduction in the frequency of seizures and total seizures (all types), the number of patients with a response equal to or greater than 50%, and the impression of clinical improvement by the patient or caregiver, adverse events, and tolerability to treatment.

As the analyses showed homogeneous results (low heterogeneity), the results of the three clinical situations were kept together for common outcomes. The quality of the evidence will be expressed using GRADE terminology. The use of CBD was compared to placebo in patients with Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex in a follow-up period of 12–16 weeks.

Benefit

- Shows an absolute reduction in seizure frequency of 33%; being necessary to treat three patients for a benefit (number need to treat [NNT]=3). Moderate quality of evidence.
  - Increases the number of patients with a ≥50% reduction in the frequency of seizures by 20% (NNT=5). High quality of evidence.
  - Increases the number of patients with no seizures by 3% (NNT=33). Moderate quality of evidence.
  - Improvement in caregiver – or patient – rated clinical impression by 21% (NNT=5). High quality of evidence.

Damage

- Increases serious adverse events by 16% (number need to harm [NNH]=6). Moderate quality of evidence.
  - Increases the risk of abandoning treatment by 12% (NNH=8). High quality of evidence.

Benefit/harm ratio

For patients who maintain adherence to treatment with CBD, a relevant reduction in the number of monthly seizures is estimated, assuming the risk of adverse events is severe, with a negative NNT/NNH ratio of 0.83 (NNT/NNH: 5/6), favorable to the adoption of the treatment.

Recommendation

This evaluation, with meta-analysis, supports the use of CBD in the treatment of patients with convulsive crises, originating in the Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex, who are resistant to the usual drugs, presenting satisfactory benefits in the reduction of convulsive crises and tolerable toxicity.

COMPASSIONATE MEDICINAL USE OF CANNABIS DERIVATIVES[4-59]

In patient health care, we are faced with limits in the results of our actions in many clinical situations, despite all the therapeutic arsenal that we have today. These limits can occur in acute events with unfavorable outcomes, but they can also be present in diseases or symptoms of a chronic, recurrent, or even terminal nature. In these situations of intractability, refractoriness, or nonresponsiveness to available conventional treatments, the individuality of patients plays a fundamental role in medical decision-making, and the term "compassionate treatment" has been used for the personalized care of these patients, through therapeutic alternatives not included among the conventional or usual treatments.

However, despite the individual and exceptional character of compassionate use, these therapeutic forms must have been studied, whether or not associated with conventional treatments, through the same parameters used for evaluating the efficacy and safety of treatments already in use today.

These parameters (see guideline for the efficacy and safety of the medicinal use of cannabis derivatives) minimally involve parallel randomized controlled clinical trials, comparing cannabis derivatives with conventional treatments or with placebo, demonstrating superiority or absence of difference in relevant and present outcomes in more than one study (aggregated data) as a manifestation of refractoriness.

This evaluation and consequently the synthesis of evidence will not express the result and analysis already expressed in the evaluation of the efficacy and safety of the medicinal use of cannabis products, in which the clinical situations directly benefited are those associated with seizures, resistant to drugs such as failure of more than 2 appropriate and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve sustained freedom from seizures, namely: in Drave syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex.

Unlike the review and meta-analysis of the efficacy and safety of medicinal use of cannabis-derived products, the synthesis of evidence in this evaluation of compassionate medicinal use of these products is not necessarily based on significant differences between cannabis and placebo, nor on the quality of minimally moderate or high evidence.

However, regardless of the superiority result or the quality of the evidence, but dependent on a result not inferior to placebo, this synthesis is based on quantified direct evidence (derived from parallel randomized clinical trials) or qualified indirect evidence (extrapolated from direct evidence, considering potential refractory outcomes that were correlated or also associated with other diseases, which were studied through crossover randomized clinical trials).

It is also necessary to remember that the clinical situations included here for compassionate use are those in which all conventional and currently available therapeutic resources have already been exhausted, and despite this, nonresponsive patients remain with refractory symptoms (outcomes) that are related to their clinical situation or underlying disease.

The clinical situations with their respective analyzed outcomes (benefit and harm) that are likely to be treated compassionately with cannabis-derived products are as follows:

1. Cancer patients (direct evidence): Low to very low quality of evidence.
    - Pain: No difference in the number of responders comparing THC: CBD (up to 16 oral sprays/day, at follow-up ranging from 2 to 5 weeks) to placebo.
    - Opioid use: No difference in opioid consumption with THC+CBD oral spray compared to placebo.
    - Nutrition: Increase in nutrition measured by intake in kcal/day favorable to oral THC treatment (at doses ranging from 0.5 to 5.0 mg/day) when compared to placebo.
    - Adverse events: 11% increased risk of adverse events (95% confidence interval [CI]+6% to+16%) with the use of THC (27 mg/ml)+CBD (25 mg/mL) (up to 16 oral sprays/day in follow-up ranging from 2 weeks to 35 days) when compared to placebo.
2. Patients with neuropathic pain – nononcological (direct evidence): Low to very low quality of evidence.
    - Reduction in intensity (>30%): Response increase by 13% (95%CI 1–25%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (9 at 24 mg/day orally), in a follow-up ranging from 15 to 52 weeks, when compared to placebo.
    - Pain (VAS): There is no difference in the visual analog scale (VAS) score with the use of THC: CBD or THC when compared to placebo.
    - Adverse events (total): 14% increased risk of total adverse events (95%CI +6% to +22%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray), in follow-up ranging from 15 to 52 weeks, when compared to placebo.
    - Adverse events (treatment-related): Increased risk of treatment-related adverse events by 26% (95%CI +15% to +38%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, of oral spray) or THC (1–4 mg/day VO)], in a follow-up ranging from 5 to 15 weeks, when compared to placebo.
3. Patients with chronic pain – nononcological (direct evidence): Low to very low quality of evidence.
    - Pain (VAS): There is no difference in pain intensity with the use of THC when compared to placebo.
    - Adverse Events: There is no difference in the risk of serious adverse events with the use of (THC: CBD or THC) when compared to placebo.
4. Patients with multiple sclerosis (direct evidence) and spinal cord injury (indirect evidence): Low to very low quality of evidence.
    - Spasticity: In patients with multiple sclerosis, response is found to be increased by 13% (95%CI 9–17%) with the use of THC: CBD [(2.7 and 2.5 mg, respectively, oral spray) or (THC 10.0–25.0 mg and CBD 5.0–25.0 mg/day VO)], in a follow-up ranging from 6 to 48 weeks, when compared to placebo. In patients with spinal cord injury, there is a reduction in spasticity (nonquantified effect and indirect evidence) with the use of THC, when compared to placebo.
    - Pain (response): Response (responders) increased by 8% (95%CI 3–14%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, oral spray) or (10–25 mg and 5–25 mg/day VO, respectively)] or THC (10 mg/day), in a follow-up ranging from 6 to 48 weeks, when compared to placebo.

- Adverse events (total): 12% increased risk of total adverse events (95%CI +7% to +17%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, oral spray) or (10.0–25.0 mg and 5.0–25.0 mg/day orally, respectively)] or THC (7–15 mg/day), in a follow-up ranging from 3 weeks to 36 months, when compared to placebo.
- Serious adverse events: There is no risk difference in serious adverse events with the use of THC: CBD or THC when compared to placebo.

5. Patients undergoing chemotherapy (direct evidence): Low to very low quality of evidence.
   - Nausea and/or vomiting (response): Response increased by 42% (95%CI 18–67%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (2.5–20 mg/day VO), in a follow-up ranging from immediate to 5 days, when compared to placebo.
   - Nausea and/or vomiting (absence): There is no difference in the absence of nausea and/or vomiting with the use of THC when compared to placebo.
   - Adverse events: Increased risk of adverse events by 28% (95%CI 3–53%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (2.5–20 mg/day orally), in a follow-up ranging from immediate to 5 days, when compared to placebo.

Recommendation

Compassionate use of cannabis-derived products can be used in the following patients with their respective refractory symptoms: cancer (pain, opioid use, and nutrition); neuropathic and chronic (noncancer) pain; multiple sclerosis (spasticity and pain); spinal cord injury (spasticity); and chemotherapy (nausea and/or vomiting). In all these clinical situations, there is an increased risk of adverse events (total or serious) with the use of cannabis-derived products. The quality of evidence is low or very low.

AUTHORS' CONTRIBUTIONS

WMB: Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **CEF:** Project administration, Supervision, Writing – review & editing. **JELD:** Writing – review & editing. **CEF, JELD, LSN, MA, CFC, RPAP, CRMR, FT, WMB:** Conceptualization, Investigation, Validation.

REFERENCES

1. Ministry of Health. Resolution of the Collegiate Board - RDC No. 03 of January 26, 2015. Ministry of Health (MS) National Health Surveillance Agency (ANVISA). Available from: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2015/rdc0003_26_01_2015.pdf
2. National Health Surveillance Agency. Technical Note Technical Note No. 01/2017/GMESP/GGMED/ANVISA – 01/09/2017. National Health Surveillance Agency (ANVISA). Available from: https://static.poder360.com.br/2017/01/mevatyl.pdf.
3. Brazilian Society of Pediatrics. Indications for cannabis use in pediatric patients with neurodevelopmental disorders and/or epilepsy: an evidence-based review. Orientation Manual. Scientific Departments of Neurology and Pediatrics of Development and Behavior (2022-2024 term). Brazilian Society of Pediatrics. No. 32, December 13, 2022. Available from: https://www.sbp.com.br/imprensa/detalhe/nid/indicacoes-para-o-uso-da-cannabis-em-pacientes-pediatricos-com- neurodevelopmental-disorders-and/or-epilepsy-an-evidence-based-review/
4. Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. J Natl Compr Canc Netw. 2012;10(4):487-92. https://doi.org/10.6004/jnccn.2012.0048
5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
6. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
7. Grade Working Group. [cited on June 2022]. Available from: https://www.gradeworkinggroup.org
8. McMaster University. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). Available from: gradepro.org.
9. Wiesmann UN, DiDonato S, Herschkowitz NN. Effect of chloroquine on cultured fibroblasts: release of lysosomal hydrolases and inhibition of their uptake. Biochem Biophys Res Commun. 1975;66(4):1338-43. https://doi.org/10.1016/0006-291x(75)90506-9
10. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39(2):167-79. https://doi.org/10.1016/j.jpainsymman.2009.06.008
11. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438-49. https://doi.org/10.1016/j.jpain.2012.01.003
12. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain. 2017;11(3):119-33. https://doi.org/10.1177/2049463717710042
13. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage. 2018;55(2):179-88.e1. https://doi.org/10.1016/j.jpainsymman.2017.09.001

14. Brisbois TD, Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22(9):2086-93. https://doi.org/10.1093/annonc/mdq727
15. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, Oñate-Ocaña LF, Zatarain-Barrón ZL, Barrón F, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. Support Care Cancer. 2018;26(9):3029-38. https://doi.org/10.1007/s00520-018-4154-9
16. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19. https://doi.org/10.1016/j.pain.2004.09.012
17. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58. https://doi.org/10.1016/S0304-3959(01)00349-9
18. Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017;377(7):699-700. https://doi.org/10.1056/NEJMc1708349
19. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90(14):e1204-11. https://doi.org/10.1212/WNL.0000000000005254
20. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. JAMA Neurol. 2020;77(5):613-21. https://doi.org/10.1001/jamaneurol.2020.0073
21. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378(20):1888-97. https://doi.org/10.1056/NEJMoa1714631
22. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-96. https://doi.org/10.1016/S0140-6736(18)30136-3
23. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2021;78(3):285-92. https://doi.org/10.1001/jamaneurol.2020.4607
24. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18(7):999-1012. https://doi.org/10.1002/j.1532-2149.2013.00445.x
25. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153(10):2073-82. https://doi.org/10.1016/j.pain.2012.06.024
26. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128-30. https://doi.org/10.2337/dc09-1029
27. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133(1-3):210-20. https://doi.org/10.1016/j.pain.2007.08.028
28. Vries M, Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, Goor H, Pain and Nociception Neuroscience Research Group. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clin Gastroenterol Hepatol. 2017;15(7):1079-86.e4. https://doi.org/10.1016/j.cgh.2016.09.147
29. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006;45(1):50-2. https://doi.org/10.1093/rheumatology/kei183
30. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich cannabis oil in people with fibromyalgia: a randomized, double-blind, placebo-controlled clinical trial. Pain Med. 2020;21(10):2212-8. https://doi.org/10.1093/pm/pnaa303
31. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004;10(5):589-95. https://doi.org/10.1191/1352458504ms1085oa
32. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. Int J MS Care. 2013;15(3):146-58. https://doi.org/10.7224/1537-2073.2012-053
33. Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. Int J Neurosci. 2019;129(2):119-28. https://doi.org/10.1080/00207454.2018.1481066
34. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-29. https://doi.org/10.1159/000481089
35. Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, et al. The cannabinoid use in progressive inflammatory brain disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015;19(12):vii-viii, xxv-xxxi, 1-187. https://doi.org/10.3310/hta19120
36. Vachová M, Novotná A, Mares J, Taláb R, Fiedler J, Lauder H, et al. A multicentre, double-blind, randomised, parallel-group, placebo-controlled study of effect of long-term Sativex® treatment on cognition and mood of patients with spasticity due to multiple sclerosis. J Mult Scler 2014; 1(2):22. https://doi.org/10.4172/2376-0389.1000122
37. Zajicek J, Ball S, Wright D, Vickery J, Nunn A, Miller D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. Lancet Neurol. 2013;12(9):857-65. https://doi.org/10.1016/S1474-4422(13)70159-5
38. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260(4):984-97. https://doi.org/10.1007/s00415-012-6739-4
39. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012;83(11):1125-32. https://doi.org/10.1136/jnnp-2012-302468

40. Notcutt W. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. Available from: ClinicalTrials.gov Identifier: NCT01606176; https://clinicaltrials.gov/ct2/show/NCT01606176
41. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. 2011;18(9):1122-31. https://doi.org/10.1111/j.1468-1331.2010.03328.x
42. Kavia RB, Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010;16(11):1349-59. https://doi.org/10.1177/1352458510378020
43. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res. 2010;32(5):451-9. https://doi.org/10.1179/016164109X12590518685660
44. Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007;14(3):290-6. https://doi.org/10.1111/j.1468-1331.2006.01639.x
45. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1664-9. https://doi.org/10.1136/jnnp.2005.070136
46. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812-9. https://doi.org/10.1212/01.wnl.0000176753.45410.8b
47. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253. https://doi.org/10.1136/bmj.38149.566979.AE
48. Levin DN, Dulberg Z, Chan AW, Hare GM, Mazer CD, Hong A. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Can J Anaesth. 2017;64(4):385-95. https://doi.org/10.1007/s12630-017-0814-3
49. Kleine-Brueggeney M, Greif R, Brenneisen R, Urwyler N, Stueber F, Theiler LG. Intravenous delta-9-tetrahydrocannabinol to prevent postoperative nausea and vomiting: a randomized controlled trial. Anesth Analg. 2015;121(5):1157-64. https://doi.org/10.1213/ANE.0000000000000877
50. Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol. 2010;70(5):656-63. https://doi.org/10.1111/j.1365-2125.2010.03743.x
51. Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007;23(3):533-43. https://doi.org/10.1185/030079907x167525
52. Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med. 1979;91(6):825-30. https://doi.org/10.7326/0003-4819-91-6-825
53. Maas AI, Murray G, Henney H, Kassem N, Legrand V, Mangelus M, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 2006;5(1):38-45. https://doi.org/10.1016/S1474-4422(05)70253-2
54. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30(3):548-54. https://doi.org/10.1097/00003246-200203000-00009
55. Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl). 2018;235(7):1923-32. https://doi.org/10.1007/s00213-018-4885-9
56. McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry. 2018;175(3):225-31. https://doi.org/10.1176/appi.ajp.2017.17030325
57. Naftali T, Bar-Lev Schleider L, Almog S, Meiri D, Konikoff FM. Oral CBD-rich cannabis induces clinical but not endoscopic response in patients with Crohn's disease, a randomised controlled trial. J Crohns Colitis. 2021;15(11):1799-806. https://doi.org/10.1093/ecco-jcc/jjab069
58. Naftali T, Mechulam R, Marii A, Gabay G, Stein A, Bronshtain M, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. Dig Dis Sci. 2017;62(6):1615-20. https://doi.org/10.1007/s10620-017-4540-z
59. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11(10):1276-80.e1. https://doi.org/10.1016/j.cgh.2013.04.034

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"The road to hell is paved with good intentions" — the cognitive bias of immobility in in-patients at risk of falling

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Patient falls are one of the most common adverse events reported in hospitals[1]. Although preventable hospital falls have been decreasing over the past years, approximately 1 in 10 falls results in serious injury[2]. Besides, inpatient falls can result in significant physical and economic burdens to the patients (increased injury and mortality rates and decreased quality of life) and to medical organizations (increased length of stay, medical care costs, and litigation)[1,2].

Consistent concerns aimed at reducing this problem have led hospitals to adopt very heterogeneous guidelines for fall prevention[3]. These guidelines usually include (1) identification of patients who are at high risk of falling and (2) decisions to which attitude of fall prevention strategies to use to reduce fall risk[1,2]. However, this approach may had led to a confused "correct approach" to fall prevention in specific settings, since the lack of clarity of prevention guidelines may add to the cognitive burden of patient care and potentially increases in-hospital patient risk.

First, the use of fall risk prediction tools is widespread, but their value in hospital fall prevention interventions is questionable[4]. In this context, it is important to distinguish between fall risk assessments and fall prediction or screening tools. Risk assessments usually consist of a checklist of risk factors for falls but do not provide a score or value for the patient's fall risk[1]. The lack of evidence supporting the use of predictive tools led *National Institute for Health and Care Excellence* and *the Agency for Healthcare Research and Quality* to recommend a caution in the routine use of fall prediction tools[1]. Despite this, fall risk screening tools are frequently used to identify patients for intervention and are recommended and required by Healthcare International Quality Agencies[5].

Second, falls in hospitals are different from falls in general, community-dwelling adult populations[3]. Inconsistencies in risk factors for falls have been identified between hospitalized and nonhospitalized older adult populations[1]. The hospitalized patients are in unfamiliar environments and routines; present pain; are commonly under the influence of psychotropic drugs, anesthetics, or opioid analgesics; are connected to drains, tubes, or venous catheters; and have a loss of locus of control in performance of personal activities and a physical dependency on staff. In this context, a recent meta-analysis identifies 11 risk factors for falls in hospitalized patients with cancer, including age, history of falls, opiates, benzodiazepines, steroids, antipsychotics, sedatives, radiation therapy, chemotherapy, the use of an assistive device, and length of hospitalization[6]. Another problem is that the trials have not preferentially evaluated hospitalized patients[1,3]. When evaluated only hospitalized patients, there were no significant reduction of risk of falls and combined clinic-level quality improvement strategies, patient-level quality improvement strategies, and multifactorial assessment and treatment relative to usual care (OR 0.78 [95%CI 0.33–1.81]) or with combined patient-level quality improvement strategies and exercise relative to exercise alone (OR 1.12 [95%CI 0.38–3.25])[7].

Third, interventions that prevent falls may not prevent injurious falls[3]. Injurious falls, particularly those requiring provision of additional healthcare services, have been found to be the key driver of overall "cost per fall" estimates. As injurious falls occur at a lower frequency than total falls, individual studies are rarely powered adequately to identify an effect on this outcome. However, one could argue that if falls are reduced, injurious falls should also reduce by a similar magnitude; thus, a reduction in falls would be seen as beneficial.

Finally, the identification of a patient at risk of falling cognitively leads the hospital staff to mobilize less the patients. Falls also lead to anxiety and distress among caregivers and relatives who perhaps believe that "something should have been done" in an apparent place of safety to prevent the falls and that "someone

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must be to blame" and, therefore, are frequently cited in both complaints and litigation. This concern is partly caused by fear of complaint or litigation or inquests, and because staff may feel guilty that they could have done more to prevent the fall and are aware that they are constantly balancing the autonomy and rehabilitation of individual patients versus the duty of care to all of those they look after. Added to that, a fall is generally poorly tolerated by managers generating punishments (need to attend root-cause meetings or to start a continuing education course) for professionals participating in the event.

The smaller number of employees available at the hospital, their lower fees, and their high turnover reduce the ability to obtain these certificates. In addition, the need to obtain and disseminate care indicators monthly forces employees to move away from patient care at the bedside. This is a key point of the problem—the patients are less mobilized. Immobility contributes to development of delirium, and the delirium contributes for greater use of physical restraints. Patients who require restraints suffer a loss of dignity and autonomy, thereby causing agitation, delirium, pressure ulcers, deconditioning, and death[1]. Furthermore, a recent meta-analysis (including 54 randomized controlled trails, 41,596 participants aged 65 years and older, 39 interventions plus usual care) showed that exercise (OR, 0.51 [95%CI 0.33–0.79]; absolute risk difference, -0.67 [95%CI -1.10 to -0.24]) was associated with a lower risk of injurious falls[7].

In summary, hospital patients have a myriad of acute and chronic illnesses that limit judgment and mobility, and they must navigate a new and unfamiliar environment. Furthermore, staffing and even unit design considerations may play into fall risk. Assessing the risk of falling in hospitalized patients could generate an unmeasured risk of immobility. In this context, when we "correctly" label the patient at risk of falling, we usually "incorrectly" immobilize them, to "correctly" follow the guidelines that we can certainly comply with "incorrectly." The unique organizational culture and leadership structures of hospitals require specific implementation of strategies. Thus, it is imperative to reexamine fall prevention intervention strategies specific to the hospital setting.

REFERENCES

1. LeLaurin JH, Shorr RI. Preventing falls in hospitalized patients: state of the science. Clin Geriatr Med. 2019;35(2):273-83. https://doi.org/10.1016/j.cger.2019.01.007
2. Oliver D, Healey F, Haines TP. Preventing falls and fall-related injuries in hospitals. Clin Geriatr Med. 2010;26(4):645-92. https://doi.org/10.1016/j.cger.2010.06.005
3. Haines TP, Waldron NG. Translation of falls prevention knowledge into action in hospitals: what should be translated and how should it be done? J Safety Res. 2011;42(6):431-42. https://doi.org/10.1016/j.jsr.2011.10.003
4. Aranda-Gallardo M, Morales-Asencio JM, Canca-Sanchez JC, Barrero-Sojo S, Perez-Jimenez C, Morales-Fernandez A, et al. Instruments for assessing the risk of falls in acute hospitalized patients: a systematic review and meta-analysis. BMC Health Serv Res. 2013;13(1):122. https://doi.org/10.1186/1472-6963-13-122
5. Mansour W, Boyd A, Walshe K. The development of hospital accreditation in low- and middle-income countries: a literature review. Health Policy Plan. 2020;35(6):684-700. https://doi.org/10.1093/heapol/czaa011
6. Zhao J, Wang G, Chen L, Yu S, Li W. Risk factors for falls in hospitalized patients with cancer: a systematic review and meta-analysis. Asia-Pacific J Oncol Nurs. 2022;9(8):100107. https://doi.org/10.1016/j.apjon.2022.100107
7. Tricco AC, Thomas SM, Veroniki AA, Hamid JS, Cogo E, Strifler L, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. JAMA. 2017;318(17):1687-99. https://doi.org/10.1001/jama.2017.15006

SHORT COMMUNICATION

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Anaphylactic risks associated with immunobiological agents in asthma therapy

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Specific monoclonal antibodies (mAbs) have been increasingly used in the management of patients with severe asthma. As of October 2022, six mAbs (omalizumab, reslizumab, benralizumab, mepolizumab, dupilumab, and tezepelumab) have been approved by the Food and Drug Administration (FDA) and are currently available for asthma management in North America[1]. Several adverse effects have been reported with the administration of these mAbs in clinical trials, which had often shown a similar incidence in the placebo-treated groups. Of particular concern are the risks of hypersensitivity/allergic reactions and anaphylaxis, as these drugs may demonstrate antigenic properties. Symptoms typically associated with these severe side effects include bronchospasm, hypotension, syncope, urticaria, angioedema of the throat/tongue, dyspnea, cough, chest tightness, cutaneous angioedema, and generalized pruritus. Anaphylaxis, a systemic and life-threatening immune reaction, may also occur, requiring immediate medical assistance and specific interventions, such as intramuscular epinephrine injection[2].

Hypersensitivity/allergic reactions due to mAbs are fundamentally driven by the immunogenic properties of their protein component. Thus, fully human mAbs, which consist of 99% human components, are usually associated with a significantly lower risk of anaphylaxis compared to humanized mAbs, as those can carry up to 10% of murine elements[3]. However, sensitization and hypersensitivity/allergic reactions may also be driven by excipient chemicals, such as polysorbates, which are usually present in mAbs formulations. Interestingly, the female sex also seems to be a potential risk factor for anaphylaxis related to mAbs used in asthma. A history of anaphylactic reactions, regardless of the etiology, is also of clinical relevance when prescribing any mAbs. Even more concerning is that asthma patients appear to have a higher risk of severe allergic reactions, including anaphylaxis, compared to those suffering from chronic urticaria during treatment with the same mAb[3].

Overall, the estimated incidence of anaphylactic reactions related to mAb therapy for severe asthma is low[3,4]. Nevertheless, according to clinical trial and post-marketing surveillance data, the risk of developing anaphylaxis may differ according to the mAb in use. It is important to consider that mAbs that have been on the market for longer periods are more likely to be associated with hypersensitivity/allergic reactions.

Omalizumab is the first mAb specifically developed for asthma management and has been in commercial use since 2003, with an incidence of anaphylaxis estimated at 0.1–0.2%. Most of these reported cases occurred within 2 h after its administration, though some delayed-onset cases have also been reported up to 24 h. Of note, anaphylaxis may be triggered by any dose of omalizumab, regardless if previous doses had been well tolerated[5,6].

Reslizumab may also cause anaphylaxis, as 0.3% of patients randomized to this mAb also experienced this side effect during phase 3 clinical trials, which was more likely to occur as early as the second dose, either during infusion or within 20 min[4].

Given these observations, it is not surprising that FDA has included a black box warning on both omalizumab and reslizumab's labels recommending in-office infusion and close monitoring after these injections. For the first three doses of omalizumab, the monitoring period recommended is 2 h, which can be decreased to at least 30 min with subsequent doses. Conversely, there are no current clear recommendations for how long patients on reslizumab should be monitored after its infusion.

Benralizumab phase 3 clinical trials reported hypersensitivity/allergic reactions in approximately 3% of subjects treated with this drug[4]. In a previous 1-year phase 3 extension study, out of 518 patients treated with this drug, only

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Table 1. Suggested recommendations for administration of monoclonal antibodies in asthma.

• All patients must sign an informed consent form prior to treatment commencement.	
• All patients must be warned regarding the potential related risks and advised to seek prompt medical assistance should they experience any symptoms suggestive of anaphylaxis.	
• These drugs must be administered in a healthcare setting capable of providing urgent and intensive care support.	
Group	**Monitoring**
Low risk Omalizumab* Reslizumab Benralizumab	• Direct medical supervision during administration and observation for at least 2 h after injection for the first three doses. Personnel should be able to recognize anaphylaxis and treat it accordingly. • Direct medical supervision during administration and observation for at least 30 min from the fourth dose onward.
Very low risk Mepolizumab	• Direct medical supervision during administration and observation for at least 30 min, regardless of the dose number.
Extremely low risk Dupilumab Tezepelumab?	• Direct medical supervision during administration and observation for at least 30 min. Dupilumab can be considered for self-administration at home, especially if no hypersensitivity/allergic reactions occur during the first three doses[3].

*Ideally, patients would be trained for using epinephrine auto-injectors.

one case of anaphylaxis was described (0.19%)[7]. However, a recent study based on post-marketing reports supports that the risk of anaphylaxis associated with benralizumab seems to be similar to that observed with omalizumab and reslizumab[3]. In this study, the risk of hospitalization due to anaphylaxis was significantly higher in patients treated with benralizumab compared to their counterparts receiving omalizumab.

For mepolizumab, while no cases of drug-related anaphylaxis were described in clinical trials, post-marketing data have reported few cases of anaphylaxis following its administration[3,8]. Hypersensitivity/allergic reactions due to dupilumab (a fully human mAb), despite being estimated in 0.1–1.0%, consist mainly of generalized urticaria[4], and no cases of anaphylaxis have been reported with this drug based on post-marketing reports[3]. Similarly, no anaphylactic reaction was described among 528 asthma patients treated with tezepelumab, another fully human mAb, in a phase 3 clinical trial[9]. However, post-marketing data on tezepelumab are still scarce, as this drug has been on the market for a short period (approved for use in the United States since December 2021).

Therefore, based on the currently available data, we propose to classify the mAbs employed in severe asthma management according to their anaphylaxis risk into the following categories: *low risk* (omalizumab, reslizumab, and benralizumab), *very low risk* (mepolizumab), and *extremely low risk* (dupilumab and, probably, tezepelumab). Specific recommendations for the administration of these mAbs are listed in Table 1. These immunobiological agents must be administered in a healthcare setting capable of providing urgent and intensive care support, including administration of epinephrine, oxygen, bronchodilators, intravenous corticosteroids, and proceed with emergency orotracheal intubation and/or initiate cardiopulmonary resuscitation if needed. All patients on immunobiological therapy for asthma should be also warned about the risk of anaphylaxis with these drugs and advised to seek prompt medical attention in case they experience any hypersensitivity/allergic side effects. Ideally, patients on omalizumab should be able to initiate anaphylaxis treatment outside hospital facilities, which mostly relies on the use of an epinephrine auto-injector[5,6]. However, this recommendation is not feasible in Brazil, given that epinephrine auto-injectors, especially in public settings, are not available to be offered to our patients. Out of the six mAbs described here, given the good safety profile of dupilumab, we agree with the possibility of its self-administration at home after no occurrence of any hypersensitivity/allergic reactions during the first three doses administered under medical supervision[3].

The recommendations presented here should and will need to be updated as new evidence becomes available. Finally, to ensure accurate pharmacovigilance, it is essential that healthcare professionals report any adverse events related to these mAbs to local health authorities.

AUTHORS' CONTRIBUTIONS

JBM: Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing. **FSLF**: Conceptualization, Writing – review & editing. **LSBC**: Conceptualization, Writing – review & editing.

REFERENCES

1. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. N Engl J Med. 2022;386(2):157-71. https://doi.org/10.1056/NEJMra2032506
2. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472. https://doi.org/10.1016/j.waojou.2020.100472
3. Li L, Wang Z, Cui L, Xu Y, Guan K, Zhao B. Anaphylactic risk related to omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. Clin Transl Allergy. 2021;11(4):e12038. https://doi.org/10.1002/clt2.12038
4. Jackson K, Bahna SL. Hypersensitivity and adverse reactions to biologics for asthma and allergic diseases. Expert Rev Clin Immunol. 2020;16(3):311-9. https://doi.org/10.1080/1744666X.2020.1724089
5. Kim HL, Leigh R, Becker A. Omalizumab: practical considerations regarding the risk of anaphylaxis. Allergy Asthma Clin Immunol. 2010;6(1):32. https://doi.org/10.1186/1710-1492-6-32
6. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol. 2007;120(6):1373-7. https://doi.org/10.1016/j.jaci.2007.09.032
7. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med. 2019;7(1):46-59. https://doi.org/10.1016/S2213-2600(18)30406-5
8. Jingo K, Harada N, Nishioki T, Torasawa M, Yamada T, Asao T, et al. Anaphylaxis to three humanized antibodies for severe asthma: a case study. Allergy Asthma Clin Immunol. 2020;16:46. https://doi.org/10.1186/s13223-020-00446-w
9. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021;384(19):1800-9. https://doi.org/10.1056/NEJMoa2034975

SHORT COMMUNICATION

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Transcranial direct current stimulation associated with pharmacological approaches in patients infected by SARS-CoV-2

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SARS-CoV-2 was considered a worldwide health problem due to its rapid spread and lethality. Almost 3 years after the beginning of the pandemic period, people who were infected and survived are still presenting sequelae. Neurological manifestations caused by SARS-CoV-2 were identified in approximately 10% of people infected and hospitalized[1]. It has been suggested that SARS-CoV-2 can infect the central nervous system through olfactory and vagus nerves. Then, it releases cytokines, increasing the sympathetic nervous system activity and maintaining the inflammatory response[2]. Anti-inflammatory exacerbated response, pain, fatigue, cognitive issues, and physical deterioration are outcomes frequently involved in the central nervous system dysfunctions after SARS-CoV-2 infection[2,3].

Noninvasive and safe strategies, such as transcranial direct current stimulation, might be an alternative to managing inflammatory response and neurological symptoms. Neuromodulation of the left dorsolateral prefrontal cortex seems to present the potentiality to decrease the recovery time of the neurological disabilities generated by SARS-CoV-2 through different mechanisms[2]. The sympathetic and parasympathetic autonomic nervous system response seems to be involved in inflammatory modulation[4]. It is important to mention that in experimental models and preliminary data in human beings, vagus nerve stimulation attenuates inflammation, modulating activity of cholinergic anti-inflammatory pathways[5].

There are at least six drugs approved by the Food and Drug Administration to treat SARS-CoV-2: paxlovid, molnupiravir, fluvoxamine[6], remdesivir, baricitinib[7], and dexamethasone[8], which have decreased the recovery time and accelerated an improvement in clinical status of patients infected by SARS-CoV-2. It has been hypothesized that their actions are related to reducing inflammatory-mediated injury and improving lymphocyte counts.

There are at least nine ongoing clinical trials registered in adults[9]. All the trials are designed to use transcranial direct current stimulation without pharmacological association to treat patients infected by SARS-CoV-2. We expect that future clinical trials are designed using transcranial direct current stimulation as an associated strategy with pharmacological treatment to generate a booster. In this sense, if transcranial direct current stimulation shows efficacy to recover central nervous system dysfunctions generated by SARS-CoV-2, we could start discussions to insert this tool in the public health system.

AUTHORS' CONTRIBUTIONS

ESF: Conceptualization, Writing – review & editing. **MEF**: Conceptualization, Writing – review & editing.

REFERENCES

1. Meppiel E, Peiffer-Smadja N, Maury A, Bekri I, Delorme C, Desestret V, et al. Neurologic manifestations associated with COVID-19: a multicentre registry. Clin Microbiol Infect. 2021;27(3):458-66. https://doi.org/10.1016/j.cmi.2020.11.005
2. Baptista AF, Baltar A, Okano AH, Moreira A, Campos ACP, Fernandes AM, et al. Applications of non-invasive neuromodulation for the management of disorders related to COVID-19. Front Neurol. 2020;11:573718. https://doi.org/10.3389/fneur.2020.573718
3. Pilloni G, Bikson M, Badran BW, George MS, Kautz SA, Okano AH, et al. Update on the use of transcranial electrical brain stimulation to manage acute and chronic COVID-19 symptoms. Front Hum Neurosci. 2020;14:595567. https://doi.org/10.3389/fnhum.2020.595567
4. Schmaußer M, Hoffmann S, Raab M, Laborde S. The effects of noninvasive brain stimulation on heart rate and heart rate variability: a systematic review and meta-analysis. J Neurosci Res. 2022;100(9):1664-94. https://doi.org/10.1002/jnr.25062
5. Azabou E, Bao G, Bounab R, Heming N, Annane D. Vagus nerve stimulation: a potential adjunct therapy for COVID-19. Front Med (Lausanne). 2021;8:625836. https://doi.org/10.3389/fmed.2021.625836

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6. Wen W, Chen C, Tang J, Wang C, Zhou M, Cheng Y, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and paxlovid) for COVID-19: a meta-analysis. Ann Med. 2022;54(1):516-23. https://doi.org/10.1080/07853890.2022.2034936

7. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795-807. https://doi.org/10.1056/NEJMoa2031994

8. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704. https://doi.org/10.1056/NEJMoa2021436

9. US National Institutes of Health. ClinicalTrials.gov; 2020 [cited on Mar 6, 2020]. Available from: https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=tdcs&cntry=&state=&city=&dist=

SHORT COMMUNICATION

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Teenage pregnancy in the first year of the COVID-19 pandemic in Brazil

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INTRODUCTION

Several factors are associated with adolescent maternity, such as hindered access to public health services, greater social vulnerability, lower income, and lower education level. It has negative consequences for adolescents, including school dropout, postponement of professional training, unemployment, and financial instability[1].

In Brazil, there was a slow and gradual decrease in adolescent mothers' live births (LB) percentage and fertility rate in all regions from 2001 onward. There was a reduction of 37.2% (23.4% in 2000 to 14.7% in 2019) and 48 births per 1,000 adolescents aged 15–19 years in 2019 (in 2000, the fertility rate in the age group 15–19 years was 81/1,000). It is observed that the LB percentage is inversely proportional to the human development index (HDI), because only the Southeast and South regions presented indicators below the country's average (38.2 and 39‰, respectively)[2]. However, the numbers of adolescent pregnancy are still very high in relation to developed countries, and there is great regional inequality within the country.

The COVID-19 pandemic caused unprecedented harm worldwide, with social, economic, cultural, and educational impacts, also on individual and community health. Recent projections of the United Nations Population Fund/United Nations Children's Fund (UNFPA/UNICEF) show that the impact of the COVID-19 pandemic could result in over 13 million child marriages, as well as 7 million unplanned pregnancies and 31 million cases of gender-based violence between 2020 and 2030[3]. In the first 3 months of social distancing, the reported increase in early pregnancy in Krachi, Gana, was nine times[4].

Several factors contributed to these projections, such as the closing of schools, greater hindrances for adolescents to access health services, turn of attention of health to COVID-19 hospitalization and treatment, and the lack of contraceptive availability. All of these factors could lead to an increase in unplanned pregnancies in this age group[5].

Regional inequality in Brazil in the cultural, social, religious, educational, and public health aspects raised the interest in studying the impact of the COVID-19 pandemic on the adolescent population. Thus, the objective of this study was to evaluate the behavior of adolescent pregnancy in the first year of the pandemic in Brazil.

METHODS

A cross-sectional study was conducted with data obtained from the Live Births Data System (SINASC), through the server of the Informatics Department of the Unified Health System (DATASUS) of the Brazilian Health Ministry, with the purpose of gathering epidemiological data on informed births in the national territory[6]. The form of declaration of live birth

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(DNV) is a document with 52 fields to be filled, referring to notary, place of occurrence, characteristics of mother, pregnancy, birth, neonate, identification, and data of the person responsible for filling the form. The filling of the DNV is mandatory and necessary for the civil register of the neonate. Data are collected directly from the mother and/or the clinical history. For this study, the following variables were used: birth according to the mother's place of residence, birth according to the region of the country, year of birth, and maternal age.

Data were obtained on the total number of LB per region and on age groups 10–14 and 15–19 years to calculate the LB rate among adolescent mothers[6]. The calculation of age-specific fertility rate (ASFR) per 1,000 adolescents in the same age group and same region and state was performed, using data from the Brazilian Institute of Geography and Statistics (IBGE) on population projection to estimate adolescent population[7]. In 2019, this population corresponded to 7,823,491 adolescents aged 10–14 years and 8,338,727 aged 15–19 years. In 2020, the estimate was 7,709,355 adolescents aged 10–14 years and 8,264,254 aged 15–19 years.

Relative and absolute frequencies of LB according to the mother's age group and year of occurrence were calculated. The percentage increase or decrease in the period was calculated using the expression: [(% of LB in 2020–% of LB in 2019)/% of LB in 2019]×100. Choropleth maps were used in the description of the results.

As SINASC is a public-access database, the project did not require a Research Ethics Committee review. The R-Project (version 5.4.0) and ArcGis (version 10.0.4) software were used.

RESULTS

In 2020, adolescent pregnancy in Brazil in 2020 represented 14% of total LB, which is equivalent to a reduction of 8.4% in relation to 2019. In 2020, there were born 381,653 babies of adolescent mothers, with 17,579 LB from mothers in the age group 10–14 years and 364,074 mothers in the age group 15–19 years. The calculation of age-specific fertility rate (ASFR) showed 2.3/1,000 births from mothers aged 10–14 years and 44.1/1,000 in the age group 15–19 years.

Figure 1 shows the ASFR in the age groups 10–14 and 15–19 years in each of the country's regions. It is observed that only in the Southeast and South regions the ASFR is lower than the national average.

.The distribution of ASFR per 1,000 adolescents in age groups 10–14 and 15–19 in all 27 Brazilian states is shown in Table 1 and Figure 2. In 2019, there was a reduction in adolescent pregnancy in all Brazilian regions. In the age group 10–14 years, the reduction was 9.0% in the North region, 7.7% in the Northeast region, 7.9% in the Southeast region, 6.2% in the South region, and 9.3% in the Center-West region. Among adolescents in the age group 15–19 years, the reduction was 7.9, 8.5, 8.3, 9.3, and 9.4%, respectively. In the North region, the states with higher ASFR were Roraima, Amazonas, and Acre, while in the Northeast region they were Maranhão and Alagoas. The lowest ASFR in the age group 15–19 years was in the Federal District (30.2‰), São Paulo (31.8‰), and Rio Grande do Sul (33.4‰) (Table 1 and Figure 2).

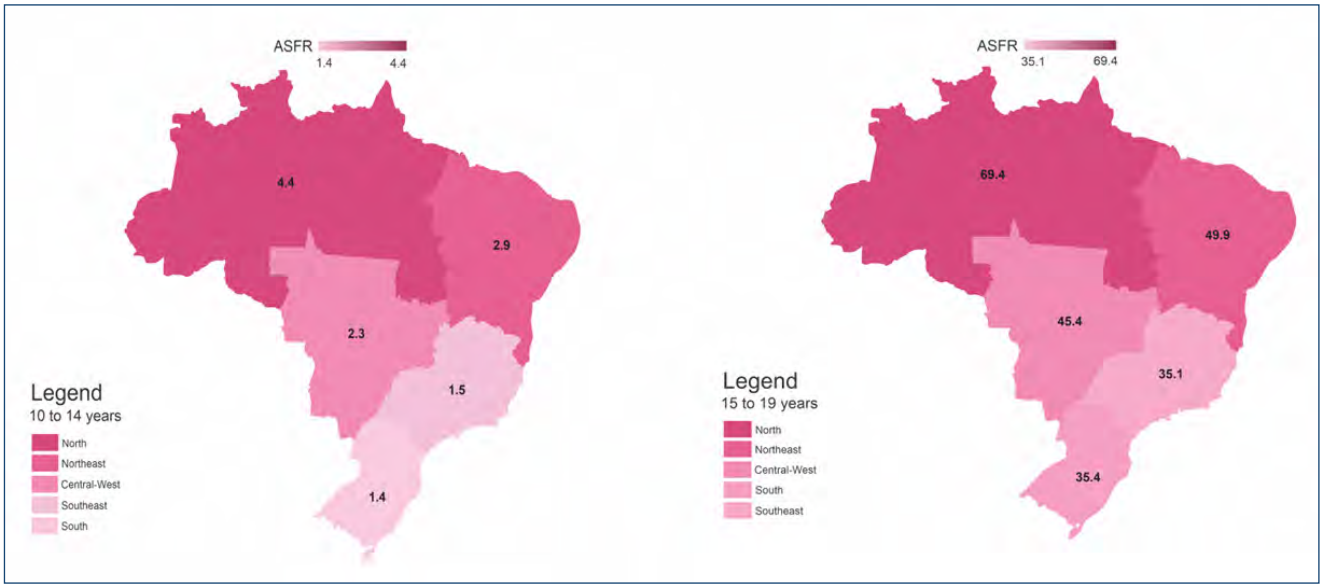

Figure 1. Distribution of age-specific fertility rate per 1,000 adolescents by region (2020). Source: DATASUS/SINASC, 2020.

DISCUSSION

The prediction was that unplanned pregnancies would have increased worldwide during the COVID-19 pandemic[3]. In South Africa, for example, the number of children born from adolescent mothers in the country's most populated province, Gauteng, increased by 60% since the start of the pandemic. The Health Department of Gauteng informed that, between April 2020 and March 2021, more than 23,000 adolescents gave birth and 934 were <14 years of age[7]. The main reasons were the lack of access to contraceptives, the possibility of having a safe

Table 1. Distribution of age-specific fertility rate (ASFR) per 1,000 adolescents by federative unit of Brazil (2019–2020).

Region	Adolescents aged 10–14 years			Adolescents aged 15–19 years		
	2019	2020	ASFR/1,000 evolution % 2019–2020	2019	2020	ASFR/1,000 evolution % 2019–2020
Brazil	**2.5**	**2.3**	**-8.0**	**48.0**	**44.1**	**-8.4**
North region	**4.8**	**4.4**	**-9.0**	**75.0**	**69.0**	**-7.9**
Rondônia	2.7	2.2	**-18.8**	55.0	49.1	**-10.7**
Acre	5.6	4.7	**-15.6**	84.6	74.5	**-11.9**
Amazonas	6.1	5.2	**-15.3**	84.6	78.8	**-6.9**
Roraima	7.3	7.2	**-1.6**	110.6	95.3	**-13.9**
Pará	4.6	4.2	**-7.4**	74.0	68.6	**-7.3**
Amapá	4.0	4.3	**7.4**	68.4	62.6	**-8.6**
Tocantins	3.4	3.7	**7.3**	59.7	56.2	**-5.9**
Northeast region	**3.1**	**2.9**	**-7.7**	**54.5**	**49.8**	**-8.5**
Maranhão	4.0	3.7	**-7.6**	72.0	64.5	**-10.4**
Piauí	3.0	3.0	**1.9**	57.4	52.1	**-9.3**
Ceará	2.7	2.7	**-1.6**	47.5	42.5	**-10.5**
Rio Grande do Norte	2.7	2.3	**-13.1**	43.7	39.7	**-9.3**
Paraíba	2.8	2.6	**-7.9**	53.2	49.2	**-7.5**
Pernambuco	2.8	2.5	**-10.3**	53.2	50.0	**-6.1**
Alagoas	3.9	3.6	**-8.0**	63.1	59.1	**-6.3**
Sergipe	3.2	3.2	**-0.6**	50.0	48.2	**-3.5**
Bahia	3.0	2.6	**-11.7**	51.0	46.5	**-9.0**
Southeast region	**1.6**	**1.5**	**-7.9**	**38.2**	**35.1**	**-8.3**
Minas Gerais	1.6	1.4	**-11.7**	38.1	34.7	**-8.7**
Espírito Santo	1.9	2.1	**10.3**	44.5	42.1	**-5.5**
Rio de Janeiro	2.3	2.1	**-7.7**	45.4	42.8	**-5.7**
São Paulo	1.3	1.2	**-8.3**	35.1	31.8	**-9.5**
South region	**1.5**	**1.4**	**-6.2**	**39.0**	**35.4**	**-9.3**
Paraná	1.8	1.6	**-10.4**	42.2	37.3	**-11.5**
Santa Catarina	1.3	1.3	**-1.0**	38.0	35.1	**-7.6**
Rio Grande do Sul	1.4	1.4	**-3.4**	36.2	33.4	**-7.7**
Center-West region	**2.6**	**2.3**	**-9.3**	**50.1**	**45.4**	**-9.4**
Mato Grosso do Sul	3.5	3.3	**-3.9**	61.6	54.0	**-12.4**
Mato Grosso	3.6	3.3	**-8.5**	64.7	59.5	**-8.1**
Goiás	2.1	1.9	**-9.8**	45.2	41.5	**-8.3**
Federal District	1.5	1.2	**-23.1**	34.4	30.2	**-12.2**

Source: DATASUS/SINASC, 2020.

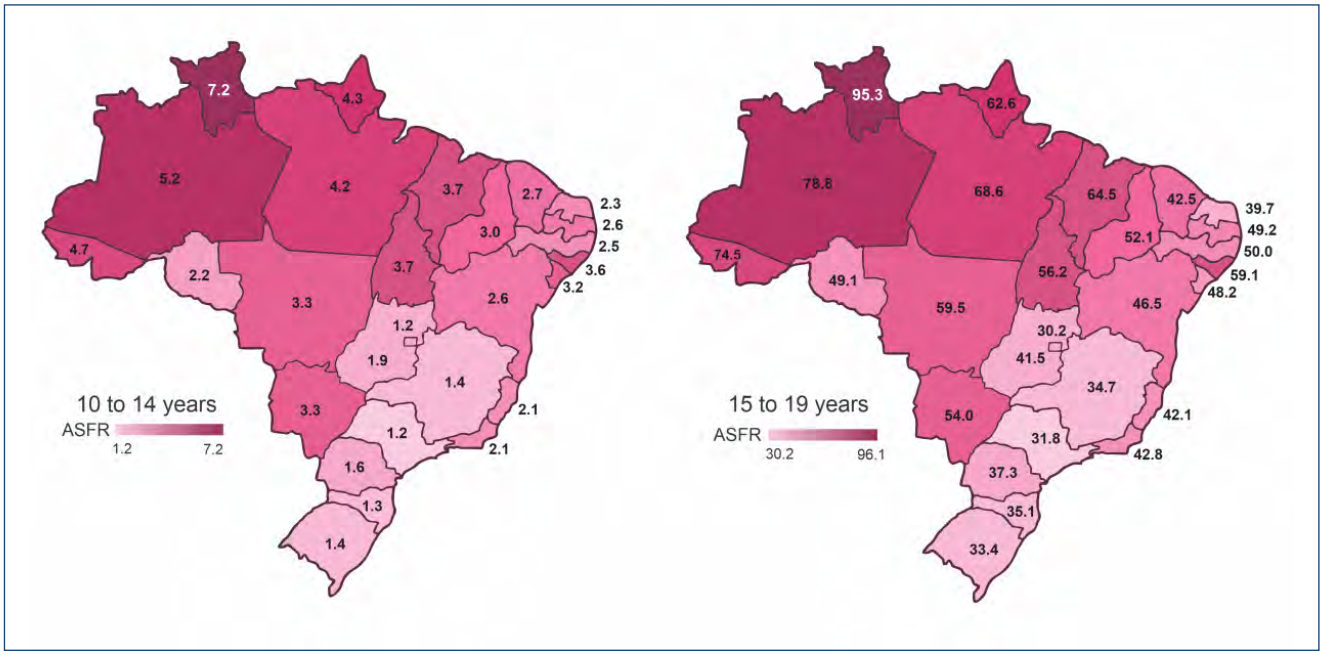

Figure 2. Map of distribution of age-specific fertility rate per 1,000 adolescents by federative units of Brazil (2020). Source: DATASUS/SINASC, 2020.

abortion, the closing of schools, and shift of healthcare attention to hospitalization and treatment of COVID-19 patients[3,7,8].

In Brazil, however, during the first year of the pandemic, there was a reduction of 8.4% in the frequency of adolescent pregnancy[5]. This reduction can be partially justified by social distancing, which made it impossible for adolescents to go to parties, social meetings, and school.

In 2020, there were 180 deaths of pregnant and puerperal adolescents, with 24 maternal deaths of adolescents caused by COVID-19[9]. Pregnant women are more vulnerable to respiratory infections, such as the one caused by COVID-19, and may develop severe symptoms that put at risk mother and baby[8]. The Ministry of Health of Brazil had been registering a decrease in deaths of pregnant and puerperal women between 2017 and 2019; however, there was an increase of approximately 25% with the start of the COVID-19 pandemic in 2020 and higher than 40% in 2021[10].

Even with the frequency of adolescent pregnancy in Brazil that has reached a reduction of 40% between 2000 and 2020, with an ASFR of 44.1/1,000 in the age group 15–19 years[6], these numbers would have to be reduced to half to be close to rates lower than 18/1,000 in North America, Europe, and a large part of Asia[11].

It is important to stress that international statistics on adolescent fertility rate refer only to the age group 15–19 years, because ASFR in the age group 10–14 years is lower than 1‰, except in Latin America and Africa[12].

According to the Pan American Health Organization (PAHO), the constant interruption of women's health services due to COVID-19 could retrocede over 20 years of advances in maternal mortality reduction and the raise of access to family planning in Latin America and the Caribbean. In the Americas, there is a highlight on socioeconomic and health impacts, with approximately 20 million women affected by the interruption of reproductive and maternal health services during the pandemic[8]. The challenges and inequalities that existed before COVID-19 have worsened during the pandemic. The protection of women's life must be a collective priority.

The closing of schools and the measures of social distancing imposed by COVID-19 had a significant impact on the lives of vulnerable adolescents in Africa because it increased 25% risk of early marriage and many girls will never return to school. Currently, early marriage and adolescent pregnancy will continue to increase in Nigeria until public policy managers conduct effective actions to reverse this unfortunate tendency[13].

In Brazil, health services continued to be provided during the social distancing period, and even with the decrease in the distribution of contraceptive methods, there has been no total interruption. It is known that the insertion of intrauterine devices (IUD) has decreased by 40% in 2020 in relation to 2019. However, the distribution of contraceptives continued, since the expenditures of the Ministry of Health with contraceptive inputs presented a reduction of only 17% in 2020[14].

As limitations of this study, we point out the fact that this research used population projection data of IBGE, containing details based on the last census conducted in Brazil in 2010, to estimate the population of adolescents[6,7].

CONCLUSION

The expected increase in pregnancies in the first year of the COVID-19 pandemic did not occur in Brazil, where there was a reduction of 8.4% in relation to 2019. The main factors that might have contributed to this reduction were social distancing, lesser exposure of adolescents to situations of risk, and the maintenance of healthcare services with the distribution of contraceptives.

ETHICAL ASPECTS

SINASC is a public-access database, it did not require a Research Ethics Committee review.

AUTHORS' CONTRIBUTIONS

DLMM: Conceptualization, Data curation, Investigation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **ADT:** Conceptualization, Writing – original draft, Writing – review & editing. **NCPR:** Conceptualization, Data curation, Investigation, Formal Analysis, Methodology. **MSCM:** Methodology, Investigation, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **IPM:** Data curation, Formal Analysis, Writing – review & editing. **ZVB:** Data curation, Investigation, Formal Analysis, Writing – original draft, Writing – review & editing. **FAS:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MFBR:** Data curation, Investigation, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. PAHO/UNICEF. Accelerating progress toward the reduction of adolescent pregnancy in Latin America and the Caribbean. Retrieved from Washington DC; 2016. [cited on Apr 07, 2021]. Available from: https://iris.paho.org/handle/10665.2/34493
2. Monteiro DLM, Monteiro IP, Machado MSC, Bruno ZV, Silveira FA, Rehme MFB, et al. Trends in teenage pregnancy in Brazil in the last 20 years (2000-2019). Rev Assoc Med Bras. 2021;67(5):759-65. https://doi.org/10.1590/1806-9282.20210265
3. Pan American Health Organization and the United Nations Population Fund. Adolescent pregnancy in Latin America and the Caribbean. Technical Brief. August 2020. Washington, DC: PAHO, UNFPA. [cited on Apr 23, 2022]. Available from: https://iris.paho.org/handle/10665.2/53133
4. ONU News. Em África, Unesco apoia retorno às aulas após casos de gravidez precoce na pandemia. Amatijane Candé, Bissau, ONU News, outubro 2020. [cited on Apr 07, 2022]. Available from: https://news.un.org/pt/story/2020/10/1728992
5. Organização Panamericana de Saúde (OPAS). Covid-19 tem impactos devastadores sobre as mulheres, afirma diretora da OPAS. [cited on Apr 29, 2022]. Available from: https://www.paho.org/pt/noticias/26-5-2021-covid-19-tem-impactos-devastadores-sobre-mulheres-afirma-diretora-da-opas
6. Ministério da Saúde/DATASUS/SINASC. Departamento de Informática do SUS. Sistema de Informações de Nascidos Vivos. Informações de Saúde - Estatísticas vitais. [cited on May 07, 2022]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinasc/cnv/nvuf.def
7. Instituto Brasileiro de Geografia e Estatística: Projeções da População | IBGE. Projeção da População das Unidades da Federação por sexo e idade: 2000-2030. [cited on May 07, 2022]. Available from: https://www.ibge.gov.br/apps/populacao/projecao/index.html
8. Schwikowski M. África: pandemia da Covid-19 fez aumentar casos de gravidez precoce. [cited on Jul 07, 2022]. Available from: https://p.dw.com/p/40B7D
9. Observatório Obstétrico Brasileiro (OOBr). OOBr Óbitos gestantes e Puérperas. [cited on Sep 06, 2022]. Available from: https://observatorioobstetricobr.org/
10. Almeida P. Mortes de gestantes crescem mais de 40% em 2021, apontam dados da saúde. [cited on Jun 07, 2022]. Available from: https://www.cnnbrasil.com.br/saude/ mortes-de-gestantes-crescem-mais-de-40-em-2021-apontam-dados-da-saude/
11. The World Bank. United Nations Population Division, World Population Prospects. Adolescent fertility rate (births per 1,000 women ages 15-19. [cited on Sep 06, 2022]. Available from: https://data.worldbank.org/indicator/SP.ADO.TFRT?view=map
12. Department of Economic and Social Affairs Population Division. World population prospects 2019 highlights. New York; United Nations, 2019. [cited on Sep 06, 2022]. Available from: https://population.un.org/wpp/publications/files/wpp2019_highlights.pdf
13. Musa SS, Odey GO, Musa MK, Alhaj SM, Sunday BA, Muhammad SM, et al. Early marriage and teenage pregnancy: the unspoken consequences of COVID-19 pandemic in Nigeria. Public Health Pract (Oxf). 2021; 2:100152. https://doi.org/10.1016/j.puhip.2021.100152
14. Relatório Luz 2022. VI Relatório Luz da Sociedade Civil Agenda 2030 de Desenvolvimento Sustentável. Brasil, junho 2022. Available from https://brasilnaagenda2030.files.wordpress.com/2022/07/pt_rl_2022_final_web-1.pdf

SHORT COMMUNICATION

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Comprehensive assessment model for patients with spinal muscular atrophy: proposal of tools for clinical practice and real-world studies

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Spinal muscular atrophy (SMA) is a rare genetic condition, with an incidence of 10 per 100,000 live births, in which an autosomal recessive alteration occurs in the motor neuron survival gene *SMN1*, leading to hypotonia, progressive weakness, developmental damage, and motor losses[1].

It is a condition with great variability in presentation and clinical course, classified into four types from I to IV based on the age of onset of symptoms and maximum motor function reached, with type I, with childhood onset, being the most severe and type IV, with late onset, having a better prognosis. Type I SMA affects infants before 6 months of age, impairs the acquisition of motor milestones, and reduces life expectancy[1]. The severity of the disease and its limitations are related to complications of the respiratory, musculoskeletal, cardiovascular, and gastrointestinal systems[2,3].

Advances in elucidating the molecular, cellular, and physiological processes of disease have allowed innovative studies with disease-modifying therapies, in combination with interdisciplinary care, that demonstrated promising results in clinical trials and real-world studies[1-3].

Among the three alternatives approved as disease-modifying therapies, Nusinersen, an antisense oligonucleotide, increases the production of the motor neuron survival protein by acting on the inclusion of exon 7 in the mRNA transcripts of the *SMN2* gene. It is a medication applied via intrathecal administration with four loading doses on days 0, 14, 28, and 63 and reinforcement every 4 months[1,4]. Safety and efficacy research and real-world studies demonstrate positive results and suggest new phenotypes[1]. However, differences in study methodologies in different countries may limit of results and indicate the need for greater standardization in evaluation[4].

The interpretation of real gains of the patients is impaired by the heterogeneity of the studies, different periods of data collection, and duration of follow-up, as well as by the use of different outcome measures and poor description of quality of life, respiratory, and nutritional outcomes[1].

A recent systematic review shows an important gap in the follow-up data of the therapeutic program of children with SMA I and highlights the need for new studies with independent publication, without conflicts of interest, that reinforce the long-term stabilization of results, functional abilities acquired, and additional characteristics of patients and multidisciplinary therapies[4].

As it is an expensive drug, such data and information reaffirm its cost- effectiveness and guarantee the treatment. In Brazil, the drug was incorporated in 2019 for patients with SMA I. The new Clinical and Therapeutic Protocol, approved in January 2022, brings recommendations for the analysis of clinical effectiveness, including the use of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)[5], Hammersmith Infant Neurological Exam-Part 2 (HINE-2)[6], and Expanded Hammersmith Functional Motor Scale (HFMSE)[7], and also the evaluation of time/modality ventilation, invasive or noninvasive (NIV), oral or alternative feeding, and anthropometric measurements[8].

There is a lack of scientific publications about Brazilian patients undergoing treatment. One study showed an increase in the CHOP INTEND score of more than 70% of the 21 patients using Nusinersen and the acquisition of new motor steps by 28% of them (cervical control and acquisition of sitting), and also reported a reduction in NIV time, corroborating data from international publications and contrasting with

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the natural history of the disease of losses, functional limitations, and early death[9].

We did not find reports demonstrating the experience of other reference services, with detailed information and a more comprehensive and long-term approach of the observed effects. There is also a question about the determination of factors that may also influence the results, in addition to the number of copies of *SMN2* and the precocity of treatment, such as performing therapies, contractures, and preexisting deformities[4].

In view of this limitation of data and correlations and based on international care recommendations and subsequent publications, we suggest an initial evaluation model supplementary to that proposed in the Clinical Protocols and Therapeutic Guidelines for the follow-up of patients with SMA type I using Nusinersen. The aspects that require further investigation and indicated measurement instruments are presented in Table 1.

As it is a multisystemic condition, there is a need for a comprehensive investigation, considering several biopsychosocial aspects[2,3]. The choice of the best tool should consider the child's age and collaboration, as well as the evaluator's knowledge regarding the criteria, application methods, and clinical implications of the findings. In our routine, patients are always evaluated before applying the next dose of medication, up to a maximum of 7 days in advance.

To verify motor function, it is recommended that the CHOP INTEND scale be used with all patients under 2 years of age and with those over 2 years without the ability to sit. The HFMSE is intended for children over 2 years of age who sit or who have a CHOP INTEND score greater than 60. In cases of scores between 50 and 60 on the CHOP INTEND, both scales must be applied. The HINE-2 should be used on patients aged up to 2 years[10].

During the respiratory assessment, not only the time of use of NIV and oxygen pulse saturation should be recorded but also aspects such as the presence of a paradoxical thoracic pattern, growth and development of the rib cage, nocturnal oximetry, lung volumes and capacities, and cough effectiveness need to be measured. These parameters also indicate the adequacy of ventilatory support levels, changes in patient autonomy, and the necessary level of assistance, which allow for better longitudinal follow-up and therapeutic programming[2,11].

The Great Ormond Street Respiratory Score for SMA I (GRS) is also a current alternative to quantify stability and need for assistance[11]. The choice for low- and/or high-cost resources, such as plethysmography, sniff nasal inspiratory pressure, and diaphragmatic ultrasound, will depend on the availability of the service.

The observation of dietary aspects is also relevant, especially with regard to nutritional adequacy and risk of bronchoaspiration, occurrence of fatigue during oral feeding, and regurgitation. The Oral and Swallowing Abilities Tool was developed for this purpose[12]. In specific cases, a study of swallowing by videofluoroscopy can also be performed.

The observation of cognitive and communication aspects allows demonstrating the child's interaction with the environment and improving educational strategies and socialization[13]. It is also interesting to assess quality of life and caregiver burden[14].

The clinical state of the patient must be described in all evaluations, including the presence of pain, contractures and deformities, previous or concomitant diseases, medications, occurrence of dysautonomia, and indication for cardiological evaluation[2,3].

Table 1. Proposed tools for evaluating patients with type I spinal muscular atrophy.

Involvement	Aspect	Assessment tools
Motor	Motor function Motor developmental stages	CHOP INTEND[5] e HMFSE[6] HINE-2[7]
Respiratory	Rib cage growth	Chest circumference[15]
	Vital capacity	Ventilometry[16]
	Sleep disorders	Nocturnal oximetry, poly/polysomnography[17]
	Inspiratory pressure	Sniff nasal inspiratory pressure (SNIP)[18]
	Cough effectiveness	Cough peak flow[19]
	Diaphragmatic mobility and thickness	Diaphragmatic ultrasound[20]
	Ventilatory pattern	Plethysmography[21]
	Stability and need for support	GRS Score[11]
Nutritional	Deglutition	OrSAT[12] Swallowing videofluoroscopy

CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2: Hammersmith Infant Neurological Exam-Part 2; HFMSE: Expanded Hammersmith Functional Motor Scale; GRS: Great Ormond Street Respiratory Score for SMA1; OrSAT: Oral and Swallowing Abilities Tool.

We emphasize the importance of proactive multidisciplinary rehabilitation care, which must be included in the individual therapeutic protocol of patients with the participation of the family. There is a demand for training professionals to assess and treat patients, favoring early diagnosis and intervention, minimizing complications, and ensuring the achievement of the maximum potential of each child with SMA.

AUTHORS' CONTRIBUTIONS

LBA: Conceptualization, Writing – original draft, Writing – review & editing. **VVDL:** Conceptualization, Writing – original draft, Writing – review & editing. **RMRA:** Conceptualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Hjartarson HT, Nathorst-Böös K, Sejersen T. Disease modifying therapies for the management of children with spinal muscular atrophy (5q SMA): an update on the emerging evidence. Drug Des Devel Ther. 2022;16:1865-83. https://doi.org/10.2147/DDDT.S214174
2. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197-207. https://doi.org/10.1016/j.nmd.2017.11.004
3. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(3):103-15. https://doi.org/10.1016/j.nmd.2017.11.005
4. Erdos J, Wild C. Mid- and long-term (at least 12 months) follow-up of patients with spinal muscular atrophy (SMA) treated with nusinersen, onasemnogene abeparvovec, risdiplam or combination therapies: a systematic review of real-world study data. Eur J Paediatr Neurol. 2022;39:1-10. https://doi.org/10.1016/j.ejpn.2022.04.006
5. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010;20(3):155-61. https://doi.org/10.1016/j.nmd.2009.11.014
6. Romeo DM, Cowan FM, Haataja L, Ricci D, Pede E, Gallini F, et al. Hammersmith infant neurological examination for infants born preterm: predicting outcomes other than cerebral palsy. Dev Med Child Neurol. 2020. 63(8):939-46. https://doi.org/10.1111/dmcn.14768
7. O'Hagen JM, Glanzman AM, McDermott MP, Ryan PA, Flickinger J, Quigley J, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 2007;17(9-10):693-7. https://doi.org/10.1016/j.nmd.2007.05.009
8. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Portaria Conjunta Nº03, de 18 de Janeiro de 2022. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Atrofia Muscular Espinhal 5q tipos 1 e 2. https://www.gov.br/saude/pt-br/assuntos/protocolos-clinicos-e-diretrizes-terapeuticas
9. Holanda Mendonça R, Jorge Polido G, Ciro M, Jorge Fontoura Solla D, Conti Reed U, Zanoteli E. Clinical outcomes in patients with spinal muscular atrophy type 1 treated with nusinersen. J Neuromuscul Dis. 2021;(2):217-24. https://doi.org/10.3233/JND-200533
10. Pierzchlewicz K, Kępa I, Podogrodzki J, Kotulska K. Spinal muscular atrophy: the use of functional motor scales in the era of disease-modifying treatment. Child Neurol Open. 2021;8:2329048X211008725. https://doi.org/10.1177/2329048X211008725
11. Edel L, Grime C, Robinson V, Manzur A, Abel F, Munot P, et al. A new respiratory scoring system for evaluation of respiratory outcomes in children with spinal muscular atrophy type1 (SMA1) on SMN enhancing drugs. Neuromuscul Disord. 2021;31(4):300-9. https://doi.org/10.1016/j.nmd.2021.01.008
12. Berti B, Fanelli L, Sanctis R, Onesimo R, Palermo C, Leone D, et al. Oral and swallowing abilities tool (OrSAT) for type 1 SMA patients: development of a new module. J Neuromuscul Dis. 2021;8(4):589-601. https://doi.org/10.3233/JND-200614
13. Polido GJ, Miranda MMV, Carvas N, Mendonça RH, Caromano FA, Reed UC, et al. Cognitive performance of children with spinal muscular atrophy: a systematic review. Dement Neuropsychol. 2019;13(4):436-43. https://doi.org/10.1590/1980-57642018dn13-040011
14. Lloyd AJ, Thompson R, Gallop K, Teynor M. Estimation of the quality of life benefits associated with treatment for spinal muscular atrophy. Clinicoecon Outcomes Res. 2019;25:11:615-22. https://doi.org/10.2147/CEOR.S214084
15. Ropars J, Barnerias C, Hully M, Chabalier D, Peudenier S, Barzic A, et al. Thoracic circumference: a new outcome measure in spinal muscular atrophy type 1? Neuromuscul Disord. 2019;29(6):415-21. https://doi.org/10.1016/j.nmd.2019.03.003
16. Bach JR, Tuccio MC, Khan U, Saporito LR. Vital capacity in spinal muscular atrophy. Am J Phys Med Rehabil. 2012;91(6):487-93. https://doi.org/10.1097/PHM.0b013e31824fa5dd
17. Hilbert J. Sleep-disordered breathing in neuromuscular and chest wall diseases. Clin Chest Med. 2018;39(2):309-24. https://doi.org/10.1016/j.ccm.2018.01.009
18. Miller K, Mayer OH. Pulmonary function testing in patients with neuromuscular disease. Pediatr Pulmonol. 2021;56(4):693-9. https://doi.org/10.1002/ppul.25182
19. Toussaint M, Chatwin M, Gonzales J, Berlowitz DJ; ENMC Respiratory Therapy Consortium. 228th ENMC International Workshop: airway clearance techniques in neuromuscular disorders Naarden, The Netherlands, 3–5 March, 2017. Neuromuscul Disord. 2018;28(3):289-98. https://doi.org/10.1016/j.nmd.2017.10.008
20. Buonsenso D, Berti B, Palermo C, Leone D, Ferrantini G, Sanctis R, et al. Ultrasound assessment of diaphragmatic function in type 1 spinal muscular atrophy. Pediatr Pulmonol. 2020;55(7):1781-8. https://doi.org/10.1002/ppul.24814
21. LoMauro A, Aliverti A, Mastella C, Arnoldi MT, Banfi P, Baranello G. Spontaneous breathing pattern as respiratory functional outcome in children with spinal muscular atrophy (SMA). PLoS One. 2016;11(11):e0165818. https://doi.org/10.1371/journal.pone.0165818

ORIGINAL ARTICLE

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Effect of protection of enoxaparin against experimental ischemia/reperfusion injury in the rat ovary on in vitro fertilization outcomes

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SUMMARY

OBJECTIVE: The study aimed to investigate the protection of enoxaparin (E) against experimental ischemic (I) and ischemic-reperfusion (I/R) injury in rat ovaries on in vitro fertilization outcomes.

METHODS: In total, 56 adult female Sprague-Dawley albino rats were randomly assigned to 6 groups of 8 animals each: Sham, Ischemia, I/R, Sham+E, I+E, and I/R+E. Ischemia groups were subjected to bilateral adnexal torsion for 3 h. In contrast, I/R and I/R+E groups received subsequent detorsion for 3 h. Enoxaparin (0.5 mg/kg s.c.) was administered 30 min prior to ischemia (I+platelet-rich plasma) or reperfusion (I/R+I+platelet-rich plasma). Ovaries were stimulated through intraperitoneal injection of 150–300 internal units IU/kg pregnant mare serum gonadotropin. Anti-Müllerian hormone levels were measured before and after surgery in all groups.

RESULTS: When the number of metaphase II oocytes was evaluated, statistically significant differences were observed between the I and I+E (p=0.001) and I/R and I/R+E (p=0.000) groups. When both I and I+E groups and I/R and I/R+E groups were compared, it was found that E application increased the number of fertilized oocytes. The number of embryos on the second day was higher in the I/R+E group than that in the I/R group. Statistically significant differences were found in the number of grade 1 embryos between the I/R and I/R+E groups (p=0.003). In comparing anti-Müllerian hormone values within the group, the highest decrease was observed in the I and I/R groups.

CONCLUSION: Enoxaparin effectively minimizes ovarian damage and preserves ovarian reserve following ovarian torsion.

KEYWORDS: Fertilization in vitro. Reperfusion injury. Ovarian torsion. Enoxaparin.

INTRODUCTION

Adnexal torsion is a surgical emergency resulting from partial or complete rotation of the ovary, fallopian tube, or both[1]. It has an annual prevalence of approximately 2–6%, commonly in women of reproductive age[2].

It may occur in normal ovaries, with the conditions such as ovarian and/or paratubal cysts, hyperlaxity of the utero-ovarian or infundibulopelvic ligaments, as well as ovulation induction[3]. Timely diagnosis and subsequent surgical intervention for detorsion are crucial to preserving ovarian function and future fertility[3]. The most successful strategy for preserving ovarian tissue is detorsion of the twisted tissues with early surgical intervention[4]. While the ischemic injury is the possible cause of adnexal damage that occurs as the initial result of torsion, ischemia/reperfusion (I/R) injury[5]. Oxidative stress causes tissue damage due to the imbalance between the free radicals formed and the antioxidant defense mechanisms[6]. For this reason, it was determined that the treatment performed as detorsion alone was insufficient, and it was stated that an effective antioxidant and anti-inflammatory treatment could be effective[7].

Enoxaparin (E) sodium, a low-molecular-weight heparin (LMWH), is an anticoagulant agent and has been shown to protect ovarian reserve against ovarian I/R injury by evaluating histopathological damage scores in a rat ovarian torsion model[8].

The protective effects of many agents against I- and I/R-related damage to the ovarian tissue due to ovarian torsion have been demonstrated by histopathological or serum biochemical markers[6,8].

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Although histopathological and biochemical results were obtained in these studies, they do not provide sufficient information about the number of oocytes, embryo number, and quality that result in reproductive physiology.

Therefore, we planned to evaluate the number and quality of embryos obtained by oocyte retrieval and in vitro fertilization (IVF) to predict reproductive outcomes. We aimed to support the situation by evaluating the serum anti-Müllerian hormone (AMH) level.

METHODS

Ethics and animals

The study was conducted in Sakarya University's SÜDETAM laboratory under the authority of Sakarya University's experimental animal ethics committee on 05/05/2021 under decision No. 25. Applications for all research animals were carried out according to the "The European Commission Directive 86/609/ECC guideline" protocol.

The study consisted of a total of 36 virgin Sprague-Dawley albino rats (weighing 220–260 g) and 1 male Sprague-Dawley albino rat (weighing 300 g). Animals were fed ad libitum and tap water in 13 separate cages, using controlled ambient conditions of 20–24°C and 50–60% humidity, with a 12-h light/dark cycle.

Surgical procedures and experimental protocol

The rats were arbitrarily categorized into six groups of six animals each: Sham (S) operation, Ischemia (I) (3 h), I/R (3 h ischemia plus 3 h reperfusion), S+E (0.5 mg/kg enoxaparin s.c. 30 min before surgery), I+E (0.5 mg/kg enoxaparin s.c. 30 min before surgery, 3 h ischemia), and I/R+E (3 h ischemia and 3 h reperfusion with 0.5 mg/kg enoxaparin s.c. before reperfusion).

Ketamine hydrochloride (30 mg/kg Ketalar; Eczacıbaşı, İstanbul, Turkey) and xylazine hydrochloride (15 mg/kg Rompun; Bayer Türk_Ilaç Ltd., İstanbul, Turkey) were used for anesthesia applied to rats[9]. A preoperative blood sample (AMH1) was taken from each rat. Uterine horns and adnexa were observed after a 2-cm longitudinal midline incision. The abdominal wall was closed with 3/0 silk sutures in the S group after 2 min observation. In group I, the ovarian pedicles were rotated 360° clockwise and fixed to the abdominal wall. In the I/R group, the 3 h ischemia period. In the S+E group, enoxaparin 0.5 mg/kg (s.c.) was administered intraperitoneally (i.p.) 30 min before the sham operation. In the I+E group, adnexal torsion was performed, as described, 30 min after 0.5 mg/kg enoxaparin (s.c.) administration. In the I/R+E group, 0.5 mg/kg enoxaparin (s.c.) was followed 30 min later by sequential bilateral adnexal torsion and detorsion.

Rats were prepared for ovulation induction and IVF after waiting for three consecutive estrous cycles. On the day of stimulation, female rats were sacrificed, and their oocytes were collected (Figure 1). Oocytes were classified as germinal vesicle, metaphase I (MI), and metaphase II (MII) stages. To compare the meiotic progression in the maturation process of oocytes in different systems, the mean times taken by each stage of nuclear progression as previously described by Sirard et al. were used[10].

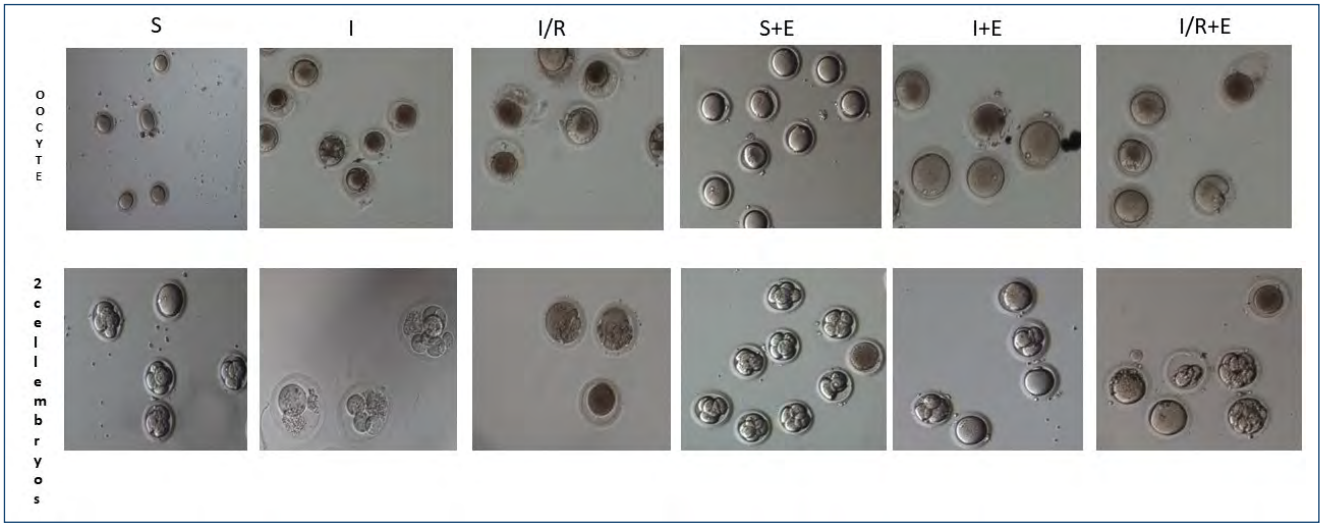

Figure 1. Oocytes and second-day embryos of the groups are seen; 100× magnification. The second-day embryo counts, oocytes maturation and embryo quality in the S and S+E groups were quite good compared to the other groups. It is seen that the quality and number of oocytes and embryos on the second day are significantly better in the I+E and I/R+E groups compared to the I and I/R groups, respectively. S: Sham operation; I: Ischemia; I/R: Ischemia and reperfusion; S+E: Sham+Enoxaparin; I+E: Ischemia+Enoxaparin; I/R+E: Ischemia and reperfusion+Enoxaparin.

Stimulation and collection of oocytes

For ovarian stimulation, 150–300 IU/kg pregnant mare serum gonadotropin (Chronogest/PMSG, Intervet, Istanbul, Turkey) was administered using i.p. injection, followed by 150–300 IU/kg human chorionic gonadotropin (hCG; Gonatropin, Chorulon ® Intervet, Istanbul, Turkey) approximately 48 h later. Notably, 15 IU Pregnant Mare Serum Gonadotropin (PMSG) was administered 17–19 h after hCG administration[11]. After anesthesia was applied to all rats, they were immobilized on a standard operating board, blood samples (AMH2) were taken, ovaries were removed, and the oocytes to be used in the study were collected from the ovaries. A human tubal fluid medium (Cat. No. 90166, Irvine Scientific, USA) was used for sperm pre-incubation, fertilization, and embryo transfer. After fertilization control, fertilized embryos were washed and transferred to culture drops, and the resulting embryos were followed up to the two-cell stage[11]. Before the oocyte collection, male rat testicles were excised under appropriate anesthesia. The epididymis was carefully peeled off using forceps, and the sperm were transferred into petri dishes and incubated at 37°C for 30 min before IVF[12]. After pre-incubating the sperm for 15–60 min, the final sperm concentration was found to be approximately 4.5 to 6×10^5 mL.

After transferring them to culture medium containing sperm in cumulus-oocyte complexes, they were incubated in culture medium at 37°C and 5% CO_2 for 10 h. Oocytes with two pronuclei (2PN) and at least one sperm tail in the ooplasm under the inverted microscope used for fertilization control were considered fertilized[13]. Total cell count was counted as described by Ahumada as an embryo evaluation criterion[14]. Embryo grade assessment was performed based on Veeck's cleavage-stage embryo score using blastomere symmetry and fragmentation rate[15].

Hormonal assays

Serum concentrations of AMH were quantified using enzyme-linked immunosorbent assay (ELISA) AMH kit according to the manufacturer's instructions (BT LAB Biotech Co. Ltd., Shanghai, Cat. No. E0456Ra). The sensitivity of the AMH ELISA was 0.1–40 ng/mL.

Statistical analysis

Statistical analyses were performed using the SPSS version 24.0 package program (SPSS Inc. and Lead Tech. Inc., Chicago, USA). The Shapiro-Wilk test was used for the normal distribution of the data. The Kruskal-Wallis test compared more than two variables that did not show normal distribution. The Kruskal-Wallis comparison was performed using the Mann-Whitney U test for pairwise comparisons between groups in the parameters that differed. Since AMH1 and AMH2 values showed normal distribution, dependent groups were compared using the paired-sample t-test. All results are presented as mean±SD. Results with $p<0.05$ were considered significant.

RESULTS

The group with the highest oocyte collection had an average of 10.13±0.64 in the S group, while the lowest number of oocytes was seen in the I/R group with 2.38±0.51. With the effect of enoxaparin, it was observed that the number of collected oocytes increased in the I and I+E ($p=0.000$) and I/R and I/R+E ($p=0.001$) groups (Figure 2).

When the number of MII oocytes was evaluated, statistically significant differences were observed between the I and I+E ($p=0.001$) and I/R and I/R+E ($p=0.000$) groups (Figure 2). When we compared the I and I+E and I/R and I/R+E groups, statistically significant differences were observed between the fertilized oocytes numbers. The order of p-values was 0.021 when I and I+E groups were compared and 0.011 when I/R and I/R+E groups were compared. Statistically significant differences were also observed between the groups in the number of two-cell embryos ($p=0.000$). While the number of two-cell embryos did not show statistically significant differences between S and S+E and I and I+E groups ($p>0.05$), the number of embryos on the second day was higher in the I/R+E group than in the I/R group (Figure 2).

While there was no statistically significant difference between the number of grade 2, grade 3, and grade 4 embryos between the I and I+E groups ($p>0.05$), there was a significant difference between the number of grade 1 embryos ($p=0.003$). Statistically significant differences were found in the number of grade 1 embryos between the I/R and I/R+E groups ($p=0.003$). When the number of grade 2, grade 3, and grade 4 embryos of the same groups were compared, no significant differences were observed ($p>0.05$).

To compare the effects of E application on AMH values, we examined the correlation between AMH1 and AMH2 values of the S+E, I+E, and I/R+E groups. It was observed that E application had positive effects on AMH concentration in the S+E, I+E, and I/R+E groups. A high degree of correlation was observed between AMH1 and AMH2 values in all three groups. The p-values were the same in all three groups ($p=0.000$ for both groups) (Figure 3).

DISCUSSION

The current management of ovarian torsion is to perform a surgical detorsion procedure to preserve ovarian reserve for

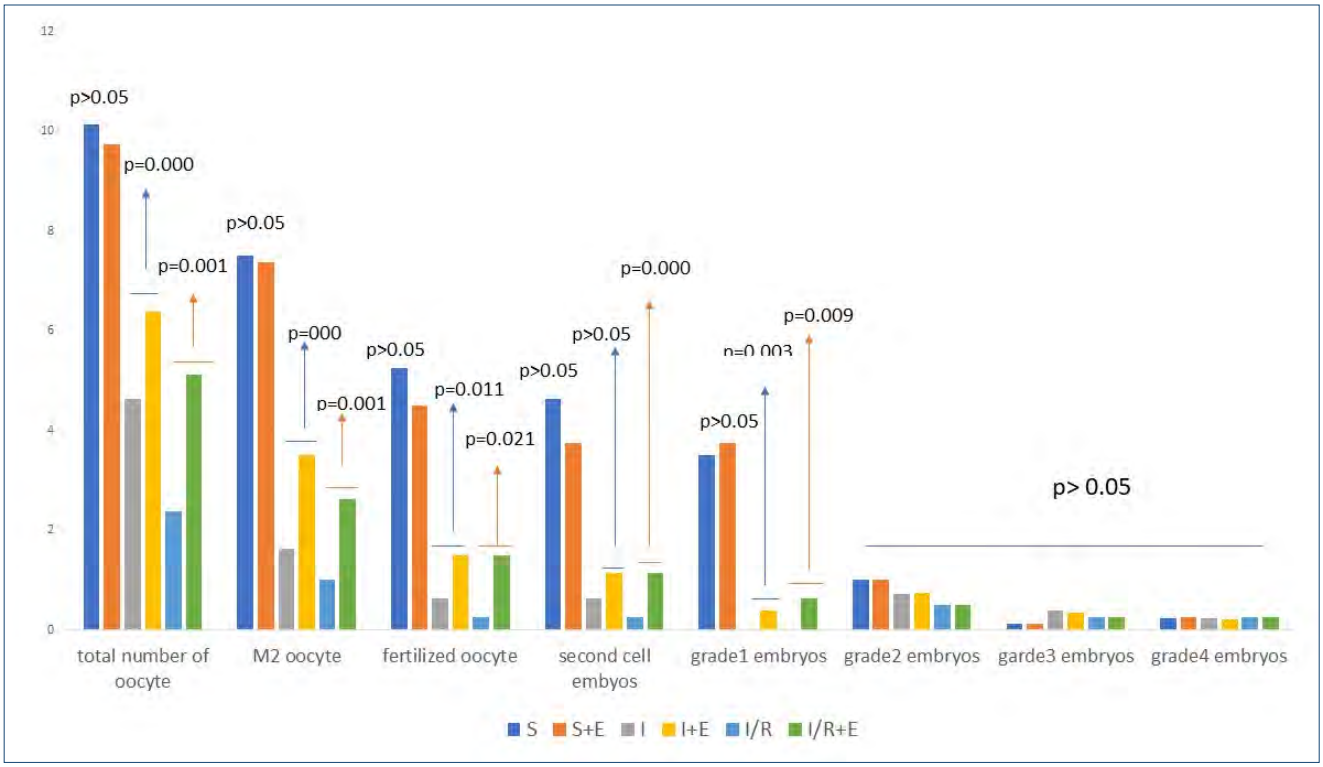

Figure 2. Comparison of the study groups' total oocyte count, metaphase II, fertilized oocyte counts, two-cell embryo, and embryo grade score. Statistical analysis between all groups was performed with the Kruskal-Wallis test. Pairwise comparisons were made with the Mann-Whitney U test (p<0.05 was considered statistically significant). All parameters were statistically significant between groups (p=0.000). No significant difference was observed in all parameters in pairwise comparisons between S and S+E groups. While the embryo Grade 1 score showed statistical differences between I-I/E and I/R-I/R+E groups, there was no statistical difference between grade 2, grade 3, and grade 4 embryos. S: Sham operation; I: Ischemia; I/R: Ischemia and reperfusion; S+E: Sham+Enoxaparin; I+E: Ischemia+Enoxaparin; I/R+E: Ischemia and reperfusion+Enoxaparin; M2: metaphase II.

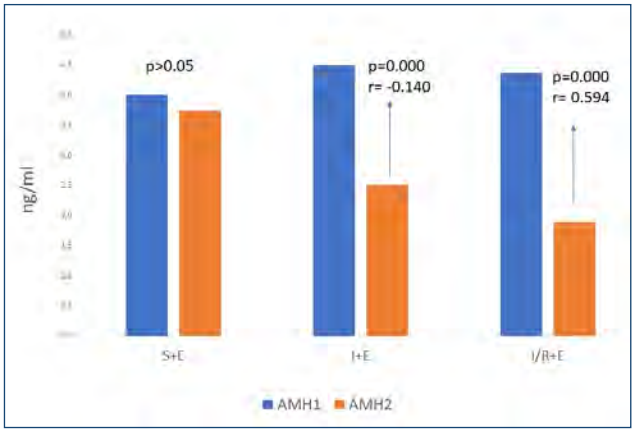

Figure 3. Anti-Müllerian hormone correlation graph between S+E, I+E, and I/R+E groups. There was no correlation between AMH1 and AMH2 values in the S+E group (p>0.05). A high level of correlation was observed between AMH1 and AMH2 concentrations in the I+E and I/R+E groups. AMH: anti-Müllerian hormone (ng/mL). Analysis was performed with the paired sample test (p<0.05 was considered statistically significant). S+E: Sham+Enoxaparin; I+E: Ischemia+Enoxaparin; I/R+E: Ischemia and reperfusion+Enoxaparin; AMH1: preoperative serum anti-Müllerian hormone level; AMH2: postoperative serum anti-Müllerian hormone level.

the continuation of fertility[4]. Reperfusion injury, called I/R injury, that occurs after surgical correction provided by detorsion can also cause serious problems on ovarian reserve. After detorsion, the reestablishment of oxygen in the ischemic cellular environment can trigger tissue injury by the activation of the proapoptotic signaling cascade and complement systems[16]. There are also studies on LMWHs and other molecules, in which the protective effect against oxidative stress in ovarian torsion is demonstrated by changes in histopathological and serum AMH levels[8,17,18].

In earlier tissue I/R studies, such as in cerebral I/R injury, and cardiac and hepatic toxicity models, LMWHs helped prevent cellular damage[19,20]. Enoxaparin has an anti-inflammatory effect in addition to acting as an anticoagulant[21]. This effect is mainly due to its ability to bind proteins such as chemokines, growth factors, enzymes, and adhesion molecules involved in the inflammatory process[21].

In the literature, it has been shown by vascular congestion and hemorrhage scores and histopathological and serum biochemical markers that LMWHs have a protective effect

in ovarian torsion cases[8,22]. These results do not include the number of oocytes obtained later and the number and status of embryos after fertilization. In our study, it is seen that the number of MII oocytes is lower in the I and I/R groups when compared to the I+E and I/R+E groups. It shows that E effectively prevents the effects of torsion and detorsion.

In our study, when I and I/R groups and I+E and I/R+E groups are compared, the number of grade 1 embryos is higher in E group. It shows that E treatment is protective against ovarian reserve damage, and this situation also affects the embryo quality. Evaluating the number of oocytes, the number of fertilized embryos, and their quality instead of histopathological evaluation in predicting fertility is the strength of our study. However, the most critical limitation of the study is that it does not show implantation rates and birth rates after embryo transfer, and there is no human study, although it is an animal study that provides usefulness in predicting clinical outcomes.

The decline of AMH concentrations in experimental ovarian torsion/detorsion injury has been reported in previous studies[8,23]. In our study, the decrease in AMH values was significantly higher in the I and I/R groups than in the I+E and I/R+E groups. To the best of our knowledge, this study reveals more meaningful results in terms of long-term effects, as it includes ovulation induction and IVF with three estrus cycles, rather than the early results provided by the histopathological evaluation performed in other torsion.

CONCLUSION

This is the first experimental study investigating the effects of enoxaparin therapy on ovarian reserve with IVF results. Enoxaparin has a protective effect against ovarian reserve damage caused by torsion and subsequent detorsion.

AUTHORS' CONTRIBUTIONS

MSB: Conceptualization (lead), Data curation (equal), Formal Analysis (equal), Funding acquisition (equal), Investigation (lead), Methodology (lead), Project administration (lead), Resources (equal), Software (equal), Supervision (equal), Validation (lead), Writing – original draft (lead), Writing – review & editing (lead). **ÖB:** Conceptualization (equal), Investigation (equal), Methodology (equal), Writing – original draft (equal), Writing – review & editing (equal). **HÇ:** Investigation (equal), Methodology (equal), Resources (equal). **OK:** Methodology (equal), Software (equal), Supervision (equal), Validation (equal), Visualization (equal). **ÖD:** Investigation (equal), Software (equal). **EÇ:** Methodology (equal), Software (equal), Supervision (equal), Validation (equal).

REFERENCES

1. Vijayalakshmi K, Reddy GM, Subbiah VN, Sathiya S, Arjun B. Clinico-pathological profile of adnexal torsion cases: a retrospective analysis from a tertiary care teaching hospital. J Clin Diagn Res. 2014;8(6):Oc04-7. https://doi.org/10.7860/JCDR/2014/8167.4456
2. Houry D, Abbott JT. Ovarian torsion: a fifteen-year review. Ann Emerg Med. 2001;38(2):156-9. https://doi.org/10.1067/mem.2001.114303
3. Bar-On S, Mashiach R, Stockheim D, Soriano D, Goldenberg M, Schiff E, et al. Emergency laparoscopy for suspected ovarian torsion: are we too hasty to operate? Fertil Steril. 2010;93(6):2012-5. https://doi.org/10.1016/j.fertnstert.2008.12.022
4. Taskin O, Birincioglu M, Aydin A, Buhur A, Burak F, Yilmaz I, et al. The effects of twisted ischaemic adnexa managed by detorsion on ovarian viability and histology: an ischaemia-reperfusion rodent model. Hum Reprod. 1998;13(10):2823-7. https://doi.org/10.1093/humrep/13.10.2823
5. Jennings RB, Murry CE, Steenbergen C Jr, Reimer KA. Development of cell injury in sustained acute ischemia. Circulation. 1990;82(3 Suppl):II2-12. PMID: 2394018
6. Bostancı MS, Bakacak M, İnanc F, Yaylalı A, Serin S, Attar R, et al. The protective effect of G-CSF on experimental ischemia/reperfusion injury in rat ovary. Arch Gynecol Obstet. 2016;293(4):789-95. https://doi.org/10.1007/s00404-015-3878-8
7. Ozler A, Turgut A, Soydinç HE, Sak ME, Evsen MS, Alabalik U, et al. The biochemical and histologic effects of adnexal torsion and early surgical intervention to unwind detorsion on ovarian reserve: an experimental study. Reprod Sci. 2013;20(11):1349-55. https://doi.org/10.1177/1933719113485300
8. Kaya C, Turgut H, Cengiz H, Turan A, Ekin M, Yaşar L. Effect of detorsion alone and in combination with enoxaparin therapy on ovarian reserve and serum antimüllerian hormone levels in a rat ovarian torsion model. Fertil Steril. 2014;102(3):878-84.e1. https://doi.org/10.1016/j.fertnstert.2014.06.007
9. Dair EL, Simoes RS, Simões MJ, Romeu LR, Oliveira-Filho RM, Haidar MA, et al. Effects of melatonin on the endometrial morphology and embryo implantation in rats. Fertil Steril. 2008;89(5 Suppl):1299-305. https://doi.org/10.1016/j.fertnstert.2007.03.050
10. Sirard MA, Florman HM, Leibfried-Rutledge ML, Barnes FL, Sims ML, First NL. Timing of nuclear progression and protein synthesis necessary for meiotic maturation of bovine oocytes. Biol Reprod. 1989;40(6):1257-63. https://doi.org/10.1095/biolreprod40.6.1257
11. Agca Y, Critser JK. Chapter 7 - Assisted reproductive technologies and genetic modifications in rats. In: Suckow MA, Weisbroth SH, Franklin CL, editors. The laboratory rat. 2nd ed. Burlington: Academic Press; 2006. p. 165-89.
12. Seed J, Chapin RE, Clegg ED, Dostal LA, Foote RH, Hurtt ME, et al. Methods for assessing sperm motility, morphology, and counts in the rat, rabbit, and dog: a consensus report. ILSI Risk Science Institute Expert Working Group on Sperm Evaluation. Reprod Toxicol. 1996;10(3):237-44. https://doi.org/10.1016/0890-6238(96)00028-7

13. Seita Y, Sugio S, Ito J, Kashiwazaki N. Generation of live rats produced by in vitro fertilization using cryopreserved spermatozoa. Biol Reprod. 2009;80(3):503-10. https://doi.org/10.1095/biolreprod.108.072918

14. Ahumada A, Olmedo SB, Liebermann J, Mauri AL, Medina R, Posada MN, et al. Manual de procedimentos. Laboratório de Reprodução Assistida. In: Franco Junior JG, editor. São Paulo: Red Latinoamericana de Reproducción Asistida; 2006.

15. Hsu MI, Mayer J, Aronshon M, Lanzendorf S, Muasher S, Kolm P, et al. Embryo implantation in in vitro fertilization and intracytoplasmic sperm injection: impact of cleavage status, morphology grade, and number of embryos transferred. Fertil Steril. 1999;72(4):679-85. https://doi.org/10.1016/s0015-0282(99)00320-9

16. Maneechote C, Palee S, Chattipakorn SC, Chattipakorn N. Roles of mitochondrial dynamics modulators in cardiac ischaemia/reperfusion injury J Cell Mol Med. 2017;21(11):2643-53. https://doi.org/10.1111/jcmm.13330

17. Karakaş S, Kaya C, Güraslan H, Sakiz D, Süzen Çaypinar S, Cengiz H, et al. Effect of metformin and detorsion treatment on serum anti-Müllerian hormonelevels and ovarian histopathology in a rat ovarian torsion model. Turk J Med Sci. 2020;50(2):455-63. https://doi.org/10.3906/sag-1803-196

18. Güney G, Kaya C, Yildirim S, Oto G, Ekin S, Özdemir H. Investigation of allium sativum's protective effect on ovarian reserve in an experimental ovarian injury model. Int J Morphol. 2018;36(2):395-401. https://doi.org/10.4067/S0717-95022018000200395

19. Deepa PR, Varalakshmi P. Protective effect of low molecular weight heparin on oxidative injury and cellular abnormalities in adriamycin-induced cardiac and hepatic toxicity. Chem Biol Interact. 2003;146(2):201-10. https://doi.org/10.1016/j.cbi.2003.08.003

20. Zhang ZG, Zhang QZ, Cheng YN, Ji SL, Du GH. Antagonistic effects of ultra-low-molecular-weight heparin against cerebral ischemia/reperfusion injury in rats. Pharmacol Res. 2007;56(4):350-5. https://doi.org/10.1016/j.phrs.2007.08.004

21. Manduteanu I, Dragomir E, Voinea M, Capraru M, Simionescu M. Enoxaparin reduces H2O2-induced activation of human endothelial cells by a mechanism involving cell adhesion molecules and nuclear transcription factors. Pharmacology. 2007;79(3):154-62. https://doi.org/10.1159/000098952

22. Sahin Ersoy G, Eken M, Tal R, Oztekin D, Devranoglu B, Isik Kaygusuz E, et al. N-acetylcysteine leads to greater ovarian protection than enoxaparin sodium in a rat ovarian torsion model. Reprod Biomed Online. 2016;33(1):93-101. https://doi.org/10.1016/j.rbmo.2016.03.009

23. Dasgupta R, Renaud E, Goldin AB, Baird R, Cameron DB, Arnold MA, et al. Ovarian torsion in pediatric and adolescent patients: a systematic review. J Pediatr Surg. 2018;53(7):1387-91. https://doi.org/10.1016/j.jpedsurg.2017.10.053

ORIGINAL ARTICLE

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Overweight status, abdominal circumference, physical activity, and functional constipation in children

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SUMMARY

OBJECTIVE: The aim of this study was to assess the prevalence of functional constipation and its relationship with the food intake, overweight status, and physical activity of children.

METHODS: This cross-sectional study included students from two public schools in the municipality of Osasco, which is located in the metropolitan area of São Paulo. Functional constipation was diagnosed if the clinical manifestations of the Rome IV criteria were present for more than 2 months. A 24-h recall survey was used to determine the daily food intake. Weight, height, abdominal circumference, and bioelectrical impedance were used to evaluate the weight status. Active commuting to school and physical activity scores were assessed using a questionnaire that has been validated in Brazil.

RESULTS: A total of 452 children, aged 6–12 years, were evaluated. Functional constipation was observed in 22.3% of participants. A greater abdominal circumference was associated with functional constipation in girls (p=0.036) in the bivariate analysis but not in the logistic regression model. Boys with functional constipation consumed higher quantities of fats (p=0.041). There was no statistically significant relationship between functional constipation and overweight status (44.6 and 34.5% of children with and without constipation, respectively; p=0.083) and active commuting to school (48.5 and 56.7% of children with and without constipation, respectively; p=0.179).

CONCLUSION: Functional constipation was associated with a greater abdominal circumference in girls in the bivariate analysis, however, without association in the logistic regression model. Boys with functional constipation consumed higher quantities of fat. No association was found between functional constipation, overweight status, and physical activity.

KEYWORDS: Child. Constipation. Eating. Pediatric obesity. Exercise. Sagittal abdominal diameter.

INTRODUCTION

Functional constipation is a functional gastrointestinal disorder that is a highly prevalent health issue in children[1-3]. Functional constipation is caused by the interaction of biopsychosocial factors such as genetic features, intestinal motility disturbance, low dietary fiber intake, low fluid intake, physical inactivity, and a vicious cycle of painful evacuation leading to fecal retention due to the inhibition of bowel movements[1-6].

In adolescents and adults, constipation is more frequent in females; however, in children, there is no consensus on the distribution of constipation between the sexes[1,4].

Increasing the intake of dietary fiber and water is recommended to treat and prevent functional constipation[6-8]. However, the effects of energy intake and different types of dietary nutrients as factors associated with functional constipation have not been completely explored[9,10].

Although few studies have indicated that overweight status is a risk factor for functional constipation[2-11], the scientific evidence is controversial[2,11]. An association between visceral body fat and irritable bowel syndrome in adult women was recently reported[12]. However, the relationship between abdominal circumference and functional constipation has not been evaluated in the pediatric age range. Furthermore, the effects of physical activity and its intensity on functional constipation in children and adolescents have not been widely investigated[13-15]. This study was conducted to assess the prevalence of functional constipation and its relationship with food intake, overweight status, and physical activity of children.

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METHODS

Study design

This cross-sectional study included students from two public schools in the municipality of Osasco, which is located in the metropolitan area of São Paulo. Functional constipation was diagnosed based on the clinical manifestations of the Rome IV criteria for more than 2 months. Food intake was evaluated using the 24-h dietary recall. Overweight status was evaluated using anthropometric and electrical bioimpedance measurements. Physical activity was evaluated based on the active commuting of the students to school and physical activity scores were obtained using a questionnaire validated in Brazil. The study was approved by the Research Ethics Committee of the Federal University of São Paulo (CEP 2.250.658).

Participants

Data were collected between November 2014 and 2015. The Department of Education selected the schools where greater collaboration and adherence of employees was expected to carry out the study. The only inclusion criterion was the enrollment in the schools included in the study by the Secretary of Education of the Municipality of Osasco. Therefore, all students were invited to participate in the study, regardless of their sex, nutritional status, race, or economic status. Patients with severe genetic, neurologic, cardiopulmonary, inflammatory, endocrine, or chronic kidney diseases were excluded from the data analysis.

A total of 1,770 students between 6 and 12 years of age attended the two designated schools. A presentation on the topic of the study was made to all parents and/or guardians. Authorization to participate in the study was requested from all parents or guardians. The parents of 480 (27.1%) children signed an informed consent form, while one student refused to participate in this study. The parents of 25 students could not be interviewed to provide information for the study. Two students were excluded because of severe disease (one with myelomeningocele and one with cerebral palsy). Finally, a total of 452 participants were included in this study.

Method

Functional constipation diagnosis

Functional constipation was diagnosed when the children had two or more of the following six clinical manifestations of the Rome IV criteria[3] for a minimum of 2 months[5]: two or fewer defecations per week in the toilet for a child of developmental age (at least 4 years of age); at least one episode of fecal incontinence per week; history of retentive posturing or excessive volitional stool retention; history of painful or hard bowel movements; and history of large-diameter stools that can obstruct the toilet[3,5].

Parents answered questions about the Rome IV criteria during the face-to-face interviews. The questions used in the interview were in Portuguese, and they had been tested for comprehension and were successfully used to identify functional constipation[16] in accordance with the Rome criteria[3,5].

Food intake analysis

The 24-h dietary recall survey, answered by parents/guardians, was used to obtain data for the quantitative analysis[17]. The nutrient calculations were performed using the Nut Win version 2.5 software developed by the Health Information Technology Department of the Federal University of São Paulo (São Paulo, Brazil).

Weight, height, and abdominal circumference measurements

Weight and height were measured as recommended[18]. Abdominal circumference was measured with an inelastic tape from the midpoint between the last rib and the upper border of the iliac crest (hip bone)[18]. The height-for-age z-scores and the relationship between the body mass index and age were calculated by the Anthro plus software version 1.0.4 (World Health Organization, Geneva, Switzerland).

Electrical bioimpedance analysis

The electrical bioimpedance test was performed using electrode placement (101 Quantum; RJL Systems, Miami, FL, USA) and BC software version 1.038 (RJL Systems, Miami, FL, USA) to estimate the body fat mass and lean mass.

Physical activity analysis

To evaluate physical activity, the children received illustrated questionnaires with drawings related to the activities they might have performed the previous day. The previous day's version improves measurements and reduces the child's need for recall by preventing craving behavior responses[19]. During the first part, they identified the means of transportation used to go to school (on foot, or by bicycle, public bus, car, or school bus). Then, the answer was rated as active or inactive commuting to school[19,20].

During the second part of the test, the participants were asked to choose the intensity level of each type of activity (low, medium, or high). The survey illustrated 11 possible types of

activities (dancing, walking/running, biking, performing chores, going up the stairs, playing soccer, jumping rope, swimming, gymnastics, skating, and playing with a dog). The score for each activity was determined by assigning 1 point for low intensity, 3 points for medium intensity, and 9 points for high intensity; the maximum score for all activities was 99[19,20].

Statistical analysis

Parametric and nonparametric statistical tests were performed according to the variable distribution to analyze the results along with the Sigma Plot version 11.2 software (Systat Software, San Jose, CA, USA). For all the tests, the significance level was set at 5% or 0.05.

RESULTS

The prevalence of functional constipation was 22.3% (101/452) for the total population, with a rate of 23.9% (65/273) for girls and 20.1% (36/179) for boys (p=0.419). The mean age was similar in children with (9.4 years±1.3) and without (9.2 years±1.5) constipation (p=0.257). Logistic regression showed a statistically significant effect (p=0.011) on the interaction between sex and age. Up to 9 years of age, the proportion of constipation was similar in both sexes; however, from 10 years onward, it was more frequent (p<0.05) in females.

Food intake was similar between children with and without functional constipation; however, fat intake was higher for boys with functional constipation (Table 1). The body mass index, height-for-age z-scores, lean mass, and fat mass did not differ between children with and without functional constipation (Table 2). The abdominal circumference was larger for girls with functional constipation than for boys.

Overweight status was more frequent in boys and girls with functional constipation (44.6%; 45/101) than in those without constipation (34.5%; 121/351). However, the difference was not statistically significant (p=0.083); a total of 46.2% (30/65) and 37.0% (77/208) of girls with and without functional constipation, respectively, were overweight (p=0.242). Furthermore, 41.7% (15/36) and 30.8% (44/143) of boys with and without functional constipation, respectively, were overweight (p=0.296). There was no difference in the frequency of active commuting to school or in the physical activity scores of the groups with and without functional constipation (Table 3).

The logistic regression model including sex, age, overweight, and functional constipation did not confirm the association between abdominal circumference and functional constipation (p=0.705) in female students as found in the bivariate analysis.

Table 1. Food intake of children according to sex and the presence of functional constipation.

	Functional constipation		p-value[a]
	Yes	No	
Energy (kcal)			
Girls	1960.7±906.7	1980.1±750.4	0.615
Boys	2199.2±631.5	2049.6±771.5	0.071
Total	2045.7±823.9	2008.4±758.7	0.571
Protein (g)			
Girls	89.2±45.0	93.7±44.7	0.258
Boys	101.8±37.2	101.4±57.0	0.416
Total	93.7±42.7	96.8±50.2	0.689
Lipid (g)			
Girls	54.0±40.2	56.3±29.8	0.255
Boys	62.8±24.2	55.6±26.7	**0.041**
Total	57.2±35.5	55.9±28.5	0.770
Carbohydrate (g)			
Girls	280.7±126.8	275.7±110.9	0.909
Boys	307.3±105.2	285.6±102.5	0.240
Total	290.2±119.7	279.7±107.5	0.474
Water (mL)			
Girls	1212.3±506.9	1216.6±453.8	0.579
Boys	1348.7±445.7	1286.2±488.9	0.618
Total	1260.9±488.2	1244.9±468.9	0.926
Dietary fiber (g)			
Girls	25.9±15.2	28.3±17.5	0.466
Boys	33.1±19.3	29.8±18.2	0.444
Total	28.5±17.1	28.9±17.8	0.828
Calcium (mg)			
Girls	597.7±323.2	611.7±337.7	0.612
Boys	639.4±300.7	673.8±395.0	0.825
Total	612.6±314.5	637.0±362.9	0.607
Iron (mg)			
Girls	9.7±5.3	9.9±4.5	0.362
Boys	11.5±4.3	10.8±5.1	0.176
Total	10.3±5.0	10.3±4.8	1.000
Vitamin A (IU)			
Girls	622.2±1140.0	509.9±480.2	0.832
Boys	550.7 ± 397.4	834.2±3057.4	0.993
Total	596.7 ± 942.5	641.9±1988.5	0.883
Vitamin C (mg)			
Girls	69.5±91.9	81.5±119.1	0.333
Boys	76.1±88.2	62.0±76.7	0.443
Total	71.9±90.2	73.6±104.2	0.738
Cholesterol (mg)			
Girls	217.1±112.5	265.3±185.3	0.141
Boys	263.2±125.0	262.6±206.1	0.272
Total	233.5±118.6	264.2±193.7	0.605

Number of children with constipation: 65 girls and 36 boys. Number of children without constipation: 208 girls and 143 boys. Mean±standard deviation. [a]Student's t-test was performed for independent samples. Bold indicates statistically significant p-values.

Table 2. Body mass index, height-for-age z-score, abdominal circumference, abdominal circumference for height, and body composition of children according to sex and the presence of functional constipation.

	Functional constipation		p-value[a]
	Yes	No	
Body mass index (kg/m^2)			
Girls	19.0±3.5	18.2±3.4	0.074
Boys	18.2±3.7	17.9±3.3	0.616
Total	18.7±3.6	18.1±3.4	0.079
Height for age (z-score)			
Girls	0.3±1.1	0.4±0.9	0.590
Boys	0.3±0.9	0.3±1.1	0.806
Total	0.3±1.0	0.3±1.0	0.578
Abdominal circumference (cm)			
Girls	64.5±9.2	61.9±8.8	**0.036**
Boys	62.9±9.4	62.5±8.9	0.693
Total	63.9±9.3	60.2±8.9	0.054
Abdominal circumference[a] / height (cm)			
Girls	0.47±0.1	0.46±0.1	0.274
Boys	0.47±0.1	0.46±0.0	0.524
Total	0.47±0.1	0.46±0.1	0.202
Lean mass (%)			
Girls	74.2±7.8	74.9±7.3	0.541
Boys	76.3±7.3	77.0±0.6	0.705
Total	74.9±7.7	75.7±7.1	0.283
Fat mass (%)			
Girls	25.8±7.8	25.0±7.1	0.470
Boys	23.7±7.3	22.9±6.7	0.701
Total	25.0±7.7	24.2±6.9	0.268

Number of children with constipation: 65 girls and 36 boys. Number of children without constipation: 208 girls and 143 boys. Mean±standard deviation. [a]Student's t-test was performed for independent samples. Bold indicates statistically significant p-values.

Table 3. Physical activity of children according to sex and the presence of functional constipation.

	Functional constipation		p-value
	Yes	No	
Physical activity score			
Girls	15.4±8.1	16.4±10.4	0.901[a]
Boys	20.7±16.3	18.7±10.1	0.792[a]
Total	17.3±11.9	17.3±10.3	0.601[a]
Active commuting to school			
Girls	44.6% (29/65)	52.9% (110/208)	0.307[b]
Boys	55.6% (20/36)	62.2% (89/143)	0.587[b]
Total	48.5% (49/101)	56.7% (199/351)	0.179[b]

Number of children with constipation: 65 girls and 36 boys, n=36. Number of children without constipation: 208 girls and 143 boys. Mean±standard deviation. [a]Student's t-test was performed for independent samples, [b]Pearson's chi-square test.

DISCUSSION

The prevalence of functional constipation in the present study was similar to that reported by other studies in Brazil[1] and other countries[4].

For boys, a higher fat intake was observed, which was in concordance with a study on Japanese children[9]. This finding suggests that there might be an abnormal gastrocolic reflex response with prolonged retrograde phasic contraction after eating a fat-rich meal[9]. This mechanism may be related to dysmotility in functional constipation. No additional differences were observed in the intake of other nutrients, including dietary fiber, between the groups with and without functional constipation. However, studies showed that children with functional constipation had a lower intake of total dietary fiber, insoluble dietary fiber, vegetables, fruits, and fluids[15,21]. The absence of relationships between functional constipation and other nutrients observed during this study may be related to the fact that the participants had mild functional constipation.

Our results are also in agreement with those of studies performed in Brazil[22] and Colombia[11] that did not demonstrate any association between functional constipation and overweight status; however, this result differed from those of studies performed in developed countries. Moreover, this discrepancy can be explained by hormonal, emotional, and genetic factors, as well as by eating habits, lifestyle, and financial status in different countries[11], in addition to the severity of functional constipation.

This study is the first to show the relationship between increased abdominal circumference and functional constipation in children, specifically in girls. This result agrees with the amount of visceral fat observed using abdominal tomography in adult women with irritable bowel syndrome[12]. The fact that fecal incontinence was not observed in patients with functional constipation suggests that there was insufficient fecal retention in the colon that could increase the abdominal circumference. Notably, the relationship between functional constipation and abdominal circumference observed during our study agrees with the results of another study in Brazil that demonstrated a higher correlation between metabolic syndrome and abdominal

circumference in relation to the ratio of the abdominal circumference to height[23].

The relationship between increased abdominal circumference and functional constipation dysmotility may be related to increased intra-abdominal pressure caused by excess visceral fat. Another possible mechanism is related to the amount of adipokines and cytokines secreted by the visceral adipose tissue, which cause low-grade tissue inflammation in the gut. Inflammation may result in abnormal epithelial secretion, visceral hypersensitivity, smooth muscle dysfunction syndrome, dysmotility, and pain perceived by the enteric nervous system[11,22]. However, further studies are required to explore and support this hypothesis.

In contrast to the literature[15,24,25], no connection between less physical activity and functional constipation was observed. Research involving children and teenagers in Iceland has shown a connection between these two factors for children older than 10 years[24]. However, the children and teenagers studied in Iceland were older than the children evaluated during our study.

A limitation of this study is its cross-sectional design that does not allow for establishing a cause–effect relationship. The study was performed in only one city and thus does not represent the entire Brazilian population. The results of the present study justify the development of future projects in not only public but also private schools. In addition, there is a need for further studies on the intensity of physical activity and constipation in children to elucidate whether there is a relationship.

CONCLUSION

The prevalence of functional constipation was similar to that observed in other epidemiological studies. Functional constipation was associated with a greater abdominal circumference in girls in the bivariate analysis; however, there was no association in the logistic regression model. Boys with functional constipation consumed higher quantities of fat. No association was found among functional constipation, overweight status, and physical activity.

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AUTHORS' CONTRIBUTIONS

FCD: Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **SNB:** Data curation, Visualization, Writing – review & editing. **ST:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **LM:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **MBM:** Conceptualization, Formal Analysis, Project administration, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Morais MB, Maffei HVL. Constipação intestinal. J Pediatr (Rio J). 2000;76:S147-56.
2. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem. World J Gastroenterol. 2016;22(30):6864-75. https://doi.org/10.3748/wjg.v22.i30.6864
3. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, Van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1527-37. https://doi.org/10.1053/j.gastro.2016.02.015
4. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr. 2018;198:121-30.e6. https://doi.org/10.1016/j.jpeds.2018.02.029
5. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527-37. https://doi.org/10.1053/j.gastro.2005.08.063
6. Tabbers MM, Dilorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58(2):258-74. https://doi.org/10.1097/MPG.0000000000000266
7. National Collaborating Centre for Women's and Children's Health (UK). Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. London: RCOG Press; 2010.
8. Lindberg G, Hamid SS, Malfertheiner P, Thomsen OO, Fernandez B, Garisch JJ, et al. World gastroenterology organisation global guideline: constipation – a global perspective. J Clin Gastroenterol. 2011;45(6):483-7. https://doi.org/10.1097/MCG.0b013e31820fb914
9. Fujitani A, Sogo T, Inui A, Kawakubo K. Prevalence of functional constipation and relationship with dietary habits in 3- to 8- year-old children in Japan. Gastroenterol Res Pract. 2018;2018:3108021. https://doi.org/10.1155/2018/3108021

10. Benninga MA, Tabbers MM. Constipation in children: fibre and probiotics. BMJ Clin Evid. 2015;2015:0303. PMID: 25758093
11. Koppen IJ, Velasco-Benítez CA, Benninga MA, Di Lorenzo C, Saps M. Is there an association between functional constipation and excessive bodyweight in children?. J Pediatr. 2016;171:178-82.e1. https://doi.org/10.1016/j.jpeds.2015.12.033
12. Lee CG, Lee JK, Kang YS, Kim JH, Lim YJ, Koh MS, et al. Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. Am J Gastroenterol. 2015;110(2):310-9. https://doi.org/10.1038/ajg.2014.422
13. Huang R, Ho SY, Lo WS, Lam TH. Physical activity and constipation in Hong Kong adolescents. PLoS One. 2014;9(2):e90193. https://doi.org/10.1371/journal.pone.0090193
14. World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010.
15. Chien L-Y, Liou YM, Chang P. Low defaecation frequency in Taiwanese adolescents: association with dietary intake, physical activity and sedentary behaviour. J Paediatr Child Health. 2011;47(6):381-6. https://doi.org/10.1111/j.1440-1754.2010.01990.x
16. Sangalli CN, Dos Santos Leffa P, De Morais MB, Vitolo MR. Infant feeding practices and the effect in reducing functional constipation 6 years later: a randomized field trial. J Pediatr Gastroenterol Nutr. 2018;67(5):660-5. https://doi.org/10.1097/MPG.0000000000002075
17. Freudenheim JL. A review of study designs and methods of dietary assessment in nutritional epidemiology of chronic disease. J Nutr. 1993;123(2 Suppl):401-5. https://doi.org/10.1093/jn/123.suppl_2.401
18. Sociedade Brasileira de Pediatria. Manual de orientação: avaliação nutricional da criança e do adolescente. São Paulo: Sociedade Brasileira de Pediatria. Departamento Científico de Nutrologia; 2021. p.120.
19. Costa FF, Liparotti JR. Reliability of a new questionnaire for the evaluation of habitual physical activity and food consumption in children. Rev Bras Cineantropom Desempenho Hum. 2010;12(1):21-8. https://doi.org/10.5007/1980-0037.2010v12n1p21
20. Barros MVG, Assis MAA, Pires MC, Grossemann S, Vasconcelos FAG, Luna MEP, et al. Validity of physical activity and food consumption questionnaire for children aged seven to ten years old. Rev Bras Saúde Matern Infant. 2007;7(4):437-48. https://doi.org/10.1590/s1519-38292007000400011
21. Okuda M, Kunitsugu I, Yoshitake N, Sasaki S. The relationship between functional constipation and dietary habits in school-age Japanese children. J Nutr Sci Vitaminol. 2019;65(1):38-44. https://doi.org/10.3177/jnsv.65.38
22. Costa ML, Oliveira JN, Tahan S, Morais MB. Overweight and constipation in adolescents. BMC Gastroenterol. 2011;11:40. https://doi.org/10.1186/1471-230X-11-40
23. Pereira PF, Serrano HMS, Carvalho GQ, Lamounier JA, Peluzio MCG, Franceschini SCC, et al. Circunferência da cintura e relação cintura/estatura: úteis para identificar risco metabólico em adolescentes do sexo feminino? Rev Paul Pediatr. 2011;29(3):372-7. https://doi.org/10.1590/S0103-05822011000300011
24. Seidenfaden S, Ormarsson OT, Lund SH, Bjornsson ES. Physical activity may decrease the likelihood of children developing constipation. Acta Paediatr. 2017;107(1):151-5. https://doi.org/10.1111/apa.14067
25. Driessen LM, Kiefte-de Jong JC, Wijtzes A, de Vries SI, Jaddoe VW, Hofman A, et al. Preschool physical activity and functional constipation: the generation R study. J Pediatr Gastroenterol Nutr. 2013;57(6):768-74. https://doi.org/10.1097/MPG.0b013e3182a313fc

ORIGINAL ARTICLE

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Effect of contrast medium on early detection and analysis of mediastinal lymph nodes in computed tomography

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SUMMARY

OBJECTIVE: This study aimed to evaluate the diagnostic efficiency of contrast-to-noise and signal-to-noise ratios created by the contrast medium in detecting lymph nodes.

METHODS: In this study, 57 short-axis subcentimeter lymph nodes in 40 cardiac computed tomography patients with noncontrast- and contrast-enhanced phases were evaluated. The contrast-to-noise ratios and signal-to-noise ratios of noncontrast- and contrast-enhanced lymph node-mediastinal fat and aortic-mediastinal fat tissues were determined. In addition, lymph nodes in noncontrast- and contrast-enhanced series were evaluated subjectively.

RESULTS: There was a significant difference in lymph node-mediastinal fat signal-to-noise values between the contrast and noncontrast phases (p=0.0002). In the contrast phase, aortic density values were found to be 322.04±18.51 HU, lymph node density values were 76.41±23.41 HU, and mediastinal adipose tissue density values were -65.73±22.96 HU. Aortic-mediastinal fat contrast-to-noise ratio value was 20.23±6.92 and the lymph node-mediastinal fat contrast-to-noise ratio value was 6.43±2.07. A significant and moderate correlation was observed between aortic-mediastinal fat and lymph node-mediastinal fat contrast-to-noise ratio values in the contrast phase (r=0.605; p<0.001). In the contrast-enhanced series, there was a significant increase in the subjective detection of lymph nodes (p=0.0001).

CONCLUSION: In the detection of paratracheal lymph nodes, the contrast agent increases the detection of short-axis subcentimeter lymph nodes quantitatively and qualitatively. Contrast enhances and facilitates the detection of paratracheal lymph nodes.

KEYWORDS: Lymph nodes. Contrast media. Computed tomography. Mediastinum.

INTRODUCTION

Lung cancer is the leading cause of death from cancer[1]. Mediastinal lymph node evaluation is important in the diagnosis, treatment, and follow-up of lung cancer because lung cancer often causes mediastinal and hilar lymph node involvement[1,2]. In particular, lymphoscintigraphic evaluations revealed that the dominant route in lymphatic drainage was the bilateral paratracheal area[3]. Therefore, the detection of paratracheal lymph nodes is an important factor in tumor staging[3]. Lymph node diagnosis, staging, and treatment protocol may vary[4,5]. A short axis >1 cm is an important criterion in the definition of the pathological lymph node[6]. However, some studies have shown that lymph nodes with a short axis <1 cm can also be pathological[7-9]. Therefore, determining the early metastatic involvement of the lymph nodes is very important for the patient's prognosis[5]. In addition, suspicious lymph nodes should not be overlooked in lymph node surgeries. Detection of large lymph nodes is relatively easy during imaging and surgical procedures, while detection of small lymph nodes is quite difficult. The most accurate detection of small lymph nodes can change the staging of the patient[7,10]. Thus, a patient's surgery, treatment protocol, and prognosis may change.

Many imaging methods are used in the detection, staging, and follow-up of mediastinal lymph nodes. Methods such as computed tomography (CT), positron emission tomography, magnetic resonance imaging (MRI), and endobronchial ultrasonography can be used[1,11-13]. However, these methods have difficulties in detecting small lymph nodes, and their effectiveness decreases[10]. Therefore, optimizing shooting techniques and increasing the efficiency of these methods by determining the factors affecting image quality are important problems in engineering and radiology sciences.

MRI has the advantage over CT that it is radiation free. However, since MRI does not provide evaluation of lung parenchyma, CT is still used more effectively in the lung and mediastinal area[14]. CT is an effective and important test in the diagnosis of early-stage lung cancer[15]. However, since it has the disadvantage of containing radiation dose, it should be

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done with optimal and correct techniques. Thus, the patient is exposed to less radiation dose[15]. For this reason, protocols are being made for lung and mediastinal evaluation, and these protocols are being developed day by day[16].

In our study, we aimed to evaluate the effect of vascular contrast material on contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) in CT and its effectiveness in subcentimetric lymph node diagnosis.

METHODS

Patient selection

This study was approved by the Atatürk University Scientific Ethics Committee (dated February 24, 2022; decision no. 2/26). In this study, the images of the patients who had no known malignancy and who had 62 cardiac extractions were reviewed retrospectively. Notably, 5 patients with body mass index >30, 3 patients with mediastinal calcified lymphadenopathies, 3 patients whose lymph node evaluation was not performed due to artifacts, and 11 patients whose mediastinal paratracheal lymph nodes were not detected were excluded from the study. Only individuals with mediastinal subcentimetric lymph nodes were used in the study. Patients with lung pathology that may cause mediastinal lymph node formation and an increase in number were excluded from the study. Thus, the cardiac patient group in which only cardiac imaging was performed due to cardiac complaints and the mediastinal area was evaluated was selected. In total, 40 individuals who met the criteria were evaluated. In addition, 57 lymph nodes with a short axis <1 cm were evaluated in 40 patients.

Computed tomography protocol

CT examinations were performed with a 256-section CT scanner (Somatom Definition Flash®, Siemens Healthcare, Forscheim, Germany). Prospective ECG-gated high-pitch "flash spiral" technique was used to acquire the images with the following parameters: 120 kVp; 3 mm slice thickness; 256×0.6 mm slice collimation; z-flying focal spot; 280 ms gantry rotation time; 3.4 pitch; 75 msn temporal resolution; tube current of 80–140 mA; and topogram-based automatic tube current selection (CareDose 4D®, Siemens Healthcare). The contrast amount was 90–100 mL, and the injection rate was 4–5 mL/s.

Image analysis

Noncontrast and 15-s images of 40 patients in the aorta were evaluated in the mediastinal window (window width, 350 HU; level, 50 HU). Evaluations were made for lymph nodes located 1 cm below the short axis at the paratracheal level. Hounsfield unit mean density and standard deviation (SD) values were determined by applying 0.10–0.15 cm^2 to a region of interest (ROI) from the aortic lumen, paratracheal adipose tissue, and paratracheal lymph nodes in the cortical area. Aortic-mediastinal fat and paratracheal lymph node-mediastinal fat CNRs and SNRs were determined with the following formulas for contrast and noncontrast series. The SNR (Equation 1)

is found by dividing the signal intensity (SI) by the SD. The CNR (Equation 2) is found by dividing the difference between the lesion and background ROI values by the square root of half the sum of the squares of the SD.

$$\mathrm{SNR} = \frac{\mathrm{SI(ROIa)}}{\mathrm{SD(ROIa)}} \quad (1)$$

$$\mathrm{CNR} = \frac{\mathrm{ROI(organ)} - \mathrm{ROI(background)}}{\sqrt{\frac{1}{2}\left(\mathrm{SD(organ)}^2 + \mathrm{SD(background)}^2\right)}} \quad (2)$$

In addition, the lymph nodes were evaluated subjectively by two observers according to the clarity of the lymph node mediastinal fat border separation. Image quality was evaluated by two reviewers for lymph node and mediastinal adipose tissue separation. They were instructed to report lesion conspicuity on a 4-point scale (1, barely perceptible with presence debatable; 2, subtle finding but likely a lesion; 3, definite lesion detected; and 4, strikingly evident and easily detected)[17,18]. The conspicuity of undetected lesions was recorded as 0. The final data were obtained by averaging the data of two reviewers.

Statistical analysis

The normality of the data was checked using the D'Agostino-Pearson test. The correlation between aortic-mediastinal adipose tissue CNR data and lymph node-mediastinal adipose tissue CNR values was evaluated using the Spearman's correlation test. The relationship between CNR, SNR, and subjective evaluation between the contrast and noncontrast groups was evaluated using the Wilcoxon test.

RESULTS

The mean age of 40 patients was 49.05 years; 20 patients were male and 20 patients were female, with a female-to-male ratio of 1. In 40 patients, 57 lymph nodes with a short axis <1 cm were evaluated. In the noncontrast phase, aortic density value was 39.53±13.35 HU, lymph node density value was 29.3±15.85 HU, and mediastinal adipose tissue density value was -69.74±26.52 HU. Aortic-mediastinal fat CNR value was 5.18±1.49; lymph node-mediastinal fat CNR value was 4.58±1.85. In the noncontrast

phase, a significantly high correlation was observed between aortic-mediastinal fat and lymph node-mediastinal fat CNR values (r=0.833; p<0.0001) (Figure 1A). The noncontrast lymph node SNR was 2.23±1.68, and the aortic SNR was 3.85±4.63. No correlation was observed between lymph node SNR values and aortic SNR values in noncontrast series (r=0.164, p=0.31).

In the contrast phase, aortic density value was found to be 322.04±18.51 HU, lymph node density value was 76.41±23.41 HU, and mediastinal adipose tissue density value was -65.73±22.96 HU. Aortic-mediastinal fat CNR value was 20.23±6.92; lymph node-mediastinal fat CNR value was 6.43±2.07. A significant and moderate correlation was observed between aortic-mediastinal fat and lymph node-mediastinal fat CNR values in the contrast phase (r=0.605; p<0.001) (Figure 1B). The contrast-enhanced lymph node SNR was 6.43±2.07, and the aortic SNR was 20.2±6.92. A significant moderate correlation was observed between contrast-enhanced lymph node SNR values and aortic SNR values (r=0.5, p=0.001) (Table 1).

There was a significant difference in lymph node-mediastinal fat CNR values between the contrast and noncontrast phases (p=0.0002) (Figure 1C). As the signal rate created by the contrast increases, there is an increase in the mediastinal lymph node signal (Figure 2). Contrast-enhanced lymph node SNR values were also significantly higher than nonenhanced lymph node SNR values (p<0.0001) (Table 1).

In the subjective evaluation of lymph nodes among reviewers, an agreement was high in terms of noncontrast- and contrast-enhanced groups (kappa 0.81 and 0.86, respectively). In the pre-contrast subjective evaluation of lymph nodes, the mean rating was 3.19±0.9, and in the post-contrast evaluation, the mean rating was 3.41±0.7. There was a significant increase in the subjective detection of the lymph node in the contrast-enhanced series (p=0.0001).

DISCUSSION

Our study showed that as the vascular contrast agent and its signal strength increase, the signal strength of lymph nodes also increases. Thus, the detectability of lymph nodes increases significantly. Detection and follow-up of lymph nodes are important in many lung diseases, especially lung cancer[1,13]. Therefore, imaging methods, techniques, and evaluation criteria are also very important[10]. CT is an important one among these methods. In fact, with the detection power of CT, changes in staging guidelines have to be made[19]. However, lymph node detection in CT has not reached optimal levels. At this point, the specificity of CT is still 81%, while the sensitivity is still 55%.[20] Although PET-CT increases this sensitivity and specificity, its effectiveness in small lymph nodes is still low[21]. In addition, PET-CT contains a high radiation dose, and false-positive rates are high[22].

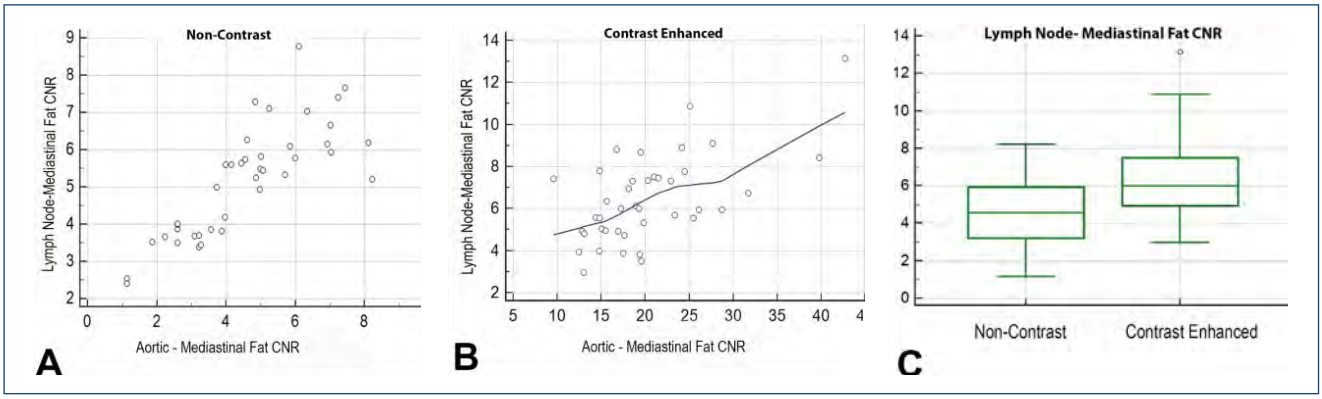

Figure 1. There was a correlation between aortic contrast-to-noise ratio values and lymph node contrast-to-noise ratio values in noncontrast-enhanced (A) and contrast-enhanced (B) series. In the contrast-enhanced series, there was a significant increase in lymph contrast-to-noise ratio (C).

Table 1. Statistical analysis of contrast-to-noise ratio and signal-to-noise ratio values.

	CNR		Correlation value	SNR		Correlation value
	Aortic	Lymph node		aortic	lymph node	
Contrast phase	20.23±6.92	6.43±2.07	r=0.605 p<0.001	20.2±6.92	6.43±2.07	r=0.5 p=0.001
Noncontrast phase	5.18±1.49	4.58±1.85	r=0.833 p<0.0001	3.85±4.63	6.43±2.07	r=0.164 p=0.31
p-value	–	0.0002	–	–	<0.0001	–

Therefore, lymph node biopsy is still the gold standard for diagnosis[23]. At this point in the biopsy, it is an invasive procedure and can cause complications[23]. Some studies have shown that even respiratory activity during a CT scan can affect the detection of lymph nodes[24]. Therefore, it is necessary to increase the efficiency of the techniques and to develop them continuously, and new protocols are created. This is the first study in the literature to determine the effect of vascular CNR on lymph node CNR.

Studies are carried out to use MRI in the staging of lung cancer. Many studies show that MRI plays an important role in detecting mediastinal lymph nodes[25]. However, studies that will establish many standardizations regarding MRI are still required[1,25]. In addition, CT is a feature that can be used as an advantage as it provides faster evaluation than MRI.

Huang et al. observed that the densities of metastatic and nonmetastatic lymph nodes increased significantly in contrast-enhanced CT images[6]. In our study, these data supported the increase in lymph node density in contrast-enhanced series. In addition, we showed that the CNR of the lymph nodes with the ground mediastinal adipose tissue increased. Huang et al. found no significant difference between the arterial and venous phases of the contrast medium in lymph nodes[6]. In our study, we examined the effect of the signal strength created by the contrast agent in the aorta on the contrast signal strength of the lymph nodes, independent of the contrast phase. We found a moderately significant correlation between the vascular CNR and the lymph node CNR.

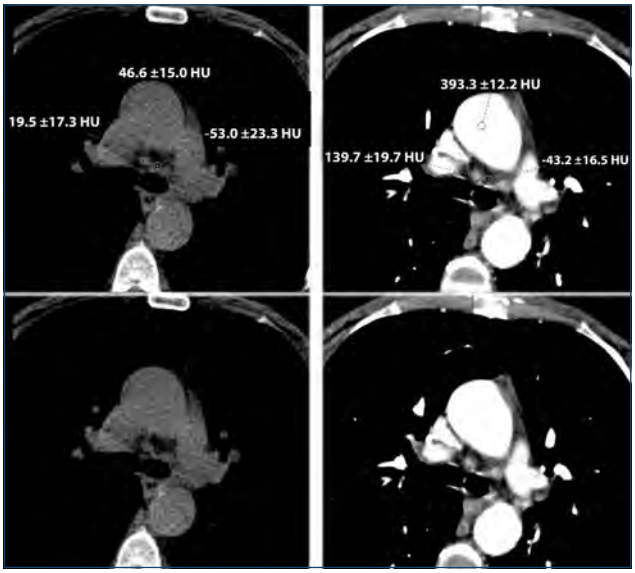

Figure 2. Noncontrast-enhanced aortic-mediastinal fat contrast-to-noise ratio value 5.18, lymph node-mediastinal fat contrast-to-noise ratio ratio 4.58; the contrast-enhanced aortic-mediastinal fat contrast-to-noise ratio value was 20.23, and the contrast-enhanced lymph node-mediastinal fat ratio was 6.43. In subjective evaluations, the mean of the lymph node was 3.19 in the noncontrast-enhanced image, and 3.41 in the contrast-enhanced image.

Choi et al. found a significant increase in the CNR of lymph nodes in contrast-enhanced images[18]. This study supports the increase in lymph node CNR, as we obtained in the contrast-enhanced series in our study. In addition, our study is important in terms of showing the effect of signal strength in the aortic lumen on the lymph node signal CNR in contrast-enhanced series. Aortic contrast signal strength can be affected by individual differences between individuals, as well as by contrast delivery protocols (weight, blood pressure, cardiac rate, etc.). Choi et al. found an increase in the degree of lesion salience in the subjective evaluation of the lymph node in the contrast-enhanced series of reviewers[18]. Our study shows a significant increase in subjective evaluation and supports these data.

Our study also showed a high correlation between aortic-mediastinal fat CNR values and lymph node-mediastinal fat CNR values in noncontrast series. In addition, the lymph node SNR value in the contrast-enhanced phase was also significantly higher than in the noncontrast phase. Many studies in the literature show that nonmetastatic lymph nodes are vascular dense[26,27]. The presence of this dense vascularity may explain the high correlation of lymph nodes with major vascular structures such as the aorta in terms of CNR. However, in contrast-enhanced series, the moderate correlation between aortic CNR and lymph node CNR indicates that the increase in the signal created directly by the contrast in the vascular structure is not as much as the increase in the signal created in the lymph node. As seen in our data, the density increase created by the contrast in the aorta is about 8 times, while the increase in the density created in the lymph node is about 2.5 times. However, this density increase rate provided data that would affect the qualitative evaluation.

As a limitation of our study, we evaluated the detectability of nonmetastatic lymph nodes. Therefore, since the metastatic lymph nodes are on a variable pathological spectrum (increased or decreased vascularity, necrosis, etc.), the effect of aortic signal on the CNR varies[28,29].

CONCLUSION

The contrast agent increases the detection of lymph nodes quantitatively and qualitatively. In addition, an increased aortic CNR facilitates lymph node detection. Contrast enhances and facilitates the detection of paratracheal lymph nodes.

AUTHORS' CONTRIBUTIONS

GP: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **MP:** Formal Analysis, Investigation, Writing – review & editing. **EM:** Resources, Writing – review & editing.

REFERENCES

1. Zhang L, Wu F, Zhu R, Wu D, Ding Y, Zhang Z, et al. Application of computed tomography, positron emission tomography-computed tomography, magnetic resonance imaging, endobronchial ultrasound, and mediastinoscopy in the diagnosis of mediastinal lymph node staging of non-small-cell lung cancer: a protocol for a systematic review. Medicine (Baltimore). 2020;99(9):e19314. https://doi.org/10.1097/MD.0000000000019314
2. Yu J, Ouyang W, Li C, Shen J, Xu Y, Zhang J, et al. Mapping patterns of metastatic lymph nodes for postoperative radiotherapy in thoracic esophageal squamous cell carcinoma: a recommendation for clinical target volume definition. BMC Cancer. 2019;19(1):927. https://doi.org/10.1186/s12885-019-6065-7
3. Sakao Y, Suzuki K, Takeo S, Hayashi A, Tsuchida M, Hirono T, et al. Oncological issues in staging mediastinal lymph node metastasis for left lung cancer. Asian J Surg. 2022;45(1):143-7. https://doi.org/10.1016/j.asjsur.2021.04.003
4. Iskender I, Kadioglu SZ, Cosgun T, Kapicibasi HO, Sagiroglu G, Kosar A, et al. False-positivity of mediastinal lymph nodes has negative effect on survival in potentially resectable non-small cell lung cancer. Eur J Cardiothorac Surg. 2012;41(4):874-9. https://doi.org/10.1093/ejcts/ezr054
5. Camidge DR, Mandair D, Morgan R, Amini A, Rusthoven CG. Quantifying the medical impact of a missed diagnosis of non-small cell lung cancer on chest imaging. Clin Lung Cancer. 2022;23(5):377-85. https://doi.org/10.1016/j.cllc.2022.03.006
6. Huang S, Meng H, Cen R, Ni Z, Li X, Suwal S, et al. Use quantitative parameters in spectral computed tomography for the differential diagnosis of metastatic mediastinal lymph nodes in lung cancer patients. J Thorac Dis. 2021;13(8):4703-13. https://doi.org/10.21037/jtd-21-385
7. Almeida FA, Uzbeck M, Ost D. Initial evaluation of the nonsmall cell lung cancer patient: diagnosis and staging. Curr Opin Pulm Med. 2010;16(4):307-14. https://doi.org/10.1097/MCP.0b013e32833ab0b6
8. Nguyen P, Bhatt M, Bashirzadeh F, Hundloe J, Ware R, Fielding D, et al. Comparison of objective criteria and expert visual interpretation to classify benign and malignant hilar and mediastinal nodes on 18-F FDG PET/CT. Respirology. 2015;20(1):129-37. https://doi.org/10.1111/resp.12409
9. Wang S, Zimmermann S, Parikh K, Mansfield AS, Adjei AA. Current diagnosis and management of small-cell lung cancer. Mayo Clin Proc. 2019;94(8):1599-622. https://doi.org/10.1016/j.mayocp.2019.01.034
10. Wang H, Zhou Z, Li Y, Chen Z, Lu P, Wang W, et al. Comparison of machine learning methods for classifying mediastinal lymph node metastasis of non-small cell lung cancer from (18)F-FDG PET/CT images. EJNMMI Res. 2017;7(1):11. https://doi.org/10.1186/s13550-017-0260-9
11. Ayub II, Mohan A, Madan K, Hadda V, Jain D, Khilnani GC, et al. Identification of specific EBUS sonographic characteristics for predicting benign mediastinal lymph nodes. Clin Respir J. 2018;12(2):681-90. https://doi.org/10.1111/crj.12579
12. Liu J, Hoffman J, Zhao J, Yao J, Lu L, Kim L, et al. Mediastinal lymph node detection and station mapping on chest CT using spatial priors and random forest. Med Phys. 2016;43(7):4362. https://doi.org/10.1118/1.4954009
13. Udoji TN, Phillips GS, Berkowitz EA, Berkowitz D, Ross C, Bechara RI. Mediastinal and hilar lymph node measurements. Comparison of multidetector-row computed tomography and endobronchial ultrasound. Ann Am Thorac Soc. 2015;12(6):914-20. https://doi.org/10.1513/AnnalsATS.201312-430OC
14. Ohno Y, Nishio M, Koyama H, Miura S, Yoshikawa T, Matsumoto S, et al. Dynamic contrast-enhanced CT and MRI for pulmonary nodule assessment. AJR Am J Roentgenol. 2014;202(3):515-29. https://doi.org/10.2214/AJR.13.11888
15. Svahn TM, Sjöberg T, Ast JC. Dose estimation of ultra-low-dose chest CT to different sized adult patients. Eur Radiol. 2019;29(8):4315-23. https://doi.org/10.1007/s00330-018-5849-5
16. Byrne SC, Hammer MM. Use of diagnostic ct and patient retention in a lung cancer screening program. J Am Coll Radiol. 2022;19(1 Pt A):47-52. https://doi.org/10.1016/j.jacr.2021.09.027
17. Shuman WP, Green DE, Busey JM, Mitsumori LM, Choi E, Koprowicz KM, et al. Dual-energy liver CT: effect of monochromatic imaging on lesion detection, conspicuity, and contrast-to-noise ratio of hypervascular lesions on late arterial phase. AJR Am J Roentgenol. 2014;203(3):601-6. https://doi.org/10.2214/AJR.13.11337
18. Choi JW, Cho YJ, Ha JY, Lee SB, Lee S, Choi YH, et al. Generating synthetic contrast enhancement from non-contrast chest computed tomography using a generative adversarial network. Sci Rep. 2021;11(1):20403. https://doi.org/10.1038/s41598-021-00058-3
19. Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45(5):787-98. https://doi.org/10.1093/ejcts/ezu028
20. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S-e250S. https://doi.org/10.1378/chest.12-2355
21. Wang J, Welch K, Wang L, Kong FM. Negative predictive value of positron emission tomography and computed tomography for stage T1-2N0 non-small-cell lung cancer: a meta-analysis. Clin Lung Cancer. 2012;13(2):81-9. https://doi.org/10.1016/j.cllc.2011.08.002
22. Seol HY, Kim YS, Kim SJ. Predictive value of 18F-fluorodeoxyglucose positron emission tomography or positron emission tomography/computed tomography for assessment of occult lymph node metastasis in non-small cell lung cancer. Oncology. 2021;99(2):96-104. https://doi.org/10.1159/000509988
23. Yasufuku K, Pierre A, Darling G, Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011;142(6):1393-400.e1. https://doi.org/10.1016/j.jtcvs.2011.08.037
24. Lin WY, Hsu WH, Lin KH, Wang SJ. Role of preoperative PET-CT in assessing mediastinal and hilar lymph node status in early stage lung cancer. J Chin Med Assoc. 2012;75(5):203-8. https://doi.org/10.1016/j.jcma.2012.04.004
25. Pereiro-Brea T, Alegría AM, Valdés L, Golpe-Gómez A, Carreira-Villamor JM, Ruano-Raviña A. Magnetic resonance imaging for the study of mediastinal adenopathies in lung cancer: comparison with standard tests. J Cancer Res Ther. 2021;17(4):917-24. https://doi.org/10.4103/jcrt.JCRT_1626_20

26. Kato T, Uehara K, Ishigaki S, Nihashi T, Arimoto A, Nakamura H, et al. Clinical significance of dual-energy CT-derived iodine quantification in the diagnosis of metastatic LN in colorectal cancer. Eur J Surg Oncol. 2015;41(11):1464-70. https://doi.org/10.1016/j.ejso.2015.08.154

27. Rizzo S, Radice D, Femia M, Marco P, Origgi D, Preda L, et al. Metastatic and non-metastatic lymph nodes: quantification and different distribution of iodine uptake assessed by dual-energy CT. Eur Radiol. 2018;28(2):760-9. https://doi.org/10.1007/s00330-017-5015-5

28. Li X, Meng X, Ye Z. Iodine quantification to characterize primary lesions, metastatic and non-metastatic lymph nodes in lung cancers by dual energy computed tomography: an initial experience. Eur J Radiol. 2016;85(6):1219-23. https://doi.org/10.1016/j.ejrad.2016.03.030

29. Liu H, Yan F, Pan Z, Lin X, Luo X, Shi C, et al. Evaluation of dual energy spectral CT in differentiating metastatic from non-metastatic lymph nodes in rectal cancer: Initial experience. Eur J Radiol. 2015;84(2):228-34. https://doi.org/10.1016/j.ejrad.2014.11.016

ORIGINAL ARTICLE

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Eating habits, anthropometry, lifestyle, and hypertension of a group of non-village indigenous women in Amazon, Brazil

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SUMMARY

OBJECTIVE: The aim of this study was to describe the anthropometric characteristics, eating habits, and lifestyle of non-village indigenous women living in Manaus, AM, and their association with hypertension.

METHODS: This cross-sectional (descriptive-analytical) study was carried out from January 2020 to December 2021 using a questionnaire for clinical, sociodemographic, and behavioral data. Non-pregnant women who belonged to Parque das Tribos for more than a year, declared themselves indigenous, and were over 18 years of age were included in the study.

RESULTS: In total, 21 ethnicities were identified, and 95 indigenous women were evaluated. The average age group was 36±12.1 years, the average height was 157 cm, and the body mass index was 28.8 kg/m^2. The prevalence of systemic arterial hypertension was ±40%, and 68.5% had excess weight, with 29.1% having class I obesity. In all, 35.8% consumed a lot of salt, sugar, and industrialized foods, and 88.4% were sedentary.

CONCLUSION: Much of the sample presented excess weight, and almost all were sedentary. More than one-third had unappropriated eating habits. Hypertension was present in more than one-third of these indigenous women. There was an association between higher body mass index and hypertension. Knowing the characteristics of this group of non-village indigenous women may help determine the best health approach. The data demonstrate the necessity of preventive measures.

KEYWORDS: Anthropometry. Obesity. Comorbidity. Indigenous peoples.

INTRODUCTION

Relocating to urban centers can be seductive for indigenous people. This relocation is due to expectations regarding improving living conditions, access to health and education, the labor market, and the goods and services offered[1]. On the contrary, indigenous people have a different lifestyle from Western people, with the former having more physical activity and considerable energy expenditure[2]. In addition, this change has created a local scenario of socio-environmental vulnerability. It has exposed these indigenous people to consuming industrialized products and ultra-processed foods of low nutritional value, which are high energy, dense, low in fiber and micronutrients and rich in preservatives and industrial additives[3]. Greater exposure to salt, sugar, and industrialized foods associated with a sedentary lifestyle may cause excess weight[3]. Sedentarism, obesity, and overweight were also detected in several indigenous ethnic groups in the midwest region of Brazil[4-6]. It is crucial to highlight the association between the growing relevance of obesity and comorbidities in indigenous populations[4-6].

Another significant issue is the knowledge about the living and beliefs of the indigenous people. Identifying and understanding indigenous cultures has been linked with enhanced social and health care[7].

In Manaus, there are three areas of occupation, not legally regulated, where many indigenous people live[8]. These occupations are in public and private areas; currently, they are not exclusively indigenous occupations[9,10].

The first indigenous neighborhood of Manaus, Tribes Park, is in the West zone of Manaus, with approximately 20 ethnic groups. It is a place representative of non-village indigenous people[11]. Given the nutritional situation of the indigenous population, particularly considering the rapid nutritional transition in progress[4,6], it is essential to emphasize the need to carry out studies to collect data on this issue. The present study aimed to describe the anthropometric characteristics, eating habits, and lifestyle of non-villages indigenous women living in Manaus, AM, and their association with hypertension.

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METHODS

Study design

This is a cross-sectional study with a group of indigenous women living in the urban area of Manaus (Tribes Park), in which a questionnaire was applied to collect clinical, sociodemographic, and behavioral data. In addition, weight, height, body mass index (BMI), and blood pressure were recorded.

Sample size calculation

The sample size was calculated based on the partial census organized by the indigenous leaders of Tribes Park. A total of 124 women who had the profile and presented the indigenous self-declaration or Administrative Indigenous Birth Registry (RANI), aged over 18 years, resided in Tribes Park for over a year were included. The sampling error was 5.0% with a 95% confidence level, totaling a minimum sample of 94 indigenous people.

Data collection location

The initial meeting location was the main tent built next to the Chief's house, where public service is offered. Meetings were held to present the study proposal, in which they got to know and discussed the importance of the research in the study population. After the initial meeting, the same researcher and collaborator set the day to collect data for each family. The place for the data collection was the house of each indigenous woman. All those women who met the inclusion criteria and accepted to participate were included in our analysis.

Inclusion criteria

The study included nonpregnant women belonging to the Tribes Park for more than a year who had self-declaration as indigenous people or the RANI; who were over 18 years of age; who communicated in Portuguese or understood its translation, without recent surgery in the torso area; and who did not have internal organ diseases that increased waist circumference.

Exclusion criteria

Women who were incapable to communicate in Portuguese, who had no self-declaration as indigenous people or the RANI, and who were below 18 years old were excluded.

Subjects and methods

Method of anthropometric and blood pressure data collection

A portable stadiometer measured the height, with the women standing barefoot, and requested to have their back to the marker in an anatomical position. An electronic platform scale (Altis®, portable, 20 g precision, maximum load 150 kg) was used to determine body weight, wearing light clothing. BMI was then calculated.

Blood pressure was measured using an automatic digital blood pressure device (OMRON HEM-742INTC®), in only 1 day, taken three times, considering the average of the three readings on different occasions, according to the protocol of the Brazilian Guidelines on Arterial Hypertension[12].

Data were collected using a questionnaire to assess sociodemographic, behavioral (eating, exercising, way of sleeping, and beliefs), and clinical variables. The questions asked about eating habits were if women often maintain the traditional foods used in the indigenous village, often use traditional white man food, and use large amounts of salt, sugar, and processed foods.

Data processing and analysis

The results were statistically analyzed using the R software version 4.0.5. Quantitative variables were described by measures of centrality and dispersion, while qualitative variables were summarized in absolute and relative frequencies.

Ethical aspects

The ethics committee approved this research – CONEP, research CAEE 12193319.1.0000.5020 – and strictly followed the Resolutions of the National Council of Health n°466 of 2012 and n° 304 of 2000 and Resolution N.304/2000 (items 2.2 and 2.3) that deal with research of indigenous peoples. All women included in the present study signed a consent form.

RESULTS

There were 21 identified ethnic groups among the women: Apurinã, Kuripako, Marubo, Miranda, Munduruku, Mura, Piratapuia, Sateré Mawé, Tariano, Tikuna, Baniwa, Tukano, Tupinnamba, Wanano, Kokama, Baré, Dessano, Kanamary, Karapanã, Kulina, and Witoto. The Tukano ethnic group was the most frequently observed in the sample, with 18 indigenous women representing 18.9% of the interviewees, followed by 13 (13.7%) women from Baré and 10 (10.5%) from the Kokama and Munduruku ethnic groups. The average age was 36±12.1 years (mean/SD), and almost half (44.2%) of the women were homemakers. The average age at which they had their first child was 18.5 (±3.3). According to the sociodemographic form, 93.6% were married. The average number of people living in the same household was 4.9 (5.16%). The houses were occupied by couples, children, and their relatives. Notably, 66.3% of the women reported that they knew about sexually transmitted diseases. Concerning the clinical profile of the participants,

27 (39%) indigenous women were classified as hypertensive. Seven reported having type II diabetes, three high glycemia (>100 and <126 mg/dL), three hypercholesterolemia, and three were diagnosed with cholelithiasis. Table 1 shows the characteristics of the population and morbidities.

Table 1. Characteristics of the population and morbidities (n=95).

Age	Years
Mean±SD	36±12.1
Median	34
Minimum	18
Maximum	74
Occupation (work with or without payment)	**(%)**
Artisan	27.4
Housewife	44.2
Others	28.4
Education (years of schooling)	(%)
<4	4.2
4–11	40.0
≤11	55.8
Ethnicity	**Morbidities (%)**
Apurinã, Dessano	3.2
Kuripako, Marubo, Miranha, Mura, Witoto	1.1
Munduruku, Kokama	10.5
Piratapuia, Sateré Mawé	4.2
Tariano	8.4
Tikuna, Tupinnamba, Wanano, Kanamary, Karapana, Kulina	2.1
Baniwa	5.3
Tukano	18.9
Baré	13.7

SD: standard deviation. Occupation represents work with or without remuneration. Alcohol consumption represents intake once or more times a week. Physical activity referring to weekly practice – once or more times.

According to BMI classification, we identified women who were overweight and obese. The median height was 157 cm; the maximum was 170 cm and the minimum was 138 cm. Overweight and obesity were reported in 68.5% (overweight 23.2%, obesity class I 29.5%, class II 14.7%, and class III 1.1%). Table 2 shows the classification of groups according to anthropometry (BMI) and the presence of hypertension (p<0.001).

Concerning the data on their weekly eating habits, 22.1% maintained consuming traditional food in the indigenous settlement. A total of 42.1% often consumed a standard Westernized diet. Regularly, 35.8% used a significant amount of salt, especially with fish. They also said having excess sugar and consuming industrialized foods (soft drinks and processed meat). Table 3 illustrates the dietary and behavioral profile of non-village indigenous women.

DISCUSSION

The present study evaluated the anthropometric characteristics, eating habits, and lifestyle of non-village indigenous women living in Tribes Park in Manaus, Brazil, and their association with hypertension. A total of 21 ethnicities were identified, and 95 indigenous women were evaluated.

Over one-third of the women consumed a lot of salt, sugar, and industrialized foods, and almost 90% were sedentary. Overweight and obesity were reported in 68.5% of the interviewers, which was higher than non-indigenous women from Manaus, Amazonas[13]. Other studies with non-village indigenous women presented the same problem[4,14-16]. Besides preserving some beliefs, losing original indigenous territory is related to weight gain. Physical activity is not practiced enough since they no longer need to walk long distances searching for food[2,11].

Aspects related to excess weight in Brazilian capitals, including those who self-declared as indigenous, revealed a prevalence of overweight in 55.9%, which was linked to arterial hypertension and diabetes mellitus[17,18].

Table 2. Classification of groups according to anthropometry (body mass index) and the presence of hypertension.

Variable	Total n=95	Hypertension 39%		PR (95%CI)	p-value
		Negative n=58	Positive n=37		
BMI					
Mean (SD)	29.2 (7.04)	24.5 (4.14)	32.2 (4.8)	6.20 (4.1–8.3)	<0.001
Minimum–maximum	19.00–40.1	19.0–38.8	20.9–40.1		
Mean (SD)	89 (16.3)	79.5 (7.41)	100 (16.3)		
Minimum–maximum	67.00–141.00	67.00–105.00	68.00–141.00		

BMI: body mass index; PR: prevalence ratio; CI: confidence interval; SD: standard deviation.

Table 3. Dietary and behavioral profile of non-village indigenous women (n=95).

Variable	(%)
What is your weekly food routine?	
Maintains the traditional food used in the indigenous village	22.1
Often use traditional white man food	42.1
Frequently uses large amounts of salt, sugars, and processed foods. Like soft drinks, fish preserved in salt, and preserves	35.8
Smoking	
No	94.7
Past/never smoked	5.3
Alcohol consumption	
Yes	15.8
No	84.2
Practice of regular physical activity	
Yes	11.6
No	88.4
Sleep in hammock	
Yes	54.7
No	45.3

Alcohol subjective intake criteria once or more times a week; Physical activity referring to weekly practice once or more times a week.

The prevalence of arterial hypertension is close to 40% in women from Tribes Park, and there was a significant association between a group with a higher BMI and hypertension. Another study among indigenous women observed that overweight or obese respondents had approximately 50% higher hypertension prevalence than those with low or average weight[4].

More than half of the interviewees had 11 or more years of schooling. This aspect is unusual among indigenous women, and other studies point out a low level of education among them. In Mato Grosso do Sul, Brazil, 82% of the women, with an average age of 35.5 years, had 4 or fewer years of education[4]. The unmet needs of the village population's low education level may be due to requirements not being fulfilled, such as teacher shortages in language and intercultural matters[19]. Souza Filho et al., in a study of indigenous people from the Thura ethnic group in Amazonas, with a sample of 121 women, found that 19.8% had education for 11 years[20]. The reason that Tribes Park has a higher level of education could be due to the assistance provided by the Municipal Department of Education through the Management of Indigenous School Education [Gerência de Educação Escolar Indígena (Geei)], with 17 teachers[21].

The average fertility rate was three children per indigenous woman from Parque das Tribos. The fertility of indigenous people is decreasing, even among those residing in indigenous lands. However, pregnancy of indigenous adolescents, without much differentiation according to the urban or rural residence, remains at very high levels[22]. Nevertheless, the present study did not evaluate pregnancy below 18 years.

The alcohol intake among indigenous women was 15.8%. In line with this finding, other research evaluated 283 indigenous women of the ethnic groups Guarani and Terena in Dourados. Almost 90.0% of the women did not smoke or drink alcohol[4]. Nevertheless, another study found excessive alcohol consumption perceived as an essential issue among indigenous people[23]. However, indigenous women's alcohol use is at an early stage[17,23,24].

The present study indicated an average height of 157 cm, which may be related to the 21 different ethnic groups found in the Tribes Park. Studies with 72 Yanomamis indigenous women from the Amazon indicated that 68.1% had less than 145 cm[25].

As a limitation, the findings presented in this study do not directly represent any specific indigenous ethnic group in Brazil. The data were collected in Tribes Park, where 21 ethnicities were identified. In addition, some information was based on interviews with possible bias. The diagnosis of hypertension was based on three measures of blood pressure on different occasions in only 1 day. Finally, the study's cross-sectional nature precludes inferring causality from associated risk factors. However, for the strengths of this study, we can include the fact that the data concerning the population of Tribes Park are unprecedented. We highlight that there are few studies on anthropometric characteristics, eating habits, lifestyle, and hypertension of non-village indigenous women.

CONCLUSION

Many non-village indigenous women living in Tribes Park, Manaus, had unhealthy eating habits. Much of the sample presented excess weight, and almost all were sedentary. Hypertension was present in more than one-third of these indigenous women, and there was an association between higher BMI and hypertension.

The findings from this study may contribute to indigenous women's health policies, especially with the early use of educational campaigns on the importance of physical activity and healthy eating.

ETHICAL ASPECTS

We declare that we have no conflict of interest in disseminating data from this research and do not present direct or indirect conflicts concerning the research with the studied population. This research was approved by the ethics and research

committee on July 10, 2019. We inform that the Ethics Committee approved this research – CONEP, research CAEE 12193319.1.0000.5020 – and strictly followed the Resolutions of the National Health Council nº 466 of 2012 and nº 304 of 2000 and Resolution nº 304/2000 (items 2.2 and 2.3) that deal with research patterns in the area of indigenous peoples.

AUTHORS' CONTRIBUTIONS

ALSF: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AV:** Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **KPLR:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **HAP:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **QS:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Ministério da Justiça e Segurança Pública. Povos indígenas: quem são? [Internet]. Brasília: Ministério da Justiça e Segurança Pública; 2021 [cited on Nov 15, 2021]. Available from: https://www.gov.br/funai/pt-br/atuação/povos-indígenas/quem-são
2. Rocha ESC, Toledo NN, Pina RMP, Fausto MCR, D'Viana AL, Lacerda RA. Primary health care attributes in the context of indigenous health. Rev Bras Enferm. 2020;73(5):e20190641. https://doi.org/10.1590/0034-7167-2019-0641
3. Fraser B. Head of Indian Affairs Foundation fired in Brazil. Lancet. 2019;393(10190):2481. https://doi.org/10.1016/S0140-6736(19)31468-0
4. Almeida JB, Kian KO, Lima RC, Souza MC. Total and abdominal adiposity and hypertension in indigenous women in midwest Brazil. PLoS One. 2016;11(6):e0155528. https://doi.org/10.1371/journal.pone.0155528
5. Hursting SD, Digiovanni J, Dannenberg AJ, Azrad M, Leroith D, Demark-Wahnefried W, et al. Obesity, energy balance, and cancer: new opportunities for prevention. Cancer Prev Res (Phila). 2012;5(11):1260-72. https://doi.org/10.1158/1940-6207.CAPR-12-0140
6. Mazzeti CMS. Estado nutricional dos indígenas Pataxó de 5 aldeias de Minas Gerais, Brazil [dissertação] [Internet]. Belo Horizonte: Escola de Enfermagem, Universidade Federal de Minas Gerais; 2020 [cited on Mar 6, 2020]. Available from: http://hdl.handle.net/1843/ANDO-9VFNS5
7. Shepherd SM, Delgado RH, Sherwood J, Paradies Y. The impact of indigenous cultural identity and cultural engagement on violent offending. BMC Public Health. 2017;18:50. https://doi.org/10.1186/s12889-017-4603-2
8. Nascimento RL, Carvalho FO, Araujo FS, Melo-Marins D, Carneiro MVO, Saraiva LC, et al. Anthropometric and hemodynamic indicators associated with arterial hypertension in sedentary people. Res Soc Dev. 2021;30(2):55-78. https://doi.org/10.33448/rsd-v10i7.16603
9. Pereira JCM. Indígenas na metrópole: lutas multiétnicas e identidade coletiva na cidade de Manaus (AM). Rio de Janeiro: PPGAS/MN/UFRJ; 2018.
10. Pereira, JCM. Indígenas na cidade de Manaus (AM). Novos Cad NAEA. 2021;23(3):11-31. https://doi.org/10.5801/ncn.v23i3.8257
11. Santos GS. Territórios pluriétnicos em construção: a proximidade, a poiesis e a praxis dos indígenas em Manaus [tese]. Manaus: Universidade Federal do Amazonas; 2016.
12. Corrêa MM, Tomasi E, Thumé E, Oliveira ERA, Facchini LA. Waist-to-height ratio as an anthropometric marker of overweight in elderly Brazilians. Cad Saude Publica. 2017;33(5):e00195315. https://doi.org/10.1590/0102-311X00195315
13. Jayedi A, Soltani S, Zargar MS, Khan TA, Shab-Bidar S. Gordura central e risco de todas as causas de mortalidade: revisão sistemática e meta-análise dose-resposta de 72 estudos prospectivos de coorte. BMJ. 2020;370:m3324.
14. Soares LP, Fabbro ALD, Silva AS, Sartorelli DS, Franco LF, Kuhn PC, et al. Cardiovascular risk in Xavante indigenous population. Arq Bras Cardiol. 2018;110(6):542-50. https://doi.org/10.5935/abc.20180090
15. Cervantes A, Singh RG, Kim JU, Souza SV, Petrov MS. Relationship of anthropometric indices to abdominal body composition: a multiethnic New Zealand magnetic resonance imaging study. J Clin Med Res. 2019;11(6):435-46. https://doi.org/10.14740/jocmr3820
16. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise em Saúde e Vigilância de Doenças Não Transmissíveis. Vigitel Brazil 2019: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde; 2020.
17. Oliveira RC, Nicolau BF, Levine A, Mendonça AVM, Videira V, Vargas AMD, et al. "Tihik quando bebe Kaxmuk não tem pai, nem mãe, nem irmão": percepções sociaisdas consequências do uso da cachaça no povo indígena Maxakali/MG/Brazil. Cienc Saude Colet. 2019;24(8):2883-94. https://doi.org/10.1590/1413-81232018248.16992017
18. Sousa APM, Pereira IC, Araujo LL, Rocha MR, Bandeira HMM, Lima LHO. Prevalência e fatores associados ao excesso de peso em adultos nas capitais e no Distrito Federal, Brazil, 2019. Epidemiol Serv Saude. 2021;30(3):e2020838. https://doi.org/10.1590/S1679-49742021000300014
19. Mizetti MCF, Krolow IRC, Teixeira MRF. Access of indigenous peoples to formal education: science education: a challenge, a reality. Pro-Posições. 2020;31:e20170147. https://doi.org/10.1590/1980-6248-2017-0147
20. Souza Filho ZA, Ferreira AA, Dos Santos J, Meira KC, Pierin AMG. Cardiovascular risk factors with an emphasis on hypertension in the Mura Indians from Amazonia. BMC Public Health. 2018;18(1):1251. https://doi.org/10.1186/s12889-018-6160-8
21. Araujo B. Projeto educacional resgata cultura indígena no Parque das Tribos. Em tempo [Internet]. 9 Mar 2020 [cited on Nov 3, 2021]. Available from: http://www.povosindigenas.blog.

br/v1/2020/03/04/am-projeto-educacional-resgata-cultura-indigena-no-parque-das-tribos/

22. Wong LLR. Tendências da fecundidade dos povos indígenas nos Censos Demográficos brasileiros de 1991 a 2010. Rev Bras Estud Popul. 2016;33(2):399-421. https://doi.org/10.20947/S0102-30982016a0038

23. Souza RSB, Oliveira JC, Araújo VE, Teodoro MLM. Instrumentos para a avaliação do uso de álcool em comunidades indígenas – revisão sistemática. Temas Psicol. 2018;26(3):1589-603. https://doi.org/10.9788/TP2018.3-16En

24. Mendes APM, Alfonso J-OR, Langdon EJ, Grisotti M, Martínez-Hernáez A. Representações e práticas de cuidado dos profissionais da saúde indígena em relação ao uso de álcool. Cienc Saude Colet. 2020;25(5):1809-18. https://doi.org/10.1590/1413-81232020255.34442019

25. Orellana JDY, Marrero L, Alves CLM, Ruiz CMV, Hacon SS, Oliveira MW, et al. Associação de baixa estatura severa em crianças indígenas Yanomami com baixa estatura materna: indícios de transmissão intergeracional. Cienc Saúde Colet. 2019;24(7):2778-83. https://doi.org/10.1590/1413-81232018245.17062017

ORIGINAL ARTICLE

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Maternal visceral adiposity and fetal biometry in women with obesity and diabetes

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SUMMARY

OBJECTIVE: The aim of this study was to compare the correlation of maternal visceral adiposity with sonographic variables related to fetal biometry in the second trimester of pregnancy in mothers who were previously obese versus nonobese and gestational diabetic versus nondiabetic.

METHODS: This cross-sectional study included 583 pregnant women who received prenatal care between October 2011 and September 2013 at the *Instituto de Medicina Integral Prof. Fernando Figueira*, northeast of Brazil. Maternal visceral adiposity was measured by ultrasound examination at the same time as fetal biometry. Gestational age was 14.9±3.2 weeks. The correlation between maternal visceral adiposity and fetal biometric variables was evaluated using Pearson's correlation coefficient. Among the groups, the correlation coefficients were compared using Fisher's Z-test. This test was also used to evaluate the null hypothesis of correlation coefficients between pairs of variables.

RESULTS: Maternal visceral adiposity positively correlated with fetal abdominal circumference, estimated fetal weight, head circumference, femur length, and biparietal diameter in pregnant women with obesity, nonobesity, gestational diabetes, and nondiabetes, but the correlation coefficients were statistically similar among the groups.

CONCLUSION: Maternal visceral adiposity positively correlated with fetal biometry in the second trimester of pregnancy in the same manner in pregnant women previously obese and nonobese, as well as in pregnant women with gestational diabetes and nondiabetes.

KEYWORDS: Intra-abdominal fat. Body composition. Ultrasonography, prenatal. Diabetes, gestational. Obesity. Fetal weight.

INTRODUCTION

Obesity and diabetes are major public health concerns that can affect pregnant women and cause adverse maternal and fetal outcomes worldwide. Normal pregnancy is characterized by an insulin resistance state in order to supply the increasing metabolic demands of the developing fetus. The consequence of such physiological insulin resistance is an increase in insulin secretion, and failure to do so leads to gestational diabetes mellitus (GDM)[1]. It is important to note that overweight and obese individuals are more insulin-resistant than their lean counterparts and also more susceptible to beta-cell dysfunction in the pancreas[2].

It is known that the nutritional status of the mother and the consequent hyperglycemia and hyperinsulinemia can directly influence fetal growth. Excessive fetal growth is probably the most frequent and important outcome of GDM. Likewise, the association between maternal obesity and birth weight is also well documented[3]. Both maternal obesity and gestational diabetes have been associated with newborn adiposity[3-5]. Pre-pregnancy and during pregnancy, maternal body composition can influence the body fat mass of the offspring from fetal life through adolescence and can predict the risk of obesity in adulthood[6,7].

Studies suggest that central adiposity has a stronger association with complications related to obesity compared to peripheral adiposity. During pregnancy, there is also evidence that central adiposity, compared to the peripheral, is associated with glucose intolerance, gestational diabetes, and increased birth weight[8,9]. In addition, it has been demonstrated that maternal visceral adiposity has a stronger association with birth weight than maternal body mass index (BMI)[9].

Despite the wide evidence of maternal body composition and metabolism's influence on offspring body composition and cardiometabolic risk, little is known about their role in fetal growth and fat accumulation. The effect of maternal visceral adiposity on fetal growth and body composition is not yet well established, and there is no data on the effect of maternal visceral adiposity on fetal growth among obese and diabetic pregnant women. This study aimed to investigate and compare

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the correlation of maternal visceral adiposity with sonographic parameters of fetal biometry in the second trimester of pregnancy in obese, nonobese, gestational diabetic, and nondiabetic pregnant women.

METHODS

This retrospective cross-sectional study included pregnant women who received prenatal care at the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP) between October 2011 and September 2013, and who started their prenatal care before the 28th week of gestation. Participants were excluded from the study if they had pre-pregnancy diabetes mellitus, multiple gestations, mental disability, the absence of a legal representative in adolescents, and fetal abnormalities.

The variables studied to characterize the population were age, gestational age, ethnicity, income, and schooling. The independent variable was maternal visceral adiposity. The dependent variables were the fetal measurements [biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), estimated fetal weight (EFW), femur length (FL), and the ratios BPD/FL, HC/AC, FL/HC, EFW/BPD, and EFW/HC], obesity, and GDM.

Obese women were considered those with a pre-pregnancy BMI ≥30 kg/m^2. Pre-pregnancy BMI was determined using the informed pre-pregnancy weight and height measured at prenatal care. In the first prenatal care visit, fasting glucose was obtained. It was considered clinical diabetes during pregnancy if the fasting blood glucose was ≥126 mg/dl, if the glycated hemoglobin (HbA1c) was ≥6.5%, or if a random plasma glucose of ≥200 mg/dl was detected. Between the 24th and 28th gestational weeks, those with values <92 mg/dl underwent the oral glucose tolerance test with 75 g intake (OGTT-75g). For this test, fasting values ≥92 mg/dl or ≥180 mg/dl within the first hour, or ≥153 mg/dl in the second hour, were considered GDM[10].

During routine ultrasound examination, maternal visceral adiposity was assessed by ultrasonography, performed by a single qualified sonographer (A.S.R.S.), once for each patient. The thickness of visceral fat was measured in centimeters (cm) from the inner edge of the rectus abdominis muscle, at the linea alba level, in mesogastric region, to the anterior wall of the abdominal aorta (Figure 1)[11]. The measurement was made using Philips 22Ui equipment with a 5- to 9-MHz transducer (Koninklijke Philips, Amsterdam, the Netherlands). Fetal biometry measurements were performed on the same occasion, by the same operator. This technique has been validated[12,13].

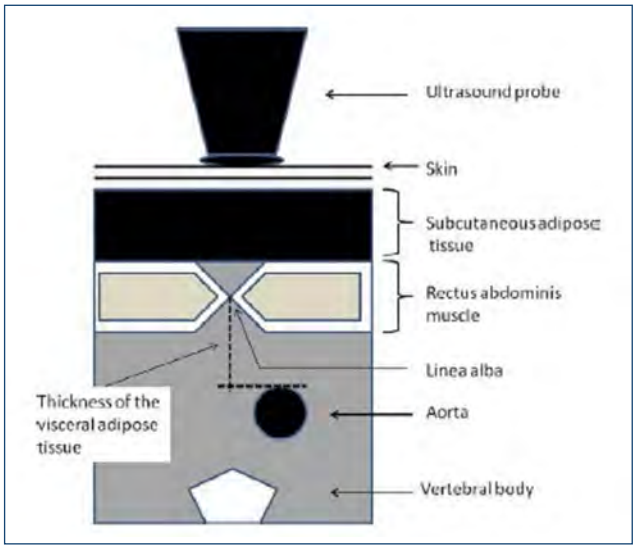

Figure 1. Visceral fat measurement.

Sample size was based on a previous study by these same authors, who evaluated the correlation between maternal visceral adiposity and fetal biometry[14]. The correlations between maternal visceral adiposity and fetal biometric variables were evaluated using Pearson's correlation coefficient. Among the groups, the correlation coefficients were compared using Fisher's Z-test. This test was also used to test the null hypothesis of correlation coefficients between pairs of variables. To test the null hypothesis of adjusted correlation coefficients (partial correlation coefficients), the Student's t-test was used. Statistical analysis was performed with STATA 12.1 SE (StataCorp, Texas, USA). A p-value of less than 0.05 was considered statistically significant.

Participants gave written informed consent, and the research protocol was approved by the IMIP Ethics Committee before the study began, CAAE number 48051515.5.0000.5201, October 15, 2015.

RESULTS

A total of 583 participants were included in the study. The age of pregnant women ranged from 16 to 41 years (mean 26±3 years), and the median number of years of schooling was 12 years. Most of them described themselves as mulattos, and 90% had a mensal income of up to two minimum wages (U$400.00). Of the 583 participants, obesity and gestational diabetes were observed in 163 (35.7%) and 71 (12.2%), respectively. Gestational diabetes was more frequent in pregnant women with obesity as compared to pregnant women without obesity [30/163 (18.4%) versus 31/420 (7.3%), p<0.001]. The ultrasound measurement of maternal visceral

adiposity and fetal biometry was performed at a mean gestational age of 14.9 (±3.2) weeks of amenorrhea, median age of 15.2 weeks, and interquartile range from 13 to 17.2 weeks. The mean visceral adiposity was 7.6 (±1.84) cm. Notably, 14.4% of women were obese (BMI ≥30 kg/m^2), 26.6% were overweight (BMI ≥25 and <30 kg/m^2), and 10.4% developed gestational diabetes.

Maternal visceral adiposity positively correlated with fetal AC, EFW, HC, FL, and BPD in obese, nonobese, gestational diabetic, and nondiabetic pregnant women (Table 1). There was a negative correlation between the ratios of BPD/FL and HC/AC (Table 1). The correlation coefficients were statistically similar among the groups (Table 1). The analysis of the correlation of maternal visceral adiposity and fetal biometric parameters remained statistically significant after controlling for age, gestational age, ethnicity, income, and schooling (Table 2).

DISCUSSION

The present study showed that there was a statistically significant correlation between maternal visceral adiposity and fetal biometric parameters in the second trimester of pregnancy, even after controlling for gestational age, in groups of obese, nonobese, gestational diabetic, and nondiabetic women. There was no statistical difference when the correlation coefficient of the previously obese and nonobese groups was compared. Neither there was a statistical difference when the correlation coefficient of the gestational diabetic and nondiabetic groups was compared.

Obesity and gestational diabetes are strongly associated with neonatal macrosomia and adiposity[3,4]; therefore, one would expect a greater correlation between fetal biometry and maternal visceral adiposity in these groups, compared to controls. However, the exact roles of fetal growth determinants remain to be elucidated. There is evidence of the association between

Table 1. Pearson's correlation coefficients between maternal visceral adiposity and fetal sonographic parameters in the second trimester of pregnancy in obese, nonobese, diabetic, and nondiabetic women.

Fetal biometric parameters	Obese		Nonobese		p††	Diabetic		Nondiabetic		p††
	r (n)	p†	r (n)	p†		r (n)	p†	r (n)	p†	
Abdominal circumference (AC)	0.60 (82)	<0.001	0.54 (501)	<0.001	0.424	0.67 (38)	<0.001	0.49 (443)	<0.001	0.132
Estimated fetal weight (EFW)	0.57 (80)	<0.001	0.54 (491)	<0.001	0.677	0.70 (38)	<0.001	0.50 (429)	<0.001	0.072
Head circumference (HC)	0.59 (82)	<0.001	0.53 (501)	<0.001	0.475	0.64 (38)	<0.001	0.49 (443)	<0.001	0.182
Femur length (FL)	0.58 (82)	<0.001	0.52 (501)	<0.001	0.477	0.62 (38)	<0.001	0.48 (443)	<0.001	0.248
Biparietal diameter (BPD)	0.58 (82)	<0.001	0.54 (501)	<0.001	0.617	0.65 (38)	<0.001	0.49 (443)	<0.001	0.194
Ratio BPD/FL	-0.27 (82)	0.013	-0.28 (501)	<0.001	0.971	-0.31 (38)	0.062	-0.28 (443)	<0.001	1.110
Ratio HC/AC	-0.43 (79)	<0.001	-0.27 (493)	<0.001	1.868	-0.37 (38)	0.021	-0.24 (432)	<0.001	1.585
Ratio FL/AC	0.01 (82)	0.903	0.14 (501)	0.002	1.688	0.01 (38)	0.950	0.14 (443)	0.003	1.542
Ratio EFW/BPD	0.69 (44)	<0.001	0.54 (264)	<0.001	0.124	0.71 (25)	<0.001	0.51 (246)	<0.001	0.156
Ratio EFW/HC	0.66 (44)	<0.001	0.52 (264)	<0.001	0.206	0.71 (25)	<0.001	0.51 (246)	<0.001	0.149

†Fisher's Z-test to test the hypothesis that Pearson's correlation coefficient was zero. ††Fisher's Z-test to test the hypothesis of equality of Pearson's correlation coefficients.

Table 2. Pearson's partial correlation coefficients between maternal visceral adiposity and fetal sonographic parameters in the second trimester of pregnancy in obese, nonobese, diabetic, and nondiabetic women, after adjusting for age, gestational age, ethnicity, income, and schooling.

Fetal biometric parameters	Obese		Nonobese		p††	Diabetic		Nondiabetic		p††
	r (n)	p†	r (n)	p†		r (n)	p†	r (n)	p†	
Abdominal circumference (AC)	0.59 (58)	<0.001	0.54 (322)	<0.001	0.615	0.73 (32)	<0.001	0.53 (400)	<0.001	0.078
Estimated fetal weight (EFW)	0.60 (58)	<0.001	0.57 (316)	<0.001	0.755	0.74 (32)	<0.001	0.55 (391)	<0.001	0.085

†Student's t-test (Stata 12.1: command pcorr). ††Teste Z.

maternal obesity and fetal body composition in the third trimester of pregnancy[12], while another study found no association between maternal obesity and fetal growth in the third and second trimesters[13,14]. Another interesting study evaluated the association between newborn adiposity and fetal growth[14-17]. They demonstrated an association of newborn adiposity with EFW in the third trimester, but not in the second trimester[18]. In contrast, fetal growth in the third trimester was not associated with adiposity in adulthood. One study evaluated the relationship between birth weight and the growth rate in the third trimester with body composition and metabolism of glucose in adulthood using differences between pairs of twins. Birth weight was inversely associated with both visceral and subcutaneous fat in adulthood; on the contrary, there was no association with insulin resistance. In contrast, fetal growth rate during the third trimester was not associated with visceral or subcutaneous fat in adults. These data suggest that distinct metabolic and anthropometric trajectories, which influence the risk of developing type 2 diabetes in adults, are determined according to the period of growth restriction during pregnancy[18]. In the present study, fetal biometry was measured during the second trimester, at a mean gestational age of 22 weeks. It is possible that the effect of maternal obesity, and especially gestational diabetes, on fetal growth is more evident later in pregnancy.

One question that arises is whether the increased risk of adverse fetal outcome in obese women is associated with obesity alone or with an increased risk of developing GDM. The Hyperglycemia and Adverse Pregnancy Outcome study included more than 23,000 pairs of mothers and babies and showed a strong linear association between fasting glucose and post-glucose load with the incidence of macrosomia and neonatal adiposity[4]. An European multicenter study involving seven countries also showed that both maternal obesity and the presence of GDM are independent risk factors for perinatal complications. However, maternal obesity has a greater relative influence on the risk of macrosomia[19]. Because of the interrelated effect of obesity and diabetes on fetal growth, in the present study, we compared the correlation coefficients of the obese and gestational diabetic groups with a control group of nonobese and nondiabetic pregnant women, but there was still no statistical difference (data not shown) between the groups.

Considering the determinants of fetal growth, it has also been documented that there is a positive correlation between fetal AC and glucose levels in maternal blood in nonobese and nondiabetic pregnant women[20]. In this regard, there seems to be a trend toward increased fetal AC in fetuses of pregnant women with GDM, when compared to controls at the beginning of the last trimester (p=0.077) and at delivery (p=0.078)[21]. Together, these data suggest that the metabolic determinants of fetal growth would have a more important role in fetal tissues sensitive to insulin, such as adipose tissue, as represented by AC measurement. However, in the present study, maternal visceral adiposity positively correlated with fetal biometric parameters representing tissues that were both sensitive and nonsensitive to insulin. Although there was no statistical difference, in the present study, there was a tendency of greater AC and EFW in the gestational diabetic group. It is possible that in larger studies, and maybe in studies during the third trimester, this difference will become significant.

The distribution of fat is very important when analyzing outcomes associated with obesity[22] and is commonly categorized as central adiposity (visceral) when there is an excess of fat in the thoracoabdominal area and peripheral when the accumulation of fat occurs in the subcutaneous tissue, particularly in the hips, thighs, and legs[23]. Maternal obesity is usually defined as a high pre-pregnancy BMI and is associated with adverse outcomes[24]. However, BMI does not adequately differentiate the contributions of the muscles and the abdominal or visceral fat to body weight[22]. It is known that central visceral fat is more related to the risk of metabolic disease when compared to subcutaneous fat[25].

On this subject, central adiposity predicts more accurately than the BMI the risk for type 2 diabetes[26] and insulin resistance development in adults. On the contrary, peripheral fat seems to have a dampening effect or to shield some risks related to weight[25]. Regarding fetal growth, recent data, including 740 pregnant women, report no correlation between pre-pregnancy BMI and fetal biometric parameters such as HC, AC, BPD, and EFW in the second trimester of pregnancy, although maternal visceral adiposity is positively correlated with all those parameters[14]. In the present study, maternal visceral adiposity positively correlated with CC, CA, DBP, and EFW in the second trimester of obese, nonobese, diabetic, and nondiabetic mothers.

Our study has some limitations. First, it had a sectional design. Visceral fat and fetal biometry were measured only once, although the recommended techniques had been followed. Second, fat distribution during fetal life may be influenced by gender, and we could not identify this variable. In fact, the effect of gender on the fat distribution of the fetus is not completely known. Third, many variables influence fetal growth and can potentially alter the distribution of fetal fat. Unfortunately, we could not control them all. However, our study has strengths. The study addressed a topic not yet studied, and an adequate sample was studied; besides that, validated techniques were used.

Several studies point to an association between maternal nutrition during pregnancy and fetal development, influencing the body composition of the offspring[24]. This body composition in early life may influence the development of obesity in childhood and adulthood. However, little is known about the role of growth trajectories and intrauterine body composition as determinants of adverse metabolic outcomes in extrauterine life.

CONCLUSION

The present study found no significant difference between the correlation of maternal visceral adiposity and fetal biometric parameters when comparing obese and nonobese mothers, or gestational diabetic and nondiabetic mothers in the second trimester of pregnancy. Larger studies that investigate these correlations in the second and third trimesters may contribute to a better understanding of the exact role and timing of each factor in determining fetal growth.

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AUTHORS' CONTRIBUTIONS

KRML: Conceptualization, Data curation, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. **JGA:** Conceptualization, Formal Analysis, Methodology, Resources, Supervision, Writing – review & editing. **ASRS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

REFERENCES

1. Reece EA, Leguizamón G, Wiznitzer A. Gestational diabetes: the need for a common ground. Lancet. 2009;373(9677):1789-97. https://doi.org/10.1016/S0140-6736(09)60515-8
2. Giacca A, Xiao C, Oprescu AI, Carpentier AC, Lewis GF. Lipid-induced pancreatic β-cell dysfunction: focus on in vivo studies. Am J Physiol Endocrinol Metab. 2011;300(2):E255-62. https://doi.org/10.1152/ajpendo.00416.2010
3. Tan HC, Roberts J, Catov J, Krishnamurthy R, Shypailo R, Bacha F. Mother's pre-pregnancy BMI is an important determinant of adverse cardiometabolic risk in childhood. Pediatr Diabetes. 2015;16(6):419-26. https://doi.org/10.1111/pedi.12273
4. Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care. 2009;32(9):1639-43. https://doi.org/10.2337/dc09-0688
5. Logan KM, Gale C, Hyde MJ, Santhakumaran S, Modi N. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2017;102(1):F65-72. https://doi.org/10.1136/archdischild-2015-309750
6. Hull HR, Thornton JC, Ji Y, Paley C, Rosenn B, Mathews P, et al. Higher infant body fat with excessive gestational weight gain in overweight women. Am J Obstet Gynecol. 2011;205(3):211.e1-7. https://doi.org/10.1016/j.ajog.2011.04.004
7. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. Am J Obstet Gynecol. 2008;198(4):416.e1-6. https://doi.org/10.1016/j.ajog.2007.10.796
8. Martin AM, Berger H, Nisenbaum R, Lausman AY, MacGarvie S, Crerar C, et al. Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. Diabetes Care. 2009;32(7):1308-10. https://doi.org/10.2337/dc09-0290
9. Cisneiros RM, Dutra LP, Silveira FJ, Souza AR, Marques M, Amorim MM, et al. Visceral adiposity in the first half of pregnancy predicts newborn weight among adolescent mothers. J Obstet Gynecol Can. 2013;35(8):704-9. https://doi.org/10.1016/S1701-2163(15)30860-4
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2011;34(Suppl 1):S62-9. https://doi.org/10.2337/dc11-S062
11. Arcaro G, Zamboni M, Rossi L, Turcato E, Covi G, Armellini F, et al. Body fat distribution predicts the degree of endothelial dysfunction in uncomplicated obesity. Int J Obes Relat Metab Disord. 1999;23(9):936-42. https://doi.org/10.1038/sj.ijo.0801022
12. Ribeiro-Filho FF, Faria AN, Azjen S, Zanella MT, Ferreira SR. Methods of estimation of visceral fat: advantages of ultrasonography. Obes Res. 2003;11(12):1488-94. https://doi.org/10.1038/oby.2003.199
13. Mauad FM, Chagas-Neto FA, Benedeti ACGS, Nogueira-Barbosa MH, Muglia VF, Carneiro AAO, et al. Reprodutibilidade da avaliação da gordura abdominal pela ultrassonografia e tomografia computadorizada. Radiol Bras. 2017;50(3):141-7. https://doi.org/10.1590/0100-3984.2016.0023
14. Lopes KRM, Souza ASR, Figueiroa JN, Alves JGB. Correlation between pre-pregnancy body mass index and maternal visceral adiposity with fetal biometry during the second trimester. Int J Gynaecol Obstet. 2017;138(2):133-7. https://doi.org/10.1002/ijgo.12202
15. Grivell RM, Yelland LN, Deussen A, Crowther CA, Dodd JM. Antenatal dietary and lifestyle advice for women who are overweight or obese and the effect on fetal growth and adiposity: the LIMIT randomised trial. BJOG. 2016;123(2):233-43. https://doi.org/10.1111/1471-0528.13777
16. Canavan TP, Deter RL. The effect of maternal body mass index on fetal growth: use of individualized growth assessment and two-level linear modeling. J Clin Ultrasound. 2014;42(8):456-64. https://doi.org/10.1002/jcu.22158
17. Breij LM, Steegers-Theunissen RP, Briceno D, Hokken-Koelega AC. Maternal and fetal determinants of neonatal body composition. Horm Res Pædiatrics. 2015;84(6):388-95. https://doi.org/10.1159/000441298
18. Pilgaard K, Hammershaimb Mosbech T, Grunnet L, Eiberg H, Van Hall G, Fallentin E, et al. Differential nongenetic impact of birth weight versus third-trimester growth velocity on glucose metabolism and magnetic resonance imaging abdominal obesity in young healthy

twins. J Clin Endocrinol Metab. 2011;96(9):2835-43. https://doi.org/10.1210/jc.2011-0577

19. Vellinga A, Zawiejska A, Harreiter J, Buckley B, Di Cianni G, Lapolla A, et al. Associations of body mass index (maternal BMI) and gestational diabetes mellitus with neonatal and maternal pregnancy outcomes in a multicentre european database (diabetes and pregnancy vitamin D and lifestyle intervention for gestational diabetes mellitus. ISRN Obes. 2012;2012:424010. https://doi.org/10.5402/2012/424010
20. Parretti E, Mecacci F, Papini M, Cioni R, Carignani L, Mignosa M, et al. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth. Diabetes Care. 2001;24(8):1319-23. https://doi.org/10.2337/diacare.24.8.1319
21. Zornoza-Moreno M, Fuentes-Hernández S, Prieto-Sánchez MT, Blanco JE, Pagán A, Rol MA, et al. Influence of gestational diabetes on circadian rhythms of children and their association with fetal adiposity. Diabetes Metab Res Rev. 2013;29(6):483-91. https://doi.org/10.1002/dmrr.2417
22. Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. BMJ. 2001;322(7288):716-20. https://doi.org/10.1136/bmj.322.7288.716
23. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev. 2006;2(4):367-73. https://doi.org/10.2174/1573399810602040367
24. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord. 2001;25(8):1175-82. https://doi.org/10.1038/sj.ijo.0801670
25. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes. 1996;45(5):633-8. https://doi.org/10.2337/diab.45.5.633
26. Bray GA, Jablonski KA, Fujimoto WY, Barrett-Connor E, Haffner S, Hanson RL, et al. Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. Am J Clin Nutr. 2008;87(5):1212-8. https://doi.org/10.1093/ajcn/87.5.1212

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Effects of maternal anxiety on fetal and maternal circulation

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the association between maternal anxiety in the third trimester and changes in fetal and maternal circulation assessed by Doppler velocimetry.

METHODS: This is a prospective, cross-sectional study. The inclusion criteria were good health, a singleton pregnancy, maternal age between 18 and 40 years, and gestational age between 34 and 40 weeks. Doppler measurements included mean uterine artery pulsatility index, fetal middle cerebral artery pulsatility index, peak of systolic velocity, umbilical artery, and umbilical vein. The Beck Anxiety Inventory questionnaire, validated for the Brazilian population, with 21 self-reported items, was applied.

RESULTS: The study included 34 pregnant women, and 6 (17.7%) presented a total Beck Anxiety Inventory score showing moderate or severe maternal anxiety. The mean maternal age was 28.1 years (SD 5.7 years); the mean gestational age at interview was 36.5 weeks (SD 1.8 weeks), and the mean Beck Anxiety Inventory total score was 12.3 (SD 9.8). The group with moderate or severe anxiety, compared to the group with minimal or mild anxiety, presented an association with lower maternal age (median 21.5 vs. 29.5 years, p=0.019), lower fetal umbilical vein blood flow (median 189.4 vs. 249.5 mL/min, p=0.047), and lower umbilical vein-corrected blood flow (median 68.5 vs. 84.9 mL/kg/min, p=0.038).

CONCLUSION: Maternal anxiety may affect fetal circulation patterns in late pregnancy and is associated with reduced blood flow in the fetal umbilical vein. The underlying physiopathology needs further investigation.

KEYWORDS: Anxiety. Maternal health. Placental circulation. Umbilical veins.

INTRODUCTION

Several physiological, anatomical, and psychological changes occur in women during gestation that are essential to ensure adequate fetal growth and development. During the pregnancy, expectant mothers usually present anxiety related to the acceptance of body changes, growth of the fetus, and, at the third trimester, maternal anxiety increases related to fear of labor and the need for readjustment of lifestyle with others and the new baby.

Few studies have been done regarding an association between maternal psychological status and maternal-fetal circulation. Fu et al. concluded that poor mental health during pregnancy is found to have an adverse effect on umbilical artery and fetal cerebral circulation evaluated by Doppler ultrasound[1]. Levine et al.[2], in a systematic review, concluded that there is limited evidence that prenatal stress is associated with changes in circulation. In particular, studies of life stress during pregnancy and birth outcomes confirm that the mother's emotional status affects the developing baby. High levels of perceived maternal stress and anxiety are also associated with preterm birth[3], birth weight[4,5], and small-sized infants for gestational age[6].

Doppler velocimetry results of uterine artery (UtA), umbilical artery (UA), fetal middle cerebral artery (MCA), and fetal venous circulation have been linked with adverse perinatal outcomes. However, few studies have assessed their potential relationship with prenatal maternal anxiety. This study was conducted in order to evaluate the association between maternal anxiety in the third trimester and changes in fetal and maternal circulation assessed by Doppler velocimetry.

METHODS

A prospective comparative study was carried out at the prenatal clinic of the University Hospital. The study was approved by the Local Human Research Ethics Committee (CAAE 56059116.9.0000.5505), and all participants signed an informed consent form. The inclusion criteria were pregnant women presenting good health, a singleton pregnancy, maternal age between 18 and 40 years, gestational age between 36 and 40 weeks, and no regular use of medication.

Gestational age was based on the last menstrual period and confirmed by first-trimester ultrasound. Each woman was initially evaluated by ultrasound, and measurements were obtained for fetal biometry and the amniotic fluid index. Fetal Doppler velocimetry measurements were taken of the UtA,

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UA, MCA, and umbilical vein (UV). Doppler measurements were carried out using a real-time ultrasound Voluson 730 Pro (GE Healthcare, Solingen, Germany) with a 2.5-MHz curved-array probe using pulsed and color Doppler options. The high-pass filter was set at minimum, and the sample volume size was adapted to the vessel diameter. All of the recordings used for analysis were obtained in the absence of fetal body and breathing movements at insonation angles as low as possible and always close to 0°. A pulsed Doppler examination of the UA was performed at the free loop of the umbilical cord, and the pulsatility index (PI) was obtained. The MCA could be seen as a major lateral branch in the circle of Willis, and a Doppler sample gate was placed on the proximal portion to obtain waveforms and measure PI. The Doppler assessment of UtA was performed on both the left and right branches, and the mean value of PI was obtained for analysis.

The UV was identified in its intra-abdominal portion, and waveforms were plotted for the straight part. The venous Doppler parameters included time-averaged maximum velocities (TAMxV) measured with insonation along the vessel axis. The evaluation of TAMxV was not recorded simultaneously to adjacent arterial vessels; the measurements were performed during the mean time to include five or more heart cycles. The UV diameter was measured in insonation perpendicular to the vessel wall with the color Doppler mode switched off and the vessel image zoomed in. The blood flow (Q) was calculated as follows: $Q=\pi(D/2)^2\times h\times TAMxV$, where D is the vein diameter and h is the coefficient for the blood velocity profile (0.5)[7].

The intra- and interobserver variability of UV measurements was previously assessed. Intraclass correlation coefficient for the UV TAMxV mean measures was 0.938 (95% confidence interval [CI] 0.888–0.969) and interclass correlation coefficient for the UV TAMxV mean measures was 0.798 (95%CI 0.635–0.889)[8].

Following the Doppler ultrasound measurements, the Beck Anxiety Inventory (BAI) questionnaire was handed out; it is easy to apply and is answered by pregnant women. The BAI is a questionnaire with 21 self-reported items for assessing the severity of a woman's anxiety. Each item describes a common symptom of anxiety and is rated on a 4-point Likert scale, ranging from 0 (for not at all) to 3 (for severely). The respondent is asked to rate each symptom and then the total score is calculated (0–63). A high overall score indicates a high level of anxiety. Score from 0 to 10 reflects minimal anxiety; from 11 to 19, mild anxiety; from 20 to 30, moderate anxiety; and from 31 to 63, severe anxiety. The Brazilian version of the BAI used in this study was validated using the Brazilian population[9].

Data were analyzed using the MedCalc program, version 11.5.1.0 (MedCalc Software, Belgium). Descriptive statistics are presented as mean and standard deviation (SD), median and range, or frequency and percentage. The sample size was estimated based on the study of Fu et al.[1] to detect a difference of 0.20 in the UA-PI, and it was verified that a minimum sample size of 30 cases was required. Data were compared using the Mann-Whitney U test for independent samples, the chi-square test, or the Fisher's exact test. A statistical significance level was set at $p<0.05$.

RESULTS

The study included 34 pregnant women, and 6 (17.7%) presented a total BAI score showing moderate or severe maternal anxiety. Table 1 displays the maternal characteristics and the main Doppler results. The mean BAI total score was 12.3 (SD 9.8). No preterm delivery occurred and all babies had adequate parameters for their gestational age at birth.

Table 1. Maternal, perinatal characteristics, and Doppler parameters at third trimester (n=34).

Characteristic	Value
Maternal age (years)	28.1 (5.7)
Nulliparity	21 (61.8%)
Gestational age at exam (weeks)	36.5 (1.7)
Estimated fetal weight (g)	2,852 (488)
Amniotic fluid index (cm)	12.9 (2.5)
UtA PI	0.72 (0.67–0.77)
UA PI	0.81 (0.16)
MCA PI	1.62 (0.25)
MCA PSV	51.2 (10.1)
UV TAMxV (cm/s)	20.42 (3.79)
UV flow (mL/min)	226.3 (197.0–269.9)
UV flow, normalized (mL/min/kg)	79.7 (69.2–96.1)
Total BAI score	10.5 (7.0–13.0)
Maternal anxiety	
Minimal	17 (50.0%)
Mild	11 (32.4%)
Moderate	4 (11.8%)
Severe	2 (5.9%)

Data expressed as n (%), mean (SD), or median (95%CI for the mean). UtA: uterine artery; PI: pulsatility index; UA: umbilical artery; MCA: middle cerebral artery; PSV: peak systolic velocity; UV: umbilical vein; TAMxV: time averaged maximum velocity; BAI: Beck Anxiety Inventory.

Table 2 presents the results of Doppler parameters in the group of moderate or severe anxiety, compared to the group of minimal or mild anxiety, and presents an association with lower maternal age (p=0.019), lower fetal UV blood flow (p=0.047), and lower UV-corrected blood flow (p=0.038). No significant association was found between moderate or severe maternal anxiety and fetal growth (p=0.651), mean UtA PI (p=0.175), UA PI (p=0.752), MCA PI (p=0.401), and MCA PSV (p=0.191). No significant differences were detected regarding the type of delivery when comparing the groups: the cesarean section rate was 33.3% (n=2) in the group with moderate or severe anxiety and 32.1% (n=9) in the group with mild or minimal anxiety (p=1.0, Fisher's exact test).

Figure 1 shows the median fetal UV blood flow and UV-corrected blood flow in both groups of moderate or severe anxiety, compared to group of minimal or mild anxiety. A reduction in the UV blood flow occurs in the mothers presenting anxiety.

Table 2. Maternal characteristics and Doppler values of uterine artery, umbilical artery, middle cerebral artery, and umbilical vein according to maternal anxiety.

Characteristics	Minimal or mild anxiety (n=28)	Moderate or severe anxiety (n=6)	p-value*
Maternal age (years)	29.5 (25.3–34.8)	21.5 (18.6–29.2)	0.019
Nulliparity	18 (64.3)	3 (50.0)	0.855
Gestational age at exam (weeks)	36.5 (35.3–37.7)	35.5 (34.3–38.1)	0.442
Amniotic fluid index (cm)	13.0 (11.6–14.3)	12.5 (10.0–15.6)	0.910
Estimated fetal weight (g)	2940 (2499–3139)	2583 (2234–3517)	0.651
UtA PI	0.72 (0.68–0.81)	0.64 (0.55–0.75)	0.175
UA PI	0.85 (0.75–0.91)	0.78 (0.65–0.96)	0.712
MCA PI	1.59 (1.49–1.70)	1.69 (1.37–1.77)	0.401
MCA PSV	49.5 (43.9–54.6)	54.6 (45.4–71.3)	0.191
UV TAMxV (cm/s)	20.9 (19.5–22.1)	18.2 (15.8–23.2)	0.343
UV flow (mL/min)	249.5 (201.3–294.1)	189.4 (133.8–249.7)	0.047
UV flow, normalized (mL/min/kg)	84.9 (73.0–103.3)	68.5 (59.9–76.2)	0.038
Total BAI score	8.0 (6.0–11.0)	25.0 (22.0–45.1)	<0.001

*Mann-Whitney U test. Data expressed as n (%) or median (95%CI for the mean). UtA: uterine artery; UA: umbilical artery; PI: pulsatility index; MCA: middle cerebral artery; PSV: peak systolic velocity; UV: umbilical vein; TAMxV: time averaged maximum velocity; BAI: Beck Anxiety Inventory.

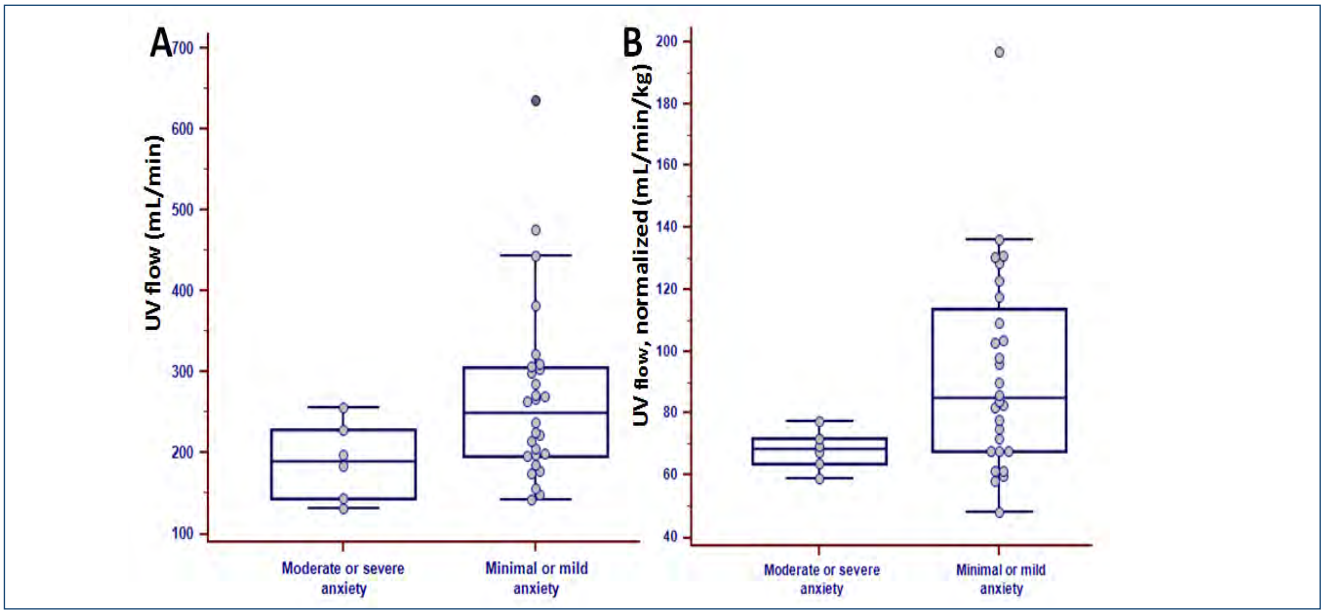

Figure 1. Box-and-whisker plot for median and 95%CI of umbilical vein flow (A) and normalized umbilical vein flow by estimated fetal weight (B) according to maternal anxiety.

DISCUSSION

In our study, fetal UV circulation patterns are associated with maternal anxiety. Maternal anxiety appears to be related to reduced UV blood flow. These changes suggest that the fetal supply of oxygenated blood flow may be reduced in conditions of moderate or severe maternal anxiety. Color Doppler ultrasound is a sensitive and safe technique for examining changes in fetal blood flow and provides a comprehensive and objective assessment of the fetus[10].

No difference is found with the UtA, UA, and MCA changes in both groups, according to maternal anxiety. It agrees with Kent et al.[11] Interestingly, as opposed to the study of Fu et al.[1], we found no difference in Doppler velocimetry indices in the UA. Possible reasons might be the small sample size or an unknown possible physiological mechanism of how maternal stress affects the fetus.

Anxiety is increasing in our society due to several factors and represents an important health problem. Maternal anxiety in the first trimester is a risk factor for later development of fetal complications. A study was performed to identify the biopsychosocial risk associated with the development of adverse obstetric outcomes. Ramiro-Cortijo et al.[12] found women with fetal complications showed a significantly higher score in anxiety compared to women without fetal complications. Our data show that maternal psychological features like anxiety exert an influence on fetal UV blood flow.

Elevated maternal psychological distress during pregnancy is linked to adverse outcomes. Prenatal brain development in the setting of elevated maternal distress has adverse infant social and cognitive outcomes. Wu et al.[13] studied mother-infant dyads and found an association between prenatal maternal stress and infant cognitive outcome mediated by fetal left hippocampal volume. McGuinn et al.[14] found that higher levels of pregnancy-specific anxiety in the mother were associated with higher anxiety symptoms in the child. Changes in fetal circulation due to maternal anxiety may be related to long-term effects on the offspring.

The different positions adopted by pregnant women may affect the maternal uteroplacental blood flow and interfere in fetal circulation[15]. As uterine blood flow may change in the maternal supine position, the exams in the present study were performed to avoid this aspect.

The strength of this study is the prospective examination of fetal venous blood flow in a population of pregnant women attending for routine care and assessment of maternal anxiety. The main limitation of the study is the limited number of cases and the data confined to the third trimester of pregnancy. The sample size of the groups does not allow the analysis of changes in Doppler flow regarding anxiety that may affect the fetus and play a role in medical decision-making. Studies with a larger number of cases are needed to better understand the effects of maternal anxiety on the fetus that may influence obstetric management.

CONCLUSION

Maternal anxiety may affect fetal circulation patterns in late pregnancy and is associated with reduced blood flow in the fetal UV. Effective use of these Doppler indices allows fetal assessment of changes in maternal characteristics and medical history that affect these measurements in normal pregnancies. However, the underlying physiopathology of these changes needs further investigation.

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AUTHORS' CONTRIBUTIONS

RMYN: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **TFJ:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Fu J, Yang R, Ma X, Xia H. Association between maternal psychological status and fetal hemodynamic circulation in late pregnancy. Chin Med J (Engl). 2014;127(13):2475-8. PMID: 24985586
2. Levine TA, Alderdice FA, Grunau RE, McAuliffe FM. Prenatal stress and hemodynamics in pregnancy: a systematic review. Arch Womens Ment Health. 2016;19(5):721-39. https://doi.org/10.1007/s00737-016-0645-1
3. Rondó PH, Ferreira RF, Nogueira F, Ribeiro MC, Lobert H, Artes R. Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. Eur J Clin Nutr. 2003;57(2):266-72. https://doi.org/10.1038/sj.ejcn.1601526

4. Khashan AS, Everard C, McCowan LM, Dekker G, Moss-Morris R, Baker PN, et al. Second-trimester maternal distress increases the risk of small for gestational age. Psychol Med. 2014;44(13):2799-810. https://doi.org/10.1017/S0033291714000300
5. Kaitz M, Mankuta D, Rokem AM, Faraone SV. Moderate antenatal anxiety symptoms and birth outcomes of boys and girls. J Psychosom Obstet Gynaecol. 2014;35(4):116-23. https://doi.org/10.3109/0167482X.2014.952279
6. Class QA, Lichtenstein P, Långström N, D'Onofrio BM. Timing of prenatal maternal exposure to severe life events and adverse pregnancy outcomes: a population study of 2.6 million pregnancies. Psychosom Med. 2011;73(3):234-41. https://doi.org/10.1097/PSY.0b013e31820a62ce
7. Acharya G, Wilsgaard T, Rosvold Berntsen GK, Maltau JM, Kiserud T. Reference ranges for umbilical vein blood flow in the second half of pregnancy based on longitudinal data. Prenat Diagn. 2005;25(2):99-111. https://doi.org/10.1002/pd.1091
8. Ortigosa C, Nomura RM, Costa VN, Miyadahira S, Zugaib M. Fetal venous Doppler in pregnancies with placental dysfunction and correlation with pH at birth. J Matern Fetal Neonatal Med. 2012;25(12):2620-4. https://doi.org/10.3109/14767058.2012.711394
9. Cunha JA. Manual da versão em português das escalas Beck: BDI, BAI, BHS e BSI. São Paulo: Casa do Psicólogo; 2001.
10. Wu M, Lin Y, Lei F, Yang Y, Yu L, Liu X. Diagnostic value of prenatal ultrasound for detecting abnormal fetal blood flow. Am J Transl Res. 2021;15;13(5):5094-100. PMID: 34150097
11. Kent A, Hughes P, Ormerod L, Jones G, Thilaganathan B. Uterine artery resistance and anxiety in the second trimester of pregnancy. Ultrasound Obstet Gynecol. 2002;19(2):177-9. https://doi.org/10.1046/j.0960-7692.2001.00546.x
12. Ramiro-Cortijo D, de la Calle M, Benitez V, Gila-Diaz A, Moreno-Jiménez B, Arribas SM, et al. Maternal psychological and biological factors associated to gestational complications. J Pers Med. 2021;11(3):183. https://doi.org/10.3390/jpm11030183
13. Wu Y, Espinosa KM, Barnett SD, Kapse A, Quistorff JL, Lopez C, et al. Association of elevated maternal psychological distress, altered fetal brain, and offspring cognitive and social-emotional outcomes at 18 months. JAMA Netw Open. 2022;5(4):e229244. https://doi.org/10.1001/jamanetworkopen.2022.9244
14. McGuinn LA, Tamayo-Ortiz M, Rosa MJ, Harari H, Osorio-Valencia E, Schnaas L, et al. The influence of maternal anxiety and cortisol during pregnancy on childhood anxiety symptoms. Psychoneuroendocrinology. 2022;139:105704. https://doi.org/10.1016/j.psyneuen.2022.105704
15. Silva KP, Hamamoto TENK, Nomura RMY. Transient fetal blood redistribution associated with maternal supine position. J Perinat Med. 2017;45(3):343-7. https://doi.org/10.1515/jpm-2016-0288

ORIGINAL ARTICLE

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Investigation of associations between apolipoprotein A5 and C3 gene polymorphisms with plasma triglyceride and lipid levels

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SUMMARY

OBJECTIVE: The aim of this study was to determine frequency and associations between *APOA5* c.56C>G, -1131T>C, c.553G>T, and *APOC3* -482C>T and *SstI* gene polymorphisms with hypertriglyceridemia.

METHODS: Under a case-control study model, 135 hypertriglyceridemic and 178 normotriglyceridemic control participants were recruited. Polymerase chain reaction and restriction fragment length polymorphism methods were utilized for genotyping. Statistical calculations were performed by comparing allele and genotype frequencies between groups. Clinical characteristics were compared between groups and intra-group genotypes.

RESULTS: *APOC3* gene -482C>T and *SstI* polymorphic genotypes and allele frequencies were significantly higher in hypertriglyceridemic group (genotype frequencies, p=0.035, p=0.028, respectively). Regression analysis under unadjusted model confirmed that *APOC3* -482C>T and *SstI* polymorphisms were significantly contributing to have hypertriglyceridemia (p=0.02, odds ratio [OR]=1.831 (95% confidence interval [CI] 1.095–3.060); p=0.04, OR=1.812 (1.031–3.183), respectively). *APOA5* c.56C>G was in complete linkage disequilibrium with *APOA5* c.553G>T polymorphism (D'=1).

CONCLUSION: For the first time in a population sample from Turkey, among the five polymorphisms of *APOA5* and *APOC3* genes investigated, *APOC3* -482C>T and *SstI* polymorphisms were associated with elevated serum TG levels, while *APOA5* c.56C>G, -1131T>C, and c.553G>T polymorphisms were not.

KEYWORDS: Apolipoprotein A-V. Apolipoprotein C-III. Lipids. Apolipoproteins. Genetic variation.

INTRODUCTION

Hypertriglyceridemia (HTG) is characterized by significantly elevated serum triglyceride (TG) levels[1]. HTG was directly associated with coronary artery disease (CAD) risk[2]. Genetic factors are known to be responsible for increased serum lipid levels, especially TG. *APOA5* gene is the latest discovered gene that influences serum TG levels. It was shown that *APOA5* overexpressing mice displayed significantly lower serum TG levels, while *APOA5* knockout mice displayed significantly higher serum TG levels[3]. It was also reported that combined effect of *APOA5* -1131T>C and c.56C>G polymorphic alleles on elevated serum TG levels was twice as influential compared to normal alleles[4]. Apolipoprotein C-III (apoC-III) was discovered much earlier than apoA-V and influences serum lipid levels by inhibiting lipoprotein lipase enzyme (LPL)[5]. ApoC-III is a component of mainly high-density lipoproteins (HDL) and TG-rich lipoproteins while apoA-V is a component of HDL and very low density lipoproteins (VLDL).

Association of *APOA5* and *APOC3* genes with serum TG levels was shown in various ethnicities around the world[2,6-10]. However, there are also reports showing that there is no association between *APOC3* and *APOA5* with serum lipid levels[11]. These conflicting results may arise from selection criteria of the study sample, ethnic differences, and environmental factors like population lifestyle habits.

METHODS

Study subjects

Unrelated 135 hypertriglyceridemic and 178 normolipidemic control Caucasians were recruited from a hospital of Ondokuz Mayıs University, Samsun, Turkey, and Ünye community health care center number 1, Ordu, Turkey. Assoc. Prof. Dr. (MD) M. Kamil Turan contributed by referring and diagnosing the patients and clinical specimens based on the patient's clinical laboratory characteristic results. Inclusion criteria for control group was having fasting TG level under 2.26 mmol/L and for case group above 2.26 mmol/L. Individuals who were relatives, using lipid lowering medication, and had any CAD or any metabolic disease were excluded. All participants signed the informed written consent for participation in the study. The study was approved

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by the ethics committee of Ondokuz Mayıs University, Faculty of Medicine, with registration number 100, Date: 20.4.2005.

Genotyping

A 2 mL of venous blood was drawn to EDTA-containing tubes after overnight fasting. Genomic DNA was extracted from whole blood by salting-out method described previously and stored in TE solution at -20°C[12]. Before genotyping procedures, extracted DNA was diluted with pure water to yield optimum polymerase chain reaction (PCR) amplification. Genotyping of all single nucleotide polymorphisms (SNPs) was carried out using PCR and restriction fragment length polymorphism (RFLP) assay. For the sake of simplicity, used PCR primers and restriction enzymes were not given here, although primers for PCR and enzyme names for RFLP can be shared upon request. All PCR reactions were performed in 25 µL of total volume over 30–35 cycles depending on the polymorphism and primer and may be shared upon request. PCR amplicons were digested with RFLP enzymes overnight at 37°C. 2 µL of amplicons and restriction fragments were visualized in 2% standard agarose gel electrophoresis that stained with ethidium bromide under computerized UV system.

Biochemical analysis

Blood TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), and LDLC levels were measured after overnight fasting with automated hospital analyzer instruments of biochemistry laboratory. Hormone levels were measured using the Siemens ADVIA Centaur® XP electrochemiluminescence assay.

Statistical analysis

Statistical analyses were performed using SPSS (SPSS Inc., IL, Chicago) software. Continuous variables were expressed as mean±standard deviation (SD). Statistically significance alpha level was p=0.05. The Kolmogorov-Smirnov test was used to determine normally distributed data. Genotype and allele frequencies were determined by gene counting. Differences of genotype and allele frequencies between groups were evaluated by chi-square analysis. Mann-Whitney U test and Student's t-test were used to test significant differences in clinical characteristics. ANOVA test was used to evaluate differences in lipid levels between genotypes. Logistic regression analysis was used to evaluate the effect of polymorphisms on having HTG. Haplotype analysis and pairwise linkage disequilibrium (LD) were calculated using the SHEsis software (http://analysis.bio-x.cn). Haplotypes with frequencies less than 0.03 were excluded. LD values equal to 1 are accepted as complete LD.

RESULTS

A comparison of clinical characteristics is shown in Table 1. HTG group had significantly higher TC and body mass index (BMI) levels compared to controls (p<0.05). Mean HDLC level of control group was significantly higher than HTG group since subjects in control group had more balanced serum lipid composition compared to HTG group (p<0.05). There was no significant difference between groups in terms of age and male-female ratio.

Genotype and allele frequencies are given in Table 2. All these *APOA5* polymorphic (c.56C>G, -1131T>C, and c.553G>T) genotype allele frequencies were not significantly different between groups (p>0.05 for all). Among all subjects, only one heterozygous c.553G>T polymorphism participant was detected, while the homozygous polymorphic genotype was not detected at all. However, polymorphic genotype and allele frequencies of both *APOC3* gene -482C>T and *SstI* polymorphisms were significantly higher in HTG group compared to control group (genotype frequencies, p=0.035, p=0.028, respectively).

Logistic regression analysis results are shown in Table 3. Compatible with the chi-square association analysis as shown in Table 2, none of the three *APOA5* polymorphisms had an effect on having HTG under both additive and dominant models (p>0.05). However, in the unadjusted model, both *APOC3* -482C>T and *SstI* heterozygous polymorphic genotypes significantly contribute to have HTG (p=0.02, odds ratio [OR]=1.831 (95% confidence interval [CI]=1.095–3.060); p=0.04, OR=1.812 (1.031–3.183), respectively). In the adjusted model (adjusted for age and sex), heterozygous polymorphic genotype of *APOC3* -482C>T was also contributing to having HTG with a greater OR than the unadjusted model (p=0.01, OR=2.065 (95%CI 1.187–3.592). However, significant contribution of APOC3 *SstI* polymorphism on having HTG was disappeared in the adjusted model with a borderline alpha

Table 1. Basic characteristics of subjects.

	HTG	Controls	p-value
Gender (M/F)	70/65	58/78	>0.05
Age (years)	46.07±11	43.93±11	>0.05
TG (mmol/L)	3.61±1.38	1.34±0.48	<0.05
TC (mmol/L)	5.50±1.08	4.54±0.91	<0.05
HDLC (mmol/L)	1.01±0.24	1.18±0.33	<0.05
LDLC (mmol/L)	2.85±1.00	2.74±0.74	>0.05
BMI (kg/m^2)	28.72±3.94	26.64±4.15	<0.05

Standard deviation is given after ± symbol. TG: triglyceride; TC: total cholesterol; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; BMI: body mass index.

Table 2. Comparison of genotypes and allelic frequencies of *APOA5* and *APOC3* polymorphisms between HTG and control groups.

		HTG	Controls	p-value
APOA5 c.56C>G n (%)	CC	102 (78.5)	115 (85.8)	0.286
	CG	26 (20.0)	18 (13.4)	
	GG	2 (1.5)	1 (0.8)	
Allele frequencies C/G		0.88/0.12	0.93/0.07	0.11
APOA5 -1131T>C n (%)	TT	62 (79.5)	43 (71.7)	0.536
	TC	13 (16.7)	13 (21.7)	
	CC	3 (3.8)	4 (6.7)	
Allele frequencies T/C		0.88/0.12	0.82/0.18	0.21
APOA5 c.553G>T n (%)	GG	132 (99.2)	135 (100)	0.496
	GT	1 (0.8)	0 (–)	
	TT	0 (–)	0 (–)	
Allele frequencies G/T		0.992/0.008	1/0	*
APOC3 -482C>T n (%)	CC	44 (33.8)	66 (49.3)	**0.035**
	CT	72 (55.4)	59 (44.0)	
	TT	14 (10.8)	9 (6.7)	
Allele frequencies C/T		0.62/0.38	0.71/0.29	**0.018**
APOC3 SstI n (%)	CC	68 (59.6)	84 (73.7)	**0.028**
	CG	44 (38.6)	30 (26.3)	
	GG	2 (1.8)	0 (–)	
Allele frequencies C/G		0.79/0.21	0.87/0.13	**0.025**

Bold indicates statistically significant p-values. *Not available.

significance level (p=0.06). In the unadjusted model, both -482C>T and *SstI* polymorphisms were more effective than additive model on having HTG (p=0.01, OR=1.897 (95%CI 1.154–3.117); p=0.03, OR=1.894 (1.082–3.317), respectively). Similarly, both polymorphisms were still effective with greater odd ratios in the adjusted model (p=0.01, OR=2.052 (95%CI 1.205–3.494); p=0.04, OR=1.851 (1.022–3.352), respectively).

DISCUSSION

The vast majority of previous *APOA5* and *APOC3* polymorphism studies were mainly focused on the association of the disease with CAD. However, the direct involvement of *APOA5* and *APOC3* polymorphisms in the development of CAD remained controversial, possibly due to too many influential factors involved in CAD that are uncontrollable in a case-control study. Thus, it may be more effective to know whether *APOA5* and *APOC3* are involved in HTG. In addition, studies that include nonalcoholic fatty liver disease (NAFLD), which may occur as a result of excess TG accumulation, investigated the possible relations between genetic factors and NAFLD. In one of these studies, it was reported that genetic mutations as well as oxidative stress may lead to necrotic inflammation in the liver[13]. They also added that mostly genetic background of the individuals is significant in the development of NAFLD. Additionally, Toman et al.[14] reported that obesity, a condition that is related to elevated serum TG and cholesterol levels, may cause NAFLD. However, it was also reported that obesity may be protective in patients with lung lobectomy[15].

In a study from Morocco where the case group was composed of CAD patients, under the dominant model, *APOA5* c.56C>G polymorphism was found to be associated with elevated TG and TC levels (p<0.05 for both)[16]. This result may be comparable with ours due to multifactorial nature of CAD, since when all subjects are included, it may be accepted as a population sample. c.56C>G polymorphism of the *APOA5* gene was reported to be associated with HTG also in a Caucasian population sample previously[17]. However, like ours, there are studies that did not find any association between c.56C>G and HTG in several ethnicities[16]. In intragroup comparisons, we detected a borderline significant TC decrease of CG+GG genotypes compared to CC genotype in HTG group under dominant model, which may be explained by lipid-raising effect of this polymorphism (p=0.043) (data not shown). G allele of the c.56C>G is very less frequent in Asian ethnicity (0.01–0.03), while it does not exist in Korean ethnicity[18]. In our study, the G allele frequency of c.56C>G was 0.12 in HTG group and 0.07 in control group, displaying a similar general population sample frequency to Asian and Korean populations. As expected, the G allele frequency of our cohort was higher from Asian ethnicity, closer to Eastern ethnicities.

The C allele frequency of -1131T>C polymorphism was 0.3 in Chinese and Japan ethnicities, while it was 0.1 in Caucasian ethnicity[18,19]. In our study, the C allele frequency of -1131T>C was 0.12 in HTG group and 0.18 in control group, displaying an overall frequency between Asian and Caucasian ethnicities, with an insignificant p-value of 0.21. In a Spanish population sample, the C allele of the APOA5 -1131T>C polymorphism was not associated with elevated serum TG levels. In Chinese population, polymorphic C allele carriers of -1131T>C showed approximately 25% higher serum TG level compared to non-carriers, where this difference was 27% and significant in our study (p=0.004)[11]. The C allele frequency of *APOA5* -1131T>C in various ethnicities around the globe differs between 13 and 41%[20]. In our study, T allele frequency was below 1%, which

Table 3. Binary logistic regression analysis.

Additive model					
Genotype		Unadjusted		Adjusted[a]	
		OR (95%CI)	p-value	OR (95%CI)	p-value
APOA5 c.56C>G	CC	1		1	
	CG	1.629 (0.844–3.143)	0.15	1.655 (0.824–3.324)	0.16
	GG	2.255 (0.201–25.237)	0.51	2.012 (0.179–22.629)	0.57
APOA5 -1131T>C	TT	1		1	
	TC	0.694 (0.293–1.642)	0.4	0.745 (0.285–1.944)	0.55
	CC	0.520 (0.111–2.443)	0.41	0.371 (0.060–2.305)	0.29
APOA5 c.553G>T	GG	1		1	
	GT	*	*	*	*
	TT	*	*	*	*
APOC3 -482C>T	CC	1		1	
	CT	1.831 (1.095–3.060)	**0.02**	2.065 (1.187–3.592)	**0.01**
	TT	2.333 (0.930–5.856)	0.07	1.982 (0.751–5.231)	0.17
APOC3 SstI	CC	1		1	
	CG	1.812 (1.031–3.183)	**0.04**	1.768 (0.972–3.215)	0.06
	GG	*	*	*	*
Dominant model					
Genotype		Unadjusted		Adjusted[a]	
		OR (95%CI)	p-value	OR (95%CI)	p-value
APOA5 c.56C>G	CC	1		1	
	CG+GG	1.662 (0.876–3.153)	0.12	1.678 (0.853–3.301)	0.13
APOA5 -1131T>C	TT	1		1	
	TC+CC	0.653 (0.298–1.432)	0.29	0.648 (0.269–1.559)	0.33
APOA5 c.553G>T	GG	1		1	
	GT+TT	*	*	*	*
APOC3 -482C>T	CC	1		1	
	CT+TT	1.897 (1.154–3.117)	**0.01**	2.052 (1.205–3.494)	**0.01**
APOC3 SstI	CC	1		1	
	CG+GG	1.894 (1.082–3.317)	**0.03**	1.851 (1.022–3.352)	**0.04**

[a]Adjusted for age, gender, and BMI. *Since there was only one heterozygote and no homozygous polymorphic genotype in both HTG and control groups, the p-value cannot be calculated. Bold indicates statistically significant p-values.

is an extremely low percentage compared to Chinese studies. We detected only one heterozygous participant and did not detect a nonhomozygous polymorphic genotype among all subjects (particularly in HTG group). This finding is compatible with the nonexistence of *APOA5* c.553G>T polymorphism in Caucasians[17].

In Chinese population, T allele of *APOC3* -482C>T polymorphism was found to be associated with increased serum TG and decreased HDLC levels (p=0.012 and p=0.012, respectively)[21]. However, this population sample was recruited from healthy subjects, unlike our case-control study design; thus, we cannot directly compare our results. We have also checked whether polymorphic genotypes of -482C>T have an influence on serum lipid levels and BMI in both HTG and control groups and interestingly observed that under additive model, this polymorphism was showing a significant TG-lowering effect in the HTG group (p=0.025) and BMI-lowering effect in the control group (p=0.017) (data not shown). This result is not compatible with previously reported results and may be explained by intergenic interactions like LD with other polymorphisms.

APOC3 *SstI* polymorphism was associated with increased serum TG levels in Bogalusa Heart Study, whose participants were from the USA with a large sample size[22]. Polymorphic allele frequency was detected at 30–43% in Chinese, 25–48% in Japanese, and 16% in Indians[23]. However, there are also studies in European populations that did not encounter any association between APOC3 *SstI* polymorphism and serum TG levels[24]. We have detected an association between APOC3 *SstI* polymorphism and HTG, with a significantly higher frequency of polymorphic genotypes in HTG group than in controls (p=0.028). We have also confirmed by regression analysis that there is a significant effect of *APOC3 SstI* polymorphism on having HTG under dominant model under both unadjusted and adjusted models (p=0.03, OR=1.894 (95%CI 1.082–3.317); p=0.04, OR=1.851 (95%CI 1.022–3.352), respectively).

Haplotype analysis showed that none of the haplotype frequencies were significantly different between case and control groups (p>0.05, all) (data not shown). A weak LD (D'=0.29) between *APOA5* 1131T>C and *APOC3* 482C>T was observed in a Chinese population[21]. Similar to the mentioned Chinese sample, in our study, the D' value between *APOA5* -1131T>C and *APOC3* -482C>T was very weak (D'=0.03). It was reported that *APOC3* -482C>T with *APOA5* c.56C>G, *APOA5 -1131C>T*, and *APOC3 SstI* has strong LD[25]. Our result was compatible with the abovementioned study, with a strong LD between *APOC3* -482C>T and *APOC3 SstI* (D'=0.87). Yin et al.[23] reported that in a Chinese population sample, *APOC3 SstI* was in LD with *APOA5* -1131T>C (r^2=0.359). In our study, *APOA5* c.56C>G and *APOA5* c.553G>T showed complete LD (D'=1) (data not shown). The other strong LD were observed between *APOA5* c.553G>T and *APOC3* -482C>T (D'=0.96), APOA5 c.553G>T and *APOC3 SstI* (D'=0.99), and *APOC3* -482C>T and *APOC3 SstI* (D'=0.87) (data not shown).

Limitations of this study that should be addressed are lack of serum apoA-V and apoC-III protein measurements and relatively small sample size due to low cost.

CONCLUSIONS

The investigated polymorphisms in this study represent divergent frequencies and associations with HTG in previous studies that were conducted with several other ethnicities. Representing a sample who live in Black Sea coast, in the current study, we show that *APOC3* polymorphisms -482C>T and *SstI* are associated with HTG. However, we did not encounter any association between *APOA5* polymorphisms c.56C>G, -1131T>C, and HTG. Additionally, the homozygous polymorphic genotype of *APOA5* c.553G>T was not seen in our cohort. Finally, *APOA5* c.56C>G and c.553G>T polymorphisms are observed in complete LD.

AUTHORS' CONTRIBUTIONS

ET: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **HB:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **MKT:** Data curation, Methodology, Resources, Writing – review & editing.

REFERENCES

1. Oh RC, Trivette ET, Westerfield KL. Management of hypertriglyceridemia: common questions and answers. Am Fam Physician. 2020;102(6):347-54. PMID: 32931217
2. Goyal S, Tanigawa Y, Zhang W, Chai JF, Almeida M, Sim X, et al. APOC3 genetic variation, serum triglycerides, and risk of coronary artery disease in Asian Indians, Europeans, and other ethnic groups. Lipids Health Dis. 2021;20(1):113. https://doi.org/10.1186/s12944-021-01531-8
3. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, et al. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001;294(5540):169-73. https://doi.org/10.1126/science.1064852
4. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. Hum Mol Genet. 2002;11(24):3031-8. https://doi.org/10.1093/hmg/11.24.3031
5. Hansen SEJ, Madsen CM, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Genetic variants associated with increased plasma levels of triglycerides, via effects on the lipoprotein lipase pathway, increase risk of acute pancreatitis. Clin Gastroenterol Hepatol. 2021;19(8):1652-1660.e6. https://doi.org/10.1016/j.cgh.2020.08.016
6. Dai W, Zhang Z, Yao C, Zhao S. Emerging evidences for the opposite role of apolipoprotein C3 and apolipoprotein A5 in lipid metabolism and coronary artery disease. Lipids Health Dis. 2019;18(1):220. https://doi.org/10.1186/s12944-019-1166-5
7. Girelli D, Piubelli C, Martinelli N, Corrocher R, Olivieri O. A decade of progress on the genetic basis of coronary artery disease. Practical insights for the internist. Eur J Intern Med. 2017;41:10-7. https://doi.org/10.1016/j.ejim.2017.03.019

8. Dib I, Khalil A, Chouaib R, El-Makhour Y, Noureddine H. Apolipoprotein C-III and cardiovascular diseases: when genetics meet molecular pathologies. Mol Biol Rep. 2021;48(1):875-86. https://doi.org/10.1007/s11033-020-06071-5
9. Matsunaga A, Nagashima M, Yamagishi H, Saku K. Variants of lipid-related genes in adult japanese patients with severe hypertriglyceridemia. J Atheroscler Thromb. 2020;27(12):1264-77. https://doi.org/10.5551/jat.51540
10. Dron JS, Hegele RA. Genetics of triglycerides and the risk of atherosclerosis. Curr Atheroscler Rep. 2017;19(7):31. https://doi.org/10.1007/s11883-017-0667-9
11. You Y, Wu YH, Zhang Y, Zhang L, Song Y, Bai W, et al. Effects of polymorphisms in APOA5 on the plasma levels of triglycerides and risk of coronary heart disease in Jilin, northeast China: a case-control study. BMJ Open. 2018;8(6):e020016. https://doi.org/10.1136/bmjopen-2017-020016
12. Kalousová M, Levová K, Kuběna AA, Jáchymová M, Franková V, Zima T. Comparison of DNA isolation using salting-out procedure and automated isolation (MagNA system). Prep Biochem Biotechnol. 2017;47(7):703-8. https://doi.org/10.1136/bmjopen-2017-020016
13. Toman D, Sengul I, Pelikán A, Sengul D, Vavra P, Ihnát P, et al. Hepatocellular carcinoma *versus* nonalcoholic fatty liver disease: metabolic, environmental, and genetic association? *De facto*? Rev Assoc Médica Bras. 2022;68(5):708-11. https://doi.org/10.1590/1806-9282.20220147
14. Toman D, Sengul I, Pelikán A, Sengul D, Vavra P, Ihnat P, et al. A narrative review on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis versus hepatocellular carcinoma: do you mind? Rev Assoc Médica Bras. 68(6):871-4. https://doi.org/10.1590/1806-9282.20220268
15. Tulinský L, Sengul I, Ihnát P, Ostruszka P, Toman D, Guňková P, et al. Obesity in cases undergoing the surgical procedure of lung lobectomy: risk or benefit Rev Assoc Med Bras. 2022;68(8):1090-5. https://doi.org/10.1590/1806-9282.20220526
16. Morjane I, Charoute H, Ouatou S, Elkhattabi L, Benrahma H, Saile R, et al. Association of c.56C > G (rs3135506) apolipoprotein A5 gene polymorphism with coronary artery disease in Moroccan subjects: a case-control study and an updated meta-analysis. Cardiol Res Pract. 2020;2020:5981971. https://doi.org/10.1155/2020/5981971
17. Hubacek JA, Adamkova V, Prusikova M, Snejdrlova M, Hirschfeldova K, Lanska V, et al. Impact of apolipoprotein A5 variants on statin treatment efficacy. Pharmacogenomics. 2009;10(6):945-50. https://doi.org/10.2217/pgs.09.17
18. Lai CQ, Tai ES, Tan CE, Cutter J, Chew SK, Zhu YP, et al. The APOA5 locus is a strong determinant of plasma triglyceride concentrations across ethnic groups in Singapore. J Lipid Res. 2003;44(12):2365-73. https://doi.org/10.1194/jlr.M300251-JLR200
19. Baum L, Tomlinson B, Thomas GN. APOA5-1131T>C polymorphism is associated with triglyceride levels in Chinese men. Clin Genet. 2003;63(5):377-9. https://doi.org/10.1034/j.1399-0004.2003.00063.x
20. Mahrooz A, Zargari M, Ansari V, Makhlough A, Hashemi-Sooteh MB. Association of APOA5 gene promoter region -1131T>C polymorphism (rs662799) to plasma triglyceride level in patients with type 2 diabetic nephropathy. J Clin Diagn Res JCDR. 2016;10(5):BC09-13.
21. Li GP, Wang JY, Yan SK, Chen BS, Xue H, Wu G. Genetic effect of two polymorphisms in the apolipoprotein A5 gene and apolipoprotein C3 gene on serum lipids and lipoproteins levels in a Chinese population. Clin Genet. 2004;65(6):470-6. https://doi.org/10.1111/j.1399-0004.2004.00251.x
22. Hallman DM, Srinivasan SR, Chen W, Boerwinkle E, Berenson GS. Longitudinal analysis of haplotypes and polymorphisms of the APOA5 and APOC3 genes associated with variation in serum triglyceride levels: the Bogalusa heart study. Metabolism. 2006;55(12):1574-81. https://doi.org/10.1016/j.metabol.2006.07.018
23. Yin RX, Li YY, Lai CQ. Apolipoprotein A1/C3/A5 haplotypes and serum lipid levels. Lipids Health Dis. 2011;10:140. https://doi.org/10.1186/1476-511X-10-140
24. Kee F, Amouyel P, Fumeron F, Arveiler D, Cambou JP, Evans A, et al. Lack of association between genetic variations of apo A-I-C-III-A-IV gene cluster and myocardial infarction in a sample of European male: ECTIM study. Atherosclerosis. 1999;145(1):187-95. https://doi.org/10.1016/s0021-9150(99)00066-0
25. Talmud PJ, Hawe E, Martin S, Olivier M, Miller GJ, Rubin EM, et al. Relative contribution of variation within the APOC3/A4/A5 gene cluster in determining plasma triglycerides. Hum Mol Genet. 2002;11(24):3039-46. https://doi.org/10.1093/hmg/11.24.3039

ORIGINAL ARTICLE

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Evaluation of comorbid diseases in obstructive sleep apnea syndrome

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SUMMARY

OBJECTIVE: It is known that obstructive sleep apnea syndrome affects many systems due to hypoxemia and hypercarbia. We aimed to demonstrate with the utilization of well-standardized questionnaire tools and electrophysiological tests that cognitive impairment, depression, autonomic dysfunction, and metabolic syndrome may occur in association with obstructive sleep apnea syndrome.

METHODS: The electrophysiological examination protocol of autonomic nervous system functions was performed with sympathetic skin response and R-R Interval. Patients were administered Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Montreal Cognitive Assessment, and Hamilton Depression Rating Scale by physicians in face-to-face interviews.

RESULTS: This study included 148 participants, consisting of 73 patients and 75 controls. There was a statistically significant difference between the patient group and control group with regard to sympathetic skin response, R-R Interval, post-hyperventilation R-R Interval, and R-R Interval variation ($p<0.001$). A statistically significant difference was observed between the patient group and control group in terms of median Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and Montreal Cognitive Assessment scores. It was observed that the control group achieved significantly better scores than the patient group in delayed recall ($p<0.001$) and language ($p<0.05$) categories.

CONCLUSION: Obstructive sleep apnea syndrome patients should be screened for diseases, especially in the cardiovascular system, that cause serious morbidity and impair functionality such as dementia and depression. We believe that many comorbid diseases encountered in obstructive sleep apnea syndrome patients can be prevented with early diagnosis and continuous positive airway pressure treatment.

KEYWORDS: Sleep apnea, obstructive. Cognitive dysfunction. Autonomic nervous system diseases.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and often a decrease in blood oxygen saturation[1,2]. Major symptoms include excessive daytime sleepiness, witnessed apnea, and loud snoring[3-5].

OSAS has been associated with many comorbid conditions such as hypertension, diabetes mellitus, coronary artery disease, metabolic syndrome, and cognitive impairment[6-8]. The effect of OSAS on the autonomic nervous system (ANS) plays an important role in the pathogenesis of complications of the cardiovascular system. As a result of recurrent apnea, hypoxemia and hypercarbia cause increased sympathetic activation via both peripheral and central chemoreceptors.

Studies have demonstrated that OSAS is associated with both neurocognitive dysfunction and mood disorders. The main complaints reported by OSAS patients include decreased stress sensitivity and a significant negative impact on job performance, driving safety, education, and daily household activities[9-11].

This study aimed to demonstrate with the utilization of well-standardized questionnaire tools and electrophysiological tests that cognitive impairment, depression, autonomic dysfunction, and metabolic syndrome may occur in association with OSAS.

METHODS

In this study, patients who applied to our center with complaints of snoring, excessive daytime sleepiness, and witnessed apnea, who were diagnosed with OSAS after PSG in the sleep laboratory, and who were staged as moderate or severe according to the American Academy of Sleep Medicine (AASM) international scoring were evaluated. Apnea-hypopnea index (AHI) ≥5 and less than 15 was classified as mild, ≥15 and less than 30 as moderate, and ≥30 as severe OSAS. Ethics approval was obtained from our university's clinical studies and ethics committee (approval no. 80558721/231). The study included 73 patients and 75 healthy individuals as the control group. Participants with factors that could affect ANS functions, such as diabetes,

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peripheral vascular disease, heart failure, chronic renal and liver failure, alcoholism, polyneuropathy, and drug use (anticholinergic, beta-blocker, etc.) were excluded. Consent was obtained from all study participants. The electrophysiological examination protocol of ANS functions was performed with SSR (sympathetic skin response) and RRIV (R-R Interval) calculated both at rest and during deep breathing. SSR was obtained from both upper extremities with a Medtronic brand EMG device. RRIV was performed according to the method described by Stalberg.

Patients were administered Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Montreal Cognitive Assessment (MoCA), and Hamilton Depression Rating Scale (HAM-D) by physicians in face-to-face interviews. Waist circumference, weight, height, and arterial blood pressure of the patients were measured. Body mass index (BMI) was calculated as weight/height (kg^2/m^2). For the evaluation of metabolic syndrome, blood samples were taken from the patients, and their fasting blood glucose, HDL, and triglyceride blood levels were assessed.

Statistical analysis

Statistical analyses were performed using the SPSS for Windows 21 package program. Descriptive statistics were expressed as percentages for qualitative variables and as mean ± standard deviation or median (interquartile range) for quantitative variables. A chi-square test was used to analyze the differences between groups in terms of categorical variables. For measurable variables, those with normal distribution were compared using the Independent samples t-test, and those without normal distribution were compared using the Mann-Whitney U test. $p<0.05$ was considered statistically significant for all analyses.

RESULTS

The study included 148 participants, consisting of 73 patients and 75 controls. Mean age was 50.3±12.1 years in the patient group and 43.6±11.9 years in the control group (p=0.063). In the patient group, 32 (44%) patients had moderate OSAS and 41 (56%) patients had severe OSAS. Mean AHI was 37.8±19.8 in the patient group.

Triglyceride, fasting blood glucose levels (p=0.004), waist circumference, and BMI were significantly higher, while HDL was significantly lower in the patient group compared to the control group (p<0.001). There was a statistically significant difference between the groups in terms of the presence of metabolic syndrome (p<0.001) (Table 1).

A statistically significant difference was observed in terms of median ESS, PSQI, and MoCA scores (p<0.001) (8 (5–12), 4 (2–6) for ESS; 5 (3–7), 3 (2–4) for PSQI; and 27 (25–28), 29 (27–30) for MoCA) (Table 1). In the analysis of MoCA subdomains (visuoconstructional skills, naming, attention, verbal fluency, abstraction, delayed recall, and orientation), it was observed that the control group achieved significantly better scores than the patient group in delayed recall (p<0.001) and verbal fluency (p<0.05) categories (Table 2).

There was a statistically significant difference between the patient group and control group with regard to SSR (p<0.05), RRIV, post-hyperventilation RRIV, and RRIV variation (p<0.001) (Table 3).

Table 1. Comparison of demographic characteristics and Epworth Sleepiness Scale, Pittsburgh Sleep Quality Scale, Hamilton Depression Scale, and MoCA of the patient group and the control group.

	OSAS (n=73)	Control (n=75)	p-value
Female/male	24/49	28/47	–
Age	50.3±12.1	43.6±11.9	0.63
BMI	29±5	25±4	**<0.001**
HDL	44±11.2	55±17.6	**<0.001**
Triglyceride	130±52	96±53	**<0.001**
Fasting blood sugar	95±11	89±11	**0.004**
Waist circumference	102±12	87±16	**<0.001**
Metabolic syndrome	26 (78.8%)	7 (21.2%)	**<0.001**
Epworth Sleepiness Scale	8 (5–12)	4 (2–6)	**<0.001**
Pittsburgh Sleep Quality Scale	5 (3–7)	3 (2–4)	**<0.001**
Hamilton Depression Scale	6 (4–14)	7 (3–11)	0.279
MoCA	27 (25–28)	29 (27–30)	**<0.001**

Bold indicates statistically significant p-values.

Table 2. Comparison of groups according to MoCA subdomains.

		OSAS (n=73)	Control (n=75)	Total	p-value
Language	**1.00**	1 (100%)	0 (0.0%)	1 (100%)	**<0.05**
	2.00	22 (68.7%)	10 (31.3%)	32 (100%)	
	3.00	50 (43.2%)	65 (56.8%)	115 (100%)	
Delayed recall	**0.00**	2 (100%)	0 (0.0%)	2 (100%)	**<0.001**
	1.00	5 (71.4%)	2 (28.6%)	7 (100%)	
	2.00	10 (100%)	0 (0.0%)	10 (100%)	
	3.00	23 (59.0%)	16 (41.0%)	39 (100%)	
	4.00	26 (43.3%)	34 (56.7%)	60 (100%)	
	5.00	7 (23.3%)	23 (76.7%)	30 (100%)	

Bold indicates statistically significant p-values.

Table 3. Comparison of SSR latency, SSR amplitude, RRIV, Post-hyperventilation RRIV, and RRIV variation.

	OSAS (n=73)	Control (n=75)	p-value
SSR latency (ms)	1,984 (1,635–2,210)	1,858 (1,568–2,184)	0.47
SSR amplitude (mV)	1.59 (0.9–2.9)	1.32 (0.6–2.3)	**<0.05**
RRIV (%)	35 (24–48)	24 (15–33)	**<0.001**
Post-hyperventilation RRIV (%)	66 (46–93)	45 (30.5–65)	**<0.001**
RRIV variation (%)	39 (25–53)	27 (17–37)	**<0.001**

Bold indicates statistically significant p-values.

DISCUSSION

Mean BMI was 25.3±4.5 in the control group and 29.4±5 in the patient group (p<0.01). Truncal obesity reduces chest compliance and functional residual capacity, leading to increased oxygen demand[12]. Obesity is a significant risk factor for the development and progression of OSAS[13]. Moreover, individuals with OSAS who lost 10% of their baseline weight had a sixfold reduction in OSAS progression and more than a 20% reduction in OSAS severity[12].

Lower HDL levels were detected in the patient group, and a highly significant difference was observed between the OSAS group and control group in terms of triglyceride, waist circumference, and total cholesterol values (p<0.001). This emphasizes the need for routine biochemical screening to detect treatable metabolic disorders in all OSAS patients.

In our study, metabolic syndrome was detected in 26 (35.6%) individuals in the OSAS group and 7 (9.3%) individuals in the control group (p<0.001) Considering that 20–30% of the adult world population is affected by metabolic syndrome and that it is one of the most important causes of mortality and morbidity worldwide[14], this should always be kept in mind by clinicians.

The combination of obstructive sleep apnea and metabolic syndrome is referred to as "Syndrome Z"[15]. Although there is no clear consensus, changes in the hypothalamic-pituitary axis, recurrent hypoxia, inflammation, and generation of reactive oxygen species caused by adipokines are thought to be responsible for the changes seen at the cellular level in OSAS and metabolic syndrome[16]. In a cohort study by Marshall et al., while the prevalence of diabetes was 4.7% in the nonapnea group, this rate was 17.7% in the severe apnea group. The calculated odds ratio for severe apnea was 4.37. In a 4-year period, the incidence of diabetes was 2.2% in those without apnea and 20% in those with severe apnea[17]. Comparison between the groups demonstrated that fasting blood glucose was significantly increased in the OSAS group compared to the control group (p<0.01). Accordingly, the presence of undiagnosed diabetes should be kept in mind and screened in patients with OSAS or suspected OSAS, and it may be unregulated despite the diagnosis.

While there was no statistically significant difference between the groups in terms of HAM-D scores, there were 16 participants in the OSAS group and 7 participants in the control group who scored between 16 and 28. It is known that hypoxemia and sleep disruptions have direct effects such as excessive daytime sleepiness, fatigue, and irritability; it is assumed that these symptoms are similar to depressive-somatic symptoms, but do not cause depression alone[18].

In our study, the total MoCA score of the OSAS group was significantly lower than the control group [27 (25–28) vs. 29 (27–30), respectively] (p<0.001). One study indicated that cognitive impairment caused by OSAS resulted from neuronal apoptosis due to chronic exposure to hypoxia[19]. This finding is consistent with animal studies demonstrating that exposure to intermittent hypoxia is associated with increased apoptosis in the hippocampus in rodents[20]. Furthermore, hypoxemia with voxel-based morphometry revealed gray matter volume reduction in brain regions that are responsible for memory and executive functions (e.g., frontal, parietal, and temporal regions and the hippocampus)[21]. These findings suggest that intermittent hypoxia in OSAS may play an important role in cognitive dysfunction and gray matter volume reduction, which may contribute to the development of dementia. Second, mice exposed to hypoxic conditions have shown increased cerebral amyloid plaque formation and tau phosphorylation[22,23]. β-Amyloid accumulation and tau phosphorylation in the brain are common features of Alzheimer's disease that may contribute to the link between OSAS and dementia.

In our study, MoCA subscores in the language and delayed recall domains were significantly lower in OSAS patients than in the control group (p<0.05 and p<0.001, respectively). The frontal lobe is responsible for the motor function of speech, while the temporal lobe performs the function of understanding and naming speech. Previous studies suggest that intermittent hypoxia particularly affects the frontal white matter and temporal lobe[21]. Recent studies have shown that cognitive dysfunction can improve with the application of at least 4 weeks of continuous positive airway pressure (CPAP) therapy[24]. According to the results of our study, we believe that OSAS patients should be evaluated in a multidisciplinary approach; the temporal, frontal, and hippocampal regions in particular are more sensitive to hypoxia and these symptoms may regress with CPAP treatment.

There are few EMG studies in the literature evaluating autonomic dysfunction in OSAS. Ito et al. conducted a study using RRIV, corrected QT interval, and heart rate variability to demonstrate the relationship between OSAS and ANS, as well as treatment response, and the reported findings indicating that OSAS had an impact on the ANS that regressed with treatment[25]. According to the results of our study, RRIV at rest and post-hyperventilation RRIV values were significantly lower in the OSAS group compared to the control group ($p<0.001$). While there was no significant difference between the groups in terms of SSR latency, SSR amplitude was found to be significantly higher in the OSAS group ($p<0.05$). Sympathetic hyperactivity has been demonstrated in OSAS patients. As a result, the increase in sympathetic activity increases the resting heart rate and decreases RRIV variation of ECG. Since comorbid diseases such as increased sympathetic activity, susceptibility to arrhythmias, hypertension, and coronary artery disease can determine mortality in OSAS, it is important to follow-up patients in this regard.

CONCLUSION

Recurrent apnea in OSAS can lead to oxygen desaturation and sleep disruptions, resulting in significant neurobehavioral and cardiac consequences. These consequences can affect all systems in the body at a cellular level, and we recommend that OSAS patients should be screened for diseases, especially in the cardiovascular system, that cause serious morbidity and impair functionality such as dementia and depression. We believe that many comorbid diseases encountered in OSAS patients can be prevented with early diagnosis and CPAP treatment.

AUTHORS' CONTRIBUTIONS

FGA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology ,Project administration, Resources, Writing – original draft, Writing – review & editing. **DIA:** Conceptualization, Data curation, Formal Analysis, Software. **OOE:** Conceptualization, Data curation, Formal Analysis, Supervision, Validation, Writing – original draft, Writing – review & editing.

REFERENCES

1. Kuvat N, Tanriverdi H, Armutcu F. The relationship between obstructive sleep apnea syndrome and obesity: a new perspective on the pathogenesis in terms of organ crosstalk. Clin Respir J. 2020;14(7):595-604. https://doi.org/10.1111/crj.13175
2. Prabhakar NR, Peng YJ, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. J Clin Invest. 2020;130(10):5042-51. https://doi.org/10.1172/JCI137560
3. Park DY, Kim JS, Park B, Kim HJ. Risk factors and clinical prediction formula for the evaluation of obstructive sleep apnea in Asian adults. PLoS One. 2021;16(2):e0246399. https://doi.org/10.1371/journal.pone.0246399
4. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. JAMA. 2020;323(14):1389-400. https://doi.org/10.1001/jama.2020.3514
5. AlRumaih HS, Baba NZ, AlShehri A, AlHelal A, Al-Humaidan A. Obstructive sleep apnea management: an overview of the literature. J Prosthodont. 2018;27(3):260-5. https://doi.org/10.1111/jopr.12530
6. Wang F, Xiong X, Xu H, Huang H, Shi Y, Li X, et al. The association between obstructive sleep apnea syndrome and metabolic syndrome: a confirmatory factor analysis. Sleep Breath. 2019;23(3):1011-9. https://doi.org/10.1007/s11325-019-01804-8
7. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. Curr Cardiol Rep. 2020;22(2):6. https://doi.org/10.1007/s11886-020-1257-y
8. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, et al. Obstructive sleep apnea, depression and cognitive impairment. Sleep Med. 2020;72:50-8. https://doi.org/10.1016/j.sleep.2020.03.017
9. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc. 2004;10(5):772-85. https://doi.org/10.1017/S1355617704105134
10. Roure N, Gomez S, Mediano O, Duran J, Peña ML, Capote F, et al. Daytime sleepiness and polysomnography in obstructive sleep apnea patients. Sleep Med. 2008;9(7):727-31. https://doi.org/10.1016/j.sleep.2008.02.006
11. Nowak M, Kornhuber J, Meyrer R. Daytime impairment and neurodegeneration in OSAS. Sleep. 2006;29(12):1521-30. https://doi.org/10.1093/sleep/29.12.1521
12. Nastałek P, Polok K, Celejewska-Wójcik N, Kania A, Sładek K, Małczak P, et al. Impact of bariatric surgery on obstructive sleep apnea severity and continuous positive airway pressure therapy compliance-prospective observational study. Sci Rep. 2021;11(1):5003. https://doi.org/10.1038/s41598-021-84570-6
13. Dong Z, Xu X, Wang C, Cartledge S, Maddison R, Islam SMS. Association of overweight and obesity with obstructive sleep apnoea: a systematic review and meta-analysis. Obes Med. 2020;17:100185. https://doi.org/10.1016/j.obmed.2020.100185
14. Engin A. The definition and prevalence of obesity and metabolic syndrome. Obes Lipotoxicity. 2017:1-17. https://doi.org/10.1007/978-3-319-48382-5_1
15. Sureja BR, Bhambhani GD. The prevalence of syndrome Z (the interaction of obstructive sleep apnoea with the metabolic syndrome) in a tertiary care center, Gujarat, India. Int J Adv Med. 2018;5(6):1476. https://doi.org/10.18203/2349-3933.ijam20184760
16. Nieuwenhuizen AG, Rutters, F. The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. Physiol Behav. 2007;94(2):169-77. https://doi.org/10.1016/j.physbeh.2007.12.011

17. Marshall NS, Wong KK, Phillips CL, Liu PY, Knuiman MW, Grunstein RR. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med. 2009;5(1):15-20. PMID: 19317376

18. Means MK, Lichstein KL, Edinger JD, Taylor DJ, Durrence HH, Husain AM, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. Sleep Breath. 2003;7(1):31-42. https://doi.org/10.1007/s11325-003-0031-x

19. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011;306(6):613-9. https://doi.org/10.1001/jama.2011.1115

20. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. J Neurosci. 2001;21(7):2442-50. https://doi.org/10.1523/JNEUROSCI.21-07-02442.2001

21. Baril AA, Martineau-Dussault MÈ, Sanchez E, André C, Thompson C, Legault J, et al. Obstructive sleep apnea and the brain: a focus on gray and white matter structure. Curr Neurol Neurosci Rep. 2021;21(3):11. https://doi.org/10.1007/s11910-021-01094-2

22. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive sleep apnea and its treatment in aging: Effects on Alzheimer's disease biomarkers, cognition, brain structure and neurophysiology. Neurobiol Dis. 2020;145:105054. https://doi.org/10.1016/j.nbd.2020.105054

23. .Zhang Y, Zhang Y, Zeng Y, Chen X, Wang W, Lin Z, et al. Medical image analysis of telmisartan-induced protection in hippocampal CA1 after chronic intermittent hypoxia. J Med Imaging Health Info. 2020;10(12):2849-54. https://doi.org/10.1166/jmihi.2020.3251

24. .Wang G, Goebel JR, Li C, Hallman HG, Gilford TM, Li W. Therapeutic effects of CPAP on cognitive impairments associated with OSA. J Neurol. 2020;267(10):2823-8. https://doi.org/10.1007/s00415-019-09381-2

25. Ito R, Hamada H, Yokoyama A, Oshima M, Katayama H, Ohnishi H, et al. Successful treatment of obstructive sleep apnea syndrome improves autonomic nervous system dysfunction. Clin Exp Hypertens. 2005;27(2-3):259-67. PMID: 15835389

ORIGINAL ARTICLE

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Is there a correlation between dizziness and intracranial artery calcification?

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SUMMARY

OBJECTIVE: This study aimed to investigate the correlation between dizziness and intracranial artery calcification.

METHODS: A total of 107 consecutive patients were recruited for this study. These patients were categorized into first (case) and second (control) groups. The first and second groups had complaints of dizziness and headache, respectively. All the patients had noncontrast cranial computed tomography images. Bilateral internal carotid arteries, bilateral vertebral arteries, and basilar arteries were evaluated for detecting burden of intracranial artery calcification. Finally, demographic characteristics, stroke risk factors, and burden of intracranial artery calcification of these two groups were compared. The Mann-Whitney U test, chi-square test, and Spearman's correlation were performed to analyze the study.

RESULTS: It was found that the first and second groups included 39 and 68 patients, respectively. The mean age of the first group was significantly higher than that of the second group. The mean burden of intracranial artery calcification of the posterior circulation in the first and second groups were not statistically different from each other (p=0.555). The mean burden of intracranial artery calcification of the anterior circulation in the first group was found to be significantly higher than the second group (p=0.005). However, no significant difference was found between the two groups in terms of burden of intracranial artery calcification of anterior or posterior circulation, when the age variable was synchronized in both groups.

CONCLUSION: Although this study found a limited correlation between dizziness and intracranial artery calcification, this situation was basically related to aging.

KEYWORDS: Carotid arteries. Tomography. Ischemia. Cerebrovascular circulation. Vascular diseases.

INTRODUCTION

Dizziness is a nonspecific term that refers to a sense of disorientation without a false sense of motion. It varies from vertigo to a general feeling of instability and generally affects elderly people[1-5]. Etiologies of dizziness include metabolic, cardiovascular, neurologic, and psychiatric diseases. However, no objective evidence of the etiology is found. Nevertheless, vascular causes should not be neglected, as they can be mortal[3-5]. Therefore, a decrease in blood perfusion of the anterior or posterior circulation due to stenosis or occlusion may cause the symptom of dizziness[1,2,5,6]; however, some authors find no evidence to support this pathophysiology[2].

Dizziness is a common complaint in outpatient clinics and is found in approximately 5% of patients as a primary symptom. Previous studies have suggested that many of these patients have abnormalities in the vertebrobasilar and carotid arteries associated with dizziness, especially in the elderly patients[5,7,8]. However, dizziness with vascular etiology seldom requires surgical treatment[7].

Intracranial artery calcification (IAC) is a noninvasive imaging marker that is incidentally detected on brain computed tomography (CT), especially in advanced age[9-11]. The author supposes that arterial calcification (AC) is caused by the accumulation of calcium-phosphate complexes in the vessels.

Some studies claim that AC is a part of the active process of atherosclerosis and may be affected by aging, diabetes mellitus, and chronic kidney disease[9,11-14]. AC may occur in up to 90% of atherosclerotic lesions in vessels[13]. Therefore, it can be hypothesized that IAC may be a potential predictor of future ischemic stroke[15,16]. Moreover, IAC may be associated with transient ischemic attacks, epileptic seizures, and cognitive decline[11,14]. However, a relationship between IAC and dizziness has not yet been reported in the literature. Hence, this study aimed to investigate whether or not there is a correlation between ICA and dizziness.

METHODS

Patients

A total of 107 consecutive patients (53 males and 54 females) with complaints of dizziness (first group) or headache (second group) and noncontrast cranial CT images were recruited for this study. The first group was determined the main (or the

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case) group, and the second group was accepted as the control group. The patients who had no or insufficient CT images were not included in this study. The data of these two groups, which were gathered during 2-year periods from our hospital automation system, were analyzed. This study was performed retrospectively, and animals or human subjects were not included. Therefore, informed consent was not required.

Measurement of intracranial arterial calcification

Hyperdense lesions over 130 Hounsfield units observed on the noncontrast cranial CT images were assumed to be intracranial arterial calcification (IAC). Bilateral internal carotid arteries (ICAs), bilateral vertebral arteries (VAs), and basilar arteries (BAs) were evaluated. Of the patients with circular calcification on the intracranial arterial walls in the axial section on the noncontrast cranial CT, those with calcification below 50% of the arterial diameter were given one point, and those with 50% or above were given two points (Figure 1). Those without calcifications were given zero points. For each patient, the burden of IAC (BIAC) of anterior (bilateral ICAs) or posterior (bilateral VAs and BAs) circulation was calculated by summing all these points.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS) 26.0 (SPSS Inc., Chicago, IL, USA) program was used for evaluating data. Demographic characteristics, stroke risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease [CAD], chronic kidney disease, atrial fibrillation, smoking, and stroke history), and BIAC of these two groups were compared. The Mann-Whitney U test was used for continuous variables, the chi-square test for categorical variables, and Spearman's rho test for correlation. A p-value of <0.05 was considered statistically significant in all analyses.

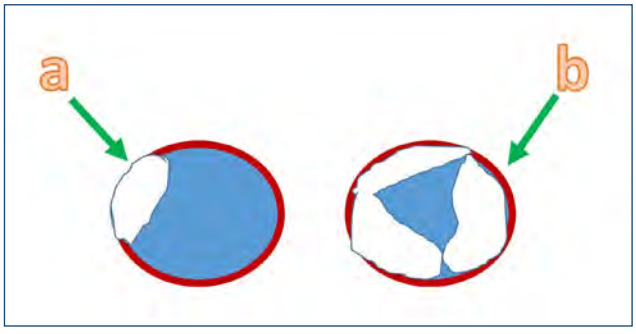

Figure 1. Calcifications observed in intracranial arteries (green arrow). (a) Calcifications that narrow the diameter of intracranial artery below 50%. (b) Calcifications that narrow the diameter of intracranial artery above 50%.

RESULTS

In this study, 39 and 68 patients were consecutively included in the first and second groups, respectively. The sex distribution of these two groups was found to be close to each other (chi-square test; p=0.784). However, the mean age of both groups was found to be significantly different from each other (Mann-Whitney U test; p<0.001). There was no significant difference between these two groups in terms of stroke risk factors (chi-square test; p>0.05), except for CAD (chi-square test; p<0.001). The comparison of the two groups in terms of gender, age, and stroke risk factors is summarized in Table 1.

In this study, calcifications were detected in the posterior circulation in 23 VAs on the right and 26 VAs on the left, along with 3 BAs. However, calcifications were observed in the anterior circulation in 58 and 54 ICAs on the right and left sides, respectively. The mean BIAC of the posterior circulation was found 0.76±1.31, and the mean BIAC of the anterior circulation was calculated 1.78±1.79. The mean BIAC of the posterior circulation of the first and second groups were similar (Mann-Whitney U test; p=0.555); however, the mean BIAC of the anterior circulation of the first group was significantly higher than that of the second group (Mann-Whitney U test; p=0.005). In addition, a strong positive correlation was found between age and the BIAC of the anterior or posterior circulation (p<0.001). Table 2 shows the comparison of the two groups according to BIAC and the correlation of age with BIAC. To dismiss the effect of the age variable, only patients over 40 years old were included in the first and second groups (n=35 vs. n=39, respectively). Then, the analysis was repeated regarding the new sample size. However, no significant difference was

Table 1. Comparison of the two groups in terms of sex, age, and stroke risk factors.

Variables	First group	Second group	p-value
Age (years)	64.72±15.13	48.68±19.79	**<0.001**
Sex (m/f)	20/19	33/35	0.784
DM (%)	25.6%	19.1%	0.429
HTN (%)	51.3%	33.8%	0.076
CAD (%)	41%	10.3%	**<0.001**
AF (%)	7.7%	2.9%	0.352
Stroke (%)	25.6%	11.8%	0.065
CKD (%)	15.4%	11.8%	0.593
HL (%)	12.8%	14.7%	0.787
Smoking (%)	12.8%	2.9%	0.097

DM: diabetes mellitus; m: male; f: female; HTN: hypertension; CAD: coronary artery disease; AF: atrial fibrillation; CKD: chronic kidney disease; HL: hyperlipidemia. Bold indicates statistically significant p-values.

Table 2. Comparison of the two groups according to burden of intra-arterial calcification and correlation of age with burden of intra-arterial calcification.

	First group	Second group	p-value	Age (Spearman correlation)	p-value
Anterior BIAC	2.41±1.74	1.41±1.73	**0.005**	rho=0.746	**<0.001**
Posterior BIAC	0.82±1.33	0.73±1.30	0.555	rho=0.622	**<0.001**

BIAC: burden of intra-arterial calcification; rho: correlation coefficient. Bold indicates statistically significant p-values.

found between the two groups in terms of BIAC of the anterior or posterior circulation (Mann-Whitney U test; p=0.674 vs. p=0.221, respectively).

DISCUSSION

In this study, intra-arterial calcifications were detected in a total of 112 arteries in the anterior circulation and 52 arteries in the posterior circulation. It was observed that the anterior total BIAC was higher than that in the posterior circulation. Moreover, the mean anterior BIAC was found to be significantly higher in the first group than that in the second group, statistically. However, it was found that this significant difference disappeared when the age variable was equalized in both groups. Previous studies reported that male patients were more associated with IAC than female ones[11,13]. Our study showed that there was no significant sex difference between the two groups.

Arterial calcification is a vascular lesion that mainly affects the intima or media layers of the vessel wall and is generally changed by aging and common cardiovascular risk factors[11]. Consistent with the literature, our study revealed a strong positive correlation between age and the BIAC. However, there was a significant difference between these two groups according to only CAD. AC can be found in various vessels and causes different hemodynamic changes or outcomes. An unenhanced CT is thought to be the best tool for detecting calcifications[13]. A density ≥130 HU on CT imaging is generally accepted as a diagnostic criterion for calcification[9,10].

Several studies have demonstrated that the intracranial carotid artery and VA are the most affected vessels, respectively[9,10,13,17]. Therefore, some authors claim that AC, specifically heavier calcifications, may increase the risk of stroke by changing arterial flow and enhancing arterial stiffness[9-11,13,14,18]. They also claim that IAC may be accepted as an indicator of atherosclerosis[13]. However, the pathophysiological relationship between calcification and ischemia is still controversial[12,14,17]. Furthermore, some researchers assume that calcified plaque is less related to ischemic symptoms than noncalcified plaque in preventing plaque rupture. They have also observed that patients with intimal IAC tend to have good collateral circulations before endovascular treatment[19].

Previous reports show that calcifications are found mainly in the cavernous or siphon segments of ICAs and the intracranial segment of VAs. Hence, our study focuses on these parts of vessels to calculate BIAC clearly. Some studies have also shown that calcifications are found more frequently in the left VA than in the right side[17]. In this study, there were no significant differences between both sides. In the literature, various methods have emerged to calculate the severity of calcification[13]. However, different methods may preclude the comparison of findings from various studies. Therefore, the present study used a new simple visual grading method related to the narrowing of the vessel lumen by calcification.

Dizziness is a common symptom in outpatient clinics and accounts for over half of vestibular system diseases[4,8]. Within cerebrovascular diseases, severe carotid artery stenosis (CAS) may be one of the significant nonvestibular causes of dizziness. However, the relationship between CAS and dizziness is not clearly understood, and some conflicts between studies are still emerging. On the one hand, some authors claim that severe CAS can decrease perfusion through the carotid circulation; on the other hand, others accept dizziness as an asymptomatic symptom, although there is an occluded carotid artery[2,5,7,8,20]. In the literature, although there are a lot of reports about the relationship between CAS and dizziness, there have been no studies about the relationship between calcification and dizziness.

Our study has some limitations. First, the study is designed retrospectively. Second, the flow rate and volume of vessels (ICAs and VAs), which may be disturbed by the calcifications, are not included in the study. Finally, a new visual grading method, whose validity has not yet been proven, is used to calculate the severity of AC.

CONCLUSION

This study found that the group with dizziness had much more calcifications than the control group. However, we found that dizziness was not associated primarily with IAC when the age variable was equalized in both groups. To the best of our knowledge, both dizziness and IAC are usually seen in old patients. Therefore, they can occur coincidentally with aging. As a result, prospective studies with a large sample size are needed in the future to investigate the relationship between IAC and dizziness comprehensively.

REFERENCES

1. Della-Morte D, Rundek T. Dizziness and vertigo. Front Neurol Neurosci. 2012;30:22-5. https://doi.org/10.1159/000333379
2. Weinberger J, Biscarra V, Weisberg MK. Hemodynamics of the carotid-artery circulation in the elderly "dizzy" patient. J Am Geriatr Soc. 1981;29(9):402-6. https://doi.org/10.1111/j.1532-5415.1981.tb02378.x
3. Malak W, Hagiwara M, Nguyen V. Neuroimaging of dizziness and vertigo. Otolaryngol Clin North Am. 2021;54(5):893-911. https://doi.org/10.1016/j.otc.2021.06.001
4. Voetsch B, Sehgal S. Acute dizziness, vertigo, and unsteadiness. Neurol Clin. 2021;39(2):373-89. https://doi.org/10.1016/j.ncl.2021.01.008
5. Chen H, Shi Z, Feng H, Wang R, Zhang Y, Xie J, et al. The relationship between dizziness and cervical artery stenosis. Neuroreport. 2015;26(18):1112-8. https://doi.org/10.1097/wnr.0000000000000478
6. Burulday V, Doğan A, Akgül MH, Alpua M, Çankaya I. Is there a relationship between basilar artery tortuosity and vertigo? Clin Neurol Neurosurg. 2019;178:97-100. https://doi.org/10.1016/j.clineuro.2019.02.006
7. Fisher FS, Aumiller BJ. Dizziness and carotid artery stenosis: what is the relationship? J Family Med Prim Care Open Acc. 2018;2:108. https://doi.org/10.29011/JFOA-108. 100008
8. Hsu LC, Chang FC, Teng MM, Chern CM, Wong WJ. Impact of carotid stenting in dizzy patients with carotid stenosis. J Chin Med Assoc. 2014;77(8):403-8. https://doi.org/10.1016/j.jcma.2014.05.005
9. Wang X, Chen X, Chen Z, Zhang M. Arterial calcification and its association with stroke: implication of risk, prognosis, treatment response, and prevention. Front Cell Neurosci. 2022;16:845215. https://doi.org/10.3389/fncel.2022.845215
10. Yang WJ, Wasserman BA, Zheng L, Huang ZQ, Li J, Abrigo J, et al. Understanding the Clinical implications of intracranial arterial calcification using brain CT and vessel wall imaging. Front Neurol. 202;12:619233. https://doi.org/10.3389/fneur.2021.619233
11. Bartstra JW, van den Beukel TC, Van Hecke W, Mali W, Spiering W, Koek HL, et al. Intracranial arterial calcification: prevalence, risk factors, and consequences: JACC review topic of the week. J Am Coll Cardiol. 2020;76(13):1595-604. https://doi.org/10.1016/j.jacc.2020.07.056
12. Chen XY, Lam WW, Ng HK, Fan YH, Wong KS. Intracranial artery calcification: a newly identified risk factor of ischemic stroke. J Neuroimaging. 2007;17(4):300-3. https://doi.org/10.1111/j.1552-6569.2007.00158.x
13. Wu XH, Chen XY, Wang LJ, Wong KS. Intracranial artery calcification and its clinical significance. J Clin Neurol. 2016;12(3):253-61. https://doi.org/10.3988/jcn.2016.12.3.253
14. Wu X, Wang L, Zhong J, Ko J, Shi L, Soo Y, et al. Impact of intracranial artery calcification on cerebral hemodynamic changes. Neuroradiology. 2018;60(4):357-63. https://doi.org/10.1007/s00234-018-1988-2
15. Kockelkoren R, Vos A, Van Hecke W, Vink A, Bleys RL, Verdoorn D, et al. Computed tomographic distinction of intimal and medial calcification in the intracranial internal carotid artery. PLoS One. 2017;12(1):e0168360.https://doi.org/10.1371/journal.pone.0168360
16. Yang WJ, Zheng L, Wu XH, Huang ZQ, Niu CB, Zhao HL, et al. Postmortem study exploring distribution and patterns of intracranial artery calcification. Stroke. 2018;49(11):2767-9. https://doi.org/10.1161/strokeaha.118.022591
17. Du H, Yang W, Chen X. Histology-verified intracranial artery calcification and its clinical relevance with cerebrovascular disease. Front Neurol. 2021;12:789035. https://doi.org/10.3389/fneur.2021.789035
18. Dorobisz K, Dorobisz T, Zatoński T. The assessment of the balance system in cranial artery stenosis. Brain Behav. 2020;10(9):e01695. https://doi.org/10.1002/brb3.1695
19. Luijten SPR, van der Donk SC, Compagne KCJ, Yo LSF, Sprengers MES, Majoie C, et al. Intracranial carotid artery calcification subtype and collaterals in patients undergoing endovascular thrombectomy. Atherosclerosis. 2021;337:1-6. https://doi.org/10.1016/j.atherosclerosis.2021.10.005
20. Gillett RC Jr. Should carotid artery stenosis be examined as a cause of dizziness? Am Fam Physician. 2011;83(8):879; author reply 80. PMID: 21524027

ORIGINAL ARTICLE

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Evaluation of first- and third-trimester afamin levels in preeclampsia

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SUMMARY

OBJECTIVE: The aim of this study was to investigate serum afamin levels in the first and third trimesters in preeclampsia.

METHODS: Serum samples from 118 patients in the first and third trimesters were analyzed. Serum samples were collected from pregnant women who had enrolled in the first trimester. Blood was then collected from pregnant women who had developed preeclampsia and from healthy controls in the third trimester. The collected blood samples were resolved for analysis, and serum afamin concentrations were measured in the first and third trimesters. Preeclampsia and healthy controls were compared.

RESULTS: There was no significant difference between the control and preeclampsia groups in terms of age, body mass index, and smoking. Afamin levels in the first and third trimesters were higher in the preeclampsia group than in the control group ($p<0.05$). In the subgroup analysis of the preeclampsia group, afamin levels were higher in the early-onset preeclampsia group than in the late-onset preeclampsia group in the first and third trimesters ($p<0.05$). In the receiver operating characteristic analysis afamin levels were 96.23 ng/mL in the first trimester and 123.57 ng/mL in the third trimester as cut-off values for preeclampsia.

CONCLUSION: Serum afamin levels are useful for predicting preeclampsia in the first trimester in pregnant women and can be used in clinical practice as a supportive biomarker for the diagnosis of preeclampsia in the third trimester. Meta-analyzes are needed to investigate the effect of afamin levels in the prediction and diagnosis of preeclampsia and to determine the cut-off value.

KEYWORDS: Pre-eclampsia. Proteinuria. Hypertension. Biomarker. Pregnancy trimester, first.

INTRODUCTION

Preeclampsia (PE) is a hypertension [blood pressure (BP) ≥140/90 mmHg] disorder that occurs after 20 weeks of gestation (but no hypertension before pregnancy) and also causes proteinuria (proteinuria≥300 mg/24 h), but the presence of proteinuria is not always observed for PE[1]. The presence of systemic findings along with hypertension (liver dysfunction, renal failure, presence of hemolysis and thrombocytopenia, pulmonary edema, and visual and cerebral findings) indicates PE without proteinuria[1]. Although it is thought to be caused by PE trophoblast invasion disorder and impaired placental blood supply, the pathogenesis is not fully understood. Impaired placental development, increased placental oxidative stress, apoptosis, and necrosis cause endothelial dysfunction, proteinuria, and maternal hypertension[2].

Afamin (also called α-albumin), which is a vitamin E-binding glycoprotein, has been identified as the fourth member of the human albumin gene family after albumin, α-fetoprotein, and vitamin D-binding protein[3]. Vitamin E is an important protective lipophilic antioxidant that protects against oxidative stress during pregnancy and postpartum[4]. Serum afamin concentrations have previously been reported to increase in response to high oxidative stress[3].

During normal pregnancy, plasma afamin concentration approximately increases two times and decreases to pre-pregnancy levels soon after delivery[5]. High afamin concentrations have been associated with insulin resistance (IR) and components of metabolic syndrome[6]. In the literature, there are few studies on the association between PE and afamin. To the best of our knowledge, in English literature, there is no study that examined afamin, which is associated with oxidative stress, in both the first and third trimesters.

The aim of this study was to evaluate the role of afamin in predicting PE by comparing afamin levels in the first and third trimesters of the PE and control groups.

METHODS

Pregnant patients who presented to the Obstetrics and Gynecology Outpatient Department of Samsun Training and Research Hospital between January 2021 and January 2022

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were enrolled in the study. Prior to the study, approval was obtained from the ethics committee of our hospital (Dated September 23, 2021/No. KAEK 2021/418).

Routine evaluations were performed on the pregnant women who presented to the outpatient clinic in the first trimester. Serum samples taken from the pregnant women for the study were stored at -80°C for subsequent biochemical analyses. Patients were followed until delivery, and pregnancy outcomes were recorded. Prenatal serum samples were collected from the patients who developed PE in the third trimester. The control group consisted of pregnancies whose blood was collected and stored in the first trimester, who did not develop PE or any complications during pregnancy follow-up, and who delivered at term (37–41 weeks). Multiple pregnancies, fetal anomalies, and patients with systemic diseases (chronic hypertension, vascular diseases, and diabetes mellitus) diagnosed before or after pregnancy were accepted as criteria for exclusion from the study.

It was planned to include age, gravidity, parity, body mass index (BMI), smoking, type of delivery (cesarean section/normal vaginal delivery), presence of meconium, neonatal intensive care unit (NICU) requirement, systolic blood pressure (SBP), diastolic blood pressure (DBP), birth weight, APGAR 0 min, APGAR 5 min, serum afamin level in the first and third trimesters, and birth weight. Week of gestation was confirmed by ultrasound using the first day of the last menstrual period (LMP) or first-trimester ultrasound measurements in patients whose LMP was unknown.

Preeclampsia was defined as BP ≥140/90 mmHg associated with proteinuria in two separate measurements of at least 4 h after the 20th week of gestation in a woman whose BP was previously within normal limits. Proteinuria was detected in ≥+1 protein by dipstick test or ≥300 mg in a 24-h urine test. The study included 2,852 pregnant women in the first trimester. Serum samples from 118 patients in the first and third trimesters were analyzed in the study. Of the patients whose serum samples were taken, 74 patients were diagnosed with PE and these patients were included in the study group, while 44 pregnant women were included in the control group.

A subgroup analysis of the PE group was performed. The PE group was divided into two groups according to the week of delivery: less than 34 weeks (early-onset) and 34 weeks and more (late-onset). Stored serum samples were measured for serum afamin concentrations using a commercially available kit. Afamin levels were expressed in ng/mL.

Statistical analyses were performed using SPSS 22 (IBM SPSS Statistics 22, an IBM Co, Somers, NY). The continuous variables were reported as mean and standard deviation. The categorical variables were expressed as percentage and frequency. The chi-square test was used to compare categorical data between groups. The independent samples t-test was used to compare the distribution of variables between groups. Receiver operating characteristic analysis (ROC) was used to evaluate the diagnostic performance of afamin in the first and third trimesters in PE. The p-value<0.05 was considered significant.

RESULTS

There was no significant difference between the control and PE groups in terms of patient age, BMI (p=0.059), and smoking (p=0.458). Gravida and parity numbers were lower in the PE group than in the control group. SBP, DBP, and cesarean section rates were lower in the control group than in the PE group. As for neonatal outcomes, the presence of meconium and the need for NICU were lower in the control group, while APGAR first-fifth min scores and birth weight were higher. Afamin levels in the first and third trimesters were lower in the control group than in the PE group. The demographic characteristics and serum analysis results of the patients are shown in Table 1.

Table 1. Demographic characteristics of the patients and results of serum analysis.

	Preeclampsia (n=74)	Control (n=44)	p-value
Age (year)	27.31±4.88	29.23±6.03	0.062
Gravida	1.99±1.03	2.7±1.44	**0.002**
Parity	0.68±0.72	1.18±1.19	**0.005**
Type of birth			
C/S	44 (59.5%)	15 (34.1%)	**0.008**
VD	30 (40.5%)	29 (65.9%)	
Presence of meconium	17 (23%)	3 (6.5%)	**0.024**
NICU	17 (23%)	3 (6.5%)	**0.036**
SBP (mmHg)	155±21.03	117.27±8.99	**<0.001**
DBP (mmHg)	97.43±17.23	65.45±6.97	**<0.001**
Birth weight	2899.26±787.71	3349.89±316.75	**<0.001**
Week of birth	36.61±2.99	39.14±0.88	**<0.001**
Apgar 1 min	7.53±1.67	9.2±1.02	**<0.001**
Apgar 5 min	8.2±1.52	9.7±1.02	**<0.001**
First trimester afamin	217.47±231.72	53.57±23.37	**<0.001**
Third trimester afamin	467.08±359.76	79.38±26.25	**<0.001**

Data are presented as mean±standard deviation or as numbers and percentages. The significance test of the difference between the two means or the Pearson chi-square test was used. BMI: body mass index; C/S: cesarean section; VD: vaginal delivery; NICU: neonatal intense care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure. Bold indicates statistically significant p-values.

In the subgroup analysis of 74 patients in the PE group, 23 patients delivered below 34 weeks of gestation (early-onset PE), and 51 patients delivered at or above 34 weeks of gestation (late-onset PE). There was no significant difference between the early and late PE groups in terms of patient age, parity (p=0.058), BMI (p=0.065), and smoking (p=0.122). Gravida was lower in the early PE group compared to the late PE group. SBP, DBP, and cesarean section rates were found to be lower in the late-onset PE group than in the early-onset PE group. When neonatal outcomes were evaluated, the presence of meconium and the need for NICU were higher in the early PE group, while APGAR 1–5 min scores and birth weight were significantly lower. Afamin levels in the first and third trimesters were lower in the late-onset PE group than in the early-onset PE group. Demographic characteristics and serum analysis results of PE patients are given in Table 2.

In the ROC, an afamin level of 96.23 ng/mL [sensitivity (59%) and specificity (95%)] in the first trimester and 123.57 ng/mL [sensitivity (81%) and specificity (99%)] in the third trimester was set as the cutoff value for PE. The area under the curve (AUC) was 0.73 (95%CI 0.64–0.81) in the first trimester and 0.90 (95%CI 0.84–0.95) in the third trimester. ROC curves are shown in Figure 1.

Table 2. Demographic characteristics and serum analysis results of the preeclampsia patients.

	<34 weeks (early-onset PE) (n=23)	34 weeks and above (late-onset PE) (n=51)	p-value
Age (year)	28.65±4.95	26.71±4.77	0.113
Gravida	2.52±1.12	1.75±0.89	**0.002**
Type of birth			
C/S	23 (100%)	21 (41.2%)	
VD	0 (0%)	30 (58.8%)	**<0.001**
Presence of meconium	11 (47.8%)	6 (11.8%)	**0.001**
NICU	17 (47.8%)	6 (11.8%)	**0.001**
SBP (mmHg)	169.78±12.66	148.33±20.73	**<0.001**
DBP (mmHg)	110.22±9.83	91.67±6.97	**<0.001**
Birth weight	2054.57±624.26	3280.2±508.15	**<0.001**
Week of birth	33.22±2.54	38.14±1.60	**<0.001**
Apgar 1 min	6.57±1.62	7.96±1.52	0.001
Apgar 5 min	7.43±1.59	8.55±1.36	0.003
First-trimester afamin	377.33±264.16	145.38±175.03	**<0.001**
Third-trimester afamin	800.43±261.73	316.75±290.96	**<0.001**

Data are presented as mean±standard deviation or as numbers and percentages. The significance test of the difference between the two means or the Pearson chi-square test was used. BMI: body mass index; C/S: cesarean section; VD: vaginal delivery; NICU: neonatal intense care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure. Bold indicates statistically significant p-values.

DISCUSSION

This study compared serum afamin levels in the first and third trimesters between patients with and without PE in predicting PE. This is the first study that we know of that evaluated both first- and third-trimester afamin levels in PE patients. Serum afamin levels were found to be higher in patients with PE compared to patients without PE in both first and third trimesters. For patients with PE, 96.23 ng/mL in the first trimester and 123.57 ng/mL in the third trimester were set as cut-off values. In the PE subgroup analysis, higher serum afamin levels were found in both first and third trimesters in early-onset (<34 weeks) PE compared with late-onset (≥34 weeks) PE.

Afamin, a plasma glycoprotein, belongs to the albumin gene family and has been identified as an alternative carrier protein for vitamin E[7]. In addition, it functions as a transfer protein responsible for the exchange of lipoproteins such as cholesterol, triglycerides, and ApoB[8]. It has also been found to correlate highly with the prevalence of metabolic syndrome[9]. Köninger et al., found an association between afamin and gestational diabetes mellitus[6]. A meta-analysis found a high correlation between afamin and type 2 diabetes mellitus[10]. According to Hubalek et al., maternal serum afamin concentrations increase

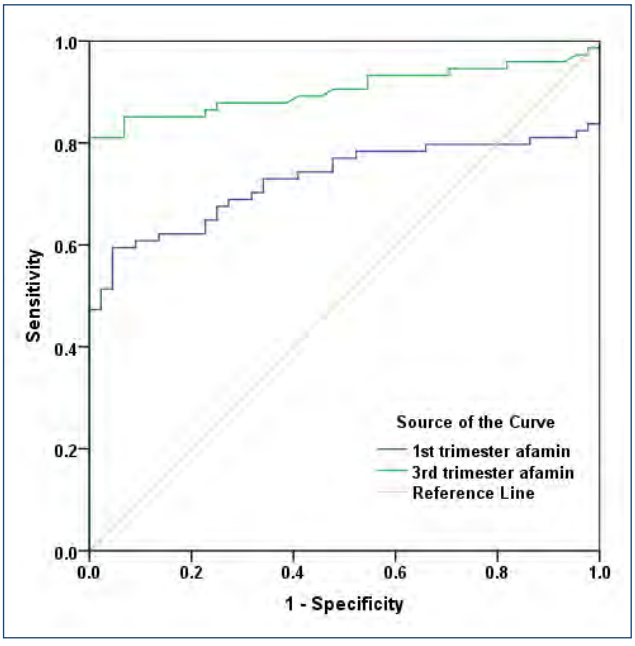

Figure 1. Receiver operating characteristic analysis curves.

linearly during the three trimesters in uncomplicated pregnancies[5]. It is not clear why serum afamin concentrations increase as pregnancy progresses. There are few studies of afamin in PE.

Tramontana et al., involving 30 PE patients and Köninger et al., involving 39 PE patients in their studies found that the first-trimester afamin levels were lower in patients in control compared to the PE group[11,12]. Caliskan et al., in a study of 39 PE patients found that PE developed in those who had high second-trimester afamin levels[3]. Our study differs from other studies in that it detects and reveals high levels of afamin in both first and third trimesters. Although early diagnosis is important for predicting PE, detection of high afamin levels in the third trimester may be useful in diagnosing PE cases that cannot be definitively diagnosed. Caliskan et al., found no difference in serum afamin levels in early-onset and late-onset patients with PE[3]. Köninger et al., detected higher afamin levels in the first trimester in the late-onset patients with PE compared with the early-onset patients with PE, but there was no difference in afamin levels in the early-onset patients with PE compared with the control group[7]. In our study, afamin levels were lower in patients with the early-onset PE compared with patients with the late-onset PE. This result is consistent with the literature. Although increased maternal serum afamin concentrations have been described in patients with PE, the mechanism of any causal relationship is not clear.

The strengths of our study are that afamin levels were not checked in the second trimester, afamin levels were not checked in the cord blood of patients with PE, the number of patients with PE was higher than in other studies, and 2,852 pregnant women were followed until delivery.

CONCLUSION

Serum afamin levels are useful for predicting the first-trimester PE in pregnant women and can be used in clinical practice as a supportive biomarker in the diagnosis of third-trimester PE. Prospective studies with larger patient groups and meta-analyses will be necessary to investigate the effect of serum afamin level on the prediction and diagnosis of PE and to determine the cut-off value.

ETHICAL APPROVAL

Prior to the study, approval was obtained from the Ethics Committee of Samsun Training and Research Hospital (September 23, 2021//No. KAEK 2021/418).

AUTHORS' CONTRIBUTIONS

SG: Conceptualization, Formal Analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **SÇ:** Conceptualization, Formal Analysis, Writing – original draft. **GU:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122-31. https://doi.org/10.1097/01.AOG.0000437382.03963.88
2. Gülücü S, Güçlü M, Çelik S, Can İS, Soyer Çalışkan C, Çelik S. İlk trimester vitamin D, vitamin B12 ve ferritin seviyelerinin preeklampsi ile ilişkisi. Ahi Evran Med J. 2021;5(3):229-35. https://doi.org/10.46332/aemj.865619
3. Çalışkan CS, Celik S, Avcı B. Is afamin a potential early biomarker for subsequent development of preeclampsia? A nested case-control study. J Matern Fetal Neonatal Med. 2021;34(12):2006-11. https://doi.org/10.1080/14767058.2020.1818201
4. Erol SA, Tanacan AT, Anuk AT, Tokalioglu EO, Biriken D, Keskin HL, et al. Evaluation of maternal serum afamin and vitamin E levels in pregnant women with COVID-19 and its association with composite adverse perinatal outcomes. J Med Virol. 2021;93(4):2350-8. https://doi.org/10.1002/jmv.26725
5. Hubalek M, Buchner H, Mortl GM, Schlembach D, Huppertz B, Firulovic B, et al. The vitamin E-binding protein afamin increases in maternal serum during pregnancy. Clin Chim Acta. 2014;434(100):41-7. https://doi.org/10.1016/j.cca.2014.03.036
6. Köninger A, Mathan A, Mach P, Frank M, Schmidt B, Schleussner E, et al. Is Afamin a novel biomarker for gestational diabetes mellitus? A pilot study. Reprod Biol Endocrinol. 2018;16(1):30. https://doi.org/10.1186/s12958-018-0338-x
7. Dieplinger H, Dieplinger B. Afamin – a pleiotropic glycoprotein involved in various disease states. Clin Chim Acta. 2015;446:105-10. https://doi.org/10.1016/j.cca.2015.04.010
8. Chen S, Liu Z, Cen L, Wang J, Zhang J, Zhang X, et al. Association between serum afamin levels with nonalcoholic associated fatty liver disease. Can J Gastroenterol Hepatol. 2022;2022:7175108. https://doi.org/10.1155/2022/7175108
9. Kronenberg F, Kollerits B, Kiechl S, Lamina C, Kedenko L, Meisinger C, et al. Plasma concentrations of afamin are associated with the prevalence and development of metabolic syndrome. Circ Cardiovasc Genet. 2014;7(6):822-9. https://doi.org/10.1161/CIRCGENETICS.113.000654
10. Kollerits B, Lamina C, Huth C, Marques-Vidal P, Kiechl S, Seppala I, et al. Plasma concentrations of afamin are associated with prevalent and incident type 2 diabetes: a pooled analysis in more than 20,000 individuals. Diabetes Care. 2017;40(10):1386-93. https://doi.org/10.2337/dc17-0201
11. Tramontana A, Dieplinger B, Stangl G, Hafner E, Dieplinder H. First trimester serum afamin concentrations are associated with the development of pre-eclampsia and gestational diabetes mellitus in pregnant women. Clin Chim Acta. 2018;476:160-6. https://doi.org/10.1016/j.cca.2017.11.031
12. Köninger A, Enekwe A, Mach P, Andrikos D, Schmidt B, Frank M, et al. Afamin: an early predictor of preeclampsia. Arch Gynecol Obstet. 2018;298(5):1009-16. https://doi.org/10.1007/s00404-018-4897-z

ORIGINAL ARTICLE

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A logarithmic model for hormone receptor-positive and breast cancer patients treated with neoadjuvant chemotherapy

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the predictive importance of the previously validated log(ER)*log(PgR)/Ki-67 predictive model in a larger patient population.

METHODS: Patients with hormone receptor positive/HER-2 negative and clinical node positive before chemotherapy were included. Log(ER)*log(PgR)/Ki-67 values of the patients were determined, and the ideal cutoff value was calculated using a receiver operating characteristic curve analysis. It was analyzed with a logistic regression model along with other clinical and pathological characteristics.

RESULTS: A total of 181 patients were included in the study. The ideal cutoff value for pathological response was 0.12 (area under the curve=0.585, p=0.032). In the univariate analysis, no statistical correlation was observed between luminal subtype (p=0.294), histological type (p=0.238), clinical t-stage (p=0.927), progesterone receptor level (p=0.261), Ki-67 cutoff value (p=0.425), and pathological complete response. There was a positive relationship between numerical increase in age and residual disease. As the grade of the patients increased, the probability of residual disease decreased. Patients with log(ER)*log(PgR)/Ki-67 above 0.12 had an approximately threefold increased risk of residual disease when compared to patients with 0.12 and below (odds ratio: 3.17, 95% confidence interval: 1.48–6.75, p=0.003). When age, grade, and logarithmic formula were assessed together, the logarithmic formula maintained its statistical significance (odds ratio: 2.47, 95% confidence interval: 1.07–5.69, p=0.034).

CONCLUSION: In hormone receptor-positive breast cancer patients receiving neoadjuvant chemotherapy, the logarithmic model has been shown in a larger patient population to be an inexpensive, easy, and rapidly applicable predictive marker that can be used to predict response.

KEYWORDS: Patients. Breast neoplasms. Neoadjuvant therapy. Antineoplastic agents. Receptors, progesterone. Receptors, estrogen.

INTRODUCTION

Breast tumors show different behaviors based on the biological characteristics of the cells from which they originate[1]. Frequently used markers in tumor biology classification are estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor (HER-2). Generally, hormone receptor (HR)-negative tumors (ER and PgR negative) or HER-2-positive tumors are sensitive to chemotherapy and respond well to neoadjuvant chemotherapy (NACT)[2]. NACT enables axillary downstaging, breast conserving surgery, and evaluation of early in vivo response to chemotherapy in most of these patients[3]. However, HR-positive/HER-2-negative breast cancer (ER or PgR positive) cases respond poorly to NACT, pathological complete response rate (pCR) is significantly lower, and there is a relationship between residual tumor characteristics and survival after treatment[4]. Nevertheless, some subgroups of HR-positive patients may have good responses to NACT; therefore, the establishment of methods which can aid treating physicians to distinguish patients will benefit from NACT is of utmost importance[5].

At present, there is no inexpensive, reliable, and easily accessible predictive marker for the HR-positive/HER-2-negative patient group for obtaining pCR with NACT. Although genome sequencing tests such as Mammaprint and Oncotype can be used as validated methods for predicting benefit from NACT, they are expensive, and the cost of their application makes them inaccessible for large patient populations. On the contrary, relative cost-effective methods such as immunohistochemical determination of Ki-67 levels still remain far from standardization, and there can be significant differences between the immunohistochemical methods and pathology laboratories in the evaluation processes of Ki-67; there is still a need for predictive methods that are cost-effective, are easily reproducible, and can be validated.

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The European Society for Medical Oncology (ESMO) divides HR-positive breast tumors into two as luminal A-like and luminal B-like according to receptor percentages. In patients with ER >1, a PGR of less than 20% or a high Ki-67 (an indeterminate cutoff) is referred to as luminal B-like[6]. In contrast, ASCO defines ER between 1 and 10% as low ER positivity and does not accept Ki-67 as a tumor marker[7]. Due to such uncertainties, there is a need for a new classification using important markers such as ER, PgR, and Ki-67 to classify HR-positive/HER-2-negative patients according to NACT responses.

In a previous study, we found that the formula log(ER)*log(PgR)/Ki-67 was predictive of NACT response in 126 HR-positive/HER-2-negative patients. In this study, we aimed to investigate the predictive value of our logarithmic index in a larger patient population and confirm its accuracy[8].

METHODS

In our study, the data of HR-positive/HER-2-negative breast cancer patients who received NACT between February 1, 2014, and May 1, 2022 were evaluated retrospectively. Inclusion criteria were as follows: receiving a standard chemotherapy regimen [four cycles of cyclophosphamide+epirubicin (or doxorubicin) followed by either docetaxel (75 mg/m^2) every 3 weeks for 4 cycles or paclitaxel (80 mg/m^2) every 12 cycles week], and being clinically node positive before treatment. Patients who were metastatic, male, and unable to complete the neoadjuvant regimen and who received different chemotherapy regimens were excluded from the study (Figure 1). Clinical and pathological tumor staging was based on the TNM Classification of Malignant Tumors, 8th edition. Polymerase chain reaction (PCR) was defined as ypT0/ypTis, ypN0. The cutoff value for Ki-67 was determined as 18 in the separation of luminal A-like and luminal B-like.

In the formula log(ER)*log(PgR)/Ki-67, log(ER) defines the base 10 logarithm of the ER level, log(PgR) defines the base 10 logarithm of the PgR level, and Ki-67 defines the proliferation index without "%." Values with ER zero (0) or PgR zero (0) are considered 0, as they do not cut the logarithm curve.

The SPSS Statistical version 24 (SPSS Inc., Chicago, III) software was used for all statistical analyses. The specificity-sensitivity along with the ideal cutoff value for PCR and non-PCR discrimination of the logarithmic formula were determined by receiver operating characteristic (ROC) analysis. The relationships between logarithmic formula, pCR, and other clinical-pathological characteristics were assessed with the chi-square test. Univariate and multivariate analyses were calculated using binary logistic regression analysis. Odds ratio (OR) was reported with the corresponding 95% confidence intervals (CIs), and $p<0.05$ was considered statistically significant.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and approved by the Non-Interventional Ethics Committee (Approval no. 2022.86.05.13).

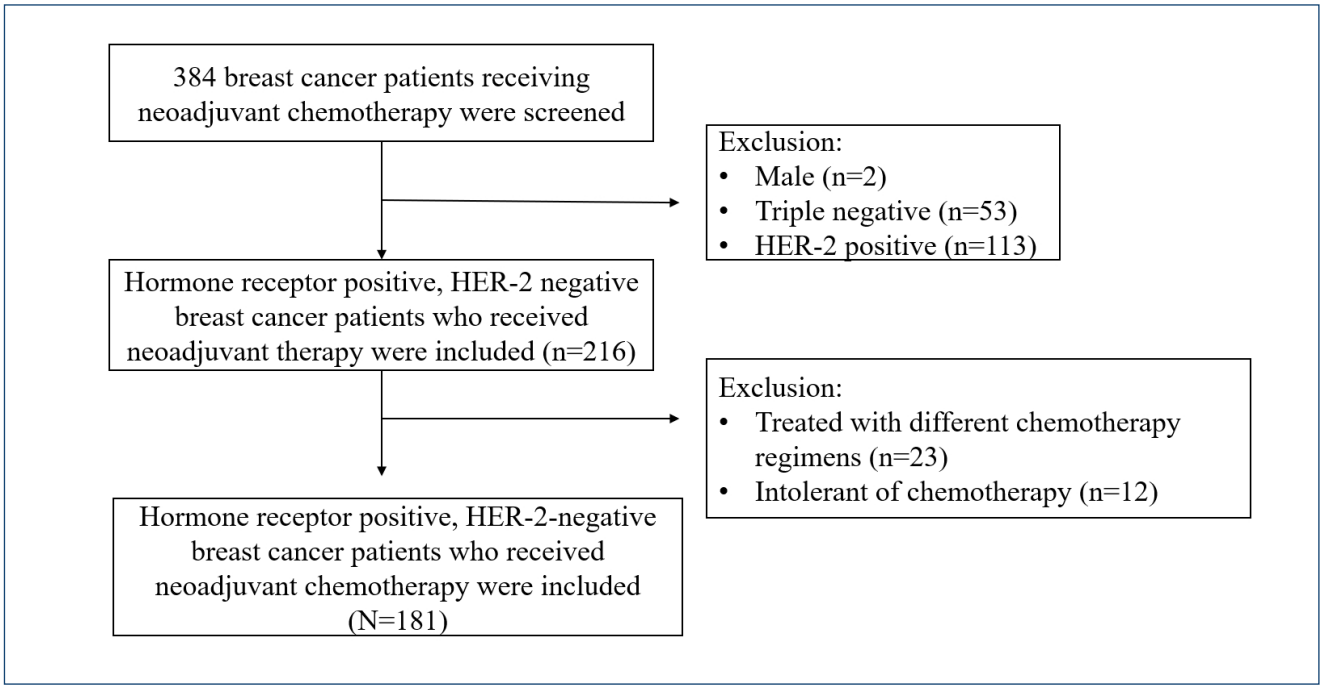

Figure 1. Flow chart documenting selection criteria for patients.

RESULTS

Patient characteristics and treatment responses by characteristics

The data of 181 patients were analyzed. The median age of the patients was 50 (min–max: 25–79) years. When the patients were separated according to their molecular subtypes, 39 (21.5%) patients were luminal A-like and 142 (78.5%) patients were luminal B-like. Histologically, 151 (83.4%) patients had invasive ductal carcinoma and 30 (16.6%) patients had other histological subtypes; 142 (78.5%) patients were found to have residual tumor (non-pCR) and 39 (21.5%) patients were found to have pCR among the patients who underwent surgery after NACT. The highest pCR was observed in patients aged less than 50 (27.4%) years, and the least pCR was observed in grade 1 tumors (0%) (Table 1).

Pathological and clinical characteristics according to log(ER)*log(PgR)/Ki-67

The ideal cutoff value, which distinguishes patients who had pCR and those who did not, was determined as 0.12 using the ROC analysis (Figure 2). This value allows identifying two separate populations: cutoff ratio^{low} (<0.12), 86 (47.5%) patients and cutoff ratio^{high} (≥0.12), 95 (52.5%) patients (n=181, AUC=0.585, p=0.032). The sensitivity and specificity of this value to identify non-PCR patients were 58.5 and 69.2%, respectively.

When treatment responses were analyzed using the univariate logistic regression analysis, no statistical relationship was found between pCR and luminal subtype (0.294), histological subtype (0.238), clinical t-stage (0.927), PgR receptor level (0.261), and Ki-67 cutoff value (0.425). There was

Table 1. Comparison of treatment responses according to patients' clinical and pathological characteristics.

Variables	Total (n=181)	Non-pCR (n=142)	Non-pCR (%) (78.5%)	pCR (n=39)	pCR (%) (21.5%)	p-value
Age						
<50	68	61	72.6	7	27.4	0.076
≥50	113	81	83.5	32	16.5	
Molecular subtype						
Luminal A-like	39	33	84.6	6	15.4	0.291
Luminal B-like	142	109	76.8	33	23.2	
Histological type						
Ductal	151	116	76.8	35	23.2	0.231
Others	30	26	86.7	4	13.3	
PgR						
<20	54	40	74.1	14	25.9	0.350
≥20	127	102	80.3	25	19.7	
Ki-67						
<18	51	42	82.4	9	17.6	0.424
≥18	130	100	76.9	30	23.1	
Grade						
Grade 1	8	8	100	0	0	0.072
Grade 2	121	98	81.0	23	19.0	
Grade 3	52	36	78.5	16	21.5	
Clinical T stage						
T1	50	39	78.0	11	22.0	0.927
T2-T3	131	103	78.6	28	21.4	
Log(ER)*log(PgR)/Ki-67						
Cutoff ^{low} (<12%)	86	59	68.6	27	31.4	0.002
Cutoff ^{high} (≥12%)	95	83	87.4	12	12.6	

pCR: pathological complete response; Non-pCR: non-pathological complete response; PgR: progesterone receptor.

a positive relationship between numerical increase in age and residual disease (OR 1.032, 95%CI 1.000–1.065, p=0.048). Probability of residual disease decreased as the grade of the patients increased (OR 0.457, 95%CI 0.230–0.908, p=0.025). Patients with log(ER)*log(PgR)/Ki-67 above 0.12 (cutoff ratio^{high}) had an approximately threefold increased risk of having residual disease (OR 3.17, 95%CI 1.48–6.75, p=0.003) compared to patients with a value of 0.12 and below (cutoff ratio^{low}). When age, grade, and logarithmic formula were evaluated together, the logarithmic formula maintained its statistical significance (OR 2.47, 95%CI 1.07–5.69, p=0.034) (Table 2).

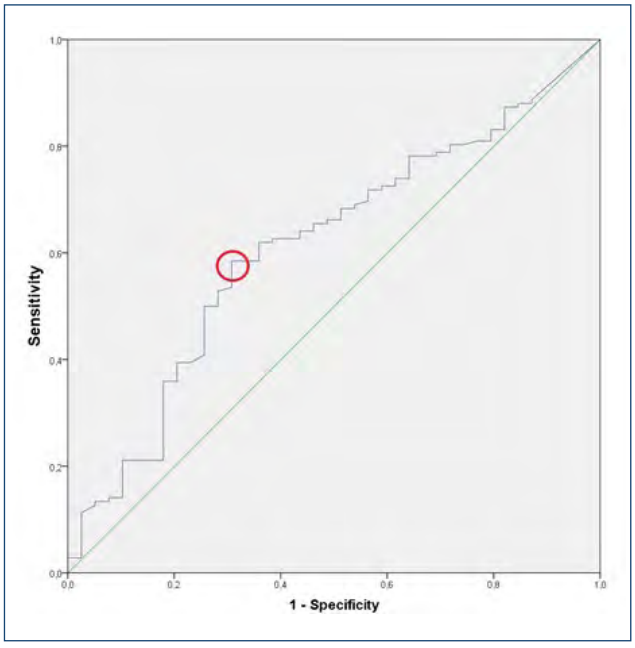

Figure 2. Receiver operating characteristic curve to determine the ideal cut-off value for the logarithmic model (the red circle indicates the cut-off value).

DISCUSSION AND CONCLUSION

Luminal-like breast cancer is considered chemotherapy resistant relative to triple-negative and HER-2-positive subtypes. However, NACT is being increasingly utilized as a method for increasing the rate and improving the outcome of breast and axillary conserving surgery; therefore, it is important to be able to delineate the patients who can most benefit from NACT[6]. pCR can be chosen as a decisive parameter for the description of HR-positive/HER-2-negative BC patients who have an increased chance of showing a response to NACT. As a result of the investigation of tumor genetics, such as Oncotype DX® and Mammaprint® along with the next generation sequencing method, the selection of the right patients to be the candidates for chemotherapy is beneficial[9,10]. However, the use of these tests for NACT is limited and sometimes cannot give clear results in the selection of patients who may benefit from chemotherapy. In addition, it is expensive and the results can be obtained only after a long time[11]. Therefore, these markers cannot be used routinely, especially in developing countries.

In a previous study, we developed an easily accessible model in all clinics, which demonstrated its predictive effectiveness[8]. In this study, it was aimed to investigate the clinical and pathological characteristics of the patients, along with the predictive importance of the log(ER)*log(PgR)/Ki-67 formula in a larger patient population (n=181) in HR-positive/HER-2-negative patients. When assessed with a univariate analysis, patients with cutoff ratio^{high} had approximately three times more complete responses than those with cutoff ratio^{low}.

Table 2. Univariate and multivariate logistic regression analysis of clinical and pathological markers for residual disease after neoadjuvant chemotherapy in HR-positive/HER-2-negative breast cancer patients (n=181).

Variable	Category	Univariate analysis		Multivariate analysis	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Age	Continuous	1.03 (1.00–1.07)	**0.048**	1.02 (0.99–1.05)	0.276
Luminal type	Luminal A/B (HER-2 negative)	0.60 (0.23–1.56)	0.294		
Histological type	Ductal/others	1.96 (0.64–6.00)	0.238		
Clinical T stage	t1/t2/t3	1.04 (0.47–2.28)	0.927		
Log(ER)*log(PgR)/Ki-67	Low/high	3.17 (1.48–6.75)	**0.003**	2.47 (1.07–5.69)	**0.034**
Ki-67	<18/≥18	0.71 (0.31–1.63)	0.425		
PgR	Continuous	1.01 (1.00–1.02)	0.261		
Nuclear grade	1/2/3	0.46 (0.23–0.91)	**0.025**	0.72 (0.34–1.53)	0.390

Significant values are indicated in bold.

Age and histological grade are known as predictive factors for NACT in breast cancer[12]. In this study, in accordance with the literature, age and grade predicted residual disease after NACT. The logarithmic formula maintained its statistical significance as an independent predictor of response to NACT even when age and grade were included in the multivariate analysis.

In the 2011 Gallen Consensus, it was reported that the luminal classification can be used to predict prognosis, risk of recurrence, and pCR in HR-positive/HER-2-negative breast cancer patients[13]. However, current studies show that the luminal A and B breast cancer classification alone is inadequate to identify patients who might benefit from NACT[14,15]. Consistently, luminal classification was not found to be predictive for pCR in our study, which included only luminal breast cancer patients. In addition, the logarithmic formula was predictive for the NACT response, while also detecting residual disease with higher accuracy than the classical luminal classification.

In many studies, it has been reported that an increase in Ki-67 and a decrease in ER caused a higher rate of pCR as well[16,17]. There is a mathematically inverse relationship between Ki-67 proliferation index and ER and PR HR expression levels in terms of treatment response, and these three biomarkers can be evaluated in the context of a continuum within a formula. The reference ranges of these three biomarkers are between 1 and 100, and the pathologists still specifying the level manually, despite automated systems, make standardization difficult. The literature also proposes logarithmic transformation of predictively skewed data in breast cancer[18,19]. The standardization of reporting of HR depression levels and reduction of inconsistencies between different centers of ER levels and reducing differences between centers can be achieved with application of log-transformation formulas[20]. In our study, besides hormone expression levels, the Ki-67 expression levels were also included in the formula. This innovative approach helped eliminate the Ki-67 cutoff uncertainty problems and enabled the categorization of continuous variables such as ER-PgR.

There are some limitations to our study. First is the retrospective analysis of the data. Second, our study could not exclude the possibility of neoadjuvant selection bias, even though the choice of treatment for all patients in the study was decided by the multidisciplinary breast cancer tumor board. The strengths of our study were that all patients received a single NACT regimen and that the data were homogeneous because the pathology specimens were assessed by the same pathologist.

In conclusion, we confirmed that the log(ER)*log(PgR)/Ki-67 formula can be used as a predictive marker for pCR in a larger patient population. We think that our new predictor formula, which is easily accessible, inexpensive, and powerful, may have a decisive role in the selection of patients who can benefit from NAC.

ETHICS STATEMENT

Approval no: 2022.86.05.13 (Non-Interventional Ethics Committee of Tekirdağ Namık Kemal University).

AUTHORS' CONTRIBUTIONS

EŞŞ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration. **Yİ:** Conceptualization, Writing – original draft, Writing – review & editing. **EÇ:** Conceptualization, Writing – original draft, Writing – review & editing. **KK:** Conceptualization, Writing – original draft, Writing – review & editing. **OA:** Conceptualization, Writing – original draft, Writing – review & editing. **AY:** Conceptualization, Writing – original draft, Writing – review & editing. **SÖG:** Conceptualization, Writing – original draft, Writing – review & editing. **MÖ:** Conceptualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol. 2014;5(3):412. https://doi.org/10.5306/wjco.v5.i3.412
2. Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of pathological complete response after neoadjuvant therapy for breast cancer. Breast Cancer (Auckl). 2016;10:103-6. https://doi.org/10.4137/BCBCR.S33163
3. Piato JR, Andrade RD, Chala LF, Barros N, Mano MS, Melitto AS, et al. MRI to predict nipple involvement in breast cancer patients. AJR Am J Roentgenol. 2016;206(5):1124-30. https://doi.org/10.2214/AJR.15.15187
4. Gomes Cunha JP, Goncalves R, Silva F, Aguiar FN, Mota BS, Chequim BB, et al. Validation of the Residual Cancer Burden Index as a prognostic tool in women with locally advanced breast cancer treated with neoadjuvant chemotherapy. J Clin Pathol. 2021; jclinpath-2021-207771. https://doi.org/10.1136/jclinpath-2021-207771
5. Torrisi R, Marrazzo E, Agostinetto E, Sanctis R, Losurdo A, Masci G, et al. Neoadjuvant chemotherapy in hormone receptor-positive/HER2-negative early breast cancer: when, why and what? Crit Rev Oncol Hematol. 2021;160:103280. https://doi.org/10.1016/j.critrevonc.2021.103280
6. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194-220. https://doi.org/10.1093/annonc/mdz173

7. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2020;38(12):1346-66. https://doi.org/10.1200/JCO.19.02309
8. Iriagac Y, Cavdar E, Karaboyun K, Tacar SY, Taskaynatan H, Avci O, et al. A new predictive marker for predicting response after neoadjuvant chemotherapy in hormone receptor positive/HER2-negative patients: a logarithmic model. J BUON. 2021;26(6):2274-81. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85123687967&partnerID=40&md5=c1ca8222edc33d471241f8e685fdc766
9. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;141(1):13-22. https://doi.org/10.1007/s10549-013-2666-z
10. Mook S, Van't Veer LJ, Rutgers EJ, Piccart-Gebhart MJ, Cardoso F. Individualization of therapy using Mammaprint®: from development to the MINDACT Trial. Cancer Genomics Proteomics. 2007;4(3):147-55. PMID: 17878518
11. Chandler Y, Schechter CB, Jayasekera J, Near A, O'Neill SC, Isaacs C, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018;36(6):554-62. https://doi.org/10.1200/JCO.2017.74.5034
12. Huober J, Minckwitz G, Denkert C, Tesch H, Weiss E, Zahm DM, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat. 2010;124(1):133-40. https://doi.org/10.1007/s10549-010-1103-9
13. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736-47. https://doi.org/10.1093/annonc/mdr304
14. Collins PM, Brennan MJ, Elliott JA, Abd Elwahab S, Barry K, Sweeney K, et al. Neoadjuvant chemotherapy for luminal a breast cancer: factors predictive of histopathologic response and oncologic outcome. Am J Surg. 2021;222(2):368-76. https://doi.org/10.1016/j.amjsurg.2020.11.053
15. Zhang Z, Zhang H, Li C, Xiang Q, Xu L, Liu Q, et al. Circulating microRNAs as indicators in the prediction of neoadjuvant chemotherapy response in luminal B breast cancer. Thorac Cancer. 2021;12(24):3396-406. https://doi.org/10.1111/1759-7714.14219
16. Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer. 2011;11:486. https://doi.org/10.1186/1471-2407-11-486
17. Chen X, He C, Han D, Zhou M, Wang Q, Tian J, et al. The predictive value of Ki-67 before neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. Futur Oncol. 2017;13(9):843-57. https://doi.org/10.2217/fon-2016-0420
18. Chapman JW, Murray D, McCready DR, Hanna W, Kahn HJ, Lickley HL, et al. An improved statistical approach: can it clarify the role of new prognostic factors for breast cancer? Eur J Cancer. 1996;32(11):1949-56. https://doi.org/10.1016/0959-8049(96)00232-8
19. Feng C, Wang H, Lu N, Chen T, He H, Lu Y. Log-transformation and its implications for data analysis. Shanghai Arch psychiatry. 2014;26(2):105-9. https://doi.org/10.3969/j.issn.1002-0829.2014.02.009
20. Chapman JA, Mobbs BG, Hanna WM, Sawka CA, Pritchard KI, Lickley HL, et al. The standardization of estrogen receptors. J Steroid Biochem Mol Biol. 1993;45(5):367-73. https://doi.org/10.1016/0960-0760(93)90005-h

ORIGINAL ARTICLE

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Predicting response to neoadjuvant therapy with glucose transporter-1 in breast cancer

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SUMMARY

OBJECTIVE: Glucose transporter-1 is a marker involved in energy transport in cancer cells. It has been shown to be a poor prognostic factor in many cancer types, including breast cancer. However, there is no satisfactory parameter predicting treatment in breast cancer patients receiving neoadjuvant therapy. This study investigated the effect of glucose transporter-1 in predicting the treatment response of patients receiving neoadjuvant therapy.

METHODS: In this study, glucose transporter-1 immunohistochemistry was applied to tru-cut biopsy of patients who were diagnosed with breast cancer and received neoadjuvant therapy between 2010 and 2021. A built-in scoring system was used to evaluate both the pattern and intensity of glucose transporter-1 immunohistochemistry staining. The relationship between glucose transporter-1 immunohistochemistry staining and other clinicopathological parameters was examined. In addition, the relationship of glucose transporter-1 with response to treatment was investigated.

RESULTS: A relationship was found between high glucose transporter-1 expression and other clinicopathological parameters (such as estrogen and progesterone receptor negativity, high Ki-67, triple-negative, and Her2 status). Cases with high glucose transporter-1 expression had either a complete or a partial pathologic response. The result was statistically significant.

CONCLUSION: Glucose transporter-1 has the potential to be a biomarker that can be evaluated more objectively as an alternative to Ki-67 labeling index in evaluating the response to treatment in patients receiving neoadjuvant therapy.

KEYWORDS: Glucose transporter type 1. Breast. Cancer. Immunohistochemistry. Neoadjuvant therapy.

INTRODUCTION

Breast cancer (BC) is the most common tumor worldwide with a high mortality rate among women. Some parameters, such as tumor stage, molecular subtyping, and hormone receptor status, are used in the selection of treatment and in predicting the prognosis[1]. Molecular subtyping is the most important parameter that predicts the response to neoadjuvant therapy (NT)[2]. Molecular subtyping alone is insufficient to predict treatment. However, more parameters are needed. Therefore, it is important to investigate different biomarkers that will shed light on new agents in predicting the prognosis, response of patients, and even in choosing treatment method.

Glucose transporters are membrane transporter proteins that catalyze the facilitative bidirectional transfer of their substrates across membranes[3]. Glucose transporter-1 (Glut-1) is the first identified member of the glucose transporter family as well as the most common of all membrane transport proteins[4]. It is highly expressed in the endothelium of tissues where selective glucose transfer from blood to tissues is important, such as the central nervous system, retina, iris, ciliary muscle, and endoneurium. Moreover, Glut-1 is also expressed in erythrocytes physiologically[5], and pathologically, it mediates basal glucose transport in cancer cells, which require considerably higher energy levels than normal cells, and provides glucose for energy metabolism[6]. Various studies have also investigated whether insulin resistance, which regulates glucose metabolism in the body, is a risk factor in BCs. Some of these studies have defined a high risk of BC in obese and diabetic patients. However, the mechanisms are not clear[7]. As a result, Glut-1 has been found to be overexpressed in various types of cancer, including prostate, stomach, lung, and BC; squamous cell carcinoma of the head and neck[8-11]; and its overexpression is a poor

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prognostic parameter[12,13]. Therefore, it has been thought that tumor progression can be prevented via Glut-1 mechanism.

In the present study, we aimed to investigate the potential use of Glut-1 antibody in tru-cut biopsy (TCB) as a new biomarker to predict the response and prognosis before NT. In addition, we studied the relationship between Glut-1 expression and clinicopathological parameters, such as hormone receptor status and Ki-67 labeling index (LI).

METHODS

Study design and case selection

In our retrospectively planned study, patients with a diagnosis of breast carcinoma and received NT between 2010 and 2021 were retrieved from the hospital electronic system.

Patient data

The age, details of NT protocol, the status of recurrence or distant metastasis, and survival status were retrieved from the hospital and national electronic database. Tumor size, status of hormone receptor and Her2 expression, Ki-67 LI, and the presence of lymphovascular and perineural invasion were obtained from pathological reports.

Histopathological and immunohistochemical staining

Hematoxylin and eosin-stained slides of both TCB and resection were retrieved from the pathology archive. Cases that did not have tumor slides or clinical data were excluded. H&E and immunohistochemical slides were re-evaluated by three different pathologists (SDÖ, ÇÖ, and GA). All cases were classified according to their molecular and histological subtypes according to the World Health Organization classification[14-16]. The cutoff value for Ki-67 LI was accepted as 14%.

The best representative tumor block was selected from both TCB and resections, and 4-µm sections were obtained. The Ventana Medical Systems (SN: 714592, Ref: 750-700 Arizona, USA) automated immunohistochemistry device was used. Immunohistochemical staining was performed using the Ultra-view Universal DAB Detection Kit (REF: 760-500, Ventana) and Glut-1 antibody (PA1-46152, 1/200 diluted, Glut-1 Rabbit Polyclonal Antibody).

An established scoring system that evaluates both the pattern and intensity of staining was used. Membranous and cytoplasmic staining were considered positive. Briefly, the staining pattern was scored according to the percentage of cells that showed cytoplasmic and/or membranous staining as follows: 0=less than 1%, 1+=1–10%, 2+=11–50%, 3+=51–80%, and 4+=over 80%. The intensity was scored as 1: weak, 2: moderate, and 3: strong. Blinded assessment was done by two different observers (SDO and OO). The overall score was then calculated as (1+intensity/3)×pattern[17]. Tumor cells were scored as negative if no immunopositive cells were present after immunostaining. The total score was based on the percentage of positive tumor cells and the degree of immunostaining intensity[18].

Statistically, the median value for staining score was 3.9. Score <4 was accepted as low, while score ³4 was accepted as high (Figure 1).

ETHICAL APPROVAL

Ethics committee approval for our study was obtained from the ethics committee of the Recep Tayyip Erdogan University Faculty of Medicine, non-interventional clinical research (E-40465587-050.01.04-352). The study was conducted in accordance with the Declaration of Helsinki, the ethical standards of the institutional research committee, and the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guideline[19].

STATISTICAL ANALYSIS

Statistical post-hoc power and effect size were calculated by using the G*Power version 3.1.9.7 software[20]. Statistical analyses were performed using IBM SPSS Statistics, Version 22.0 (SPSS Inc., Chicago, USA). Each group's descriptive statistics were reported as frequency and percentages within the group (n, %). Whether there was a correlation between the groups in terms of categorical variables was evaluated using the chi-square (Pearson's chi-square) and Fisher's exact test. The Kaplan-Meier method was used for survival analysis and was evaluated with the log-rank test. For statistical significance, the p-value was accepted as <0.05.

RESULTS

Clinicopathological parameters

A total of 65 cases were included, and the median age was 58 years (range, 33–84 years). Estrogen receptor (ER) and progesterone receptor (PR) positivity were observed in 45 (69%) and negative in 41 (63%) cases. In all, 50 (77%) cases had high Ki-67 LI (≥15%). Complete and partial pathologic responses were observed in 25 (38%) and 31 (48%) cases, respectively, while 9 (14%) had no response to NT.

Association of glucose transporter-1 expression with clinicopathological parameters in tru-cut biopsy before neoadjuvant therapy

High Glut-1 expression was present in 31 of 65 cases. Glut-1 expression was high in cases that had no expression of ER and PR (p=0.016 and p=0.004, respectively). There was a statistically significant relationship between Glut-1 expression and high Ki-67 LI (p=0.001) (Figure 1). Glut-1 expression was statistically higher in cases that were classified as luminal A and luminal B compared to Her2 and triple-negative (TN) ones (p=0.032). Glut-1 expression was statistically low in cases with lymphovascular invasion (p=0.002) and lymph node metastasis (p=0.017). Cases with high Glut-1 expression had either a complete or a partial pathologic response. The result was statistically significant (p=0.028) (Table 1).

Relationship between glucose transporter-1expression and prognosis

The median follow-up for the entire cohort was 36 months (range, 1–88 months). Notably, seven (11%) cases were died of

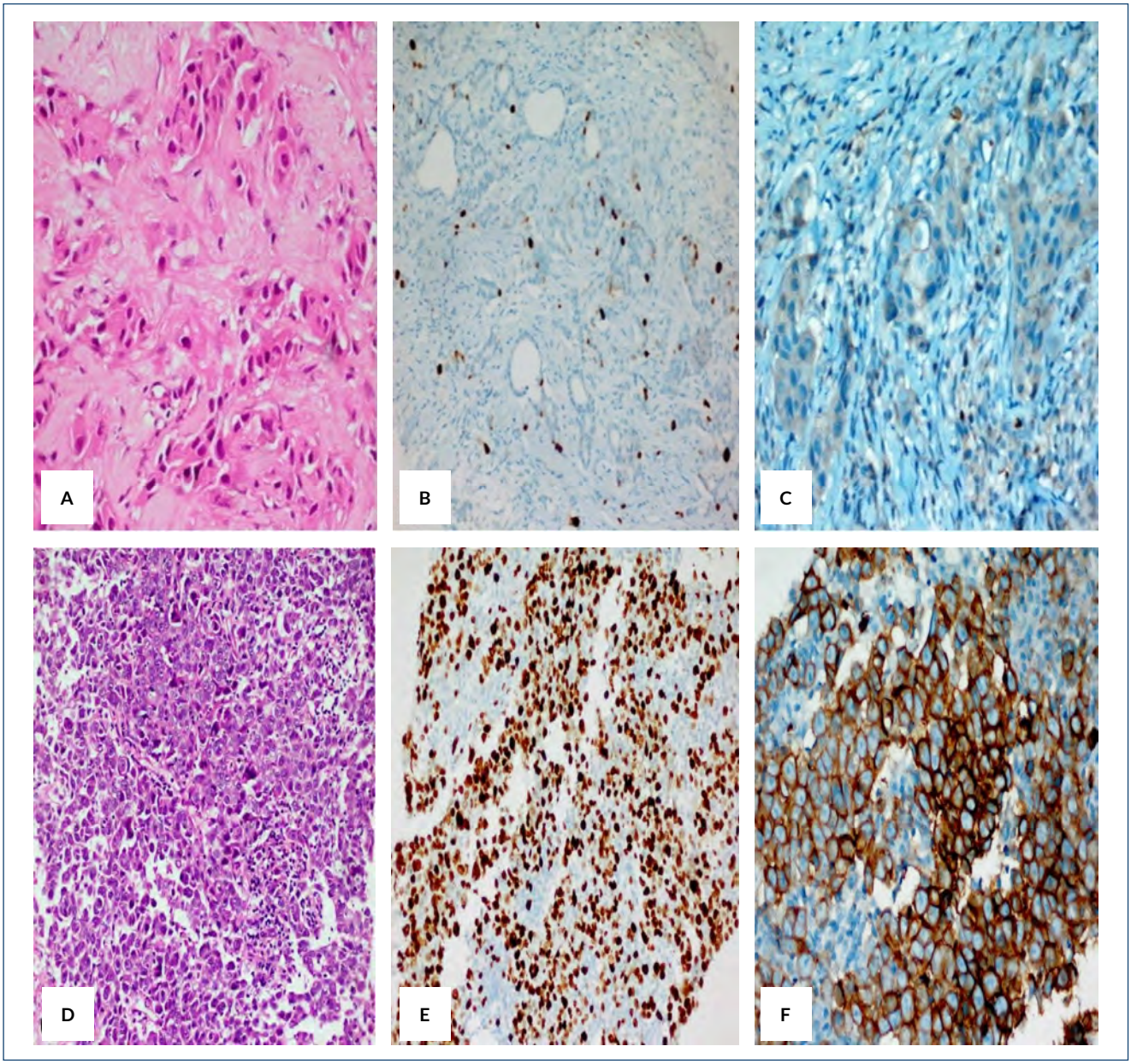

Figure 1. **(a)** Microscopic image of invasive breast carcinoma (H&E 200×). **(b)** Tumor labeling index (200×) with Ki-67. **(c)** Low glucose transporter-1 expression (400×). **(d)** Microscopic view of invasive breast cancer (H&E 200×). **(e)** Tumor labeling index (200×) with Ki-67. **(f)** High glucose transporter-1 expression (200×).

disease, and two (29%) had high Glut-1 expression. Distant organ metastases were observed in 14 (22%) cases, and Glut-1 expression was low in 12 (86%) of them. Statistically, Glut-1 expression was found to be associated with disease-free survival (DFS), but no correlation was found with overall survival (OS) (log-rank p=0.014 and p=0.469, respectively) (Figure 2).

DISCUSSION

Glut-1, a member of the glucose transporter family, expression is controlled by different transcription factors. For example, hypoxia-inducible factor (HIF-1 alpha) has been reported to regulate Glut-1 expression in hypoxic conditions. Moreover, c-Myc plays a role in Glut-1 expression in many different tumors[21]. Abnormal expression of Glut-1 is also affected by the PI3K/Akt pathway. Changes in the stability of Glut-1 transcription are associated with changes in glucose concentration, the structure of growth factors, cytokines, and some hormones[22]. The Glut-1 expression reflects increased glycolytic metabolism, so there is Glut-1 upregulation in many cancers to maintain high glucose levels in neoplastic cells[23].

Glut-1 has been shown as an optimal biomarker in various types of cancer[24], and it has been reported that agents providing Glut-1 inhibition in BC can be used in targeted therapy in different studies[21-27]. Moreover, this is the first study regarding Glut-1 expression in BC patients receiving NT.

BC is the most common type of cancer with a high mortality rate among women[11]. Some parameters, such as tumor

Table 1. The relationship between glucose transporter-1 expression and clinicopathological parameters in tru-cut biopsies before neoadjuvant therapy.

		Glut-1		
		<4	≥4	p-value
		n (%)	n (%)	
Histological subtypes	Invasive ductal carcinoma	32 (94.1)	29 (93.5)	1.000
	Invasive lobular carcinoma	2 (5.9)	2 (6.5)	
Response to treatment	No response	8 (23.5)	1 (3.2)	0.028
	Partial/complete response	26 (76.5)	30 (96.8)	
Molecular subtypes	Luminal A + Luminal B	28 (82.4)	18 (58.1)	0.032
	Her2 + Triple negative	6 (17.6)	13 (41.9)	
Estrogen receptor	Negative	6 (17.6)	14 (45.2)	0.016
	Positive	28 (82,4)	17 (54.8)	
Progesterone receptor	Negative	7 (20.6)	17 (54.8)	0.004
	Positive	27 (79.4)	14 (45.2)	
Her2	Negative	19 (55.9)	19 (61.3)	0.141
	Positive	11 (32.4)	12 (38.7)	
	Unknown	4 (11.8)	0 (0)	
Ki-67 proliferation index	Low	12 (36.4)	1 (3.3)	0.001
	High	21 (63.6)	29 (96.7)	
Lymphovascular invasion	Absent	16 (47.1)	26 (83.9)	0.002
	Present	18 (52.9)	5 (16.1)	
Perineural invasion	Absent	28 (82.4)	29 (93.5)	0.262
	Present	6 (17.6)	2 (6.5)	
Axillary lymph node metastasis	Absent	13 (38.2)	21 (67.7)	0.017
	Present	21 (61.8)	10 (32.3)	
Distant organ metastasis	Absent	22 (64.7)	29 (93.5)	0.005
	Present	12 (35.3)	2 (6.5)	
Dead of disease	Alive	29 (85.3)	29 (93.5)	0.43
	Exitus	5 (14.7)	2 (6.5)	

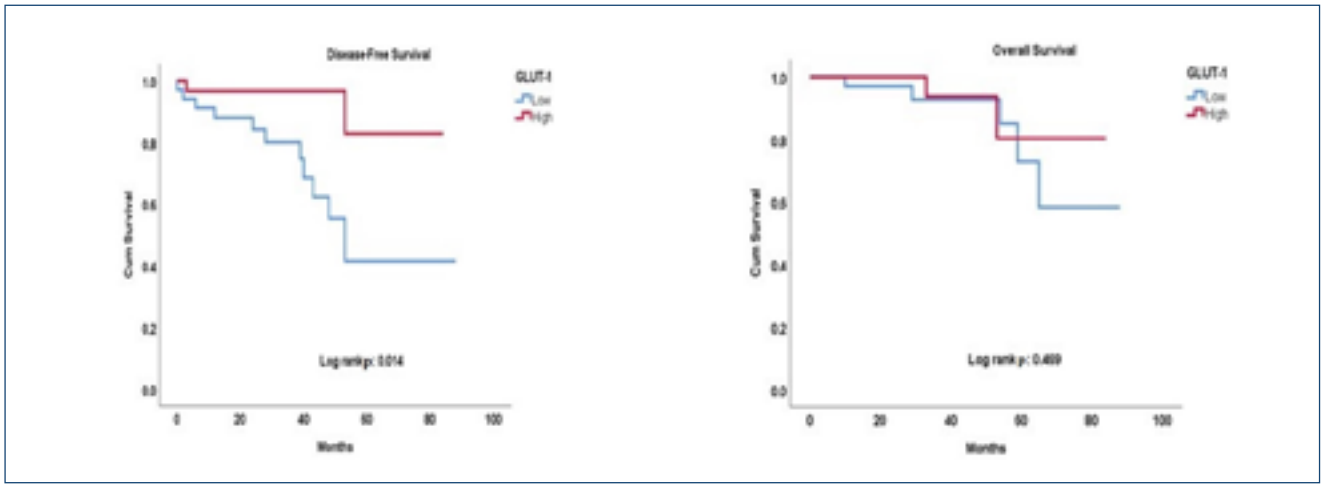

Figure 2. The relationship of glucose transporter-1 expression of cases with disease-free survival and overall survival by Kaplan-Meier analysis.

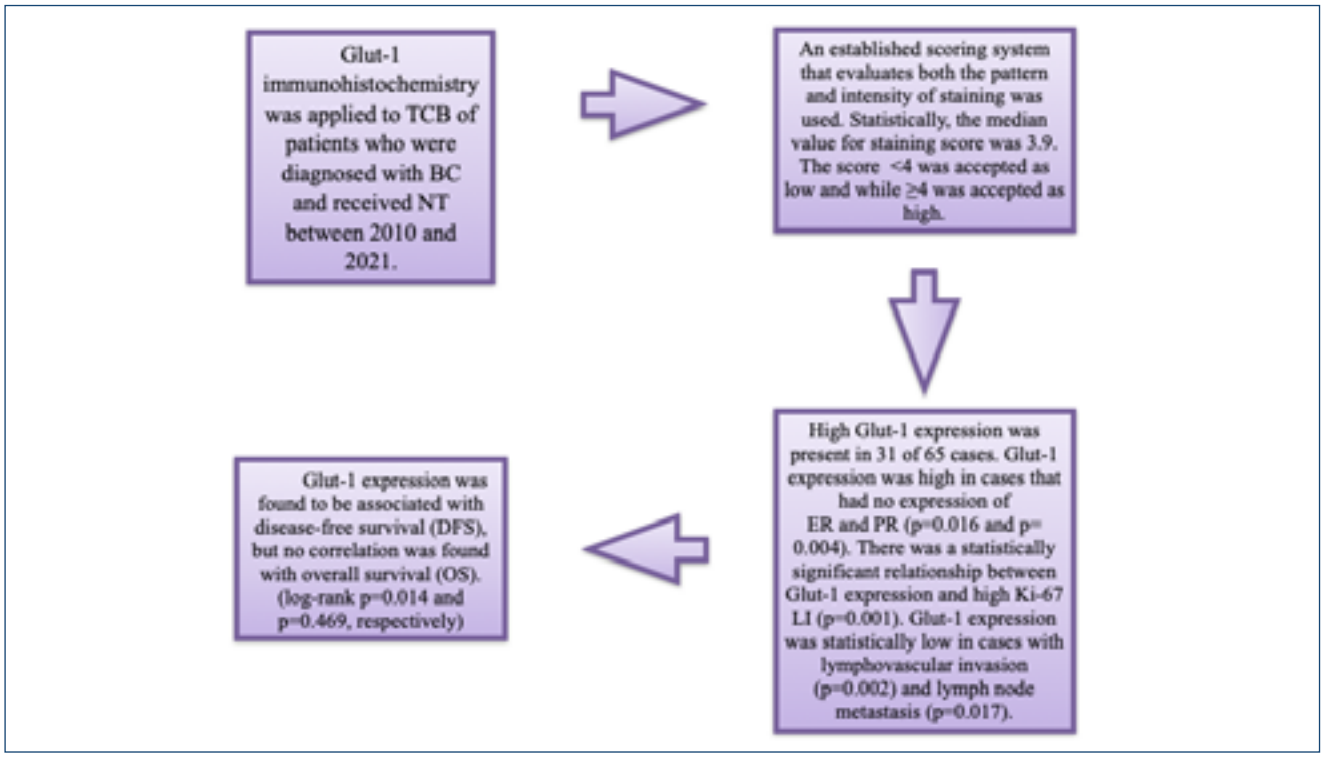

Figure 3. Flowchart of the research.

stage, molecular subtype, and hormone receptor status, have been used in daily practice to choose the treatment method and predict the prognosis.

To the best of our knowledge, there has been no study regarding Glut-1 expression in BC patients receiving NT.

According to Deng Y et al., Glut-1 expression was associated with higher tumor grade, ER, and PR negativity in BC patients who did not receive NT (1). In the current study, overexpression of Glut-1 was significantly related to the negative hormone receptor. In addition, higher expression was found in Her2 and TN BCs compared to luminal subtype. As a result, high expression of Glut-1 may indirectly be a sign of poor prognosis, since it is associated with hormone receptor negativity.

In our study, there was a statistically significant relationship between high Glut-1 expression and high Ki-67 LI (Figure 3). In a study by Alba et al., BC patients with a high LI had a complete response to NT. As in the studies of Alba et al., other studies advocate the predictive use of the Ki-67 LI to predict response

to chemotherapy in identifying patients with pathological complete response. In this way, the use of Ki-67 is very useful in determining the patient group with a long prognosis[25]. On the contrary, Ki-67 LI in breast carcinomas is assessed by eyeballing method by choosing three hotspot areas, counting 10 different high-magnification areas, and taking the average of the values. Therefore, this assessment is highly subjective among pathologists. In our study, Glut-1 expression was high in almost all of the cases with complete response to treatment. With these results, we can suggest that the evaluation of Glut-1 expression, which is an objective parameter that can be easily done in routine practice, can be used to predict response to treatment, as well as Ki-67.

In the meta-analysis by Yu Deng et al., the prognostic role of Glut-1 in BC was widely investigated but the results are reported to be inconsistent[1]. Hussein et al. reported that Glut-1 expression was not associated with OS in BC[26]. However, other researchers have presented significant associations between Glut-1 expression and poor prognosis in BC[1,27]. In our study, there was a statistically significant relationship between Glut-1 expression and DFS, but no relationship was found between its expression and OS. Glut-1 expression has not been studied in neoadjuvant patients before, and we think that higher expression can be used as a good prognostic marker in patients receiving NT. A significant correlation was found between low Glut-1 expression and lymphovascular invasion, perineural invasion, lymph node metastasis, and distant organ metastasis in patients receiving NT. This result also supports that high Glut-1 expression can be indirectly used as an indicator of good prognosis in patients receiving NT.

There were some limitations in our study; for example, our cases did not show a homogeneous distribution in terms of molecular subtype, hormone receptor status, response to treatment and had a short follow-up time. Another limitation of our study is the small number of cases.

In conclusion, cancer with high Glut-1 expression has a better response to NT. This is the first and pioneering study regarding Glut-1 expression in BC patients receiving NT. As a result, we suggest that Glut-1 could be used as an alternative biomarker to Ki-67 in objective evaluation of treatment response among BC patients.

AUTHORS' CONTRIBUTIONS

SDÖ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **ÇÖ:** Conceptualization, Data curation, Methodology, Resources, Supervision, Writing – review & editing. **OO:** Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **GA:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **RB:** Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **BŞ:** Data curation, Formal Analysis, Software, Validation, Writing – review & editing.

REFERENCES

1. Deng Y, Zou J, Deng T, Liu J. Clinicopathological and prognostic significance of GLUT1 in breast cancer: a meta-analysis. Medicine. 2018;97(48): e12961. https://doi.org/10.1097/MD.0000000000012961
2. Mozarowski P, Rasaiah B, Reed M, Lewis A, Walde N, Voutsadakis IA. Prognostic role of tumor budding in breast cancer patients receiving neo-adjuvant therapy. J Clin Med. 2021;10(4):827. https://doi.org/10.3390/jcm10040827
3. Saier MH Jr, Beatty JT, Goffeau A, Harley KT, Heijne WH, Huang SC, et al. The major facilitator superfamily. J Mol Microbiol Biotechnol. 1999;1(2):257-79. PMID: 10943556
4. Carruthers A, DeZutter J, Ganguly A, Devaskar SU. Will the original glucose transporter isoform please stand up! Am J Physiol Endocrinol Metab. 2009;297(4):E836-48. https://doi.org/10.1152/ajpendo.00496.2009
5. Rastogi K, Singh L, Khan NA, Goyal S, Khatri A, Gupta N. Benign vascular anomalies: a transition from morphological to etiological classification. Ann Diagn Pathol. 2020;46:151506. https://doi.org/10.1016/j.anndiagpath.2020.151506
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. https://doi.org/10.1016/j.cell.2011.02.013
7. Trinconi AF, Filassi JR, Soares JM Jr, Baracat EC. Evaluation of the insulin-like growth factors (IGF) IGF-I and IGF binding protein 3 in patients at high risk for breast cancer. Fertil Steril. 2011;95(8):2753-5. https://doi.org/10.1016/j.fertnstert.2011.02.014
8. Yang J, Wen J, Tian T, Lu Z, Wang Y, Wang Z, et al. GLUT-1 overexpression as an unfavorable prognostic biomarker in patients with colorectal cancer. Oncotarget. 2017;8(7):11788-96. https://doi.org/10.18632/oncotarget.14352
9. Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S, et al. Overexpression of Glut-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma. Cancer. 2003;97(4):1015-24. https://doi.org/10.1002/cncr.11159
10. Maki Y, Soh J, Ichimura K, Shien K, Furukawa M, Muraoka T, et al. Impact of GLUT1 and Ki-67 expression on early-stage lung adenocarcinoma diagnosed according to a new international multidisciplinary classification. Oncol Rep. 2013;29(1):133-40. https://doi.org/10.3892/or.2012.2087

11. Tohma T, Okazumi S, Makino H, Cho A, Mochizuki R, Shuto K, et al. Overexpression of glucose transporter 1 in esophageal squamous cell carcinomas: a marker for poor prognosis. Dis Esophagus. 2005;18(3):185-9.https://doi.org/10.1111/j.1442-2050.2005.00489.x
12. Yin C, Gao B, Yang J, Wu J. Glucose transporter-1 (GLUT-1) expression is associated with tumor size and poor prognosis in locally advanced gastric cancer. Med Sci Monit Basic Res. 2020;26:e920778-1. https://doi.org/10.12659/MSMBR.920778
13. Minami K, Saito Y, Imamura H, Okamura A. Prognostic significance of p53, Ki-67, VEGF and Glut-1 in resected stage I adenocarcinoma of the lung. Lung Cancer. 2002;38(1):51-7. https://doi.org/10.1016/s0169-5002(02)00108-3
14. Cirqueira MB, Moreira MA, Soares LR, Cysneiros MA, Vilela MH, Freitas-Junior R. Effect of Ki-67 on immunohistochemical classification of luminal A to luminal B subtypes of breast carcinoma. Breast J. 2015;21(5):465-72. https://doi.org/10.1111/tbj.12441
15. Rakha E, Allison K, Ellis I, Horii R, Masuda S, Penault-Llorca F. Invasive breast carcinoma: general overview. Breast tumours WHO classification of tumours. 5th ed. Lyon: World Health Organization; 2019. p. 82-101.
16. Bandyopadhyay S, Bluth MH, Ali-Fehmi R. Breast carcinoma: updates in molecular profiling 2018. Clin Lab Med. 2018;38(2):401-20. https://doi.org/10.1016/j.cll.2018.02.006
17. Basturk O, Singh R, Kaygusuz E, Balci S, Dursun N, Culhaci N, et al. GLUT-1 expression in pancreatic neoplasia: implications in pathogenesis, diagnosis, and prognosis. Pancreas. 2011;40(2):187-92. https://doi.org/10.1097/MPA.0b013e318201c935
18. Panzan MQ, Mattar R, Maganhin CC, Simões Rdos S, Rossi AG, Motta EL, et al. Evaluation of FAS and caspase-3 in the endometrial tissue of patients with idiopathic infertility and recurrent pregnancy loss. Eur J Obstet Gynecol Reprod Biol. 2013;167(1):47-52. https://doi.org/10.1016/j.ejogrb.2012.10.021
19. Sauerbrei W, Taube SE, McShane LM, Cavenagh MM, Altman DG. Reporting recommendations for tumor marker prognostic studies (REMARK): an abridged explanation and elaboration. J Natl Cancer Inst. 2018;110(8):803-11. https://doi.org/10.1093/jnci/djy088
20. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91. https://doi.org/10.3758/bf03193146
21. Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, et al. Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. J Biol Chem. 2000;275(29):21797-800. https://doi.org/10.1074/jbc.C000023200
22. Melstrom LG, Salabat MR, Ding XZ, Milam BM, Strouch M, Pelling JC, et al. Apigenin inhibits the GLUT-1 glucose transporter and the phosphoinositide 3-kinase/Akt pathway in human pancreatic cancer cells. Pancreas. 2008;37(4):426-31. https://doi.org/10.1097/MPA.0b013e3181735ccb
23. Oh S, Kim H, Nam K, Shin I. Glut1 promotes cell proliferation, migration and invasion by regulating epidermal growth factor receptor and integrin signaling in triple-negative breast cancer cells. BMB Rep. 2017;50(3):132-7. https://doi.org/10.5483/bmbrep.2017.50.3.189
24. Zambrano A, Molt M, Uribe E, Salas M. Glut 1 in cancer cells and the inhibitory action of resveratrol as a potential therapeutic strategy. Int J Mol Sci. 2019;20(13):3374. https://doi.org/10.3390/ijms20133374
25. Alba E, Lluch A, Ribelles N, Anton-Torres A, Sanchez-Rovira P, Albanell J, et al. High proliferation predicts pathological complete response to neoadjuvant chemotherapy in early breast cancer. Oncologist. 2016;21(2):150-5. https://doi.org/10.1634/theoncologist.2015-0312
26. Hussein YR, Bandyopadhyay S, Semaan A, Ahmed Q, Albashiti B, Jazaerly T, et al. Glut-1 expression correlates with basal-like breast cancer. Transl Oncol. 2011;4(6):321-7. https://doi.org/10.1593/tlo.11256
27. Jang SM, Han H, Jang KS, Jun YJ, Jang SH, Min KW, et al. The glycolytic phenotype is correlated with aggressiveness and poor prognosis in invasive ductal carcinomas. J Breast Cancer. 2012;15(2):172-80. https://doi.org/10.4048/jbc.2012.15.2.172

ORIGINAL ARTICLE

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Revisiting type II diabetes mellitus in pregnancy and pregnancy outcomes such as in thyroidology: do you mind?

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SUMMARY

OBJECTIVE: There is an increase in the prevalence of pre-gestational diabetes in the past decades, mainly due to the increase in the prevalence of obesity in the general population and consequently type 2 diabetes among women of reproductive age.

METHODS: This study purposed to describe the delivery characteristics, pregnancy complications, and outcomes among women in Serbia with the pre-gestational type 2 diabetes in the past decade, as well as their pregnancy complications, deliveries, and neonatal outcomes. The study included data from all the pregnant women with pre-gestational type 2 diabetes in Belgrade, Serbia during the period between 2010 and 2020. The final sample consisted of 138 patients.

RESULTS: More than half, i.e., 70 (50.7%) had a vaginal delivery, while 48 (34.8%) had elective and 20 (14.5%) had emergency caesarean sections. Throughout the period, there was 1 patient with preeclampsia (0.7%), 5 with pregnancy-induced hypertension (3.6%), 7 had newborns with small for gestational age (5.1%), 28 with macrosomia (20.3%), 12 (8.7%) had preterm births, and one-fifth, i.e., 28 (20.3%) of the newborns had Apgar score under 8.

CONCLUSION: The present study revealed that women with type 2 diabetes in pregnancy have a significant burden of pregnancy complications, related to pregnancy, delivery, and newborns.

KEYWORDS: Diabetes mellitus. Diabetes mellitus, type 2. Pregnancy. Thyroid gland. Pregnancy outcome.

INTRODUCTION

Diabetes, *per se*, is the most common chronic illness affecting pregnant women. Approximately 85% of diabetic cases in pregnancy are gestational diabetes mellitus (GDM)[1]. There has been an increase in the prevalence of pre-gestational diabetes (pre-GDM) in the past decades, mainly due to the increase in the prevalence of obesity in the general population and consequently type 2 diabetes (T2DM) among women of reproductive age[2,3]. A study from the United Kingdom (UK) showed that the prevalence of T2DM in pregnancy increased by 354% in the period between 1995 and 2012, from 0.2% in 1995 to 1.06% in 2012[3]. According to the national UK data, T2DM in 2016 represented half of all cases of pre-GDM[4]. Of note, pregnancies with pre-GDM have a higher frequency of pregnancy complications compared to pregnancies with GDM. Another dimension important for the increase in the prevalence of pre-GDM is that if the diabetes is diagnosed in the first trimester or early in the second trimester, it is considered pre-GDM[5]. This increase also has a societal influence, as diabetes is associated with a decrease in quality of life[6].

Prevalence of pre-gestational diabetes (pre-GDM) is associated with a decrease in fertility[1], but there are more data on the type 1 diabetes mellitus (T1DM), though the same is presumed with T2DM due to the higher prevalence of obesity and polycystic ovarian syndrome among women with T2DM compared to the general population[1,6-9]. Pre-GDM is associated with maternal and neonatal morbidity and mortality[2]: higher likelihood of spontaneous abortions, caesarean deliveries, operative vaginal deliveries, lacerations, perinatal asphyxia, different congenital anomalies, and higher perinatal mortality or venous

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thromboembolism[3,5,10]. As such, the adverse pregnancy outcomes among women with pre-GDM are more frequent than among women with GDM[11,12]. Women with T2DM are at higher risk for adverse pregnancy outcomes compared to women with T1DM, with four times higher perinatal mortality[13] and generally poorer pregnancy outcomes[14]. Pregnancies with pre-gestational T2DM are commonly complicated by chronic hypertension, the main risk factor for preeclampsia that is reported in almost one in five pregnancies with pre-gestational T2DM[11]. Additionally, chronic hypertension is also a risk factor for uteroplacental insufficiency and stillbirth. There is also a higher rate of preterm births, small for gestational age (SGA) infants, large for gestational age (LGA) infants, hypoglycemia and cardiac anomalies in infants[2,11,15], respiratory distress syndrome, polycythemia, organomegaly, electrolyte disturbances, and hyperbilirubinemia[2].

The important issues for the obstetricians in charge of patients with T2DM during pregnancy are the timing and type of delivery. The factors influencing this decision include, but are not limited to, fetal size, the presence of medical comorbidities, and placental insufficiency[16]. T2DM in pregnancy, *per se*, is associated with uteroplacental malperfusion, which can be presented as placental infarction, vasculopathy in deciduas, and earlier maturation of villi[17]. The adequate timing and mode of delivery aim to reduce the rates of intrauterine death, which are higher among women with T2DM compared to women with other types of diabetes in pregnancy and healthy populations. Consequently, the most common timing for delivery of infants of mothers with T2DM is between 37+0 and 38+6 weeks, compared to the usually targeted timing of 40 weeks among women with GDM[16].

At present, there is growing evidence that many consider T2DM a benign condition, and it seems that there is a general lack of concern among patients[17]. The present study aimed to describe the delivery characteristics, pregnancy complications, and outcomes, including thyroidology, among women in Serbia with pre-gestational T2DM over the past decade, as well as their pregnancy complications, deliveries, and neonatal outcomes.

METHODS

Study design

The study included data from all the pregnant women with pre-gestational T2DM in Belgrade, Serbia, during the period between 2010 and 2020. The final sample consisted of 138 patients, and the study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade, Serbia (No. 1322/IX-80). The data for this study were routinely gathered for all the pregnant patients in the health care system in Belgrade. The data from the Birth database for Belgrade, City Institute of Public Health were the age, type of delivery, the presence of chronic hypertension, preeclampsia, pregnancy-induced hypertension (PIH), newborns' birth weight, newborns' birth length in centimeters, gestational age at delivery, and Apgar score.

To this end, the type of delivery was classified as vaginal (including spontaneous vaginal, forceps, and vacuum-assisted vaginal delivery), elective caesarean section, and emergency caesarean section. Based on the newborn's birth weight, newborns were classified as small for gestational age (SGA), adequate for gestational age (AGA), and large for gestational age (LGA). The pre-term birth was defined as birth before 37 weeks of gestation[18]. The ponderal index was calculated using the following formula:

[PI=birth weight×100/(birth height in centimeters)^3][19].

Statistical analyses

Statistical analyses were done using the methods of descriptive and analytical statistics. The numerical data were presented as means± standard deviations, and the categorical data were presented as relative numbers (percentages). The differences between the groups on numerical variables were examined using the Student's t-test and univariate variance analysis (ANOVA). The statistical analyses were done using Statistical Software for Social Sciences (SPSS) 22.0.

RESULTS

There were a total of 138 pregnant women with T2DM treated in any health care facility in Belgrade, Serbia, during the 11 years. The average age of the patients was 31.88±5.38 years. More than half, i.e., 70 (50.7%) had a vaginal delivery, 48 (34.8%) had elective caesarean sections, and 20 (14.5%) had emergency caesarean sections. There was 1 patient with preeclampsia (0.7%), 5 with pregnancy-induced hypertension (3.6%), 7 had newborns with SGA (5.1%), 28 with macrosomia (20.3%), 12 (8.7%) had preterm births, and one-fifth, i.e., 28 (20.3%) newborns had Apgar score under 8. The characteristics of the women included in the study are presented in Table 1.

There were significant differences in the average Apgar scores between the newborns of women with different types of delivery, women with and without preeclampsia, and women with a gestational age of under and over 37 weeks at delivery. There were significant differences between the women with preeclampsia and the women without preeclampsia in the average newborns' birth weight. The newborns' birth weight differed significantly between the women with gestational age at delivery of <37 weeks and >37 weeks. The differences in Apgar scores and newborns' birth weights between the patients with different medical and obstetric complications are presented in Table 2.

DISCUSSION

A posteriori, reproductive functions are affected by some conditions, such as T2DM, L-thyroxine (3,5,3′,5′-tetraiodothyronine, T4), and L-triiodothyronine (3,5,3′-triiodothyronine, T3), which are crucial for the normal reproductive function of human and animals *via* the ovarian, uterine, and placental tissues through specific nuclear receptors, modulating their development and metabolism in thyroidology[20-22].

The present study incorporated a total of 138 women with T2DM during the study period, comprising 2% of the total population of women with diabetes in pregnancy in Belgrade, Serbia. The average age of pregnant women with T2DM in Belgrade in our study was 31.9 years, similar to the age reported in the studies in the UK[3] and Denmark[13]. In addition, the prevalence of elective cesarean sections has increased in recent decades[23]. The data from 15 years in Scotland showed the prevalence of elective caesarean sections at 30.5%, which is similar to our results of 34.8%, but the prevalence of emergency caesarean sections in the present study was two times lower compared to the Scottish data, 14.5 vs. 29%, respectively[24]. The treatment and control of diabetes in pregnancy have been improved since the beginning of the data gathering in Scotland, and the differences in the prevalence of emergency caesarean sections can be explained by these improvements, as the start of our data collection was delayed for more than a decade[2,17,18].

Table 1. The characteristics of women in the study design.

Characteristics	n (%)
Age in years (X±SD)	31.88±5.38
Type of delivery	
Vaginal delivery	70 (50.7)
Elective caesarean section	48 (34.8)
Emergency caesarean section	20 (14.5)
Chronic hypertension	
Yes	14 (10.1)
No	124 (89.9)
Preeclampsia	
Yes	1 (0.7)
No	137 (99.3)
Pregnancy-induced hypertension	
Yes	5 (3.6)
No	133 (96.4)
Newborns' birth weight in grams (X±SD)	3423.01±596.27
Newborns' birth weight	
SGA	7 (5.1)
Normal weight	103 (74.6)
Macrosomia	28 (20.3)
Newborns' birth lenght in cms (X±SD)	51.11±2.95
Gestational age at delivery in weeks (X±SD)	38.53±1.78
Gestational age at delivery	
<37 weeks	12 (8.7)
≥37 weeks	126 (91.3)
Apgar score (X±SD)	8.71±0.88
Apgar score	
<8	28 (20.3)
≥8	110 (79.7)
Ponderal index (X±SD)	2.55±0.27

More than 1 in 10 pregnant women in our study reported pre-gestational chronic hypertension, and an additional 3.6% were diagnosed with PIH, which is more than three times lower prevalence of hypertension compared to the TODAY study[11] and similar to the prevalence of hypertension in the cohort of women in California[14]. The risk factors for preeclampsia among pregnant women with T2DM are less examined than the risk factors for preeclampsia among pregnant women with T1DM[16], as the risk for preeclampsia is higher among women with T1DM[19]. Preeclampsia is considered a significant complication associated with both maternal and fetal adverse pregnancy outcomes[16] and the frequency of preeclampsia among women with T2DM is just below 10%[19]. Only one case in the present study had preeclampsia, comprising less than 1% of the sample, but the differences between the studies can be explained by the sample size in our study, which may be insufficient in order of describing the actual prevalence of preeclampsia in this population. The low prevalence of preeclampsia in our study may also indicate improvements in glycemic and cardiovascular control among women with T2DM achieved in recent years[2].

One in five newborns in our study were LGA, similar to the study from California[14], and the prevalence was almost two times lower than that in the Scottish study, although the mean birth weight was almost identical in both studies[24].

The mean gestational age at delivery was above 38 weeks in the present study, which is in the range of the advised time for adequate delivery for women with T2DM for minimization of the risks for stillbirth, and the prevalence of preterm birth in our cohort was below 10%, significantly lower than previously reported for women with T2DM in pregnancy. This prevalence was significantly higher compared to the prevalence of preterm birth among all livebirths in neighboring Bosnia and Herzegovina. One-fifth of the newborns in our study had an Apgar score of less than 8, and the average score of 8.7 is likely previously reported. Finally, newborns of women with emergency caesarean sections had significantly lower Apgar scores compared to the newborns

Table 2. The differences in the Apgar scores and newborns' birth weight.

Characteristics	Apgar score (X±SD)	p	Newborns' birth weight (X±SD)	p
Type of delivery				
Vaginal delivery	8.81±0.80	**0.001**	3397.57±475.90	0.876
Elective caesarean section	8.85±0.46		3454.06±562.45	
Emergency caesarean section	8.00±1.45		3437.50±976.50	
Chronic hypertension				
No	8.69±0.92	0.330	3423.63±560.97	0.971
Yes	8.93±0.27		3417.50±877.14	
PIH				
No	8.71±0.89	0.777	3407.63±590.53	0.119
Yes	8.60±0.55		3832.00±672.40	
Preeclampsia				
No	8.74±0.79	**<0.001**	3437.77±572.57	**<0.001**
Yes	4.00		1400.00	
Gestational age at delivery				
<37 weeks	8.08±1.50	**0.009**	2769.17±858.21	**<0.001**
≥37 weeks	8.77±0.78		3485.28±529.06	

Bold indicates statistically significant p-values.

of women with vaginal and elective caesarean deliveries, as did preterm newborns compared to term newborns. One newborn born to a mother who developed preeclampsia had a significantly lower birth weight compared to the other newborns and a lower Apgar score, but this was the newborn born at 30 weeks of gestation, compared to the average of 38+3 weeks[14,16,24,25].

Limitations

This study has a few possible limitations. First of all, it possesses a descriptive study design. The differences between the examined groups are cross-sectional, and we could not establish a causal relationship. The number of women included in the study is low, which limits the possibility of the statistics. The aforementioned study encompasses the largest study on pregnancies with T2DM in the Serbian population, and the longitudinal design allowed us to describe the large cohort covering the entire decade. Unlike the majority of studies examining the characteristics of pregnant women with pre-GDM that obtain data from clinical settings, the data included in this study are obtained from a population-based registry and reflect the general population of pregnant women with T2DM.

CONCLUSION

This study revealed that women with T2DM in pregnancy have a significant burden of pregnancy complications related to pregnancy, delivery, and newborns. Herewith, we might recommend adequate follow-up and strict glycemic control, which must be enforced among these patients in order to minimize the risks for both mothers and their newborns. This issue merits further investigation.

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AUTHORS' CONTRIBUTIONS

JT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, and Writing—original draft. **SD:** Data curation, Investigation, Methodology, Project administration, Resources, Software, Validation, and Visualization. **DS:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, and Writing—review & editing. **DSt:** Investigation, Methodology, Project administration, Validation, and Visualization. **DAD:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, and Writing—review & editing. **IS:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization,

Writing—original draft, and Writing—review & editing. **ECAV:** Investigation, Methodology, Project administration, Validation, Visualization, and Writing—review & editing. **ZTS:** Project administration, Resources, Validation, and Visualization. **BD**: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, and Visualization. **MG**: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, and Visualization.

REFERENCES

1. Egan AM, Dunne FP. Epidemiology of gestational and pregestational diabetes mellitus. Front Diabetes. 2019;28:1-10. https://doi.org/10.1159/000480161
2. Caughey AB, Kaimal AJ, Gabbe SG. ACOG practice bulletin: pregestational diabetes. Am Coll Obstet Gynecol. 2018;132(60):228-48.
3. Coton SJ, Nazareth I, Petersen I. A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. BMJ Open. 2016;6(1):1-6. https://doi.org/10.1136/bmjopen-2015-009494
4. NHS Digital. National pregnancy in diabetes audit report 2016: England, Wales and the Isle of Man. 2016;(October):5678. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/national-pregnancy-in-diabetes-annual-report-2016
5. Yefet E, Jeda E, Tzur A, Nachum Z. Markers for undiagnosed type 2 diabetes mellitus during pregnancy—a population-based retrospective cohort study. J Diabetes. 2020;12(3):205-14. https://doi.org/10.1111/1753-0407.12985
6. Grujic-Vujmilovic D, Gavric Z. Quality of life of patients with diabetes mellitus: social domain of health. Sanamed. 2014;9(2):151-9.
7. Forslund M, Landin-Wilhelmsen K, Trimpou P, Schmidt J, Brännström M, Dahlgren E. Type 2 diabetes mellitus in women with polycystic ovary syndrome during a 24-year period: importance of obesity and abdominal fat distribution. Hum Reprod Open. 2020;2020(1):hoz042. https://doi.org/10.1093/hropen/hoz042.
8. Al-Rifai RH, Majeed M, Qambar MA, Ibrahim A, Alyammahi KM, Aziz F. Type 2 diabetes and pre-diabetes mellitus: a systematic review and meta-analysis of prevalence studies in women of childbearing age in the Middle East and North Africa, 2000-2018. Syst Rev. 2019;8(1):268. https://doi.org/10.1186/s13643-019-1187-1
9. Kakoly NS, Earnest A, Teede HJ, Moran LJ, Joham AE. The impact of obesity on the incidence of type 2 diabetes among women with polycystic ovary syndrome. Diabetes Care. 2019;42(4):560-7. https://doi.org/10.2337/dc18-1738
10. Isabey EP, Pylypjuk CL. The relationship between fetal abdominal wall thickness and intrapartum complications amongst mothers with pregestational type 2 diabetes. J Diabetes Res. 2021;2021:5544599. https://doi.org/10.1155/2021/5544599
11. TODAY study group. Pregnancy outcomes in young women with youth-onset type 2 diabetes followed in the TODAY study. Diabetes Care. 2022;45(5):1038-45. https://doi.org/10.2337/dc21-1071
12. Sugiyama T, Saito M, Nishigori H, Nagase S, Yaegashi N, Sagawa N, et al. Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes first diagnosed in pregnancy: a retrospective multi-institutional study in Japan. Diabetes Res Clin Pract. 2014;103(1):20-5. https://doi.org/10.1016/j.diabres.2013.10.020
13. Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care. 2005;28(2):323-8. https://doi.org/10.2337/diacare.28.2.323
14. Allen AJ, Snowden JM, Lau B, Cheng Y, Caughey AB. Type-2 diabetes mellitus: does prenatal care affect outcomes? J Matern Neonatal Med. 2018;31(1):93-7. https://doi.org/10.1080/14767058.2016.1276558
15. Pylypjuk C, Sellers E, Wicklow B. Perinatal outcomes in a longitudinal birth cohort of first nations mothers with pregestational type 2 diabetes and their offspring: the Next Generation Study. Can J Diabetes. 2021;45(1):27-32. https://doi.org/10.1016/j.jcjd.2020.05.001
16. Mukerji G, Bacon S, Feig DS. Gestational diabetes and type 2 diabetes during pregnancy. Maternal-fetal and neonatal endocrinology: physiology, pathophysiology, and clinical management. Elsevier Inc.; 2019. p. 371-388.
17. Kapustin RV, Kopteyeva EV, Tral TG, Tolibova GK. Placental morphology in different types of diabetes mellitus. J Obstet Women's Dis. 2021;70(2):13-26. https://doi.org/10.17816/JOWD57149
18. Cheung NW, McElduff A, Ross GP. Type 2 diabetes in pregnancy: a wolf in sheep's clothing. Aust New Zeal J Obstet Gynaecol. 2005;45(6):479-83. https://doi.org/10.1111/j.1479-828X.2005.00480.x
19. Gill SV, May-Benson TA, Teasdale A, Munsell EG. Birth and developmental correlates of birth weight in a sample of children with potential sensory processing disorder. BMC Pediatr. 2013;13(1):1. https://doi.org/10.1186/1471-2431-13-29
20. Fayyaz J. Ponderal index. J Pak Med Assoc. 2005;55(6):228-9. PMID: 16045088
21. Yeagle KP, O'brien JM, Curtin WM, Ural SH. Are gestational and type ii diabetes mellitus associated with the apgar scores of full-term neonates? Int J Womens Health. 2018;10:603-7. https://doi.org/10.2147/IJWH.S170090
22. Sahinturk H, Turhan CS, Selvi OC, Yilmaz AA, Uysalel A. Factors affecting anaesthesia preferences of the gravid women who are to deliver by caesarean section. Sanamed. 2019;14(1):13-20. https://doi.org/10.24125/sanamed.v14i1.271
23. Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, et al. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia. 2018;61(5):1081-8. https://doi.org/10.1007/s00125-017-4529-3
24. Persson M, Cnattingius S, Wikström AK, Johansson S. Maternal overweight and obesity and risk of pre-eclampsia in women with type 1 diabetes or type 2 diabetes. Diabetologia. 2016;59(10):2099-105. https://doi.org/10.1007/s00125-016-4035-z
25. Skokic F, Hotic N, Muratovic S, Skokic M, Hadzic D, Cosickic A, et al. Perinatal outcome of preterm infants in Federation of Bosnia and Herzegovina. Sanamed. 2015;10(1):15-22. https://doi.org/10.24125/sanamed.v10i1.12

ORIGINAL ARTICLE

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The effect of perceived social support levels on coping methods for urinary incontinence in elderly men

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SUMMARY

OBJECTIVE: This study aimed to determine the effect of the perceived social support level on coping methods for urinary incontinence among men aged 65 years and over with urinary incontinence.

METHODS: A total of 92 male patients over the age of 65 years with urinary incontinence and adequate cognitive levels were included in the study. The coping methods, the environmental support, and the Multidimensional Scale of Perceived Social Support were used to collect data.

RESULTS: The most common method of coping was changing clothes (64 [69.6%]). The Multidimensional Scale of Perceived Social Support total mean score was 55.83±14.8, which was considered above the medium-level support. The perception level of social support caused significant differences in coping methods in individuals with urinary incontinence.

CONCLUSION: The view that urinary incontinence is a problem related to aging is regarded as an obstacle to seeking healthcare. Society should be made aware that urinary incontinence is not a normal condition related to aging and that it is not an insoluble problem that the elderly must endure.

KEYWORDS: Social support. Men. Urinary incontinence.

INTRODUCTION

Aging causes changes in many organs and bodily systems, and it can affect the functioning of those systems[1]. The management of diseases such as diabetes[2,3], hypertension[4], and cancer[5,6] is more difficult in elderly patients. Urinary incontinence (UI) is a difficult condition to accept, often hidden by those who experience it, and is referred to as a "silent epidemic"[7]. The risk of UI steadily increases with increasing age and decreasing physical and mental performance. The worldwide prevalence of UI varies between 20 and 68%[8]. Prior to the age of 80 years, UI is 1.3–2 times more common in women than in men; after the age of 80 years, its prevalence is similar among both genders.

UI causes psychosocial problems, such as the fear of smelling bad, anxiety, feelings of dirtiness, unhappiness, stigma, deterioration in body image, and depression[9]. Individuals, especially the elderly, rarely report UI, as it is considered a natural consequence of aging. Additional negative consequences, such as anxiety, depression, decreased sexual life, decreased physical activity, poorer quality of life, social isolation, and the loss of self-confidence, can affect those who hide their UI[10].

Social support is defined as the emotional, financial, and information support that an individual receives from their environment. Perceived social support is an individual's overall impression of the support they receive from their social environment. Although the importance of environmental support for health-seeking behavior and health promotion is known, to the best of our knowledge, there are no studies in the literature examining the levels of environmental support and perceived social support among individuals with UI. This study aimed to determine the effect of the perceived social support level on coping methods for UI among men aged 65 years and over with UI.

METHODS

This cross-sectional study was conducted in the Urology Outpatient Clinic of Necmettin Erbakan University Meram Medical Faculty Hospital between December 2021 and May 2022. Ninety-two male patients over the age of 65 years with UI and adequate cognitive levels were included in the study. Patients with impermanent UI, active infection, impaired cognitive function, or malignancy were not included in the study.

A personal information form and the Multidimensional Scale of Perceived Social Support (MSPSS) were used to collect data. The personal information form consisted of 28 structured questions to determine the state of being affected by incontinence,

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the support received from the environment, the expectation from the environment, coping methods, and sociodemographic characteristics. Ten of these questions examined introductory features, and 18 gathered information about UI.

The MSPSS, developed by Zimet et al.[11], consists of 12 items. Each item is answered using a 7-point Likert-type scale that ranges from 1 ("Very Strongly Disagree") to 7 ("Very Strongly Agree"). The scale consists of 3 subdimensions, namely, friend, family, and special person support, that examine an individual's support system. Each subdimension includes 4 items. The score for each subdimension ranges from 4 to 28, while the score for the entire scale ranges from 12 to 84. Higher scores indicate higher levels of perceived social support. Eker et al.[12] examined the scale's validity and reliability in Turkey. The scale's internal consistency and reliability were found to be high, with Cronbach's alpha coefficient between 0.80 and 0.95. In our study, the results of the scale were found to be very good for factor analysis (Kaiser-Meyer-Olkin value: 0.84; Bartlett test: chi-square=1284.5, df=66, p<0.001), and a three-factor structure was detected in the factor analysis of the scale. Our study is similar to the original scale. These three factors explained 87% of the total variance of the MSPSS. Ethics committee approval was obtained from the Ethics Committee for our study (approval no. 2022/002).

Statistical analysis

The SPSS software (21.0 version) was used to analyze the data. The participants' characteristics were given as percentages and frequencies. Skewness and kurtosis were used to test the normality of the scale scores. The comparison of homogeneously distributed parameters was performed with an independent sample t-test and analysis of variance. The Games-Howell *post hoc* analysis was used to evaluate the subgroups. The significance level was set at p<0.05.

RESULTS

The participants' median age was 69 (65–83) years, and the median duration of UI was 3 (0.5–10) years. The sociodemographic characteristics are presented in Table 1. Notably, 54 (58.7%) participants indicated that their UI was due to old age, 26 (28.3%) indicated that it was due to benign prostate gland enlargement, and 5 (5.4%) indicated that it was due to both. Seven (7.6%) subjects did not know the cause of their UI (Table 1).

With respect to the impact of UI on daily life, it most frequently affected the participants' daily activities (57% [62%]) and least frequently affected their work lives (5 [5.4%]). The additional affected daily activities and their frequencies were as follows: sleeping (50 [54.3%]), going out (34 [37%]), worshiping (33 [35.9%]), traveling (11 [12%]), and visiting friends (5 [5.4%]). Of note, 69 (75%) participants shared their UI status with other people, while 23 (25%) did not disclose this information to anyone. Individuals most commonly shared this information with their spouses (29 [42%]) and least commonly shared it with their caregivers (2 [2.9%]). The most common method of coping was changing clothes (64 [69.6%]). It was determined that the use of special panties was never preferred

Table 1. Demographic characteristics of patients with urinary incontinence (UI) in the study (n=92).

Features	Groups	n	%
Marital status	Single	32	34.8
	Married	60	65.2
Working status	No	80	87
	Yes	12	13
Income level status	Income less than expenses	21	22.8
	Income equals expense	49	53.3
	Income more than expenses	22	23.9
Living place	City	46	50
	Districts	25	27.2
	Village	21	22.8
Health insurance	No	11	12
	Yes	81	88
Family type	Elementary family	72	78.3
	Extended family	20	21.7
Live with at home	Alone	25	27.2
	Spouse	44	48.8
	Spouse and child	23	25
The status of UI causing problems in daily life	Sometimes	53	57.6
	Most of the time	32	34.8
	Always	7	7.6
Frequency of UI	Once a day	10	10.9
	Several times a day	19	20.7
	Once a week or less	26	28.3
	Two/three times a week	29	31.5
	Always	8	8.7
Reasons for UI	Aging	54	58.7
	Prostate hypertrophy	26	28.3
	Unknowing	7	7.6
	Aging and prostate hypertrophy	5	5.4

as a coping method. The frequency of other coping methods was given as follows: going to the doctor, 58 (63%); using medications, 46 (50%); trying to drink less water, 46 (50%); going to the toilet more often, 46 (50%); using a pad/cloth/napkin, 23 (25%); foot keeping warm, 37 (40.2%); and exercising, 2 (2.2%).

The total mean score of the respondents on the MSPSS was 55.83±14.8. The lowest score was 16, whereas the highest score was 82. These findings suggest that the perception of individuals with UI regarding social support was above the medium level. Social support from family and special person was considered high, but that from friends was of a moderate level. With respect to the perception of family support, the scores of UI patients who applied fluid intake were significantly higher than those who did not adopt this coping method (p=0.04) (Table 2). In terms of the perception of support from friends, however, the scores of these individuals were significantly lower than those who did not use fluid intake-related coping method (p=0.001) (Table 2). The total MSPSS score and the subdimension scores of patients who rarely changed clothes as a coping method were significantly higher than those who used this method (p>0.05, for all) (Table 2). The total MSPSS score and the special person support scores among patients who visited their doctors were significantly higher than those who did not consult physicians (p=0.029 and p=0.027, respectively). No difference was found among the patients in terms of their total MSPSS score and subdimension scores on drug use as a coping method (p>0.05) (Table 2).

The total MSPSS score, family support scores, and special person support scores of married patients were significantly higher than those of single patients (p>0.05) (Table 2). No significant difference was found between these individuals in terms of scores on the perception of friend support and marital status (p=0.097). The same absence of significant differences was identified with regard to the scores on support from family, friends, and special individuals and the total support scores of

Table 2. Comparison of the Multidimensional Scale of Perceived Social Support and subdimensions scores with coping methods.

Coping methods		Multidimensional Scale of Perceived Social Support (Mean±SD)			
		Family support	Friend support	Special person support	Total support
Trying to drink less fluids	Yes	22.1±4.8	14.4±5.8	18±5.3	54.7±10.7
	No	19.5±6.9	18.5±5.9	18.8±6.7	56.9±18
	t/p*	**-2.085/0.04**	**3.325/0.001**	0.601/0.55	0.723/0.47
Going to the toilet more often	Yes	20.5±6.7	15.8±7	18.3±6.8	54.7±17.2
	No	21.2±5.4	17±5.2	16.6±5.2	56.9±12
	t/p*	0.544/0.58	0.939/0.35	0.257/0.79	0.723/0.47
Using pad/cloth/napkin	Yes	22.5±4.6	17±7.2	19.8±5.2	59.4±12.4
	No	20.3±6.4	16.3±5.8	18±6.2	54.6±15.4
	t/p*	-1.798/0.07	-0.463/0.6	-1.287/0.2	-1.352/0.18
Frequent laundry changes	Yes	20±6.6	15.5±6.1	17.4±5.9	53±15.1
	No	22.8±4	18.5±5.9	20.8±5.8	62.3±11.9
	t/p*	**2.543/0.013**	**2.182/0.032**	**2.581/0.011**	**2.888/0.005**
Keep feet warm	Yes	21.5±6.1	16.4±5.4	17.8±6.1	55.8±13.4
	No	20.4±6.1	16.5±6.7	18.8±6	55.8±15.7
	t/p*	-0.835/0.4	0.058/0.95	0.746/0.45	-0.015/0.98
Medication	Yes	21.2±6.2	17.1±6.3	19.4±6.1	57.8±16
	No	20.55±6	15.7±6	17.5±5.8	53.8±13.3
	t/p*	-0.510/0.61	-1.109/0.27	-1.509/0.13	-1.293/0.19
Visit the doctor	Yes	21.2±5.9	17.2±6.1	19.3±6.1	57.9±15.5
	No	20.2±6.3	15.1±6.1	16.9±5.6	52.2±12.8
	t/p*	**-0.822/0.46**	**-1.623/0.11**	**-1.877/0.027**	**-1.793/ 0.029**

*Independent sample t-test. Bold values indicate statistical significance.

nuclear and extended families (p>0.05 for all) (Table 3). Similar scale scores were derived by working and nonworking groups (Table 3). The friend support scores of patients with comorbidities were significantly lower than those without comorbidities (p=0.02). However, no difference was found among the comorbidity and family support scores, special person support scores, and total support scores (p>0.05 for all, Table 3).

DISCUSSION

In this study, it was found that the participants shared their UI most frequently with their spouses, they used the change of clothes most frequently as their coping method, and they exhibited a moderate perception of social support. In addition, it was observed that this level of perception of social support gave rise to significant differences in coping methods.

In a previous study, 45.5% of the participating women and 52.8% of the participating men reported that they first shared their UI problem with their spouses, families, or friends/neighbors[7]. Of the elderly participants, 43.7% shared their UI issues with their relatives[13]. In another study, 59% of UI patients talked to the people around them, mostly relatives, but only 23.2% consulted a professional. In this study, individuals mostly shared their UI with their close relatives. The evaluation of UI frequency showed that 10% of the participants experienced this condition once a week, 23.3% had it two to three times a week, 30% experienced it once a day, and 36.6% encountered it more than once a day[14]. Other researchers reported a

Table 3. Comparison between Multidimensional Scale of Perceived Social Support and subdimensions scores and marital status, family type, comorbidity status, and working status.

Subdimension scores	Marital status		
	Married (n=60) Mean±SD	Single (n=32) Mean±SD	p-value*
Family support	23±5.19	16.9±5.78	**<0.001**
Friend support	17.16±6.54	15.18±5.38	0.097
Special person support	19.65±6.53	16.25±6.54	**0.004**
Total	69.81±14.94	48.37±11.42	**<0.001**
Subdimension scores	**Family type**		
	Elementary (n=72) Mean±SD	Extended (n=20) Mean±SD	p-value*
Family support	20.2±6.3	23.2±4.5	0.056
Friend support	16.3±6.4	16.8±5.3	0.76
Special person support	18±6.2	20±5.3	0.2
Total	54.6±15.4	60±11.3	0.15
Subdimension scores	**Comorbidity status**		
	No (n=24) Mean±SD	Yes (n=68) Mean±SD	p-value*
Family support	21.5±5.6	20.6±6.2	0.57
Friend support	19±6.8	15.5±5.7	**0.02**
Special person support	19.2±7.1	18.1±5.6	0.44
Total	59.7±16.2	54.4±14.1	0.12
Subdimension scores	**Working status**		
	No (n=80) Mean±SD	Yes (n=12) Mean±SD	p-value*
Family support	20.9±5.9	20.8±7.6	0.97
Friend support	16.1±6.1	18.7±6.4	0.17
Special person support	18.1±5.9	20.4±6.3	0.23
Total	55.2±14	60±19.5	0.29

*Independent sample t-test. Bold values indicate statistical significance.

UI frequency of one or more times a day (72.6%)[15]. In our study, for the most part, the respondents experienced UI only occasionally. UI frequency differs depending on the target population and ethnicity, as well as study design[16]. As individuals with UI typically prefer to conceal their problems, the results of face-to-face studies and confidential surveys may vary[17,18]. The findings of this research, whose data were collected face to face, are compatible with the literature. Shaw et al.[18] indicated that 68.6% of individuals with UI believe that the condition is a normal consequence of aging. Regardless of the type of society, UI due to old age is perceived as a natural result of physical regression and loss of power.

The literature indicated that the level of perception of social support among married individuals is higher than that among their single counterparts[19,20]. It has been reported that there is no significant difference in the perception of social support between individuals with and without comorbidities[20]. Individuals with UI prefer to share their problems with their spouses because they are ashamed of this condition. In our study, the feeling of shame was predicted to be effective. The results correspond with the literature. Nevertheless, considering that individuals with chronic diseases may have minimal socialization, in addition to grappling with UI, low perceptions of social support can be expected. This possibility highlights the importance of family support.

No studies have been devoted to perceptions of social support among elderly male individuals with UI. As perceived social support levels decrease, the severity of internalized stigma increases[21]. Studies have indicated that a high perception of social support exerts a positive effect on individuals' adaptation to and recovery from the disease[21,22]. Social support also has a favorable influence on coping[21]. The findings of this research on the patient group exhibiting a moderate perception of social support and using positive coping methods, such as doctor consultations, support the literature.

CONCLUSION

The view that UI is a problem related to aging is regarded as an obstacle to seeking healthcare. Society should be made aware that UI is not a normal condition related to aging and that it is not an insoluble problem that the elderly must endure.

AUTHORS' CONTRIBUTIONS

ZK: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Validation, Writing – Original Draft. **BB:** Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. **IG:** Data Curation, Formal Analysis, Resources, Software, Supervision, Validation, Visualization, Writing – Review & Editing. **HHT:** Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – Review & Editing.

REFERENCES

1. Blokzijl F, Ligt J, Jager M, Sasselli V, Roerink S, Sasaki N, et al. Tissue-specific mutation accumulation in human adult stem cells during life. Nature. 2016;538(7624):260-64. https://doi.org/10.1038/nature19768
2. Kocak MZ, Aktas G, Duman TT, Atak BM, Bilgin S, Kurtkulagi O, et al. Type 2 diabetes mellitus is more commonly well controlled in younger men compared to older men. Aging Male. 2020;23(5):906-10. https://doi.org/10.1080/13685538.2019.1621833
3. Alaca B, Kocak MZ, Gürler M. Clinical significance and prevalence of frailty syndrome in type 2 diabetes patients. Osmangazi Med J. 2022;44(2):169-76. https://doi.org/10.20515/otd.986794
4. Atik F, Aktas G, Kocak MZ, Erkus E, Savli H. Analysis of the factors related to the blood pressure control in hypertension. J Coll Physicians Surg Pak. 2018;28(6):423-6. https://doi.org/10.29271/jcpsp.2018.06.423
5. Kocak MZ. Comment on "frailty screening by geriatric-8 and 4-meter gait speed test is feasible and predicts postoperative complications in elderly colorectal cancer patients". J Geriatr Oncol. 2021;12(4):685. https://doi.org/10.1016/j.jgo.2021.02.017
6. Kocak MZ. Letter to the editor regarding the article 'frailty and skeletal muscle in older adults with cancer'. J Geriatr Oncol. 2020;11(6):1041. https://doi.org/10.1016/j.jgo.2020.02.009
7. Bilgic D, Kizilkaya Beji N, Ozbas A, Çavdar İ, Aslan E, Yalcin O. Coping and help-seeking behaviors for management of urinary incontinence. Low Urin Tract Symptoms. 2017;9(3):134-41. https://doi.org/10.1111/luts.12120
8. Seshan V. Coping strategies & self measures adopted by the women with urinary incontinence & its effects on QOL. Obstet Gynecol Int J. 2016;5:00187. https://doi.org/10.15406/ogij.2016.05.00187
9. Schluter PJ, Ward C, Arnold EP, Scrase R, Jamieson HA. Urinary incontinence, but not fecal incontinence, is a risk factor for admission to aged residential care of older persons in New Zealand. Neurourol Urodyn. 2017;36(6):1588-95. https://doi.org/10.1002/nau.23160
10. Pizzol D, Demurtas J, Celotto S, Maggi S, Smith L, Angiolelli G, et al. Urinary incontinence and quality of life: a systematic review and meta-analysis. Aging Clin and Exper Res. 2021;33(1):25-35. https://doi.org/10.1007/s40520-020-01712-y
11. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess. 1988;52:30-41. https://doi.org/10.1207/s15327752jpa5201_2

12. Eker D, Arkar H. Factor structure, validity and reliability of multidimensional perceived social support scale. Turk J Psychol.1995;10:45-55.
13. Bulga M, Avcı İA. Awareness of urinary incontinence in elderly patients and affecting factors and methods of coping with urinary incontinence. J Nursol. 25:1-6. https://doi.org/10.54614/JANHS.2022.729980
14. Jafarizadeh H, Maghsoudi Z, Namadi F, Mohammadpour Y, Moradi Y. The effect of pelvic floor muscles training, bladder exercises and lifestyle modification on urinary incontinence in elderly men. J Nephropathol. 2022;11(1):e8. https://doi.org/10.34172/jnp.2022.08
15. El Gayar N, Ahmed S, Abou-Raya S, Mohamed A, Mahmoud H. Prevalence, impact and correlates of treatment-seeking for urinary incontinence in elderly patients attending main university hospital of Alexandria, Egypt. NILES J Geriatr Gerontol. 2022;5(1):150-76. https://doi.org/10.21608/niles.2022.211777
16. Murukesu RR, Singh DK, Shahar S. Urinary incontinence among urban and rural community dwelling older women: prevalence, risk factors and quality of life. BMC Public Health. 2019;19(Suppl 4):529. https://doi.org/10.1186/s12889-019-6870-6
17. Veronese N, Smith L, Pizzol D, Soysal P, Maggi S, Ilie P-C, et al. Urinary incontinence and quality of life: a longitudinal analysis from the english longitudinal study of ageing. Maturitas. 2022;160:11-15. https://doi.org/10.1016/j.maturitas.2022.01.010
18. Shaw C, Rajabali S, Tannenbaum C, Wagg A. Is the belief that urinary incontinence is normal for ageing related to older canadian women's experience of urinary incontinence? Inter Urogynecol J. 2019;30(12):2157-60. https://doi.org/10.1007/s00192-019-03906-z
19. Ozvurmaz S. Relationship between the loneliness levels of elderly individuals and their perceptions of social support. Adnan Menderes University Faculty of Health Sciences Journal. 2018;2:118-25.
20. Yanik A, Saglam Y. Evaluation of life satisfaction and social support perception of elderly individuals. J Health Scien Profes. 2019;6(3):501-12.
21. Chen L, Alston M, Guo W. The influence of social support on loneliness and depression among older elderly people in China: coping styles as mediators. J Com Psychol. 2019;47(5):1235-45. https://doi.org/10.1002/jcop.22185
22. Szymona-Pałkowska K, Janowski K, Pedrycz A, Mucha D, Ambroży T, Siermontowski P, et al. Knowledge of the disease, perceived social support, and cognitive appraisals in women with urinary incontinence. BioMed Res Int. 2016;2016:3694792. https://doi.org/10.1155/2016/3694792

ORIGINAL ARTICLE

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A propensity score-matched retrospective cohort study of hysterectomies for benign disease during the COVID-19 pandemic

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SUMMARY

OBJECTIVE: This study aimed to evaluate how the pandemic might have affected the number of elective and urgent hysterectomies for benign gynecological pathologies in a single-care tertiary center in the State of São Paulo, Brazil, and to identify if there were any changes in the need for blood transfusions.

METHODS: This is a single-center retrospective cohort study. It involved all non-puerperal and non-oncological hysterectomies from October 2018 to July 2021. Patients were divided into two groups, namely, the pandemic group (46 patients) and the control group (92 patients). Data were collected by reviewing the physical and electronic patient records. We carried out the statistical analysis using the RStudio software.

RESULTS: The number of planned hysterectomies was 82 in the pre-pandemic group and 23 in the analysis group, representing a 71.9% decrease. When considering only urgent surgeries, 10 of them happened in the pre-pandemic group, while 23 occurred in the pandemic group, representing an increase of 130%.

CONCLUSION: Elective hysterectomies may improve the quality of life of women, reducing abnormal bleeding and pelvic pain. Treatment delay can worsen patients' physiological and biological conditions, such as lower labor production, humor, and social aspects, increasing costs to the healthcare system.

KEYWORDS: COVID-19. Hysterectomy. Pandemics. Gynecologic surgical procedures.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic started on May 2019 in the city of Wuhan, Hubei Province, China[1]. In Brazil, the first case was reported in March 2020 in the city of São Paulo[2]. Governments, fearing a collapse of health systems, started social distancing policies. Healthcare facilities had to postpone outpatient appointments and elective surgeries in order to prioritize resources to treat patients with acute respiratory syndrome (ACR) caused by the novel coronavirus (SARS-CoV-2)[3-7].

Among the postponed surgeries, hysterectomies are included. This procedure is widely used to treat several gynecological diseases, most coursing with abnormal uterine bleeding, and may be performed by different access points, such as vaginal, laparotomy, or laparoscopy[7,8].

The number of deaths and people directly affected by the COVID-19 pandemic worldwide has been widely investigated. However, the full burden of the outbreak remains unknown, especially regarding changes in the treatment of other diseases[9,10].

The goal of this study was to evaluate how the pandemic might have affected the number of elective and urgent hysterectomies for benign gynecological pathologies in a single-care tertiary center in the State of São Paulo, Brazil, and to identify if there were any changes in the need for blood transfusions.

METHODS

We performed a single-center retrospective cohort study. We included all non-puerperal hysterectomies performed from October 2018 up to July 2021. From March 2020 to July 2021, our Outpatient Clinic of Gynecology was closed as a restrictive measure due to the COVID-19 pandemic. Therefore, patients who needed immediate medical care had to seek our emergency department. Thus, we divided patients into two groups: the pre-pandemic group contains patients who underwent hysterectomy from October 2018 to February 2020 and the pandemic group represents patients who had their surgeries performed from March 2020 to July 2021. Thus, both groups spanned

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a period of 17 months. Exclusion criteria were patients with planned oncological hysterectomies and missing data.

Our main hypothesis is that patients having surgery during the pandemic period had different pre-surgical hemoglobin levels and required different amounts of blood transfusions when compared to patients in the control group. Furthermore, we also analyzed the proportion of elective and urgent surgeries during each period.

Data were collected by reviewing physical and electronic patient records. All data were collected by one of the researchers, and it was checked for inconsistencies by two other different researchers. In case of inconsistencies, patient records were reviewed again.

For each patient, we recorded information regarding ethnicity, education level, marital status, type of surgery (elective or urgent), surgical operative time in hours, hemoglobin level before surgery, and volume of blood transfusion before, during, and after the surgery, if any. Blood transfusion was included when occurring 30 days before or after the surgery.

Since there were more patients in the group whose surgery happened before the pandemic, we used propensity score matching with a ratio of 2 controls per 1 case to compare both groups. Equal variables for matching were ethnicity, marital status, educational level, type of surgery, and surgery length[11]. Nominal variables were adjusted for this method. The race was adjusted to a binary variable, as either white or non-white ethnicity, since the majority of patients belonged to this group. Marital status was also converted into a binary variable, either in a relationship with a partner or without a relationship. Education was maintained as an ordinal variable with seven degrees, namely, no education, incomplete primary grade, complete primary grade, incomplete high school education, complete high school education, incomplete college education, or complete college education. We used a linear regression model to test the correlation between the amount of blood transfusion required and the aforementioned variables. The same procedure was carried out for pre-surgical hemoglobin levels and the study variables. This process was repeated for an exploratory subgroup analysis among all urgent surgery patients in the study. Finally, the number of planned and urgent surgeries in both groups of the total cohort was compared with the exact Poisson test, with the period of 17 months being equal in both groups. We carried out the statistical analysis using the RStudio version 4.1.1 software (dated 2021-08-10).

This research follows the STROBE guideline. The study began after ethical approval by the local research ethics committee (CAAE 51821921.8.0000.5413). We followed the Declaration of Helsinki.

RESULTS

Initially, we included 262 patients. Following exclusion criteria, we removed 81 patients who were planned oncological surgeries. One patient was excluded due to missing data. Of the 180 patients included, 46 patients underwent surgeries during the pandemic, which were matched to 92 controls, for a total of 138 patients analyzed in this research.

The number of planned hysterectomies was 82 in the pre-pandemic group and 23 in the analysis group, representing a 71.9% decrease. The exact Poisson test is statistically significant in this analysis, with a p-value <0.01. When considering only urgent surgeries, 10 happened in the pre-pandemic group, while 23 occurred in the pandemic group, representing an increase of 130%. The Poisson exact test for the number of urgent surgeries demonstrated a higher-than-expected value during the outbreak, and the p-value was 0.03.

Linear regression models applied to the matched cohort identified a statistically significant association between the amount of blood transfusion and both surgery type (p<0.01) and surgery length (p<0.01). Pre-surgical hemoglobin values in the linear regression model were correlated exclusively to surgery type (p<0.01). In both cases, surgery before or during the COVID-19 pandemic as an individual variable was not associated with the amount of blood transfusion required or pre-surgical hemoglobin. This group is presented in Table 1.

Analysis continued in the urgency hysterectomy group, which had a total of 33 patients. In the linear regression model, no variable was found to be associated with either the amount of blood transfusion required or the pre-surgical hemoglobin levels. Characteristics of this subgroup are summarized in Table 2.

DISCUSSION

There was a reduction in the number of surgeries performed during the pandemic period. This finding is probably related to health policies to prioritize resources to deal with the pandemic, such as operating rooms, individual protection equipment, and medications. On the contrary, an increase in urgent surgeries was found, as well as a positive association between urgent surgeries and lower pre-surgical hemoglobin values and the amount of blood transfusion required. Moreover, there was a delay in outpatient clinic appointments and elective surgeries to avoid a collapse of the healthcare system[12-16].

Our findings are similar to a study that evaluated the total number of gynecological procedures performed in 2019 and 2020, due to benign and malign pathologies, in a large teaching hospital system. In that study, a reduction of 75% in the number of surgeries performed was found as a consequence of

the delay of elective surgeries[3]. Another study evaluated hospital admission in 18 teaching hospitals in Germany, and comparing 2018 to 2020, hysterectomies due to benign conditions suffered a reduction of 78.8%[4].

Although we observed a reduction in hysterectomies, we also found an increase of 130% in the number of urgent hysterectomies during the pandemic. Moreover, urgent surgeries were associated with the necessity of blood transfusion and lower pre-surgical hemoglobin values. Therefore, it is possible that the delay in appointments and surgeries worsened the gynecological condition that demanded a hysterectomy[17].

It is important to note that if, on the one hand, the delay of appointments and surgeries probably helped dealing with the pandemic, on the other hand, other conditions were neglected. The increase in the need for blood transfusions, in a scenario of a global decrease in blood donations, shows us that health policies must consider several variables[18,19].

As the strengths of this study, we point out that we collected data from a large number of uniform patient electronic records. As limitations, our findings represent the reality of the region assisted by our service and may not represent what was observed in our state or country.

CONCLUSION

Elective hysterectomies may improve the quality of life of women, reducing abnormal bleeding and pelvic pain. Treatment delay can worsen patients' physiological and biological conditions, such as lower labor production, humor, and social aspects, increasing costs to the healthcare system[3,4,20].

Table 1. Characteristics of a cohort of patients submitted to hysterectomy before and during the COVID-19 pandemic.

	Pandemic (n=46)	Pre-pandemic (n=92)	Overall (n=138)
Ethnicity			
Non-white	15 (32.6%)	22 (23.9%)	37 (26.8%)
White	31 (67.4%)	70 (76.1%)	101 (73.2%)
Marital status			
No relationship with partner	16 (34.8%)	29 (31.5%)	45 (32.6%)
Relationship with partner	30 (65.2%)	63 (68.5%)	93 (67.4%)
Education level			
No education	0 (0%)	2 (2.2%)	2 (1.4%)
Incomplete primary grade	20 (43.5%)	42 (45.7%)	62 (44.9%)
Complete primary grade	12 (26.1%)	14 (15.2%)	26 (18.8%)
Incomplete high school	1 (2.2%)	5 (5.4%)	6 (4.3%)
Complete high school	9 (19.6%)	20 (21.7%)	29 (21.0%)
Incomplete college education	1 (2.2%)	2 (2.2%)	3 (2.2%)
Complete college education	3 (6.5%)	7 (7.6%)	10 (7.2%)
Surgery length			
Mean (SD)	3.03 (0.883)	2.85 (1.04)	2.91 (0.989)
Median [min, max]	2.75 [1.67, 5.50]	2.75 [1.00, 6.58]	2.75 [1.00, 6.58]
Surgery type			
Planned	23 (50.0%)	82 (89.1%)	105 (76.1%)
Urgent	23 (50.0%)	10 (10.9%)	33 (23.9%)
Pre-surgical hemoglobin			
Mean (SD)	10.8 (3.15)	12.8 (2.29)	12.2 (2.78)
Median [min, max]	11.2 [4.90, 16.5]	13.2 [5.90, 23.7]	12.6 [4.90, 23.7]
Blood bags used			
Mean (SD)	1.39 (2.21)	0.348 (1.35)	0.696 (1.75)
Median [min, max]	0 [0, 9.00]	0 [0, 10.0]	0 [0, 10.0]

Table 2. Characteristics of a subgroup of patients submitted to urgent hysterectomy before and during the COVID-19 pandemic.

	Pandemic (n=23)	Pre-pandemic (n=10)	Overall (n=33)
Ethnicity			
Non-white	7 (30.4%)	4 (40.0%)	11 (33.3%)
White	16 (69.6%)	6 (60.0%)	22 (66.7%)
Marital status			
No relationship with partner	9 (39.1%)	2 (20.0%)	11 (33.3%)
Relationship with partner	14 (60.9%)	8 (80.0%)	22 (66.7%)
Education level			
No education	0 (0%)	2 (20.0%)	2 (6.1%)
Incomplete primary grade	11 (47.8%)	4 (40.0%)	15 (45.5%)
Complete primary grade	5 (21.7%)	1 (10.0%)	6 (18.2%)
Incomplete high school	0 (0%)	0 (0%)	0 (0%)
Complete high school	5 (21.7%)	3 (30.0%)	8 (24.2%)
Incomplete college education	1 (4.3%)	0 (0%)	1 (3.0%)
Complete college education	1 (4.3%)	0 (0%)	1 (3.0%)
Surgery length			
Mean (SD)	3.02 (0.844)	3.88 (1.30)	3.28 (1.06)
Median [min, max]	2.75 [2.25, 5.50]	3.54 [2.50, 6.17]	2.83 [2.25, 6.17]
Pre-surgical hemoglobin			
Mean (SD)	8.73 (2.64)	10.4 (3.05)	9.24 (2.83)
Median [min, max]	8.40 [4.90, 14.2]	11.6 [5.90, 14.1]	8.90 [4.90, 14.2]
Blood bags used			
Mean (SD)	2.57 (2.59)	2.60 (3.31)	2.58 (2.77)
Median [min, max]	2.00 [0, 9.00]	1.50 [0, 10.0]	2.00 [0, 10.0]

AUTHORS' CONTRIBUTIONS

IBL: Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **NJWMJ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project admnistration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **VCM:** Data curation, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **LBBGM:** Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **FJCR:** Methodology, Writing – original draft, Writing – review & editing.

REFERENCES

1. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-6. https://doi.org/10.1016/j.ijsu.2020.02.034
2. Oliveira RDP, Santos MCL, Moreira CB, Fernandes AFC. Detection of breast cancer: knowledge, attitude, and practice of family health strategy women. J Canc Educ. 2018;33(5):1082-7. https://doi.org/10.1007/s13187-017-1209-4
3. Gupta S, Maghsoudlou P, Ajao M, Ivar Einarsson J, Perkins King L. Analysis of COVID-19 response and impact on gynecologic surgery at a large academic hospital system. JSLS. 2021;25(4):e2021.00056. https://doi.org/10.4293/JSLS.2021.00056
4. Kapsner LA, Kampf MO, Seuchter SA, Gruendner J, Gulden C, Mate S, et al. Reduced rate of inpatient hospital admissions in 18 German university hospitals during the COVID-19 lockdown. Front Public Health. 2021;8:594117. https://doi.org/10.3389/fpubh.2020.594117

5. Shehata IM, Elhassan A, Jung JW, Urits I, Viswanath O, Kaye AD. Elective cardiac surgery during the COVID-19 pandemic: proceed or postpone? Best Pract Res Clin Anaesthesiol. 2020;34(3):643-50. https://doi.org/10.1016/j.bpa.2020.07.005
6. Gilat R, Haunschild ED, Tauro T, Cole BJ. Recommendations to Optimize the Safety of Elective Surgical Care While Limiting the Spread of COVID-19: Primum Non Nocere. Arthrosc Sports Med Rehabil. 2020;2(3):e177–83. https://doi.org/10.1016/j.asmr.2020.04.008
7. Chrysostomou A, Chrysostomou M. COVID-19 pandemic: which hysterectomy? 2020;2(1):4.
8. Kaye K, Paprottka F, Escudero R, Casabona G, Montes J, Fakin R, et al. Elective, Non-urgent procedures and aesthetic surgery in the wake of SARS-COVID-19: considerations regarding safety, feasibility and impact on clinical management. Aesthetic Plast Surg. 2020;44(3):1014-42.https://doi.org/10.1007/s00266-020-01752-9
9. Leandro PHF. Escola de Saúde Pública Do Ceará Hospital Geral de Fortaleza Programa De Residência Médica Em Urologia. 2021;20.
10. Mendes FF. COVID-19 e a retomada das cirurgias eletivas. Como voltaremos à normalidade? Braz J Anesthesiol. 2020;70(5):455-6. https://doi.org/10.1016/j.bjan.2020.09.001
11. Miguel L, Silva JCRE, Poli Neto OB, Tiezzi DG, Andrade JM, Reis FJCD. A propensity score-matched case-control study of laparoscopy and laparotomy for endometrial cancer. Rev Assoc Med Bras. 2021;67(5):753-8. https://doi.org/10.1590/1806-9282.20210194
12. Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. BMJ. 2020:m1106. https://doi.org/10.1136/bmj.m1106
13. Metelmann IB, Busemann A. Elective surgery in times of COVID-19: a two-centre analysis of postponed operations and disease-related morbidity and mortality. Z Evid Fortbild Qual Gesundhwes. 2020;158-9:62-5. https://doi.org/10.1016/j.zefq.2020.10.003
14. Almeida ALC, Santo TM do E, Mello MSS, Cedro AV, Lopes NL, Ribeiro APMR, et al. Repercussões da Pandemia de COVID-19 na Prática Assistencial de um Hospital Terciário. Arquivos Brasileiros de Cardiologia [Internet]. 17 de setembro de 2020 [citado 29 de outubro de 2022]; Disponível em: http://abccardiol.org/en/article/repercussions-of-the-covid-19-pandemic-on-the-care-practices-of-a-tertiary-hospital/
15. Gangbe E, Cai E, Penta R, Mansour FW, Krishnamurthy S. Effects of surgical delay due to COVID-19 on women requiring emergency gynaecological surgery. J Obstet Gynaecol Can. 2021;43(11):1296-300. https://doi.org/10.1016/j.jogc.2021.05.016
16. Rocco M, Oliveira BL, Rizzardi DAA, Rodrigues G, Oliveira G, Guerreiro MG, et al. Impact of the COVID-19 pandemic on elective and emergency surgical procedures in a University Hospital. Rev Col Bras Cir. 2022;49:e20223324. https://doi.org/10.1590/0100-6991e-20223324-en
17. Al-Jabir A, Kerwan A, Nicola M, Alsafi Z, Khan M, Sohrabi C, et al. Impact of the coronavirus (COVID-19) pandemic on surgical practice - Part 1. Int J Surg. 2020;79:168-79. https://doi.org/10.1016/j.ijsu.2020.05.022
18. Coutinho F, Nascimento C, Miranda L, Ramos M, Rodrigues A, Berg A. Impactos da pandemia de COVID-19 na doação de sangue no Brasil: análise histórica dos anos de 2011-2020. Hematology, Transfusion and Cell Therapy. outubro de 2021;43(1):S525. https://doi.org/10.1016/j.htct.2021.10.907
19. Magalhães N, Silva-Malta M, Chaves D, Ribeiro M, Cioffi J, Martins M, et al. Impacto da COVID-19 na rede hemoterápica: experiência da fundação hemominas. Hematol Transfus Cell Ther. 2021;43:S523. https://doi.org/10.1016/j.htct.2021.10.903
20. Nepogodiev D, Martin J, Biccard B, Makupe A, Bhangu A; National Institute for Health Research Global Health Research Unit on Global Surgery. Global burden of postoperative death. The Lancet. 2019;393(10170):401. https://doi.org/10.1016/S0140-6736(18)33139-8

ORIGINAL ARTICLE

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Girls victims of sexual aggression in Baixada Fluminense

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SUMMARY

OBJECTIVE: This study aimed to describe the current situation of sexual aggression and assess the adhesion to ambulatory care follow-up.

METHODS: This is a cross-sectional study involving female children and adolescents aged 0–19 years, treated at the Center for Multiprofessional Care of Sexual Violence of the General Hospital of Nova Iguaçu, from 2014 to 2018.

RESULTS: Of the 453 children and adolescents, 264 (58.3%) were <14 years of age and 189 (41.7%) were 14–19 years of age. In both groups, 78% were black. School delay of >2 years was found in 15.6% of children in the age group <14 years and 40.5% of adolescents in the age group 14–19 years [p<0.001; OR=3.7 (2.1–65)]. In girls aged £13 years, abuse usually occurred at home (73.2%), which was perpetrated by one aggressor (91%) and known to the victim (91.2%). In adolescents aged ≥14 years, 84.1% of rapes occurred outside the home, practiced by one aggressor (74.8%), 57.8% were unknown, and in 91.2% of cases, there was use of physical force and/or verbal threats. The victims aged <14 years have 14 times more chance of experiencing aggression within the family setting [p<0.001; OR=14.3 (8.2–25.6)] and 16 times more chance of experiencing aggression from known persons [p<0.001; OR=16.2 (9.2–29.8)]. On the contrary, adolescents aged ≥14 years have three times more chance of being abused by more than one aggressor [p<0.001; OR=3.3 (1.8–6.1)].

CONCLUSION: Black girls, especially those aged <14 years, are in a situation of greater vulnerability for sexual violence, have less adhesion to follow-up, and often experience aggression in the household setting.

KEYWORDS: Sex offenses. Gender-based violence. Rape.

INTRODUCTION

Sexual violence is defined as any type of activity of an erotic or sexual nature that disrespects the rights of one of the involved persons[1]. Regarding children and adolescents aged <14 years, it is a crime to rape a vulnerable person, and it has a strong negative effect on mental health, sociability, and neurodevelopment problems[2].

It is estimated that 120 million girls worldwide experience some type of forced sexual contact before the age of 20 years[3]. In Brazil, in 2020, there were 60,926 cases of sexual violence reported, 86.9% of the victims were females, and 44,879 (73.7%) of those cases occurred against girls under the age of 14 years. Although in 2020 social distance measures imposed by the COVID-19 pandemic caused under-notification of sexual violence registration, which makes it impossible to confirm if the number of cases of rape has increased, data indicate that the victims were younger than in 2019, and this profile is confirmed year after year. In 2021, there was an increase of 3.7% in the number of registrations of rape and rape of the vulnerable, with a mean rate of 51.8 per 100,000 women[4,5].

The younger the victim, the greater the possibility that the aggression is perpetrated by an aggressor who is close to or is a member of the family and that it takes place in a household setting. This fact tends to favor abuse chronicity and impairments to make a registration of the violence experienced[4]. It is also known that the younger the victim is, the greater the chances of negative effects, such as the occurrence of sexually transmitted infections and psychic damages, among which the most frequent are post-traumatic stress disorder, schizophrenia, drugs use, and sexual dysfunction[4,6,7]. Therefore, continued care is necessary for this phenomenon, especially for girls aged <14 years, because this is the most affected age group.

Multiprofessional care for victims of rape is crucial for the reduction of complications resulting from this event. Besides emergency measures, ambulatory care follow-up for 6 months is imperative to achieve this objective. Therefore, one of the challenges is to provide such services to these girls in an anticipatory and opportune way. The literature has few studies on the adhesion to medical follow-up after sexual violence. It is estimated

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that this rate varies between 10 and 31%. Factors associated with the quality-of-care services impede adherence to ambulatory care follow-up[8]. Therefore, it is important to estimate the parcel of victims with access to emergency care, those who remain for follow-up, and, if possible, assess the obstacles to this process.

The scope of this study was to contextualize the situation of aggression against female children and adolescents treated at a reference center in Baixada Fluminense, in the Rio de Janeiro metropolitan region, Brazil, by comparing age groups <14 years and ≥14 years, and to assess the adhesion to ambulatory care follow-up after the first urgent care.

METHODS

This is a cross-sectional study including female children and adolescents aged 0–19 years, who were treated at the General Hospital of Nova Iguaçu (HGNI) emergency sector and/or followed up at the ambulatory of its Center for Multiprofessional Care of Sexual Violence (CAMVIS), which delivers long-term care to victims of sexual crimes. Data were obtained from emergency care reports and medical records of 453 victims from the CAMVIS follow-up ambulatory in the period of 2014–2018.

As emergency care is objective and carried out through the application of a semi-structured questionnaire, details of sexual aggression are not available. Patients who seek the multidisciplinary follow-up ambulatory present a detailed description of the characteristics of the aggression setting, which is registered on the medical record. For the analysis of the age at the violence occurrence, the group was divided into those aged £13 years and those aged 14–19 years.

The analyzed variables are a place of occurrence, number of aggressors involved, connection with the aggressor, use of force/threat, history of abuse situations, victim's relatives knowing the aggression, use of a condom, the aggressor being under the effect of drugs, and police registration of the offense.

The collected variables were used in the comparative analyses to identify the odds ratio (OR). Data were described through proportions, means, standard deviations, and medians, and the respective confidence intervals (CI) of 95% were estimated. The associations between sexual violence and possible risk factors were evaluated through statistical tests. The magnitude of the associations was observed through the calculation of measures of associations (odds ratio) and the respective CI of 95%. The process of data entry and statistical analysis was performed through the Epi Info 3.5.2 program. The study was approved by the Ethics Committee of the HGNI.

RESULTS

Of the 453 female children and adolescents treated during the period, 264 (58.3%) were <14 years old and 189 (41.7%) were ≥14 years old. There was no difference in color or race between the groups, with the majority being the black race (78%). For the education level, 85% of the girls aged £13 years present an adequate level for their age, and 15% have a delay of >2 years. School delay is more accentuated in the age group ≥14 years (40.5%), corresponding to a 3.7-fold increase in the likelihood of school delay [p<0.001; OR=3.7 (95%CI 2.1–6.5); Table 1].

In general, girls aged £13 years were abused at home (73.2%), perpetrated by one aggressor (91%), known to the victim (91.2%), with 31.1% being the father/stepfather and 39.1% a friend/acquainted, and the girls denied using physical and/or verbal aggression in 53.1% of the episodes. On the contrary, with adolescents aged ≥14 years, 84.1% of rapes occurred on the streets, practiced by one aggressor (74.8%), over half of whom were unknown (57.8%), and in 91.2% of cases, there was use of physical force and/or verbal aggression. In both groups, more than 90% of the reports denied the use of a condom and drugs by the aggressor (97.6 and 78.7%, respectively; Table 2).

Table 1. Sociodemographic characteristics of victims.

Characteristics	<14 years	≥14 years	p-value	OR (95%CI)
	Freq/n (%)	Freq/n (%)		
Age	264/453 (58.3)	189/ 453 (41.7)		
Color/race				
Black	112/144 (77.8)	102/130 (78.5)	0.9	0.9 (0.5–1.7)
White	32/144 (22.2)	28/130 (21.5)		
School delay >2 years				
Yes	24/154 (15.6)	49/121 (40.5)	<0.001	3.7 (2.1–6.5)*
No	130/154 (84.4)	72/121 (59.5)		

*p significant.

Table 2. Characteristics of sexual aggression.

Characteristics	<14 years	≥14 years	p-value	OR (95%CI)
	Freq/n (%)	Freq/n (%)		
Place of aggression				
Own home	142/194 (73.2)	21/132 (15.9)	<0.001	14.3 (8.2–25.6)*
Outside home	52/194 (26.8)	111/132 (84.1)		
Number of aggressors				
1	192/211 (91.0)	116/155(74.8)	<0.001	3.3 (1.8–6.1)*
2 or more	19/211 (9.0)	39/155(25.2)		
Aggressor unknown				
Yes	187/205 (91.2)	65/154 (42.2)	<0.001	16.2 (9.2–29.8)*
No	18/205 (8.8)	89/154 (57.8)		
Connection				
Friend/Acquainted	79/202 (39.1)	41/151 (27.2)		
Father	30/202 (14.8)	3/151 (2.0)		
Stepfather	33/202 (16.3)	5/151 (3.3)		
Mother	3/202 (1.5)	0		
Brother	7/202 (3.5)	1/151 (0.7)		
Caregiver	27/202 (13.4)	1/151 (0.7)		
Boyfriend	5/202 (2.5)	3/151 (2.0)		
Ex-spouse	0	1/151 (0.7)		
Institutional relationship person	0	3/151 (2.0)		
Unknown	18/202 (8.9)	93/151 (61.6)		
Use of force				
Yes	45/96 (46.9)	104/114 (91.2)	<0.001	0.09 (0.04–0.18)*
No	51/96 (53.1)	10/114 (8.8)		
Previous violence				
Yes	55/73 (75.3)	19/43 (44.1)	<0.001	3.8 (1.7–8.7)*
No	18/73 (24.6)	24/43 (55.8)		
Relatives know				
Yes	238/240 (99.1)	109/111 (98.1)	0.5	2.2 (0.2–21.2)
No	2/240 (0.8)	2/111 (1.8)		
Condom				
Yes	9/114 (7.9)	3/82 (3.6)	0.2	2.3 (0.6–10.6)
No	105/114 (92.1)	79/ (96.3)		
Use of drugs by aggressor(s)				
Yes	3/123 (2.4)	17/80 (21.2)	<0.001	0.09 (0.02–0.3)*
No	120/123 (97.6)	63/80 (78.7)		
Police report				
Yes	114/133 (85.7)	116/150 (77.3)	0.07	1.7 (0.94–3.3)
No	19/133 (14.3)	34/150 (22.7)		

*p significant. Source: The authors.

The victims aged <14 years had 14 times more chance of experiencing aggression by household members (p<0.001; OR=14.3 (95%CI 8.2–25.6)) and 16 times more chance of knowing the aggressor [p<0.001; OR=16.2 (95%CI 9.2–29.8)]. On the contrary, being aged ≥14 years triples the chance of being abused by more than one aggressor [p<0.001; OR=3.3 (95%CI 1.8–6.1)].

It was observed that 75.3% of patients aged £13 years had experienced previous situations of sexual violence, compared to 44.1% of those aged ≥14 years. In both groups, more than 75% of the victims reported the offense to the police, and in more than 98% of cases, the relatives knew about the rape (Table 2).

The comparison between the two groups shows an association between the place of aggression [p<0.001; OR=14.3 (95%CI 8.2–25.6)], the aggressor being acquainted [p<0.001; OR=16.2 (95%CI 9.2–29.8)], the use of force at the moment of the violence (p<0.001; OR=0.09 (95%CI 0.04–0.18)), and the occurrence of violence previously to the aggression [p<0.001; OR=3.8 (95%CI 1.7–8,7); Table 2].

Regarding medical care after sexual exposure in victims aged <14 years, 71.3% received only initial care at the emergency unit, with no ongoing ambulatory care follow-up. In the age group ≥14 years, 57.6% continued ambulatory care (Table 3).

DISCUSSION

Child-adolescent sexual violence is a severe and chronic situation with great repercussions for the victim's health and life, and it is virtually invisible, especially in children younger than 14 years, because it is committed by known individuals within the household setting.

This study identified that the majority of rape crimes occurred against girls aged <14 years, who are incapable of consenting to the act, denominated rape of vulnerable by Law 12015/2018. This crime is on the rise in Brazil, because in 2018, over half of the victims were £13 years of age, increasing to 70% in 2019 and 77% in 2020[4].

In this analysis, 78% of victims in both groups were black girls and adolescents. The distribution by color or race is one feature of the profile of victims of rape aged ≤19 years in Brazil which differs from that observed in other crimes. Racial inequality is not as present as in intentional violent deaths. In the age group between 0 and 4 years, most victims are white. In the other age groups, the majority are black. But, in the age group between 10 and 13 years, 56% are black and 42% are white. Considering all victims from 0 to 19 years, 52% are black and 46% are white[4].

The fact that victims aged <14 years are subjected to aggression by household members, often without the use of physical or verbal aggression, reaffirms what happens in Brazil, where 85.2% of the perpetrators are known to the victims[4]. The aggressor with some emotional connection uses the trust relationship with the child/adolescent to practice acts that are initially considered as demonstrations of affection, and when the victim starts to understand the situation as abnormal, the aggressor requires silence through all types of threats[9].

This study demonstrates that school delay is higher for victims aged ≥14 years and that these adolescents have four times more chance of having educational delay. The participation of the school is acknowledged as important for the promotion of actions against sexual violence, identification, and support for the victims. Children who participate in school programs of sexual abuse prevention have greater knowledge about the subject and are three times less likely to become victims as adults[10].

On the contrary, recent years have been atypical due to the coronavirus pandemic, imposing circulation restrictions and rigorous social isolation measures. For children and adolescents, these changes involved classroom lessons suspension, a reduction in the frequency of public services, and for those who live in an aggressive setting, it meant a reduction in possible protection networks and an increase in exposure to violence[4].

It is known that children who experience sexual violence have a higher probability of re-victimization throughout their lives[4]. The results of this research point out that more than two-thirds (75.3%) of girls aged <14 years had experienced some situation of previous violence, which can be justified by the context of social vulnerability in which they are inserted and by their proximity to the aggressors, hampering the registration and favoring the chronicity of those acts.

Table 3. Care after sexual exposure.

Care	<14 years	≥14 years	p-value	OR (95%CI)
	Freq/n (%)	Freq/n (%)		
Urgency	159/223 (71.3)	70/165 (42.4)	p<0.001	OR=3.4(2.2–5.2)*
Urgency+Ambulatory	64/223 (28.7)	95/165 (57.6)		

*p significant. Source: The authors.

This study was conducted at the largest hospital complex in the town of Nova Iguaçu, which delivers health care to the local population and that of the surrounding municipalities of Baixada Fluminense. The region concentrates 22.6% of the population of the State of Rio de Janeiro (RJ) and is characterized by poverty, social inequality, and a predominance of violence[11], similar to what occurs in most of the national territory. In 2020, the Baixada Fluminense area presented one of the highest mean rates of rape per 100,000 women in RJ (77.6), even higher than the mean rate in RJ (67.5). In 2021, the mean rate of RJ was 50.5, similar to that of Brazil (51.8)[5,12].

In this analysis, most aggressors were not under the effect of drugs and/or alcohol. In the aggression against the age group 14–19 years, the consumption of such substances by the aggressor(s) was 21.2%, and in the age group <14 years was 2.4%, probably due to the aggressor's profile and the setting being often different in the two groups. The literature has been pointing out a relation between the consumption of drugs and/or alcohol with sexual violence, e.g., in extrafamilial sexual aggression alcohol ingestion increases the victim's vulnerability due to cognitive and motor effects[13].

Immediate care after sexual exposure and the specialized ambulatory care follow-up by a multiprofessional team are the determinants for the reduction of physical and emotional repercussions in the victim's life, both in short and long term.

Despite the promising advances with the creation of reference centers, formulation of protocols, and the mandatory delivery of these services by the Brazilian Unified Health System (SUS), many obstacles hamper the adequate follow-ups, such as non-adherence to the proposed therapy and the continuity of the ambulatory care follow-up, because a considerable number of patients do not return after the first visit. In this study, less than 30% of girls aged <14 years continued with the ambulatory care follow-up, similar to the rates described in other studies, between 10 and 31%[9]. These data demonstrate the need to improve the work of family health teams, tutelary councils, juvenile courts, and other institutions that can constitute an integrated protection network, in the sense of conducting active searches of these girls who are victims of violence, thus enabling more effective follow-up, aiming to minimize the impacts of the violence experienced and to prevent further occurrence, because most of it happens in the family setting.

Factors related to the victim, such as low socioeconomic level, change of address, victim's psychic condition, and association of the care with what motivated it may also jeopardize the adhesion. Further studies are necessary for the improvement of adhesion strategies.

There was difficulty in obtaining data in the urgency/emergency reports due to the objectivity of the description of the aggression scene, which represents a limitation of this study. In the group with ambulatory care follow-up, the description was more detailed, enabling better access to the data of the analyzed variables.

CONCLUSION

Black girls, especially those in the age group <14 years, are more vulnerable to sexual violence and re-victimization because they present lesser adhesion to health care follow-up and experience aggression mostly in the family setting.

This public health problem requires continuous efforts to broaden the network of protection for victims and gradually improve multidisciplinary care because adhesion to the preconized treatment and follow-up consists of challenges of this type.

AUTHORS' CONTRIBUTIONS

ARA: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **DLMM**: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **ESPA**: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **SRT**: Methodology, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **NCPR**: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing.

REFERENCES

1. Conselho Federal de Medicina. Sociedade de Pediatria de São Paulo. Sociedade Brasileira de Pediatria. Manual de atendimento às crianças e adolescentes vítimas de violência. 2nd ed. Brasília (DF): Conselho Federal de Medicina; 2018.
2. Barbara G, Collini F, Cattaneo C, Facchin F, Vercellini P, Chiappa L, et al. Sexual violence against adolescent girls: labeling it to avoid normalization. J Womens Health (Larchmt). 2017;26(11):1146-9. https://doi.org/10.1089/jwh.2016.6161
3. World Health Organization. Global status report on preventing violence against children. Geneva: World Health Organization; 2020 [cited on Apr 15, 2022]. Available from: https://www.unicef.org/sites/default/files/2020-06/Global-status-report-on-preventing-violence-against-children-2020.pdf
4. Fórum Brasileiro de Segurança Pública. Anuário Brasileiro de Segurança Pública. 15th ed. São Paulo (SP): Fórum Brasileiro de Segurança Pública; 2021 [cited on Apr 15, 2022]. Available from: https://forumseguranca.org.br/wp-content/uploads/2021/10/anuario-15-completo-v7-251021.pdf

5. Fórum Brasileiro de Segurança Pública. Violência contra mulheres em 2021. São Paulo (SP): Fórum Brasileiro de Segurança Pública; 2021 [cited on Apr 24, 2022]. Available from: https://forumseguranca.org.br/wp-content/uploads/2022/03/violencia-contra-mulher-2021-v5.pdf
6. Siebra DX, Barroso ML, Melo AMD, Landim JMM, Oliveira GF. Os prejuízos causados à saúde mental e à vida sexual adulta das mulheres vítimas de abuso sexual na infância. Rev Mult Psic. 2019;13(46):359-78. https://doi.org/10.14295/idonline.v13i46.1890
7. Hailes HP, Yu R, Danese A, Fazel S. Long-term outcomes of childhood sexual abuse: an umbrella review. Lancet Psychiatry. 2019;6(10):830-9. https://doi.org/10.1016/S2215-0366(19)30286-X
8. Oshikata CT, Bedone AJ, Papa MSF, Santos GB, Pinheiro CD, Kalie AH. Características das mulheres violentadas sexualmente e da adesão ao seguimento ambulatorial: tendências observadas ao longo dos anos em um serviço de referência em Campinas, São Paulo, Brasil. Cad Saúde Pública. 2011;27(4):701-13. https://doi.org/10.1590/S0102-311X2011000400009
9. Pfeiffer L, Salvagni EP. Visão atual do abuso sexual na infância e adolescência. J Pediatr. 2005;81(5):197-204. https://doi.org/10.1590/S0021-75572005000700010
10. Pelisoli C, Benvegnu P. Prevenção do abuso sexual infantil: estratégias cognitivo comportamentais na escola, na família e na comunidade. Rev Bras Ter Cogn. 2010;6(1):108-36.
11. Federal Intervention Cabinet. Observatório Legislativo da Intervenção Federal na Segurança Pública do Rio de Janeiro. Desigualdade na Baixada Fluminense; 2022 [cited on Apr 10, 2022]. Available from: http://olerj.camara.leg.br/retratos-da-intervencao/desigualdade-na-baixada-fluminense
12. Instituto de Segurança Pública. Dossiê Mulher 2021. 16th ed. Rio de Janeiro (RJ): Instituto de Segurança Pública; 2021 [cited on Apr 24, 2022]. Available from: https://arquivo.proderj.rj.gov.br/isp_imagens/uploads/DossieMulher2021.pdf
13. Valle R, Bernabé-Ortiz A, Gálvez-Buccollini JA, Gutiérrez C, Martins SS. Intrafamilial and extrafamilial sexual assault and its association with alcohol consumption. Rev Saude Publica. 2018;52:86. https://doi.org/10.11606/S1518-8787.2018052000539

ORIGINAL ARTICLE

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Most Cochrane systematic reviews and protocols did not adhere to the Cochrane's risk of bias 2.0 tool

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SUMMARY

OBJECTIVE: The aim of this study was to identify the frequency of Cochrane systematic reviews and Cochrane systematic reviews protocols using (or planning to use) the risk of bias 2.0 tool to assess the risk of bias of the included randomized clinical trials.

STUDY DESIGN: This is a meta-research study.

METHODS: We included Cochrane systematic reviews or Cochrane systematic reviews protocols that planned to include randomized clinical trials. We assessed the Cochrane Database of Systematic Reviews and screened for issues published after the launch of risk of bias 2.0 tool (2019–2022). Two independent investigators performed the study selection and data extraction.

RESULTS: We analyzed 440 Cochrane systematic reviews and 536 Cochrane systematic reviews protocols. Overall, 4.8% of the Cochrane systematic reviews and 28.5% of the Cochrane systematic reviews protocols used or planned to use risk of bias 2.0 tool. Although low, adherence is increasing over time. In 2019, 0% of Cochrane systematic reviews used risk of bias 2.0 tool, compared to 24.1% in 2022. In Cochrane systematic reviews protocols, adherence increased from 6.9% in 2019 to 41.5% in 2022. A total of 274 (62.1%) Cochrane systematic reviews had their protocols published before 2018; only one used risk of bias 2.0 tool and reported the change of versions in the "Differences between protocol and revision" section.

CONCLUSION: The Cochrane's risk of bias 2.0 tool has low adherence among Cochrane protocols and systematic reviews. Further efforts are necessary to facilitate the implementation of this new tool.

KEYWORDS: Systematic review. Research report. Publications. Methods. Systematic reviews as topic.

INTRODUCTION

Assessing the risk of bias of individual studies is an essential step in developing a systematic review and a key component of the assessment that grades the certainty of the body of evidence. Ignoring potential biases can directly impact the estimated effects of the intervention and lead to uncertain conclusions[1-3]. Since 2008, when Cochrane introduced the Risk of Bias (RoB) tool[4], authors from systematic reviews of interventions were encouraged to use it to assess the internal validity of the included randomized clinical trials (RCTs). This tool was developed to fill gaps in the available methodological assessment instruments and evaluate the extent of confidence one can have in the RCT methodological steps and its influence on the results[1,4].

The original RoB tool comprises seven domains, and the judgment of the risk of bias is performed individually, where each domain can be classified as high, unclear, and low risk of bias. It is worth mentioning that the recommendation for some domains (blinding of participants, personnel and outcome assessors, and incomplete outcome data) is to be assessed not only at the individual study level but separately for each outcome analyzed in the review[4]. After the Cochrane Handbook updates in 2018[3], the original RoB tool was replaced by the RoB version 2.0. This new instrument assesses the risk of bias no longer through individual studies and outcomes but by synthesizing study results (analytical level assessment). Like the original version, the new tool is structured in domains, through which bias can be introduced in the study result. In addition, there

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are "signaling questions," which involve additional information relevant to the risk of bias assessment[5]. The answer options for these questions are: "yes," "probably yes," "probably not," "no," "no information," and "not applicable." Definitive "yes" and "no" answers often indicate that robust evidence is available. The "not applicable" option is only available for nonmandatory questions. Throughout the application of the tool, the responses fulfill some algorithms that determine the risk of bias for each domain as high risk of bias, low risk of bias, or any concern about bias[3,5].

Despite the improvement in the interpretation of bias and its influence on the RCT results, RoB 2.0 has a more complex structure than its original version, and there is a growing discussion around its applicability and usability, which seems to limit its wide adoption[6]. Thus, this meta-research study aimed to identify the frequency of Cochrane systematic reviews (CSR) and CSR protocols using (or planning to use) the RoB 2.0 to assess the risk of bias of the included RCTs.

METHODS

Eligibility criteria

We included any CSR or CSR protocols that planned to include RCTs and were published between 2019 and 2022. Updated reviews and network meta-analyses were not considered.

Retrieval strategy

We assessed the Cochrane Database of Systematic Reviews and screened for issues published between January 2019 and March 2022. CSR and CSR protocols were then screened to see if they fulfilled our eligibility criteria. Two independent investigators performed this process. A third investigator solved the disagreements.

Data extraction

We extracted the following data from included reports using a pre-designed Excel spreadsheet:

- publication date of CSR and its respective protocol
- publication data of CSR protocols
- the version of the risk of bias tool used (CSR) or planned to use (CSR protocols)
- descriptions of the change of RoB versions in the section "Differences between protocol and review" (for CSR whose protocol has been published before 2018).

Two independent investigators performed the data extraction process, and a third investigator solved the disagreements.

Data synthesis and presentation

We summarized information using common descriptive statistics. Data were presented in tables. Stata v17 was used for data management and all descriptive analysis.

RESULTS

Considering the eligibility criteria, a total of 440 CSR and 536 CSR protocols were analyzed. Overall, 4.8% (21/440) of the CSR and 28.5% (153/536) of the CSR protocols used or planned to use the RoB 2.0. Table 1 presents the main findings.

Figures 1 and 2 compared the adoption of the two versions of the RoB table by CSR and CSR protocols published between 2019 and 2022.

A total of 274 (62.1%) CSRs had their protocols published prior to the introduction of RoB 2.0 (2018), but only one review used RoB 2.0 to assess the risk of bias of included RCTs and also reported the change of versions in the "Differences between protocol and revision" section, as follows:

RoB 2 tool used (had planned to use the risk of bias tool). Therefore, this section has been re-written in accordance with the editorial checklist for the RoB 2 tool.[7]

DISCUSSION

This meta-research study analyzed 440 CSR and 536 CSR protocols regarding the use of the new tool proposed for assessing the risk of bias, the RoB 2.0. The findings showed that a small proportion of complete reviews and protocols adopted or planned to adopt the RoB 2.0 in assessing their included RCTs. However, there has been increased adherence to RoB 2.0 over the years since its implementation.

Table 1. Adherence to risk of bias 2.0 tool from Cochrane systematic reviews and Cochrane systematic reviews protocols.

	RoB table (original version)	RoB 2.0
CSR (n=440)	419 (95.2%)	21 (4.8%)
2019 (n=258)	258 (100%)	0 (0%)
2020 (n=40)	40 (100%)	0 (0%)
2021 (n=113)	99 (97.6%)	14 (12.4%)
2022 (n=29)	22 (75.9%)	7 (24.1%)
CSR protocols (n=536)	383 (71.5%)	153 (28.5%)
2019 (n=116)	108 (93.1%)	8 (6.9%)
2020 (n=169)	136 (80.5%)	33 (19.5%)
2021 (n=210)	115 (54.8%)	95 (45.2%)
2022 (n=41)	24 (58.5%)	17 (41.5%)

n: number of studies.

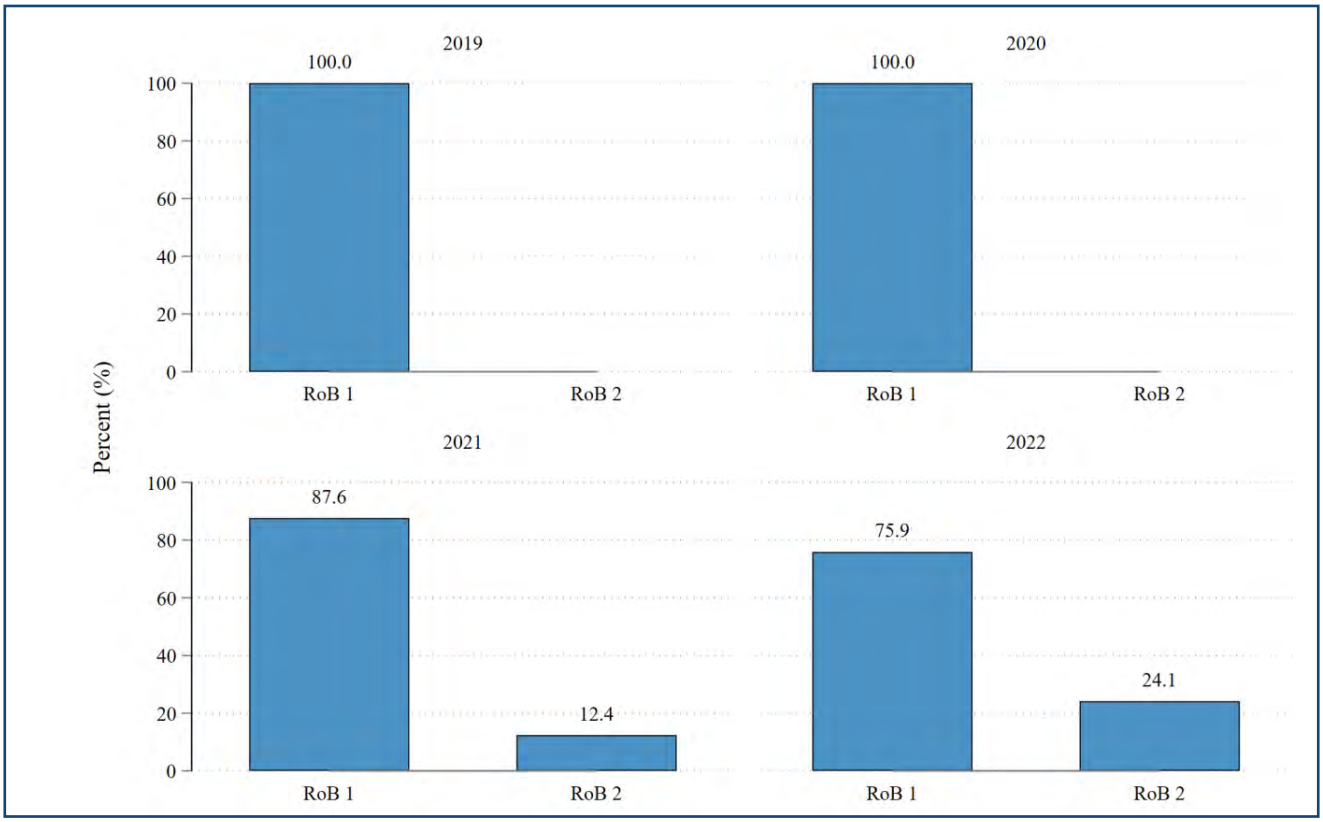

Figure 1. Risk of bias 2.0 tool adoption by year of publication of Cochrane review.

Figure 2. Risk of bias 2.0 tool adoption by year of publication of Cochrane review protocols.

Despite the methodological improvements that this new version offered in terms of results and bias interpretation, its structure and application are more complex than the original version, which may contribute to the lower adhesion of Cochrane reviewers. An inter-rater reliability study[6] found poor agreement among experienced examiners in the overall RoB 2.0 judgment, ranging from slight to moderate for single domains. The complexity of the implementation was attributed to the difficulties in understanding the questions and applying the tool, mainly due to the new terminology and different approaches for some domains, such as "deviations from intended intervention" and "selection of reported results," and also the conditionality of signaling questions that can raise the risk of wrong interpretation.

Furthermore, some critical issues have been removed and will likely impact the final risk of bias assessment. For example, in Rob 2.0, the absence of selective reporting and assessment of outcomes (reporting bias) has been discussed. In RCTs, the outcomes of interest must be defined in advance and disclosed. Selective reporting bias occurs in numerous situations, such as when planned outcomes and/or their results are not reported, are reported incompletely, or are reported in the final publication of the study, leading to possible overestimation of benefits and underestimation of harm of interventions.

Given the importance of assessing the risk of bias for the applicability of the results of a systematic review, it is important to question why most Cochrane reviewers chose not to use the RoB 2.0. Future survey studies can be a good way to hear from the reviewers themselves about the difficulties and challenges they encountered in applying the tool. Understanding the different versions of this important tool and how to interpret its results helps the review authors critically evaluate the RCTs included in a systematic review and an individual analysis per study. In addition, it is essential to understand the limitations of the current version compared to the original and the need for future adjustments and considerations regarding its use in practice.

CONCLUSIONS

The Cochrane's RoB 2.0 tool has low adherence among Cochrane protocols and systematic reviews. Further efforts are necessary to facilitate the implementation of this new tool.

HIGHLIGHTS

- We conducted a meta-research study to assess the frequency of CSR and CSR protocols using (or planning to use) the RoB 2.0 tool to assess the risk of bias of the included RCTs.
- A total of 440 CSR and 536 CSR protocols were analyzed. Overall, 4.8% (21/440) of the CSR and 28.5% (153/536) of the CSR protocols used or planned to use the RoB 2.0.
- Although low, adherence is increasing over time. In 2019, 0% of CSR used RoB 2.0, compared to 24.1% in 2022. In CSR protocols, adherence increased from 6.9% in 2019 to 41.5% in 2022.
- The Cochrane's RoB 2.0 tool has low adherence among Cochrane protocols and systematic reviews. Further efforts are necessary to facilitate the implementation of this new tool.

AUTHORS' CONTRIBUTIONS

ALCM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **RLP:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Writing – review & editing. **GMS:** Investigation, Writing – original draft. **EMS:** Investigation, Writing – original draft. **KMM:** Investigation, Writing – original draft. **RR:** Methodology, Project administration, Resources, Supervision, Validation, Visualization.

REFERENCES

1. Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, et al. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. BMJ. 2009;339:b4012. https://doi.org/10.1136/bmj.b4012
2. Verhagen AP, Vet HC, Bie RA, Boers M, Brandt PA. The art of quality assessment of RCTs included in systematic reviews. J Clin Epidemiol. 2001;54(7):651-4. https://doi.org/10.1016/s0895-4356(00)00360-7
3. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane; 2022.
4. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011.
5. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366:l4898. https://doi.org/10.1136/bmj.l4898
6. Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. J Clin Epidemiol. 2020;126:37-44. https://doi.org/10.1016/j.jclinepi.2020.06.015
7. Clark B, Whitall J, Kwakkel G, Mehrholz J, Ewings S, Burridge J. The effect of time spent in rehabilitation on activity limitation and impairment after stroke. Cochrane Database Syst Rev. 2021;10(10):CD012612 https://doi.org/10.1002/14651858.CD012612.pub2

ORIGINAL ARTICLE

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Assessment of pain and quality of life in patients undergoing cardiac surgery: a cohort study

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SUMMARY

OBJECTIVE: This study aimed to evaluate postoperative pain and quality of life in patients undergoing median sternotomy.

METHODS: A cohort study was carried out on a sample of 30 patients who underwent elective cardiac surgery by longitudinal median sternotomy. Patients were interviewed at Intensive Care Unit discharge and hospital discharge, when the Visual Numeric Scale and the Brief Pain Inventory were applied, and 2 weeks after hospital discharge, when the World Health Organization Quality of Life-Bref questionnaire was administered. The normality of the results was analyzed by the Shapiro-Wilk test, and Wilcoxon Rank Sum and McNemar tests were utilized for the analysis of numerical and categorical variables. For correlation between numerical variables, Spearman's linear correlation test was applied. To compare numerical variables, Mann-Whitney U and Kruskal-Wallis tests were applied. Differences between groups were considered significant when the p-value was <0.05.

RESULTS: Between Intensive Care Unit and hospital discharge, there was a reduction in median pain intensity assessed by the Visual Numeric Scale from 5.0 to 2.0 (p<0.001), as well as in eight Brief Pain Inventory parameters: worst pain intensity in the last 24 h (p=0.001), analgesic relief (p=0.035), and pain felt right now (p=0.009); and in interference in daily activities (p<0.001), mood (p=0.017), ability to walk (p<0.001), relationship with other people (p=0.005), and sleep (p=0.006). Higher pain intensity at Intensive Care Unit discharge was associated with worse performance in the psychological domain of quality of life at out-of-hospital follow-up.

CONCLUSION: Proper management of post-sternotomy pain in the Intensive Care Unit may imply better quality of life at out-of-hospital follow-up.

KEYWORDS: Pain. Quality of life. Postoperative care. Sternotomy. Cardiac surgical procedures.

INTRODUCTION

Moderate-to-severe post-sternotomy pain is reported by up to 75% of patients in the first 4 days of surgery, and persistent pain is reported by 58% in the first month and 39% in the first year. Adequate analgesia in the postoperative period can reduce the incidence of chronic pain and improve the patient's quality of life[1-4].

Quality of life is a broad concept, comprising "an individual's perception of his or her place in life in the context of the culture and value systems in which he or she lives and concerning his or her goals, expectations, standards, and concerns"[5]. Improving the quality of life is the ultimate goal of cardiac surgery[6].

However, the improvement in cardiovascular symptoms cannot be associated with post-sternotomy pain, as the improvement in quality of life caused by the reduction in cardiovascular symptoms can be minimized by the chronicity of pain in the postoperative period.

Many recent initiatives have been focused on limiting opioid use in surgical patients, since excessive administration of opioids for pain treatment after surgery has been recognized as an important concern for public health and a potential contributor to patterns of opioid misuse and related harm[7-11]. However, in developing countries, the problem with these surgeries seems to be different. There is undertreatment of pain due to a lack of resources[9]. This context becomes even more evident in the postoperative period, in which adequate pain management could promote positive outcomes in patient recovery.

Besides, poorly controlled pain is associated with an increased hormonal response to stress. This may contribute to the multiple postoperative adverse events[12], causing a worsening of quality of life.

The present study aimed to analyze the incidence and characteristics of postoperative pain after median sternotomy, identify possible associated variables, and assess the impact of pain intensity and duration on postoperative quality of life.

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METHODS

This is a cohort study, with a convenience sample, conducted in a university hospital in Brazil. The sample was composed of patients of both genders aged ≥18 years, who underwent elective cardiac surgery with longitudinal median sternotomy in the period between August 2020 and April 2021. Patients undergoing previous sternotomy, urgent or emergency surgery, chronic pain, or using analgesics 2 weeks before surgery were not included.

Patients were evaluated at three moments in the postoperative period: at discharge from the Intensive Care Unit (ICU) (T0), at hospital discharge (T1), and at home 14–28 days after discharge (T2). At T0 and T1, pain intensity was characterized by the Visual Numerical Scale (VNS) and Brief Pain Inventory (BPI). At T2, to assess the postoperative quality of life, the World Health Organization Quality of Life Questionnaire – Bref (WHOQoL-Bref) was used.

The Visual Numerical Scale is a quick, practical, and easily applied instrument. It consists of a 0–10 visual scale that rates the intensity of pain the patient reports feeling anywhere in the body. Pain is classified as mild (0 to 3), moderate (4 to 6), and severe (7 to 10).

The Brief Pain Inventory is a more detailed multidimensional questionnaire. It starts with two screening questions about the presence and location of pain and is then divided into two main scales, namely, pain intensity and pain interference. As for the first scale, the questions: "worst pain in the last 24 hours", "use of analgesics", "intensity of analgesic improvement", and "pain felt now" were selected. The anchors of the pain intensity scale are 0="no pain" and 10="worst pain imaginable." As for the pain interference scale, the questions addressed the influence of pain on general activity, mood, ability to walk, relationship with other people, sleep, and ability to enjoy life. The anchors of this scale are 0="no interference" and 10="completely interferes."

The WHOQoL-Bref standardized structured questionnaire of quality of life, developed by the World Health Organization, is an abbreviated version of the WHOQoL-100, composed of the 26 questions that obtained the best psychometric performances of the original questionnaire, containing two general quality-oflife-questions and 24 other questions representing each of the 24 facets that compose the following four domains: physical (7 items), psychological (6 items), social relations (3 items), and environment (8 items)[13]. The higher the score, the better the quality of life.

Data were tabulated and analyzed in the statistical program SPSS 25.0®. For the analysis of results, numerical variables were presented as mean and standard deviation, median, and range (minimum and maximum), and categorical variables as absolute (n) and relative (%) frequencies. Normality was checked using the Shapiro-Wilk test. To compare numerical and categorical variables at T0 and T1, the Wilcoxon and McNemar tests were applied, respectively. For correlation between numerical variables, Spearman's linear correlation test was applied. To compare numerical variables with metrics in up to two categories, the Mann-Whitney U test was applied, and in three categories or more, the Kruskal-Wallis test was applied. Differences between groups were considered significant when the p-value was <0.05.

The present study was approved by the Research Ethics Committee of the institution (No. 23523.023901/2018-1/CAAE:14783119.5.0000.5087) and was conducted in accordance with the Declaration of Helsinki. All participants signed the informed consent form.

RESULTS

The sample included 30 patients, mostly females (60%, n=18) and in the age range of 46–59 years (40%, n=12), ranging from 18 to 78 years (49.73±16.60 years). The most frequent surgical procedures were coronary artery bypass grafting (40%, n=12) and valvular replacement (40%, n=12). The mean times of surgery, cardiopulmonary bypass (CPB), and aortic cross-clamping were 209±65 min (120 to 343), 91.86±33.91 min (18 to 154), and 75±34.56 min (32 to 175), respectively. The most commonly observed American Society of Anesthesiologists preoperative physical status classification was ASA III (40%, n=12), followed by II (36%, n=11). Mean ICU and in-hospital stays (including the preoperative period of clinical stabilization of baseline conditions) were 6.45±6.25 days (2 to 26 days) and 32.10±19.34 days (7 to 93 days), respectively (Table 1).

At T0, 10 (33.3%) patients had severe pain, and 7 (23.33%) patients had moderate pain (median: 5, 0–10). At T1, 10% had severe pain and 16.67% had moderate pain (median 2, 0–10). Between these two moments, clinical improvement was observed in all parameters assessed by the BPI, except "pain interference with the ability to enjoy life" (p=0.161) (Table 2). The most commonly reported areas of pain were sternal, scapular, and lumbosacral. However, no statistically significant differences were observed between the moments of the interview.

The female gender was correlated with higher pain intensity and parameters interference, both at T0 and T1, but with statistical significance only for interference in general activity (p=0.052; Mann-Whitney U test) and walking ability (p=0.044; Mann-Whitney U test) at T0 and for pain now (p=0.028; Mann-Whitney U test) at T1.

Table 1. Sociodemographic, clinical, and surgical aspects of patients undergoing median sternotomy in a referral hospital.

Variables	n
Gender	
Female	18 (60.0%)
Male	12 (40.0%)
Age (years)	
18–30	5 (16.7%)
31–45	6 (20.0%)
46–59	12 (40.0%)
60 and over	7 (23.3%)
Mean±SD	49.7±16.6
Color	
Brown	19 (63.3%)
White	7 (23.3%)
Black	4 (13.3%)
Habits	
Physical activity	2 (6.7%)
Current alcoholism	1 (3.3%)
Previous alcoholism	11 (36.7%)
Current smoking	1 (3.3%)
Previous smokig	7 (23.3%)
BMI[a] (kg/m²)	25.4±5.3
Heart disease	
Mitral insufficiency	12 (40.0%)
Heart failure	8 (26.7%)
Mitral stenosis	4 (13.3%)
Aortic insuficciency	4 (13.3%)
Tricuspid insufficiency	4 (13.3%)
CAD[b]	5 (16.7%)
Aortic stenosis	3 (10.0%)
ASD[c]	3 (10.0%)
Surgical procedures	
Valvular replacement	12 (40.0%)
CABG[d]	12 (40.0%)
Closure of ASD[e]	4 (13.3%)
Valve repair or replacement	1 (3.3%)
Combined procedures	1 (3.3%)
Surgery time (min)	209±65
ICU[f] stay (days)	6.4±6.3
Hospitalization (days)	32.1±19.3
Cross clamping (min)	75.0±34.6
CPB[g] (min)	91.9±33.9
ASA[h]	
I–II	12 (40.0%)
III	18 (80.0%)
Analgesia	
Morphine	29 (96.7%)
Tramadol	8 (26.7%)
Codein	8 (26.7%)
Dipyrone	26 (86.7%)
Paracetamol	11 (36.7%)
Analgesia-related symptoms	
Constipation	11 (36.7%)
Altered appetite	8 (26.7%)
Altered diuresis	10 (33.3%)

[a]Body Mass Index; [b]Coronary Artery Disease; [c]Atrial Septal Defect; [d]Coronary Artery Bypass Graftin; [e]Atrial Septal Defect; [f]Intensive Care Unit; [g]Cardiopulmonary bypass; [h]American Society of Anesthesiologists.

The longer time of aortic cross-clamping was associated with greater interference with mood (p=0.011; Spearman's correlation), walking ability (p=0.026; Spearman's correlation), and relationship with other people (p=0.003; Spearman's correlation) at T0, and with interference with general activity (p=0.028; Spearman's correlation) and again with mood (p=0.007; Spearman's correlation) at T1.

The most commonly used analgesics were morphine (96.7%, n=29), dipyrone (86.7%, n=26), and/or paracetamol (36.7%, n=11). The total daily dose in the first 24 h postoperatively was 3.29±2.27 mg morphine and 5.12±1.64 g dipyrone.

The total dose of morphine during the ICU stay and on the ward was 221 and 5 mg, respectively, for the group with mild pain at ICU discharge, 38 and 7 mg for moderate pain, and 90 and 18 mg for severe pain.

At T2, the WHOQoL-Bref questionnaire was self-administered 19.32±9.48 days after hospital discharge. The median overall quality of life was 70.27, ranging from 36.76 to 86.62. The worst performing domain was physical (12.93±2.76), followed by environment (13.15±2.03). Pain intensity at ICU discharge (T0) was associated with more unfavorable parameters in the psychological domain (p=0.022). This relationship was not observed with pain intensity at hospital discharge (T1) (Table 3).

DISCUSSION

The vast majority of patients achieved a significant improvement in key BPI parameters between ICU discharge and hospital discharge. However, important pain values persisted during hospitalization. The post-sternotomy pain of moderate intensity at ICU discharge and mild at hospital discharge is in agreement with the results of other studies[13-17], showing that there is still room for improvement in analgesic techniques, especially in the first postoperative days[13].

The systematic use of opioids in the immediate postoperative period was verified; however, the total daily dose may have been insufficient for adequate analgesia. One of the factors for the inadequacy of post-sternotomy pain control is the fear of side effects of intravenous opioids, which should be the preferred choice in this context, associated with a second type of analgesic therapy[12].

There is evidence in the literature of a relationship between post-sternotomy pain and younger age, female gender, and higher BMI[19]. In this study, it was found that age was correlated positively with the intensity of analgesic relief at hospital discharge.

The female gender was associated with greater pain interference in daily activities and walking ability at ICU discharge,

Table 2. Comparison of responses to the Visual Numerical Scale and Brief Pain Inventory, at Intensive Care Unit discharge (T0) and hospital discharge (T1), of patients submitted to median sternotomy for cardiac surgery in a tertiary hospital.

Variáveis		T0	T1	p§
		#	#	
Visual Numerical Scale		5.0 (0–10)	2.0 (0–10)	0.001
Brief Pain Inventory				
Intensity	The worst pain in the last 24 hours	5.0 (0–10)	1.5 (0–10)	0.001
	From pain relief	8.0 (0–10)	10.0 (5–10)	0.035
	Of the pain felt now	1.0 (0–10)	0.0 (0–7)	0.009
Pain influence	On general activity	5.0 (0–10)	0.5 (0–10)	0.001
	Mood	3.5 (0–10)	0.0 (0–10)	0.017
	Ability to walk	7.0 (0–10)	0.0 (0–10)	0.001
	Relationship with other people	0.5 (0–10)	0.0 (0–10)	0.005
	Sleep	6.0 (0–10)	3.0 (0–10)	0.006
	Ability to enjoy life	2.0 (0–10)	0.0 (0–10)	0.161

§Wilcoxon; #Median (min–max).

Table 3. Relationship between the Visual Numerical Scale at Intensive Care Unit discharge (T0) and hospital discharge (T1) with the post-discharge Quality of Life (World Health Organization Quality of Life Questionnaire – Bref) (T2) of patients submitted to median sternotomy for cardiac surgery in a reference hospital.

WHOQoL-Bref		Visual Numeric Scale			p¥
		Mild pain (0–3)	Moderate pain (4–6)	Severe pain (7–10)	
		#	#	#	
T0	Physical domain	13.7 (7.4–20.0)	13.1 (9.7–17.1)	12.3 (9.1–14.3)	0.431
	Psychological domain	16.0 (6.7–20.0)	14.0 (11.3–16.0)	13.3 (11.3–14.7)	0.022
	Social relations domain	14.7 (10.7–18.7)	14.7 (10.7–17.3)	14.7 (8.0–16.0)	0.633
	Environmental domain	13.5 (8.0–18.0)	13.0 (11.5–15.0)	12.5 (10.5–15.0)	0.374
T1	Physical domain	13.7 (7.4–20.0)	12.6 (10.3–13.7)	12.0 (9.1–13.7)	0.371
	Psychological domain	15.0 (6.7–20.0)	12.7 (12.0–14.7)	14.0 (12.0–14.7)	0.211
	Social relations domain	14.7 (10.7–18.7)	14.7 (8.0–17.3)	14.7 (10.7–16.0)	0.814
	Environmental domain	13.2 (8.0–18.0)	12.0 (11.5–13.0)	12.5 (12.0–15.0)	0.383

¥Kruskal-Wallis; #Median (min–max).

and with pain intensity at hospital discharge. Females were associated with greater areas of pain at the end of the first week of cardiac surgery[14], more postoperative complications and length of stay, more symptoms 2 weeks after discharge, and lower quality of life for 6 months after surgery[19].

Thus, as observed in this study, surgery may imply some degree of impairment of psychological function during the first weeks because patients have to face the challenges of a new life phase that may be accompanied by physical and mental deterioration[20]. However, the psychological consequences of sternotomy and anginal pain, including depression and anxiety, may be clinically evident for up to a year after surgery[21]. This wide time interval of unfavorable manifestations in the psychological domain is another indication of the complexity of the consequences of pain caused by the punctual surgical event, which has repercussions on the quality of life in the short and long term, requiring readjustments in lifestyle.

In our sample, we observed a correlation between CPB time and the parameter interference in relationships with other people (T0) and mood (T1). Another study observed that CPB time <60 min was associated, with statistical significance, with a lower incidence of moderate to severe pain[2].

Comparing the data found with those of another author who investigated the mean BPI values in 70 patients at ICU discharge, equivalent to T0, higher values were found for influence of pain on walking (7×6.67) and sleep (6×5.37) and lower

values for worst pain in 24 h (5×4.66), pain now (1×2.61), influence of pain on activities (5×7. 30), mood (3.5×4.16), relationship (0.5×1.54), and enjoy life (2×3.04). As for the parameter "influence on the ability to enjoy life", it decreases according to the pain relief score[17].

In the elderly group, cardiac surgery has less effect on increasing life expectancy, while its impact on improving quality of life is relevant. The variables associated with greater gains in quality of life in the elderly are poor preoperative physical status, female gender, older age, and longer hospital stay[22].

The most frequent location of acute postoperative pain is in the sternal region[2,3,4,14,15], sometimes accompanied by significant impairment of lung function[4]. In our study, there was no significant variation in pain location at T0 and T1.

Several analgesic techniques can be used. Pharmacological techniques, such as opioids and anti-inflammatory drugs, infiltration with local anesthetics, nerve blocks, and spinal analgesia[12], and non-pharmacological techniques, such as heat/cold application, massage, hypnosis, and distraction techniques, exist. Continuous infusion of local anesthetics can reduce the intensity of acute postoperative pain, opioid use, mechanical ventilation time, hospital stay, and atelectasis, and it is a simple and effective method for treating pain after median sternotomy[23].

The patient with pain tends to have greater physical and emotional exhaustion, reduce his movement, remain in dorsal decubitus, maintain more superficial ventilation, and awaken from sleep. Thus, it is reinforced that pain control must be seen as a priority in health care[24].

Among the limitations of the study, the coronavirus pandemic (SARS-CoV-2) reduced the number of elective surgeries, leading to a reduction of the sample, the prolongation of the length of hospital stay, and the wide range of T2 follow-up, which can lead to significantly different pain findings at days 14 and 28. Future studies with higher samples are needed for a better comparison of findings.

As the relevance of this study, one can highlight the use of validated questionnaires to assess pain and quality of life, the follow-up performed with three interviews in the postoperative period, delimiting the short-term postoperative follow-up, as well as the execution in the reference service of the region.

CONCLUSION

The persistence of postoperative pain had an unfavorable impact on the quality of life after hospital discharge in the short term, especially in the psychological domain. The correct management of post-sternotomy pain in the ICU is necessary to relieve the patient's discomfort during hospitalization, minimize clinical complications associated with pain, and improve the quality of life in out-of-hospital follow-up.

AUTHORS' CONTRIBUTIONS

LBRV: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **EJSGO:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **CMBO:** Conceptualization, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **ECRM:** Conceptualization, Writing – original draft, Writing – review & editing. **LHLV:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **VJSN:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **EF:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **PCL:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

REFERENCES

1. Ziyaeifard M, Azarfarin R, Golzari SE. A review of current analgesic techniques in cardiac surgery. is epidural worth it? J Cardiovasc Thorac Res. 2014;6(3):133-40. https://doi.org/10.15171/jcvtr.2014.001
2. Raksamani K, Wongkornrat W, Siriboon P, Pantisawat N. Pain management after cardiac surgery: are we underestimating post sternotomy pain? J Med Assoc Thai. 2013;96(7):824-8. PMID: 24319854
3. Sethares KA, Chin E, Costa I. Pain intensity, interference and patient pain management strategies the first 12 weeks after coronary artery bypass graft surgery. Appl Nurs Res. 2013;26(4):174-9. https://doi.org/10.1016/j.apnr.2013.07.005
4. Giacomazzi CM, Lagni VB, Monteiro MB. A dor pós-operatória como contribuinte do prejuízo na função pulmonar em pacientes submetidos à cirurgia cardíaca. RBCCV. 2006;21(4). https://doi.org/10.1590/S0102-76382006000400008
5. Fleck MPA, Louzada S, Xavier M, Chachamovich E, Vieira C, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". Rev Saúde Pública. 2000;34(2):178-83. https://doi.org/10.1590/S0034-89102000000200012
6. Araújo HV, Figueirêdo TR, Costa CR, Silveira MM, Belo RM, Bezerra SM. Quality of life of patients who undergone myocardial revascularization surgery. Rev Bras Enferm. 2017;70(2):257-64. https://doi.org/10.1590/0034-7167-2016-0201

7. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018;360:j5790. https://doi.org/10.1136/bmj.j5790
8. Ladha KS, Neuman MD, Broms G, Bethell J, Batheman BT, Wijeysundera DN, et al. Opioid prescribing after surgery in the United States, Canada, and Sweden. JAMA Network Open. 2019;2(9):e1910734. https://doi.org/10.1001/jamanetworkopen.2019.10734
9. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. Lancet. 2016;387(10028):1644-56. https://doi.org/10.1016/S0140-6736(16)00161-6
10. Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. Lancet. 2019;393(10180):1547-57. https://doi.org/10.1016/S0140-6736(19)30428-3
11. Lappin R. CDC Guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2019;65(4):150-1.
12. Huang AP, Sakata RK. Pain after sternotomy - review. Braz J Anesthesiol. 2016;66(4):395-401. https://doi.org/10.1016/j.bjane.2014.09.013
13. Aguiar MI, Farias DR, Pinheiro ML, Chaves ES, Rolim IL, Almeida PC. Quality of life of patients that had a heart transplant: application of Whoqol-Bref scale. Arq Bras Cardiol. 2011;96(1):60-8. https://doi.org/10.1590/s0066-782x2010005000133
14. Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chioléro R, von Segesser LK. Pain location, distribution, and intensity after cardiac surgery. Chest. 2000;118(2):391-6. https://doi.org/10.1378/chest.118.2.391
15. Öğüt S, Sucu Dağ G. Pain characteristics and pain interference among patients undergoing open cardiac surgery. J Perianesth Nurs. 2019;34(4):757-66. https://doi.org/10.1016/j.jopan.2018.10.009
16. Zencir G, Eser I. Effects of cold therapy on pain and breathing exercises among median sternotomy patients. Pain Manag Nurs. 2016;17(6):401-10. https://doi.org/10.1016/j.pmn.2016.05.006
17. Mathai AT, Sams LM. Assessment of quality of pain and contributing factors affecting level of pain among patients who had undergone cardiac surgery in selected hospitals, Mangalore. Asian Pacific J Nurs. 2015;2(1):8-11.
18. Borges JBC, Ferreira DLM P, Carvalho SMR, Martins AS, Andrade RR, Silva MA M. Avaliação da intensidade de dor e da funcionalidade no pós-operatório recente de cirurgia cardíaca. RBCCV. 2006;21(4):393-402. https://doi.org/10.1590/S0102-76382006000400009
19. Bjørnnes AK, Parry M, Lie I, Fagerland MW, Watt-Watson J, Rustøen T, et al. Pain experiences of men and women after cardiac surgery. J Clin Nurs. 2016;25(19-20):3058-68. https://doi.org/10.1111/jocn.13329
20. Perrotti A, Ecarnot F, Monaco F, Dorigo E, Monteleone P, Besch G, et al. Quality of life 10 years after cardiac surgery in adults: a long-term follow-up study. Health Qual Life Outcomes. 2019;17(1):88. https://doi.org/10.1186/s12955-019-1160-7
21. Yüksel V, Gorgulu Y, Cinar RK, Huseyin S, Sonmez MB, Canbaz S. Impact of experiencing acute coronary syndrome prior to open heart surgery on psychiatric status. Braz J Cardiovasc Surg. 2016;31(4):281-6. https://doi.org/10.5935/1678-9741.20160064
22. Coelho PNMP, Miranda LMRPC, Barros PMP, Fragata JIG. Quality of life after elective cardiac surgery in elderly patients. Interact Cardiovasc Thorac Surg. 2019;28(2):199-205. https://doi.org/10.1093/icvts/ivy235
23. Pala AA, Urcun YS, Çiçek ÖF, Şahin S. Can continuous local anesthetic infusion after median sternotomy reduce opioid use? Cureus. 2020;12(9):e10711. https://doi.org/10.7759/cureus.10711
24. Ribeiro SBF, Pinto JCP, Ribeiro JB, Felix MMS, Barroso SM, Oliveira LF, et al. Dor nas unidades de internação de um hospital universitário. Rev Bras Anestesiol. 2012;62(5):605-11. https://doi.org/10.1590/S0034-70942012000500001

COMMENTARY

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Comment on "Early results of novel robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction by using Da Vinci XI: initial clinical experience"

Zhengtao Wu[1], Yangfen Zhang[2], Han Li[2], Jian Huang[1*]

Dear Editor,

We are pleased to read the article entitled "Early results of novel robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction by using Da Vinci XI: initial clinical experience" by Çakır et al.[1]. In this study, the authors evaluated the early outcomes of robotic surgery-assisted anterior resection for low rectal cancer and transvaginal specimen extraction (TVSE). The authors explained the importance of TVSE for women in two aspects: it can bring good cosmetic effect and effectively reduce the complications related to additional skin incision. However, there are still some problems that need our further thinking and exploration.

Both transvaginal extraction and transanal extraction belong to natural orifice specimen extraction (NOSE). In this article, TVSE was used, and the research object was limited to women. As we know, different genders have different human structures. The rectum is the last segment of the bowel, which is connected with the sigmoid colon on the upper part and the anus on the lower part. In female, the uterus and vagina are located in the front of rectum, and in male, the bladder, seminal vesicle, and prostate lie in front of the rectum. In clinical practice, many studies[2,3] used transanal specimen extraction. Comparing the two methods of NOSE, transanal specimen extraction technology is more applicable to a wide range of people (both men and women). To the best of our knowledge, the authors illustrates the importance of TVSE for women, but we suggest comparing the two methods of NOSE in terms of operation time, operation and early postoperative complications, hospital stay, blood loss, etc. to highlight the disadvantages and advantages of TVSE.

Vagina is very important for women and it is closely related to some diseases and sexual life[4] of women. The complications of some TVSE (e.g., sexual intercourse difficulties, infection, infertility, pelvic structural trauma[5]) may have a significant impact on the postoperative life of some special women. Therefore, when using TVSE, patients should be carefully screened to avoid unexpected injury. In addition, further studies on which women (e.g., sexual dysfunction, difficulty in pregnancy) are not suitable for TVSE are also needed.

Compared with traditional laparoscopic methods (unstable view, enlarged hand tremor, uncomfortable ergonomic position of the surgeon[6]), the robot method has some advantages to help rectal cancer surgery, including three-dimensional vision, less fatigue, tremor filtering, and seven degrees of wrist-like motion[7,8]. However, the robot can only act as a more advanced technology and means in the current stage of surgery, and, in essence, it still needs human operation ideas and arrangements.

AUTHORS' CONTRIBUTIONS

ZW: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration. **YZ:** Conceptualization, Writing – original draft. **HL:** Conceptualization, Writing – original draft. **JH:** Conceptualization, Writing – review & editing.

REFERENCES

1. Çakır T, Aslaner A. Early results of novel robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction by using Da Vinci XI: initial clinical experience. Rev Assoc Med Bras (1992). 2021;67(7):971-4. https://doi.org/10.1590/1806-9282.20210325

2. D'Hoore A, Wolthuis AM. Laparoscopic low anterior resection and transanal pull-through for low rectal cancer: a natural orifice specimen extraction (NOSE) technique. Colorectal Dis. 2011;13(Suppl. 7):28-31. https://doi.org/10.1111/j.1463-1318.2011.02773.x

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3. Zhang J, Li W, Li Y, Amin B, Zhang N, Sun Z, et al. Short- and long-term outcomes as well as anal function of transanal natural orifice specimen extraction surgery versus conventional laparoscopic surgery for sigmoid colon or rectal cancer resection: a retrospective study with over 5-year follow-up. Wideochir Inne Tech Maloinwazyjne. 2022;17(2):344-51. https://doi.org/10.5114/wiitm.2022.113567
4. Schober JM, Alguacil NM, Cooper RS, Pfaff DW, Meyer-Bahlburg HF. Self-assessment of anatomy, sexual sensitivity, and function of the labia and vagina. Clin Anat. 2015;28(3):355-62. https://doi.org/10.1002/ca.22503
5. Bayraktar O, Esen E, Bengür FB, Erenler Bayraktar İ, Aytaç E, Bilgin İA, et al. Transvaginal specimen extraction in minimally invasive colorectal resections: initial experience of a tertiary referral hospital. ACU Saglik Bil Derg. 2019;10(2):231-5. https://doi.org/10.31067/0.2019.130
6. Cui B, Lei S, Liu K, Yao H. Robotic low anterior resection plus transanal natural orifice specimen extraction in a patient with situs inversus totalis. BMC Surg. 2018;18(1):64. https://doi.org/10.1186/s12893-018-0394-3
7. Xiong B, Ma L, Zhang C, Cheng Y. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a meta-analysis. J Surg Res. 2014;188(2):404-14. https://doi.org/10.1016/j.jss.2014.01.027
8. Watanabe T, Hata K. Robotic surgery for rectal cancer with lateral lymph node dissection. Br J Surg. 2016;103(13):1755-7. https://doi.org/10.1002/bjs.10412

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