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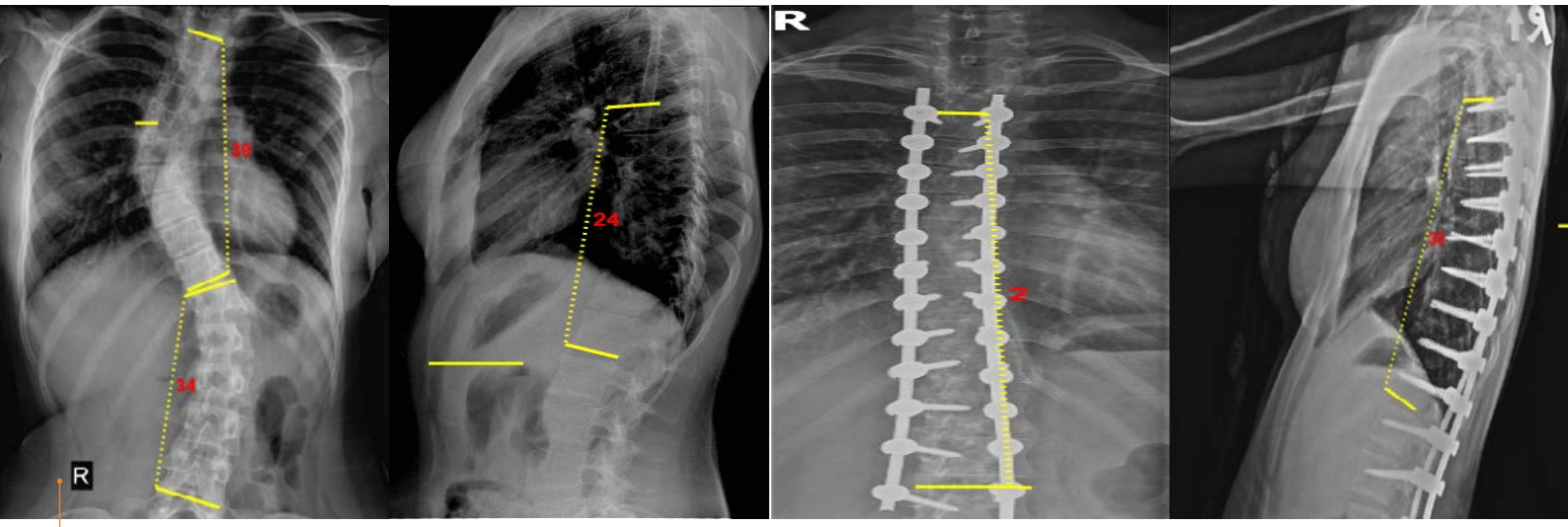

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RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA (JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

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EDITORIAL

Healthcare and Teaching Hospitals

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In order to improve healthcare for Brazilians, the Brazilian Health System (SUS) should guarantee a wide range of services, which include healthcare promotion, prevention, treatment and rehabilitation actions carried out in a long productive chain, from the small family healthcare unit to the large specialized hospital, which means from vaccination to organ transplantation, from analgesic to expensive surgical prostheses.

Each SUS service has its own characteristics, with specific techniques, ranging from behavioural approaches to the intensive use of equipment, with different degrees of complexity. They need trained professionals, technically and administratively, whose learning places are varied, with emphasis on teaching hospitals (TH).

The changes in the SUS thus include TH due to their participation in the training in the 14 professional healthcare categories and also because they constitute the most costly and complex SUS services[1].

The healthcare sector is subject to the effects of demographic, epidemiological, technological, sociocultural, geopolitical and even climatic transitions, resulting in new and more costly demands on the system. These conditions increase the importance (and cost) of TH in researching and teaching new skills and medium and long-term strategies that make SUS sustainable[2].

TH are classified in university hospital, hospital school and auxiliary teaching hospital. The first is owned or managed by universities and the second one by the medical school, while the third one is arranged with a higher education institution.

They are exponential organizations due to the constant and intense disruption and innovation of the technology used. It has high fixed costs for the capital invested in specific physical area, equipment whose technology is rapidly renewed, professionals of notorious specialization, expenses with research and education, high consumption of inputs, public utility and maintenance items, longer length of stay in hospital and minor turnover of beds.

There are in the country (connected to SUS) 200 TH certified, of which 51 are in the State of São Paulo (ESP), 11 belonging to the State Government.

In 2017, the 51 TH admitted 710,000 patients (28.5% of hospitalizations in the 614 hospitalization units of SUS/SP). The average of procedures of high complexity in SUS/SP is 8.4%; in TH, it is 18.4%. The mean value of hospitalization for TH is twice as high

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as the hospitalization value of other hospitals in the SUS/SP (according to the SUS table, which has very outdated values).

The monitoring of these units, both qualitative and quantitative, is carried out with information from both DATASUS and the Teaching Hospitals Evaluation System (SAHE)[3].

The triad care, research and education do not include individualized assessments of quality, productivity and costs, new ways of measuring the operational outcome, which would allow better management and financing. Evaluation of qualitative and quantitative, institutional and professional performance, with publicity and transparency, give returns to society on the feasibility of programs and services mentioned.

The disorderly search of the population for TH services, recognized for their quality, as well as deficiencies in the SUS network generate operational problems. Cases of low complexity that could be better cared in less costly units, overcrowd their emergencies and ambulatories. The use of their beds as the back-end system for chronic and elderly patients reduce the access of more complex cases. Citizens covered by Supplementary Health (SS) use the TH services without the corresponding compensation.

Archaic models of administration also collaborate for poor indicators of turnover and hospital stay, for the lack of standardization of conducts and the use of materials and inputs, which make services more expensive.

The definition of lines of research based on healthcare policies will enable the integration between the objectives of the SUS, educational institutions, researchers and TH, leading to the rationalization of the use of research resources. These resources should be clearly separated from the care expenses, (which is still a precarious fact), which would allow the good administrative performance of the unit.

Direct support from the government and through the development agencies (CAPES, FINEP, CNPq and FAPESP) and other entities has been fundamental for the advancement in this area. However, in the State of São Paulo, in 2017, 17 of the 51 TH have requested funds from FAPESP, which is lower than desired, but this has been increasing since 2006 when it began to be evaluated.

In the training of healthcare professionals, many measures need to be taken, in particular in TH. SUS managers, providers, professional trainers need to dialogue to decide on the profile of the healthcare professional that SUS needs for care and management[4]. The multi-professional participation of experts from the exact, social, biological and human sciences, makes possible the answer to the challenges. It is necessary to make a decision on load of knowledge, years of study and retraining for the type of action, practice and academic.

The offer of vacancies in specialization for trainee doctors, should be based on predictive scenarios, such as in countries that have studied trends from two to three decades onwards, defining residence and research funding bases. While institutions and TH are not aligned with the SUS and SS, hardly the new epidemiological and social challenges will be overcome. The state provides 6,600 medical residency grants for 53 programs, investing 270 million reais annually.

The use of public hospitals by private colleges is a practice that has been important, especially in ESP (with 59 medical schools), sometimes with more than one college using the same TH, a common fact in Brazil. It is essential to have an adequate 'student per bed' relation, giving respect and safety to the patient, learning opportunities, ethical and humanitarian aspects. Specific budgeting is imperative.

TH must have new models and administrative experiences, with flexible organizational structures, capable of promoting governability and sustainability, adaptive to the dynamics of the transitions and integration to SUS and SS. International experiences, partnerships and information exchange are necessary.

REFERENCES

1. Nogueira, D L, Lira, G V, Izabelle Albuquerque, I M A N, Linhares M S C. Avaliação dos Hospitais de Ensino no Brasil: uma Revisão Sistemática. Revista Brasileira de Educação Médica, 39 (1): 151-158; 2015
2. Mendes, J D V, Bittar, O J N V. Perspectivas e desafios na gestão pública do SUS, Rev. Fac. Ciênc. Méd. Sorocaba, v. 16, n. 1, p. 35 - 39 2014.
3. Bittar, O J N V, Magalhães A, Gouveia, R C A, Mendes, J D V. Saúde e protocolos de qualidade. Bol. Epidemiológico Paulista, BEPA Janeiro 2016; 13 (145): 19-32
4. Oliveira, M P R, Menezes I H C F, Sousa, L M, Peixoto, M R G. Formação e Qualificação de Profissionais de Saúde: Fatores Associados à Qualidade da Atenção Primária. Maria. Revista Brasileira de Educação Médica, 547 40 (4): 547-559; 2016

Microcephaly caused by Zika virus and viral detection in maternal urine

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Dear Editor

We read the publication on "*Microcephaly caused by congenital Zika virus infection and viral detection in maternal urine during pregnancy*" with great interest [1]. It reported "*a case of virus infection in a 25-year-old woman during the first trimester of her pregnancy, confirmed by laboratory tests only for the detection of viral particles in maternal urine, with imaging studies demonstrating the progression of cranial and encephalic changes in the foetus and later in the new-born, such as head circumference reduction, cerebral calcifications and ventriculomegaly.*" In fact, this report is a classical finding of Zika virus disease. The infection is usually asymptomatic and the detection of the virus in the body secretion including to urine is possible [2]. According to this report, we might conclude that there are co-incidence of detection of Zika virus in maternal urine and there is an abnormal infant with microcephaly. However, the interesting concern is whether we can assume that finding of Zika virus in maternal urine in asymptomatic pregnant mother has any clinical predictive clue for congenital microcephaly in infant. As mentioned, asymptomatic Zika virus infected mothers are common and not all asymptomatic infected mothers give birth to abnormal child. In our country, in tropical Asia, there has never been any abnormal child born to asymptomatic Zika virus infected pregnant women[3].

REFERENCES

1. Regadas VC, Silva MCE, Abud LG, Labadessa LMPL, Oliveira RGG, Miyake CH, et al. Microcephaly caused by congenital Zika virus infection and viral detection in maternal urine during pregnancy. Rev Assoc Med Bras. 2018;64(1):11-4.
2. Wiwanitkit S, Wiwanitkit V. Afebrile, asymptomatic and non-thrombocytopenic Zika virus infection: don't miss it! Asian Pac J Trop Med. 2016;9(5):513.
3. Joob B, Wiwanitkit V. Congenital Zika virus infection: the tropical Asian perspective. Clin Neurophysiol. 2017;128(2):289.

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Living donor nephrectomy

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Living donor nephrectomy can be carried out through conventional open access, mini-incision, laparoscopy, assisted by robotics, single-site (LESS), or natural orifices (NOTES). The purpose of this guideline is to present the doctors, specialists and healthcare establishments with the prominent evidence available on the best technique for living donor nephrectomy. For this, a systematic review of the literature was performed, without period restriction, in the Medline database, retrieving 322 papers, of which 28 were selected to respond to clinical doubt. The details about the methodology and the results are set out in Appendix I.

INTRODUCTION

LIVING DONOR NEPHRECTOMY can be carried out through conventional open access, mini-incision, pure or hand-assisted laparoscopy (transperitoneal or retroperitoneal), assisted by robotics, single-site (LESS), natural orifices (NOTES). Regardless of the technique, the choice of kidney must comply with severe anatomical criteria and the healthier kidney must always remain with the donor. In cases of equal health conditions, the priority is to remove the left kidney.

In conventional open nephrectomy, the patient is positioned in lateral decubitus, and an oblique lumbar incision is made. The peritoneum is bluntly dissected and medially reflected, gaining access to the retroperitoneal space and the kidney. For an open nephrectomy through mini-incision, the patient is placed in the same previous position, and the mini-incision is made, which can be subcostal, horizontal or vertical. Separation without incision is preferred to muscle section and the extraction of ribs is avoided. When we opt for a transperitoneal laparoscopic nephrectomy, after the complete separation of the kidney, ureter, and renal vessels, a mini Pfannenstiel incision is made, through which the organ will be removed. Renal vessels should be, preferably, connected using, at least, two clamps on each of them.

In retroperitoneal laparoscopic nephrectomy, with the patient in lateral decubitus, the workspace is created through digital or balloon dilation. The trocars are placed, and renal and vascular dissection is conducted as previously described. Hand-assisted laparoscopic nephrectomy can be conducted via a

trans or retroperitoneal approach. The surgery begins with an incision to place the device and introduce the hand. The kidney and the vessels are laparoscopically dissected with manual aid. Renal extraction is made through the hand-insertion device. In robot-assisted laparoscopic nephrectomy, the donor is laterally positioned, and four portals are used, two for the surgeon, one for the camera and another for the assistant. The surgeon operates outside the surgical field, with a magnified 3D view, and the robotic arms offer an amplitude of movements similar to those of the human fist. Surgery lengths are the same as described and the kidney can be removed through a midline incision. Single-site (LESS) or natural orifices (NOTES) laparoscopic nephrectomy, with fewer or no scars, has also been used in living donor nephrectomy. The procedure requires special equipment, but its steps are similar to the ones previously described.

RESULTS

Is there an advantage in living donor nephrectomy through mini-incision over lumbotomy?

Several randomized studies have been published comparing living donor nephrectomy through mini-incision and conventional and laparoscopic open surgery. The mini-incision can be anterior, flank, or posterior. When compared with the conventional lumbotomy, the mini-incision showed: increase in surgery time (p=0.02), less bleeding (p=0.01), reduction in the use of analgesics and decrease in length of hospital stay (p<0.0001). There was no difference in the number of postoperative complications (p=1.00) and significant difference in the level of serum creatinine in the receiver after up to 30 days[1,2] **(B)**. When compared with the laparoscopic surgery, in two studies, there was an increase in: use of analgesics, length of surgery and recovery, as well as warm ischemia time (p<0.05 for all comparisons). No differences were found in the results from kidney function on the receiver and in the number of postoperative and surgical complications for any of the three techniques[3,4] **(A)**.

In a recent retrospective cohort study, the mini-incision, compared with laparoscopic surgery, reduced the length of surgery (53.9 min [40-75] versus 93.7 minutes (75-140), p<0.001), warm ischemia time (2.14 vs 2.66 min min; p<0.001), and length of hospital stay (2.44 vs 3.28 days; p<0.001). There were no significant differences in the scores for pain, graft function, or quality of life between the two groups[5] **(B).**

RECOMMENDATION

Nephrectomy through mini-incision is an acceptable alternative to conventional lumbotomy for living donors. (A)

Are there advantages in using hand-assisted laparoscopic or pure laparoscopic nephrectomy, for living donors, in comparison with the conventional open approach?

Hand-assisted vs. Open

A retrospective cohort study compared the hand-assisted laparoscopic nephrectomy with a living donor (HALN) and conventional open nephrectomy (ON). In comparison with ON, HALN reduced intraoperative bleeding (274.4 ± 198.1 vs 202.99 ± 157.1 ml; p<0.05), and length of hospital stay (5.58 ± 2.2 vs. 4.23 ± 1.8, p<0.05), but increased the length of surgery (270 vs 217 ± 60.1 ± 57.5 minutes, p<0.05) and the warm ischemia time (4.62 ± 2.7 vs 2.12 ± 1.4 minute, p<0.05). There were no significant differences in surgical complications after up to 30 days or in need for transfusion (p>0.05 for both comparisons). There was no reported loss of graft and no difference in kidney function between the groups, at days 1-2, or months 1, 6, or 12, after the nephrectomy[6] **(B)**.

The living donor HALN was compared with the laparoscopic nephrectomy (LN) in a meta-analysis (two randomized clinical trials [RCTs] and 14 cohort studies). No difference was found in the number of complications, conversion to open nephrectomy, blood loss, graft function (assessed by four cohort studies), and length of hospital stay. Manual assistance reduced surgery lengths and warm ischemia time in the comparison with pure LN DM = -18.3, 95% CI -32.9 to -3.6, R2 = 94% and DM = -52.9, 95% CI -91.6 To -14.3, R2 = 96%, respectively)[7,8] **(A)**.

There were no differences in the number of complications when hand-assisted techniques (HALN and hand-assisted retroperitoneal laparoscopic nephrectomy [HARLN]) were combined and compared with the fully laparoscopic approach (OR=0.52, 95% CI 0.33-0,83, R2=46%)[7] **(A)**.

Laparoscopy vs. Open

Despite the greater length of hospital stay and warm ischemia time, laparoscopic nephrectomy presented a shorter length of hospital stay and postoperative recovery, as well as less pain and blood loss. Return to daily activities is faster and, most impor-

tantly, the laparoscopic nephrectomy provides the best quality of life to the donor, in comparison with conventional open surgery or even with the mini-incision approach. It presents low rates of complications and conversion[8-10]**(A)**. The warm ischemia time is longer in laparoscopic nephrectomy when compared with open surgery; however, there is no difference in the final graft function[8,9,11]**(A)**[12]**(B)**.

Transperitoneal vs. Retroperitoneal Approach

The transperitoneal laparoscopy approach (TPLN) is technically more straightforward, with better defined anatomical references and a larger area for work than the retroperitoneal approach.

The use of the retroperitoneal approach (RPLN) in living donor nephrectomy has the advantages of easy access to the renal vessels, improved view of the lumbar vessels, and lower interference in the abdominal organs.

A recent meta-analysis comparing both approaches showed no difference in surgery length, warm ischemia time, blood loss, intestinal lesion, chylous ascites, rates of repeated procedures, ureteral complications, and loss of graft. However, in comparison with the transperitoneal approach, the retroperitoneal approach reduced the rates of blood transfusion, the incidence of delayed graft function, vascular lesion and conversion to an open surgical approach. The length of hospital stay was longer when the retroperitoneal approach was used. Therefore, for living donor nephrectomy, RPLN might be better than TPLN[13]**(A)**.

Another meta-analysis compared the hand-assisted retroperitoneal laparoscopic approach (HARPLN) with TPLN for living donor nephrectomy. Seven studies (498 patients) were included in the final analysis.

HARPLN was better than TPLN in reducing the length of surgery (SMD = -0.84, 95% CI [-1.18 to -0.50]) and warm ischemia time (SMD = -0.93, 95% CI [-1.13 to -0.72]). There was no difference between HARPLN and TPLN in blood loss (SMD = 0.13, CI 95% [-0.50 to 0.76]), hospital stay (SMD = -0.27, 95% CI [-0.70 to 0.15]) or graft survival (RR = 0.97, 95% CI [0.92 to 1.02]). There were also no differences in risk of intraoperative complications between the groups (RR = 0.62, 95% CI [0.31 to 1.21]). When the complications from both retroperitoneal approaches (HARPLN and RPLN) were combined and compared with the transperitoneal approach, the retroperitoneal ones showed reduced complications (OR = 0.52, 95% CI 0.33-0.83, r2 = 0%)[14]**(A)**.

RECOMMENDATION

Living donor laparoscopic nephrectomy (transperitoneal or retroperitoneal) is a safe procedure with minimal associated mortality. (A)

Are there restrictions for living donor laparoscopic nephrectomy in special situations?

There is a discussion around right/left living donor nephrectomy. The left side is preferred because it presents a longer renal vein, whereas the right side is associated with thrombosis of the renal vein and shorter vessels.

A retrospective study identified 58,599 living-donor transplants, of which 50,483 (86.1%) were left donor nephrectomy (LDN), and 8,116 (13.9%) right donor nephrectomy (RDN). There was a higher incidence of delay in graft function in receptors of RDN, with an odds ratio (OR) of 1.38 (95% CI: 1.24–1.53, p<0.0001). The rates of primary failure (loss of graft within 30 days from the transplant) were similar. In the RDN group, graft thrombosis as the leading cause of graft failure, with OR of 1.48 (95% CI: 1.18 to 1.86, p=0.0004), and graft survival was significantly lower (p=0.006 log-rank test). For the living donor results, the conversion from laparoscopy to open was greater in the RDN group, with an OR of 2.02 (95% CI: 1.61-2.52, p<0.00001). There were no differences in vascular complications or the need for reoperation due to bleeding. Reoperations and readmissions were higher in the LDN group. Therefore, there are differences regarding the effectiveness and safety of right and left kidney donor nephrectomy regarding receptor studies, but these are extremely small[15]**(A)**.

The effectiveness and safety of right living donor laparoscopic nephrectomy (RDLN) versus the left (LDLN) were assessed using a meta-analysis. A total of 15 studies with 3,073 patients were included (left, 2,420 patients [78%]; right, 653 patients [22%]). In comparison with the LDLN, RDLN presented shorter length of surgery (weighted mean difference [DMP] -13.44 min, 95% CI -4.15 to -22.73 min; p=0.005) and less blood loss (DMP -10.53 mL; 95% CI -3.64 to -17.43 ml; p=0.003). There were higher intraoperative donor complication rates in LDLN OR = 0.53; 95% CI, 0.31 to 0.92; p=0.03). There were no differences between groups regarding the length of hospital stay, delayed graft function, loss of graft after one year, conversion to open nephrectomy, need of blood transfusion for the donor, and donor or receiver postoperative complications. We can conclude that right and left living

donor laparoscopic nephrectomy are similar in surgical outcomes and postoperative graft function[16]**(A)**.

The studies show that multiple-artery donor laparoscopic nephrectomy is feasible and safe. The multiplicity of arteries could be linked with a higher incidence of ureteral complications for the receiver, especially in cases of polar arteries[17-20]**(B)**.

A body mass index (BMI) of over 35 is usually considered a contraindication to being a donor. To determine if this is justified, a systematic review with meta-analysis compared the perioperative outcome of living donor nephrectomy between donors with high and low BMIs. Of the 14 studies analyzed, eight donor perioperative outcomes were meta-analyzed, out of which five showed no differences for different categories of BMI. Three outcomes showed mean differences (DM) favoring donors with low BMI (≤29.9 kg/m2). A higher BMI increased the length of surgery (DMP 16.91 min; 95% CI 9.06 to 24.76; l2 = 29%), donor serum creatinine (pre/postoperative) (DM 0.05 mg/dl; 95% CI 0.01 to 0.09; R2 = 56%) and the risk of conversion (RR = 1.69; 95% CI 1.12 to 2.56, r2=0%). Thus, a high body mass index (BMI), alone, does not constitute a contraindication for nephrectomy with living donor regarding short-term outcomes[21]**(A)**.

RECOMMENDATION

Evidence supports laparoscopic nephrectomy, regardless of the side (right or left) and for donors with multiple arteries. As for the laparoscopic nephrectomy using obese donors ((BMI ≥ 35 kg/m2), a careful risk assessment should be conducted, and its use should not be generalized. (A)

Are there any advantages of robot-assisted living donor laparoscopic nephrectomy?

A controlled randomized clinical trial compared the robot-assisted laparoscopic nephrectomy in living donor (RALN) and the pure laparoscopic nephrectomy (LN). A total of 45 donors (27 in the right subgroup, and 18 in the left) were randomized into two groups following the ratio of 1: 2. There were no intraoperative complications in both groups. Compared with LN, RALN reduced pain (VAS) at 6, 24, and 48 hours after the surgery (p<0.001 for all comparisons), the need for analgesics (mg of tramadol, p<0.001) and length of hospital stay (p<0.001). There was a preservation of a longer arterial length of the graft when using the robot-assisted approach on the right side (p=0.03), but not on the left (p=0.77). The warm ischemia time is longer in the total RALN group (right + left nephrectomy). In the analysis of the subgroups, there was an increase in the warm ischemia time for left nephrectomy (p=0.01), but it wasn't different from the LN in the right nephrectomy (p=0.24). There was no difference between groups regarding total length of surgery (p=0,14), a decrease in hemoglobin (p=0.97), postoperative donor complications (p=0.97) and the estimated rate of glomerular filtration of the receiver at 9 months (p=0.64). Therefore, RALN is safe and facilitates the preservation of a longer length of the renal artery on the right side. However, the left RALN is associated with a longer warm ischemia time, although with no adverse outcomes of the graft[22]**(A)**.

A retrospective cohort study with 05 live kidney donors who underwent right robot-assisted laparoscopic nephrectomy and 20 who underwent the conventional approach showed no difference in blood loss (p=0.07), length of surgery (p=0.61) and warm ischemia time (p=0.44). It showed no difference in the early postoperative glomerular filtration rates of the donor (p=0.26) and the glomerular filtration of the receiver in the analysis at six months (p=0.53) [23]**(B)**.

A second retrospective cohort study with 13 living kidney donors who underwent robot-assisted laparoscopic nephrectomy and 13 who underwent the open approach showed an increase in surgery length (p=0.0001) and in warm ischemia time (p=0.0001) for the robot-assisted approach. There was no difference in blood loss (p>0.05) and creatinine clearance in the receivers five days after the transplant (p>0.05). The robot-assisted approach reduced the length of hospital stay (5.84 ± 1.8 d x 9.69 ± 2.2 d, p=0.0001)[24]**(B)**.

RECOMMENDATION

Robot-assisted laparoscopic nephrectomy, in living kidney donors, can be an alternative approach to open nephrectomy or pure laparoscopy.

Are there advantages in using single-site laparoscopic nephrectomy in comparison with conventional laparoscopy (l)?

A recent systematic review with meta-analysis included three controlled randomized clinical trials [25-27]**(A)** (179 living donors), which compared single-site laparoscopic nephrectomy in donors (LESS-DN) with pure donor laparoscopic nephrectomy in adults.

There were no differences between LESS-DN and donor laparoscopic nephrectomy regarding mean surgery length (two studies, 79 participants: MD 6.36 min, 95% CI -11.85 to 24.57), intraoperative blood loss (two studies, 79 participants: MD -8.31 ml, 95% CI -7.09 to 23.70) or number of complications (three studies, 179 participants: ARR = 0.05, 95% CI -0.04 to 0.14).

Pain scores at discharge were lower in the LESS-DN group (two studies, 79 participants: MD -1.19, 95% CI -2.17 to -0.21).

For all other outcomes, (length of hospital stay, time to return to daily activities, blood transfusions, conversion to other types of surgery, warm ischemia time, the total need of analgesics, loss of graft), there were no differences [28]**(A)**.

RECOMMENDATION

Any advantage of the single-site laparoscopic nephrectomy over the conventional laparoscopic nephrectomy in uncertain. (A)

APPENDIX I

Clinical question

What is the best technique for living donor nephrectomy?

Eligibility criteria

The main reasons for exclusion were: they did not respond to the PICO and study design.

Narrative reviews, case studies, series of cases, studies with preliminarily results presentations were, initially, excluded.

Search for papers

Database

The scientific database consulted was Medline (via PubMed) and the references of the selected studies.

Identification of descriptors

P	Living kidney donor
I	Nephrectomy
C	Different nephrectomy techniques
O	Benefit or damage

P (Patient); **I** (Intervention or Exposure); **C** (Comparison); **O** (Outcome)

Research strategy

Searches conducted until March 4th, 2018.

Medline via PubMed

#1 (Kidney Transplantation OR Nephrectomy) AND Living Donors

#2 (Laparotomy OR Laparoscopy OR Endoscopy OR Retroperitoneal Space OR Robotic Surgical Procedures OR robotic OR Robot-Assisted OR Robotic-Assistence OR Hand-Assisted Laparoscopy OR open donor nephrectomy OR ODN OR open nephrectomy OR laparoscopic live donor nephrectomy OR LDN)

#3 (Random* OR Comparative study OR Comparative studies OR systematic[sb])

#4: #1 AND #2 AND #3 = 322 studies

#5 (Nephrectomy AND Living Donors) AND (Renal Artery OR multiple Renal Artery OR multiple renal arteries) = 301 studies

#6 (Nephrectomy AND Living Donors) AND (BMI OR Obesity) = 119 studies

#5 OR #6 = 408 studies

Total studies included = 28 studies

Central (Cochrane)

(Kidney Transplantation OR Nephrectomy) AND Living Donors - Included 0

Others

(Kidney Transplantation OR Nephrectomy) AND Living Donors - Included 0

Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question to gather information in medicine to standardize approaches and assist in decision-making.

Reliability - Internal validity

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted, in total accordance with the inclusion and exclusion criteria. Finally, the studies with potential relevance were separated. When the title and the summary were not enlightening, we sought for the full article.

Only studies with texts available in its entirety were considered for critical evaluation.

No restriction was made regarding the year of publication.

Languages: Portuguese, English, and Spanish.

Results application - External validity

The level of scientific evidence was classified by type of study according to Oxford[29] (**Table 1**).

TABLE 1: GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT) and submitted to an appropriate critical evaluation checklist (**Table 2**). The critical evaluation of RCT allows to classify it according to the Jadad score[30], considering Jadad trials < three (3) as inconsistent (grade B) and those with score ≥ three (3) consistent (grade A).

When the evidence selected was defined as a comparative study (observational cohorts, or non-randomized clinical trial), it was subjected to an adequate critical assessment checklist (**Table 3**), allowing for the classification of the study according to the Newcastle Ottawa ScaleE[31], which considered consistent cohort studies with scores ≥ 6, and inconsistent < 6.

TABLE 2 - GUIDE FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, Jadad, level of evidence	**Sample size calculation** Estimated differences, power, significance level, total number of patients
Patient selection Inclusion and exclusion criteria	**Patients** Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	**Patient follow-up** Time, losses, migration
Treatment protocol Intervention, control, and blinding	**Analysis** Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	**Results** Benefits or harmful effects in absolute data, benefits or harmful effects on average

A MeaSurement Tool to Assess Reviews (Amstar)[32] was used to evaluate the quality of the systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, in which 11 represents a review of the highest quality. Quality categories were determined as follows: low (0 to 3 score), medium (4 to 7 score) and high (8 to 11 score). SRs of low and medium quality were excluded.

Method of extraction and result analysis

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be explicitly defined whenever possible.

The results will be presented preferably in absolute data, absolute risk, the number needed to treat (NNT) or number needed to harm (NNH) and, eventually, in mean and standard deviation values (**Table 4**).

TABLE 4 - WORKSHEET USED FOR DESCRIBING AND PRESENTING THE RESULTS FOR EACH STUDY

Evidence included
Study design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ration, mean

Results

Studies returned (05/2018)

TABLE 5 - NUMBER OF PAPERS RETURNED FROM THE SEARCH METHODOLOGY USED IN EACH OF THE SCIENTIFIC DATABASES

DATABASE	NUMBER OF PAPERS
Primary	
PubMed-Medline	322

Application of evidence - Recommendation

The recommendations will be elaborated by the authors of the review, with the primary characteristic of the synthesis of evidence, being subject to validation by all authors who participated in creating the guideline.

TABLE 3 - GUIDE FOR CRITICAL EVALUATION OF COHORT STUDIES

Representativeness of the exposed and selection os the non-exposed (Max. 2 points)	Exposure definition (Max. 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (Max. 1 point)	Comparability from the design or the analysis (Max. 2 points)	Outcome assessment (Max. 1 point)	Adequate follow-up time (Max. 2 points)	Scores and level of evidence

The available evidence will follow some principles of exposure– it will be by outcome and will have as components: number of patients, type of comparison, magnitude, and precision (standard deviation and 95% CI).

Its strength will be estimated (Oxford[29]/Grade[33]) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate weak, or very weak.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician, responsible for the conduct to be followed, given the reality and clinical condition of each patient.

REFERENCES

1. Kok NF, Alwayn IP, Schouten O, Tran KT, Weimar W, Ijzermans JN. Mini-incision open donor nephrectomy as an alternative to classic lumbotomy: evolution of the open approach. Transpl Int. 2006;19(6):500-5.
2. Neipp M, Jackobs S, Becker T, zu Vilsendorf AM, Winny M, Lueck R, et al. Living donor nephrectomy: flank incision versus anterior vertical mini-incision. Transplantation. 2004;78(9):1356-61.
3. Dols LF, Ijzermans JN, Wentink N, Tran TC, Zuidema WC, Dooper IM, et al. Long-term follow-up of a randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy. Am J Transplant. 2010;10(11):2481-7.
4. Kok NF, Lind MY, Hansson BM, Pilzecker D, Mertens zur Borg IR, et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ. 2006;333(7561):221.
5. Yadav K, Aggarwal S, Guleria S, Kumar R. Comparative study of laparoscopic and mini-incision open donor nephrectomy: have we heard the last word in the debate? Clin Transplant. 2016;30:328-34. PMID: 26780835
6. Villeda-Sandoval CI, Rodríguez-Covarrubias F, Cortés-Aguilar G, Alberú-Gómez J, Vilatobá-Chapa M, Sotomayor M, et al. Hand-assisted laparoscopic versus open donor nephrectomy: a retrospective comparison of perioperative and functional results in a tertiary care center in Mexico. Transplant Proc. 2013;45:3220-4. PMID: 24182788
7. Özdemir-van Brunschot DM, Koning GG, van Laarhoven KC, Ergün M, van Horne SB, Rovers MM, et al. A comparison of technique modifications in laparoscopic donor nephrectomy: a systematic review and meta-analysis. PLoS One. 2015 27;10:e0121131. PMID: 25816148
8. Yuan H, Liu L, Zheng S, Yang L, Pu C, Wei Q, et al. The safety and efficacy of laparoscopic donor nephrectomy for renal transplantation: an updated meta-analysis. Transplant Proc 2013;45:65-76. PMID: 23375276
9. Greco F, Hoda MR, Alcaraz A, Bachmann A, Hakenberg OW, Fornara P. Laparoscopic living-donor nephrectomy: analysis of the existing literature. Eur Urol. 2010;58(4):498-509
10. Wilson CH, Sanni A, Rix DA, Soomro NA. Laparoscopic versus open nephrectomy for live kidney donors. Cochrane Database Syst Rev. 2011;(11):CD006124.
11. Dols LF, Kok NF, Ijzermans JN. Live donor nephrectomy: a review of evidence for surgical techniques. Transpl Int. 2010;23(2):121-30.
12. Maroun M, Anthony KC, Samir R, Fouad A, Fouad N, David A, Samir M, Chebl M. LIVING DONOR NEPHRECTOMY: OPEN vs LAPARASCOPY. Renal Function and Complications. J Med Liban. 2015;63:144-9. PMID: 26591194
13. He B, Bremner A, Han Y, Hamdorf JM. Determining the Superior Technique for Living-donor Nephrectomy: the Laparoscopic Intraperitoneal Versus the Retroperitoneoscopic Approach. Exp Clin Transplant 2016;14:129-38. PMID: 27015530
14. Elmaraezy A, Abushouk AI, Kamel M, Negida A, Naser O. Should hand-assisted retroperitoneoscopic nephrectomy replace the standard laparoscopic technique for living donor nephrectomy? A meta-analysis. Int J Surg 2017;40:83-90. PMID: 28216391
15. Khalil A, Mujtaba MA, Taber TE, Yaqub MS, Goggins W, Powelson J, et al. Trends and outcomes in right vs. left living donor nephrectomy: an analysis of the OPTN/UNOS database of donor and recipient outcomes--should we be doing more right-sided nephrectomies? Clin Transplant 2016;30:145-53. PMID: 26589133
16. Wang K, Zhang P, Xu X, Fan M. Right Versus Left Laparoscopic Living Donor Nephrectomy: A Meta-Analysis. Exp Clin Transplant 2015;13:214-26. PMID: 26086831
17. Bandín Musa AR, Montes de Oca J. Hand-assisted Laparoscopic Nephrectomy in Living-donor Kidneys With Multiple Arteries: Experience of a Transplant Center Exp Clin Transplant. 2016;14:153-6. PMID: 27015532
18. Cooper M, Kramer A, Nogueira JM, Phelan M. Recipient outcomes of dual and multiple renal arteries following 1000 consecutive laparoscopic donor nephrectomies at a single institution. Clin Transplant 2013;27:261-6. PMID: 23305411
19. Carter JT, Freise CE, McTaggart RA, Mahanty HD, Kang SM, Chan SH, et al. Laparoscopic procurement of kidneys with multiple renal arteries is associated with increased ureteral complications in the recipient. Am J Transplant 2005;5:1312-8.
20. Hsu TH, Su Li, Ratner LE, Trock BJ, Kavoussi LR. Impact of renal artery multiplicity on outcomes of renal donors and recipients in laparoscopic donor nephrectomy. Urology 2003;61:323-7.
21. Lafranca JA, Hagen SM, Dols LF, Arends LR, Weimar W, Ijzermans JN, et al. Systematic review and meta-analysis of the relation between body mass index and short-term donor outcome of laparoscopic donor nephrectomy. Kidney Int 2013;83(5):931-9. PMID: 23344469
22. Bhattu AS, Ganpule A, Sabnis RB, Murali V, Mishra S, Desai M. Robot-Assisted Laparoscopic Donor Nephrectomy vs Standard Laparoscopic Donor Nephrectomy: A Prospective Randomized Comparative Study. J Endourol 2015;29:1334-40. PMID: 26414847
23. Liu XS, Narins HW, Maley WR, Frank AM, Lallas CD. Robotic-assistance does not enhance standard laparoscopic technique for right-sided donor nephrectomy. JSLS 2012;16:202-7.
24. Renoult E, Hubert J, Ladriere M, Billaut N, Mourey E, Feuillu B, et al. Robot-assisted laparoscopic and open live-donor nephrectomy: a comparison of donor morbidity and early renal allograft outcomes. Nephrol Dial Transplant 2006;21:472-7.
25. Aull MJ, Afaneh C, Charlton M, Serur D, Douglas M, Christos PJ, et al. A randomized, prospective, parallel group study of laparoscopic versus laparoendoscopic single site donor nephrectomy for kidney donation. Am J Transplant 2014;14:1630-7. PMID: 24934732
26. Kurien A, Rajapurkar S, Sinha L, Mishra S, Ganpule A, Muthu V, et al. First prize: Standard laparoscopic donor nephrectomy versus laparoendoscopic single-site donor nephrectomy: a randomized comparative study. J Endourol 2011;25:365-70.
27. Richstone L, Rais-Bahrami S, Waingankar N, Hillelsohn JH, Andonian S, Schwartz MJ, et al. Pfannenstiel laparoendoscopic single-site (LESS) vs conventional multiport laparoscopic live donor nephrectomy: a pro-

spective randomized controlled trial. BJU Int 2013;112:616-22. PMID: 23826907

28. Gupta A, Ahmed K, Kynaston HG, Dasgupta P, Chlosta PL, Aboumarzouk OM. Laparoendoscopic single-site donor nephrectomy (LESS-DN) versus standard laparoscopic donor nephrectomy. Cochrane Database Syst Rev 2016;(5):CD010850. PMID: 27230690

29. Levels of Evidence and Grades of Recommendations - Oxford Centre for Evidence Based Medicine. Disponível em http://www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based medicine-levels-evidence-march-2009.

30. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1-12

31. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Disponível em: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

32. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; 62:1013-20. PMID: 19230606 (http://amstar.ca/Amstar_Checklist.php)

33. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest 2006;129(1):174-81. PMID: 16424429

Fibrin sealant repair of a double-necked femoral pseudoaneurysm

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SUMMARY

Pseudoaneurysms are rare, but femoral artery false aneurysms have increased in recent decades. They are related to endovascular procedures performed on patients with increased risk for this complication. Pseudoaneurysms generally present with only one neck. This paper describes a femoral artery pseudoaneurysm with two necks that occurred after an endovascular procedure and was successfully treated by duplex-guided fibrin sealant. Pseudoaneurysms are rare, but femoral artery pseudoaneurysms have increased with a discrepant incidence reported from 0.5% to almost 4%, mainly related to the increase of endovascular procedures in recent decades. The double-necked pseudoaneurysm identification was of utmost importance to guide the clinical decision-making and allowed good outcomes for the patient.

KEYWORDS: *Aneurysm, False. Fibrin Tissue Adhesive. Ultrasonography, Interventional. Vascular Diseases.*

INTRODUCTION

Pseudoaneurysms are an uncommon clinical entity, generally arising after trauma or surgical procedures. However, pseudoaneurysms may affect up to 3% of vascular access for endovascular procedures, mainly in patients that present risk factors for local complication of the procedure[1,2]. Most of these pseudoaneurysms have only one neck and are first-line treated with compression (blind or ultrasound-guided)[3]. The presence of a second neck could contribute to the failure of this initial treatment by the additional flow in the pseudoaneurysm and also contribute to complications such as deep venous thrombosis, because it requires more intense or prolonged compressions. Ultrasound-guided thrombin injection is reserved for those in whom the compression procedure fails[3]. Even in the treatment with thrombin injection, the two-neck pseudoaneurysm presents additional challenges. Flow in the second neck may also be an additional pathway for distal embolization (main complication of this treatment). The physi-

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cian who performs those procedures must be alert to identify the patients at risk of complications, predict complications as compression failure, and treat them as soon as they arise with the best available alternative[2-5]. After physical examination, duplex ultrasound remains the cornerstone imaging test for better clinical decision-making in the treatment of femoral pseudoaneurysm, especially in the detection of morphological alterations that affect clinical outcomes, such as the presence of more than one neck[2]. Following the CARE statements, a topical case is described that exemplifies the importance of detailed pre-treatment evaluation[6,7].

CASE

A 32-year-old woman, body mass index of 33 kg/m^2, who presented a non-sustained ventricular tachycardia during pregnancy, was submitted to an endovascular cardiac ablation 40 days after delivery. The endovascular procedure was performed with difficulty due to the patient's obesity. Five puncture attempts were required and a 5F introducer was used. Six hours after the end of the endovascular procedure, she was evolved with a pulsatile mass at the puncture site in the right groin, associated with pain and paraesthesia of the right lower inferior limb. Colour Doppler ultrasonography (9 MHz linear transducer, Logic P6, GE healthcare, Wauwatosa, USA) was performed and showed signs of a pseudoaneurysm (Ying-Yang sign) of 1.7 x 2.6 x 2.3 cm (10 ml) localised between the femoral and deep femoral arteries (Figure 1). The false aneurysm had two necks, one at the femoral artery and the other at the deep femoral artery, with a length of 0.55 cm and 0.33 cm, and a width of 0.24 cm and 0.44 cm, respectively (Figure 1).

Firstly, following the diagnosis and pain control with opioids, ultrasound-guided compression was performed on the right groin during two 40-minute attempts. Since the false aneurysm remained at the one-hour duplex control, an ultrasound-guided fibrin sealant injection of 2 mL was performed under local anaesthesia. The fibrin sealant was a commercial tissue adhesive containing fibrinogen and thrombin (Tisseel Lyo®, Baxter AG, Vienna, Austria), and it was injected into the sac of the pseudoaneurysm avoiding the injection in the necks. The immediate control with duplex ultrasound revealed an almost complete

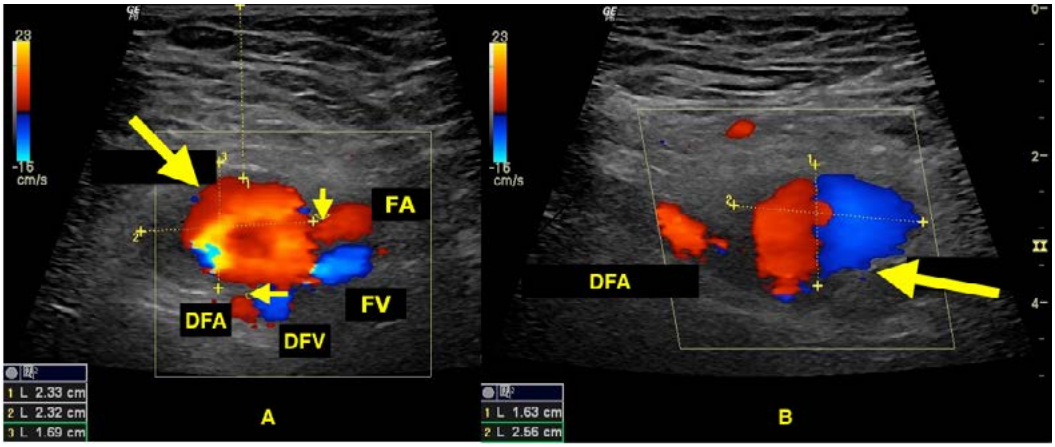

FIGURE 1
Colour Doppler ultrasonography before fibrin sealant repair. A: transversal section of groin vessels; big arrow = pseudoaneurysm; small arrows = necks. B: longitudinal section of groin vessels; big arrow = Ying-Yang sign inside the pseudoaneurysm, D F A = d e e p femoral artery, D F V = d e e p femoral vein, FA = femoral artery and FV = femoral vein.

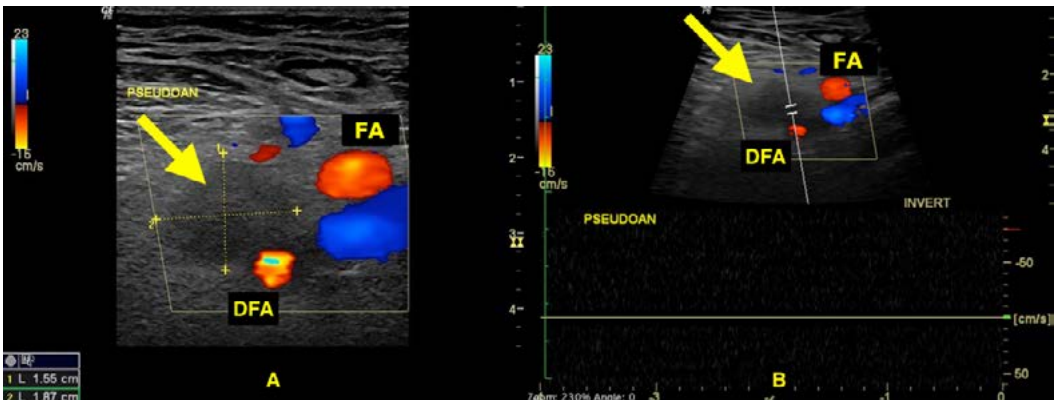

FIGURE 2
Colour Doppler ultrasonography after fibrin sealant repair at 24-h control. A: transversal section of groin vessels; big arrow = o c c l u d e d pseudoaneurysm. B: transversal section of groin v e s s e l s w i t h duplex ultrasound; big arrow = occluded pseudoaneurysm, D F A = d e e p femoral artery and FA = f e m o r a l artery.

occlusion of the pseudoaneurysm and no sign of distal embolization. The 24-h duplex control showed a complete occlusion of the pseudoaneurysm, without colour imaging and without any waveform inside the lesion (Figure 2). All distal arteries of the right lower limb were maintained previously. One month after the procedure, under no indication of pain or paraesthesia, another duplex control confirmed the right femoral artery false aneurysm occlusion without any distal embolization, and no sign of haematoma.

DISCUSSION

Pseudoaneurysms are rare, but femoral artery pseudoaneurysms have increased with a discrepant incidence reported from 0.5% to almost 4%, mainly related to the increase of endovascular procedures in recent decades[1,8,9]. One of the main purpose of endovascular procedures is reducing surgical risks and complications, such as pseudoaneurysm at the vascular access site. Pseudoaneurysms at the vascular access site are associated with several risk factors, including advanced age (>75 years old), female gender, elevated body mass index, degree of arterial calcification, platelet depletion, the use of anticoagulants, the urgency of the procedure, the site of arterial cannulation, and the use of combined arterial and venous access[2,5,10]. The presence of a second neck is a rare finding in femoral pseudoaneurysms but should be included in the list of risk factors for complications, especially since it can contribute to the failure of initial compression, to thrombosis and to distal embolization. Further care should be taken, as in this case, to avoid the necks of the pseudoaneurysm in the injection of fibrin sealant in order to avoid arterial thrombosis or distal embolization.

Patient physical examination with the presence of a pulsatile mass at the groin region or the presence of a non-pulsatile inguinal mass and superficial haematoma must lead the physician to the pseudoaneurysm diagnosis hypothesis[10]. Diagnostic confirmation is achieved by the use of duplex ultrasound to determine the presence of a vessel defect, its measures, the presence of hypo-echoic collection, and the colour and spectral modes to make the distinction between a haematoma and a pseudoaneurysm. Systematic reviews of randomised controlled trials suggest that femoral artery pseudoaneurysms must be treated firstly by compression (blind or ultrasound-guided) and after an unsuccessful attempt, duplex-guided thrombin injection seems to be the best choice[3]. This report describes a case of femoral artery pseudoaneurysm with two necks after an endovascular procedure in an obese and female patient that was successfully treated by duplex-guided fibrin sealant. The double-necked pseudoaneurysm identification was of utmost importance to guide the clinical decision-making and allowed good outcomes for the patient.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series until the time of manuscript submission.

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Informed consent

Written informed consent was obtained from the patient for her anonymised information to be published in this article.

Contributors

RLF, HJGN, STA, JEA, LCN - study design, data collection, data analysis and writing. YLG, CGP - data collection and writing

RESUMO

Os pseudoaneurismas são raros, mas os aneurismas falsos da artéria femoral aumentaram nas últimas décadas. Eles estão relacionados aos procedimentos endovasculares realizados em pacientes com risco aumentado para esta complicação. Os pseudoaneurismas geralmente apresentam apenas um colo. Este artigo descreve um pseudoaneurisma da artéria femoral com dois colos que ocorreu após um procedimento endovascular e foi tratado com sucesso por selante de fibrina guiado por duplex. Os pseudoaneurismas são raros, mas os pseudoaneurismas da artéria femoral aumentaram com uma incidência discrepante relatada de 0,5% a 4%, principalmente relacionada ao aumento dos procedimentos endovasculares nas últimas décadas. A identificação do pseudoaneurisma de colo duplo foi de extrema importância para orientar a tomada de decisão clínica e permitiu bons resultados para o paciente.

PALAVRAS-CHAVE: *Falso aneurisma. Adesivo tecidual de fibrina. Ultrassonografia de intervenção. Doenças vasculares.*

REFERENCES

1. Hirano Y, Ikuta S, Uehara H, Nakamura H, Taniguchi M, Kimura A, et al. Diagnosis of vascular complications at the puncture site after cardiac catheterization. J Cardiol. 2004;43(6):259-65.
2. Stone PA, Campbell JE, AbuRahma AF. Femoral pseudoaneurysms after percutaneous access. J Vasc Surg. 2014;60(5):1359-66.
3. Tisi PV, Callam MJ. Treatment for femoral pseudoaneurysms. Cochrane Database Syst Rev. 2013;(11):CD004981.
4. Yoo T, Starr JE, Go MR, Vaccaro PS, Satiani B, Haurani MJ. Ultrasound-guided thrombin injection is a safe and effective treatment for femoral artery pseudoaneurysm in the morbidly obese. Vasc Endovascular Surg. 2017;51(6):368-72.
5. Ocke Reis PE, Roever L, Ocke Reis IF, Azambuja Fontes F, Rotolo Nascimento M, Nunes dos Santos L, et al. Endovascular stent grafting of a deep femoral artery pseudoaneurysm. EJVES Short Rep. 2016;33:5-8.
6. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. BMJ Case Rep. 2013;2013. pii: bcr2013201554.
7. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218-35.
8. Standard for diagnostic arteriography in adults. Standards of Practice Committee of the Society of Cardiovascular and Interventional Radiology. J Vasc Interv Radiol. 1993;4(3):385-95.
9. Moll R, Habscheid W, Landwehr P. The frequency of false aneurysms of the femoral artery following heart catheterization and PTA (percutaneous transluminal angioplasty). Rofo. 1991;154(1):23-7.
10. Mlekusch W, Haumer M, Mlekusch I, Dick P, Steiner-Boeker S, Bartok A, et al. Prediction of iatrogenic pseudoaneurysm after percutaneous endovascular procedures. Radiology. 2006;240(2):597-602.

Male with myelofibrosis and ulceronecrotic lesions

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SUMMARY

Granulocytic sarcoma also called myeloid sarcoma is an extramedullary tumour of immature granulocytic cells. It is a rare entity, and mostly accompanied by acute myeloid leukaemia. It is observed during the course of myeloproliferative disorders especially in chronic myeloid leukaemia and myelodysplastic syndromes. Here, we report a case of a 60-year-old male with past history of myelofibrosis admitted to the emergency room due ulceronecrotic lesions, fever and dysphagia. We emphasize the importance of recognizing this entity and its severity.

KEYWORDS: *Sarcoma, Myeloid. Leukaemia. Primary myelofibrosis.*

CASE

A 60-year-old man was admitted to the emergency room due ulceronecrotic lesions, fever and dysphagia in the last 15 days. He was in follow-up of hypertension and myelofibrosis for three years without complications. On physical examination, periorbital oedema, ulceronecrotic lesions in ocular, oral and genital mucosae (Figure 1), erythematous and purplish lesions on lower limbs, toes (Figures 2 and 3) and face, cervical, axillary, and inguinal lymph node enlargement, and hepatosplenomegaly were observed. Histopathology of a skin lesion on right thigh showed perivascular inflam-

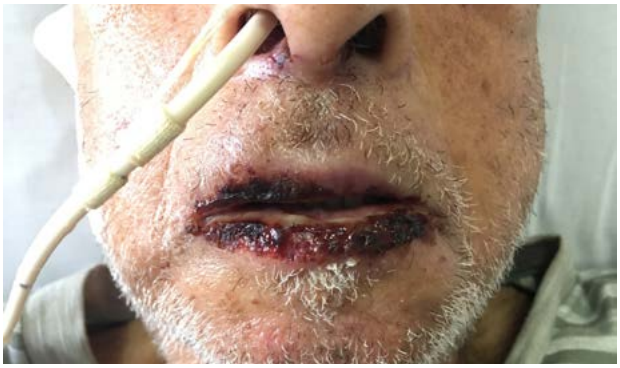

FIGURE 1: MULTIPLE EROSIONS AND CRUSTS ARE PRESENT ON THE LIPS AND NASAL VESTIBULES.

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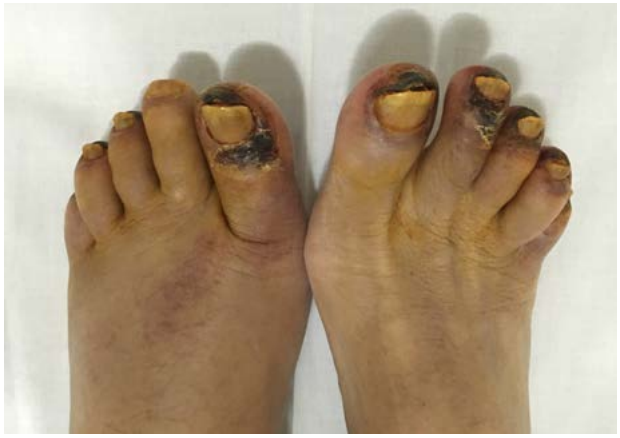

FIGURE 2: ERYTHEMATOUS, CYANOTIC LESIONS AND BLACKENED ERYTHEMATOUS LESIONS ON THE TOES.

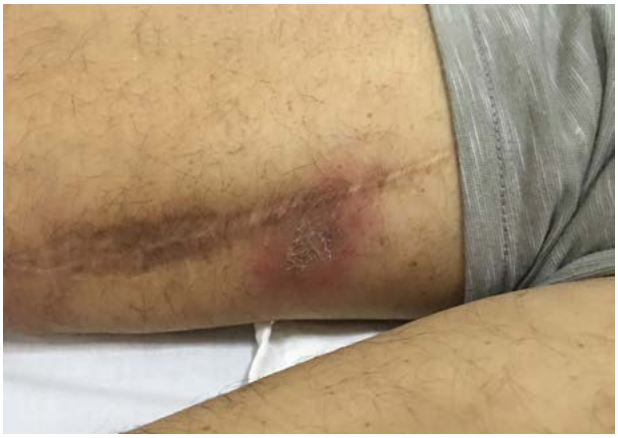

FIGURE 3: INFILTRATED ERYTHEMATOUS PLAQUE ON THE RIGHT THIGH.

matory infiltrate of granulocytic cells in the dermis and subcutaneous with areas of necrosis; no signs of vasculitis. In immunohistochemical evaluation, there was staining for CD3, CD34, CD117, and myeloperoxidase; CD20 was negative.

DISCUSSION

Granulocytic sarcoma, chloroma or extramedullary myeloid tumour, is a tumour mass of myeloblasts or immature myeloid cells that appears in extramedullary sites, especially bone tissue.[1] It is a rare variant of myeloid neoplasia, formerly known as chloroma, because of its greenish colour, secondary to the expression of myeloperoxidase.[1,2]

Cutaneous lesions in patients with myelodysplastic syndrome can be separated into non-specific (vasculitis, infections, neutrophilic dermatosis, ecchymosis, panniculitis and erythema multiform) and specific lesions defined by the presence of malignant hematopoietic cells in the skin.[2,3] The occurrence of cutaneous granulocytic sarcoma in the context of myelodysplastic syndromes is rare and often a sign of poor prognosis.[2] Clinicians must hence be aware to diagnose these lesions early because they can precede peripheral blood and bone marrow transformation to acute myelogenous leukaemia.

RESUMO

O sarcoma granulocítico, também chamado de sarcoma mieloide, é um tumor extramedular de células granulocíticas imaturas. É uma entidade rara, e principalmente acompanhada de leucemia mieloide aguda. É observado durante o transtorno mieloproliferativo, especialmente na leucemia mieloide crônica e síndromes mielodisplásicas. Aqui, relatamos um caso de um homem de 60 anos com antecedente de mielofibrose admitida na sala de emergência devido a lesões ulceronecróticas, febre e disfagia. Enfatizamos a importância de reconhecer essa entidade e sua gravidade.

PALAVRAS-CHAVE: *Sarcoma mieloide. Leucemia. Mielofibrose primária.*

REFERENCES

1. Nizery-Guermeur C, Le Gall-Ianotto C, Brenaut E, Couturier MA, Talagas M, Andrieu-Key S, et al. Cutaneous granulocytic sarcoma and Koebner phenomenon in a context of myelodysplastic syndrome. JAAD Case Rep. 2015;1(4):207-11.
2. Orofino N, Cattaneo D, Bucelli C, Pettine L, Fabris S, Gianelli U, et al. An unusual type of myeloid sarcoma localization following myelofibrosis: a case report and literature review. Leuk Res Rep. 2017;8:7-10.
3. Farah C, Bulai Livideanu C, Jegu J, Paul C, Viraben R, Lamant L, et al. Prevalence and prognostic value of cutaneous manifestations in patients with myelodysplastic syndrome. J Eur Acad Dermatol Venereol. 2010;24(10):1171-5.

An unusual cause of acute abdomen: wandering spleen with infarction

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KEYWORDS: *Wandering Spleen. Splenic Diseases. Splenic Infarction.*

CASE

An 18-year-old woman presented with 7-day history of fever and left lower quadrant abdominal pain. She had past history of Hirschsprung's disease operated on childhood. Positive findings on physical examination included marked lower abdominal tenderness mainly over the left flank and left iliac fossa. Laboratory testing was remarkable for elevated white blood cells at 18,100/mm^3 and C-reactive protein of 95.6 mg/dl. The hypotheses of renal colic and diverticulitis were raised.

An abdominal computed tomography with contrast was performed and showed an enlarged spleen located in the anterior pelvis with stretching and torsion of its vascular pedicle, densification of the fat adjacent to the organ, and small amount of free fluid in the pelvis. The suggested diagnosis was of a wandering spleen and torsion of its pedicle with infarction, confirmed after abdominal surgery with splenectomy and subsequent anatomopathological study (acute ischemia with intraparenchymal haemorrhage of the spleen was observed).

DISCUSSION

Wandering or ectopic spleen is a rarely diagnosed clinical entity. The nature of the illness is only recognized when complications have occurred and often diagnosed in an emergency setting.[1] In adulthood, the presentations vary from splenic incidentaloma to acute abdominal emergency or chronic gastrointestinal complaints. Due to the unspecific clinical features of abdominal pain, imaging modalities play a crucial role in diagnosing ectopic spleen.[1-3] Clinicians should consider wandering spleen in the differential

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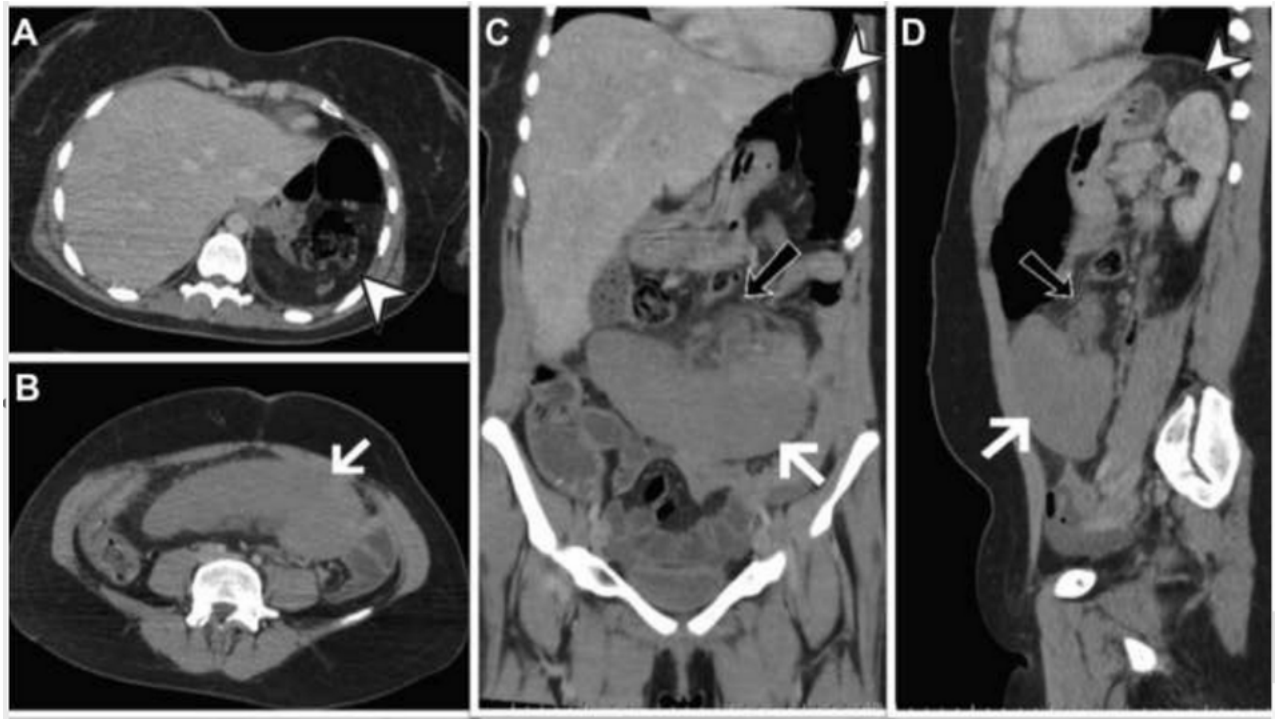

FIGURE 1 Tomographic sections in the axial plane (A and B), coronal (C) and sagittal (D), portal phase after the intravenous contrast, showing the left hypochondriac without a splenic image (head of the cursor), and the spleen being identified in the right iliac fossa (thin white arrow), of discretely increased dimensions,low contrasted, with vascular engorgement and tenuous densification of the adipose tissue with its hilum (black arrow).

diagnosis of acute abdomen. Upon diagnosis, treatment is usually surgical either splenopexy or splenectomy, depending on the degree of torsion and splenic infarction.[1-3]

PALAVRAS CHAVE: *Baço errante. Esplenopatias. Infarto esplênico.*

REFERENCES

1. Reisner DC, Burgan CM. Wandering spleen: an overview. Curr Probl Diagn Radiol. 2018;47(1):68-70.
2. Chauhan NS, Kumar S. Torsion of a wandering spleen presenting as acute abdomen. Pol J Radiol. 2016;81:110-3.
3. Carvalho CG, Vale CEP, Castro Jr PC, Frade TB. Baço migratório em hérnia paraestomal. Rev Col Bras Cir. 2008;35(5):349-50.

Upper vena cava syndrome secondary to giant atrial myxoma

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SUMMARY

Cardiac myxoma is a benign neoplasm, which corresponds to the most common primary heart tumour, responsible for about 50% of the cases. In general, 75-80% of myxomas are located in the left atrium, 18% in the right atrium, and more rarely in the ventricles or multicentric. Right atrial myxoma, in particular, can obstruct the tricuspid valve, causing symptoms of right heart failure, peripheral oedema, hepatic congestion, and syncope. Systemic embolization occurs in 30% of cases, by either tumour fragmentation or total tumour detachment. In the present report, we present a case of a symptomatic patient, who showed a large right intra-atrial lesion, with consequent superior vena cava syndrome, and then underwent surgical resection at admission.

KEYWORDS: *Myxoma. Venae cavae. Heart Neoplasms.*

INTRODUCTION

Primary heart tumours are rare to be found. Of these, myxomas are the most common primary benign neoplasms of the heart and approximately 75% of them are located in the left atrium. Myxomas are more common among women and often occur between 30 and 60 years of age. The signs and symptoms may be nonspecific and with a predominance of constitutional symptoms, and may be manifested by symptoms arising from the obstruction of atrioventricular valves or embolization phenomena.[1] Thus, diagnosis is rarely performed only by physical examination and clinical history. Presentation as superior vena cava syndrome is uncommon and rarely described in literature.[2]

A 55-year-old female, black patient admitted with a complaint of dyspnoea on minimal exertion and oedema of the face and upper limbs for 2 months. She reported a personal history of systemic arterial hypertension, haemorrhagic stroke 7 years ago and she was a former smoker. Physical examination found heart rate at 100 beats per minute, blood pressure of 130x70 mmHg, respiratory

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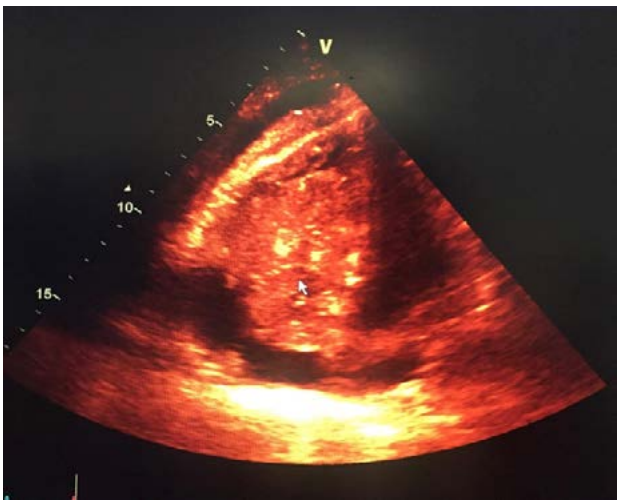

FIGURE 1. IMAGE OF TWO-DIMENSIONAL TRANSTHORACIC ECHOCARDIOGRAPHY, SHOWING A LARGE AND IRREGULAR MASS IN THE RIGHT ATRIUM.

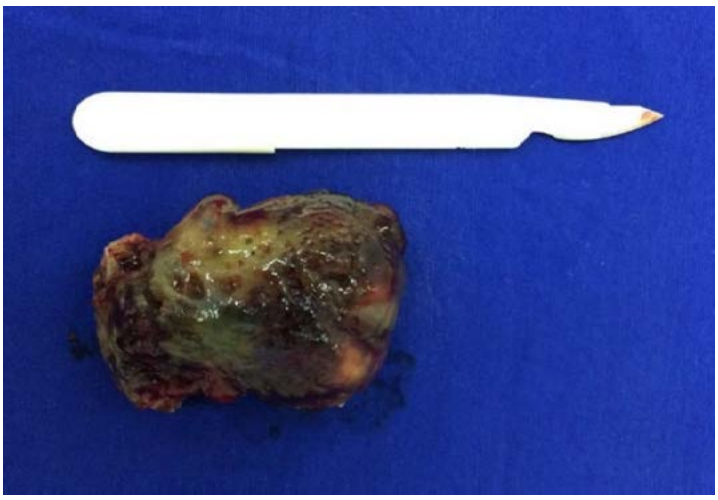

FIGURE 2. SAMPLE OBTAINED FROM THE PATIENT DURING SURGERY.

rate of 25 incursions per minute, arterial saturation 90% in ambient air, capillary filling time <3 s, rhythmic and normophonetic sounds without murmurs, vesicular murmurs present with bibasilar crackles and oedema +4/+4 on the face, upper limbs, cervical region and trunk. At that time, the diagnosis of superior vena cava syndrome and heart failure was made. Electrocardiogram showed sinus rhythm with diffuse alteration of ventricular repolarization. Transthoracic echocardiography revealed a large mass inside the right chambers (8.0 x 4.0 cm), surface and irregular borders, very mobile, hyperechogenic, heterogeneous, passing through the tricuspid valve to the right ventricle, adhered to the interatrial septum (figure 1). Diagnostic hypothesis of superior vena cava syndrome due to intra-cardiac neoplasia. The patient was referred to the surgical centre for resection of the tumour, removing all the mass and the blade of the oval fossa, in addition to closing the intra-atrial communication. The surgical description reported excision of a giant tumour of the right atrium, with invasion of the right ventricle and intense restriction of that. The margins were macroscopically free of neoplastic involvement and the patient left cardiopulmonary bypass without difficulty after 33 minutes and with anoxia of 21 minutes. The resected material was sent to anatomopathological study and confirming the diagnosis of myxoma. In the postoperative period, the patient evolved uneventfully, being discharged from the intensive care unit on the 2nd day. The oedema regressed significantly and she was discharged on the 5th postoperative day.

DISCUSSION

Tumours that originate from the heart are rare, found in less than 0.1% of the population. Of the primary cardiac tumours, 80% are considered benign. Of these, myxoma is the most frequent one, constituting 50% of benign primary cardiac tumours. It occurs most often between 30 and 60 years of age and in females. It usually occurs sporadically, although family cases of multifocal location associated with Carney's syndrome are described. Fibroelastomas and papillary lipomas are other types of benign cardiac tumours in adults but rarer than myxomas.[3] In the case reported above, it occurred in a 55-year-old woman with no records of similar cases in the family.

Cardiac myxomas are usually pedunculated, with fixation of the fibrovascular stem to the subendothelial base. The common site of fixation is the interatrial septum, in the region of the oval fossa. In contrast to other cardiac tumours, such as lipoma and rhabdomyoma, which are typically not pedunculated.[4]

Rarely the cardiac myxoma can directly involve the heart valves. Most have diameters ranging from 4 to 8 cm, although their diameter can reach 16 cm. Its average weight is of 37 g with variation of 15 to 180 g. Approximately, half of myxomas have a villous surface. Evidence suggests that myxomas with villous surface are more likely to embolize.[5] The tumour de-

scribed in this case presented it (8.0 x 4.0 cm), being already called giant myxoma (figure 2). The location was typical, however, obstruction of the tricuspid ring with manifestation of vena cava syndrome is what makes the case uncommon.

The most common clinical manifestations are constitutional or systemic, known as myxoma syndrome such as fatigue, fever, weight loss, arthralgia, myalgia, erythematous rash and laboratory abnormalities such as anaemia and elevated sedimentation rate, C-reactive protein and globulins, have been related in a discordant way with the size and the location of the tumour. It is believed that these manifestations are related to the production and release of IL-6 by the tumour cells themselves, and it is also suggested the relation with phenomena of intratumoral haemorrhage, microembolism or the release of tumour fragments, which stimulate an immune response in the patient. In any case, the systemic manifestations resolve after removal of the tumor.[6]

Symptoms of intracardiac obstruction, heart failure, embolism, syncope or sudden death (due to complete mitral valve obstruction or coronary artery embolization) may also be present. Heart failure is more common in septum-related solid tumours, whereas systemic embolization is more frequent in papillary tumours of extra septal origin.[7]

In the case presented, the patient evolved with symptoms of heart failure such as dyspnoea at minimal progressive efforts and oedema of the face and upper limbs that suggested superior vena cava syndrome. Such obstruction can be caused by invasion or extrinsic compression by contiguous pathological processes involving the right lung, lymph nodes and other mediastinal structures, or by intraluminal thrombosis.[5] The clinical manifestations of right atrial myxoma result mainly from tricuspid valve stenosis and pulmonary embolism. Tricuspid valve stenosis causes systemic venous congestion without pulmonary congestion while pulmonary embolism produces dyspnoea and pulmonary hypertension causing right heart failure.[8]

We did not find in the literature a similar report caused by myxoma. We believe that due to the mobility of the tumour, such manifestation usually does not occur since the obstruction to the flow would be intermittent. This form of presentation probably infers a greater degree of fixed obstruction and gravity.

Non-invasive methods, such as echocardiography and computed tomography of the chest, have made a great contribution to the diagnosis of intracardiac myxomas. In addition to confirming the diagnosis, they allow the establishment of the best surgical technique.[9] Transthoracic echocardiography, although less invasive, has shown 95% sensitivity in the detection of myxomas.[10] In some cases clinical echocardiographic data may not collaborate in the distinction between structures, and may be aided by computed tomography of the chest and magnetic resonance imaging. The use of transesophageal echocardiography seems to provide additional and more accurate information regarding transthoracic echocardiography, including intraoperative echocardiography to better delineate the surgical margins.[1]

Another factor of fundamental importance is the investigation of all cardiac chambers. In addition to biatrial approach, biventricular approach may also be necessary, not only to avoid relapse, but also the risk of embolization. As in the case reported in which the tumour had originated in the right atrium with invasion of the right ventricle.[9]

Due to risks previously mentioned as risks of embolization, valvular or outflow tract obstruction and arrhythmogenesis, the most common treatment approach is surgery in patients with myxomas and the results are generally favourable. Therefore, surgical excision should be planned as soon as the diagnosis is confirmed. Thromboembolic events are rare postoperatively and atrial arrhythmias are the most common complications after surgery for myxoma removal. Myxomas can be resected with low early mortality and excellent long-term survival. Although tumour recurrence is rare, imaging follow-up is recommended because the recurrence rate is significantly higher in the first 10 years after surgery.[1]

CONCLUSION

The report of superior vena cava syndrome by atrial myxoma with tricuspid valve obstruction is unique. However, it is completely reversible after surgery.

Conflict of interest

The authors declare that they agree with the publication, have no conflicts of interest and do not have funding for the study in question.

RESUMO

O mixoma cardíaco é uma neoplasia benigna, que corresponde ao tumor primário mais comum do coração, responsável por cerca de 50% dos casos. De modo geral, 75 a 80% dos mixomas estão localizados no átrio esquerdo, 18% no átrio direito, e mais raramente, nos ventrículos ou multicêntricos. O mixoma atrial direito, em particular, pode obstruir a válvula tricúspide, causando sintomas de insuficiência cardíaca direita, edema periférico, congestão hepática e síncope. A embolização sistêmica ocorre em 30% dos casos, quer pela fragmentação do tumor ou pelo desprendimento total do mesmo. No presente relato, apresentamos um caso de uma paciente sintomática, que evidenciou grande lesão intra-atrial direita, com consequente síndrome da veia cava superior, sendo, então, submetida a ressecção cirúrgica na internação.

PALAVRAS-CHAVE: *Mixoma. Veias cavas. Neoplasias Cardíacas.*

REFERENCES

1. Kavakli AS, Kavrut Ozturk N. Determination of residual mass in left ventricle by intraoperative transesophageal echocardiography after a giant and floating left atrial myxoma resection. Rev Bras Anestesiol. 2017. pii: S0034-7094(17)30137-X.
2. Pires NF, Morais A, Queiroga H. Superior vena cava syndrome as tumour presentation. Rev Port Pneumol. 2010,16(1):73-88.
3. Bowman JN, Treece J, Bhattad PB, Bochis M, Bajaj K. Giant left atrial myxoma masquerading as cough-syncope syndrome. J Investig Med High Impact Case Rep. 2017;5(3):2324709617724177.
4. Choi CH, Park CH, Kim JS, Jeon YB, Lee JI, Park KY. Giant biatrial myxoma nearly obstructing the orifice of the inferior vena cava. J Cardiothorac Surg. 2013;8:148.
5. Bonow RO, Mann D, Zipes D, Libby P. Braunwald's heart disease: a textbook of cardiovascular medicine. 9th ed. Philadelphia:Saunders Elsevier; 2011.
6. Marta L, Peres M, Alves M, Ferreira da Silva G. Giant left atrial myxoma presenting as acute myocardial infarction. **Rev Port Cardiol**. 2012;31(12):815-9.
7. Kuroda T, Yokoyama Y, Yuhara S, Okawa H, Hasegawa H, Yokote J, et al. Giant biatrial myxoma with two different gross findings. Gen Thorac Cardiovasc Surg. 2018;66(6):358-60.
8. Nakabayashi K, Murata S, Kato H, Oka T. The differentiation of giant right atrial myxoma from metastatic cancer with the use of multiple imaging modalities. Intern Med. 2016;55(8):925-8.
9. Dias RR, Stolf NA, Malbouisson LM, Fernandes F, Ramirez FJ, Mady C, et al. Morbidity and embolic potential of left atrial cardiac tumors. Thorac Cardiovasc Surg. 2006;54(6):400-3.
10. Vale MP, Freire Sobrinho A, Sales MV, Teixeira MM, Cabral KC. Giant myxoma in the left atrium: case report. **Rev Bras Cir Cardiovasc**. 2008;23(2):276-8.

Nasopharyngeal linguatulosis or halzoun syndrome: clinical diagnosis and treatment

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SUMMARY

Halzoun syndrome, also known as nasopharyngeal linguatulosis, is a rare entity that is mostly prevalent in Eastern Mediterranean countries. The consumption of raw ovine liver and lymph nodes infested with Linguatula serrata nymphs remains a major cause of the nasopharyngeal symptoms and discomfort associated with the disease. Halzoun syndrome is a clinical diagnosis based on history and presentation. Treatment of this disease is still debated; however, our experience reveals that alcohol gargle can be a good option. Proper counselling on the hazards of eating raw liver in endemic areas is needed. Moreover, physicians should be aware of the sequence of events in the disease in order not to delay or miss the diagnosis. This communication presents a rare Lebanese case of Halzoun syndrome that offers medical implications in the clinical diagnosis and treatment of the nasopharyngeal symptoms of this syndrome, with a review of the literature.

KEYWORDS: *Pentastomida. Lebanon. Nasopharyngitis. Parasitic Diseases.*

INTRODUCTION

Halzoun syndrome was originally described in Lebanon, in 1905. It is a rare clinical disease that manifests as an acute allergic-like reaction involving the upper respiratory tract and nasopharyngeal mucosa after the consumption of raw sheep or goat liver, a popular food presentation in Lebanon and other countries of the Eastern Mediterranean region.[1] At first, this condition was thought to be due to *Fasciola hepatica*;[2] alternative suggestions such as *Dicrocoelium dendriticum*,[3] *Clinostomum complanatum*[4] and, most recently, *Linguatula serrata*[5] have also been made. Consequently, Halzoun is often referred to as nasopharyngeal linguatulosis.

On the basis of clinical presentation, Lebanese Halzoun is congruent with the Marrara syndrome in Sudan.[6] Marrara is linked to the ingestion of various raw visceral organs of sheep, goats, cattle or camels. In both diseases, discomfort and a pricking sensation deep in the throat occur minutes to hours post prandial (Figure 1). However, expectoration of worms is rarely observed in patients with the Lebanese Halzoun whereas it is quite common in Marrara syndrome.[7]

Few reports exist in the literature exploring Halzoun syndrome (Table 1).[1,7-21] In this paper, we explore the case of a Lebanese patient presenting

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TABLE 1: DOCUMENTED CASES OF HALZOUN SYNDROME AND SIMILAR PRESENTATIONS. NB: ALL CASES REPORTED IMPROVEMENT OF SYMPTOMS WITH TIME.

Author	Year	Case	Source	Treatment	Country
Roy and Ganguly[8]	1940	Female with coughing, sneezing, pain over the region of the frontal sinuses and discharge of white motile worms	Domestic dog	No treatment	India
Unat and Sahin[9]	1950	Female with sneezing, coughing, severe itching in the throat and nasal discharge of motile organisms	Improperly cooked ovine mesenteric lymph nodes	No treatment	Turkey
Watson and Kerim[10]	1956	23 cases with pharyngeal irritation (Halzoun attack)	Raw sheep or goat liver	-	Lebanon
Papadakis and Hourmouziadis[11]	1958	29-year-old female with acute attack of cough and sneezing, with much rhino-pharyngeal secretion, and allergic symptoms. Worm-like pieces were expelled several times with the secretions from the rhino-pharyngeal cavities	-	No treatment	Greece
Le Corroller and Pierre[12]	1959	A case with nasopharyngeal linguatulosis	-	-	Morocco
Schacher et al.[1]	1965	26 patients with pain in the throat, severe itching in the external auditory canals, pain in the ears, tinnitus, paroxysmal coughing, hoarseness, dyspnoea, paroxysmal sneezing, lachrymation, coryza, haemoptysis, epistaxis, submandibular oedema, and temporary hearing loss	Raw goat liver	No treatment (One patient needed oxygen)	Lebanon
Schacher et al.[6]	1969	17-year-old female with itching and tingling in the throat, dyspnoea, coughing, sneezing and discharging white worms from the nasals and the mouth 29-year-old male with a foreign body sensation in the mouth, coughing, hoarseness, dyspnoea and discharge of a white organism from the mouth	Raw liver or lymph nodes of domestic herbivores	No treatment	Lebanon
Buslau et al.[13]	1990	37-year-old German tourist with coughing, hoarseness, dysphagia, anosmia, frontal headache, epistaxis and a papular non-itching exanthema	Improperly cooked meat	No treatment	Tunisia
El-Hassan et al.[14]	1991	28-year-old female with itching of the nose, palate and throat, running from the nose and eyes, and dysphonia	Raw goat liver	No treatment	Sudan
Yagi et al.[15]	1996	24 patients who presented with dyspnoea, sneezing, coughing, dysphagia, dysphonia, facial oedema, headache, fever, vomiting, itching in the throat and nose, unilateral conductive deafness, tinnitus and facial palsy	Raw viscera of goats or sheep	Antihistamines Antibiotics	Sudan
Morsy et al.[16]	1999	20-year-old male with fever, urticaria (face and neck), coughing, vomiting and passage of worm-like structures in his nasal discharge and vomitus	-	Symptomatic treatment Praziquantel (1 dose)	Egypt
Maleky[17]	2001	28-year-old female with pharyngeal symptoms	-	Removal	Iran
Siavashi et al.[18]	2002	A 27-year-old male and two females aged 23 and 43 years with discomfort and a prickling sensation deep in throat which extended to the ears, coughing, sneezing, yellow nasal discharge, dyspnoea, dysphagia and frontal headache	Undercooked sheep liver	Forceps removal of worms from larynx, nose and gums	Iran
Yilmaz et al.[19]	2011	26-year-old female with expectoration of few worms about 4 cm long from the oral cavity, sore throat, partial voice loss, pharyngeal pain, coughing, sneezing and vomiting	-	No treatment Gargling with saline solution	Turkey
Hamid et al.[20]	2012	A 34-year-old mother and her 12-year-old daughter with discomfort and pricking sensation in throat with expansion to the ears, coughing, sneezing, yellow nasal and ear discharges were appeared, epigastric pains, movement of something in their nose and ears, and discharge of several organisms through coughing and sneezing	Raw goat liver	No treatment	Iran
Khalil et al.[7]	2013	32 patients with moderate to severe pharyngitis, itchiness of throat and nose, nasal congestion and discharge and lacrimation	Raw/undercooked ovine (sheep or goat) liver ingestion	Methylprednisolone (40–80 mg intramuscular or intravenous) injections	Lebanon
Yazdani et al.[21]	2014	32-year-old woman with burning sensation and itching of the nasopharyngeal region and throat, sneezing, coughing and respiratory discharges	Raw sheep liver	Cetirizine and Flixonase aqueous nasal spray Saline solution (nasal wash)	Iran

with clinical symptoms of Halzoun syndrome, and discuss the diagnostic and curative aspects of the disease with a review of the literature.

REPORT

A 20-year-old female, previously healthy, was referred with nasopharyngeal symptoms of two days duration. Described symptoms were discomfort and a bolus sensation deep in the throat. The symptoms were associated with severe rhinorrhoea, coughing, sneezing and mild dyspnoea, and were severe enough to awaken the patient at night. Nausea, vomiting and other gastrointestinal manifestations were not reported. The patient stated that her symptoms started 6-hours after eating raw ovine liver, with five other family members. All family members developed similar symptoms; however, three siblings consumed alcohol during their meal. Their symptoms resolved within 24 hours. The remaining three family members (father, mother and patient) did not consume alcohol during the meal. Before presentation, the patient sought external medical advice and was prescribed oral corticosteroids with no significant improvement. Routine clinical examination and nasopharyngeal check-up showed no significant findings. Based on the clinical symptoms and manifestations, Halzoun syndrome was suspected. She was advised to gargle with alcohol every 4 to 6 hours. Upon follow-up, one week later, the patient reported significant improvement of symptoms. Due to the fact that alcohol gargle is an uncommon and peculiar regimen, the patient sought the advice of another practitioner who prescribed Albendazole for 3 days, despite her improvement.

DISCUSSION

Halzoun syndrome continues to manifest itself occasionally in the form of an allergic-like pharyngitis. Most of the previously described cases reported a history of raw sheep or goat liver intake (Table 1). Raw liver is a traditional Lebanese dish that is popularly served as part of the Lebanese "Mezza". Often, the symptoms of Halzoun can be mistaken for typical allergies and corticosteroids may be prescribed. The patient did not benefit from oral corticosteroids after two days of adequate steroid administration. Therefore, diagnosis based on clinical presentation and history is crucial.

Nasopharyngeal discomfort, coughing and sneezing are often common during Halzoun attacks. Other symptoms like pain and itching in the external auditory canals, tinnitus, hoarseness, lacrimation, coryza, haemoptysis, epistaxis, headache, submandibular oedema, temporary hearing loss, and papular rash may also be encountered;[1,16] our patient did not report any of these symptoms.

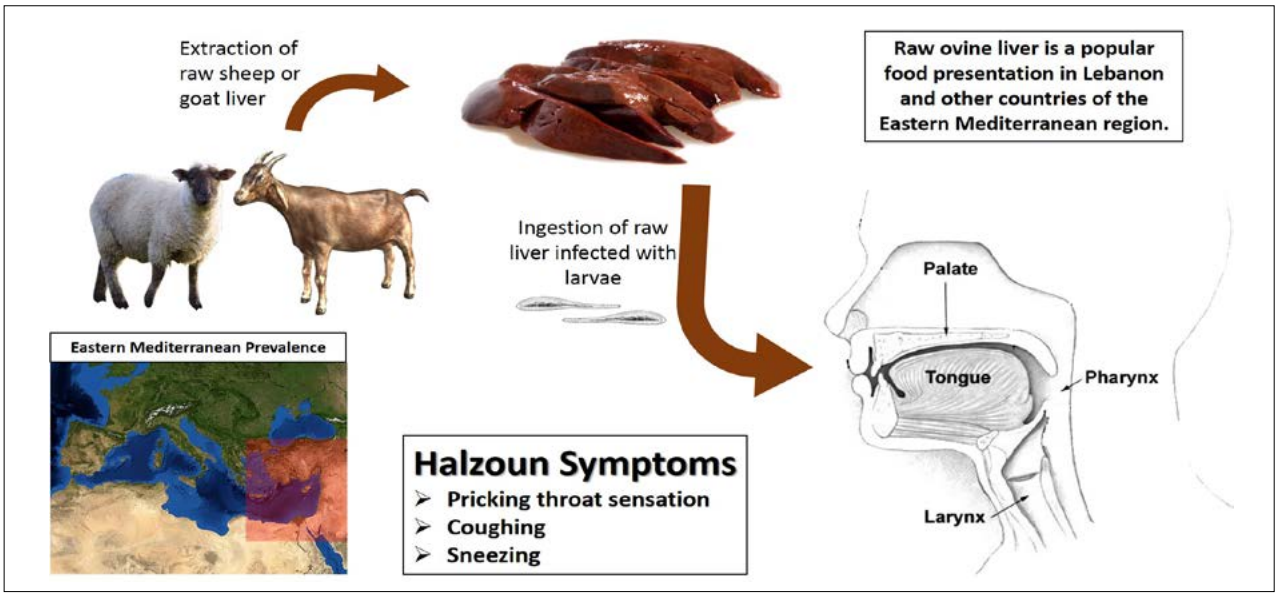

FIGURE 1 Halzoun Syndrome is a result of a buccopharyngeal infection mostly occurring in Lebanon and other Eastern Mediterranean countries. It is thought to be caused by Linguatula serrata worms which attach by their suckers to the soft palate, pharynx and larynx of the human host, after ingestion of infected raw liver or lymph nodes from sheep or goats. Most common symptoms of Halzoun include picking sensation in the throat, coughing and sneezing.

Resolution of symptoms within 24 hours in family members who ingested alcohol during their meal was a clue to the diagnosis. Other reports suggest that the patient might improve without treatment and that he/she may cough or sneeze the infested worms (Table 1). In Lebanese Halzoun, there are often no worms or only very few non-mobile worms found in the mouth, nasal secretions or throat of patients, making it difficult to expel or retrieve proper samples for pathogen identification.[7] For this reason, some suggested the administration of emetics that will lead to the expulsion of parasites in the vomitus,[2] while others suggested the insufflation of lemon powder into the throat to detach parasites from the mucosa.[10] We believe that alcohol will neutralize the parasites and that the gargle action will help in detaching them.

CONCLUSION

Alcohol gargle seems to be a good option for the treatment of Halzoun syndrome amid the lack of consensus on other alternative regimens. Proper counselling about the hazards of eating raw liver in endemic areas is needed. Moreover, physicians should be alerted to the chronology of events in the disease in order not to delay or miss the diagnosis.

Ethical Approval

Patient granted full permission to share and publish all information present.

Conflict of Interests

None declared.

Funding: None.

RESUMO

Esta comunicação apresenta um caso libanês raro de síndrome de Halzoun que oferece implicações médicas no diagnóstico clínico e no tratamento dos sintomas nasofaríngeos desta síndrome, com uma revisão da literatura. A síndrome de Halzoun, também conhecida como linguatulose nasofaríngea, é uma entidade rara predominante nos países do Mediterrâneo Oriental. O consumo de linfonodos ovinos e linfáticos ovinos infestados com ninfas Linguatula serrata continua a ser uma das principais causas dos sintomas nasofaríngeos e do desconforto associado à doença. A síndrome de Halzoun é um diagnóstico clínico baseado na história e na apresentação. O tratamento dessa doença ainda é debatido; no entanto, nossos resultados revelam que o gargarismo de álcool pode ser uma boa opção. É necessário um aconselhamento adequado sobre os perigos de comer fígado cru em áreas endêmicas. Além disso, os médicos devem estar cientes da sequência de eventos na doença, a fim de não atrasar ou perder o diagnóstico.

PALAVRAS-CHAVE: *Pentastomídeos. Líbano. Nasopharyngitis. Doenças parasitárias.*

REFERENCES

1. Schacher JF, Khalil GM, Salman S. A field study of halzoun (parasitic pharyngitis) in Lebanon. J Trop Med Hyg. 1965;68(9):226-30.
2. Khouri A. Le halzoun. Arch Parasitol. 1905;9:78-94.
3. Brumpt E. Précis de parasitologie. 5th ed. Paris:Masson et Cie:1936. p.572-3.
4. Witenberg G. What is the cause of the parasitic laryngo-pharyngitis in the near East ("halzoun")?. Acta Med Orient. 1944;3(6):191-2.
5. Khalil GM, Schacher JF. Linguatula serrata in relation to halzoun and the marrara syndrome. Am J Trop Med Hyg. 1965;14(5):736-46.
6. Schacher JF, Saab S, Germanos R, Boustany N. The aetiology of halzoun in Lebanon: recovery of Linguatula serrata nymphs from two patients. Trans R Soc Trop Med Hyg. 1969;63(6):854-8.
7. Khalil G, Haddad C, Otrock ZK, Jaber F, Farra A. Halzoun, an allergic pharyngitis syndrome in Lebanon: the trematode Dicrocoelium dendriticum as an additional cause. Acta Trop. 2013;125(1):115-8.
8. Roy DN, Ganguly SK. Linguatulid infection in man. Ind Med Gaz. 1940;75(8):478.
9. Unat EK, Sahin V. Linguatula serrata sur felerile husule gelen bir infestasiyon hastaligi dolaysile. Istanbul: Universitesi tip Facultesi Mecmuasi; 1950. p.362-9.
10. Watson JM, Kerim RA. Observations on forms of parasitic pharyngitis known as halzoun in the Middle East. J Trop Med Hyg. 1956;59(7):147-54.
11. Papadakis AM, Hourmouziadis AN. Human infestation with Linguatula serrata: report of a case. Trans R Soc Trop Med Hyg. 1958;52(5):454-5.
12. Le Corroller Y, Pierre JL. On a case of human linguatulosis in Morocco. Bull Soc Pathol Exot Filiales. 1959;52:730-3.
13. Buslau M, Kühne U, Marsch WC. Dermatological signs of nasopharyngeal linguatulosis (halzoun, Marrara syndrome): the possible role of major basic protein. Dermatologica. 1990;181(4):327-9.
14. el-Hassan AM, Eltoum IA, el-Asha BM. The Marrara syndrome: isolation of Linguatula serrata nymphs from a patient and the viscera of goats. Trans R Soc Trop Med Hyg. 1991;85(2):309.
15. Yagi H, el Bahari S, Mohamed HA, Ahmed el-R S, Mustafa B, Mahmoud M, et al. The Marrara syndrome: a hypersensitivity reaction of the upper respiratory tract and buccopharyngeal mucosa to nymphs of Linguatula serrata. Acta Trop. 1996;62(3):127-34.
16. Morsy TA, El-Sharkawy IM, Lashin AH. Human nasopharyngeal linguatuliasis (Pentasomida) caused by Linguatula serrata. J Egypt Soc Parasitol. 1999;29(3):787-90.
17. Maleky F. A case report of Linguatula serrata in human throat from Tehran, central Iran. Indian J Med Sci. 2001;55(8):439-41.
18. Siavashi MR, Assmar M, Vatankhah A. Nasopharyngeal pentastomiasis (Halzoun): report of 3 cases. Iran J Mol Sci. 2002;27:191-2.
19. Yılmaz H, Cengiz ZT, Çiçek M, Dülger AC. A nasopharyngeal human infestation caused by Linguatula serrata nymphs in Van province: a case report. Turkiye Parazitol Derg. 2011;35(1):47-9.
20. Hamid T, Hossein YD, Mehran BB, Masood FS, Hamid E. A case report of Linguatula serrata infestation from rural area of Isfahan city, Iran. Adv Biomed Res. 2012;1:42.
21. Yazdani R, Sharifi I, Bamorovat M, Mohammadi MA. Human linguatulosis caused by Linguatula serrata in the city of Kerman, South-eastern Iran: case report. Iran J Parasitol. 2014;9(2):282-5.

ORIGINAL ARTICLE

Cobalt chromium-Titanium rods versus Titanium-Titanium rods for treatment of adolescent idiopathic scoliosis; which type of rod has better postoperative outcomes?

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SUMMARY

OBJECTIVE; *Compare the outcome of spinal deformity correction between Ti-Ti and CrCo-Ti rods for the treatment of spinal Adolescent Idiopathic Scoliosis (AIS) using rods mentioned with all pedicle screws and translation technique.*

METHOD; *59 patients operated for spinal deformity (Lenke 1 or 2) AIS. The patients were divided into two groups by random allocation using Ti-Ti rods (n = 29) and CrCo-Ti rods (n = 30) and the alone difference among them in the surgical procedure was rod material (Ti-Ti or CrCo-Ti rods) and finally, radiological outcomes were compared preoperatively, postoperatively and at last follow-up for 12 months.*

RESULTS; *Patients' main curve correction after surgical procedure regardless type of rod was 48.95±11.04 (13-75) degree. Success rate of spinal deformity correction following surgical procedure regardless of type of administered rod was 86.76 ± 11.30 percent (62.5-100%). Mean of deformity correction rate was 91.49±10.67% using CrCo-Ti rods versus 81.86±9.88% using Ti-Ti rods (P-value=0.01). Angle change was 3.29±6.60 for kyphosis angle and 0.59±7.76 for lordosis angle. Rate of main curve correction was not significantly different considering patients' gender (P-value0.657). Main curve correction success rate was in association with patients' age and type of rod (P-value=0.054, r=-1.863 and P-value=0.001, r=8.865 respectively).*

CONCLUSION; *CrCo-Ti rods have the ability to produce higher correction rates in AIS compared to Ti-Ti rod of the same diameter. CrCo-Ti rods provide significant and stable spinal correction, especially in correction of main curve. This rate was associated with patients' age and type of rod administered but not gender.*

KEYWORDS: *Adolescent. Scoliosis. Chromium Alloys. Titanium. Treatment Outcome.*

INTRODUCTION

Commonly, adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) spinal deformity with hypokyphosis in sagittal plane and major curve in obligatory rotation (coronal plane) causing various complications[1] as well as in different countries, AIS prevalence is estimated between 0.47-5.2%. Genetic factors, gender and age of onset are major features determining prevalence and curve pattern in patients.[2,3]

The customary treatment of AIS is spinal fusion with instrumentation using rigid rods. In parallel, agents such as, curve magnitude, points of fixation, *level instrument selection*, curve flexibility, kind of anchor rods used for patients and post-operative care are the main factors affecting the outcome of surgery[4]. Furthermore, correcting and preserving the ability of the rod is one of the most important factor

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in choosing the best alloy for this surgery. Titanium Ti6Al4V(Ti), Stainless steel A316L (SS), and CrCoMoC (CrCo) are the most commonly used alloys of this surgery, each of them with different properties such as stiffness, radiologic features, postoperative complications, and effectiveness[5,6]. Ti rods, due to lower risk of infection after surgery and fewer artefacts in radiographic imaging are better than the SS rods previously used. However, Ti rods are more flexible and cannot modify the deformation as much as SS rods. Recently, the CrCo rods used have lower risk of postoperative infection and less artefacts in radiographic imaging than SS rods. Moreover, CrCo rods effectively correct the scoliosis and preserve better correction toward the mentioned alloys[5-7]. Therefore, in this study, we have aimed to compare the outcomes of spinal deformity correction using different alloys of Ti-Ti and CrCo-Ti rods for the treatment of spinal AIS using translation technique.

METHOD

Ethical Committee

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences.

Design and participants

This randomized clinical trial study was conducted between April 2012 and August 2107 in Alzahra Hospital-Isfahan, Iran. Patients were randomized in 2 groups, in 1:1 ratio, undergoing posterior spinal fusion surgery using CrCo-Ti rod and Ti--Ti rod in both sides, using all pedicle screw fixation technique. Patients with AIS with Lenke classification type I or II, indicated for posterior spinal fusion surgery with instrumentation that have not had spinal surgery previously, were included in this study after obtaining informed written consent. Patients who had not been followed up for 12 months or underwent further surgery were excluded from study.

Surgery procedure and management

The surgery in all patients has been done by a single surgeon and in the same institution. The procedure was done in prone position with the trunk supported at the upper thorax and thighs, while, abdomen was left free. Patients were put in a general anaesthesia and neuromonitoring control for every patient was done. Pedicles were fixed with polyaxial pedicle screws (Zimmer, Inc USA) with 4.5 or 5.5 mm diameter and between 25-45 mm in length, in both sides (Fig1). In the beginning, the uppermost and lowermost vertebrae's pedicles were screwed, and then vertebrae between them were screwed as well. Afterwards, the pre-bend rods were placed in these screws. At last, pre-bend rods were straightened up by pulling them from the sides through translation technique. Rods specifications were Ti or CrCo-Ti (Zimmer, Inc USA) with 5.5mm diameter.

In the intervention group, CoCr-Ti rod was placed in the working side (concave side) and Ti rod was placed in the resting side (convex side). In the control group, Ti rods were placed in both sides. All patients were operated under sensory evoked potential monitoring. Patients have used bracing for 3 months after surgery. First post-up radiography was done before

FIGURE 1: PREOPERATIVE AND POSTOPERATIVE RADIOGRAPHS OF AIS PATIENTS CORRECTED BY TRANSLATION TECHNIQUE WITH ALL PEDICLE SCREW AND TITANIUM -COCR RODS

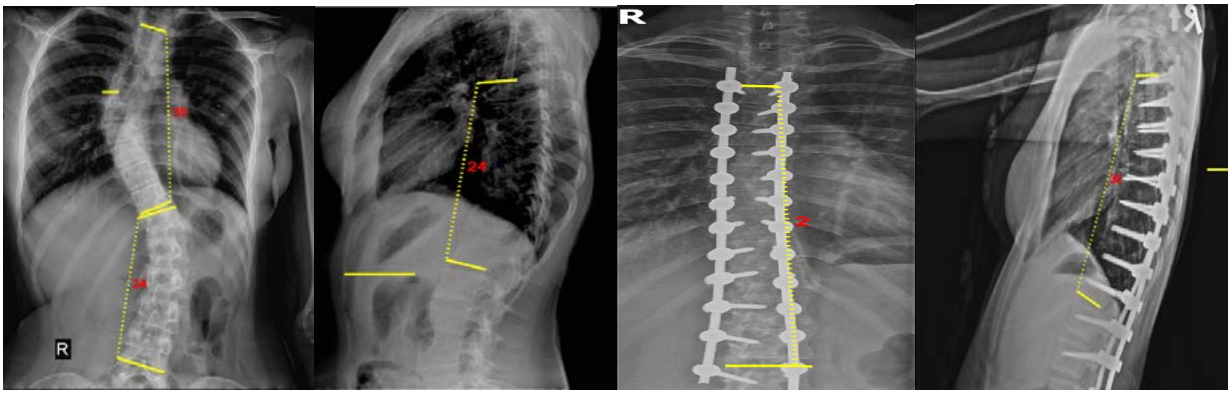

TABLE 1: DEMOGRAPHIC INFORMATION OF PARTICIPANTS

Variables		Mean ± SD		P-value
		CrCo-Ti	Ti-Ti	
Sex	Female*	18 (60.0%)	19 (65.5%)	0.661**
	male*	12 (40.0%)	10 (34.5%)	
Age (year)		13.93 ± 1.26	14.34 ± 1.54	0.265 $
Risser		3.93 ± 0.70	4.28 ± 0.65	0.055 $
Level of Fusion		9.77 ± 1.98	10.28 ± 1.91	0.318 $
Main Curve (grade)		55.17 ± 10.91	57.69 ± 11.56	0.392 $
Kyphosis Angle (grade)		38.63 ± 7.48	37.07 ± 6.40	0.392 $
Lordosis Angle (grade)		53.53 ± 8.64	51.17 ± 8.90	0.305 $
Flexibility (%)		31.80 ± 20.80	34.44 ± 20.40	0.624 $

* n (%). ** Chi-square test. $ t_independent samples

TABLE 2: MAIN CURVE, KYPHOSIS AND LORDOSIS CHANGES REGARDLESS OF THE TECHNIQUE OF SURGERY

Variables	Mean ± SD		P-value*
	Before Surgery	After Surgery	
Main Curve	56.41 ± 11.21	7.46 ± 6.66	< 0.001
Kyphosis	37.86 ± 6.95	34.58 ± 3.70	< 0.001
Lordosis	52.37 ± 8.77	51.78 ± 5.98	0.559

* paired t-test

discharge of patient. Regular post-up visit for every patient according to standard program was done.

Data collection and imaging analysis

On admission, patient's demographic information including age, gender, curve flexibility and curve class according to Lenke classification, was recorded. Coronal and sagittal imaging of thoracic and lumbar region of spine were obtained in full-standing x-ray and bending supine PA radiography was done for each patient to evaluate curve specifications, respectively. After analysis of images using surgical map software (Surgimap®, a Nemaris Inc.), Cobb angle of main curve and secondary curves were calculated. Iliac crest X-ray images were obtained due to estimate skeletal maturity according to Risser system of grading. Patients were visited again after surgery (1.5, 3, 6, 12, 24 months) in order to evaluate surgery efficiency and stability results, clinically and radiographically, as mentioned, again. Postoperative correction was calculated with the following formula:

POC%= ((preoperative full-standing Cobb angle-postoperative full-standing Cobb angle)/ postoperative full-standing Cobb angle). All measurements and assessments were done by a single experienced person and by surgical map software (Surgimap®, a Nemaris Inc.).

Statistical analysis

Collected data was analysed with independent t-test, paired t-test and univariate analysis of variance (ANOVA) in IBM SPSS20 - United States software. Results with significant P<0.05 were reported.

RESULTS

In the current study, 59 patients including 37 (62.7%) females and 22 (37.3%) males with diagnosis of AIS participated. Included patients had the mean age of 14.14±1.41 years old with the range of 12-17 years. Mean age of participating females was 14.03±1.24 and for males, it was 14.32±1.76 years (P-value=0.477). Patients' Risser grading was 4.10±0.70 with the range of 3-5. In addition, their fusion level was 10.02±1.94 (Range of 4-13). Flexibility of main curve was 33.10 ± 20.47 percent with range of 11-55 degree.

In order of deformity correction, patients were randomly divided into two groups using CrCo-Ti rod for 30 patients of first group and Ti-Ti rod for the remaining 29 patients of second group. Table-1 is showing the demographic variables of patients. Based on findings of Table-1, patients' distribution based on age and gender was not statistically different in both groups (P-value= 0.256 and 0.661, respectively). Success rate of spinal deformity correction follow-

TABLE 3: MAIN CURVE, KYPHOSIS, AND LORDOSIS ANGLES BEFORE AND AFTER SURGERY REGARDING ROD TYPE

Variables	Mean ± SD		P-value*	Mean ± SD		P-value*
	CrCo-Ti			Ti-Ti		
	Before Surgery	After Surgery		Before Surgery	After Surgery	
Main Curve	55.17 ± 10.91	4.76 ± 5.80	< 0.001	57.69 ± 11.56	10.34 ± 6.34	< 0.001
Kyphosis	38.63 ± 7.48	33.67 ± 3.31	< 0.001	37.07 ± 6.40	35.52 ± 3.90	0.177
Lordosis	53.53 ± 8.64	51.30 ± 6.10	0.117	51.17 ± 8.90	52.28 ± 5.90	0.447

* paired t-test

ing surgical procedure regardless of type of administered rod was 86.76 ± 11.30 percent (48.95±11.04 degree). Mean of deformity correction rate was 91.49±10.67%, using CrCo-Ti rods versus 81.86±9.88% using Ti-Ti rods (P-value=0.01). Mean deformity correction percentage was 86.30±12.82 in females and 87.53±8.36 for males (P-value=0.657). For kyphotic change, mean angle was 3.29 (3.29±6.60) degrees, regardless of type of rod used. Table-2 is showing effects of spinal deformity correction surgery regardless of type of rod used for the surgical procedure. According to these results, the main curve and kyphosis had statistically changed after surgery in comparison to its status prior to surgical procedure. Table-3 and Table-4 are showing mean changes of angles prior to and after surgical procedure and final detected curves of both groups respectively.

On the other hand, Univariate test showed that patients' age and type of rod are predicting factors for deformity correction success. By controlling the type of rod and age, prediction of successes of main curve correction is the following: P-value=0.054, r=-1.863. And by controlling age, use of CrCo-Ti rod is superior to Ti-Ti rods as follows: P-value=0.001, r=8.865.

DISCUSSION

In this study, our data showed that using CrCo-Ti and Ti-Ti rods for treatment of AIS, the success rate of spinal deformity correction was higher with CrCo-Ti rods and also, these findings suggest that the rate mentioned was related to age and type of patients, but not to gender.

On the other hand, for many years, CoCr has an extremely high particular strength and rigidity and it is generally used in gas turbines, dental implants and orthopaedic implants[8,9]. CoCr rods have the ability to exert high corrective forces on the spine with relatively small amounts of rod deformation. This material also has the highest potential of plastic deformation in a highly rigid spine[10,11]. In our experience, the group using CoCr-Ti rods revealed a notably greater increase in spinal kyphosis than Ti-Ti group.

A study by Hwang et al.[12] showed maintenance of coronal and sagittal plane correction between 2- and 5-year follow up using screw constructs in AIS. Our data confirms the capability of the whole-pedicle screw construct to prevent deformity improvement while maintaining balance in kyphotic patients. Furthermore, different studies in recent years have shown that efficiency of pedicle screws for achieving acceptable sagittal alignment in translation technique. In this correction technique, the importance of rod mechanical property should be steeply considered. In this term, by pedicle screw, the spine should be brought to the pre-contoured rods. It has been presented that CrCo rods have the ability of main curve correction and preventing sagittal change from deviations due to its balance between stiffness and flexibility[13-15].

Lamerain *et al.*[10], with study on 90 patients ,suggested CoCr rods have the ability to produce higher correction rates in frontal plane compared to SS rods of the same diameter as well as Lamerain *et al.*[16] with another study on 61 patients treated by posterior spinal fusion and instrumentation, using all-pedicle screw constructs have indicated CoCr rods can produce sagittal corrections in hypokyphotic adolescent idiopathic scoliosis patients and they confirm the benefit of combining all-pedicle screw constructs

On the other hand, we have also revealed that main curve correction percentage was over 86% (86.76± 11.30%) and plus, we observed notable correction of main curve angle in groups treated with CrCo-Ti rods and Ti-Ti rods. This rate was significantly higher with CrCo-Ti rod. The final main curve was significantly higher in the CrCo-Ti rods than Ti-Ti rod. This difference shows higher main curve angle correction using CrCo-Ti rods. In addition, in the other perspective of the findings of this study, for kyphotic change, the average angle was 3.29 (3.29±6.60) degrees, regardless of the type of rod used. Patients treated with CrCo-Ti rods exhibited significant postoperative kyphotic changes but these postoperative changes with Ti-Ti rods were not significant. These kyphotic changes resulted from CrCo-Ti rod and they can be attributed to higher stiffness of CrCo rod added to acceptable flexibility of Ti rod. A study by Angelliaume *et al.*[11] reported the success rate of 71% in sagittal correction of AIS patients. This success rate was similar

TABLE 4: COMPARISON OF ANGLE CHANGES USING TI-C-CR OR TI-TI ROD

Variables	Mean ± SD		P-value*
	CrCo-Ti	Ti-Ti	
Main Curve	4.67 ± 5.80	10.34 ± 6.34	0.001
Kyphosis	33.67 ± 3.31	35.52 ± 3.90	0.054
Lordosis	51.30 ± 6.10	52.28 ± 5.90	0.535

* t_independent samples

to those described earlier of over 65%[14,17]. In contrast to our findings, Angelliaume *et al.*[11] found no differences between CrCo-Ti rods in comparison to Ti-Ti rods. In addition, kyphotic angle change was not statistically different comparing the two types of rods. Another research by Han et al. compared operated adults with main complaint of spinal deformity comparing CrCo rods with Ti rods. They did not observe statistical differences between the two types of rods in terms of sagittal vertical axis, thoracic kyphosis, lumbar lordosis and pelvic incidence. Another point in this remarkable study is the change in lumbar lordosis, which was over 35 degrees in the participants regardless of the type of rod.[18]

In conclusion, our findings showed that CrCo-Ti and Ti-Ti rods provide similar significant main curve correction in flexible spinal AIS, but the success rate of CrCo-Ti rods was significantly superior on spinal deformity correction. Moreover, our data also revealed that the use of CrCo-Ti and Ti-Ti rods associated with all-pedicle screw construct is the best association to provide the highest correction rate in idiopathic scoliosis correction procedures. This is the first study in Iran to describe the clinical use of CrCo-Ti rod that shows marked radiographic improvement in coronal and sagittal alignment. Furthermore, we found better restoration of kyphotic angle change with the use of CrCo-Ti rods compared with Ti-Ti rods. In the CrCo-Ti group, the rate of postoperative kyphotic angle change was significantly higher than in the Ti-Ti group.

Study conducted at Isfahan University of Medical Sciences, Isfahan, Iran

RESUMO

OBJETIVO: *Comparar o resultado da correção da deformidade da coluna vertebral com ligas de Ti-Ti e CrCo-Ti para o tratamento da Escoliose Idiopática do Adolescente (EIA) na coluna usando as ligas mencionadas com todos os parafusos pediculares e técnica de tradução.*

MÉTODO: *59 pacientes operados por EIA com deformidade da coluna vertebral (Lenke 1 ou 2). Os pacientes foram divididos em dois grupos por alocação aleatória usando ligas de Ti-Ti (n = 29) e ligas de CrCo-Ti (n = 30) e a única diferença entre eles no procedimento cirúrgico foi o material da liga (ligas de Ti-Ti ou CrCo-Ti) e, finalmente, resultados radiológicos foram comparados no pré-operatório, pós-operatório e no último retorno por 12 meses.*

RESULTADOS: *A correção da curva principal do paciente após o procedimento cirúrgico, independentemente do tipo de liga, foi de 48,95±11,04 (13-75) graus. A taxa de sucesso da correção da deformidade da coluna vertebral após o procedimento cirúrgico, independentemente do tipo de liga administrada, foi de 86,76 ± 11,30% (62,5-100%). A média da taxa de correção da deformidade foi de 91,49±10,67% usando ligas de CrCo-Ti e 81,86±9,88% usando ligas de Ti-Ti (valor de P = 0,01). A mudança de ângulo foi de 3,29±6,60 para o ângulo de cifose e de 0,59±7,76 para o ângulo de lordose. A taxa de correção da curva principal não foi significativamente diferente considerando o sexo dos pacientes (Valor de P 0,657). A taxa de sucesso da correção da curva principal foi associada à idade do paciente e ao tipo de liga (valor de P=0,054, r=-1,863 e valor de P=0,001, r=8,865, respectivamente).*

CONCLUSÃO: *As ligas de CrCo-Ti têm a capacidade de produzir taxas de correção mais altas em EIA em comparação com a liga de Ti-Ti do mesmo diâmetro. As ligas de CrCo-Ti fornecem uma correção espinhal significativa e estável, especialmente na correção da curva principal. Essa taxa foi associada à idade e ao tipo de liga administrada, mas não ao sexo.*

PALAVRAS-CHAVE: *Adolescente. Escoliose. Ligas de Cromo. Titânio. Resultado do Tratamento.*

REFERENCES

1. Delorme S, Labelle H, Aubin CE, Guise JA, Rivard CH, Poitras B, et al. A three-dimensional radiographic comparison of Cotrel–Dubousset and Colorado instrumentations for the correction of idiopathic scoliosis. Spine (Phila Pa 1976). 2000;25(2):205-10.
2. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. Lancet. 2008;371(9623):1527-37.
3. Miller N. The role of genetic factors in the etiology of idiopathic scoliosis. Spine. 2000;14(2):313-8.
4. Asher MA, Burton DC. Adolescent idiopathic scoliosis: natural history and long term treatment effects. Scoliosis. 2006;1(1):2.
5. Riedel MD. What's the evidence? Systematic literature review of risk factors and preventive strategies for surgical site infections following pediatric spine surgery. 2012 AAP National Conference and Exhibition; 2012: American Academy of Pediatrics.
6. Serhan H, Mhatre D, Newton P, Giorgio P, Sturm P. Would CoCr rods provide better correctional forces than stainless steel or titanium for rigid scoliosis curves? J Spinal Disord Tech. 2013;26(2):E70-4.
7. Sales de Gauzy J, Jouve JL, Ilharreborde B, Blondel B, Accadbled F, Mazda K. Use of the Universal Clamp in adolescent idiopathic scoliosis. Eur Spine J. 2014;23(Suppl 4):S446-51.
8. Al Jabbari YS. Physico-mechanical properties and prosthodontic applications of Co-Cr dental alloys: a review of the literature. J Adv Prosthodont. 2014;6(2):138-45.
9. Miller A, Islam K, Grannum S, Morris S, Hutchinson J, Nelson I, et al. Cobalt chromium versus titanium alloy: has the change in scoliosis implant material improved deformity correction? Orthopaedic Proceedings 2018:96(Supp 6):20.
10. Lamerain M, Bachy M, Delpont M, Kabbaj R, Mary P, Vialle R. CoCr rods

provide better frontal correction of adolescent idiopathic scoliosis treated by all-pedicle screw fixation. Eur Spine J. 2014;23(6):1190-6.

11. Angelliaume A, Ferrero E, Mazda K, Le Hanneur M, Accabled F, Gauzy JS. Titanium vs cobalt chromium: what is the best rod material to enhance adolescent idiopathic scoliosis correction with sublaminar bands? Eur Spine J. 2017;26(6):1732-8.

12. Hwang CJ, Lee CK, Chang BS, Kim MS, Yeom JS, Choi JM. Minimum 5-year follow-up results of skipped pedicle screw fixation for flexible idiopathic scoliosis. J Neurosurg Spine. 2011;15(2):146-50.

13. Abul-Kasim K, Karlsson MK, Ohlin A. Increased rod stiffness improves the degree of deformity correction by segmental pedicle screw fixation in adolescent idiopathic scoliosis. Scoliosis. 2011;6:13.

14. Mazda K, Ilharreborde B, Even J, Lefevre Y, Fitoussi F, Penneçot GF. Efficacy and safety of posteromedial translation for correction of thoracic curves in adolescent idiopathic scoliosis using a new connection to the spine: the Universal Clamp. Eur Spine J. 2009;18(2):158-69.

15. Acar N, Karakasli A, Karaarslan AA, Ozcanhan MH, Ertem F, Erduran M. The mechanical effect of rod contouring on rod-screw system strength in spine fixation. J Korean Neurosurg Soc. 2016;59(5):425-9.

16. Lamerain M, Bachy M, Dubory A, Kabbaj R, Scemama C, Vialle R. All-pedicle screw fixation with 6-mm-diameter cobalt-chromium rods provides optimized sagittal correction of adolescent idiopathic scoliosis. Clin Spine Surg. 2017;30(7):E857-63.

17. Bridwell KH, Hanson DS, Rhee JM, Lenke LG, Baldus C, Blanke K. Correction of thoracic adolescent idiopathic scoliosis with segmental hooks, rods, and Wisconsin wires posteriorly: it's bad and obsolete, correct? Spine (Phila Pa 1976). 2002;27(18):2059-66.

18. Han S, Hyun SJ, Kim KJ, Jahng TA, Lee S, Rhim SC. Rod stiffness as a risk factor of proximal junctional kyphosis after adult spinal deformity surgery: comparative study between cobalt chrome multiple-rod constructs and titanium alloy two-rod constructs. Spine J. 2017;17(7):962-8.

ORIGINAL ARTICLE

Measurement properties of the questionnaire "Mosaic of opinions on induced abortion": a multicenter study in seven Brazilian hospitals

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SUMMARY

In Brasil, abortion is legal in cases of rape, when there is a risk of maternal death, and in cases of fetal anencephaly. However, the literature reports that some doctors refuse to care for women with such demands or come to perform it in a discriminatory manner.

OBJECTIVE: *Pretest, test and evaluate the measurement properties of the "Mosaic of Opinions on Induced Abortion," a questionnaire developed to investigate the perspectives of Brazilian healthcare professionals about the morality of abortion.*

METHODS: *Firstly, the questionnaire was pretested in an intentional sample of specialists. Secondly, it was tested in a randomized sample of 32 healthcare professionals. Finally, we conducted a multi-center study in seven university hospitals to evaluate the measurement properties of the questionnaire.*

RESULTS: *Combined samples of the three phases totalized 430 individuals. In pretest and test, all the evaluated aspects obtained satisfactory results. In the multicenter phase, confirmatory factorial analysis led to an important reduction of the questionnaire, which also obtained good indicators of reliability, beyond the validation of construct and criteria.*

CONCLUSION: *Questionnaire has been validated and is suitable for use in other surveys in Brasil.*

KEYWORDS: *Validation Studies. Abortion, Induced. Attitude of Health Personnel. Ethics. Surveys and Questionnaires.*

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HIGHLIGHTS

- MOSAI evaluates the opinions of healthcare professionals on induced abortion;
- MOSAI has been validated and is suitable for use in other surveys in Brazil;
- After an evaluation of measurement properties, we reduced the questionnaire from 42 to 32 items;
- The questionnaire has content, construct and criterion validity;
- All constructs obtained high composite reliability coefficients (minimum of 0.770).

INTRODUCTION

Providing care to women in situations of induced abortion constitutes one of the most challenging ethical problems for healthcare professionals, especially for gynecological and obstetric doctors. This challenge is reflected in the fact that, in Brazil, although permitted by the Penal Code of 1940, access to legal abortion is still problematic, mainly when the pregnancy results from rape. In some reference services, prevails a regime of constant suspicion about the veracity of the woman's narrative on rape: her story is not sufficient for getting access to the procedure, being necessary to prove herself as a victim of aggression and to present subjective traits that characterize her as such.[1] Obstruction to legal abortion also occurs through the obligation to present a series of documents not required by law, such as police reports, forensic reports, and court orders.[2] Frequently, the patient receives no guidance on the procedures performed or on the care that will be needed after the procedure, such as subsequent contraception.[3] A survey of 19 women who had aborted in private clinics found that they were exposed to a condition of total vulnerability and human rights violations, such as the submission to painful medical procedures without anesthesia, like curettage and vacuum suction.[4]

Although abortion techniques are safe, effective and inexpensive and have been well known for many decades, health care professionals (HCP) lack adequate knowledge of laws and norms around the theme, such as the misconception about the need to denounce the woman when there signs of illegal interruption.[2,5] Alongside the inefficient knowledge of the legislation on the subject, the provision of abortion care constitutes a tremendous ethical challenge to HCP. Even in cases where it is permitted by law, "the concept that it is a crime carries a stigma that is worse than that associated with other acts qualified by law as crimes."[6] In this context, the existence of a validated questionnaire to investigate the opinions of HCP could contribute to the production of systematized information on the subject, which could guide the development of new public health policies to combat barriers to access legal and safe abortion in Brazil.

We provide the "Mosaic of Opinions on Induced Abortion" (abbreviated in Portuguese by the acronym "MOSAI")[1]; the one presented was created as a candidate to meet this demand.[7] Although other studies have investigated the moral perspectives of Brazilian HCP on abortion, their methods were exclusively qualitative, which means that their samples had few professionals.[5] On the other hand, MOSAI is predominantly quantitative and can be applied on large samples. Similar scales of evaluation of the morality of abortion have been elaborated in some countries with restrictive laws on its practice,[8,9] but they are intended to be used by people in general (not only by HCP) and are not validated to the specificities of the Brazilian context.

Thereby, the objectives of this study were to pretest, test and evaluate the measurement properties of the questionnaire MOSAI.

METHODS

Study design, sampling, and questionnaire

We performed a methodological study comprised of three interlinked phases. In all of them, we applied the questionnaire online through the Lime Survey website. All the subjects received the link to MOSAI via e-mail, after they were personally invited by the researchers and consented with being included in it.

The present study uses the terminology established by the COSMIN initiative (COnsensus-based Standards for the selection of health Measurement INstruments), according to which the term "properties of the measure" refers to a set of quality indicators of an instrument, including validity (content, criteria and construct), reliability and responsiveness.[10]

In this study, we used the brief version of the MOSAI questionnaire, which contains three vignettes about women considering interrupting the pregnancy. Those vignettes are based on the situations in which abortion is allowed in Brazil: necessary abortion (when there is a risk of death to the mother), humanitarian abortion and anencephalic fetus. After these

vignettes, MOSAI presents some short affirmative phrases (from now on referred to as "items") based on patterns of views on the morality of abortion, which must be classified employing a concordance scale. The questionnaire's complete version has six vignettes and, beyond the demands mentioned above, includes cases of social abortion, contraceptive failure, and fetus with trisomy 21. [7]

Concerning the factorial structure of the questionnaire, MOSAI was created and had its content validated with 14 constructs.[7] However, in the present study, since we used its brief version, we reassembled these 14 constructs into eight new ones. The process of regrouping consisted in the separation of items characterized by a liberal or a conservative moral alignment regarding the possibility of someone performing an abortion. This process resulted in the two large groups of items, the Liberal and the Conservative. After that, we formed eight subgroups of items, four liberals and four conservatives, as defined below:

1. Psychological Aftereffects of Abortion (PAA): Appeal to the possible psychological aftereffects of abortion, or to the familiar approval or disapproval of having an abortion. Although the relationship between post-traumatic stress and abortion is questioned in some studies,[11] in Brazil, a study found that women in situations of abortion had a higher prevalence of depression.[12]

2. Conservative Emotional Appeal (CEA): Use of shocking expressions and images (like "murder" and "cruelty") or by the equalization of the fetus and the embryo to a born child.

3. Sacredness of Life (SOL): Argument that abortion is always morally reprehensible, either because human life is sacred (even in the early stages), or because the fetus is a potential person.

4. Conservative Deontology (CDE): Argument that parents have a moral duty to protect the fetus or that abortion is wrong if the woman lies about having been raped (to have access to legal abortion), or if she supposedly had any behavior that could be considered risky for rape (by people who agree with this reasoning).

5. Women's Reproductive Autonomy (WRA): Argument that women should have the right to decide whether to abort or not, according to her values and interests. The concept of autonomy occupies a central position in this construct.

6. Liberal Emotional Appeal (LEA): Invocation of shocking expressions and images in favor of the right to induce an abortion, like "torture" and "assassination" of the mother.

7. Sexual and Reproductive Rights (SRR): Argument that the denial of abortion care violates women's fundamental human rights and promotes a public health problem.

8. Fetal Personhood Problematization (FPP): Argument that the human unborn does not have moral status (at least in some circumstances) or that its life is not sacred.

Testing Phases

MOSAI was pre-tested in an intentional sample of researchers in health sciences and humanities from the State University of Campinas (UNICAMP). Using some auxiliary questions presented at the end of MOSAI, we evaluated: 1) The presence of wording errors; 2) The questionnaire functionality; 3) Its ease of using; 4) Its content comprehensibility; and 5) The satisfaction with the necessary time to answer it. Subjects also could freely write about the evaluated aspects through an open question. The saturation of the qualitative data defined the sample size.

The test phase was developed in the "Woman's Hospital Prof. Dr. J. A. Pinotti-CAISM," which belongs to UNICAMP. We employed a version of MOSAI containing changes identified as necessary during the pre-test. Even so, the objective of this phase was to reevaluate the same aspects evaluated before. The sample was randomly selected (using the software SPSS 20) from the list of physicians, nurses, psychologists, social workers and pharmacists of the hospital. The sample size was defined in 32 subjects, following the recommendation for questionnaire tests.

The Multicenter Phase

After the testing phases, we conducted a multi-center study aiming to evaluate the measurement properties of MOSAI. This stage of the research was conducted in seven hospitals selected from the Brazilian Network of Reproductive and Perinatal Health, namely: 1. Woman's Hospital of Recife; 2. Maternity School Assis Chateaubriand; 3. Hospital of Clinics of Porto Alegre; 4. Hospital of Clinics of Federal University of Paraná; 5. University Hospital of the Jundiaí Medical School; 6. Sumaré State Hospital-UNICAMP; and 7. Woman's Hospital Prof. Dr. J. A. Pinotti-CAISM). The sample was constituted of physicians, nurses, psychologists, social workers,

and pharmacists, selected by a convenience sampling method. We adopted the sample size calculation for factor analysis proposed by Hair *et al*., which suggest a ratio of 5 respondents per item of the scale and a minimum of 100 items in total.[13] To ensure a better quality of the data collected, we removed all the questionnaires answered incompletely or which had at least one item answered with the "do not know" option.

Validation of the measurement properties was performed employing a Confirmatory Factorial Analysis (CFA) with the software Smart PLS 2.0. We hypothesized that the questionnaire had a second order factorial structure, that is, a structure organized through two layers of latent constructs.[13] The composition of these layers followed the so-called "a priori criterion," used when the number of factors is already known.[13] The first layer has two great constructs: Liberal and Conservative orientations. The second layer contains the eight patterns described previously.

Analysis of the factorial model comprised two steps: analysis of the convergent and discriminant validity of the proposed model. In the case of convergent analysis, initially, we obtained the results from the mean extracted variance (AVE) for each of the model factors. AVE values higher than 0.5 indicate considerate satisfactory.[13] Subsequently, we evaluated the values of factorial loads between the items and their respective factors, assuming that items with results lower than 0.5 were candidates to leave the factorial model.[13] Discriminant validity was first evaluated by the Fornell-Larcker criterion.[14] This method compares the square root of the AVEs with the correlation values between the factors. The model has discriminant validity if the square roots of the AVEs are higher than the correlations between the factors. Discriminant validity was also evaluated through a cross-loadings analysis. It was observed whether the factorial load of a given item was higher in its factor than in the other factors. To obtain the internal consistency of the questionnaire, we calculated the composite reliability, considering that values above 0.7 would be satisfactory.[13] Finally, validation by known groups was performed by comparing MOSAI scores between religious and non-religious subjects, using the non-parametric test of Mann-Whitney.[15] We hypothesized that, compared to non-religious subjects, religious subjects would have higher scores in the conservatives constructs. In all analyzes, the level of statistical significance was set at 5%.[15]

Ethical Aspects

This project was reviewed and approved by the Research Ethics Committee of the State University of Campinas (UNICAMP), as well as by the Institutional Review Board of each site enrolled in the multi-center phase. Before enrolment, an individual Informed Consent form was electronically signed by each subject after understanding and accepting the study conditions. To assure the confidentiality, we excluded from the data analysis the subject's names or any other variable that could identify them.

RESULTS

Testing

The questionnaire was pre-tested in a sample of 10 subjects, six women and four men. The mean age was 39.0 years (max. 51.0 and min. 29.0). Subjects had a degree in Philosophy (1), Letters (1), Statistics (4), Social Sciences (2), Pharmacy (1) and Biology (1). No participant reported technical difficulties with the questionnaire, but a spelling error was identified and corrected. One subject reported that it was necessary to restart the questionnaire, due to an error in his browser. Both the "ease of use" and the "writing comprehensibility" were classified as "easy" or "very easy" by most of the subjects. Most the sample classified the time spent as moderately satisfactory.

After the pre-test, the corrected version of MOSAI was tested in a sample of 32 HCP. They were 25 women and 7 men, distributed among the following professional categories: Physicians (12), Nurses (11), Social Workers (3), Pharmacists (3) and Psychologists (3). The mean age was 39.7 years (max. 56.0 and min. 23.0). Catholicism was the most common religion among the participants (17), followed by Spiritism (7) and Protestantism (3). Five subjects were atheists or not religious (5). Almost all participants positively evaluated the grammatical, spelling, online functionality, ease of use and comprehensibility of MOSAI. The time required to answer it received the lowest classification among all the evaluated aspects, but none classified it as "bad" or "very bad."

The detailing of the pre-test and test results are not presented in this article. However, such data may be made available by the authors upon request.

Measurement properties validation

The initial sample for statistical validation consisted of 388 subjects: 133 were excluded because

they answered at least one item with the "do not know" option and 133 were excluded because they did not respond to at least one questionnaire item. Once the exclusion criterion was applied, the final sample consisted of 122 subjects. When comparing the excluded subjects with those maintained in the analysis, it was verified that there was no statistically significant difference between the characteristics of age, profession, and religiosity. However, these samples were different for gender (p = 0.0332), with a higher proportion of women in the excluded group (78.63% vs. 66.67%); and marital status (p = 0.0438), with a higher percentage of people in stable union in the group included in the analysis (71.9% vs. 59.85%). As shown in Table 1, most of the subjects kept in the study were women (66.7%), the mean age was 38.0 years (max. 69.0 min. 21.0), the most common religion was Catholicism (57.1%), and the main marital status was married (57.9%). Almost 80.0% of the sample was post-graduate, and 78.1% were physicians, most of them specialized in gynecology and obstetrics. Approximately half of the sample worked in general hospitals and half of them in hospitals specialized in women's health.

TABLE 1: DESCRIPTION OF THE SAMPLE OF HEALTH PROFESSIONALS WHO PARTICIPATED IN THE EVALUATION OF THE MOSAI MEASUREMENT PROPERTIES

Information	N	%
Gender		
Female	80	66.67
Male	40	33.33
Age (Mean/SD)	38(±11)	-
Religion		
Religious [1]	97	81.51
Not Religious	22	18.49
Marital Status		
Married or Cohabitating	86	71.07
Single or Divorced	34	28.10
Widower	1	0.83
Schooling		
Postgraduate	85	77.27
Graduate	21	19.09
High School + Technical	4	3.64
Occupation		
Physician (Gyn-Obst)	64	52.03
Nurse	20	16.26
Doctor (Other Specialty)	16	13.01
Resident Doctor [2]	16	13.01
Pharmaceutical	4	3.25
Psychologist	2	1.63
Social Worker	1	0.81

[1] Catholicism (68), Spiritism (16), Protestant Religions (12) and Judaism (1). [2] Gyn-Obst and other specialties.

The first step of CFA was the exclusion of item Q11 (Abortion should be based on a reliable diagnosis of anencephaly, that is, the certainty that the unborn child will never have a future), which had a negative load in the proposed construct. To obtain the convergent validity, we excluded the items Q20 (It is psychologically difficult for a health care professional to have to terminate the pregnancy of a healthy fetus) and Q08 (Women who interrupt pregnancy in cases of anencephaly may be under pressure from their partners), whose low factorial loads caused their respective constructs to have AVEs lower than 0.50. After that, all constructs obtained AVEs greater than 0.50, as shown in Table 2.

To obtain the discriminant validity, we applied the Fornell-Larcker criteria and removed the items Q5 (If the Federal Supreme Court had not authorized abortion in cases of anencephaly, women like Jussara would recourse to illegal abortion), Q09 (The laws that regulate life in society cannot be based on religious beliefs of specific groups), Q16 (The high mortality rates for pregnant women with this disease justify abortion to protect the mother's life), Q29 (The right to abortion in rape cases is an important way to combat maternal mortality), Q35 (Marina must keep in mind that life is sacred regardless of how it was generated), Q36 (Legal abortion in cases of rape frees the victims of the horror of carrying a life created in an act of terrible violence) and Q38 (Discontinuation of a healthy fetus's pregnancy can be considered a form of violence against the weakest).

TABLE 2: MOSAI'S EXTRACTED AVERAGE VARIANCE AND COMPOSITE RELIABILITY

Constructs	AVE	Composite Reliability
Conservative Constructs		
Psychological Aftereffects of Abortion (PAA)	0.612	0.824
Conservative Emotional Appeal (CEA)	0.586	0.808
Sacredness of Life (SOL)	0.582	0.892
Conservative Deontology (CDE)	0.522	0.813
Liberal Constructs		
Women's Reproductive Autonomy (WRA)	0.622	0.891
Liberal Emotional Appeal (LEA)	0.627	0.770
Sexual and Reproductive Rights (SRR)	0.634	0.912
Fetal Personhood Problematization (FPP)	0.531	0.771

Once these adjustments were made, the final model was composed of 32 items, whose constructs and respective factor loads are shown in Table 3. In the next step, we calculated the composite reliability. As shown in Table 2, all the constructs obtained scores higher than 0.70. To receive the validation of criteria, we observed that religious group presented higher scores in most of the constructs with conservative orientation arguments, including CEA, SOL, and CDE. In contrast, the non-religious group showed higher scores in two liberal-oriented domains, including WRA and FPP (p-value <0.05). Detailed results of validation by known groups are not presented but may be made available by the authors upon request. Besides, the database analyzed was made available to "R da A M B" at the time of the article submission. This database may also be made available to readers upon request.

DISCUSSION

Testing

In testing stages, all the evaluated aspects obtained satisfactory results. Although the time spent received the lowest rating among all aspects, no subject classified it as "bad" or "very bad." This is a significant result since the quality of filling in questionnaires tends to be inversely proportional to the time

TABLE 3: MOSAI'S FINAL FACTORS LOADING MATRIX.

Item	Constructs							
	Psychological Aftereffects of Abortion (PAA)	Conservative Emotional Appeal (CEA)	Sacredness of Life (SOL)	Conservative Deontology (CDE)	Women's Reproductive Autonomy (WRA)	Liberal Emotional Appeal (LEA)	Sexual and Reproductive Rights (SRR)	Fetal Personhood Problematization (FPP)
Q30	0.844	0.477	0.503	0.475	-0.423	-0.233	-0.349	-0.346
Q14	0.820	0.333	0.492	0.382	-0.393	-0.251	-0.341	-0.309
Q23	0.672	0.317	0.332	0.261	-0.214	-0.141	-0.154	-0.128
Q04	0.439	0.809	0.584	0.472	-0.530	-0.466	-0.481	-0.356
Q32	0.388	0.803	0.590	0.449	-0.553	-0.231	-0.490	-0.373
Q17	0.281	0.678	0.529	0.457	-0.397	-0.319	-0.443	-0.190
Q19	0.443	0.594	0.827	0.502	-0.567	-0.379	-0.581	-0.373
Q22	0.403	0.544	0.826	0.531	-0.618	-0.486	-0.686	-0.414
Q06	0.417	0.568	0.784	0.495	-0.713	-0.433	-0.629	-0.501
Q31	0.515	0.663	0.778	0.621	-0.633	-0.346	-0.587	-0.474
Q02	0.358	0.512	0.722	0.479	-0.604	-0.411	-0.541	-0.412
Q27	0.491	0.500	0.618	0.528	-0.318	-0.306	-0.340	-0.289
Q40	0.284	0.386	0.450	0.769	-0.308	-0.281	-0.310	-0.355
Q41	0.410	0.470	0.483	0.737	-0.427	-0.217	-0.333	-0.358
Q01	0.420	0.589	0.622	0.736	-0.624	-0.390	-0.478	-0.395
Q28	0.265	0.206	0.402	0.641	-0.211	-0.211	-0.123	-0.190
Q39	-0.419	-0.614	-0.630	-0.495	0.830	0.460	0.649	0.494
Q34	-0.402	-0.462	-0.538	-0.450	0.821	0.442	0.635	0.551
Q13	-0.393	-0.603	-0.680	-0.535	0.795	0.520	0.612	0.489
Q10	-0.316	-0.434	-0.619	-0.418	0.774	0.413	0.550	0.439
Q25	-0.243	-0.434	-0.533	-0.357	0.718	0.483	0.606	0.381
Q07	-0.252	-0.404	-0.453	-0.408	0.517	0.855	0.547	0.438
Q15	-0.171	-0.288	-0.358	-0.185	0.405	0.723	0.378	0.316
Q12	-0.306	-0.548	-0.715	-0.434	0.729	0.513	0.851	0.549
Q26	-0.343	-0.518	-0.645	-0.340	0.675	0.561	0.851	0.455
Q33	-0.322	-0.537	-0.624	-0.415	0.625	0.414	0.840	0.506
Q42	-0.385	-0.517	-0.544	-0.353	0.634	0.434	0.794	0.572
Q21	-0.138	-0.358	-0.455	-0.301	0.505	0.492	0.758	0.337
Q18	-0.268	-0.444	-0.532	-0.322	0.500	0.424	0.668	0.306
Q37	-0.323	-0.383	-0.434	-0.380	0.473	0.327	0.428	0.768
Q03	-0.319	-0.277	-0.421	-0.348	0.472	0.474	0.471	0.759
Q24	-0.085	-0.218	-0.316	-0.276	0.352	0.225	0.357	0.653

required to answer it.[16] Very long questionnaires may tire the subjects and compromise the uniformity of responses.

Most of the respondents rated the use of the questionnaire over the internet as "easy" or "very easy." Digital methods for data collection have some advantages over traditional methods: they broaden the sample range, reduce costs and eliminate the environmental damages associated with printing papers. However, the use of conventional questionnaires is still the preferred method for certain groups of people. One study found that the response rate for digital questionnaires was lower than for questionnaires printed in a group of physicians.[17] Nevertheless, it is argued that such preferences may be related to characteristics of the sample, especially schooling and age of the participants, as such that the collection method (online or paper) may be indifferent to the quality of the data obtained.[18]

Measurement properties validation

CFA led to an essential reduction of the questionnaire and an increase in the indicators of composite reliability, convergent validity, and divergent validity. Shorter instruments have significant advantages both in clinical practice and research: they do not require excessive interviewer time, reduce the burden of response and are beneficial when administered as part of a multipurpose battery of different questionnaires or when repeat assessments are required.[19] Shorter versions of scales achieve a higher acceptability in the population, including better response rates and lower rates of missing data.[20] Although widely recognized as beneficial, it is recommended that researchers carefully examine the effects of each item removal on the construct content validity.[21] In this study, we removed 10 items from the questionnaire applied. Item Q11 was the only exclusion due to a negative factorial load. Originally bound to construct SOL, this phrase was conceived as a conservative statement regarding the right to abortion. However, the statistical analysis evidenced that its formulation had been ambiguous, leading to a liberal interpretation. The low (but positive) factor loads of items Q8 and Q20 resulted from a different problem. Both do not appear to have been formulated ambiguously, but they pointed to narrative elements that were not addressed by any other part of the questionnaire: the husband of the pregnant woman and the healthcare professional.

Items Q5, Q09, Q16, Q29, Q35, Q36, and Q38 were excluded because they presented high correlation with domains other than those to which they belonged, compromising the discriminating validity. Items Q5 and Q29 called for an implicit idea: that women necessarily undergo an unsafe abortion when the procedure is prohibited by law. This notion is erroneous. For instance, a recent study noted that some women choose to maintain their pregnancies even in cases of sexual abuse, a condition for which abortion is permitted under Brazilian law.[22] Item Q16 formulation was problematic too. It suggested that Eisenmenger syndrome is highly incidental, but we meant to say that, in pregnancy, it is associated with high mortality rates, from 30 to 50%.[23] However, these estimates may be outdated. Although pregnancy is still discouraged in women with this syndrome, nowadays it is known that the use of sildenafil as monotherapy may allow stabilization of maternal condition and improve clinical outcomes for both mother and baby.[24]

We were not surprised by the need to exclude item Q38. Inspired by a dissident line of traditional feminist thinking, this item assumes that "a woman involuntary pregnant has a moral obligation to the now-existing dependent fetus whether she explicitly consented to it or not".[25] Self-called "pro-life feminism", this atypical perspective on the ethics of abortion was probably perceived by the sample as strange, modifying the expected pattern of response.

On the other hand, it was quite surprising that the correlation of item Q09 was greater outside than inside its construct. This item deals explicitly with the theme of secularity, which is one of the central ideas of the SRR construct. According to this argument, "religion should be a matter of private ethics, and public policies should not be based on religious mystics concerning welfare".[26] It should be noted that more than 80% of our sample considered themselves as religious, 68% of them with a Judeo-Christian orientation. That is, this important sample trait may have influenced the unexpected response pattern.

Despite the predominance of religious subjects, item Q35 also had to be excluded according to the Fornell-Larcker criterion. This item argues in favor of the sacredness of life, the idea that any form of human life has an intrinsic and sacred value. However, it should be noted that, even for a predominantly religious group, the unrestricted prohibition of abortion rights can be rejected, especially in cases such

as sexual abuse. On the other hand, it does not mean that the same group would agree with a theatrical appeal in favor of the right to abortion, like the content of item Q36.

The relationship between religiosity and abortion morality was used to obtain the validation by known groups. According to studies conducted in Brazil and other Latin American countries,[9,27-29] religious groups (especially Catholics and Protestants) show strong opposition to the right to abortion, a result also observed in the present study, which endorses the criterion validity of MOSAI. In addition to the opposing to liberal arguments, we found that the religious group showed close acceptance of conservative arguments, including those characterized by an emotional appeal.

A final point to be discussed in this paper refers to a possible role to be played by MOSAI in the context of Brazilian public health. In one of its most recurrent definitions, elaborated by the Institute of Medicine (IoM), public health is understood as "what we as a society do collectively to assure the conditions in which people can be healthy", including, as a core function, the production, and monitoring of information related to the health of the population, aiming at identifying problems and defining priorities. [30] In this sense, it can be inferred that MOSAI could become a relevant instrument in the production and monitoring of information regarding the barriers to access to legal and safe abortion in Brazil. For example, new studies developed with this questionnaire may correlate the perspectives of HCP with the practice of conscientious objection. In doing so, MOSAI may contribute to another core function of public health, which is the development of public policies, "in collaboration with community and government leaders, to solve identified local and national health problems and priorities."[30]

Limitations

The high number of missing items during the measurement properties validation can be considered the main limitation of this study. Only two-thirds of all administered questionnaires were fully answered, of which half had to be excluded because they had at least one item answered with the "do not know" option. Women had a higher proportion in the group of subjects excluded from the analysis.

Meanwhile, people in a stable relationship had a higher proportion among the subjects who duly answered the questionnaire. Although the data collected in this study do not allow us to draw further conclusions on the issue, it seems safe to infer that men and women respond to moral dilemmas related to induced abortion differently, since men and women experience this phenomenon very differently. Men do not get pregnant, do not abort. For them, answering the types of dilemmas proposed by MOSAI may be done in a cooler, distant and, therefore, more comfortable way than for women; but this is a hypothesis for future investigations. On the other hand, the differences found for the marital situation impose greater difficulty of interpretation. Why do people in stable unions respond more adequately to a questionnaire like MOSAI? The data collected in this study does not allow us to answer this question safely. However, it is possible that the variable "stable union" has measured other issues beyond what was intended, such as more or less conservatism, or more or less adherence to traditional and family values, for example. If this is the case, it seems reasonable to infer that these inclinations, measured indirectly, have influenced the quality of filling the questionnaire.

CONCLUSION

MOSAI has been validated and is suitable for use in other surveys with HCP in Brasil.

QUESTIONNAIRE (ENGLISH VERSION)

PLEASE READ THE STORY BELOW AND ANSWER QUESTIONS SUBSEQUENT

JUSSARA

Jussara and her husband wanted a baby from the very beginning of their marriage, because they felt very lonely without a child. Then, they received the news that Jussara was pregnant with great joy. However, at 16 weeks, when the first ultrasound was performed, the doctor noticed that the fetus was anencephalic, that is, it had no brain. Upon hearing the diagnosis, Jussara's first thought was to let him to be born. However, she fears that keeping her pregnancy will cause even more suffering to her, her husband, and the fetus. Being in the second trimester of pregnancy, Jussara realizes that keeping or interrupting pregnancy will be a difficult decision.

A. Are you in favor of the right to abortion in this situation?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

B. Are you in favor of the possibility of this type of abortion being performed by the Brazilian public health system?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

C. Would you perform abortion for a patient in that circumstance?

Certainly would NOT accept	Probably would NOT accept	Probably would accept	Certainly would accept	I don not know
( )	( )	( )	( )	( )

	NOW, TELL HOW MUCH YOU AGREE TO THE PHRASES BELOW [1]	I agree too much	I agree a little	Indifferent	I disagree a little	I disagree too much	I do not know
1	Jussara and her husband have become responsible for a new life and must preserve it as long as possible	O	O	O	O	O	O
2	The protection of intrauterine life should be a duty of the Brazilian State even in cases of anencephaly.	O	O	O	O	O	O
3	The fetus of Jussara can not become a full human person because it has no prospects of psychological development.	O	O	O	O	O	O
4	A child should not be killed simply because nature did not give him the form his parents would like.	O	O	O	O	O	O
5	Abortion should be based on a reliable diagnosis of anencephaly, that is, the certainty that the unborn child will never have a future	O	O	O	O	O	O
6	The authorization of the Federal Supreme Court to interrupt the pregnancy in cases of anencephaly makes the society less sensitive to the value of life.	O	O	O	O	O	O
7	Forcing Jussara to maintain the pregnancy of an anencephalic fetus is the same as torturing her for the remainder of the pregnancy.	O	O	O	O	O	O
8	Women who interrupt pregnancy in cases of anencephaly may be under pressure from their partners	O	O	O	O	O	O
9	The right to abortion in rape cases is an important way to combat maternal mortality	O	O	O	O	O	O
10	If Jussara comes to a definite position on what to do, then her will must be respected.	O	O	O	O	O	O
11	Abortion should be based on a reliable diagnosis of anencephaly, that is, the certainty that the unborn child will never have a future	O	O	O	O	O	O
12	Societies that respect the sexual and reproductive rights of their citizens allow abortion in cases of anencephaly.	O	O	O	O	O	O
13	Interrupting pregnancy in cases such as this may mitigate the suffering of the father and mother of the anencephalic fetus.	O	O	O	O	O	O
14	If you decide to interrupt the pregnancy, it is possible that Jussara will suffer from regret in the future.	O	O	O	O	O	O

[1] Gray highlights were excluded from the final questionnaire model after confirmatory factorial analysis.

PLEASE READ THE STORY BELOW AND ANSWER QUESTIONS SUBSEQUENT

GRAZIANE

Pregnant for 13 weeks, Graziane is a carrier of the rare Eisenmenger Syndrome. The problem has a high rate of maternal mortality. It leads the person to not be able to develop the simplest physical activities without feeling a lack of air and fatigue. The only form of healing it is a heart transplant combined with a lung transplant. In case of pregnancy, the medical indication is the interruption. Even abortion involves risks for women, but lower than maintaining pregnancy, especially if performed during the first trimester. Anyway, Graziane and her husband want very much to have a child. And, for the moment, the fetus is in perfect formation.

A. Are you in favor of the right to abortion in this situation?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

B. Are you in favor of the possibility of this type of abortion being performed by the Brazilian public health system?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

C. Would you perform abortion for a patient in that circumstance?

Certainly would NOT accept	Probably would NOT accept	Probably would accept	Certainly would accept	I don not know
( )	( )	( )	( )	( )

	NOW, TELL HOW MUCH YOU AGREE TO THE PHRASES BELOW [2]	I agree too much	I agree a little	Indifferent	I disagree a little	I disagree too much	I do not know
15	The maintenance of such a risky pregnancy will be the same as signing the Graziane death certificate.	O	O	O	O	O	O
16	The high mortality rates for pregnant women with this disease justify abortion to protect the mother's life	O	O	O	O	O	O
17	Indicating abortion in cases of Eisenmenger Syndrome is a cruel decision because it protects only one of the two people involved.	O	O	O	O	O	O
18	The legal possibility of abortion in such cases is an important way to combat maternal mortality.	O	O	O	O	O	O
19	The laws that allow abortion in cases of Eisenmenger's Syndrome fail to protect the unborn child.	O	O	O	O	O	O
20	It is psychologically difficult for a health care professional to have to terminate the pregnancy of a healthy fetus	O	O	O	O	O	O
21	In countries where individual freedoms are respected, pregnant women like Graziane have the right to stop pregnancy if they wish.	O	O	O	O	O	O
22	To accept abortion in such cases indicates that a banalization of the life of the unborn child has happen.	O	O	O	O	O	O
23	If Graziane decides to take the pregnancy forward, her attitude may be seen as a heroism by her family.	O	O	O	O	O	O
24	At 13 weeks' gestation, the Graziane fetus has a lower capacity to feel pain than a born person.	O	O	O	O	O	O
25	Graziane must have complete freedom to choose to abort or maintain pregnancy, because it is her life and her body that are at risk.	O	O	O	O	O	O
26	Being able to interrupt the pregnancy in case of risk of death for the pregnant woman is a fundamental right.	O	O	O	O	O	O
27	Performing abortion in cases like this affects a fetus that could have a normal future ahead of it.	O	O	O	O	O	O
28	Graziane and her husband were aware of the risks when they freely decided to fulfill the dream of having a child.	O	O	O	O	O	O

[2] Gray highlights were excluded from the final questionnaire model after confirmatory factorial analysis.

PLEASE READ THE STORY BELOW AND ANSWER QUESTIONS SUBSEQUENT

MARINA

Marina is 23 years old, evangelical and single. She was raped by a former partner at the aggressor's home. For fear, she did not seek immediate care and became pregnant because of rape. When she realized the pregnancy, she felt at risk, frightened and without alternatives. At that moment, she sought care in a basic health unit, where she was advised of the legal possibility of interrupting the pregnancy, as well as what would be necessary if she decided to perform it. However, Marina remained confused. More than once, she was told that she is responsible for the pregnancy, because she put herself in a situation of risk when visiting her former partner. In addition, the induction of abortion contradicts their religious beliefs. Deeply distressed and without any support from friends or family, Marina does not know what to do.

A. Are you in favor of the right to abortion in this situation?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

B. Are you in favor of the possibility of this type of abortion being performed by the Brazilian public health system?

Very Favorable	Favorable	A Little Favorable	A Little Contrary	Contrary	Very Contrary	I do not know
( )	( )	( )	( )	( )	( )	( )

C. Would you perform abortion for a patient in that circumstance?

Certainly would NOT accept	Probably would NOT accept	Probably would accept	Certainly would accept	I don not know
( )	( )	( )	( )	( )

	NOW, TELL HOW MUCH YOU AGREE TO THE PHRASES BELOW [3]	I agree too much	I agree a little	Indifferent	I disagree a little	I disagree too much	I do not know
29	The right to abortion in rape cases is an important way to combat maternal mortality	O	O	O	O	O	O
30	Marina is now suffering because of rape, but may suffer even more if she aborts and feels guilty.	O	O	O	O	O	O
31	The right to abortion in cases of sexual violence contravenes the constitutional principle of the defense of life.	O	O	O	O	O	O
32	The unborn child should not be killed just because Marina was unable to defend herself from the ex-boyfriend's aggression.	O	O	O	O	O	O
33	In a secular State, the possibility of terminating pregnancy in cases of sexual violence is guaranteed.	O	O	O	O	O	O
34	The right to termination of pregnancy in cases of sexual violence mitigates the suffering of women.	O	O	O	O	O	O
35	Marina must keep in mind that life is sacred regardless of how it was generated	O	O	O	O	O	O
36	Legal abortion in cases of rape frees the victims of the horror of carrying a life generated in an act of terrible violence	O	O	O	O	O	O
37	If performed in the first weeks of gestation, abortion will affect an embryo, which does not yet have brain activity.	O	O	O	O	O	O
38	Discontinuation of a healthy fetus's pregnancy can be considered a form of violence against the weakest	O	O	O	O	O	O
39	Marina's wish to have an abortion should be enough so that she could safely interrupt the pregnancy.	O	O	O	O	O	O
40	If Marina is lying, then she has no right to an abortion because her sexual relationship with the ex-boyfriend was voluntary.	O	O	O	O	O	O
41	In hospitals, it is possible that many women lie to abort, trivializing the procedure.	O	O	O	O	O	O
42	The legal possibility of abortion in cases of rape respects international agreements on sexual and reproductive human rights.	O	O	O	O	O	O

[3] Gray highlights were excluded from the final questionnaire model after confirmatory factorial analysis.

RESUMO

RESUMO: *No Brasil, o aborto induzido é permitido por lei em casos de estupro, risco de morte para a gestante e anencefalia fetal. Entretanto, a literatura relata que alguns médicos recusam atender mulheres com tais demandas, ou o fazem de maneira discriminatória.*

OBJETIVO: *Pré-testar, testar e avaliar as propriedades da medida do "Mosaico de opiniões sobre o aborto induzido", um questionário para investigar as perspectivas de profissionais da saúde brasileiros sobre a moralidade do aborto.*

MÉTODOS: *Primeiro, o questionário foi pré-testado em uma amostra intencional de especialistas. Em segundo lugar, foi testado em uma amostra aleatória de 32 profissionais da saúde. Finalmente, conduziu-se um estudo multicêntrico em sete hospitais universitários para avaliar as propriedades da medida do questionário.*

RESULTADOS: *Combinadas, as amostras das três fases totalizaram 430 sujeitos. No pré-teste e no teste, todos os aspectos avaliados obtiveram resultados satisfatórios. Na fase multicêntrica, a análise fatorial confirmatória levou a uma importante redução do questionário, que também obteve bons indicadores de confiabilidade, além da validade de construto e de critério.*

CONCLUSÕES: *O questionário foi validado e encontra-se apto para ser utilizado em outras pesquisas no Brasil.*

PALAVRAS-CHAVE: *Estudos de validação. Aborto induzido. Atitude do pessoal de saúde. Ética. Inquéritos e questionários.*

REFERENCES

1. Diniz D, Dios VC, Mastrella M, Madeiro AP. A verdade do estupro nos serviços de aborto legal no Brasil. Rev Bioet. 2014;22(2):291-8.
2. Madeiro AP, Diniz D. Legal abortion services in Brazil: a national study. Cien Saude Colet. 2016;21(2):563-72.
3. Menezes G, Aquino EML. Pesquisa sobre o aborto no Brasil: avanços e desafios para o campo da saúde coletiva. Cad Saúde Pública. 2009;25(supl.2):s193-s204.
4. Silveira P, McCallum C, Menezes G. Personal experiences with induced abortions in private clinics in Northeast Brazil. Cad Saude Publica. 2016;32(2):e00004815.
5. Cacique DB, Passini Junior R, Osis MJMD. Opiniões, conhecimento e atitudes de profissionais da saúde sobre o aborto induzido: uma revisão das pesquisas brasileiras publicadas entre 2001 e 2011. Saúde Soc. 2013;22(3):916-36.
6. Faúndes A, Miranda L. "Ethics surrounding the provision of abortion care". Best Pract Res Clin Obstet Gynaecol. 2017;43:50-57.
7. Cacique DB, Passini Junior R, Osis MJMD. Validação de conteúdo do Mosaico de Opiniões sobre o Aborto Induzido (Mosai). Rev Assoc Med Bras. 2013;59(6):576-82.
8. Shellenberg KM, Hessini L, Levandowski BA. Developing a scale to measure stigmatizing attitudes and beliefs about women who have abortions: results from Ghana and Zambia. Women Health. 2014;54(7):599-616.
9. Sorhaindo AM, Karver TS, Karver JG, Garcia SG. Constructing a validated scale to measure community-level abortion stigma in Mexico. Contraception. 2016;93(5):421-31.
10. Scholtes VA, Terwee CB, Poolman RW. What makes a measurement instrument valid and reliable? Injury. 2011;42(3):236-40.
11. Steinberg JR, Rubin LR. Psychological aspects of contraception, unintended pregnancy, and abortion. Policy Insights Behav Brain Sci. 2014;1(1):239-47.
12. Nomura RM, Benute GR, Azevedo GD, Dutra EM, Borsari CG, Rebouças MS, et al. Depression, emotional and social aspects in the abortion context: a comparison between two Brazilian capitals. Rev Assoc Med Bras. 2011;57(6):644-50.
13. Hair JF, Black WC, Babin BJ, Anderson RE, Tatham RL. Análise multivariada de dados. 6a. ed. Porto Alegre: Bookman; 2009.
14. Fornell C, Larcker DF. Evaluating structural equation models with unobservable variables and measurement error. J Mark Res. 1981;18(1):39-50.
15. Pagano M, Gauvreau K. Princípios de Bioestatística. São Paulo: Thomson; 2004.
16. Galesic M, Bosnjak M. Effects of questionnaire length on participation and indicators of response quality in a web survey. Public Opin Q. 2009;73(2):349-60.
17. Terrível J, Rodrigues AT, Ferreira M, Neves C, Roque F, Silva OABC, et al. Conhecimento dos médicos relativo à prescrição de antibióticos e à resistência microbiana: estudo piloto de comparação de questionário online vs papel. R Epidemiol Control Infect. 2013;3(3):93-8.
18. Davidov E, Depner F. Testing for measurement equivalence of human values across online and paper-and-pencil surveys. Quality & Quantity. 2011;45(2):375-90.
19. Prieto L, Alonso J, Lamarca R. Classical Test Theory versus Rasch analysis for quality of life questionnaire reduction. Health Qual Life Outcomes. 2003;1:27.
20. Grossi E, Groth N, Mosconi P, Cerutti R, Pace F, Compare A, et al. Development and validation of the short version of the Psychological General Well-Being Index (PGWB-S). Health Qual Life Outcomes. 2006;4:88.
21. Hair Jr JF, GTM Hult, Ringle CM, Sarstedt M. A primer on Partial Least Squares Structural Equation Modeling (PLS-SEM). Los Angeles: Sage Publications; 2014. 307p.
22. Godoy CLM. Vivências de mulheres que sofreram violência sexual e solicitaram interrupção legal de gestação [Tese de doutorado]. Campinas: Universidade Estadual de Campinas. Faculdade de Ciências Médicas; 2015.
23. Borges VTM, Magalhães CG, Martins AMVC, Matsubara BB. Síndrome de Eisenmenger na gravidez. Arq Bras Cardiol. 2008;90(5):e40-1.
24. Cartago RS, Alan PA, Benedicto J. Pregnancy outcomes in patients with severe pulmonary hypertension and Eisenmenger syndrome treated with sildenafil monotherapy. Obstet Med. 2014;7(1):40-2.
25. Callahan S. Pro-life feminism. In: Gensler HJ, Spurgin EWS, Swindal JC, eds. Ethics: contemporary readings. Routledge contemporary readings in philosophy. New York: Routledge - Taylor & Francis Group; 2004.
26. Diniz D. Estado laico, objeção de consciência e políticas de saúde. Cad Saúde Pública. 2013;29(9):1704-6.
27. Ogland CP, Verona AP. Religion and attitudes toward abortion and abortion policy in Brazil. J Sci Study Relig. 2011;50(4):812-21.
28. Hoga LA, Rodolpho JR, Souza Penteado PE, Borges AL, Chávez Alvarez RE. Religiosity and sexuality: counseling provided by Brazilian Protestant pastors. Sex Reprod Healthc. 2013;4(2):57-63.
29. Palermo T, Infante Erazo M, Hurtado Pinochet V. Women's opinions on the legalisation of abortion in Chile 2009-2013. Cult Health Sex. 2015;17(7):873-90.
30. Institute of Medicine (US), Committee for the Study of the Future of Public Health. The Future of Public Health. Washington: National Academies Press; 1988.

ORIGINAL ARTICLE

Quality of life and vaginal symptoms of postmenopausal women using pessary for pelvic organ prolapse: a prospective study

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SUMMARY

OBJECTIVE: *The use of pessary is an option for the conservative treatment of pelvic organ prolapse (POP). However, here are few studies assess the quality of life (QoL) after inserting the pessary for POP. We have hypothesized that the use of pessary would modify QoL in women with POP.*

METHODS: *A prospective, observational study was performed that included 19 women with advanced POP. Pessary was introduced, and the SF-36 (general quality of life) and ICIQ-VS (vaginal symptoms and quality of life subdomain) questionnaires were applied before the introduction and after six months. A single question about the satisfaction regarding the use of the device was presented (subjective impression).*

RESULTS: *The mean age of the women included was 76 years. Most of them were non-caucasian (52.6%), with no prior pelvic surgery (57.5%), with urinary symptoms (78.9%). A third of the patients reported sexual activity. After treatment, 22.2% of them presented vaginal infection, and 27.7% increased vaginal discharge. Urinary symptoms remained unaltered. Women reported 100% satisfaction after using the pessary (77.7% partial improvement; 22.3% total improvement). SF-36 had significant improvement in three specific domains: general state of health (p=0.090), vitality (p=0.0497) and social aspects (p=0.007). ICIQ-VS presented a reduction in the vaginal symptoms (p < 0.0001) and an improvement in QoL (P < 0.0001).*

CONCLUSION: *The use of pessary for six months improved the QoL and reduced vaginal symptoms for women with advanced POP.*

KEYWORDS: *Pessaries. Pelvic organ prolapse. Quality of life. Surveys and Questionnaires.*

INTRODUCTION

Pelvic organ prolapse (POP) is a disease with high prevalence among older women and may impair their quality of life (QoL) significantly. Population aging is causing an increase in this estimative [1-3]. POP symptoms can be described as pain, pelvic pressure, sexual dysfunction, urinary or bowel symptoms [4].

Two general options for treating POP are available: conservative or surgical treatment. The pessary is the most important representative of this first choice and presents a good acceptance rate (85% success report) by women, despite some reports of discomfort and expulsion[4-6]. However, there aren´t many studies focusing on this topic, especially in Brazil. A systematic review has found seven articles

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related to pessary and QoL and has concluded that the pessary produced a positive effect on women's health; they have also suggested that further studies are necessary [7]. Given that, we sought to assess, using validated questionnaires, the quality of life, symptoms, and complications of women that have used vaginal pessaries as a conservative treatment for POP.

METHODS

We performed a prospective, non-randomized study with nineteen women recruited at the Gynecology Outpatient Clinic of our Institution (CAISM-UNICAMP) from March 2015 to 2016. Institutional Review Board approved this study (CAAE - 19460013.5.0000.5404), and after signing a written informed consent, women were enrolled.

We included women with advanced POP (POP-Q stage 3 and/or 4) that would accept the use of vaginal pessary for conservative treatment. We excluded from the study women with no POP-Q clinical assessment or with cognitive dysfunctions that would disable them from answering the questionnaire.

The primary outcome was the quality of life measured by the questionnaires ICIQ-VS (International Consultation on Incontinence Questionnaire – Vaginal Symptoms) and SF-36 (Short Form 36 Health Survey). The ICIQ-VS is a validated questionnaire for Brazilian Portuguese comprising fourteen questions, divided into three independent domains: vaginal symptoms subscale (score 0-53), sexual matters subscale (score 0-58) and the overall impact on quality of life subscale (0-10) [8]. The SF-36 questionnaire is a general QoL instrument, divided into eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical functioning, emotional functioning, social functioning, mental health [9].

The secondary outcomes were: subjective impression about the use of a pessary (satisfaction), divided into cured, better, unaltered, worse; sociodemographic and clinical data; complications; and urinary symptoms.

After filling out the forms, a gynecological exam was performed with the measurement of the posterior cul-de-sac in centimeters with a colpometer and the choice of the pessary size, inserted in a gynecological position by a single health professional (S.C.A.C.). After insertion (device between the pubic bone and sacrum), the patient was oriented to walk after a spontaneous micturition. If she had no complaints, she was discharged with verbal orientations. A six-month follow-up was scheduled, and the same questionnaires were applied again during a follow-up visit.

Power calculation was performed; considering a mean difference of 17 (±6) scores from the QoL questionnaires between the pessary users and non-users, a power of 80% and 0.05 alpha, with no drop-outs, we would need 18 women to perform this study [10]. Regarding statistical analysis, simple and relative frequencies were calculated for the categorical variables and descriptive measures (mean and standard deviation) for the quantitative variables. The Wilcoxon paired test was used to compare the questionnaire scores before and after treatment. Data were analyzed by the SAS (Statistical Analysis System) for Windows, version 9.4. A significance level of 5% was stipulated.

RESULTS

Twenty-seven women were enrolled in this study; eight were discontinued from the study (one patient deceased and seven failed to retain the pessary), and 19 completed the six-month follow-up. Mean age and BMI were 76±7.9 years and 24.7(±3.5) kg/m^2, and most of the women (58%) were multiparous and non-caucasian (52.6%). The anterior (84.2%) and/or apical (74.4%) compartment were the most prevalent prolapse defects. A third of women were sexually active (Table 1).

Regarding the pessary model, all women used the ring format. Almost a third (27.8%) of the patients reported vaginal discharge. There were two cases of local pain, vaginal infection, and ulceration. No case of severe complication such as bleeding, fistula or malignant transformation was seen. About urinary symptoms, no difference was observed before and after using the pessary for six months.

When women were asked how satisfied they were with the use of the pessary, 77.7%(15/19) reported improvement and 22.3% (4/19) said they were cured. Table 2 displays the results from the applied questionnaires. The vaginal symptoms subscale from the ICIQ-VS improved significantly, with a 28-point decrease in the scores (p=.0001) as well as QoL, with a reduction of 8.1 points (p=.0001). No difference was seen concerning the sexual score; however, this subscale was underpowered (n=4) (Table 2). As for the SF-

36, a significant improvement was perceived in three specific domains: general state of health (p=.0090), vitality (p=0.0497) and social aspects (p=0.0007).

DISCUSSION

The use of the pessary had a positive effect on advanced POP, with an improvement in women´s QoL, a high success rate and no severe complications related to the use of the device. Our findings are also consistent with a systematic review previously published by our research group which showed that the pessary can produce a positive effect on women's quality of life and can significantly improve sexual function and body perception [7]. Some studies also verified an improvement of POP symptoms that was comparable to the improvement seen after surgical treatment [de Albuquerque Coelho, 2016, Female pelvic organ prolapse using pessaries: systematic review[11-13]. Moreover, other studies have shown an improvement of the POP symptoms and QoL, as well as good indexes of body image and sexual function [10,14-16].

However, we did not see any difference in the sexual matter subscale before and after treatment, probably because only a third of women were sexually active and this has perhaps underpowered the statistical analysis, increasing the risk of a type II error. A study that investigated the risk of sexual dysfunction (FSFI questionnaire) in a population of 73 women using pessaries for POP has found a significant improvement of 42.4% on the score, specifically concerning desire, lubrication and sexual satisfaction [15]. Another study has used the PISQ-12 questionnaire for the same objective and compared it with women that underwent surgery; a significative improvement was seen in both groups [13]. All women were using the ring pessary, and differently from obstructive pessaries, the ring model may be used during sexual intercourse.

We used the ICIQ-VS; its QoL subscale improved 80% after the pessary treatment; this result resembles the data from other studies that have shown an increase of at least 40% in the QoL scores, but using different questionnaires (P-QOL, PFIQ, SPS-Q) [12,14,16]. About the SF-36, a general QoL questionnaire, we

TABLE 1: BASELINE CHARACTERISTICS OF WOMEN SUBMITTED TO PESSARY TREATMENT FOR PELVIC ORGAN PROLAPSE.

Variables	N=19
Age (X± SD - years)	76±7.9
Age at menopause (X± SD - years)	48±5.2
Body mass index (kg/m2)	24.7±3.5
Educational level (years)	
< 4	17 (89.5%)
4-11	2 (10.5%)
Comorbidities	15 (78.9%)
Number of pregnancies - n(%)	
1-3	8 (42%)
4- 9	7 (37%)
> 9	4 (21%)
Spontaneous vaginal delivery - n(%)	
1-3	9 (47%)
4-9	8 (42%)
>9	2 (11%)
POP-Q staging- n(%)*	
Apical compartment	14 (74.4%)
Anterior compartment	16 (84.2%)
Posterior compartment	13 (68.4%)
Previous Pelvic Surgery - n(%)	8 (42.5%)
Sexually active - n(%)	6 (31.6%)
Urinary symptoms - n(%)*	
Stress urinary incontinence	6 (31.6%)
Urgency	8 (42.1%)
Frequency > 7 micturitions	9 (47.4%)
Nocturia	8 (42.1%)

*More than one response may apply.

TABLE 2: QUALITY OF LIFE AND VAGINAL SYMPTOMS OF WOMEN USING PESSARY FOR POP BEFORE AND AFTER TREATMENT (N=19).

Questionnaires	Before treatment*	After treatment*	Mean difference	p value**
SF 36				
Physical functioning	59.7±31.6	76.1±23.8	16.4	0.0910
Physical role	31.6±47.8	5.3±22.9	-26.3	0.1250
Pain	73.5±21.6	82.6±13.1	9.2	0.1162
General Health	74.2±19.7	82.7±17.3	8.6	0.0090
Vitality	64.7±24.3	76.1±15.5	11.3	0.0497
Social functioning	59.9±34.8	94.7±16.3	34.9	0.0007
Emotional role	29.8±45.7	5.3±22.9	-24.6	0.1250
Mental health	60.4±20.6	65.7±19.1	5.3	0.1404
ICIQ-VS				
Vaginal symptoms	30.1±8.2	2.1±3.7	-28	< 0.0001
Sexual matters***	35.5±28.1	0.0±0.0	-35.5	0.5000
Quality of life	8.5±2.1	0.4±1.8	-8.1	<0.0001

*Mean±standard deviation;**Wilcoxon test; ***n=4.

noticed a significant improvement in the general health, vitality, and social aspects domains. Other studies did not use a generic QoL questionnaire but specific ones for pelvic floor dysfunctions [10,12,13,15,17,18]. POP is a condition that impairs the QoL, and we included this questionnaire to understand more thoroughly the impact of the pessary treatment in women's lives [16,18].

The main complication found in this study after using the pessary was the increase of vaginal discharge, similar to what the literature describes. It is the most frequently referred symptom by women, followed by vaginal infection and the presence of ulceration. This increase in vaginal discharge is probably attributed to a foreign body in the vagina, as well as the possible presence of bacterial vaginosis and ulceration (19,20). We have already shown that the use of a vaginal pessary may interfere with the vaginal environment (84% of vaginal discharge in the pessary group versus 62.2% in the control group; p< 0.01) [21]. Fortunately, no severe complications (device entrapment or urogenital fistula) were seen in this study [22,23]. As for pessary expulsion, seven women presented this; it is the risk factor most often associated with the discontinuation of the treatment according to the available literature; other reported conditions are pain and discomfort [17,22,23].

The strength of this study is the application of validated questionnaires (one POP-specific and the other for general QoL assessment). As for its weaknesses, we have no control group and small sample size, even though the power calculation assures that we have recruited the minimum amount necessary to perform the study. Another point was the small percentage of sexually active women, which impaired our capacity to analyze this outcome.

CONCLUSION

Conservative treatment with the use of ring pessary for six months in women with POP presented significant improvements in the domains of two validated questionnaires of quality of life and vaginal symptoms. The SF-36 presented improvement in three specific domains: general state of health, vitality and social aspects. ICIQ-VS presented good scores in the domains of vaginal symptoms and quality of life.

Conflict of interests

None

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RESUMO

OBJETIVO: *O pessário é uma opção para o tratamento conservador do prolapso genital.*

MÉTODOS: *Um estudo prospectivo e observacional foi realizado com 19 mulheres com prolapso genital avançado. A avaliação da qualidade de vida e dos sintomas vaginais foi mensurada pelos questionários SF-36 e ICIQ-VS antes e seis meses depois da colocação do pessário. Uma pergunta simples sobre satisfação do uso do dispositivo foi também feita (impressão subjetiva).*

RESULTADOS: *A idade média das mulheres foi de 76 anos. A maioria era parda/negra (52,6%), sem cirurgias pélvicas (57,5%), com sintomas urinários (78,9%). Um terço das pacientes relatou atividade sexual. Depois do tratamento, 22,2% apresentaram infecção vaginal e 27,7% fluxo vaginal aumentado. Não houve alteração da prevalência dos sintomas urinários. As mulheres relataram 100% de satisfação (77,7% melhora parcial e 22,3% melhora completa) depois do uso do pessário. Houve melhora em três domínios do SF-36: saúde em geral (p=0,090), vitalidade (p=0,0497) e aspectos sociais (p=0,007). O ICIQ-VS apresentou redução nos sintomas vaginais (p<0,0001) e melhora da qualidade de vida (p<0,0001).*

CONCLUSÕES: *O uso do pessário por seis meses em mulheres com prolapso genital melhorou a qualidade de vida e reduziu os sintomas vaginais.*

PALAVRAS-CHAVE: *Pessários. Prolapso de órgão pélvico. Qualidade de vida. Inquéritos e questionários.*

REFERENCES

1. Ding J, Song XC, Deng M, Zhu L. Which factors should be considered in choosing pessary type and size for pelvic organ prolapse patients in a fitting trial? Int Urogynecol J. 2016;27(12):1867-71.
2. Wolff B, Williams K, Winkler A, Lind L, Shalom D. Pessary types and discontinuation rates in patients with advanced pelvic organ prolapse. Int Urogynecol J. 2017;28(7):993-7.
3. Elser DM. Recognizing and managing common urogynecologic disorders. Obstet Gynecol Clin North Am. 2017;44(2):271-84.
4. Panman CM, Wiegersma M, Kollen BJ, Burger H, Berger MY, Dekker JH. Predictors of unsuccessful pessary fitting in women with prolapse: a cross-sectional study in general practice. Int Urogynecol J. 2017;28(2):307-13.

5. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89(4):501-6.

6. Lamers BH, Broekman BM, Milani AL. Pessary treatment for pelvic organ prolapse and health-related quality of life: a review. Int Urogynecol J. 2011;22(6):637-44.

7. Albuquerque Coelho SC, Castro EB, Juliato CR. Female pelvic organ prolapse using pessaries: systematic review. Int Urogynecol J. 2016;27(12):1797-803.

8. Tamanini JT, Almeida FG, Girotti ME, Riccetto CL, Palma PC, Rios LA. The Portuguese validation of the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS) for Brazilian women with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(10):1385-91.

9. Campolina AG, Bortoluzzo AB, Ferraz MB, Ciconelli RM. Validation of the Brazilian version of the general six-dimensional short-form quality of life questionnaire (SF-6D Brazil). Cien Saude Colet. 2011;16(7):3103-10.

10. Komesu YM, Rogers RG, Rode MA, Craig EC, Gallegos KA, Montoya AR, et al. Pelvic floor symptom changes in pessary users. Am J Obstet Gynecol. 2007;197(6):620.e1-6.

11. Lone F, Thakar R, Sultan AH. One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J. 2015;26(9):1305-12.

12. Abdool Z, Thakar R, Sultan AH, Oliver RS. Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. Int Urogynecol J. 2011;22(3):273-8.

13. Mamik MM, Rogers RG, Qualls CR, Komesu YM. Goal attainment after treatment in patients with symptomatic pelvic organ prolapse. Am J Obstet Gynecol. 2013;209(5):488.e1-5.

14. Patel M, Mellen C, O'Sullivan DM, LaSala CA. Impact of pessary use on prolapse symptoms, quality of life, and body image. Am J Obstet Gynecol. 2010;202(5):499.e1-4.

15. Kuhn A, Bapst D, Stadlmayr W, Vits K, Mueller MD. Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful? Fertil Steril. 2009;91(5):1914-8.

16. Manchana T. Ring pessary for all pelvic organ prolapse. Arch Gynecol Obstet. 2011;284(2):391-5.

17. Cundiff GW, Amundsen CL, Bent AE, Coates KW, Schaffer JI, Strohbehn K, et al. The PESSRI study: symptom relief outcomes of a randomized crossover trial of the ring and Gellhorn pessaries. Am J Obstet Gynecol. 2007;196(4):405.e1-8.

18. Lone F, Thakar R, Sultan AH, Karamalis G. A 5-year prospective study of vaginal pessary use for pelvic organ prolapse. Int J Gynaecol Obstet. 2011;114(1):56-9.

19. Alnaif B, Drutz HP. Bacterial vaginosis increases in pessary users. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11(4):219-22.

20. Collins S, Beigi R, Mellen C, O'Sullivan D, Tulikangas P. The effect of pessaries on the vaginal microenvironment. Am J Obstet Gynecol. 2015;212(1):60.e1-6.

21. Coelho SCA, Giraldo PC, Florentino JO, Castro EB, Brito LGO, Juliato CRT. Can the pessary use modify the vaginal microbiological flora? A cross-sectional study. Rev Bras Ginecol Obstet. 2017;39(4):169-74.

22. Abdulaziz M, Stothers L, Lazare D, Macnab A. An integrative review and severity classification of complications related to pessary use in the treatment of female pelvic organ prolapse. Can Urol Assoc J. 2015;9(5-6):E400-6.

23. Robert M, Schulz JA, Harvey MA; Urogynaecology Committee. Technical update on pessary use. J Obstet Gynaecol Can. 2013;35(7):664-74.

ORIGINAL ARTICLE

Global costs attributed to chronic kidney disease: a systematic review

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SUMMARY

The aim of this study is to discuss the global costs attributed to chronic kidney disease (CKD) and its impact on healthcare systems of developing countries, such as Brazil. This is a systematic review based on data from PubMed/Medline, using the key words "costs" and "chronic kidney disease", in January 2017. The search was also done in other databases, such as Scielo and Google Scholar, aiming to identify regional studies related to this subject, published in journal not indexed in PubMed. Only papers published from 2012 on were included. Studies on CKD costs and treatment modalities were prioritized. The search resulted in 392 articles, from which 291 were excluded because they were related to other aspects of CKD. From the 101 remaining articles, we have excluded the reviews, comments and study protocols. A total of 37 articles were included, all focusing on global costs related to CKD. Despite methods and analysis were diverse, the results of these studies were unanimous in alerting for the impact (financial and social) of CKD on health systems (public and private) and also on family and society. To massively invest in prevention and measures to slow CKD progression into its end-stages and, then, avoid the requirement for dialysis and transplant, can represent a huge, and not yet calculated, economy for patients and health systems all over the world.

KEYWORDS: *Chronic kidney disease. Dialysis. Kidney Transplant. Health care costs.*

INTRODUCTION

Chronic kidney disease (CKD) is fast growing in Brazil and worldwide, and is associated with high financial expenditures for patients and healthcare systems. Scaling up its economic repercussions and proposing strategies to minimize the costs involved in its treatment has been configured as a challenge for the scientific community.

Defined as the presence of kidney damage or decreased kidney function for three months or more, with repercussions on the general state of the patient[1], CKD has as its main causes systemic arterial hypertension (SAH) (35%) and diabetes mellitus (DM) (30%)[2], both chronic non-communicable diseases (CNCDs) with a high impact on morbidity and mortality and with high prevalence worldwide. In addition, CKD has a strong relationship with aging[3] and, based on the Brazilian population, according to projections, by 2050, the estimated number of elderly will be 66 million, while children and adolescents will be 31.8 million, reversing the scenario of 2010,

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when values for these age groups were 19.6 and 49.9 million, respectively.[4]

In general, aging is related to the risk of multi-morbidity, that is, the individual is affected by more than one chronic illness at the same time, which generates greater use of healthcare services and a considerable increase in treatment costs, considering that these are proportional to the number of associated diseases[5]. Population aging, if analysed in isolation, already presents numerous challenges for all sectors of society and imposes the need to rethink the dimension of the supply of services needed to meet the demands of this population group in the long term[4].

In the more advanced stages of CKD, characterized by a severe decline in the glomerular filtration rate (GFR), the patient must initiate one of the modalities of renal replacement therapy (RRT), whose current options are haemodialysis (HD), peritoneal dialysis (PD) and kidney transplant. Such therapeutic options demand numerous expenses for the healthcare system because, in addition to having a high cost, its users are susceptible to prolonged hospitalizations, continuous treatment and the use of high cost medications. It is known that dialysis and kidney transplant consume disproportionate amounts of healthcare budgets, since about 5% of budgets are consumed by less than 1% of the population[1].

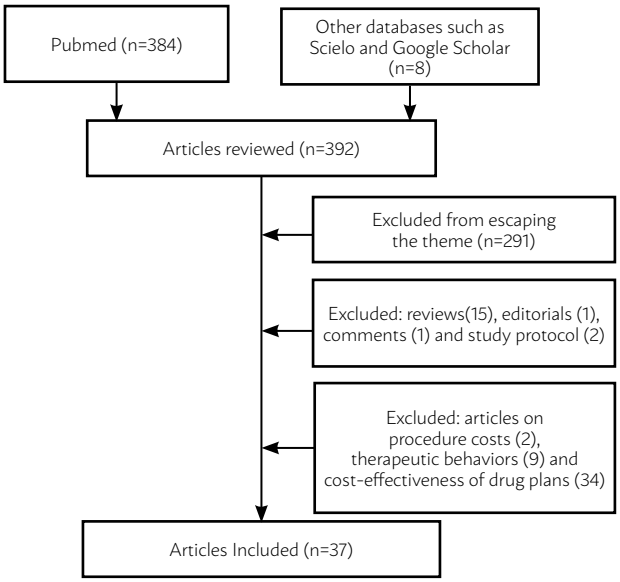
Studies of financial growth suggest that the greatest macroeconomic burden of CKD and other chronic diseases falls on low- and middle-income countries, where high prevalence and high treatment costs create a proportional burden on gross domestic product (GDP)[6]. It is known that the provision of RRT by countries has a directly proportional relation with their GDP, suggesting that poverty is an important disadvantage with respect to the access of individuals to the modalities of CKD treatment[7]. In addition, in the personal sphere, expenditures attributed to healthcare commonly affect the family financial structure, with considerable property loss, in a context of insufficient resources.

Faced with global financial instability, the uncertainties surrounding healthcare financing in developing and underdeveloped countries, the certainty of increasing life expectancy and the consequent increase in chronic health conditions, this review proposes to discuss financial costs attributed to CKD and its repercussions on healthcare systems in developing countries, such as Brazil.

MATERIALS AND METHODS

This is a systematic review carried out in the PubMed/Medline database, using the terms “costs” and “chronic kidney disease”, in January 2017. The search was expanded to other bases, such as Scielo and Google Scholar, with the purpose of identifying local studies related to this matter, published in journals not indexed in PubMed. Only articles published since 2012 have been included, considering the period of the last five years as recent. Studies focused on the costs of CKD and its treatment modalities were prioritized. The studies focused on the cost-effectiveness of drug regimens and therapeutic behaviours were excluded. The detailed selection process of the articles is described in Figure 1.

FIGURE 1: SELECTION PROCESS OF ARTICLES ON THE COSTS OF CHRONIC KIDNEY DISEASE FOUND IN THE SYSTEMATIC REVIEW AND INCLUSION/EXCLUSION CRITERIA.



RESULTS

In total, the search resulted in 392 articles (PubMed and other sources), of which 291 were excluded because they avoided the main theme of this review. Of the remaining 101, 19 articles were excluded because they were reviews, comments and study protocols, and 45 because they deal with costs of procedures, therapeutic behaviours and cost-effectiveness of specific drug regimens. The study included 37 articles focused on the overall costs related to CKD (Table 1).

TABLE 1: STUDY ON THE OVERALL COSTS RELATED TO CKD

Main Author	Year	Country	Study Model	Study Object	Primary Conclusion
Small (8)	2017	United States	Cross-sectional	Costs of CKD treatment	The costs of patients with CKD who do not go through dialysis are high and may be equal to or higher than those of cancer or CVA patients.
Damien (9)	2016	United States	Cross-sectional	Costs of CKD treatment	Therapeutic follow-up before and after the beginning of dialysis and the managing of comorbidities are potential sources of savings in CKD care.
Eriksson (10)	2016	Sweden	Cohort	Costs of CKD treatment	In comparison with the general population, the average yearly costs for CKD treatment are higher in all its modalities.
Anutrakulchai (11)	2016	Thailand	Cross-sectional	Clinical outcomes and treatment costs for CKD	The group of hospitalized CKD patients who presented the fewest benefits and highest mortality was composed of farmers, low-income, and unemployed individuals.
Silva (12)	2016	Brazil	Environmental	Socioeconomic and mortality aspects for patients with CKD	Men and the elderly presented the highest mortality. Associated with a high prevalence, kidney transplant (deceased donor) and HD presented the highest costs.
Turchetti (13)	2016	Italy	Cross-sectional	Social cost per CKD patient stages 4-5 pre-dialysis	The indirect and non-medical direct costs from CKD treatment were similar to the direct costs.
Kerr (14)	2016	England	Cross-sectional	Cause, site, and hospital costs related to the death of CKD patients	The primary causes for the death of CKD patients were not kidney related. Deaths at home are associated with a reduction of hospital costs.
Roggeri (15)	2016	Italy	Retrospective cohort	Costs of CKD treatment	CKD is associated with a high economic burden and the beginning of dialysis with an increase in direct costs with health care.
Mendu (!6)	2016	United States	Retrospective cohort	Rational clinical criteria for the diagnosis of CKD.	Some clinical criteria can guide the diagnosis of CKD and reduce its costs.
Silva (17)	2016	Brazil	Cost analysis/Literature review	Costs of CKD treatment	Kidney transplant stood out as the best alternative from a financial and clinical point of view, under the perspective of the Unified Health System (SUS).
Kulkarni (18)	2015	India	Cross-sectional	Costs of CKD treatment	The costs of HD in India are high when compared with the per capita income in the country.
Atapour (19)	2015	Iran	Cross-sectional	Costs of CKD treatment	PD presents a lower cost lower than HD.
Ferguson (20)	2015	Canada	Cost models	Operation costs for dialysis units	HD units in remote areas are more expensive, per patient, than hospital HD in urban areas.
Francis (21)	2015	Peru	Cross-sectional	CKD demographics	The high prevalence rates of CKD in Lima and Tumbes are compatible with high-income countries.
Takura (22)	2015	Japan	Cost-effectiveness analysis	Cost-effectiveness of CKD treatment.	Hemodiafiltration is a cost-effective therapy.
Wyld (23)	2015	Australia	Cohort	Costs of CKD treatment	CKD patients spend 85% more on health treatments and 50% more government subsidies than individuals with no CKD, and costs rise as the disease progresses.
Ozieh (24)	2015	United States	Cross-sectional	The costs for CKD treatment on DM patients	CKD significantly contributes to the treatment costs for individuals with DM.
Kent (25)	2015	England	Cohort	Costs of CKD treatment	RRT and vascular events are the leading causes of the rising costs in CKD treatment.
Brunelli (26)	2015	United States	Retrospective cohort	Costs for CKD treatment in individuals with autosomal dominant polycystic kidney disease.	The use and costs of health care for patients with autosomal dominant polycystic kidney disease and CKD in the terminal stage in dialysis are high.
Blanchette (27)	2015	United States	Cross-sectional	Costs for CKD treatment in individuals with autosomal dominant polycystic kidney disease.	Patients with autosomal dominant polycystic kidney disease presented higher rates of renal procedures, which can contribute to the rising costs of treatment.

Main Author	Year	Country	Study Model	Study Object	Primary Conclusion
Medway (28)	2015	Australia	Qualitative	Financial impact of CKD in children	For parents, the impossibility of keeping their jobs combined with medical and non-medical expenses where the primary factors with a financial impact.
Menezes (29)	2015	Brazil	Cross-sectional/retrospective cohort	Costs of CKD treatment	A considerable increase in the number of HD sessions and their cost was found, from 2008 to 2012.
Nassir (30)	2015	United States	Cohort	Costs of CKD treatment	No association was found between the relative costs of the treatment and the failure of the kidney grafts.
Villarreal-Rios (31)	2014	Mexico	Cross-sectional	Costs of CKD treatment	The high costs of CKD pose a serious problem for healthcare services and families. CAPD is the most cost-efficient option for both.
Satyavani (32)	2014	India	Cross-sectional	The costs for CKD treatment on DM patients	The direct costs of hospital admissions for treating CKD are considerably higher than those of the patients who suffer from the complication.
Lorenzo-Sellares (33)	2014	Spain	Cohort	Costs of CKD treatment	HD is five times more expensive than the treatment for advanced stages of CKD and three times the costs for kidney transplantation.
Moura (34)	2014	Brazil	Environmental	Incidence and prevalence of patients on dialysis who rely on public financing	During the time of the study, there was a constant increase in incidence, and prevalence rose, especially amongst the elderly.
Gador-Whyte (35)	2014	Australia	Cross-sectional	Costs for implementing protocols for CKD and DM treatment	Adherence to best practices for DM and CKD treatment was compromised by inadequate financing and matters related to the workforce.
Karopadi (36)	2014	Italy	Meta-analysis	Costs of CKD treatment	Even in the absence of a market for the local production of PD equipment, it is possible for a country to save with the provision of PD.
Vupputuri (37)	2014	United States	Retrospective cohort	The costs for CKD treatment on DM patients	The progression of CKD in DM type 2 patients substantially increases treatment costs.
Kadam (38)	2013	England	Cross-sectional	Treatment costs for chronic diseases	Multimorbidity is associated with a broad variety of treatments and different costs. CKD is one of the diseases with the highest and most expensive impact in healthcare.
Coentrão (39)	2013	Portugal	Retrospective cohort	Costs of CKD treatment	Compared with HD, PD requires fewer resources over the first year of treatment.
Essue (40)	2013	Australia	Cross-sectional	Costs of CKD treatment	A considerable proportion of the patients face difficulties due to the high costs associated with the treatment and managing od CKD.
Erdem (41)	2013	United States	Cross-sectional	Treatment costs for chronic diseases	People with chronic diseases represent a disproportionate share of Medicare payments, both for Part A and for Part B, over a period of two years. CKD is among the most expensive chronic diseases, in both parts.
Ramachandran (42)	2013	India	Cohort	Costs of CKD treatment	Kidney transplant is associated with catastrophic spendings and leads most patients who are treated in a public hospital to a serious financial crisis, as well as to school evasion and loss of employment.
Chiroli (43)	2012	Multicenter (Europe)	Retrospective cohort	Costs of CKD treatment	Secondary hyperparathyroidism increases the financial burden of CKD in Europe.
Kerr (44)	2012	England	Cross-sectional	Costs of CKD treatment	The financial impact of CKD is high, with high costs related to RRT and cardiovascular complications.

Research has warned that CKD is one of the most costly diseases in healthcare (38), and that its economic burden is already considerably high in the early stages, and can be equal to or greater than the costs attributed to cancer or cerebrovascular accident in adults[8]. With the progression of the disease and the need to initiate dialysis, there is a significant increase in direct costs related to health maintenance[15].

When comparing the financial expenditures related to the modalities of RRT, patients who are not on dialysis and kidney transplant patients are considered less costly to healthcare systems than those on dialysis[9]. Among dialysis, hemodiafiltration, a form of HD, is considered as a cost-effective therapeutic option[22]. In contrast to HD, PD stood out as a lower cost option[10,19]. In Spain, HD is five times more expensive than the treatment of the more advanced stages of CKD and three times more expensive than transplantat[33]. Continuous ambulatory peritoneal dialysis was mentioned as the most efficient use of institutional and family resources[31].

In Sweden, in relation to the healthcare costs of the general population, patients on HD, PD and kidney transplant present a 45, 29 and 11 times higher cost, respectively[14]. In Australia, CKD patients represent an 85% higher healthcare cost and require 50% more government subsidies than the general population[23].

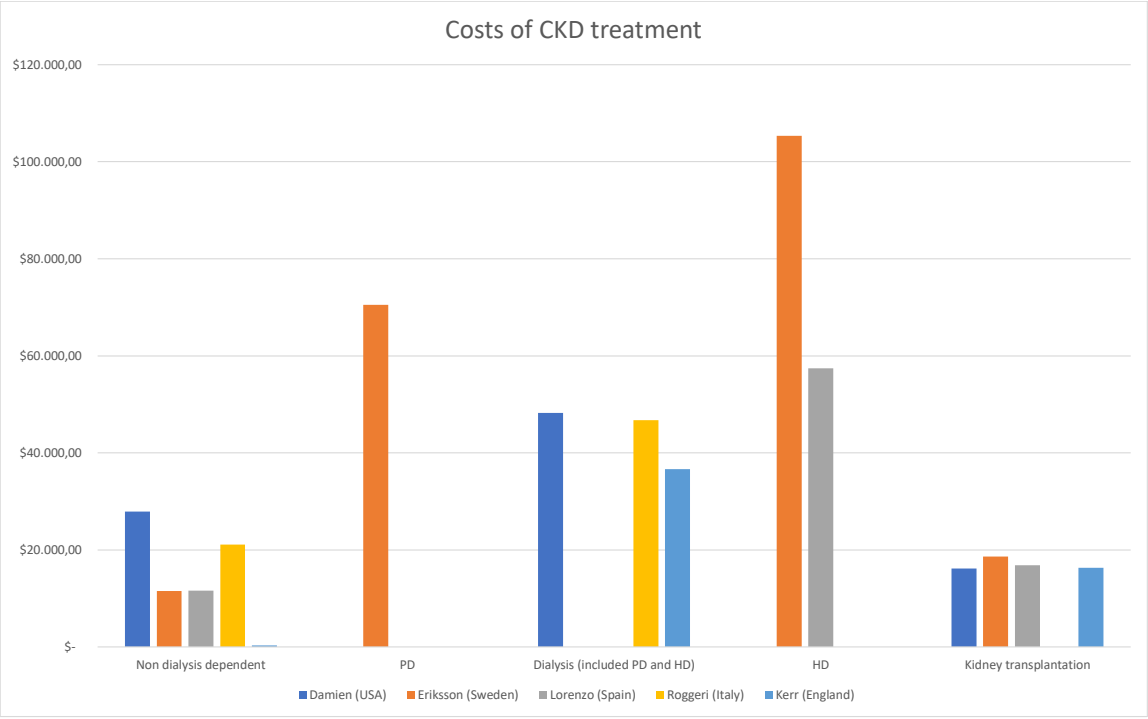
In Brazil, HD and kidney transplant stand out because of the high costs, which may be related to the high prevalence of the two modalities in the country12. In India, costs associated with transplant are considered catastrophic and are responsible for a serious financial crisis[42].

The socioeconomic profile of chronic kidney disease patients was highlighted in several articles as a relevant factor in the outcomes. Higher mortality was found among those with low income, unemployed[11], males and the elderly[12]. In addition, evidence shows that the prevalence of CKD increases considerably in the elderly[34].

A study carried out in England showed that the main causes of death in chronic kidney patients were not related to kidney problems but to heart disease, and that despite this, CKD added to hospital costs high values in the last 12 months of life[14]. In India, hospital costs of CKD patients were found to be substantially higher than those without CKD[32].

In diabetic patients, progression of CKD makes treatment more costly[37] and the direct costs of hospital admissions of patients with kidney complications are considerably higher than those without this complication[32]. In addition, CKD is responsible for the

FIGURE 2: ANNUAL COSTS (IN US DOLLARS) OF THE TREATMENT OF CHRONIC KIDNEY DISEASE (CKD) IN ITS DIFFERENT MODALITIES.



PD: peritoneal dialysis, HD: haemodialysis.

increase in expenses borne by DM patients, which strengthens the finding that it is the most expensive complication[24]. Other clinical conditions that, when associated with CKD, further increase their financial burden are autosomal polycystic kidney disease[26,27] and secondary hyperparathyroidism[43].

The financial repercussions of CKD treatment also have a strong impact on the economic structure of families[18,40]. A study points out that, for parents with chronic kidney disease children, the main culprits are the impossibility of maintaining employment and high expenses related to treatment[28]. Other research also highlights school drop-out as one of the consequences of treating the disease[42].

With a view to reducing CKD financial expenditures, studies suggest that clinical follow-up before and after initiation of dialysis and management of comorbidities are potential sources of savings in CKD care[9]. In specific cases, home death is associated with reduced hospital costs[14] and that some clinical criteria may guide the diagnosis of CKD and reduce its costs[16].

Figure 2 summarizes the annual costs of treating CKD in different modalities in different countries. Despite the characteristics of the analyses of the articles of this review, such as the variability of the factors included in the total expenditure and year of the study, when presented graphically, the costs of the CKD treatment show a significant difference between the different modalities of treatment, with haemodialysis having the highest cost.

DISCUSSION

Chronic kidney disease (CKD) has been gaining major repercussion due to its increasing incidence and prevalence worldwide, becoming a serious public health problem. The treatment of CKD is costly and, therefore, it is necessary to discuss possible cost reduction solutions, especially in Brasil, where political and economic crises are repeatedly faced. Although the methods and analyses are diverse, the results of the studies incorporated in this review are unanimous in alerting about the strong financial and social impact of CKD that affects the public and private healthcare systems, patients with the disease, family members and society as a whole. It is noted that the costs of CKD, compared to data from several countries, are higher in the long term for renal replacement therapies, especially in the haemodialysis modality. Transplant, despite being a high-cost surgical procedure, has become more cost-effective over the years, not to mention improving patient survival and quality of life.

Although the economic repercussions of CKD in developing countries are even more serious in the face of the economic difficulties faced in various sectors, it is observed that these are not different in developed countries. A study carried out in Italy concluded that annual costs for patients undergoing CKD treatment before dialysis were set at EUR 11,123 (approximately USD 13,668) versus EUR 53,764 (approximately USD 66,067) for dialysis patients, proving that prevention, early diagnosis and the consequent delay in starting dialysis could considerably reduce healthcare sector expenditures[15] also in countries with a more stable economy.

In the United States, considering the population served by Medicare, aged 65 or over, the total costs for parties A (Hospital Insurance, or HI) and B (Supplementary Medical Insurance, or SMI) increased by 11.5% to USD 227.100 million between 2008 and 2012, while such costs rose 53.6% to USD 44.6 billion among patients with CKD. The costs for patients with CKD and DM increased 70.2% between 2008 and 2012, while similar costs for patients without CKD, DM or congestive heart disease increased by only 4.1%[45].

In India, the average monthly cost of HD in the city of Mumbai, for example, was INR 6,142.33 (approximately USD 92), while the per capita income in the country was INR 5,130 (approximately USD 77) , according to data from 2011-2012, that is, the majority of patients were not able to pay for the treatment of CKD, since there are no state HD programs in the country[18], and this cost in India is significantly lower than in others countries analysed in our study, even lower than in Brasil. However, there is insufficient data to explain the reasons for this lower cost. It is estimated that in 2010 there were 2.6 million people on dialysis and 93% lived in countries with middle-high or high incomes, but the estimated number of people around the world who needed RRT was 4.9 to 9 million, indicating that approximately 2.3 million people died due to lack of access to adequate CKD care[6].

In Brasil, most of the specialized services (secondary and tertiary care) that have the treatment modalities of CKD are linked to the Brazilian Healthcare System (SUS), representing one of the biggest bottlenecks in the system, which currently faces serious management and transfer of resources prob-

lems. According to an article of the *Folha de S.Paulo* newspaper, on March 29, 2014, for every BRL 100 (approximately USD 30) invested in healthcare, BRL 54 (approximately USD 15) come from the families and corporate investment, and only BRL 46 (approximately USD 13) come from the public sector. According to experts, among the countries that adopt the universal healthcare system, Brasil is the only one where government healthcare spending is lower than private investment. It should be remembered that Brasil is the country with the largest public and universal healthcare system, and therefore should invest a much larger amount of public capital in the healthcare sector. In the United Kingdom, public sector spending accounts for 83% of the total; in Canada, 70.4% and in Argentina, 61%[46].

Regarding the Human Development Index (HDI), in the comparison between different countries, there is a proportional association with the transplant rate[47]. In 2014, Norway ranked first in the global HDI ranking (0.944) and performed 53.5 kidney transplants per million population (pmp), while in the same period, Brasil ranked 75th in the HDI (0.755) and performed 29.6 transplants pmp[48,49]. It is emphasized that the goal for the country is to reach 50 kidney transplants pmp by 2018[49].

Based on the evidence that kidney transplant is the mode of treatment for CKD with better clinical and quality of life outcomes, these data show that, although developed countries feel the financial repercussions of the CKD, their citizens are in a privileged position, in terms of access to the best therapeutic options. The HDI ratio and number of transplants also reveals the intrinsic association between CKD and financial support, because although the magnitude of the disease is transcultural, clinical outcomes are irremediably dependent on adequate funding.

Using Brasil as a reference, it was observed that in an analysis of the years 2008 and 2013 (last report available), about BRL 61.8 and BRL 189 million (approximately USD 17 and 55 million) were spent, respectively, in kidney transplants, that is, in the five-year period, the increase in expenditures was 300%[50]. However, in the same period, kidney transplants increased only 67.6%[49]. This disparity may be related to the improvement of surgical techniques, the incorporation of new less invasive technologies; to the use of new, more potent and more reliable immunosuppressive drugs, both in induction and maintenance therapy after transplant, and in the treatment of rejections; to the growth of transplant teams in number and staff; and greater longevity of patients and grafts, which generate a greater prevalence of outpatient visits in post-transplant follow-up. However, if this trend of rising charges continues, funding for the healthcare system will be seriously compromised in the future.

Given the high costs and complexity of treatments, the trend is for greater visibility to healthcare at the secondary and tertiary levels, but the results of this review point to the urgency of investing in primary care as a viable alternative for containment of expenses related to CKD.

Therapeutic interventions in the early stages of CKD are proven effective in slowing its progression. Considering that CKD, in general, is based on diseases such as hypertension and DM, continuous follow-up of patients and their families, screening new cases in the population, increasing the chances of early diagnosis, and implementing treatment for preserving kidney function are actions that need to be firmly incorporated into healthcare service practices, with emphasis on those offering basic care.

Increasing numbers of CKD and the high material and immaterial values involved in treatment modalities in a context of scarce resources have alerted to the need to develop tools and implement policies to control disease progression, aiming to reduce need for dialysis, transplant and complications.

CONCLUSIONS

It can be seen that the economic impact of CKD is global. It reaches all countries, regardless of the level of development and the model of healthcare. The studies analysed warn of the importance of primary and secondary prevention of CKD as a healthcare economy strategy. The association between population aging and the expansion of NCDs requires countries to reformulate care strategies and target their healthcare systems. The magnitude of the situation can be verified through the high incidence rates and prevalence of CKD, which is a complication of chronic diseases such as hypertension and DM. Massively investing in prevention and measures to slow the progression of CKD to the final stages, and hence avoid the need for dialysis and transplant, can represent a huge, not yet calculated, economy for patients and healthcare systems worldwide.

RESUMO

O objetivo deste estudo é discutir os custos financeiros mundiais atribuídos à doença renal crônica (DRC) e suas repercussões sobre os sistemas de saúde em países em desenvolvimento, como o Brasil. Trata-se de uma revisão sistemática realizada na base de dados do PubMed/Medline, utilizando os termos em inglês "costs" e "chronic kidney disease", em janeiro de 2017. A busca foi ampliada a outros bancos, como o Scielo e o Google Acadêmico, com o objetivo de identificar estudos locais relacionados ao assunto, publicados em revistas não indexadas no PubMed. Foram incluídos apenas artigos publicados a partir de 2012. Priorizaram-se estudos que abordavam os custos da DRC e das modalidades de tratamento. A busca resultou em 392 artigos, dos quais foram excluídos 291 por fugirem da temática principal desta revisão. Dos 101 restantes, foram excluídos revisões, comentários e protocolos. Foram incluídos 37 artigos cujo foco eram os custos globais relacionados à DRC. Apesar de os métodos e análises serem diversos, os resultados dos estudos são unânimes em alertar sobre o forte impacto, financeiro e social, da DRC que atinge os sistemas de saúde, públicos e privados, portadores da doença, familiares e a sociedade. Investir maciçamente em prevenção e nas medidas para retardar a progressão da DRC para os estágios finais e, consequentemente, evitar a necessidade de diálise e transplante, podem representar uma enorme, e ainda não calculada, economia para pacientes e sistemas de saúde do mundo todo.

PALAVRAS-CHAVE: *Insuficiência renal crônica. Diálise. Transplante de rim. Custos de cuidados de saúde.*

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter Suppl. 2013;3:1-150.
2. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Inquérito Brasileiro de Diálise Crônica 2013 - Análise das tendências entre 2011 e 2013. J Bras Nefrol. 2014;36(4):476-81.
3. Tonelli M, Riella M. Doença renal crônica e o envelhecimento da população. J Bras Nefrol. 2014;36(1):1-5.
4. Instituto Brasileiro de Geografia e Estatística (IBGE). Brasil: uma visão geográfica e ambiental no início do século XXI / Adma Hamam de Figueiredo (org). Rio de Janeiro: IBGE, Coordenação de Geografia, 2016. 435p.
5. Organização Mundial de Saúde (OMS). Relatório Mundial de Envelhecimento e Saúde (Resumo) 2015. Acesso em Fevereiro 2017. Disponível em: http://apps.who.int/iris/bitstream/10665/186468/6/WHO_FWC_ALC_15.01_por.pdf
6. Nugent RA, Fathima SF, Feigl AB, et al. The Burden of Chronic Kidney Disease on Developing Nations: A 21st Century Challenge in Global Health. Nephron Clin Pract. 2011;118:269–277.
7. Garcia-Garcia G, Jha V. CKD in Disadvantaged Populations. J Bras Nefrol. 2015;37(1):14-18.
8. Small C, Kramer HJ, Griffin KA, et al. Non-dialysis dependent chronic kidney disease is associated with high total and out-of-pocket healthcare expenditures. BMC Nephrol. 2017;18:3.
9. Damien P, Lanham HJ, Parthasarathy M, et al. Assessing key cost drivers associated with caring for chronic kidney disease patients. BMC Health Serv Res. 2016;16(1):690.
10. Eriksson JK, Neovius M, Jacobson SH, et al. Healthcare costs in chronic kidney disease and renal replacement therapy: a population-based cohort study in Sweden. BMJ Open. 2016;6:e012062.
11. Anutrakulchai S, Mairian P, Pongskul C, et al. Mortality and treatment costs of hospitalized chronic kidney disease patients between the three major health insurance schemes in Thailand. BMC Health Serv Res. 2016;16:528.
12. Silva AT, Soares LB, Magajewski FRL. Epidemiologic and Economic Aspects Related to Hemodialysis and Kidney Transplantation in Santa Catarina in the Period of 2012-2013. Transplantat Proc. 2016;48(7):2284-2288.
13. Turchetti G, Bellelli S, Amato M, et al. The social cost of chronic kidney disease in Italy. Eur J Health Econ. 2016. doi 10.1007/s10198-016-0830-1
14. Kerr M, Matthews B, Medcalf JF, et al. End-of-life care for people with chronic kidney disease: cause of death, place of death and hospital costs. Nephrol Dial Transplant. 2016;0:1–6.
15. Roggeri DP, Roggeri A, Salomone M. Chronic Kidney Disease: Evolution of Healthcare Costs and Resource Consumption from Predialysis to Dialysis in Piedmont Region, Italy. Advances in Nephrology 2014; 1-6.
16. Mendu ML, Lundquist A, Aizer AA, et al. Clinical Predictors of Diagnostic Testing Utility in the Initial Evaluation of Chronic Kidney Disease. Nephrology (Carlton). 2016;21(10): 851–859.
17. Silva SB, Caulliraux HM, Araújo CAS, et al. Uma comparação dos custos do transplante renal em relação às diálises no Brasil. Cad. Saúde Pública. 2016;32(6):e00013515.
18. Kulkarni MJ, Jamale T, Hase NK, et al. A Cross-Sectional Study of Dialysis Practice-Patterns in Patients with Chronic Kidney Disease on Maintenance Hemodialysis. Saudi J Kidney Dis Transpl 2015;26(5):1050-56.
19. Atapour A, Eshaghian A, Taheri D, et al. Hemodialysis Versus Peritoneal Dialysis, Which is Cost-effective? Saudi J Kidney Dis Transpl 2015;26(5):962-965.
20. Ferguson TW, Zacharias J, Walker SR. An Economic Assessment Model of Rural and Remote Satellite Hemodialysis Units. PLoS ONE. 2015;10(8):e0135587.
21. Francis ER, Kuo CC, Bernabe-Ortiz A, et al. Burden of chronic kidney disease in resource-limited settings from Peru: a population-based study. BMC Nephrology. 2015;16:114.
22. Takura T. Cost-effectiveness of hemodialysis in Japan. Contrib Nephrol. 2015;185:124-31.
23. Wyld MLR, Lee CMY, Zhuo X, et al. Cost to government and society of chronic kidney disease stage 1–5: a national cohort study. Intern Med J. 2015;45(7):741-7.
24. Ozieh MN, Dismuke CE, Lynch CP, et al. Medical care expenditures associated with chronic kidney disease in adults with diabetes: United States 2011. Diabetes Res Clin Pract. 2015;109(1):185–90.
25. Kent S, Schlackow I, Lozano-Kühne J, et al.What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrology. 2015;16:65.
26. Brunelli SM, Blanchette CM, Claxton AJ, et al. End-stage renal disease in autosomal dominant polycystic kidney disease: a comparison of dialysis-related utilization and costs with other chronic kidney diseases. Clinicoecon Outcomes Res. 2015;7:65–72.
27. Blanchette CM, Craver C, Belk KW, et al. Hospital-based inpatient resource utilization associated with autosomal dominant polycystic kidney disease in the US. J Med Econ. 2015;18(4):303-11.
28. Medway M, Tong A, Craig JC, et al. Parental Perspectives on the Financial Impact of Caring for a Child With CKD. Am J Kidney Dis. 2015;65(3):384-393.
29. Menezes FG, Barreto DV, Abreu RM, et al. Panorama do tratamento hemodialítico financiado pelo Sistema Único de Saúde - Uma perspectiva econômica. J Bras Nefrol 2015;37(3):367-378.
30. Nassir BA, Dean CE, Li S, et al.Variation in Cost and Quality in Kidney Transplantation. Transplantation. 2015;99(10):2150-7.
31. Villarreal-Ríos E, Cárdenas-Maldonado C, Vargas-Daza ER, et al. Institutional and familial cost of patients in continuous ambulatory peritoneal dialysis. Rev Assoc Med Bras 2014; 60(4):335-341.
32. Satyavani K, Kothandan H, Jayraman M, et al. Direct costs associated with chronic kidney disease among type 2 diabetic patients in India. Indian J Nephrol. 2014; 24(3): 141–147.
33. Lorenzo-Sellares V, Pedrosa MI, Santana-Expósito B, et al. Análisis de

costes y perfil sociocultural del enfermo renal. Impacto de la modalidad de tratamento. Nefrologia 2014;34(4):458-68.

34. Moura L, Prestes IV, Duncan BB, et al. Dialysis for end stage renal disease financed through the Brazilian National Health System, 2000 to 2012. BMC Nephrol 2014, 15:111.

35. Gador-Whyte AP, Wakerman J, Campbell D, et al. Cost of best-practice primary care management of chronic disease in a remote Aboriginal community. Med J Aust. 2014; 200(11):663-6.

36. Karopadi AN, Mason G, Rettore E, et al. The role of economies of scale in the cost of dialysis across the world: a macroeconomic perspective. Nephrol Dial Transplant. 2014;29:885–892.

37. Vupputuri S, Kimes TM, Calloway MO, Christian JB, Bruhn D, Martin AA, Nichols GA. The economic burden of progressive chronic kidney disease among patients with type 2 diabetes. J Diabetes Complications. 2014;28(1):10–16.

38. Kadam UT, Uttley J, Jones PW, et al. Chronic disease multimorbidity transitions across healthcare interfaces and associated costs: a clinical-linkage database study. BMJ Open. 2013;3(7):e003109.

39. Coentrão LA, Araújo CS, Ribeiro CA, et al. Cost analysis of hemodialysis and peritoneal dialysis access in incident dialysis patients. Perit Dial Int. 2013;33(6): 662–670.

40. Essue BM, Wong G, Chapman J, et al. How are patients managing with the costs of care for chronic kidney disease in Australia? A cross-sectional study. BMC Nephrol. 2013;14:5.

41. Erdem E, Prada SI, Haffer SC. Medicare Payments: How Much Do Chronic Conditions Matter? Medicare Medicaid Res Rev. 2013;3(2).

42. Ramachandran R, Jha V. Kidney Transplantation Is Associated with Catastrophic Out of Pocket Expenditure in India. PLoS One. 2013;8(7):e67812.

43. Chiroli S, Mattin C, Belozeroff V, et al. Impact of mineral and bone disorder on healthcare resource use and associated costs in the European Fresenius medical care dialysis population: a retrospective cohort study. BMC Nephrol. 2012; 13:140.

44. Kerr M, Bray B, Medcalf J, et al. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27(3): iii73–iii80.

45. United States Renal Data System, 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2014. [acesso em 8 Julho 2015] Disponível em: http://www.usrds.org

46. Folha de São Paulo on line. Setor privado gasta mais que o governo na área da saúde. Acesso em 27 Junho 2015. Disponível em: http://www1.folha.uol.com.br/seminariosfolha/2014/03/1432494-setor-privado-gasta-mais-que-o-governo-na-area-da-saude.shtml

47. Garcia GG, Harden P, Chapman J. O papel global do transplante renal. J Bras Nefrol 2012;34(1):1-7.

48. Programa das Nações Unidas para o Desenvolvimento no Brasil. Acesso em Janeiro de 2017. Disponível em: http://www.br.undp.org/content/brazil/pt/home/idh0/rankings/idh-global.html.

49. Associação Brasileira de Transplantes de Órgãos (ABTO). Registro Brasileiro de Transplantes 2015. Dimensionamento dos Transplantes no Brasil e em cada estado (2008-2015). Acesso em 29 dezembro 2016. Disponível em: http://www.abto.org.br/abtov03/default.aspx?mn=561&c=1086&s=0&friendly=rbt-2015

50. Portal da Saúde. Ministério da Saúde [Homepage na internet]. Orientação e Prevenção – Transplantes. Acesso em 29 dezembro 2016. Disponível em: http://portalsaude.saude.gov.br

ORIGINAL ARTICLE

Evaluation of liquid or foam sclerotherapy in small varicose veins (ceap c1) with venous clinical severity score

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SUMMARY

OBJECTIVE: *We aimed to evaluate the efficacy of liquid or foam sclerotherapy of varicose veins using venous clinical severity scores and possible complications.*

METHODS: *A total of 318 patients (268 females, 50 males) who were treated with liquid or foam sclerotherapy between January 2012 and December 2012 were included in this study.*

RESULTS: *Skin necrosis was observed in only 6 patients (1. 8%), thrombophlebitis in 10 patients (3. 1%), and hyperpigmentation in 18 patients (5. 6%) in this study group. The mean venous clinical severity score was calculated as: pain score, 1. 23 ± 0.88; varicose vein score,1.85 ± 0. 8; edema score, 0.64 ± 0.77). Pain and edema decreased at the control examination, 1 month after completion of sclerotherapy sessions. Varicose veins completely disappeared after sclerotherapy. While the decrease in edema in the foam sclerotherapy group was significantly less (P<0.001), the decline in pain showed an increasing trend (P=0.069). While skin necrosis did not develop after foam sclerotherapy, rates of pigmentation and local thrombophlebitis were similar (P>0.05).*

CONCLUSION: *In conclusion, we observed that both sclerotherapy methods are effective with a low rate of complications, alleviating the complaints of patients with small varicose veins, and providing considerable improvement in venous clinical severity scores.*

KEYWORDS: *Venous Clinical Severity Score, Reticular Veins, Sclerotherapy*

INTRODUCTION

Chronic venous insufficiency (CVI) causes considerable loss of work power, has adverse effects on the quality of life of patients and high prevalence, with 25-33% in women and 10-20% in men [1]. Furthermore, venous insufficiency associated with varicose veins cause frequent complications and cosmetic problems[2]. On the other hand, clinical, etiologic, anatomic, and pathophysiologic (*CEAP)* classification is a method of stratifying patients who have varicose veins and venous disease according to the severity of their presentation. In addition to the CEAP classification, venous clinical severity scoring system (VCSS) is also used in patients with chronic venous insufficiency [3]. This scoring system has been proposed by the American Venous Forum Ad Hoc Committee.

Telangiectasias associated with venous insuffi-

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ciency generally have diameters between 0, 1-1 mm and sclerotherapy is especially effective for this type of varicosity [4]. Complete chemical endothelial damage with inflammation develops with sclerotherapy [5]. Sclerotherapy cause transmural injury in vessel wall after endothelial damage [6]. Sclerotherapy is one of the most up-to-date approaches in the treatment of telangiectasias and varicose veins of the reticular type (1-3 mm diameter).

This study aimed to evaluate the complications and efficacy of foam and liquid sclerotherapy for telangiectasias and reticular type varicose veins of small diameter (CEAP 1 class), using VCSS and the medical literature retrospectively.

METHODS

Between January 2012 and December 2012, files of a total of 980 patients who were treated with sclerotherapy due to reticular type varicose veins or telangiectasias were screened. Before sclerotherapy, the patients were examined with venous color flow Doppler ultrasonography (CDUSG). From these patients, 318 were included in this retrospective study (268 females, 50 males; mean age 36. 7 ± 11.1 years), whose preoperative and postoperative medical records from the outpatient clinics could be found. The medical records of the patients were examined and the patients were divided into groups treated with liquid sclerosing (Group 1; 74 females, 25 males, mean age: 39.3±11 years, range 18-64) or sclerosing foam agent (Group 2; 194 females, 25 males, mean age; 35.6±10,5 years, range 18-64). Foam sclerotherapy was conducted according to the Tessari method. In the present study, 0.5%-1% polidocanol (lauromacrogol 400) (Aethoxysklerol®, Keussler Pharma, Wiesbaden, Germany) solution at a maximal dose of 0.5 ml for each vein was used, and the 2 mg/kg total dose was not exceeded. A dose of 0.5% polidocanol was administered to telangiectasias of < 1 mm diameter in both groups, while 1% polidocanol was administered to varicose veins of the reticular type of 1-3 mm diameter.

Patients with prominent venous insufficiency in CDUSG and those that received additional treatments, such as stripping, endovenous laser ablation, perforator vein ligation were excluded. There were varicose veins in both lower extremities in 44 patients (24.5%). The demographic characteristics of the patients are summarized in Table 1.

Sclerotherapy was administered to all patients with telangiectasias of 0.1-1 mm diameter or reticular veins of 1-3 mm diameter. The decision for sclerotherapy was reached after exclusion of insufficiency of the saphenous vein, deep veins and perforator veins utilizing careful physical examination and CDUSG. 30 G needles were used for sclerotherapy. Foam sclerotherapy was done while the leg was elevated at 45º, and the leg was rested at 45º for 10 minutes after the intervention. After compresses were placed over the varicose veins, the leg was wrapped with elastic straps, and compression therapy was continued for 2 days. Liquid sclerotherapy was done while the patient was lying down, and all patients were treated with compression therapy for 2 days with elastic straps. All patients returned to their normal daily activities after observation of at least half an hour at the outpatient clinics.

VCSS is based on scoring between 0 and 3 for clinical complaints and findings such as pain, varicose veins, edema, skin pigmentation, inflammation, induration, number of active ulcers, the diameter of active ulcers and past conservative treatments (compression socks and elevation) [3] . VCSS values before intervention and one month later were used in the evaluation of liquid and foam sclerotherapy in this study.

Statistical analysis

Changes in VCSS scores according to sclerotherapy method were evaluated with repeated common variable analysis. The pre-procedural characteristics of patients in the liquid and foam sclerotherapy groups were assessed by chi-square (χ^2) test (Table 1.) (p=0.029). The differences in the number of post-procedural complications of the groups were evaluated with the Mann-Whitney U test. The statistical analysis was done with SPSS 12.0 (SPSS Inc., Chicago, USA) software. P < 0.05 was considered as statistically significant.

TABLE 1. PRE-PROCEDURAL PATIENT CHARACTERISTICS

	Liquid Sclerosing Agent Treatment Group	Foam Sclerosing Agent Treatment Group	P values
Edema	1(0-3)	0.48 (0-3)	0.001
Pain	1.31(0-3)	1.19(0-3)	0.610
Varicose varices	2.11 (1-3)	1.75 (1-3)	1.120
Patient age	39.3±11	35.6±10,5	0.006
Gender F/M	74/25	194/25	0.002

P<0.05 was considered as significant with χ^2 test

RESULTS

The mean VCSS values in the pre-procedural evaluation of the patients were 1. 23 ± 0.88 for pain, 1.85 ± 0.8 for varicose veins, and 0.64 ± 0.77 for edema. The edema score, mean patient age, and proportion of male patients were higher in patients treated with liquid sclerotherapy (Table 1.). No patient in any group had pigmentation, inflammation, induration, and ulcer. Pain showed a decrease of 0.3 ± 0.45 points and edema 0.1 ± 0.12 points at the 1st-month control examination after completion of sclerotherapy sessions. Varicose veins disappeared completely (Table 2.).

Skin necrosis was observed in 6 patients (6%) who were treated with liquid sclerotherapy, thrombophlebitis in 4 (4%) and increase in pigmentation in 7 patients (7%) in the present study. Skin necrosis was not seen in patients treated with foam sclerotherapy, but pigmentation developed in 11 patients (5%), and thrombophlebitis developed in 6 patients (2.7%). Standard treatment for thrombophlebitis was administered to patients with thrombophlebitis. Local antibiotherapy and local epithelialization treatment were applied to patients with skin necrosis. Skin necrosis and thrombophlebitis were found to be improved at the control examination at the 1st month (Table 3.). Deep vein thrombosis and anaphylaxis did not occur in any patient. Local chondroitin polysulfate treatment was administered to the 15 patients (1.53%) with hyperpigmentation. Hyperpigmentation was found to be decreased at the control examination after 1 month of treatment.

Pain, temporary edema and swelling were observed in the patients for 2-3 days after sclerotherapy. Venotonic medications used in venous insufficiency and elastic bandage were administered to the patients for temporary edema, and swelling and all patients who underwent sclerotherapy were given 2x25 mg indomethacin for 5 days as analgesic/anti-inflammatory drug. Patients with very severe complaints were treated with bed rest and elevation. A mean of 1.95 sessions (range 1-8) of sclerotherapy were administered for the closure of varicose dilations.

DISCUSSION

Sclerotherapy was administered to patients without deep vein insufficiency having complaints of edema and pain in their legs, and patients with telangiectasic varicose veins who had cosmetic complaints about the appearance of their legs, by using foam and

TABLE 2. CHANGE IN VCSS ACCORDING TO SCLEROTHERAPY METHOD

		Liquid sclerosant treatment group		Foam sclerosant treatment group		P values
Symptoms	Classification	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Edema	None	32	86	137	192	0.001
	Mild	37	13	61	26	
	Moderate	28	0	19	1	
	Severe	2	0	2	0	
Pain	None	14	84	53	157	0.069
	Mild	46	14	93	61	
	Moderate	33	0	51	1	
	Severe	6	0	22	0	
Varicose veins	Mild	24	0	112	0	1
	Moderate	45	0	53	0	
	Severe	35	0	54	0	

Changes in VCSS scores were evaluated with repeated common variable analysis. P < 0.05 was considered as significant. VCSS; Venous clinical severity score

TABLE 3. COMPLICATIONS OBSERVED AFTER LIQUID SCLEROTHERAPY AND FOAM SCLEROTHERAPY

	Liquid Sclerosant Treatment Group	Foam Sclerosant Treatment Group	P values
Thrombophlebitis (regional)	4 (4%)	6 (2.7%)	0.538
Pigmentation	7 (7%)	11 (5%)	0.464
Skin necrosis	6 (6%)	0	0.001

P < 0.05 was considered as significant with Mann-Whitney U test.

liquid sclerotherapy methods. A noticeable improvement was observed in both groups regarding edema and pain, as seen in Table 2. Varicose veins completely disappeared with the use of both methods. Significant decreases in VCSS scores were recorded in comparison with baseline values with both methods.

Jia et al. [7] have reported that sclerotherapy may cause complications such as anaphylaxis, skin necrosis and ulceration, deterioration in vision, migraine, cough, minor vein thrombosis, hematoma, thrombophlebitis, skin pigmentation, and local neurological damage. Additionally, other potential complications of sclerotherapy include swelling (particularly with foot and ankle therapy), telangiectatic matting, nerve damage, painless infarction with arteriolar injection, phlebitis, and rarely deep vein thrombosis/ pulmonary embolism [8]. On the other hand, it was reported that the risk of deep venous occlusion after UGS in this series was lower when using highly diluted or undiluted sclerosant when treating veins less than 5 mm in diameter, and when restricting the volume of foam injected to less than 10 ml [9]. Deep vein thrombosis and pulmonary embolism were not observed in this study.

Herein, the most frequently encountered complications were pigmentation, local thrombophlebitis, and skin necrosis. No allergic reactions were detected in any patient. The pigmentation observed in patients decreased with time, although the duration of compression was short (2 days). Also, a similar rate of complications was seen in much of in the literature.

Özcan et al. [4] reported that skin necrosis was caused by a high concentration of sclerosing agent or the agent being injected out of the vessel. In the present study, edema decreased more with liquid sclerotherapy, and skin necrosis did not occur in the foam sclerotherapy group.

As it is well-known, telangiectasis and reticular veins develop from venous hypertension. The most crucial factor in the etiology of varicose veins is a familial predisposition, followed by other factors such as being overweight, occupations requiring continuously standing up, pregnancy, lower extremity traumas, and masses compressing on the veins [10].

Absolute contraindications for sclerotherapy include hypersensitivity against the sclerosing agent, systemic severe illness, local infection in the area where sclerotherapy is to be applied or systemic severe infections, acute superficial or deep vein thrombosis, advanced peripheral arterial disease (Fontaine stage 3 or 4), immobility, bed-ridden conditions, Hyperthyroidism (with iodine-containing sclerosants), confinement to bed and pregnancy [11]. Relative contraindications include advanced leg edema, the presence of late complications of diabetes (e.g., polyneuropathy, bronchial asthma), Fontaine stage 2 peripheral arterial disease, known hypercoagulability, poor general condition, bronchial asthma, pronounced allergic diathesis, thrombophilia (with or without a history of deep vein thrombosis) [11]. In the present study, patients were questioned on the presence of absolute or relative contraindications, and sclerotherapy was conducted on those without contraindications.

Sclerosants can be divided into three broad categories—osmotic agents, detergents, and irritant/ corrosives [12]. As well, common detergent sclerosants include polidocanol, sodium tetradecyl sulfate (STS), sodium morrhuate, and ethanolamine oleate. [12]. Polidocanol works similarly to STS as a detergent sclerosant and is used commonly in Europe [13]. On the other hand, Polidocanol usage is prevalent in Turkey. The total maximal single dose of Polidocanol for telangiectasia and reticular veins is 2 mg/kg; the dose of STS is 10 ml of 3% solution [4]. The amount of 0.5%-1% Polidocanol injection for telangiectasias and reticular veins is about 0.1-0.5 ml [4]. Özcan and Şenarslan [4] reported in their study that sclerotherapy was found inexpensive, with low complication rate, does not need hospitalization, relieves leg pain and discomfort. Polidocanol dosages used in this study are inconsistent with that study, and similar results were also found.

Rabe et al. [14] have suggested a preference of liquid sclerotherapy for C1 class reticular type varicose veins and telangiectasias according to CEAP classification, and foam sclerotherapy for C1 class varicose veins in 2013 European sclerotherapy guidelines. In the present study, liquid sclerotherapy was administered for telangiectasias, and foam sclerotherapy was preferred for reticular type varicose veins. As it is known, sclerotherapy is the standard treatment used for telangiectasic and reticular veins. Its chance of success is high if it is appropriately administered. The success of sclerotherapy depends on the administration technique, the sclerosing agent and its concentration, and the diameter of the vessel to be treated. Sclerotherapy administration became more natural as the operator administering sclerotherapy became more experienced in varicose veins of small diameter. Patients involved in this study did not require hospitalization. Also, sclerotherapy treatment

did impair the patient's ability to work. The . Ccost of this treatment technique compared to other treatment modalities for chronic venous insufficiency is lower than others.

The most important limitation of this study is the absence of optimal randomization. The cause of this is the requirement for a change of indication according to the diameters of varicose veins, which in turn led to patients with different characteristics in two groups.

CONCLUSION

In conclusion, it was observed that both sclerotherapy treatment methods are effective with a low rate of complications, alleviating the complaints of patients with small varicose veins (leg pain, irritability, decreasing analgesic requirement, cramps, and leg edema), and providing considerable improvement in VCSS scores.

Conflict of interest

The authors declare the absence of any conflicts of interest concerning any phases of preparing and publishing this manuscript.

Finance

We declare the absence of any financial support in any phase of the investigation and writing of this manuscript.

RESUMO

OBJETIVO: *Nosso objetivo foi avaliar a eficácia de líquido ou espuma na escleroterapia de varizes por meio de escores de gravidade clínica venosa e possíveis complicações.*

MÉTODOS: *Um total de 318 pacientes (268 do sexo feminino, 50 do sexo masculino) tratados com escleroterapia com espuma ou líquido entre janeiro de 2012 e dezembro de 2012 foi incluído neste estudo.*

RESULTADOS: *Necrose da pele foi observada em apenas seis pacientes (1,8%), tromboflebite em dez pacientes (3,1%) e hiperpigmentação em 18 pacientes (5,6%) neste grupo de estudo. A média do escore de gravidade clínica venosa foi calculado como: dor pontuação 1,23±0,88, veia varicosa pontuação 1,85±0,8, edema pontuação 0,64±0,77. Dor e edema reduzido no exame de controle um mês após a conclusão das sessões de escleroterapia. Varizes desapareceram completamente após a escleroterapia. Enquanto a diminuição do edema no grupo de escleroterapia com espuma foi significativamente menor (P<0,001), o decréscimo do nível de dor mostrou uma tendência a ser maior (P=0,069). Ainda que necrose da pele não tenha se desenvolvido após escleroterapia com espuma, as taxas de pigmentação e tromboflebite local foram semelhantes (P>0,05).*

CONCLUSÃO: *Observou-se que ambos os métodos de escleroterapia são eficazes, com baixa taxa de complicações, aliviando as queixas de pacientes com varizes pequenas, e proporcionando uma melhora considerável nos escores de gravidade clínica venosa.*

PALAVRAS-CHAVE: *Escore de gravidade clínica venosa. Varizes. Veias reticulares.*

REFERENCES

1. Köksal C, Alsalehi S, Kocamaz Ö, Sunar H. Kronik venöz yetmezlik tedavisi. Koşuyolu Kalp Dergisi. 2010;13:28-33.
2. İriz E, Ereren E, Oktar S, Oktar L, Halit V, İlhan M. Perforan venöz yetmezlikte miniflebektomi ile ligasyon. Türk Göğüs Kalp Damar Cer Derg. 2009;17:101-5.
3. Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G, et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg. 2003;38(2):224-8.
4. Özcan S, Şenarslan DA. Telenjiektazi ve retiküler venlerin tedavisinde skleroterapi. Bozok Tıp Dergisi. 2012;1:11-6.
5. Redondo P, Cabrera J. Microfoam sclerotherapy. Semin Cutan Med Surg. 2005;24(4):175-83.
6. Akbulut B, Tok M, Ucan Hİ, Dündar B. Sık görülen venöz sistem hastalıkları görülme sıklığı, risk faktörleri ve tedavisi. Anatolian J Clin Invest. 2009;3:113-9.
7. Jia X, Mowatt G, Burr JM, Cassar K, Cook J, Fraser C. Systematic review of foam sclerotherapy for varicose veins. Br J Surg. 2007;94(8):925-36.
8. Dietzek CL. Sclerotherapy: introduction to solutions and techniques. Perspect Vasc Surg Endovasc Ther. 2007;19(3):317-24.
9. Myers KA, Jolley D. Factors affecting the risk of deep venous occlusion after ultrasound-guided sclerotherapy for varicose veins. Eur J Vasc Endovasc Surg. 2008;36(5):602-5.
10. Soysal Ö, Gülcüler M, Cihan HB, Ege E, Gülcan Ö, Özdemir H, et al. Alt ekstremite varislerinin Polidokanol ile skleroterpisi. Turgut Özal Tıp Merkezi Dergisi. 1996;3:12-5.
11. Reich-Schupke S, Stücker M. Training in pictures: foam sclerotherapy. Phlebologie 2013;1:31-6.
12. Worthington-Kirsch RL. Injection sclerotherapy. Semin Intervent Radiol. 2005;22(3):209-17.
13. Mowatt-Larssen E. Management of secondary varicosities. Semin Vasc Surg. 2010;23(2):107-12.
14. Rabe E, Breu FX, Cavezzi A, Coleridge Smith P, Frullini A, Gillet JL, et al.; Guideline Group. European guidelines for sclerotherapy in chronic venous disorders. Phlebology. 2013;29(6):338-54.

ORIGINAL ARTICLE

Adiponectin levels and sleep deprivation in patients with endocrine metabolic disorders

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SUMMARY

BACKGROUND: *Sleep abnormalities are frequent in patients with endocrine metabolic disorders (EMD) such as arterial hypertension, diabetes and obesity. Adiponectin is a peptide largely secreted by adipocytes and has various properties e.g. anti-inflammatory, antioxidant, antiatherogenic, pro-angiogenic, vasoprotective and insulin-sensitizing. Adiponectin inversely relates to body weight and when its concentration decreases, the resistin concentration increases resulting in greater insulin resistance.*

OBJECTIVE: *The objective of this study is to examine factors influencing adiponectin levels in a population with EMD.*

METHODS: *This was a cross-sectional evaluation of 332 patients (18 to 80y) presenting arterial hypertension, pre-diabetes, diabetes, and/or obesity. Investigation included clinical evaluation of comorbidities, general blood tests and adiponectin measures (ELISA). Chronic sleep deprivation was determined if habitual sleep was <6 hours >4 days/week.*

RESULTS: *Arterial hypertension (78.5%), type-2 diabetes (82.3%), and overweight (45.0%)/obesity (38.8%) were frequent. Patients with type-2 diabetes tended to have more chronic sleep deprivation (p=0.05). Adiponectin levels increased with age and were inversely correlated with sagittal abdominal diameter (p=0.04) and fasting insulin (p=0.001). Chronic sleep deprivation was associated with higher adiponectin concentration [OR=1.34; CI=1.13-1.58; p<0.005] and this was maintained after adjustment for gender, age, body mass index, menopause, arterial hypertension, American Diabetes Association classification and physical exercise levels [OR=1.38; CI=1.14-1.66: p=0.001].*

CONCLUSION: *In patients with EMD, adiponectin is influenced not only by obesity but also by age and sleep deprivation. The latter finding may be explained by a compensatory effect or a counter regulation to minimize the harmful effects of sleep deprivation.*

KEYWORDS: *Sleep deprivation. Diabetes. Hypertension. Adiponectin. Obesity.*

INTRODUCTION

The frequent clustering of arterial hypertension, diabetes and obesity is potentially aggravated by factors such as old age, smoking, alcohol consumption, sedentary lifestyle, among others. Chronic sleep deprivation occurs in various endocrine-metabolic disorders further aggravating a cascade of harmful effects [1,2].

A recent review suggests that sleep disturbance and long sleep duration, but not short sleep duration, are associated with increases in markers of systemic inflammation[3]. Evidence suggests that sleep deprivation induces harmful effects on metabolic abnormalities, in the hypothalamic–pituitary–adrenal axis, and

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ultimately weight gain[4], In fact, an explanation for the biological changes found in patients with short or long sleep duration remains obscure. For instance, in healthy adults, sleep deprivation is associated with cognitive, neurophysiologic and endocrine changes, despite increased regional brain activity. These apparently paradoxical findings may be explained by adaptive behaviour or a compensatory effect [5].

The adipose tissue secretes several bioactive molecules, known as adipokines that are influential to whole-body homeostasis and serve as a measure of adipose tissue activity[6]. Adiponectin is the most abundant adipocytokine and has a regulatory effect on the metabolism of glucose and lipid[7,8]. High adiponectin levels have been associated with positive cardiovascular benefits; whereas low values of adiponectin are connected to obesity, metabolic syndrome, type 2 diabetes and dyslipidaemia[9]. Previously, female *diabetic showed higher adiponectin levels than male indicating a gender effect*[10]. Furthermore, higher adiponectin levels are inversely related to body weight and to insulin resistance[10]. All this evidence indicates that a complex set of variables influence adiponectin concentration.

The objective of the present study is to investigate factors influencing adiponectin expression in a population with endocrine-metabolic disorders.

METHODS

Study design and patients

This is a cross sectional evaluation of 332 patients with endocrine-metabolic disorders. We consecutively recruited patients from an outpatient clinic at *Centro Integrado de Diabetes e Hipertensão* (CIDH) in Fortaleza, Brazil. Initially, 400 subjects from the central database were examined. Sixty-eight were excluded due to difficulty of posterior examination (N=34), severe associated comorbidities (N=23) or refusal to participate in the study (N=11). Three-hundred and thirty-two of them attended the eligible criteria for the desired analyses. Plasma adiponectin levels were obtained in a subsample of 120 patients. The study involved individuals of both genders, aged from 18 to 80 years old, with a Body Mass Index (BMI) from 18.5-45.0 kg/m^2. All patients underwent clinical evaluation, investigation of comorbid disorders and blood tests. None had severe heart disease, renal insufficiency, stroke, dementia, severe depression, gastrointestinal and/or liver dysfunction or previous diagnosis of cancer. In this study, patients with type 1 diabetes and/or on use of insulin or glucocorticoids were not included. The local Research Ethics Committee (HUWC-CEP 031-04-09) approved the protocol and all included patients provided written informed consent.

Assessments

Three previously trained health workers assessed demographic and clinical information using a face-to-face interview. Endocrine-metabolic disorders were investigated. Arterial hypertension was defined as a systolic blood pressure ≥140mm Hg, diastolic blood pressure ≥90mm Hg, and/or current use of antihypertensive medications[11]. American Diabetic Association (ADA) classification rated patients as normal, with glucose intolerance or diabetes. The presence of a fastening ≥126mg/dl, post-prandial glucose concentration ≥200mg/dl, or diabetes symptoms and a plasmatic glucose concentration (last mealtime independent) ≥200mg/dl defined diabetes[12]. Intermediate plasma glucose levels situated between those considered normal and those considered diabetic characterized impaired glucose tolerance. A fasting blood glucose level of above 6.0 mmol/L or a blood glucose level of over 7.8 mmol/L 2 hours after consuming 75g of glucose established impaired glucose tolerance. Overweight was considered if Body Mass Index (BMI) ≥25 kg/m^2 and obesity if BMI ≥30 kg/m^2. Hyperlipidaemia was defined as an alteration in lipid profile, in which the Low Density Cholesterol (LDL) ≥100mg/dl, High Density Cholesterol (HDL) <40mg/dl and/or triglycerides >150mg/dl[13]. Chart review confirmed the clinical information.

Questionnaires investigated sleep duration, physical exercise and comorbidities. Patients were questioned about how many hours of sleep they usually get during the week and during the weekend. Less than six hours of sleep per day occurring at least four days per week defined the presence of *chronic sleep deprivation.* Less than 30 minutes of exercise per day and/or the absence of heavy physical exertion at home or at work, namely cleaning, hand washing clothes or other defined physical inactivity.

Biochemical analyses

Blood sampling and laboratory measurements were obtained in all patients. Samples were taken for biochemical investigations in blood collection tubes (Vacutainer - Vacuum II ®). Blood was drawn from an antecubital vein with the participants in a sitting po-

sition and was collected between 7:00 am and 9:30 AM, without stasis; the serum was separated after centrifugation for 10 minutes and stored at -70 degrees Celsius for the analyses. Adiponectin levels were determined by ELISA using commercial kits *(Kit Assay Designs Cortisol ELISA, Michigan, USA®).*

Statistical analysis

Descriptive statistics are presented as mean (standard deviation), range and frequency (percentage values). Fisher exact tests for categorical variables, Mann-Whitney *U* test for continuous variables and Student's t test for normally distributed data with equal variances compared between groups. Patients were grouped as having or not <6 hours of sleep. Adiponectin and variables were correlated (Pearson test). A logistic regression analysis model examined the associations of variables with reduced hours of sleep (<6h). In this model, gender, age, menopause, BMI, arterial hypertension, ADA classification and physical exercise level were all included. In this regression model all variables were included in a single step (enter). Statistical analysis used SPSS for Windows, version 21.0 and $p < 0.05$ was required for the statistical significance.

RESULTS

The majority of patients had arterial hypertension (78.5%), type 2 diabetes (82.3%), and overweight (45.0%) or obesity (38.8%). Menopause affected half of the women (50.6%). Patients with arterial hypertension frequently had type 2 diabetes (83.4%), were older (60.1±10.6 vs 51.2±11.2, p<0.005) and had higher BMI (29.8±5.3 kg/m^2 vs 27.9±4.1 kg/m^2, p=0.007). Table 1 depicts general characteristics of patients in the entire group of patients and according to the presence of chronic insufficient sleep (<6h). Reduced sleep time tended to be more frequent in patients with reduced glucose tolerance (ADA classification, p=0.05).

In this population, adiponectin levels were inversely to sagittal abdominal diameter (Pearson Exact Test: r=-0.176, p=0.04) and to fasting insulin levels (Pearson Exact Test: r=-0.226, p=0.008) (Figure 1A and 1B). Adiponectin levels were higher in patients with chronic sleep deprivation (4.2±2.7) than in those without (2.5±2.0) (Students' t test, p=0.001) (Figure 2). Older age [OR=1.02; CI=1.00-1.05; p=0.03] and increased adiponectin levels [OR=1.34; CI=1.13-1.58; p<0.005] were associated with reduced hours of sleep (<6h). Adiponectin concentration remained associated with sleep deprivation after adjustment for gender, age, menopause, BMI, arterial hypertension, ADA classification and physical exercise level [OR=1.38; CI=1.14-1.66: p=0.001] (Table 2).

DISCUSSION

This study shows that in patients with endocrine metabolic disorders, adiponectin levels are higher in older patients and are negatively related to sagittal abdominal diameter and fasting insulin. These findings are in agreement with previous reports demonstrating higher adiponectin levels with increasing age in both genders, regardless of the presence of obesity[14]. The role of increased adiponectin with increasing age is unclear. Kizer et al. suggest that age-related homeostatic dysregulation explains high adiponectin levels over time in long-lived adults. These higher values have been associated with greater physical disability and mortality[15].

Previous studies confirm that adiposity is negatively related to adiponectin levels[16,17]. In this work, only sagittal abdominal diameter was inversely related to adiponectin concentration indicating that this measure is a reliable predictor of visceral adiposity[18,19]. Similar to our findings, high fasting insulin was associated with lower levels of adiponectin. More precisely, increased resistin has been associated with lower adiponectin[20]. Our findings confirm that low values of adiponectin are connected to adiposity and high fasting insulin.

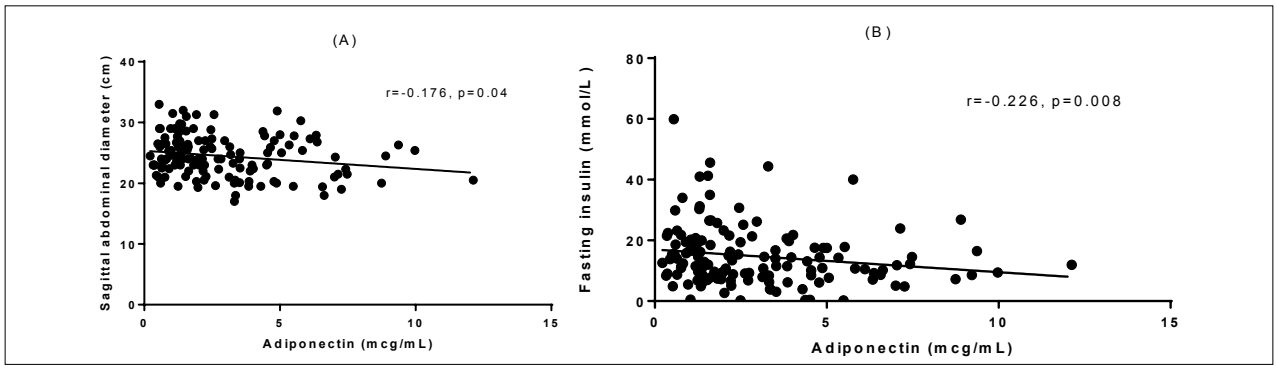
Presently, sleep deprivation was independently associated with elevated adiponectin levels. We hypothesize that the latter findings can be explained by a compensatory mechanism to limit the harmful effects of sleep deprivation. In agreement, a counter-regulatory effect mitigating further damage was previously suggested[21]. To the best of our knowledge, to date, no study reported a relationship between chronic sleep deprivation and adiponectin levels in a population with endocrine-metabolic disorder. Previous studies relating adiponectin levels with chronic sleep alterations show controversial results. In healthy young volunteers, Robertson et al. described no changes of adiponectin levels after three weeks of reduced daily sleep duration[21]. Simpson et al. reported differential effects according to gender and ethnicity[22]. Taheri et al. described, in a population of recruited volunteers, no change in adiponectin levels

TABLE 1: CLINICAL CHARACTERISTICS OF PATIENTS ACCORDING TO THE PRESENCE/ABSENCE OF SIX HOURS OF SLEEP

Variables	All cases N=322	≥6 h/sleep N=243	<6h sleep N=79	p-value
Male/Female, N/ (%)	131/191 (40.7)/(59.3)	103/140 (42.3)	28/51 (35.4)	b 0.29
Age (y), Range Mean (SD)	29-80 58.2(11.3)	29-80 57.5 (11.1)	31-79 60.6 (11.2)	a 0.36
Menopause N, %	162 (50.6)	113 (80.7)	46 (90.1)	b 0.15
Arterial Hypertension Yes/No	253 (78.5)	186 (77.8)	65 (82.3)	b 0.43
(ADA) (Normal, Red. Tolerance, Diabetes) N/%	22/35/265 (6.8/10.9/82.3)	18/21/204 (7.5/8.6/83.9)	4/14/61 (5.1/17.7/77.2)	b 0.05
Smoker (never, previous, current) N/%	210/76/36 (65.2/23.6/11.1)	157/26/58 (65.2/10.8/24.0)	51/10/18 (64.6/12.6/22.8)	b 0.86
Alcoholism N, %	28 (8.7)	24 (10.0)	4 (5.0)	b 0.42
BMI Range. Mean (SD)	19.1-50.5 29.4(5.1)	19.1-50.5 29.3 (5.2)	21.8-42.9 29.8 (4.8)	a 0.39
Hip-Waist Variation. Mean (SD)	0.84-1.77 1.05 (0.1)	0.84-1.75 1.05 (0.10)	0.89-1.77 1.05 (0.11)	a 0.87
Abdominal circumference (cm) Range Mean (SD)	59-148 103.9 (10.9)	59-148 103.5 (11.2)	87-135 105.2 (9.9)	a 0.22
Neck circumference (cm) Range Mean (SD)	24-50 38.5(3.8)	24-50 38.6 (3.8)	30.5-48 38.4 (3.9)	a 0.73
Thigh circumference (cm) Range Mean (SD)	34-103 50.8 (8.1)	34-79 50.5 (7.3)	37-103 51.5 (10.1)	a 0.34
Arterial systolic pressure Range Mean (SD)	98-220 138 (21.0)	98-220 137.5 (21.0)	100-204 140.1 (21.4)	a 0.35
Arterial diastolic pressure Range Mean (SD)	60-120 81.6 (10.7)	60-120 81.3 (10.6)	60-106 82.8 (11.0)	a 0.29
Physical activity (sedentary/mild/moderate & intense)	179/80/62	139/57/45	40/23/16	b 0.49
Sun exposure (score)	0-56 13.9(12.2)	0-56 13.7 (12.6)	0-42 14.2 (10.6)	c 0.75

Abbreviations: ADA= American Diabetic Association; BMI= Body Mass Index; SD= Standard Deviation a Student's t-test; b Fisher exact test; c Mann-Whitney test

FIGURE 1: ADIPONECTIN LEVELS WERE INVERSE TO SAGITTAL ABDOMINAL DIAMETER (A) AND TO FASTING INSULIN LEVELS (B).



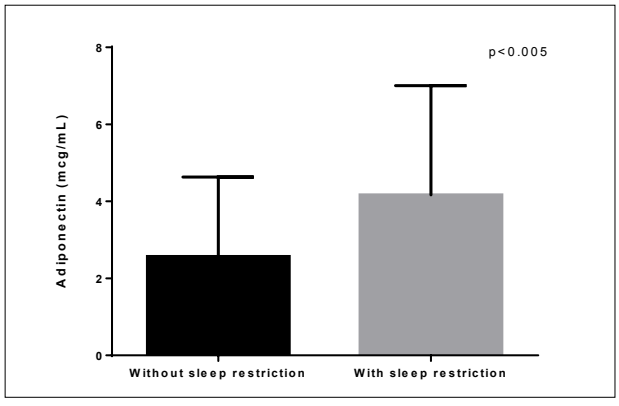


FIGURE 2: EFFECTS OF SLEEP RESTRICTION ON ADIPONECTIN LEVELS.

TABLE 2: LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH REDUCED HOURS OF SLEEP (<6H)

Variable	Exp B	CI	p-value
Gender	1.33	[0.78-2.26]	0.28
Age	1.02	[1.00-1.05]	0.03*
Menopause	1.49	[0.89-2.49]	0.12
Arterial hypertension	0.75	[0.39-1.45]	0.40
ADA Classification	0.87	[0.56-1.34]	0.53
BMI	1.02	[0.97-1.07]	0.39
Waist-Hip	1.20	[0.11-13.1]	0.87
Neck circumference	0.98	[0.92-1.05]	0.73
Vitamin D	1.00	[0.97-1.03]	0.65
Adiponectin	1.34	[1.13-1.58]	<0.005**
Sun exposure	1.00	[0.98-1.02]	0.75
Physical activity	1.14	[0.83-1.57]	0.39
Alcoholism	0.86	[0.60-1.21]	0.39
Smoker	0.99	[0.73-1.33]	0.95
Multivariate analysis (adjustments for gender, age, menopause, BMI, arterial hypertension, ADA classification, and physical exercise level, enter model)			
Adiponectin	1.457	[1.17-1.81]	0.001

Abbreviations: ADA= American Diabetic Association; BMI= Body Mass Index p<0.05* p<0.01**

in relation to chronic sleep deprivation[24]. In obese subjects, plasma low adiponectin level was associated with obstructive sleep apnea[25]. In partial agreement with the latter study, low adiponectin levels, increased levels of inflammatory markers, and atherogenic lipid profiles were found in association with obstructive sleep apnoea in hypertensive patients[26]. In opposition to the previous studies, an increase of adiponectin levels was associated with sleep apnea[25,27] Furthermore, adiponectin also shows a circadian pattern[28]. Regrettably, in the present work, sleep apnoea and circadian rhythm were not investigated. Together, all this evidence indicates that adiponectin levels are influenced by a range of factors.

In this study, patients with diabetes tended to have more sleep deprivation. Both, short and long sleep duration, and poor glucose control are reported in patients with type 2 diabetes[29,30]. In our study, no gender effect was found[23]. In opposition to our findings, higher levels of adiponectin were found in women[31,32]. In hypertensive patients, gender and renal function influenced adiponectin levels[21].

Interestingly, in this population, adiponectin measures did not correlate with anthropometric measures or to Gamma-glutamyltransferase (GGT) measures. Hsieh et al. showed that low serum adiponectin level may precipitate hepatic steatosis in patients with type 2 diabetes[33]. Another data supported a role for low circulating adiponectin in the pathogenesis of non-alcoholic fat liver disorder[34].

Limitations must to be acknowledged. In this study, chronic sleep deprivation was evaluated only by questionnaires and objective sleep measures were not recorded. Nonetheless, the strength of the present study is that it is the first to examine adiponectin levels in relation to sleep deprivation in patients with multiple endocrine-metabolic disorders.

In summary, we show that chronic sleep deprivation affects approximately 1/4 of patients with endocrine-metabolic disorders. Patients with type 2 diabetes tended to have more chronic sleep deprivation. Adiponectin levels increased with age and higher values were independently associated with chronic sleep deprivation. Increased sagittal abdominal diameter and fasting insulin levels were negatively correlated with adiponectin levels. These findings reinforce the concept that low adiponectin levels have an obnoxious effect, and multiple factors and counter-regulatory effects may influence adiponectin levels.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

RESUMO

INTRODUÇÃO: *Problemas de sono são frequentes em pacientes com distúrbios endócrino-metabólicos (DEM), como hipertensão arterial, diabetes e obesidade. A adiponectina é um peptídeo segregado por adipócitos e apresenta diversas propriedades, como por exemplo, anti-inflamatória, antioxidante, antiaterogênica, pró-angiogênica e vasoprotetora. A adiponectina relaciona-se inversamente com o peso corporal.*

OBJETIVO: *Examinar os fatores que influenciam os níveis de adiponectina em uma população com DEM.*

MÉTODOS: *Trata-se de uma avaliação transversal com 332 pacientes (18 a 80 anos) apresentando hipertensão arterial, pré-diabetes, diabetes e/ou obesidade. A investigação incluiu avaliação clínica de comorbidades, exames de sangue e medidas de adiponectina (Elisa). A restrição crônica do sono foi determinada com o sono habitual <6 horas >4 dias/semana.*

RESULTADOS: *Doenças como hipertensão arterial (78,5%), diabetes tipo 2 (82,3%) e sobrepeso (45,0%)/obesidade (38,8%) foram frequentes. Pacientes com diabetes tipo 2 apresentaram uma tendência na restrição crônica do sono (p=0,05). Os níveis de adiponectina aumentaram com a idade e foram inversamente correlacionados com o diâmetro abdominal sagital (p=0,04) e com a insulina em jejum (p=0,001). A restrição crônica do sono foi associada à maior concentração de adiponectina [OR=1,34; CI=1,13–1,58; p<0,005] e isso foi mantido após ajuste por gênero, idade, índice de massa corporal, menopausa, hipertensão arterial, classificação dos níveis da American Diabetes Association e exercício físico [OR=1,38; CI=1,14–1,66: p=0,001].*

CONCLUSÕES: *Em pacientes com DEM, a adiponectina é influenciada não apenas pela obesidade, mas também pela idade e pela restrição de sono. O último achado pode ser explicado por um efeito compensatório ou por um regulamento contrário para minimizar os efeitos nocivos da restrição do sono.*

PALAVRAS-CHAVE: *Restrição do sono. Diabetes. Hipertensão. Adiponectina. Obesidade.*

REFERENCES

1. Brum MC, Filho FF, Schnorr CC, Bottega GB, Rodrigues TC. Shift work and its association with metabolic disorders. Diabetology & metabolic syndrome. 2015;7:45
2. Broussard JL, Chapotot F, Abraham V, Day A, Delebecque F, Whitmore HR, Tasali E. Sleep restriction increases free fatty acids in healthy men. Diabetologia. 2015;58:791-798
3. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biological psychiatry. 2016;80:40-52
4. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: A novel risk factor for insulin resistance and type 2 diabetes. Journal of applied physiology (Bethesda, Md. : 1985). 2005;99:2008-2019
5. Klumpers UM, Veltman DJ, van Tol MJ, Kloet RW, Boellaard R, Lammertsma AA, Hoogendijk WJ. Neurophysiological effects of sleep deprivation in healthy adults, a pilot study. PloS one. 2015;10:e0116906
6. Check JH. The interrelationship of sleep, biologic clocks, neurotransmitters, gonadotropins and pubertal development. Clinical and experimental obstetrics & gynecology. 2013;40:7-14
7. Faraj M, Lu HL, Cianflone K. Diabetes, lipids, and adipocyte secretagogues. Biochemistry and cell biology = Biochimie et biologie cellulaire. 2004;82:170-190
8. Tao C, Sifuentes A, Holland WL. Regulation of glucose and lipid homeostasis by adiponectin: Effects on hepatocytes, pancreatic beta cells and adipocytes. Best practice & research. Clinical endocrinology & metabolism. 2014;28:43-58
9. Davis SK, Gebreab SY, Xu R, Riestra P, Khan RJ, Sumner AE, Hickson D, Bidulescu A. Association of adiponectin with type 2 diabetes and hypertension in african american men and women: The jackson heart study. BMC cardiovascular disorders. 2015;15:13
10. Aleidi S, Issa A, Bustanji H, Khalil M, Bustanji Y. Adiponectin serum levels correlate with insulin resistance in type 2 diabetic patients. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society. 2015;23:250-256
11. Alpert B, McCrindle B, Daniels S, Dennison B, Hayman L, Jacobson M, Mahoney L, Rocchini A, Steinberger J, Urbina E, Williams R. Recommendations for blood pressure measurement in human and experimental animals; part 1: Blood pressure measurement in humans. Hypertension (Dallas, Tex. : 1979). 2006;48:e3; author reply e5
12. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clinical chemistry. 2011;57:e1-e47
13. Fletcher B, Berra K, Ades P, Braun LT, Burke LE, Durstine JL, Fair JM, Fletcher GF, Goff D, Hayman LL, Hiatt WR, Miller NH, Krauss R, Kris-Etherton P, Stone N, Wilterdink J, Winston M. Managing abnormal blood lipids: A collaborative approach. Circulation. 2005;112:3184-3209
14. Schautz B, Later W, Heller M, Peters A, Muller MJ, Bosy-Westphal A. Impact of age on leptin and adiponectin independent of adiposity. The British journal of nutrition. 2012;108:363-370
15. Kizer JR, Arnold AM, Strotmeyer ES, Ives DG, Cushman M, Ding J, Kritchevsky SB, Chaves PH, Hirsch CH, Newman AB. Change in circulating adiponectin in advanced old age: Determinants and impact on physical function and mortality. The cardiovascular health study all stars study. The journals of gerontology. Series A, Biological sciences and medical sciences. 2010;65:1208-1214
16. Laughlin GA, Barrett-Connor E, May S. Sex-specific determinants of serum adiponectin in older adults: The role of endogenous sex hormones. International journal of obesity (2005). 2007;31:457-465
17. Cohen SS, Gammon MD, Signorello LB, North KE, Lange EM, Fowke JH, Hargreaves MK, Cai Q, Zheng W, Blot WJ, Matthews CE. Serum adiponectin in relation to body mass index and other correlates in black and white women. Annals of epidemiology. 2011;21:86-94
18. Pajunen P, Rissanen H, Laaksonen MA, Heliovaara M, Reunanen A, Knekt P. Sagittal abdominal diameter as a new predictor for incident diabetes. Diabetes care. 2013;36:283-288
19. Hoenig MR. Mri sagittal abdominal diameter is a stronger predictor of metabolic syndrome than visceral fat area or waist circumference in a high-risk vascular cohort. Vascular health and risk management. 2010;6:629-633
20. Siddiqui K, George TP. Serum adipokines (adiponectin and resistin) correlation in developing gestational diabetes mellitus: Pilot study. 2017:1-5
21. Mallamaci F, Zoccali C, Cuzzola F, Tripepi G, Cutrupi S, Parlongo S, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y. Adiponectin in essential hypertension. Journal of nephrology. 2002;15:507-511
22. Robertson MD, Russell-Jones D, Umpleby AM, Dijk DJ. Effects of three weeks of mild sleep restriction implemented in the home environment on multiple metabolic and endocrine markers in healthy young men. Metabolism: clinical and experimental. 2013;62:204-211
23. Simpson NS, Banks S, Arroyo S, Dinges DF. Effects of sleep restriction on adiponectin levels in healthy men and women. Physiology & behavior. 2010;101:693-698
24. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS medicine. 2004;1:e62

25. Zeng F, Wang X, Hu W, Wang L. Association of adiponectin level and obstructive sleep apnea prevalence in obese subjects. Medicine. 2017;96:e7784

26. Abdel-Fadeil MR, Abedelhaffez AS, Makhlouf HA, Al Qirshi GA. Obstructive sleep apnea: Influence of hypertension on adiponectin, inflammatory markers and dyslipidemia. Pathophysiology : the official journal of the International Society for Pathophysiology. 2017

27. Wolk R, Svatikova A, Nelson CA, Gami AS, Govender K, Winnicki M, Somers VK. Plasma levels of adiponectin, a novel adipocyte-derived hormone, in sleep apnea. Obesity research. 2005;13:186-190

28. Gomez-Abellan P, Gomez-Santos C, Madrid JA, Milagro FI, Campion J, Martinez JA, Ordovas JM, Garaulet M. Circadian expression of adiponectin and its receptors in human adipose tissue. Endocrinology. 2010;151:115-122

29. Alnaji A, Law GR, Scott EM. The role of sleep duration in diabetes and glucose control. The Proceedings of the Nutrition Society. 2016;75:512-520

30. Daniele TM, Bruin VM, Oliveira DS, Pompeu CM, Forti AC. Associations among physical activity, comorbidities, depressive symptoms and health-related quality of life in type 2 diabetes. Arq Bras Endocrinol Metabol. 2013;57:44-50

31. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: Relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes. 2003;52:1779-1785

32. Bottner A, Kratzsch J, Muller G, Kapellen TM, Bluher S, Keller E, Bluher M, Kiess W. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. The Journal of clinical endocrinology and metabolism. 2004;89:4053-4061

33. Hsieh CJ, Wang PW, Hu TH. Association of adiponectin gene polymorphism with nonalcoholic fatty liver disease in taiwanese patients with type 2 diabetes. PloS one. 2015;10:e0127521

34. Pagano C, Soardo G, Esposito W, Fallo F, Basan L, Donnini D, Federspil G, Sechi LA, Vettor R. Plasma adiponectin is decreased in nonalcoholic fatty liver disease. European journal of endocrinology. 2005;152:113-118

ORIGINAL ARTICLE

Evaluation of estrogen receptor expression in low-grade and high-grade astrocytomas

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SUMMARY

OBJECTIVE: *This study aims to compare estrogen receptor expression between low and high-grade astrocytomas.*

METHOD: *A study using paraffin blocks of glial tumors from the Anatomy Pathology archives of São Marcos Hospital was carried out and began after approval by the Review Board of the Federal University of Piaui. Specimens were histochemically marked with an anti-ER alpha antibody. Brown-stained nuclei were considered positive, regardless of reaction intensity. Data were statistically analyzed using the Mann-Whitney test and Spearman's correlation. Statistical significance was established at p<0.05.*

RESULTS: *The mean percentage of nuclei stained with anti-ER alpha in low- and high-grade astrocytomas was 0.04 and zero, respectively, while Spearman's correlation showed a strong negative association between low and high-grade tumors (p<0.001) and (r= -0.67), respectively.*

CONCLUSION: *In the current study, estrogen receptor expression was positive only in low-grade astrocytomas and nil in high-grade astrocytomas, showing that ER expression declines with the grade of tumor malignancy.*

KEYWORDS: *Astrocytoma. Glioma. Glioblastoma. Estrogen receptor beta. Estrogen receptor alpha.*

INTRODUCTION

Gliomas are the most common primary tumors of the central nervous system. These tumors have four histologic subtypes, and astrocytoma is the most prevalent type [1]. According to the World Health Organization (WHO), astrocytomas may be classified as grades 1 and 2 (low-grade or benign) and grades 3 and 4 (high-grade or malignant). High- grade astrocytomas are highly aggressive tumors. Despite adequate surgical resection, chemotherapy, and radiotherapy, high-grade tumors have a poor prognosis [1-4].

Nevertheless, high-grade gliomas may have a less poor prognosis that seems to be dependent on the understanding and manipulation of pathways that regulate aberrant tumor growth. There is a need for further diagnostic methods and new prognostic biomarkers [5-7].

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Estrogen exerts essential effects on the reproductive and gastrointestinal tracts, mammary glands, skeleton, immune system and even on the central nervous system. The majority of its effects are mainly mediated by its interaction with estrogen receptors alpha and beta (ERα and ERβ) [8,9]. However, although the primary mechanism of action of estrogen occurs through the interaction with the estrogen receptor, evidence from an in vitro study showed that substances with anti-estrogenic activity, such as tamoxifen, reduced cell proliferation through protein kinase C (PKC) [6,8-10].

The presence of estrogen receptors alpha and beta in gliomas is related to tumor aggressiveness, according to some authors [8,9]. These receptors are present in healthy brain tissue, and its expression decreases significantly with increasing histologic malignancy [11]. In contrast, a study showed an inverse result regarding ER beta expression. The study described that ER beta expression was higher in high-grade malignant neoplasms than in normal tissues and benign gliomas [12]. Therefore, the existing controversy and paucity of studies comparing estrogen receptor expression among benign and malignant astrocytomas, motivated the current study design.

METHODS

Study Design

This study used paraffin blocks of gliomas obtained from Pathology archives of São Marcos Hospital, Teresina, Brazil and began after approval by the Review Board of the Federal University of Piaui. Only astrocytomas were selected that were not submitted to any treatment before the primary surgery and stored for a maximum of five years (histopathological exams were collected between June 2012 and June 2017).

Forty cases were histologically divided into two groups (low-grade and high-grade astrocytomas). Each group had 20 cases and were chosen in a simple random manner among tumors that met the inclusion criteria.

Immunohistochemical Method

Samples of tumor tissue were fixed in buffered formalin for a period of 12-24 h and cut into 3-µm-thick sections. Tissue sections were then processed and stained with hematoxylin and eosin. Slides were deparaffinized with xylene for 15 minutes at a temperature of 60ºC, dehydrated with graded ethanol concentration 100, 95, 80 and 70% for 30 seconds each and rinsed with distilled water. For the performance of antigen retrieval, the slides were immersed in citrate buffer solution and heated in a microwave for 15 minutes at maximum power. Then, the slides were treated with 3% hydrogen peroxide in buffer solution for 10 minutes in each immersion. Slides were washed with distilled water and phosphate buffer saline solution. The slides were then placed in a BenchMark Ultra staining instrument (Ventana Medical Systems®), which used NCL-ER-6F11 monoclonal antibody (Novocastra Laboratories Ltd.) as immunohistochemical markers for estrogen receptors. Cells that displayed brown-stained nuclei, whether intensely brown or not, were considered positive.

Quantitative Method

A microscope (Nikon Eclipse E-400, optical microscope, Tokyo, Japan) attached to a color video camera (Samsung digital camera CHC-370N, Seul, Korea) was used to capture an image and transmit it to a computer equipped with the Imagelab software, version 2.3, developed by Softium Informática Ltda. (São Paulo, Brazil) for image analysis.

For estrogen receptor expression, 600 stained or non-stained cells were counted, using a magnification of 400x, starting with areas that had a higher expression of marked cells. In each slide, the percentage of cells was obtained from the ratio between the number of cells with stained nuclei and the total number of cells, multiplied by 100.

Statistical Analysis

The results were stored in Excel spreadsheets, and statistical analysis was performed by the SPSS 20.0 program. Data obtained were previously submitted to the Kolmogorov-Smirnov normality test. The mean percentage of nuclei stained for estrogen receptors between low-grade and high-grade gliomas was compared using the Mann-Whitney test. The significance level was established at $p<0.05$. The correlation between the percentage of nuclei stained for estrogen receptors and grade of astrocytic malignancy, according to WHO criteria, was performed by Spearman correlation coefficient (r). The level of significance was set at $p<0.05$.

RESULTS

Light microscopy showed a greater concentration of stained nuclei for estrogen receptors in the low-grade astrocytomas group compared to the group of high-grade astrocytomas (Fig. 1). The mean percentage of nuclei stained for estrogen receptors was 0.04 and zero in low-grade and high-grade astrocytomas, respectively (Table 1 and Fig. 2), while there was a strong negative correlation between high-grade tumors and estrogen nuclear receptor expression (r=-0.67) that was statistically significant ($p<0.01$) (Fig. 3).

DISCUSSION

Estrogen is a steroid hormone that exerts essential effects on various organs and tissues, including the central nervous system. It acts mainly by interaction with estrogen receptors. Estrogen may even influence the development and control of the growth of brain tumors, such as astrocytomas [4,8,13].

Estrogen receptors are intracellular proteins with two different subtypes (alpha and beta). Despite being produced by separate genes, these highly homologous receptors are located in chromosome 6q25.1 and 14q22-24, respectively. Although these two receptors share 97% homology in their DNA binding domains, they exhibit contradictory biological functions. ERα gene is generally believed to be an oncogene and promotes cell proliferation, whereas ERβ gene is anti-proliferative and acts as a putative tumor suppressor[9,14]. It is very well-known that ER exists and has a function in various tissues and neoplasms. However, the pathophysiology of ER is not fully understood, since few studies have shown its expression in breast, ovarian, prostate, colon cancers and astrocytic tumors [1,4].

The current study showed estrogen receptor alpha expression only in low-grade astrocytomas. In contrast, the majority of studies demonstrate the presence of estrogen receptor expression in low-grade and high-grade astrocytomas, although there is a lower proportion in high-grade astrocytoma [8,9,11,15]. Although nuclear ER expression was evaluated, the result of this study was similar to findings by Fujimoto et al.[13] which showed the presence of cytosolic estrogen receptor only in benign astrocytomas.

Despite few studies in the literature concerning ER expression in brain tissue, it is known that ER is present in hippocampal neurons, pituitary tumors, glial cells, and astrocytomas. ER expression declines with increasing malignancy, as observed in the findings of the current study. However, its specific func-

FIGURE 1: PHOTOMICROGRAPH OF THE HISTOLOGIC SECTION OF GLIOMAS, SHOWING SOME NUCLEI STAINED BROWN FOR ESTROGEN RECEPTORS IN LOW-GRADE ASTROCYTOMAS (A) AND ABSENCE OF NUCLEI STAINED IN HIGH-GRADE ASTROCYTOMAS (B).

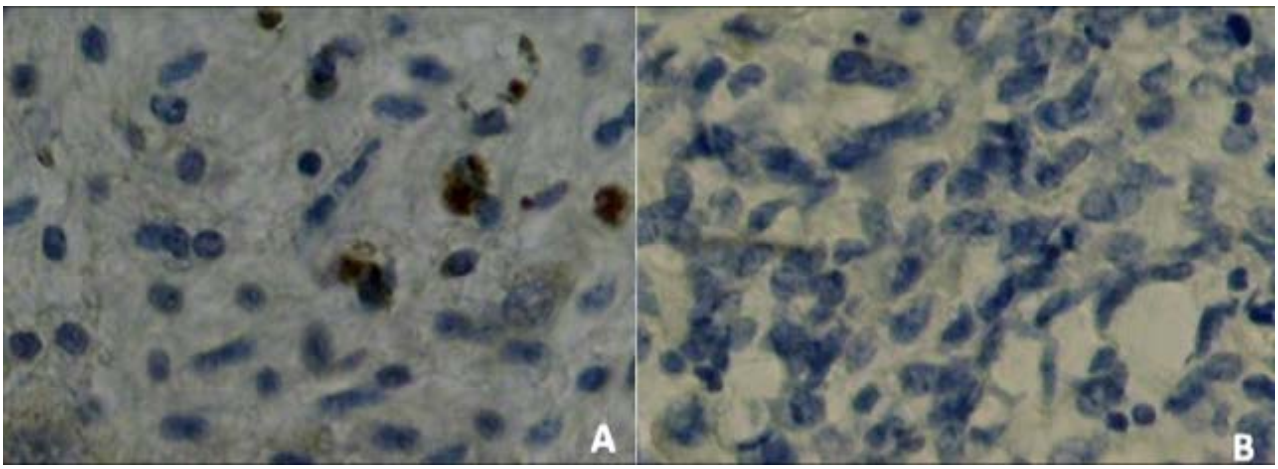


TABLE 1: MEAN PERCENTAGE OF STAINED NUCLEI OF ESTROGEN RECEPTOR PER GROUP.

Groups	N	Mean	SE Mean	Minimum	Maximum	Median
High Grade	20	0	0	0	0	0
Low Grade	20	0.04*	0.0536	0	0.1894	0.0164

*p<0.001

FIGURE 2: MEAN PERCENTAGE OF NUCLEI STAINED WITH ESTROGEN RECEPTORS IN HIGH-GRADE AND LOW-GRADE GLIOMAS.

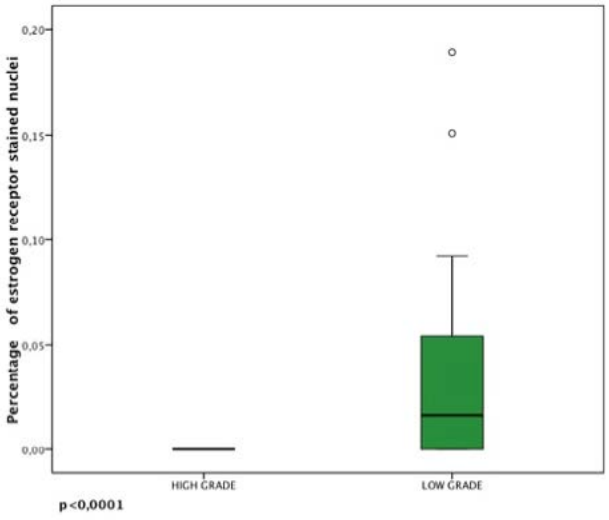
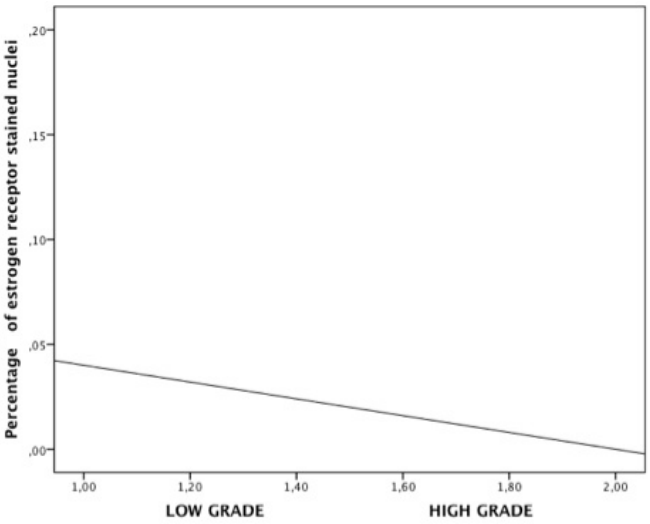


FIGURE 3: DISPERSION GRAPH BETWEEN THE EXPRESSION OF ESTROGEN RECEPTORS AND GRADE OF TUMOR MALIGNANCY IN ASTROCYTOMAS.



tion in the pathogenesis, progression, and prognosis of these neoplasms remains unknown [8,9,16].

A negative correlation was shown between ER expression and grade of astrocytoma malignancy, which is in agreement with the literature. ER is mainly expressed in normal astrocytic cells and low-grade gliomas, promoting neuroprotective role [8,9,11,16-18].

Estrogen receptors may also be used as prognostic biomarkers since a positive correlation between ER α and survival time of glioma patients has been shown [8]. Nevertheless, regression models, using the Kaplan-Meier curve have demonstrated a better prognosis and longer survival in patients with ERβ positive tumors [12,17].

Therefore, findings in the current study showed that estrogen receptor expression was positive only in low-grade and zero astrocytomas in high-grade astrocytomas, consistent with the benign glial tumor marker. However, due to the limitations of our work such as the number of paraffin blocks used and the non-assessment of estrogen receptor subtypes, further research involving a larger sample size and with immunohistochemical markers for ERα and ERβ are required.

CONCLUSIONS

In the current study, estrogen receptor expression was positive only in low-grade astrocytomas and nil in high-grade astrocytomas, showing that expression declines with increasing grade of tumor malignancy.

Conflict of interest statement

There is no conflict of interest of any of the authors with this work.

RESUMO

OBJETIVO: *O objetivo deste estudo é comparar a expressão do receptor de estrogênio entre astrocitomas de baixo e alto grau.*

MÉTODO: *Foi realizado um estudo usando blocos de parafina de tumores gliais dos arquivos de Anatomia Patológica do Hospital São Marcos e iniciado após aprovação pelo Comitê de Ética da Universidade Federal do Piauí. Os espécimes foram marcados histoquimicamente com anticorpo anti-ER alpha. Os núcleos corados em marrom foram considerados positivos, independentemente da intensidade da reação. Os dados foram analisados estatisticamente utilizando o teste de Mann-Whitney e a correlação de Spearman. A significância estatística foi estabelecida em p<0,05.*

RESULTADOS: *A porcentagem média de núcleos corados com anti-ER alfa em astrocitomas de baixo e alto grau foi de 0,04 e zero, respectivamente, enquanto a correlação de Spearman mostrou uma forte correlação negativa entre tumores de baixa e alta qualidade (p<0,001) e (r=-0,67), respectivamente.*

CONCLUSÕES: *No presente estudo, a expressão do receptor de estrogênio foi positiva apenas em astrocitomas de baixo grau e nula em astrocitomas de alto grau, mostrando que a expressão de ER diminui com o grau de malignidade tumoral.*

PALAVRAS-CHAVE: *Astrocitoma. Glioma. Glioblastoma. Receptor de estrogênio. Receptor alfa de estrogênio.*

REFERENCES

1. Pollack IF, Randall MS, Kristofik MP, Kelly RH, Selker RG, Vertosick FT Jr. Effect of tamoxifen on DNA synthesis and proliferation of human malignant glioma lines in vitro. Cancer Res. 1990;50(22):7134-8.
2. Uematsu M, Ohsawa I, Aokage T, Nishimaki K, Matsumoto K, Takahashi H, et al. Prognostic significance of the immunohistochemical index of survivin in glioma: a comparative study with the MIB-1 index. J Neurooncol. 2005;72(3):231-8.
3. Tang P, Roldan G, Brasher PM, Fulton D, Roa W, Murtha A, et al. A phase II study of carboplatin and chronic high-dose tamoxifen in patients with recurrent malignant glioma. J Neurooncol. 2006;78(3):311-6.
4. Patel S, DiBiase S, Meisenberg B, Flannery T, Patel A, Dhople A. Phase I clinical trial assessing temozolomide and tamoxifen with concomitant radiotherapy for treatment of high-grade glioma. Int J Radiat Oncol Biol Phys. 2012;82(2):739-42.
5. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer. 1983;31(1):13-20.
6. Hsu DW, Louis DN, Efird JT, Hedley-White ET. Use of MIB-1 (Ki-67) Immunoreactivity in differentiating grade II and grade III gliomas. J Neuropathol Exp Neurol. 1994;56(8):857-65.
7. Johannessen AL, Torp SH. The clinical value of Ki-67/MIB-1 labeling index in human astrocytomas. Pathol Oncol Res. 2006;12(3):143-7.
8. Batistatou A, Stefanou D, Goussia A, Arkoumani E, Papavassiliou AG, Agnantis NJ. Estrogen receptor beta (ERbeta) is expressed in brain astrocytic tumors and declines with dedifferentiation of the neoplasm. J Cancer Res Clin Oncol. 2004;130(7):405-10.
9. Batistatou A, Kyzas PA, Goussia A, Arkoumani E, Voulgaris S, Polyzoidis K, et al. Estrogen receptor beta (ERβ) protein expression correlates with BAG-1 and prognosis in brain glial tumours. J Neuro-Oncol. 2006;77(1):17-23.
10. Robins HI, Won M, Seiferheld WF, Schultz CJ, Choucair AK, Brachman DG, et al. Phase 2 trial of radiation plus high-dose tamoxifen for glioblastoma multiforme: RTOG protocol BR-0021. Neuro Oncol. 2006;8(1):47-52.
11. Liu C, Zhang Y, Zhang K, Bian C, Zhao Y, Zhang J. Expression of estrogen receptors, androgen receptor and steroid receptor coactivator-3, is negatively correlated to the differentiation of astrocytic tumors. Cancer Epidemiol. 2014;38(3):291-7.
12. Li W, Winters A, Poteet E, Ryou MG, Lin S, Hao S, et al. Involvement of estrogen receptor b5 in the progression of glioma. Brain Research. 2013;1503:97-107.
13. Fujimoto M, Yoshino E, Hirakawa K, Fujimoto J, Tamaya T. Estrogen receptors in brain tumors. Clin Neuropharmacol. 1984;7(4):357-62.
14. Cao L, Qu D, Wang H, Zhang S, Jia C, Shi Z, et al. Toosendanin exerts an anti-cancer effect in glioblastoma by inducing estrogen receptor β and p53-mediated apoptosis. Int J Mol Sci. 2016;17(11). Pii: E1928.
15. Lan YL, Zou S, Wang X, Lou JC, Xing JS, Yu M, et al. Update on the therapeutic significance of estrogen receptor beta in malignant gliomas. Oncotarget. 2017;8(46):81686-96.
16. Sareddy GR, Nair BC, Gonugunta VK, Zhang QG, Brenner A, Brann DW, et al. Therapeutic significance of estrogen receptor β agonists in gliomas. Mol Cancer Ther. 2012;11(5):1174-82.
17. Dueñas Jiménez JM, Candanedo Arellano A, Santerre A, Orozco Suárez S, Sandoval Sánchez H, Feria Romero I, et al. Aromatase and estrogen receptor alpha mRNA expression as prognostic biomarkers in patients with astrocytomas. J Neurooncol. 2014;119(2):275-84.
18. Tavares CB, Gomes-Braga F, Costa-Silva DR, Escórcio-Dourado CS, Borges US, Conde-Junior AM, et al. Expression of estrogen and progesterone receptors in astrocytomas: a literature review. Clinics. 2016;71(8):481-6.

ORIGINAL ARTICLE

Proprioceptive Stabilizer™ training of the abdominal wall muscles in healthy subjects: a quasi-experimental study

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SUMMARY

The present quasi-experimental study aimed to assess the transversus abdominis (TrA), internal oblique (IO) and external oblique (EO) thickness in healthy subjects with the proprioceptive Stabilizer™ training in abdominal wall muscles. A sample of 41 healthy participants (age: 31.9 ± 4.5 y; height: 1.7 ± 0.1 m; weight: 68.3 ± 13.1 kg; body mass index, BMI: 22.9 ± 2.7 kg/m²) were recruited to participate in this study. Ultrasound images of the EO, IO, TrA, rectus anterior (RA) and interrecti distance (IRD) were measured and analyzed by the ImageJ software. Measurements were made at rest and during the abdominal drawing-maneuver (ADIM) developed by the patients with the Stabilizer™ located in the low back holding 40 mmHg for 10 seconds with a visual stimulus provided by a circular pressure marker. Ultrasound measurements for the abdominal wall muscles showed statistically significant differences ($\Pi < .05$) for a thickness decrease of the EO, IO and a thickness increase of TrA. A proprioceptive Stabilizer™ training produced a thickness increase in TrA muscle and a thickness decrease in EO and IO muscles in healthy subjects. These findings suggest that a proprioceptive Stabilizer™ training could be useful in individuals with low back pain and lumbopelvic pain.

KEYWORDS: *Motor control. Ultrasound imaging. Proprioception*

INTRODUCTION

Abdominal wall muscles act providing protection and stability to the spine.[1] These muscles form a ring surrounding the spine, laterally 3 overlapping layers conformed by the external oblique (EO), internal oblique (IO) and transversus abdominis (TrA); moreover the rectus abdominis (RA) in the midline.[2] These muscles work in a synchronized way with lumbar multifidus, diaphragm and pelvic floor muscles, to administrate internal and external loads around the trunk and balance abdominal pressures.[1] For example, TrA is activated independently of the other abdominal wall muscles to increase the stability and preparing the spine for body movements, external loads and postural disturbances.[3] Contractions of TrA muscle do not have a conscious pattern; this activation arises automatically synchronized with deep trunk muscles to protect the lumbar spine.[3]

Dysfunction of the abdominal wall muscles

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is considered a risk factor of LBP.[4] In addiction, Hodges et al.[5] found that TrA muscle activity was decreased in subjects with lower back pain (LBP), compared with controls without LBP, and Vasseljen et al.[6] reported that the thickness of the TrA muscle during the abdominal drawing-maneuver (ADIM) was lower in individuals with chronic LBP than in controls without LBP. Teyhen et al.[7] found a decreased thickness of deep abdominal muscles during the active straight leg raise test in subjects with LPP, concluding that the spine protection mechanism does not normally work in subjects with pain. Conservative interventions have been carried out to restore morphological features, such as TrA activations in patients with LBP.[8] Besides, Vasseljen and Fladmark[6] found that an increased TrA and decreased IO thickness ratios, measured with ultrasound imaging examination (USI), in response to an 8-week exercise intervention explained 18% of the variance in temporal LBP reduction. Sihawong et al.[9] showed that an exercise program with an endurance training and muscle stretching is effective to reduce LBP in office workers. A systematic review carried out by Brumitt et al.[10] presented that motor control and general exercise program was effective in reducing pain in subacute and chronic LBP subjects. Moreover, Ferreira et al.[11] showed that patients with chronic LBP who received motor control exercise had an improvement in recruitment TrA muscle when compared with patients receiving general exercise or spinal manipulative therapy.

USI is beneficial to assess muscle changes in individuals with or without the pathology.[12] USI has been validated as a reliable tool to measure TrA morphology compared with a magnetic resonance images.[13] USI is a relatively economical, non-invasive and portable tool which can be used to provide a diagnosis and treatment.

Moreover, USI can be used to give clinical biofeedback of the abdominal wall muscles in patients with chronic LBP.[14]

A study developed by Gallego-Izquierdo et al.[15] showed that a craniocervical flexion training in patients with chronic neck pain using an air-filled pressure sensor (Stabilizer™, Chattanooga Group Inc., Tennessee, USA) (Figure 1A) produced an improvement in activation and endurance of the deep cervical flexors, as well as an improvement in pain and disability. Moreover, Stabilizer™ tool has a circular marker that allows seeing the pressure in mmHg. The present pilot study aimed to assess the TrA, IO and EO thickness in healthy subjects with the proprioceptive Stabilizer™ training in abdominal wall muscles.

METHODS

Study design

A quasi-experimental (NCT03434756) study was performed following the Template for Intervention Description and Replication (TIDierR) guidelines.[16]

Participants

A sample of 41 healthy participants (age: 31.9 ± 4.5 y; height: 1.7 ± 0.1 m; weight: 68.3 ± 13.1 kg; body mass index, BMI: 22.9 ± 2.7 kg/m^2) were recruited

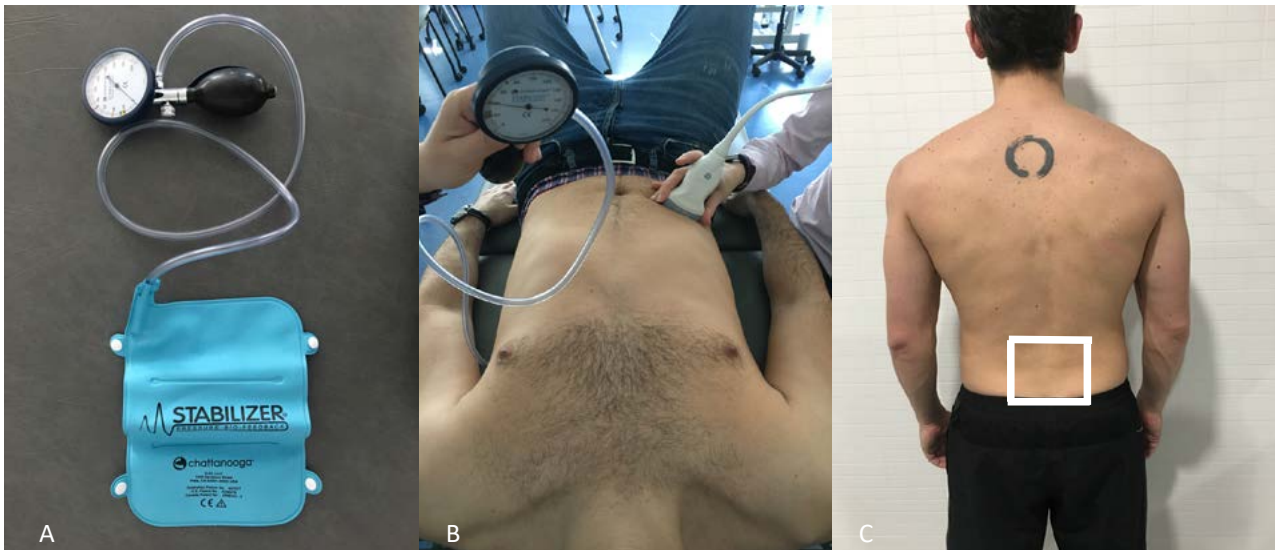

FIGURE 1 STABILIZER™ TOOL AND LOCATION AT THE PATIENTS

to participate in this study. Exclusion criteria were a BMI higher than 31 kg/m², hypocapnia,[17] any musculoskeletal condition in lumbopelvic region,[2] skin and lower limb pathology (i.e., fracture, surgery)[2].

Ethical considerations

The Scientific Committee of the European University of Madrid (CIPI/087/17) approved this study. The study also adhered to the ethical standards of the Declaration of Helsinki for human experimentation.[18]

Experimental design and data collection

Initially, baseline measurements were made following Whittaker et al.[12] guidelines to measure the thickness of the abdominal wall muscles (EO, IO, TrA, and RA). All evaluations were carried out by a single operator (B.M.P), who was a specialized physical therapist with 3 years of USI experience. A diagnostic ultrasound tool (LogiQ S7, GE Healthcare; UK) with a 3.1 to 10-MHz-range linear transducer (9L- D type; 44-mm footprint) was used for B mode ultrasound imaging. According to Whittaker et al.[12], ultrasound images of the EO, IO, and TrAb muscles were carried out with the patients in supine position, with a cross-reference point placed between the iliac crest and the inferior border of subcostal line, and the midaxillary line on the right side; RA muscle was aligned with the umbilicus, and interrecti distance (IRD) was measured just under the umbilicus. The mean measure for the thickness during rest was performed, and 3 repeated values were collected for each measure at the end of expiration, maintaining the transducer at the same point. IRD was only evaluated in the midline. Muscle thickness was considered as the distance between the inside caliper lines of each muscle border. IRD was described as the distance between the inside caliper lines of each RA muscles.[12] ImageJ software (version 2.0; US National Institutes of Health, Bethesda, Maryland, USA) was employed for measuring all the images offline. [19]

Once baseline measurements were carried out, the same measurements were made while the patients performed the exercise. This exercise specifically targets the abdominal wall muscles (EO, IO, TrA, and RA). In the beginning, patients were in a supine position (Figure 1B), the lower edge of the Stabilizer™ was placed between the posterior superior iliac spines, aligned with the sacral base (Figure 1C) and inflated up to 40 mmHg. ADIM was developed by the patients holding the 40 mmHg of pressure for 10 seconds with a visual stimulus provided by a circular pressure marker. Prior to the examination, each subject practiced the ADIM three times.[20]

Statistical analysis

SPSS 22.0 software (IBM SPSS Statistics for Windows; NY: IBM Corp.) was used for the analysis of data. An α error of 0.05 (95% confidence interval) and a desired power of 80% (β error of 0.2) were used. First, the Kolmogorov-Smirnov test was utilized to assess normality. Second, a descriptive analysis was carried out for the total sample. Finally, repeated measures t-test for independent samples were applied.

RESULTS

Regarding the Table 1, ultrasound measurements for the abdominal wall muscles showed statistically significant differences ($P < .05$) for a thickness decrease of the EO [0.65 ± 0.11 (0.02–0.10)], IO [1.10 ± 0.15 (0.05–0.15)] and a thickness increase of TrA [-0.04 ± 0.09 (-0.07–0.01)]. No statistically significant differences ($P > .05$) were observed for RA and IRD variables.

DISCUSSION

To our knowledge, this is the first study to assess whether a proprioceptive training is capable of generating an activation in deep abdominal wall muscles, such as TrA, demonstrating that it could be useful to patients who want to re-educate motor control. Our results showed that proprioceptive Stabilizer™ training with visual feedback produced a TrA activation

TABLE 1. ULTRASOUND IMAGING OF THE ABDOMINAL WALL MUSCLES

Measurement	Thickness difference*	P-value
Distance (cm)		
IRD	0.14 ± 0.09 (-0.01–0.04) *	0.355**
Thickness (cm)		
RA	-0.07. ± 0.29 (-0.17–0.16) *	0.104**
EO	0.65 ± 0.11 (0.02–0.10) *	0.001**
IO	1.10 ± 0.15 (0.05–0.15) *	0.001**
TrA	-0.04 ± 0.09 (-0.07–0.01) *	0.008**

Abbreviations: EO, external oblique; IO, internal oblique; IRD, interrecti distance; RA, rectus anterior; TrA, transversus abdominis distance; RA, rectus anterior; TrA, transversus abdominis. * Mean ± standard deviation (SD) (minimum-maximum) was applied. ** Student's t-test for independent samples was performed.

with a thickness increase and an EO and IO thickness decrease at the same time. According to Teyhen et al.[7], TrA muscle increased in thickness while the patients performed the ADIM. Springer et al.[21] showed that the TrA muscle represented 52% of the lateral abdominal muscle thickness when contracted with the ADIM, which confirms the importance of the TrA reeducation with motor control. Miura et al.[21] reported that the thickness of the TrA muscle might be associated with an activation of the muscle during a voluntary contraction with the ADIM. These findings could be an interesting starting point for clinicians to perform assessments and treatments.

In this study, we examined the thickness of the abdominal wall muscles at rest and during the ADIM. Findings for a decreased EO and IO at rest and during the ADIM in abdominal wall muscles could be explained by the automatic synergies that have to occur between deep and superficial muscles to stabilize the spine and allow a controlled movement.[3] Therefore, clinicians should establish the motor control concept into the rehabilitative training programs as one of the primary targets.

Visual feedback could be useful to improve the planning, control, and initiation of body movements supported by cortical and subcortical circuits.[22] Moreover, the visual stimulus could help to make a greater integration of the exercises in a rehabilitation training program. In our study, the visual stimulus was carried out by the circular pressure marker to provide a goal marker (40 mmHg).

Several studies demonstrated a decreased muscle thickness of TrA muscles in patients with LBP,[20,11] suggested that a motor control exercise program could be useful to improve pain and functionally. Kiesel et al.[23] reported that patients with pain in the lumbar region found it challenging to perform the ADIM. Moreover, Teyhen et al.[24] found a small TrA thickness during an active straight leg raise in individuals with LPP. In this pilot study, we found an increased TrA muscle thickness when healthy individuals performed the proprioceptive Stabilizer™ training, suggesting that this new approach based on motor control could be useful in patients with LPP and LBP.

LIMITATIONS AND FUTURES STUDIES

Several limitations should be considered in this study. First, the investigator was not blinded to the subjects. Another limitation was that we did not include a control group that did not receive any training. Finally, muscle contraction changes were not studied during functional tasks or dynamic movements.[11]

Futures studies should be developed to assess a proprioceptive Stabilizer™ training in subjects with LPP and LBP.

CONCLUSIONS

A proprioceptive Stabilizer™ training produced a thickness increase in TrA muscle and a thickness decrease in EO and IO muscles in healthy subjects. These findings suggest that a proprioceptive Stabilizer™ training could be useful in individuals with LBP, LPP and other pathologies related to the motor control of the abdominal wall muscles.

Conflicts of Interest and Source of Funding

There are no conflicts of interest or Source of Funding.

RESUMO

O objetivo do presente estudo foi avaliar o transverso abdominal (TrA), o oblíquo interno (OI) e a espessura oblíqua externa (EO) em indivíduos saudáveis com o treinamento proprioceptivo Stabilizer™ nos músculos da parede abdominal. Uma amostra de 41 participantes saudáveis (idade: 31,9±4,5 y, altura: 1,7±0,1 m; peso: 68,3±13,1 kg; índice de massa corporal, IMC: 22,9±2,7 kg / m²) foram recrutados para participar deste estudo. As imagens de ultrassom do EO, IO, TrA, reto anterior (RA) e distância interrecti (IRD) foram medidas e analisadas pelo software ImageJ. As medidas foram feitas em repouso e durante a manobra de desenho abdominal (Adim) desenvolvida pelos pacientes com o StabilizerTM localizado na parte inferior das costas segurando 40 mmHg por 10 segundos com um estímulo visual fornecido por um marcador de pressão circular. As medidas de ultrassom para os músculos da parede abdominal apresentaram diferenças estatisticamente significativas (P<0,05) para uma diminuição da espessura do EO, IO e um aumento de espessura do TrA. Um treinamento proprioceptivo Stabilizer™ produziu um aumento de espessura no músculo TrA e uma diminuição da espessura nos músculos EO e IO em indivíduos saudáveis. Esses achados sugerem que um treinamento de Stabilizer™ proprioceptivo poderia ser útil em indivíduos com dor lombar e dor lombo-pélvica.

PALAVRAS-CHAVE: *Controle motor. Imagens de ultra-som. Propriocepção*

REFERENCES

1. Brown SHM, Ward SR, Cook MS, Lieber RL. Architectural analysis of human abdominal wall muscles: implications for mechanical function. *Spine (Phila Pa 1976)*. 2011;36(5):355-362. doi:10.1097/BRS.0b013e3181d12ed7.
2. Whittaker JL, Warner MB, Stokes M. Comparison of the sonographic features of the abdominal wall muscles and connective tissues in individuals with and without lumbopelvic pain. *J Orthop Sports Phys Ther*. 2013;43(1):11-19. doi:10.2519/jospt.2013.4450.
3. Hodges PW, Moseley GL. Pain and motor control of the lumbopelvic region: effect and possible mechanisms. *J Electromyogr Kinesiol*. 2003;13(4):361-370.
4. Hides JA, Jull GA, Richardson CA. Long-term effects of specific stabilizing exercises for first-episode low back pain. *Spine (Phila Pa 1976)*. 2001;26(11):E243-8.
5. Hodges PW, Richardson CA. Delayed postural contraction of transversus abdominis in low back pain associated with movement of the lower limb. *J Spinal Disord*. 1998;11(1):46-56.
6. Vasseljen O, Fladmark AM. Abdominal muscle contraction thickness and function after specific and general exercises: a randomized controlled trial in chronic low back pain patients. *Man Ther*. 2010;15(5):482-489. doi:10.1016/j.math.2010.04.004.
7. Teyhen DS, Rieger JL, Westrick RB, Miller AC, Molloy JM, Childs JD. Changes in deep abdominal muscle thickness during common trunk-strengthening exercises using ultrasound imaging. *J Orthop Sports Phys Ther*. 2008;38(10):596-605. doi:10.2519/jospt.2008.2897.
8. Gringmuth RH, Jackson C. Therapeutic Exercise For Spinal Segmental Stabilization in Low Back Pain: Scientific Basis and Clinical Approach. *J Can Chiropr Assoc*. 2000;44(2):125.
9. Sihawong R, Janwantanakul P, Jiamjarasrangsi W. A prospective, cluster-randomized controlled trial of exercise program to prevent low back pain in office workers. *Eur spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc*. 2014;23(4):786-793. doi:10.1007/s00586-014-3212-3.
10. Brumitt J, Matheson JW, Meira EP. Core stabilization exercise prescription, part 2: a systematic review of motor control and general (global) exercise rehabilitation approaches for patients with low back pain. *Sports Health*. 2013;5(6):510-513. doi:10.1177/1941738113502634.
11. Ferreira PH, Ferreira ML, Maher CG, Refshauge K, Herbert RD, Hodges PW. Changes in recruitment of transversus abdominis correlate with disability in people with chronic low back pain. *Br J Sports Med*. 2010;44(16):1166-1172. doi:10.1136/bjsm.2009.061515.
12. Teyhen DS, Gill NW, Whittaker JL, Henry SM, Hides JA, Hodges P. Rehabilitative ultrasound imaging of the abdominal muscles. *J Orthop Sports Phys Ther*. 2007;37(8):450-466. doi:10.2519/jospt.2007.2558.
13. Hides J, Wilson S, Stanton W, et al. An MRI investigation into the function of the transversus abdominis muscle during "drawing-in" of the abdominal wall. *Spine (Phila Pa 1976)*. 2006;31(6):E175-8. doi:10.1097/01.brs.0000202740.86338.df.
14. Goldby LJ, Moore AP, Doust J, Trew ME. A randomized controlled trial investigating the efficiency of musculoskeletal physiotherapy on chronic low back disorder. *Spine (Phila Pa 1976)*. 2006;31(10):1083-1093. doi:10.1097/01.brs.0000216464.37504.64.
15. Gallego Izquierdo T, Pecos-Martin D, Lluch Girbes E, et al. Comparison of craniocervical flexion training versus cervical proprioception training in patients with chronic neck pain: A randomized controlled clinical trial. *J Rehabil Med*. 2016;48(1):48-55. doi:10.2340/16501977-2034.
16. Yamato T, Maher C, Saragiotto B, et al. The TIDieR Checklist Will Benefit the Physical Therapy Profession. *Phys Ther*. 2016;96(7):930-931. doi:10.2522/ptj.2016.96.7.930.
17. Whittaker JL. Ultrasound imaging of the lateral abdominal wall muscles in individuals with lumbopelvic pain and signs of concurrent hypocapnia. *Man Ther*. 2008;13(5):404-410. doi:10.1016/j.math.2007.03.008.
18. Holt GR. Declaration of Helsinki-the world's document of conscience and responsibility. *South Med J*. 2014;107(7):407. doi:10.14423/SMJ.0000000000000131.
19. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods*. 2012;9:671. http://dx.doi.org/10.1038/nmeth.2089.
20. Miura T, Yamanaka M, Ukishiro K, et al. Individuals with chronic low back pain do not modulate the level of transversus abdominis muscle contraction across different postures. *Man Ther*. 2014;19(6):534-540. doi:10.1016/j.math.2014.05.010.
21. Springer BA, Mielcarek BJ, Nesfield TK, Teyhen DS. Relationships among lateral abdominal muscles, gender, body mass index, and hand dominance. *J Orthop Sports Phys Ther*. 2006;36(5):289-297. doi:10.2519/jospt.2006.2217.
22. Scott SH, Cluff T, Lowrey CR, Takei T. Feedback control during voluntary motor actions. *Curr Opin Neurobiol*. 2015;33:85-94. doi:10.1016/j.conb.2015.03.006.
23. Kiesel KB, Uhl T, Underwood FB, Nitz AJ. Rehabilitative ultrasound measurement of select trunk muscle activation during induced pain. *Man Ther*. 2008;13(2):132-138. doi:10.1016/j.math.2006.10.003.
24. Teyhen DS, Williamson JN, Carlson NH, et al. Ultrasound characteristics of the deep abdominal muscles during the active straight leg raise test. *Arch Phys Med Rehabil*. 2009;90(5):761-767. doi:10.1016/j.apmr.2008.11.011.

REVIEW ARTICLE

Renal involvement in paroxysmal nocturnal haemoglobinuria: a brief review of the literature

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SUMMARY

INTRODUCTION: *Paroxysmal Nocturnal Haemoglobinuria (PNH) is an acquired genetic disorder characterized by complement-mediated haemolysis, thrombosis and variable cytopenias. Renal involvement may occur and causes significant morbidity to these patients.*

OBJECTIVE: *To review the literature about pathophysiology and provide recommendations on diagnosis and management of renal involvement in PNH.*

METHODS: *Online research in the Medline database with compilation of the most relevant 26 studies found.*

RESULTS: *PNH may present with acute kidney injury caused by massive haemolysis, which is usually very severe. In the chronic setting, PNH may develop insidious decline in renal function caused by tubular deposits of hemosiderin, renal micro-infarcts and interstitial fibrosis. Although hematopoietic stem cell transplantation remains the only curative treatment for PNH, the drug Eculizumab, a humanized anti-C5 monoclonal antibody is capable of improving renal function, among other outcomes, by inhibiting C5 cleavage with the subsequent inhibition of the terminal complement pathway which would ultimately give rise to the assembly of the membrane attack complex.*

CONCLUSION: *There is a lack of information in literature regarding renal involvement in PNH, albeit it is possible to state that the pathophysiological mechanisms of acute and chronic impairment differ. Despite not being a curative therapy, Eculizumab is able to ease kidney lesions in these patients.*

KEYWORDS: *Paroxysmal Nocturnal Haemoglobinuria, Acute Kidney Injury, Chronic Kidney Diseases.*

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria (PNH) is a haematological condition classically characterized by chronic haemolysis and thrombotic events. The incidence of PNH is 1-1.5 cases per million people and the clinical manifestations usually becomes evident between the third and fifth decades of life[1].

The main genetic abnormality in PNH is a somatic mutation of PIG-A gene, which is responsible for the final step of glycosylphosphatidylinositol (GPI) anchor production, required for the attachment of extracellular proteins to the surface of all blood cell lineages, including red blood cells (RBCs). The

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deficiency of two of those extracellular proteins is specifically relevant in PNH: CD55 and CD59. Both proteins are responsible to prevent complement-mediated RBCs opsonization and lysis.

The renal impairment in PNH is common. However, statistics are not completely reliable, once renal impairment is usually asymptomatic and studies use different definitions of renal involvement. PNH patients may present tubular concentration defects, acute kidney injury (AKI) and chronic kidney disease (CKD)[2]. In a Korean study with 301 patients with PNH, the prevalence of AKI (defined as a recorded history of AKI prior or after the definitive PNH diagnosis) was estimated at 14.6% and of CKD (defined as a GFR <60 mL/min/1.73m^2 prior or after the definitive PNH diagnosis) at 8.6%[3]. Most of the kidney impairment in PNH stems from chronic haemolysis, free haemoglobin (Hb) release in the bloodstream, and subsequent Hb renal filtration. Heme-containing pigments, such as Hb, are well stablished nephrotoxic agents, mainly due to the production of reactive oxygen species (ROS) and intratubular deposition[2,4,5]. Magnetic resonance imaging (MRI) may evidence cortical renal haemosiderosis caused by chronic haemolysis and haemoglobin filtration[5]. MRI finding is renal cortical signal reduction in T2[6]. In the development of PNH-related CKD, renal thrombotic events apparently play an even more important role than Hb filtration[5].

The diagnosis of PNH used to be made by Ham test, sucrose haemolysis test and complement lysis assay. Currently, these methods are no longer used. The gold standard diagnostic method in PNH is flow cytometry, which evaluates the presence of CD55 and CD59 and other GPI-linked proteins in red blood cells, granulocytes, and monocytes membranes. This test presents high sensitivity and specificity[7,8,9].

The mainstay of treatment is Eculizumab or hematopoietic stem cell transplantation (HSCT). HSCT is the only curative treatment. However, it is associated with high morbidity and mortality, thus it is only reserved to selected patients[10]. Eculizumab is a humanized monoclonal antibody directed against C5 that prevents the production of C5a and C5b-9 (membrane attack complex) via alternative complement system activation. C5b-9 complex is the principal culprit of intravascular haemolysis in PNH[11]. Eculizumab also has a positive impact on renal function. A cohort of PNH patients has shown an improvement or maintenance of renal function in 94.5% of patients after 36 months of therapy. Headache, nasopharyngitis, back pain, nausea, and increased susceptibility to Neisseria infections are among Eculizumab side effects, although it is generally well-tolerated[12].

METHODS

A review of literature was performed in the Medline (PubMed) database, using the following keywords: paroxysmal nocturnal haemoglobinuria; renal involvement; renal injury; Eculizumab; pathogenesis. 26 articles considered by us the most relevant were obtained from the Commission for Improvement of Higher Education Personnel (*Comissão de Aperfeiçoamento de Pessoal de Nível Superior* – CAPES) online source.

RESULTS

Pathogenesis

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disease of haematopoietic stem cells (HSC), arising most commonly from a loss-of-function mutation in the PIG-A gene (phosphatidylinositol glycan class A). PIG-A gene encodes a subunit of an enzymatic complex responsible for the assembly of GPI, a molecule that works as anchor to the attachment of extracellular proteins to plasma membrane. In PNH, due to the lack of proper GPI synthesis, GPI-anchored proteins (GPI-AP) are partially or completely absent in the surface of all haematopoietic lineages. Besides PIG-A gene mutation, any other genetic abnormality impairing proper synthesis of GPI-AP may lead to PNH, with many possible genetic mutations reported in literature. Some of the reported alternative mutated genes were PIG-M, PIG-T, PIG-V, PIG-Y, PIG-L, and CD59[2]. All haematopoietic lineages lack GPI-AP, therefore not only red blood cells (RBCs) are involved in the disease, but also leukocytes and platelets.

In healthy individuals, a small percentage of haematopoietic cells (probably colony-forming cells) may carry mutations compatible with PNH and, therefore, their derived cells are GPI-AP deficient. However, these cells are not numerous enough to produce clinical manifestations. In order to achieve an overt PNH phenotype, two other issues should be addressed. First, the cells bearing the genetic abnormalities must be HSC, which have a virtually unlimited self-renewal capacity and endless production of GPI-AP-deficient blood elements. Second, these HSC

must undergo clonal expansion[2,13,14], increasing the population of GPI-AP-deficient cells in the peripheral blood. There are mainly two hypothetical mechanisms for clonal expansion in PNH. First, it is believed that the cells bearing the mutations acquire other genetic abnormalities, which provide them a survival advantage. Second, in some cases the mechanism underlying clonal expansion requires the association of PNH and other haematological disorders, such as aplastic anaemia, in which the autoimmune destruction is mainly directed to healthy HSC, possibly because PNH-HSC lack in their membrane the target antigens[2]. Moreover, the development of PNH may also be associated with myelodysplastic syndrome[2].

Clinical manifestations

The deficiency of CD55 and CD59 is the main source of clinical manifestations in the pathogenesis of PNH. These two proteins are characterized structurally as GPI-AP (thus are absent in PNH HSC-derived blood elements) and functionally as inhibitors of the complement system. Abrogation of these proteins is followed by complement-mediated cell damage. Most of the mechanisms responsible for the clinical features found in PNH are derived from complement-mediated injury (Figures 1 and 2). Frequent manifestations of the disease are haemolytic anaemia (mechanisms of haemolysis and anaemia in PNH are summarized in Figure 1)[2,13,14,15] and thrombotic events (mechanisms of thrombosis in PNH are summarized in Figure 2)[2,13, 14, 16]. Some of the common sites of thrombosis in PNH patients are: hepatic veins (Budd-Chiari syndrome); portal, splanchnic and mesenteric veins; cavernous and sagittal sinuses; dermal veins; deep leg veins (which may progress to pulmonary embolism), and coronary and cerebral arteries. Smooth muscle dystonia may also be present. It stems from the nitric oxide (an important smooth muscle relaxant) scavenging by the free Hb molecules released by lysed red blood cells[2,13]. Smooth muscle dystonia manifests as abdominal pain, erectile dysfunction, and oesophageal spasms. Other possible clinical manifestations of the disease are fatigue and kidney injury.

Kidney injury

In 1971, Rubin[17] reported the first case of PNH with massive haemolysis causing AKI. Apart from the haemolytic crisis, the patient did not present any other condition that could explain the renal injury. Following Rubin's work, many reports showed the variety of renal lesions that could arise from PNH. The acute setting is commonly severe, frequently requiring dialysis, while chronic injury is insidious and potentially associated with high morbidity. Clark et al.[18] studied the renal function in 21 patients with PNH followed for 20 years. In this study, the authors linked the haemolytic crises with AKI, which tended to recover without providing further renal impairments, and also associated PNH with CKD and tubular reabsorption defects. Post-mortem analyses of subjects in the study suggested renal haemosider-

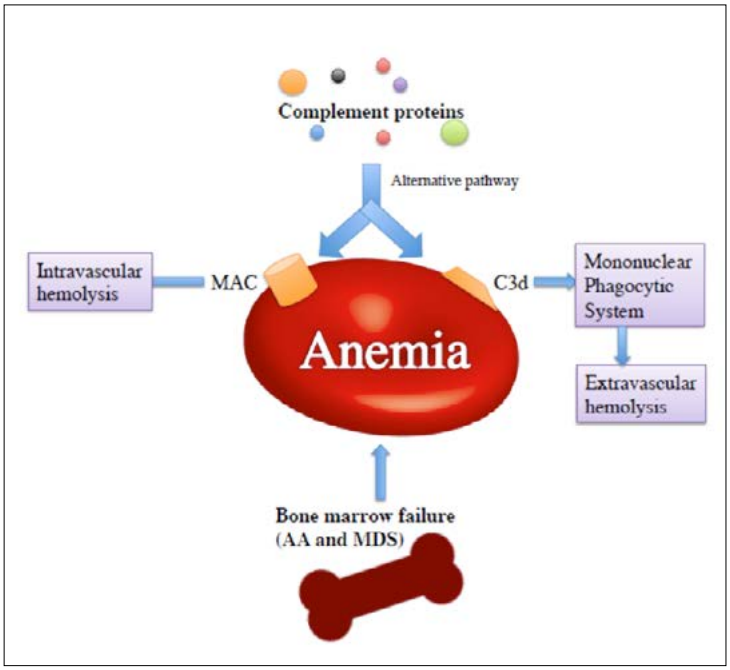

FIGURE 1 - MECHANISMS OF ANAEMIA IN PNH.

Anaemia in PNH may occur due to several factors. First, the alternative pathway activation of the complement system will lead to the formation of MAC, which will produce intravascular haemolysis, a mechanism which is the major pathogenic factor of anaemia in non-treated individuals. Second, red blood cells are marked with C3d produced by the activation of the complement system. Cells marked with this molecule are recognized and cleared from the circulation by macrophages of the mononuclear phagocytic system in a process called extravascular haemolysis, which is the primary culprit of anaemia in Eculizumab-treated individuals. Third, in patients with PNH associated with aplastic anaemia and myelodysplastic syndrome, bone marrow failure contributes to the development of anaemia.

Abbreviations: AA: aplastic anaemia; MAC: membrane attack complex; MDS: myelodysplastic syndrome. Author: Ênio Simas Macedo.

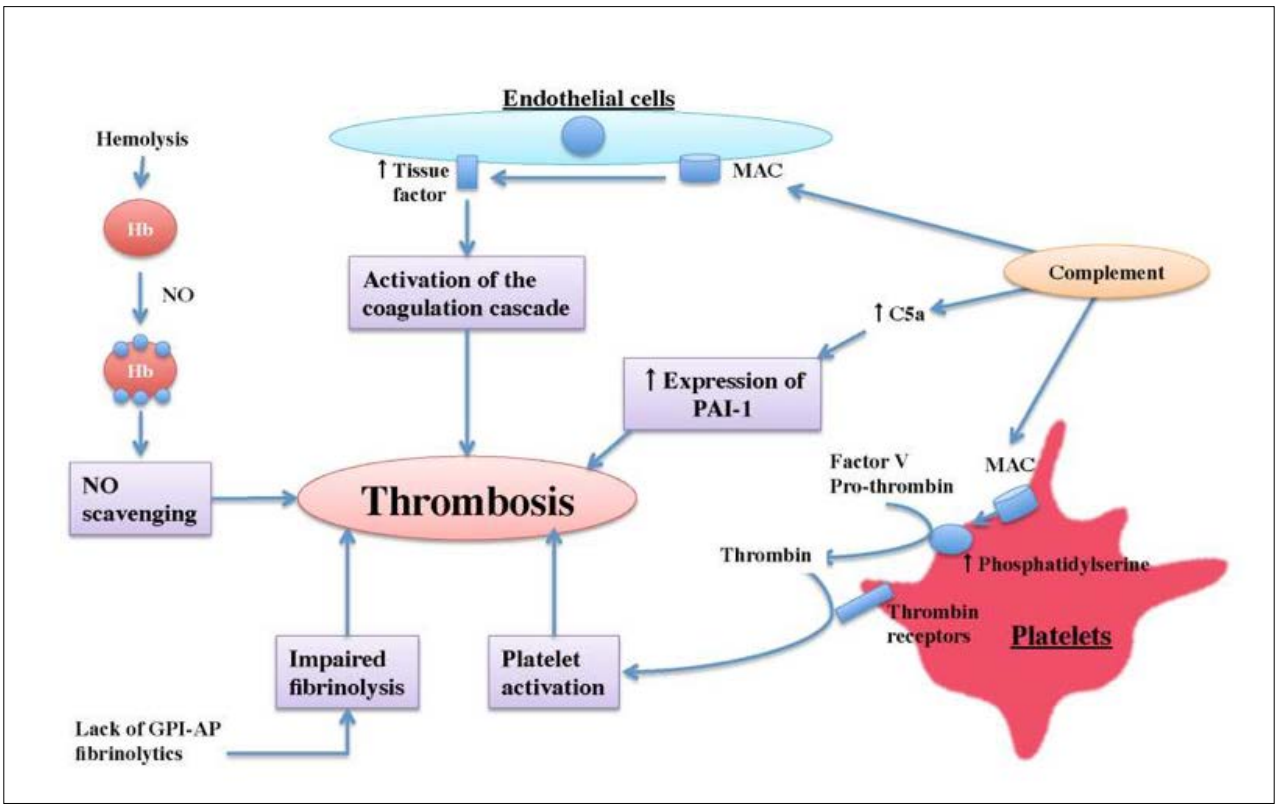

FIGURE 2 - MECHANISMS OF THROMBOSIS IN PNH.

Thrombosis in PNH is multifactorial. Complement activation leads to the formation of MAC in the surface of endothelial cells and platelets. The former cells express tissue factor in response to injury, which then activates the coagulation cascade. Platelets attacked by MAC expose in their surface phosphatidylserine, leading to factor V aggregation, followed by thrombin production. This enzyme interacts with receptors in platelets provoking the activation of these cells. Complement activation also produces C5a, which upregulates the expression of PAI-1, an inhibitor of the fibrinolytic system. Additionally, lysed red blood cells release free-Hb (which acts as a NO scavenger) and erythrocyte arginase (an enzyme that degrades arginine, the substrate of NO synthesis). Finally, the proper function of the fibrinolytic system requires some GPI-AP, which are lacking in PNH patients.

Abbreviations: GPI-AP: GPI-anchored proteins; Hb: haemoglobin; MAC: membrane attack complex; NO: nitric oxide; PAI-1: plasminogen activator inhibitor 1. Author: Enio Simas Macedo.

osis, interstitial fibrosis, and microvascular infarcts as possible pathophysiological sources of renal impairment.

Renal impairment in PNH may range from tubular concentration defects to dialytic acute kidney injury and chronic kidney disease. PNH patients have a greater than six-fold increased risk of developing CKD[2]. Furthermore, the presence of renal involvement augments mortality after 40 years of follow-up in 3-fold for patients with AKI or 6-fold for patients with CKD[3].

The mechanism involved in the development of renal damage in PNH seems to differ in acute and chronic lesions. AKI is commonly associated with episodes of haemolysis exacerbation, which may be related to infections, exercise, stress, and alcohol and drug use. As haemolysis augments, there is an increased amount of free-haemoglobin released in plasma, which is subsequently filtered by renal glomeruli. Filtered haemoglobin mediates direct toxic tubular injury, especially in the proximal convoluted tubules (PCT), by the production of reactive oxygen species (ROS). A putative mechanism that may exacerbate the PCT damage is the conversion of haemoglobin into methaemoglobin by the acidic pH of distal convoluted tubules (DCTs). Methaemoglobin, in turn, precipitates in the DCTs, leading to urinary stasis, increased PCT haemoglobin absorption and ROS-mediated damage. Moreover, ischemic features in the setting of massive haemolysis are also capable of exacerbating tubular damage. All those mechanisms may cause acute tubular necrosis, followed by AKI[5].

Mechanisms involved with CKD development are different from those of AKI. In PNH, chronic haemolysis and haemoglobin filtration lead to marked renal tubular haemosiderosis. Haemosiderin deposits are clinically observed in biopsy samples and MRI.

It is generally believed that haemosiderin may lead to interstitial fibrosis, however the exact role of these deposits in CKD development is still controversial. Classical putative mechanisms of PNH-related CKD are micro-infarcts (derived from microvascular thrombotic events) and interstitial fibrosis [5].

There have also been some reports of PNH and glomerular diseases, such as IgA nephropathy, focal segmental glomerulosclerosis, and membranous nephropathy. However, glomerular involvement in PNH is uncommon[19,20,21].

There is little experience on renal transplantation due to PNH-related end-stage CKD. Vanwalleghem et al. reported a case of a 60-year-old PNH patient, who was transfusion dependent. The patient underwent renal transplantation, with an initially significant reduction in haemolysis and no more need for transfusion. However, a new haemolytic crisis occurred within 9 months, and, posteriorly, the cortical haemosiderosis of the transplanted kidney was evidenced by MRI.

Mechanisms of renal injury in PNH were schematically summarized in figure 3.

DIAGNOSIS OF PNH

Flow cytometry is the gold standard for PNH diagnosis since it is capable of evaluating GPI-anchored proteins with high sensitivity and specificity. This technology is widely available in haematology and immunology laboratories that use flow cytometry both in research and in daily clinical practice.

The study of PNH populations is routinely performed on peripheral blood samples. Flow cytometry is performed by targeting a variety of GPI-linked proteins, and CD55 and CD59 are the most important proteins evaluated. However, false-positive diagnosis of PNH occurs if these are used alone due to the presence of rare congenital deficiencies of CD55 and CD59[2]. Ideally, at least two different monoclonal antibodies directed against two different GPI-anchored proteins on at least two different cell lineages should be used to diagnose PNH.

Previous diagnostic methods were erythrocyte-based, and included the Ham test, the sucrose haemolysis test, and the complement lysis assay. These tests have now been abandoned, especially the erythrocyte-based ones, since they can give false

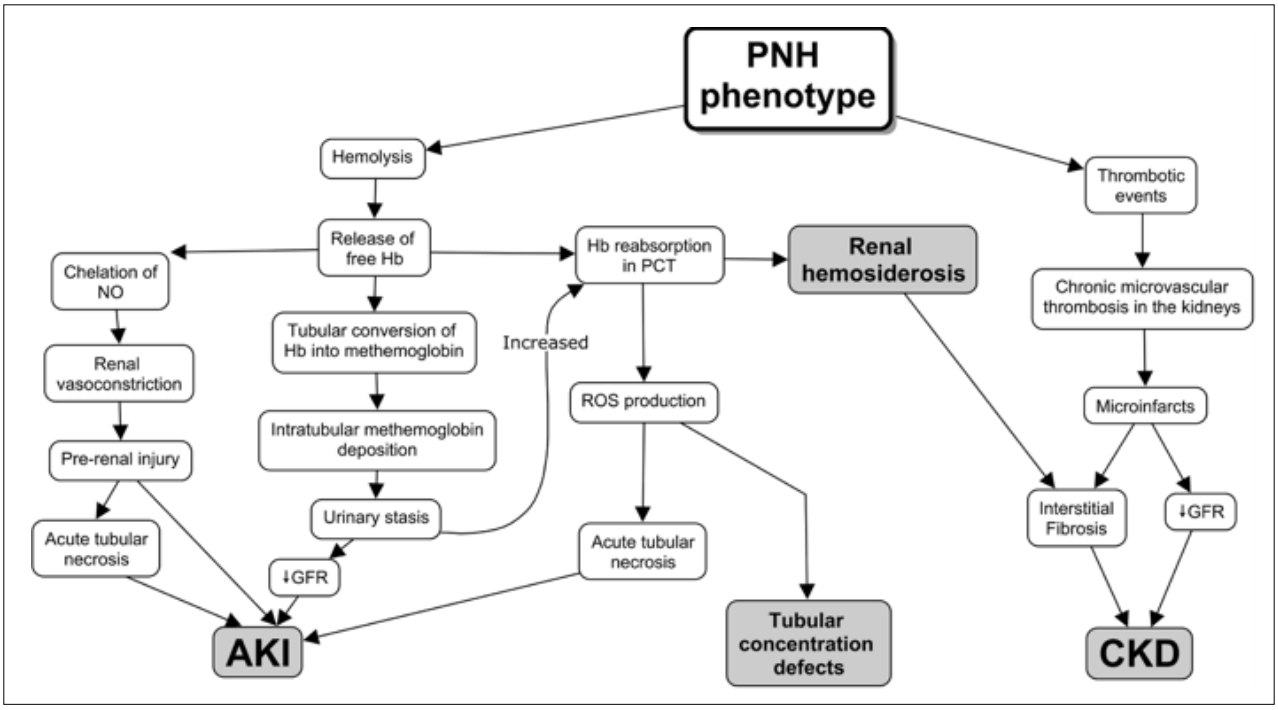

FIGURE 3 - MECHANISMS OF RENAL INJURY IN PNH.

Free haemoglobin release in haemolytic episodes, leading to renal vasoconstriction, methaemoglobin formation, renal haemosiderosis, and PCT toxicity, contribute to the development of AKI and tubular concentration defects, whereas thrombosis of the renal vasculature associated with the deleterious effects of haemosiderosis apparently plays an essential role in CKD development.

Abbreviations: AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; Hb: Haemoglobin; NO: Nitric Oxide; PCT: Proximal Convoluted Tubule; PNH: Paroxysmal Nocturnal Haemoglobinuria; RBCs: Red Blood Cells; ROS: Reactive Oxygen Species. Author: Ênio Simas Macedo.

negative results following red blood cell transfusions or haemolysis[9].

The complement lysis sensitivity test is a more specific type of test, measuring the amount of haemolysis at varying concentrations of complement. This assay showed that PNH cells lysed at lower concentrations than normal cells. This test also led to the recognition that some PNH patients have a population of cells with intermediate complement sensitivity (Type II), normal red blood cells (Type I), and the most abnormal PNH-type red blood cells (Type III)[22]. However, this test is laborious, difficult to standardize and may miss small populations of abnormal cells[7].

INDICATIONS FOR THE STUDY OF POPULATIONS OF PNH

The study of PNH is indicated in patients who present one or more of the following manifestations[8]:

- Haemolytic anaemia with negative direct Coombs test.
- Haemoglobinuria.
- Unexplained venous or arterial thrombosis in patients who meet one of the following criteria: young patients, thrombosis in unusual locations (intra-abdominal veins, Budd-Chiari syndrome, brain, dermis, etc.), evidence of haemolysis and/or cytopenia.
- Intermittent dysphagia or abdominal pain of unclear aetiology with evidence of haemolysis.
- Aplastic anaemia (at diagnosis and during annual follow-up).
- Hypoplastic myelodysplastic syndrome.
- Idiopathic and maintained cytopenias of uncertain significance.

PNH classification

The International PNH Interest Group (I-PIG) includes three main categories that cover the spectrum of disease presentation and has proposed a classification scheme for PNH [23]:

- Classical PNH, which includes haemolytic and thrombotic patients.
- PNH in the context of other primary disorders, such as aplastic anaemia (AA/PNH) or myelodysplastic syndrome (MDS/PNH).
- Subclinical PNH (scPNH), in which patients have small PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis.

However, although the overall purpose of such classification scheme is to provide a common international terminology for the disorder, it has resulted in some confusion since varying degrees of bone marrow failure underlie virtually all cases of PNH. Thus, in some cases it may be difficult to distinct between the three categories.

TREATMENT

The only available options for the treatment of PNH are the C5 inhibitor (Eculizumab) and HSCT. The latter eradicates PNH clone cells and is the only curative therapy, but is associated with a high rate of morbidity and mortality; therefore it is indicated only as frontline therapy for patients with PNH associated with aplastic anaemia. Other controversial indications are PNH in patients presenting with severe complications of the disease despite Eculizumab therapy or for those who do not have access to Eculizumab[10].

Patients who present scPNH do not typically progress to clinical PNH[10]. PNH specific therapy is not indicated in the absence of clinical manifestations. The majority of patients presenting MDS/PNH and AA/PNH have relatively small PNH clones, and haemolysis is typically an incidental finding, thus only few patients require Eculizumab treatment and the therapy must focus on the bone marrow failure syndrome[13].

Eculizumab therapy

The complement-mediated intravascular haemolysis of PNH can be inhibited by blocking the assembly of MAC. Eculizumab is a humanized monoclonal antibody against C5 that inhibits terminal complement activation. The prevention of C5 cleavage blocks the generation of the potent pro-inflammatory and cell lytic molecules, respectively C5a and C5b-9[11]. Thus, Eculizumab is highly effective in reducing intravascular haemolysis in PNH, but it does not target extravascular haemolysis and bone marrow failure. In a study with 195 patients, treatment with Eculizumab was effective to rapidly decrease lactate dehydrogenase (LDH) levels - a haemolysis marker - which was sustained as long as the patients were under treatment, although a few patients have presented a transient elevation of LDH serum. The same study showed that the percentage of patients presenting thrombotic events decreased from 32.3% to 3.6%[12].

Eculizumab is generally well tolerated. Commonly reported adverse events in clinical trials included headache, nasopharyngitis, back pain, and nausea[12]. This therapy increases the risk of *Neisseria* infections, including meningitis and sepsis. Therefore, patients must be vaccinated two weeks prior to the beginning of treatment and should be revaccinated with the tetravalent conjugate vaccine for N. meningitides every 3 years after starting the therapy[24]. Other common approach for *Neisseria* prevention is the use of continuous prophylactic penicillin.

Impact of Eculizumab in renal function

Eculizumab reduces intravascular haemolysis and haemoglobinuria events in patients presenting CKD. A cohort has shown that after 36 months of Eculizumab therapy, there was an improvement or maintenance of renal function in 94.5% of patients. Improvement in renal function was more commonly seen in patients with baseline CKD Stages 1–2 (67.1% improvement, P< 0.001). Overall, 40 (21%) of 195 patients who had renal dysfunction or damage at baseline were no longer classified as such after 18 months of treatment[25].

Future perspectives

Inhibitors of the small molecule factor D (compounds ACH-3856 and ACH-4471) significantly reduced complement-mediated haemolysis. This promising agents can be taken orally and act by blocking the alternative pathway of complement activation in PNH. Additionally, the compound ACH-4471 significantly decreased C3 fragment deposition on paroxysmal nocturnal haemoglobinuria erythrocytes, indicating a reduced potential relative to Eculizumab for extravascular haemolysis. ACH-4471 has been selected for clinical development in PNH and is currently in phase 1 clinical study[26].

CONCLUSION

There is lack of information in the literature concerning renal function in PNH. Nevertheless, we may conclude that acute and chronic renal injury mechanisms differ in the setting of the haemolysis and its repercussions. While acute injury relates with the haemolysis itself, leading to haemoglobinuria and its deleterious effects in patient's kidneys, chronic injury is mainly associated with micro-infarcts and interstitial fibrosis.

Eculizumab therapy has been proven to reduce the occurrence of haemolysis, and consequently, of haemoglobinuria, decreasing AKI incidence. Moreover, the treatment is also related with lower rates of thrombosis, and is capable of maintaining or improving renal function in patients presenting CKD.

RESUMO

INTRODUÇÃO: *A hemoglobinúria paroxística noturna (HPN) é uma doença genética adquirida, caracterizada por hemólise mediada pelo sistema complemento, eventos trombóticos e citopenias variáveis. Envolvimento renal pode ocorrer, contribuindo com morbidade significativa nesses pacientes.*

OBJETIVO: *Realização de revisão de literatura sobre o envolvimento renal na HPN.*

MÉTODOS: *Pesquisa on-line na base de dados Medline, com compilação e análise dos 26 estudos encontrados de maior relevância.*

RESULTADOS: *A HPN pode se apresentar com insuficiência renal aguda induzida por hemólise maciça, que geralmente tem apresentação grave. Em quadros crônicos, declínio insidioso da função renal pode ocorrer por depósitos tubulares de hemossiderina, microinfartos renais e fibrose intersticial. Apesar de o transplante de células-tronco hematopoiéticas permanecer como a única terapia curativa para a HPN, a droga Eculizumab é capaz de melhorar a função renal, entre outros desfechos, por meio da inibição de C5 e a subsequente ativação da cascata do complemento, que culminaria com a formação do complexo de ataque à membrana.*

CONCLUSÃO: *Há poucas informações na literatura no que concerne ao envolvimento renal na HPN, apesar de ser possível estabelecer que os mecanismos fisiopatológicos das lesões agudas e crônicas são distintos. Apesar de não ser uma terapia curativa, Eculizumab é capaz de amenizar o comprometimento renal nesses pacientes.*

PALAVRAS-CHAVE: *Hemoglobinúria paroxística noturna. Lesão renal aguda. Doenças Renais Crônicas.*

REFERENCES

1. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers 2017 May 18;3:17028.
2. Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Blood 2014;124(18):2804-2811.
3. Jang JH, Kim JS, Yoon SS, Lee JH, Kim YK, Jo DY, et al. Predictive Factors of Mortality in Population of Patients with Paroxysmal Nocturnal Haemoglobinuria (PNH): Results from a Korean PNH Registry. J Korean Med Sci 2016;31(2):214-221.
4. Zager RA, Gamelin LM. Pathogenetic mechanisms in experimental hemoglobinuric acute renal failure. Am J Physiol 1989;256(3 Pt 2):F446-455.
5. Nair RK, Khaira A, Sharma A, Mahajan S, Dinda AK. Spectrum of renal involvement in paroxysmal nocturnal haemoglobinuria: report

of three cases and a brief review of the literature. Int Urol Nephrol 2008;40(2):471-475.

6. Shinde SN, Agarwal MB. Renal low-signal intensity on magnetic resonance imaging in a case of paroxysmal nocturnal haemoglobinuria. Br J Haematol 2005;131(5):559.
7. Hall SE, Rosse WF. The use of monoclonal antibodies and flow cytometry in the diagnosis of paroxysmal nocturnal haemoglobinuria. Blood 1996;87(12):5332-5340.
8. Villegas A., Arrizabalaga B., Bonanad S., Colado E., Gaya A., González A., et al. Grupo de Trabajo de HPN de la Sociedad Española de Hematología y Hemoterapia. Consenso español para el diagnóstico y tratamiento de la haemoglobinuria paroxística nocturna. Med Clin (Barc) 2016 Mar 18; 146(6):278.e1-7.
9. Brodsky RA. How I treat paroxysmal nocturnal haemoglobinuria. Blood 2009;113(26):6522-6527.
10. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal haemoglobinuria. Hematology Am Soc Hematol Educ Program 2016;2016(1):208-216.
11. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor Eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria. Nat Biotechnol 2007;25(11):1256-1264.
12. Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, et al. Long-term safety and efficacy of sustained Eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2013;162(1):62-73.
13. Pu JJ, Brodsky RA. Paroxysmal nocturnal haemoglobinuria from bench to bedside. Clin Transl Sci 2011;4(3):219-224.
14. DeZern AE, Brodsky RA. Paroxysmal nocturnal haemoglobinuria: a complement-mediated haemolytic anemia. Hematol Oncol Clin North Am 2015;29(3):479-494.
15. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. Lancet 2009;373(9665):759-767.
16. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal haemoglobinuria. Blood 2013;121(25):4985-4996; quiz 5105.
17. Rubin H. Paroxysmal nocturnal haemoglobinuria with renal failure. JAMA 1971;215(3):433-436.
18. Clark DA, Butler SA, Braren V, Hartmann RC, Jenkins DE. The kidneys in paroxysmal nocturnal haemoglobinuria. Blood 1981;57(1):83-89.
19. Kato K, Shibata T, Mukai K, Kitazawa K, Sugisaki T. [Case of paroxysmal nocturnal haemoglobinuria complicated with IgA nephropathy who developed acute renal failure induced by haemolytic crisis]. Nihon Jinzo Gakkai Shi 2005;47(5):540-546.
20. Takahashi K, Yoshimura A, Inoue Y, Takahashi N, Sugenoya Y, Morita H, et al. [A case of paroxysmal nocturnal haemoglobinuria combined with focal segmental glomerular sclerosis]. Nihon Jinzo Gakkai Shi 2001;43(1):39-43.
21. Lee GW, Lee JH, Kim SB, Yu ES, Lee JL, Ryu MH, et al. Membranous glomerulopathy as a manifestation of chronic graft-versus-host-disease after non-myeloablative stem cell transplantation in a patient with paroxysmal nocturnal haemoglobinuria. J Korean Med Sci 2003;18(6):901-904.
22. Rosse WF, Hoffman S, Campbell M, Borowitz M, Moore JO, Parker CJ. The erythrocytes in paroxysmal nocturnal haemoglobinuria of intermediate sensitivity to complement lysis. Br J Haematol 1991;79(1):99-107.
23. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal haemoglobinuria. Blood 2005;106(12):3699-3709.
24. Alashkar F, Vance C, Herich-Terhürne D, Preising N, Dührsen U, Röth A. Serologic response to meningococcal vaccination in patients with paroxysmal nocturnal haemoglobinuria (PNH) chronically treated with the terminal complement inhibitor Eculizumab. Ann Hematol 2017;96(4):589-596.
25. Hillmen P, Elebute M, Kelly R, Urbano-Ispizua A, Hill A, Rother RP, et al. Long-term effect of the complement inhibitor Eculizumab on kidney function in patients with paroxysmal nocturnal haemoglobinuria. Am J Hematol 2010;85(8):553-559.
26. Yuan X, Gavriilaki E, Thanassi JA, Yang G, Baines AC, Podos SD, et al. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome. Haematologica 2017;102(3):466-475.

REVIEW ARTICLE

Posterior L5-S1 transdiscal screws for high grade spondylolisthesis – a systematic review

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SUMMARY

OBJECTIVE: *The surgical management of high-grade lumbar spondylolisthesis (HGLS) is complex and aims to achieve both a solid fusion that is able to support the high shear forces of the lumbosacral junction, as well as neural decompression. We performed a systematic literature review of the safety and efficacy of posterior transdiscal (PTD) screw fixation from L5S1 for HGLS and its variations.*

METHODS: *A systematic literature review following the PRISMA guidelines was performed in the PubMed database of the studies describing the use of PTD screw fixation for HGLS. Clinical and radiological data were extracted and discussed. Study quality was assessed with the Oxford Centre for Evidence-Based Medicine Levels of Evidence.*

RESULTS: *Seven studies were included and reviewed; all of them were level IV of evidence. Two of them had large case series comparing different surgical techniques: one concluded that PTD was associated with better clinical outcomes when compared with standard screw fixation techniques and the other suggesting that the clinical and radiological outcomes of PTD were similar to those when an interbody fusion (TLIF) technique was performed, but PTD was technically less challenging. The remaining five studies included small case series and case reports. All of them reported the successful useful of PTD with or without technical variations.*

CONCLUSIONS: *Our review concludes, with limited level of evidence that PTD fixation is a safe and efficient technique for treating HGLS patients. It is technically less demanding than a circumferential fusion, even though proper screw insertion is more demanding than conventional pedicle screw fixation.*

KEYWORDS: *Spondylolisthesis. Spondylolysis. Lumbar Vertebrae/surgery. Review.*

INTRODUCTION

Spondylolisthesis is a forward slip of one vertebra over the other (the word "*spondylo*" refers to "spine" and "*listhesis*" means "slippage"). According to Meyerding classification, the severity of the listhesis may be graded according to how far a vertebral body has slipped forward[1]. High grade lumbar spondylolisthesis (HGLS) includes those classified as grade III, IV and V (or spondyloptosis, when the vertebral body above has completely fallen of the vertebra below)[2-5]. HGLS may have many causes such as a congenital defect in the pars interarticularis (dysplastic origin), an acquired injury to the pars (isthmic), and, more rarely, may be due to degenerative lumbar disease[2-5].

Surgical treatment is accepted for symptomatic patients (generally for those with symptoms of radiculopathy and/or low back pain) with HGLS and, according to some authors, even for some asymptomatic cases with evidence of radiological progression[3].

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The management of these cases is complex and aims to achieve both a solid fusion that is able to support the high shear forces of the lumbosacral junction, as well as neural decompression. Additionally, improving or maintaining sagittal balance and normal or near normal spino-pelvic relations is also desired. These goals of solid arthrodesis, neurological decompression, and restoration of sagittal parameters are balanced by the risks of surgical treatment[2].

Many techniques for surgical management of HGLS have been described. The most common include:

1) Nerve root decompression with removal of the loose lamina and the fibrocartilaginous tissue (also known as Gill procedure)[6]

2) *In situ* fusion with autologous iliac crest graft (without reduction in patients with a preserved sagittal balance), with or without decompression (laminectomy)[7],

3) Posterior instrumented fusion with pedicle screws, with or without sacral dome resection for reduction[2],

4) Bohlman technique, which consists in inserting a transsacral fibular strut graft after decompression and posterior arthrodesis with iliac crest[8],

5) Posterior reduction with interbody cages and pedicle screws[5].

6) Posterior transdiscal (PTD) S1L5 screw fixation (with or without laminectomy) and arthrodesis[9].

The best technique to treat HGLS is still debated and decision-making is heavily influenced by radiological characteristics, patients' clinical symptoms and also surgeon's experience and preferences. In our practice, we have successfully treated patients with HGLS using transdiscal L5-S1 screw fixation. We performed a systematic literature review of the safety and efficacy of transdiscal screw fixation of L5S1 for HGLS and its variations.

METHODS

We performed a systematic literature review following the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines[10].

The following search entries were used in the PubMed database for search (First search), without time restriction "high grade AND spondylolisthesis AND transdiscal" (First search). Another independent search was performed using other search entries: "transvertebral AND screw" (Second search). Only articles written in English were included. Manual search of cross-references was also performed, after screening the obtained articles and their references.

Studies of the use of transdiscal L5S1 screw fixation for HGLS (Meyerding grade III, IV and V) were included, since they described in detail the surgical technique, the complications and the patients' outcome. Duplicate studies were eliminated. Studies including patients with grade I and II were also excluded.

The search was performed on May 22, 2017. Study quality was assessed with the Oxford Centre for Evidence-Based Medicine Levels of Evidence categorization[11].

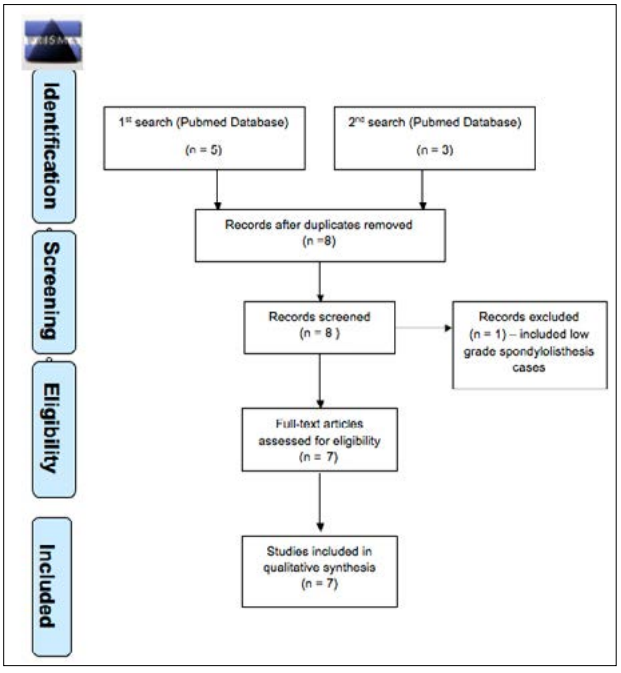
We extracted patient age and gender, clinical symptoms, description of the surgical approach and hardware used, complications and follow-up. Reduction was also documented, as well as clinical improvement or deterioration after the procedure.

A flow chart of our search mechanism is shown in Figure 1.

RESULTS

A total of five studies were obtained in the first search[12-16], and three additional studies[9,12,17] were found in the second, including the study that proposed this technique[9]. One study was not considered because it included many patients with spondylolisthesis grades I and II[16].

FIGURE 1 – FLOW DIAGRAM OF OUR SEARCH MECHANISM ACCORDING TO THE PRISMA GUIDELINES



The majority of the studies were small case series, which precluded a systematic assessment of the risk of bias. All of them were level IV of evidence.

There were two large case series comparing different surgical techniques: one from Collados-Maestre et al.[13] and the other from Rodriguez-Olaverri et al.[17]. A total of 45 cases were treated with PTD in these studies.

Collados-Maestre et al.[13] compared the outcomes of transdiscal versus conventional pedicle screw fixation for HGLS in a retrospective case-control study. Twenty-five patients had PTD fixation (mean age - 36.7 years old) and 31 had standard pedicle screw fixation (mean age – 42 years old), with a mean follow-up of 2.7 years (ranging from 2 to 5.3). Preoperative data were comparable between groups. Surgery time (p=0.598), blood loss (p=0.857), and hospital stay (0.126) were similar between groups.

PTD technique consisted in placing screws through the S1 pedicle toward the endplate of S1, crossing the disc space and the inferior endplate of L5, to finish at the L5 vertebral body. In 22 patients (88%) the instrumented level was L4S1 and in 3 (12%) the level was L5S1. Fusion without reduction was performed in 23 patients (92%) and partial listhesis reduction (manipulating the L5 vertebral body) was performed in two patients (8%). In the pedicle group, 23 patients (71%) had L4-S1 fixation and 8 patients (29%) had an L5-S1 fusion. Fusion without reduction was performed in 25 (81%) patients and 6 had some partial reduction (19%). Interbody fusion was also performed in 3 patients using L5S1 cages. Decompression was performed in both groups and posterolateral fusion was also performed using grafts from the laminectomies with additional iliac bone grafts and/or bone substitutes.

Considering the surgical technique, there were no differences in the level of instrumentation (L4-5-S1 versus L5-S1) – p=0.311 – or in the reduction rate (partial versus in situ) – p=0.276.

At the last follow-up, clinical and radiographic outcomes were significantly improved in both groups. Postoperatively, both lumbar and leg pain VAS were similar between groups, but ODI (20.2 vs. 31.6, p = 0.010), COMI (1.6 vs. 2.8, p = 0.012), and SF-12 physical (84.3 vs. 61.5, p = 0.004) and mental (81.5 vs. 69.4, p = 0.021) scores were significantly better in the transdiscal group. The neurologic complication rate was similar in both groups. There were 4 pseudoarthrosis in the pedicle group (revised using transdiscal screw technique), and none in the transdiscal group. Four patients (16%) had poor orientation of the PTD screws with one of them presenting with a L5 radiculopathy that required the removal of the screw.

The authors concluded that PTD screws resulted in improved functional outcome compared with standard screw techniques but it is technically more demanding, due to the difficulty to place them properly. The potential advantages may be attributed to its improved fixation strength.

Rodriguez-Olaverri et al.[17] compared the outcomes of patients treated for HGLS (grade III to V of Meyerding) with two different techniques: 1) unilateral transforaminal interbody fusion (TLIF) with 20 patients (Group A), and 2) transvertebral screw fixation (20 patients) (Group B). Age ranged from 19 to 48 years old (mean 33 years old) and the mean follow-up was 35 months (range, 24-48 months).

Both groups had the hip extended in order to reduce the slip angle, and horizontalize the L5 endplate. Group A patients were treated with nerve root decompression, reduction with posterior instrumentation (L4, L5, S1 and Ilium) and insertion of a TLIF. Group B patients had partial lumbosacral kyphosis reduction and received a transdiscal S1L5 screw and a L4 pedicle screw.

They reported that in Group A the median surgical time was 4.45 hours (3.45 to 5.25) in group A, with 100% fusion, with improvement, according to the SRS scores, in postoperative pain control, self-image and function. The average slip angle improved from 38.6° to 23.8° but there was no significant improvement in the percentage of slippage. Complication included seven inadvertent durotomies and 3 superficial infections.

In Group B the median surgical time was 3.25 hours (2.3 to 4.25), with 95% fusion at 6 months (19 of 20 cases), with improvement in postoperative pain control and function according to the SRS scores. The average slip angle improved from 38.2° to 23° but there was no significant improvement in the percentage of slip. Complications included one inadvertent durotomy, two superficial infections and in one instance pseudoarthrosis that resulted in implant failure. There was no neurological complication in any group.

The authors concluded that no significant differences in radiological and clinical outcomes were found between the two groups (both procedures appeared to be safe and effective). They also noted the difficulty in inserting a TLIF in HGLS, a potential increase in the risk of intraoperative complications.

The remaining five studies included small case series or case reports: Abdu et al.[9] with three cases (the technique was described in one of them), François et al.[14] with four cases and, finally, with one case report each, Beringer et al.[12], Jo et al.[18] and Palejwala et al.[15]. A total of 10 cases were performed in those five remaining studies.

Abdu et al.[9] was the first to report the use of PTD screw in three consecutive adult patients with grade III Spondylolisthesis. They named the technique "pedicular trasvertebral screw fixation", emphasizing its safety and efficacy.

The technique is described as a posterior decompression followed by screws inserted through the pedicle of S1, transfixing the L5S1 disc into the body of L5, followed by additional two pedicles of L4 and posterior fusion using autologous iliac crest graft.

The three patients were 41, 63 and 55 years old by the time they were operated. Two of them had a previous surgery (Gill procedure with Harrington rods with pseudoarthrosis in one and a Gill procedure with an in situ fusion of L4 to the sacrum). All of them had a solid fusion (documented with a bone bridge through the extension of the fusion and the absence of motion on dynamic plain radiographs). Two patients had only mild symptoms in the last follow-up and one was no longer symptomatic. No patient required further surgical exploration.

François et al.[14] reported the results of four cases of patients with HGLS treated with transdiscal screws. Patients had L4 pedicle screw fixations, without fixation of the pedicle of L5. Then, posterior transdiscal screws were placed (7 mm in diameter from S1 to L5) with rod connections and posterolateral fusion with autologous bone graft from the iliac crest. Notably, no laminectomy was reported.

Patients were respectively 30, 33, 39 and 74 years old. All had low back pain and three also had radicular symptoms. All had fusion after one year without direct complications related to the procedure and had some reduction off the slip angle postoperatively (mean slip angle preoperatively was 23.5° versus 17.5° postoperatively). The authors also reported that all four patients did have bone formation in the disc space of L5S1 in spite of no interbody fusion nor discectomy being performed.

Beringer et al.[12] reported a technical note of a modified PTD fixation. They reported an illustrative case of a 34-year-old man who had back pain with radicular pain and a grade III spondylolisthesis. An anterior retroperitoneal approach was performed, inserting an in situ L5-S1 transvertebral cage (a K wire was advanced obliquely from L5 anterosuperior region through L5 body, crossing the disc space of L5S1 and entering S1 vertebral body) and a L45 ALIF, followed by posterior transdiscal S1L5 screws and L4 pedicle screws connected with a rod and posterior decompression with posterolateral fusion from L4 to S1. The patient was still doing well after several months.

Jo et al.[18] reported a case of a lumbosacral spondyloptosis (grade V) in a 70-year-old osteoporotic woman with low back pain, radicular symptoms (2/5 motor strength for anterior tibialis and extensor hallucis longus muscle groups) and also intermittent urinary incontinence. They performed a laminectomy of the loose arch of L5, removed the scar tissue around the pars of L5, and decompressed the L5 nerve roots. After that, bilateral L2, 3, 4 and iliac screw fixation was performed, the L5S1 disc space was accessed, and an interbody spreader was used to lift the body of L5 superior and posteriorly. Then, an S1 pedicle was guided through the L5S1 disc and to the body of L5. Rods were then connected to the system and autologous bone grafts were used laterally. After seven days, a second procedure was performed, with ALIF at L34 and 45 and, using a K wire for guidance, a 6 mm diameter screw was passed from the body of L5 and directed to the body of S1. The authors reported that after 10 months of follow-up, the patient had minimal back pain and no more urinary retention, with recovery of muscle strength (grade 4/5).

Palejwala et al.[15] reported the results of a case report of an adolescent patient (12 years-old) with an L5S1 grade IV spondylolisthesis treated with bilateral transsacral transdiscal screw fixation and additional L4 pedicle screws, with decompression of the neural elements with graft obtained from the local bone decompression. The patient had progressive back pain despite conservative management. He was neurologically intact. After 14 months, the patient had significant improvement of his symptoms with a solid bone fusion. They concluded that this technique was safe and effective to treat HGLS in adolescents.

An illustrative case (Figure 2) of transdiscal screw fixation is presented.

DISCUSSION

High-grade spondylolisthesis is a rare condition that represents the minority of the cases of spondy-

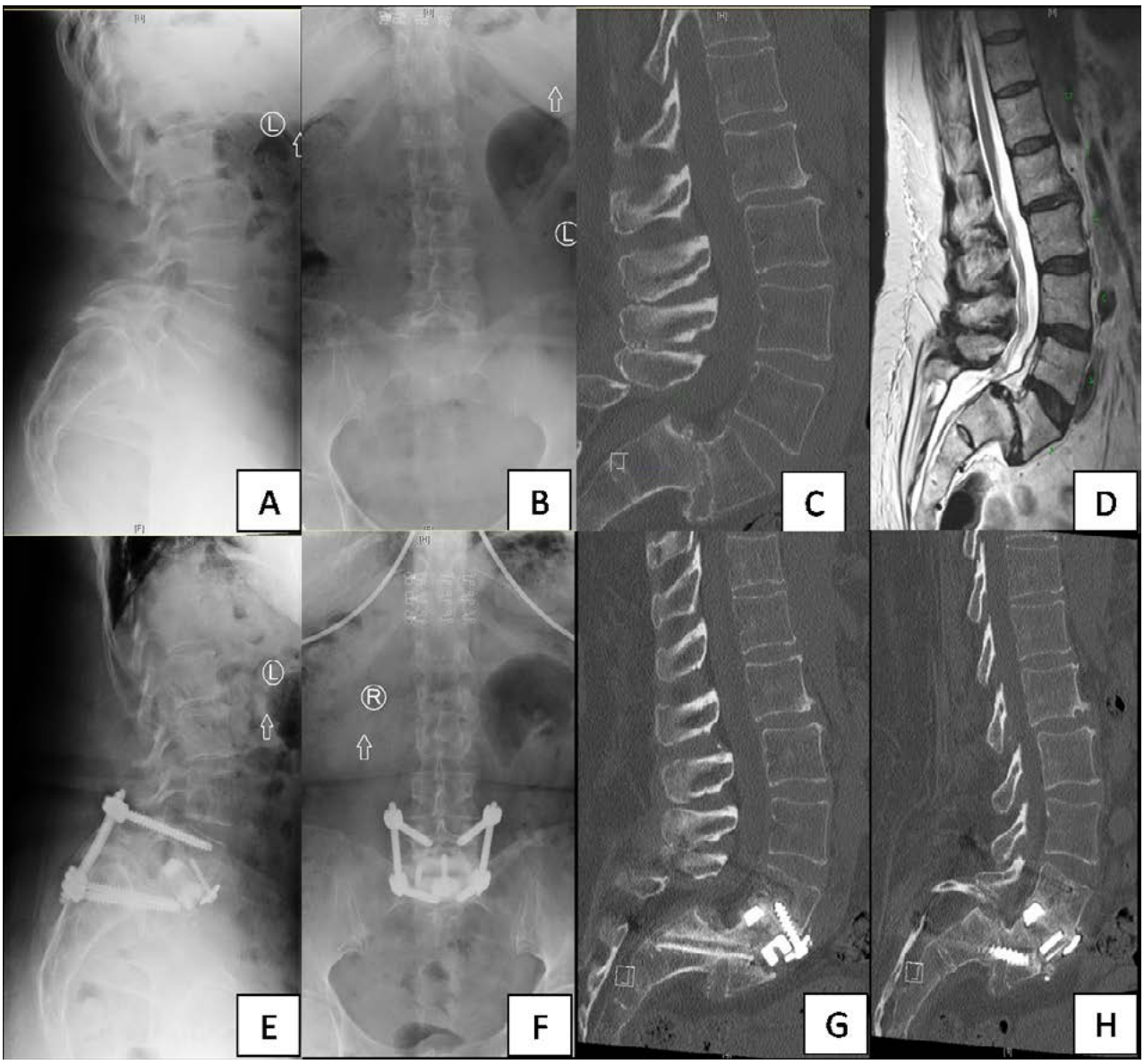


FIGURE 2 – A 65-year-old woman presented with severe episodes of acute and mechanical low back pain and leg pain. A- Lateral lumbar spine with a lytic L5 and a grade III L5S1 spondylolisthesis. B- Antero-posterior simple plain radiography. C- Sagittal midline CT scan with a narrow L5S1 disc space. D) Sagittal midline T2 sequence MRI. E) Lateral lumbar spine after an anterior lumbar interbody fusion was performed at L45 followed by posterior L4 pedicle and L5S1 transdiscal screws fixation. F- Post-operative antero-posterior simple plain radiography, G- sagittal midline CT and H- parasagittal CT in the level of the transdiscal screw fixation. The patient had a good clinical improvement after surgery.

lolisthesis[19]. Despite high grades of slippage, patients may be totally asymptomatic, and surgical indication may be accepted when progression is documented on serial radiological exams[12,14,20]. Reduction is proposed to decrease pseudoarthrosis rate, as interbody devices provide a large area of endplate surface for fusion[15]. Potential advantages of performing a slip reduction are to correct the slip angle and also restore the normal or near normal spino-pelvic relationships, which may avoid sagittal balance problems. However, in our review, none of the studies addressed comparatively spino-pelvic measurements for such analysis. On the other hand, neurological deficits, such as permanent L5 radiculopathy, were described in patients who underwent circumferential fusion with reduction of HGLS[20]. None of the patients evaluated in our review who had a PTD had permanent radicular deficits. For this reason, the evaluation of all the different techniques used for the treatment of this relatively rare and complex entity is necessary.

We reported the clinical and radiological outcome of the studies that had patients with HGLS treated with PTD screw fixation. As general conclusions, most of the studies reported that patients improved clinically

after surgery, had the intensity of their pain decreased and had no additional neurological deficits with low surgical revision rates. Many surgeons reported that *in situ* fusion for HGLS had less risk of L5 nerve root injuries and also better long-term outcomes[4,21-23].

Considering both the large series evaluated in our review, PTD is technically more demanding due to screw trajectory than traditional pedicle screw fixation. However, it is potentially more efficient and less technically demanding than a TLIF (less surgical time, less durotomies), with similar clinical outcomes[13,17].

Potential advantages are the triangular screw-to-screw secondary to the anteromedial direction of the screws through the sacral promontory, resulting in higher construction strength because of the mass of bone between the hardware instead of the amount of bone purchased by standard pedicle screw fixation[24]. Minamide et al.[25] performed a biomechanical analysis in cadaver models, whereas the construction using PTD were 1.6 to 1.8 times stiffer than conventional pedicle screw fixation.

In two case reports included in our review, authors reported an additional anterior approach combined with PTD. In the case of Beringer et al.[12], a L45 ALIF and a transvertebral anterior cage from L5S1 were performed for additional support in a 34-years-old patient. In the Jo et al.[18] case, authors performed also iliac screw fixation posteriorly, as well as a more cranial construction (L2, 3 and 4 fixation) followed by an L34 and 45 ALIF and an additional anterior screw from L5 to S1. Although additional anterior fixation may not be routinely necessary, it may be interesting in cases such as those presented by Jo et al.[18], who had a severe osteoporosis. The additional anterior support may have its rationale derived from the Bohlman technique, which a circumferential fusion was performed by a posterior only approach using a fibular graft for interbody fusion, which is inserted transsacral towards the L5 body[8].

Finally, an important limitation of our review is that the majority of the cases included did not evaluate the role of global spinal alignment and spino-pelvic relationships in their surgical planning. Further studies about transdiscal screw fixation should evaluate the spino-pelvic relationships in the outcome of high-grade spondylolisthesis management.

CONCLUSIONS

Our review concludes, with limited evidence that PTD fixation is a safe and effective technique for treating HGLS patients. It is technically less demanding that a circumferential fusion, even though proper screw insertion is more demanding than conventional pedicle screw fixation. The superiority of this technique over others for the treatment of HGLS still needs to be proven.

Conflict of interests

No funds were received in support of this study. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript. The authors have no financial interest in the subject of this article. The manuscript submitted does not contain information about medical device(s).

RESUMO

OBJETIVOS: *O tratamento cirúrgico das listeses de alto grau da coluna lombar (LAGCL) é complexo, objetivando alcançar uma fusão sólida capaz de suportar o estresse biomecânico da junção lombo-sacra, bem como descompressão do tecido neural. Realizamos revisão sistemática da literatura para avaliar a segurança e a eficácia da fixação transdiscal (FTD) L5S1 em LAGCL e suas variações.*

MÉTODOS: *Realizamos revisão sistemática conforme metodologia Prisma na base de dados PubMed dos estudos que utilizaram FTD no tratamento das LAGCL e suas variações. Dados clínicos e radiológicos foram extraídos dos trabalhos e discutidos. A qualidade dos estudos foi avaliada segundo o Oxford Centre for Evidence-Based Medicine Levels of Evidence.*

RESULTADOS: *Sete estudos foram incluídos e analisados, todos com nível IV de evidência. Dois estudos tinham séries de casos maiores, comparando diferentes técnicas cirúrgicas: um concluiu que a FTD foi associada a melhor prognóstico clínico quando comparada à fixação pedicular tradicional, e o outro sugeriu que os resultados clínicos e radiológicos com a FTD foram semelhantes à fusão intersomática, porém com menor demanda técnica na FTD. Os demais cinco estudos eram pequenas séries ou relatos de casos. Todos reportaram o uso da FTD com sucesso, com e sem variações da técnica.*

CONCLUSÃO: *Concluímos que, embora com evidências limitadas, a FTD é segura e efetiva no tratamento das LAGCL. É tecnicamente mais simples do que a fusão circunferencial (intersomática), porém com maior complexidade que a fixação pedicular convencional.*

PALAVRAS-CHAVE: *Espondilolistese. Espondilólise. Vértebras lombares/cirurgia. Revisão*

REFERENCES

1. *Meyerding* HW. *Spondylolisthesis*: surgical treatment and results. Surg Gynecol Obstet. 1932/54:371-7.
2. Ani N, Keppler L, Biscup RS, Steffee AD. Reduction of high-grade slips (grades III-V) with VSP instrumentation. Report of a series of 41 cases. Spine (Phila Pa 1976). 1991;16(6 Suppl):S302-10.
3. Kasliwal MK, Smith JS, Kanter A, Chen CJ, Mummaneni PV, Hart RA, et al. Management of high-grade spondylolisthesis. Neurosurg Clin N Am. 2013;24(2):275-91.
4. Lamberg T, Remes V, Helenius I, Schlenzka D, Seitsalo S, Poussa M. Uninstrumented in situ fusion for high-grade childhood and adolescent isthmic spondylolisthesis: long-term outcome. J Bone Joint Surg Am. 2007;89(3):512-8.
5. Roca J, Ubierna MT, Cáceres E, Iborra M. One-stage decompression and posterolateral and interbody fusion for severe spondylolisthesis. An analysis of 14 patients. Spine (Phila Pa 1976). 1994,24(7):709-14.
6. Gill GG, Manning JG, White HL. Surgical treatment of spondylolisthesis without spine fusion: excision of the loose lamina with decompression of the nerve roots. J Bone Joint Surg Br. 1955;37-A(3):493-520.
7. König MA, Boszczyk BM. Limited access surgery for 360 degrees in-situ fusion in a dysraphic patient with high-grade spondylolisthesis. Eur Spine J. 2012;21(3):390-5.
8. Bohlman HH, Cook SS. One-stage decompression and posterolateral and interbody fusion for lumbosacral spondyloptosis through a posterior approach. Report of two cases. J Bone Joint Surg Am. 1982;64(3):415-8.
9. Abdu WA, Wilber RG, Emery SE. Pedicular transvertebral screw fixation of the lumbosacral spine in spondylolisthesis. A new technique for stabilization. Spine (Phila Pa 1976). 1994;19(6):710-5.
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.
11. Oxford Centre for Evidence-Based Medicine Levels of Evidence. [cited 2015 Oct 16]. Available from: http://www.cebm.net/index.aspx?o=5653
12. Beringer WF, Mobasser JP, Karahalios D, Potts EA. Anterior transvertebral interbody cage with posterior transdiscal pedicle screw instrumentation for high-grade spondylolisthesis. Technical note. Neurosurg Focus. 2006;20(3):E7.
13. Collados-Maestre I, Lizaur-Utrilla A, Bas-Hermida T, Pastor-Fernandez E, Gil-Guillen V. Transdiscal screw versus pedicle screw fixation for high-grade L5-S1 isthmic spondylolisthesis in patients younger than 60 years: a case-control study. Eur Spine J. 2016;25(6):1806-12.
14. François J, Lauweryns P, Fabry G. Treatment of high-grade spondylolisthesis by posterior lumbosacral transfixation with transdiscal screws: surgical technique and preliminary results in four cases. Acta Orthop Belg. 2005;71(3):334-41.
15. Palejwala A, Fridley J, Jea A. Transsacral transdiscal L5-S1 screws for the management of high-grade spondylolisthesis in an adolescent. J Neurosurg Pediatr. 2016;17(6):645-50.
16. Pasha IF, Qureshi MA, Haider IZ, Malik AS, Qureshi MA, Bin Tahir U. Surgical treatment in lumbar spondylolisthesis: experience with 45 patients. J Ayub Med Coll Abbottabad. 2012;24(1):75-8.
17. Rodriguez-Olaverri JC, Zimick NC, Merola A, Vicente J, Rodriguez J, Tabuenca A, et al. Comparing the clinical and radiological outcomes of pedicular transvertebral screw fixation of the lumbosacral spine in spondylolisthesis versus unilateral transforaminal lumbar interbody fusion (TLIF) with posterior fixation using anterior cages. Spine (Phila Pa 1976). 2008;33(18):1977-81.
18. Jo DJ, Seo EM, Kim KT, Kim SM, Lee SH. Lumbosacral spondyloptosis treated using partial reduction and pedicular transvertebral screw fixation in an osteoporotic elderly patient. J Neurosurg Spine. 2012;16(2):206-9.
19. Saraste H. Long-term clinical and radiological follow-up of spondylolysis and spondylolisthesis. J Pediatr Orthop. 1987;7(6):631-8.
20. Bouyer B, Bachy M, Courvoisier A, Dromzee E, Mary P, Vialle R. High-grade lumbosacral spondylolisthesis reduction and fusion in children using transsacral rod fixation. Childs Nerv Syst. 2014;30(3):505-13.
21. Lamartina C. Posterior instrumentation, reduction and fusion in spondyloptosis. Eur Spine J. 2010;19(10):1799-800.
22. Poussa M, Remes V, Lamberg T, Tervahartiala P, Schlenzka D, Yrjönen T, et al. Treatment of severe spondylolisthesis in adolescence with reduction or fusion in situ: long-term clinical, radiologic, and functional outcome. Spine (Phila Pa 1976). 2006;31(5):583-90.
23. Transfeldt EE, Mehbod AA. Evidence-based medicine analysis of isthmic spondylolisthesis treatment including reduction versus fusion in situ for high-grade slips. Spine (Phila Pa 1976). 2007;32(19 Suppl):S126--9.
24. Ruland CM, McAfee PC, Warden KE, Cunningham BW. Triangulation of pedicular instrumentation. A biomechanical analysis. Spine (Phila Pa 1976). 1991;16(6 Suppl):S270-6.
25. Minamide A, Akamaru T, Yoon ST, Tamaki T, Rhee JM, Hutton WC. Transdiscal L5-S1 screws for the fixation of isthmic spondylolisthesis: a biomechanical evaluation. J Spinal Disord Tech. 2003;16(2):144-9.