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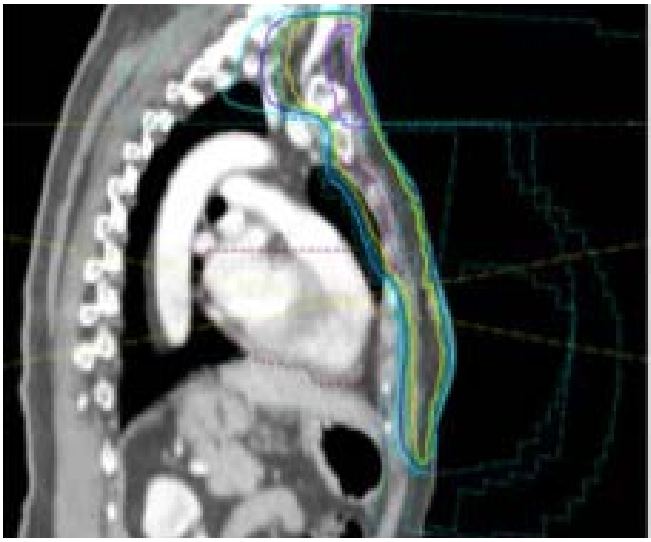

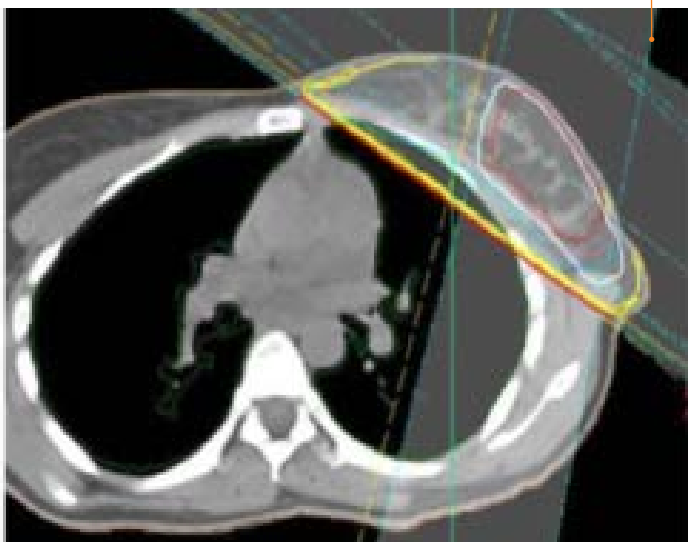

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EDITORIAL

Opinion as standard for all? Opposition to scientific evidence and thought

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Everyone is entitled to one or more opinions on a particular subject, and obviously, in medicine this is no different. In addition, of course the physician has the right and the autonomy to base his/her decisions and choices on his/her opinion.

That said, and philosophically speaking, the word *opinion* originates in the Greek (*doxa*), meaning, "the confused idea about reality and that opposes to the knowledge considered as true."

Scientifically speaking, *opinion* is the potentiated synonym of its philosophical meaning, since after thousands of years its confused ideas have been echoed thousands of times in a successful attempt to become truth. And that is also manifested in medicine.

There are many reasons for the persistency of *opinion* over the centuries[1-3]:

- At an advanced age, it disguises as outdated, uninformed weakness and without scientific thought.
- Since it is devoid of scientific proof, it is easy and inexpensive.
- Being ambivalent, it takes advantage of the ignorance, the laziness and the haste of people and nations.
- As a cultural substitute/replacement of knowledge, it is valued as a currency and an exercise of power.
- Transactions are then fuelled by non-technical, money-intoxicated agreement policies.
- Lying, it seeks to bring down the real concepts of acquired experience, autonomy, and ethics.
- Engaging a multitude of allies around its various interests, it is dedicated to the educational dissemination of these untruths.
- Finally, in an "infinite loop", beyond persisting, it diminishes scientific knowledge as necessary truth.
- By disqualifying science as standard, it inescapably strengthens its power, by simplifying the standard for everything in as "we say so".
- In medicine, this is no different, but the consequences are, since *opinion* as a standard leaves patients unprotected from lies.

However, how does scientific thinking (the source of knowledge) protect the patient from decisions regarding their lives and health[1-3]?

- Establishing standards that are independent from opinions.
- Based on consistent models of clinical research.
- Refuting direct extrapolation from animal research to humans.
- Using comparisons as the main parameter.
- Comparing the conducts already in use to identify differences.

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- Using control conducts to identify if there is effect (benefit and damage).
- And if there is an effect, what is what is its size and variation?
- Reducing the number of options for the best ones to patients.
- Paving the way for innovative comparisons
- Defining the ethical boundaries between research and deployment within the system.
- Defining the roles of industry and the State in within those boundaries.
- Fighting human trials without consent.
- Building the culture of adopting only strong evidence.
- Contributing to the organization and balance of the healthcare system.
- Stimulating the establishment of equity between public and private.
- Providing patients access to those standards.
- Assisting healthcare professionals in decision-making.
- Reducing the time spent in discussing superficial clichés.
- Reducing attention on futilities with no outcomes.
- And, in exposing confused opposition, separate wheat from chaff."

In addition, forming opinions as a way of establishing standards of conduct, exposes institutions responsible for ethical-scientific zeal and care to the blow of political winds, power and corruption, taking from them the best opportunity to safeguard the rights of adequate patient care, to positively and scientifically influence healthcare professionals, and to participate actively in the organization and strategies of the system[1-3].

After hundreds of years of effort and dedication of men and women to consolidate and establish current scientific thinking and strength of evidence, there is no reason why opinionated literature [traditional reports, case series or revisions (non-systematic)] should be minimally considered as standard into guiding any decision-making in healthcare. If one disagrees and wishes to impose their opinion to the detriment of science, as the Greeks in the past knew well, they might as well be confused about reality and it is pointless to argue an opinion[1-3].

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Homeopathy: scientific or not?

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Dear Editor

We read the publication on "Special Dossier: "Scientific Evidence for Homeopathy"" with a great interest [1] and would like to share ideas on this issue. Homeopathy has become an alternative medicine system that is presently used worldwide, but there are several comments on its scientific reliability. It is usually mentioned that homeopathy's effect is a kind of placebo effect [2]. Although there are many publications on homeopathy, the proof of scientific merit is still a controversial issue, and some medical scientists point for the "hoax" problem in those homeopathy reports [3]. Regardless of its actual biological effect, if we consider homeopathy as a kind of alternative medicine, it might psychologically support the patients at least. In addition, there are some new findings that homeopathy might be useful in preventive medicine such as prevention of tropical epidemic diseases such as dengue [4]. This becomes a new hope for several developing countries. In our experience in Thailand, a tropical country in Indochina, some local physicians already use the homeopathy technique for dengue prevention, but there are several critics from others. Regarding the present status of homeopathy, the critical question is where this alternative medicine system should be set and how to improve the quality management system for this alternative medicine practice.

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Deep brain stimulation - depression and obsessive-compulsive disorder

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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.

METHOD OF EVIDENCE COLLECTION:

This guideline followed the standard of a systematic evidence-based review based on the Evidence-Based Medicine movement, where clinical experience is integrated with the ability to critically analyse and apply scientific information rationally, thus improving the quality of medical care. EBM uses existing and currently available scientific evidence with good internal and external validity for the application of its results in clinical practice.[1,2]

Systematic reviews are currently considered the level I of evidence for any clinical issue by systematically summarizing information on a particular topic through primary studies (clinical trials, cohort studies, case-control or cross-sectional studies) using a reproducible methodology, in addition to integrating information on effectiveness, efficiency, efficacy and safety.[1,2]

We used the structured form to formulate the question synthesized by the acronym PICO, in which the **P** corresponds to the patient with **Depression or Obsessive-Compulsive Disorder**, **I** for **Deep Brain Stimulation** intervention, **C** of comparison with **Simulation of Deep Brain Stimulation**, and **O** for the clinical **Outcome**. From the structured question we identified the descriptors that formed the basis of the search for evidence in the databases Medline-PubMed, Embase and Cochrane. Thus, 21 studies were selected, after the eligibility criteria (inclusion and exclusion), to answer the clinical question (**Annex** I).

CLINICAL QUESTION:

Can patients with depression or obsessive-compulsive disorder benefit from deep brain stimulation?

Degree of recommendation and strength of evidence:

A: Experimental or observational studies of better consistency.

B: Experimental or observational studies of lower consistency.

C: Case reports/uncontrolled studies.

D: Opinion lacking critical evaluation, based on consensus, physiological studies or animal models.

Objective:

To identify the best evidence available at the present time related to the use of deep brain stimulation in patients with depression or obsessive-compulsive disorder.

Conflict of interest:

The participants have declared no conflict of interest.

INTRODUCTION

Severe depressive disorders are the most frequent form of psychiatric illness, with a prevalence of about 15%. In most cases, the disease can be effectively treated with a combination of available drugs, such as antidepressants, and psychotherapy. In approximately 10% of cases, however, the disease becomes chronic and largely refractory. These patients are candidates for non-pharmacological measures, in particular, electroconvulsive therapy (ECT) or, in specialized centres, the vagus nerve stimulation or transcranial magnetic stimulation. ECT is effective but may have a high rate of recurrence and rejection by the patient. Deep brain stimulation could potentially open up new therapeutic opportunities as an effective long-term strategy with few adverse effects[3].

Obsessive-compulsive disorder is a relatively common psychiatric illness with a prevalence of about 2%. Clinically, it manifests itself in the form of obsessive thoughts, beginning between childhood and adulthood. There is high comorbidity with depression, but also with anxiety and personality disorders. Patients with obsessive-compulsive disorder have an imbalance in conduction of the cortico-thalamic-cortical connections, with a resulting absence of inhibition. There are deregulation of the serotonergic and dopaminergic systems. These assumptions are based on the known positive effect of selective serotonin reuptake inhibitor (SSRI), clomipramine hydrochloride and some neuroleptics. In addition to these pharmacological treatment approaches, therapeutic efficacy can be achieved with cognitive-behavioural therapy. Although 70% to 80% of obsessive-compulsive disorder patients respond well to cognitive-behavioural therapy and pharmacotherapy, the remaining patients have a serious chronic illness. These patients were previously candidates for neurosurgical procedures. Among these techniques, involving the production of irreversible lesions, is bilateral anterior capsulotomy, which had the highest success rate (over 60%). This data was obtained in longitudinal studies under uncontrolled conditions. Reports of deep brain stimulation (DBS) in the treatment of patients with refractory obsessive-compulsive disorder have been published continuously since 1999. Many of the publications are case reports[3].

Deep brain stimulation (DBS) is a reversible neurosurgical procedure that involves the implantation of electrodes in specific anatomical locations and the transmission of an electric impulse of varying intensity and frequency through these electrodes. DBS induces an electric field that alters the complex patterns of neuronal action and, therefore, modifies the activity of the neural circuits. DBS has been used for the treatment of essential refractory tremor and is approved for Parkinson's disease and dystonia. In 2009, DBS was approved for the intractable treatment of obsessive-compulsive disorder (OCD) in Europe and the USA. Since the mid-1960s, it has been observed that both acute and chronic stimulation can induce mood changes, including hypomania, dysphoria and anhedonia. A number of research groups are investigating different sites for implantation of electrodes: 1. Subgenual cingulate-Brodmann 25 (SCG 25): the essential role of the subgenual cingulate cortex has been demonstrated in normal or pathological mood attitudes. In addition, other studies have indicated an association between a clinical response to antidepressants and decreased metabolism in limbic and striatal areas (subgenual cingulate cortex, hippocampus, insula and pallidum) and increased metabolism in dorsal cortical areas (parietal, prefrontal, anterior and posterior cingulate cortex); 2. Ventral internal anterior capsule/ventral striatal (VC/VS): the dorsal and ventral prefrontal cortex were defined as dysfunctional, through neuroimaging studies, in patients with mood disorders. These regions are connections of a thalamocortical-corticostriatal circuit that also includes components of the striatum and thalamus. This target for DBS was defined following gamma-knife capsulotomy studies for obsessive-compulsive disorder (OCD). In patients with primary OCD, a significant improvement was observed in depressive symptoms, leading to the investigation of this goal in depression. Functional neuroimaging studies in individuals undergoing DBS showed activation of the ventral, striatum and thalamus pre-frontal cortex during acute stimulation of the VC/VS target; 3. Nucleus accumbens (NAC) and ventral

striatum: The ventral striatum NAC circuit has been associated with drug addiction and depression. The ventral striatum NAC receives projections mainly from the anterior cingulate cortex, the insular cortex and the orbitofrontal cortex. The NAC then projects to the dorsomedial nucleus of the thalamus through the ventral tegmental area, ventral pallidum and black substance, which in turn projects back to the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, amygdala, and hypothalamus, forming the limbic circuit of the basal ganglia; 4. Inferior thalamic peduncle (ITP): ITP is a bundle of fibres that connects the thalamus system to the orbitofrontal cortex. This system induces electrocortical synchronization and allows the inhibition of irrelevant stimuli to determine selective attention. ITP was identified as a potential target for stimulation in depression; 5. Lateral habenula (LH) has been proposed as a target for DBS, since the habenular nuclei complex projects to the locus coeruleus, frontal medial dorsal cortex, orbitofrontal cortex, insula and mesolimbic areas, and ventral tegmentum/brainstem.

The implantation of DBS electrodes and batteries is a complex neurosurgical procedure. Under stereotactic guidance, two electrodes are placed in deep structures of the brain, relative to a set of anatomical landmarks. Two programmable neurostimulators are implanted in the thoracic region under the clavicle and are connected to the corresponding electrode by extension leads under general anaesthesia. Systematic outpatient adjustment of stimulation parameters (active contacts, amplitude, duration, frequency) and frequent follow-ups are required, especially during the first 6-12 months after implantation. The rates of surgical complications are quite variable, and include intracranial haemorrhage, infections and, rarely, stroke, erosion by electrode or electrode migration. From a psychiatric point of view, there is a risk of developing symptoms of mania or hypomania, anxiety, depression or aggravation, but these symptoms are generally transient and respond to changes in stimulation parameters. Suicides were reported in patients with movement disorders and depression implanted with DBS in different targets[4].

Although deep brain stimulation (DBS) is an invasive procedure, it causes few adverse effects. The spectrum of unwanted effects can be classified into three types: the complications of surgical intervention, the purely technical problems and the adverse effects of the stimulation itself. The introduction of the electrodes may result in intracerebral haemorrhage depending on the surgeon and centre, which can be expected in 0.2% to 5% of surgeries. Intracerebral haemorrhage can lead to focal neurologic symptoms such as dysarthria, hemiparesis or aphasia, or even death. Postoperative infection by the implanted materials occurs in 2% to 25% of cases, but the risk can be greatly reduced by the perioperative administration of systemic antibiotics. Problems related to the device, such as breaking the electrode and failure of the neurostimulator, are rapidly decreasing as a result of technical advances. Undesirable effects of stimulation vary widely, depending on the anatomical target, but they are reversible upon cessation of stimulation. Symptoms related to neurological stimulation, such as dyskinesia, dysarthria, palpebral apraxia and, less often, unsteady gait, often resolve spontaneously, but may regress particularly with modulation of stimulation. Attention is being given to changes in mental state. Together with descriptions of positive effects on depression and anxiety, increased use of DBS has been accompanied by an increasing number of reports of induction of behavioural changes, depressive states, and manic states. To date, however, these undesirable effects have been systematically recorded only for interventions in the subthalamic nucleus. Over a 10-year observation period, a meta-analysis of DBS in Parkinson's disease described the following psychiatric adverse effects: depression in 2% to 4% of cases, mania in 0.9% to 1.7%, emotional changes by 0.1% to 0.2%, and suicide by 0.3% to 0.7%. Subthalamic stimulation may increase the risk of suicide. Adverse effects were, as a rule, only transient, and mostly resolved by adjustment of stimulation parameters, or tolerated by patients because of the predominantly positive effects[3].

RESULTS OF SELECTED EVIDENCES

Can patients with depression benefit from deep brain stimulation?

Patients (n: 20) with major depressive disorder (over one year) and treatment-resistant (antidepressants, psychotherapy and electroconvulsive therapy) receive DBS in subcallosal cingulate gyrus (SCG). Resistance to treatment may be defined as failure to respond to a minimum of four different treatments, including sufficient antidepressant drug therapy and duration, psychotherapy, and electroconvulsive

therapy. Psychiatric evaluations and stimulator adjustments were performed one, two, and four weeks after surgery, every two weeks, for three months, and then monthly for up to 12 months. The primary outcome was the percentage of patients achieving 50% or greater reduction in severity of depression as measured by the HRSD-17 score (defined as response), with a secondary outcome of those achieving clinical remission (defined as an HRSD-17 score of 7 or less). Under local anaesthesia, a stereotaxic system was used, with implantation of quadripolar electrodes in the subcallosal cingulate gyrus (SCG). A two-channel programmable internal pulse generator has been implanted. Patients were discharged between the 2nd and 5th postoperative days. Patients received continuous monopolar stimulation in settings ranging from 3.5 V to 5.0 V, with pulse width set at 90 microseconds and 130 Hz frequency. The mean HRSD-17 score in the patients improved significantly at all time points examined, after one month or more, relative to the baseline score. After one week of stimulation, 40% of the patients were considered responders and one patient was in remission. The response rate dropped to 30% with one patient in remission, two weeks after surgery. From two weeks to six months after surgery, a growing proportion of patients improved, when 60% of patients met the response criteria and 35% of clinical remission. At 12 months, 55% of patients responded to treatment and 35% achieved or were within 1 point of remission (score of 8 or less on the HRSD-17 scale). Of the patients who fulfilled the criteria for response at six months, 72.7% also presented criteria for response at 12 months, while 33% of the patients who were not considered responders in six months had a response in 12 months. Deep brain stimulation was associated with overall improvement in depressive symptomatology measured by mood, anxiety, somatic and subcomponents of sleep. The benefit in each of the symptom groups is associated with time after beginning of the stimulus. The maximum improvement of mood component occurred after three months. Longer times were necessary to achieve maximum improvements in anxiety, sleep, and somatic symptoms. Regarding adverse events, 20% of the patients presented infection, 5% convulsion, 20% headache or pain at the implant site, 35% of the cases did not present adverse events and there was no cognitive or hypomanic effect[5](B).

Patients (n: 15) between 18 and 55 years of age, with a history of at least five years of chronic or recurrent depression (two or more years in a current episode), defined by the application of the DSM-IV instrument, and in stable psychotropic medications for at least six weeks prior to joining the study. Patients also needed at least 21 points on a 24-point scale in the Hamilton Depression Assessment (HDRS). This threshold was chosen to allow the inclusion of patients partially responsive to the current treatment. Previous treatment attempts should have included: 1) Appropriate treatments (>6 weeks maximum recommended or tolerated dose) of primary antidepressant medications of at least three different classes; 2) Adequate tests (>4 weeks) of increase/combination of strategies using a primary antidepressant with at least two other different agents; 3) At least one adequate treatment of ECT (six or more bilateral treatments) and 4) Appropriate treatment of psychotherapy (at least 20 sessions with an experienced therapist). The electrodes were implanted bilaterally in the ventral internal anterior capsule/ventral striatal VC/VS with stereotactic technique guided by the image. Implantable neurostimulators placed bilaterally under general anaesthesia were used. Intraoperative stimulation test was performed after implantation, with the patient awake and able to answer the questions. The aim of the test was to identify the contact sites that produced acute mood enhancement and anxiety reduction without significant adverse effects. Common observations during intraoperative stimulation included acute improvement of mood, spontaneity, smiling, reduced anxiety and increased energy and consciousness. Adverse effects have occurred, such as tachycardia, increased anxiety, hot feeling/sweaty, perseverance in speech, and facial motor effects. After a postoperative recovery phase (2-4 weeks), patients underwent ambulatory stimulation for several hours during several days to establish safe and effective parameters. Once the appropriate settings were identified, the individuals entered the chronic stimulation phase. During this phase, they returned at least monthly for evaluation and classification of the device. Modifications to the stimulation settings, most commonly the pulse range or width, were allowed during this phase to mitigate adverse effects and to optimize effectiveness. Multiple instruments were selected to evaluate the results: the HDRS (primary measure), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Global Assessment of Functioning (GAF) scale. The effects

of DBS treatment were also categorically evaluated, with a defined response as a reduction of 50% of the depression rating scales in relation to the preoperative baseline of each individual patient. Remission was defined as a score of 10 or lower for both MADRS and HDRS. Response and remission rates were determined separately for each rating scale. The longest follow-up period was 51 months, with a mean follow-up of 23.5 (± 14.9) months. The accumulated treatment period was 353 months of experience with DBS patients. Antidepressant regimens remained stable throughout the first six months of stimulation in 75% of patients. The mean MADRS pre-implantation score for the subjects was 34.8±7.3; baseline in the HDRS was 33.1±5.5. The scores for both measures decreased with DBS treatment (MADRS and HDRS). The sustained reduction in score was observed over time, with good agreement between these two measures. The maximum reduction in both scales (approximately 50%) was obtained in three months and maintained for 12 months. The mean reduction of 16.6±2.2 in the MADRS score was observed (between the beginning and the treatment phase), which corresponded to a mean reduction of 46.6%. Mean points in HDRS decreased by 14.4±2.0 (41.9%). In the self-assessment, the Quick Inventory of Depressive Symptomatology SR and the Patient Global Impression of disease severity were evaluated at six months. In the questionnaire for the scores of depressive symptoms there was a significant improvement from 47.47 to 33.27 in six months ($p = 0.008$). In the Patient Global Impression of disease severity, scores improved from 5.27 to 3.87 ($p = 0.006$). After three months of stimulation, mean GAF increased from 43.4±0.7 (baseline) to 58.4±2.2, with the same level of improvement maintained for 12 months. On average, an increase of 12.9±2.0 points in GAF was observed between the beginning and the end of treatment ($p < 0.0009$). After one month of active DBS, 26.7% of the patients presented 50% or more reduction in the MADRS criterion for the clinical response, with 20% reaching the corresponding criterion in HDRS. Response and remission rates at both scales were similar over time, although slightly lower for HDRS. For the patients, the response rates at three months, six months and in the last follow-up were 53.3%, 46.7% and 53.3%, respectively, in MADRS, and 46.7%, 40% and 53.3%, respectively, on HDRS. The remission rates for MADRS were 33.3% at three months, 26.6% at six months and 33.3% at the last observation. The corresponding remission rates evaluated with HDRS were 20% at three and six months and 40% at the last follow-up. The main adverse events related to DBS were occipital pain, electrode fracture and hypomania; syncope; worsening depression; and insomnia[6] **(B)**.

Patients (n = 20) with a diagnosis of major depressive disorder [DSM-IV-TR, with current depressive episode lasting >1 year, with no documented response to at least four adequate treatment attempts (pharmacotherapy, ECT and psychotherapies), and HAM-D score ≥20] received deep brain stimulation through implantation in the subcallosal cingulate gyrus. At each annual visit, the 36-item Short-Form Health Survey (SF-36), in addition to HAM-D, was applied to patients. The primary efficacy outcome was the percentage of patients who responded during follow-up period. Secondary outcomes were the percentage of patients in remission, the absolute change in HAM-D over three years, and changes in baseline functioning in the SF-36. The mean duration of post-surgical follow-up after DBS implantation was 42.1 months. Follow-up was 841 months, or 70 patient-years. The percentage of patients responding was 62.5% after one year, 46.2% after two years, 75.0% after three years and 64.3% at the last follow-up visit. In the intention-to-treat analysis, a similar pattern of response rates was observed, with 55% at one year, 45% at two years, 60% at three years and 55% at the last follow-up visit. The majority (70%) of respondents at subsequent follow-up visits had also been responders one year before. The remission rates over time also remained the same: 18.8% after one year, 15.4% after two years, 50% after three years and 42.9% at the last follow-up visit. HAM-D scores were significantly lower than at baseline ($p<0.001$), although they did not differ significantly from scores in years 1, 2 and 3. Over three years, HAM-D scores decreased significantly ($p<0.001$) relative to the baseline score. In relation to SF-36, there was a significant effect on social functioning ($p<0.05$) and mental health ($p=0.05$) domains, as well as on the physical health dimension ($p=0.05$). During follow-up, 40% of the patients were hospitalized (psychiatric or clinical reasons not related to the procedure)[7] **(B)**.

Patients (n:11) were submitted to deep brain stimulation with implantation in the Nucleus accumbens (NAC). They were between 32 and 65 years of age, with a minimum score in 28-items HDRS (HDRS28) of 21 and a score in the Global Assessment of Functioning below 45, with at least more than four epi-

sodes of major depressive disorder (MDD) or chronic depression for more than two years; 45 years after the first episode of MDD; failure to respond to adequate treatments with primary antidepressants in at least three different classes; an attempt of adequate treatment with ECT (46 bilateral treatments); an adequate attempt of individual psychotherapy (420 sessions); no psychiatric comorbidity and drug-free or under stable drug regime for at least six weeks before the beginning of DBS. Bilateral DBS electrodes were implanted. The stimulation was permanent, starting with parameters of amplitude of 2 V, pulse width of 90 ms and frequency of 130 Hz. After an intraoperative test, the stimulation was turned off for a week to allow the tissue consolidation around the electrode edges and to control microleural effects. One week after the operation, this DBS configuration was resumed and the voltage was successively increased by 2-4 V. The stimulation parameters were held constant for approximately four weeks in order to recover the observations of the first acute and subacute effects (for example, improvement in clinical impression as assessed by HDRS). The stimulation was always bilateral and symmetrical. The optimal individual configuration of DBS was kept constant in each patient, at least one month before and during the end of follow-up. Additional pharmacological treatment was kept constant for at least six weeks, before and after surgery. The primary outcome was the response to antidepressant (reduction of 50% severity of depressive symptoms assessed by HDRS28 [28-items]) or remission (HDRS-score <10). Patients were classified as responders and non-responders with respect to their response at month 12 after surgery. Secondary outcome was MADRS and the Hamilton Anxiety Rating Scale (Hama). Of the patients, 45.5% reached the criterion of response in the first year. During the second year, the status of the response remained stable in all patients. The mean total HDRS score28 was significantly better, under stimulus, at all points in time. Responses were detected after the first month of stimulation in the sample as a whole (HDRS28 score: 32.2 [DP 5.5] at baseline, 23.2 [DP 5.6] after one month) and remained stable during the follow-up period (HDRS28-score: 20.2 [DP 7.5] after one year, 19.5 [SD 9] after two years, 22.1 [DP 13.4] at the last follow-up). Responders in 12 months remained responders at 24 months and at the last follow-up, and non-responders maintained their status respectively. Adverse events were related to the surgical procedure (edemaciate eye, dysphagia, pain), directly due to changes in parameters (erythema, transient increase in anxiety or tension, sweating within minutes to a few hours), or unrelated to DBS treatment (for example, gastritis, leg fracture, disc herniation). All side effects related to DBS treatment were transient, or could be stopped immediately, by means of parameter changes, so that patients did not experience any permanent adverse effects[8](B).

The following inclusion criteria were used: age between 18 and 70 years; depression or bipolar disorder, identified through the clinical interview structured with DSM-IV8 and confirmed by psychiatrists; current depressive episode lasting at least 12 months and not responding to at least four adequate antidepressant treatments (score 3 or higher in the history of antidepressant treatment and verified by medical records); intolerance to electroconvulsive therapy or inability to receive electroconvulsive therapy; 17-items HamiIton Depression Rating Scale (HDRS) score ≥10 of 20; preoperative HDRS score ≥20 on average between four weeks preoperatively and 30% or less than the lowest score; Global Assessment of Functioning (GAF) ≤ 11 out of 50, patients (n: 17) underwent deep brain stimulation (DBS) by stereotactic technique of subcallosal cingulate gyrus (SCG). The phases of care included preoperative evaluation for four weeks; surgery; simulated stimulation for four weeks. The patients received local or general anaesthesia, and the quadripolar DBS electrodes were implanted bilaterally. Intraoperative tests of individual contacts were performed in 70% of the patients, using parameters similar to those of chronic stimulation (130 Hz, 90-ms per pulse width, 4-8 mA, approximately 2 to 5 minutes of active stimulation in each contact). After electrode placement, an implantable generator pulse was placed in the infraclavicular region, with the patient under general anaesthesia, and connected to DBS electrodes, with active stimulation for 24 weeks. Patients were discharged after three days with the stimulator off. After surgery, patients entered a four-week simulated stimulation phase with weekly assessment. Patients were informed that they were being randomized to receive active or simulated stimulation for four weeks, but all received placebo stimulation. After these four weeks, all patients received 24 weeks of stimulation, with evaluation every one to two weeks. Chronic, bilateral, monopolar stimulation was used, with initial parameters of 130 Hz, 91-µs pulse width and 4 mA

(mA) current. There was an interruption attempt for four weeks, but because of the recurrence of depressive symptoms, it was aborted, with active stimulation and monthly assessments remaining for three months, then every three months for nine months, and then every six months. Other changes in DBS parameters were allowed during this phase. In addition, changes in medication and psychotherapy were authorized at the discretion of the study team and primary care providers of psychiatric treatment. Measures of efficacy included the HDRS score, the Beck II Depression questionnaire (BDI-II) and the GAF score. For HDRS and BDI, the higher scores indicate greater severity of depression. For GAF, lower scores indicate increased severity of symptoms or dysfunction. GAF score of 50 or lower indicates severe symptoms or psychosocial dysfunction, scores of 51-60 indicate moderate symptoms/dysfunction, 61-70 indicate mild symptoms/dysfunction, and ≥71 indicate absence or transient symptoms or minimal dysfunction. At each study visit, patients were questioned in detail about adverse events (AEs) and the Young Mania Rating scale was administered. An AE was defined as an unwanted change in physical or mental state, which justifies clinical evaluation or intervention. Severe AE was defined as an AE that resulted in death, permanent loss of biological function or the need for prolonged hospitalization. Serious AEs were characterized as probably or definitely related to surgery, DBS device or stimulation. There was significant improvement in all measures, with no clinically significant, or statistically significant differences between the bipolar disorder or depression groups. The HDRS count decreased significantly from baseline to the end of the four-week simulated stimulation phase (p=0.02). Compared with the end of the simulated phase, the reduction in HDRS score after four weeks of active stimulation did not show a significant reduction (p=0.06). Compared with baseline, the mean HDRS score decreased 43.6%, 43.0% and 70.1% by the 24th week, a year and two years of follow-up time, respectively. Remission and response were observed in 18% and 41% after 24 weeks, 36% and 36% after one year, and in 58% and 92% after two years of active stimulation. HDRS cut-off points were used to group patients in remission (HDRS <8), mild depression (HDRS between 8 and 15) or moderate to severe (HDRS> 15) at each follow-up point. All patients who reached the time point of two years were in remission or had only mild depressive symptoms. None of the patients described negative effects of acute stimulation. Adverse events occurred in 65% of the patients, with 76% with at least one severe adverse event not related to active stimulation. In the intraoperative, bleeding occurred. There were also infections and suicidal ideation during the stimulation period[9](**B**).

Inclusion criteria for patients (n: 4) undergoing deep brain stimulation were: presence of major depressive disorder, as determined by the DSM-IV Structured Clinical Interview, severe depression, with a score of at least 20 (out of 52) in the 17-item Hamilton Depression Scale (HAM-D-17); resistance to treatment, as determined by the lack of response to four different classes of antidepressants, psychotherapy or treatment with electroconvulsive therapy at an adequate dose and duration, and age between 20 and 60 years. The stereotactic intervention inserted DBS quadripolar electrodes, which were implanted bilaterally in the subcallosal cingulate gyrus (SCG). After three days the DBS electrodes were connected to the implantable pulse generator, under general anaesthesia. Patients were discharged one to two days after implantation of the pulse generator with the stimulator switched off. The optimization of the electrical stimulation parameters was performed during the first three months after the implantation of the DBS system. Monopolar stimulation was applied, with pulse width (60-450 us), frequency (2-185 Hz) and amplitude (0-10.5 V) being adjusted. In the first week, each electrode was tested for immediate effects on mood using the positive and negative affective scale (Panas) 20 and the visual analogue scale (VAS). The EVA scale was used to evaluate the following moods: sadness, happiness, anger, fear, anxiety and alertness. The optimal parameter was selected with the lowest amplitude required to produce a positive effect and the highest adverse effect threshold. During weeks 2 to 7, different stimulation frequencies (0, 5, 20, 50, 130 and 185 Hz) were randomly tested, with a pulse width frequency of 90 µs and a constant 5 V amplitude, clinical and mood responses being assessed using Panas, VAS and HAM-D-17. During weeks 8 to 11, the pulse widths were changed, keeping the frequency constant at 130 Hz. Various pulse widths were tested (0, 90, 150, 270, 450 us). For pulse widths up to 150 µs, the voltage was 5 V. At week 12, optimal stimulation parameters for each patient were selected based on the specific frequency or pulse width, which was associated with a

50% reduction in HAM-D-17 score in relation to the pre-treatment baseline, and which was associated with the maximum mood response in either instrument (VAS or Panas). For a period of six months, all patients received continuous stimulation using the stimulus parameters that were considered optimal. Clinical efficacy was assessed every two weeks using the HAM-D-17, MADRS and HAM-A instruments. All patients presented a maximal response in the happy mode (VAS-H) for longer pulse widths (270 or 450 µs) and 75% of the cases showed a 50% reduction in HAM-D-17. Of the patients, 50% reached the clinical response criterion (reduction of 50% in HAM-D-17 compared to the baseline) and 25% achieved a partial reduction response of 35% in HAM-D-17. There was no response in 25% of the cases. Anxiety, with dizziness and fainting, was the adverse event that occurred in 25% of the patients[10](B).

Patients (n: 10) between 32 and 65 years of age received DBS in the Nucleus accumbens (NAC). All met diagnostic criteria for major depressive disorder (MDD), unipolar type, and were in a current episode diagnosed with the structured clinical interview for DSM-IV (Axis I [SCID-I] and Axis II [SCID -II] disorders). The minimum score in 28 items, by the Hamilton Depression Scale (HDRS28), was 21 and the Global Assessment of Functioning was below 45. Other inclusion criteria were at least four episodes of MDD or chronic episode for more than two years, and more than five years after the first episode of MDD; failure to respond to appropriate treatments (>5 weeks at the maximum recommended or tolerated dose) of primary antidepressants of at least three different classes; lack of response to adequate treatments (more than 3 weeks at the normally recommended or maximum tolerated dose) of increasing/combining a primary antidepressant using at least two different augmentation/combination agents (lithium, T3, stimulants, neuroleptics, anticonvulsants, buspirone hydrochloride or a second primary antidepressant); appropriate ECT intervention (more than six bilateral treatments); an adequate intervention of individual psychotherapy (more than 20 sessions with an experienced psychotherapist), and absence of psychiatric comorbidity, drug-free or stable drug regimen at least six weeks prior to the beginning of treatment. Bilateral DBS electrodes were implanted using a stereotactic guide. Psychiatric assessments and adjustment of parameters were performed weekly during the first and second month after beginning of stimulation and up to half a year every two weeks. From seven months to two years, patients were monitored monthly. To capture potential effects of the surgery, patients were evaluated daily, in the week after surgery, when no stimulus occurred. The primary outcome was the antidepressants response (50% reduction in severity of depression symptoms, as assessed by HDRS28) or remission (HDRS28 score less than 10). Patients were classified as responders and non-responders with respect to their response in month 12 after surgery. Secondary outcomes included the Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAMA), Beck Depression Inventory (BDI), the self-rated inventory of depressive symptoms (IDSSR), the 90-Item Symptom Checklist (SCL-90) and the list of positive activities modified according to Hautzinger. In addition, preliminary safety information on the method of treatment was recorded. The stimulation was applied with stimulating pulse starting with parameters of amplitude of 2 V, pulse width of 90 µs and frequency of 130 Hz. After an intraoperative evaluation, stimulation was turned off to allow the consolidation of the lesions. One week after surgery, DBS was resumed and tension was successively increased from 2 to 4 V. The primary measure of effectiveness was a 50% reduction in HDRS28 (responders). Patients were classified as responders and non-responders in relation to their response to DBS at 12 months. Of the patients, 50% achieved the response. For a period of one month, 30% of patients were classified as remission (HDRS28 ≤10). The mean total HDRS28 score was significantly better under stimulation at all times. Benefits were observed after one month of stimulation throughout the sample (HDRS28 score: 32.5 at baseline, 23.8 after one month) and remained stable during the follow-up period (HDRS28 score: 20.8 after one year). Adverse effects were related to the surgical procedure (ocular oedema, dysphagia, pain), with changes in parameters (erythema, transient increase in anxiety or tension, sweating) or unrelated to DBS treatment (gastritis and fracture in the leg). All side effects related to DBS treatment were transient, or could be stopped immediately, by means of parameter changes, so that patients did not experience any permanent adverse effects. There was an adverse event of a suicide attempt, not related to DBS. Both events were not related to parameter changes. Both patients had also attempted suicide previously[11](B).

Men and women (not pregnant), aged 30 to 60 years (n: 22), diagnosed with major depressive disorder, and single or recurrent episode using the DSM-IV-TR criterion derived from Mini; first episode before the age of 35; chronic disease with current episode of ≥24 months or recurrent disease with at least a total of four episodes during life (including current episode ≥12 months); documented resistance to at least four life-depression treatments; cognitive-behavioural therapy considered effective; form of treatment in the current episode: documented resistance (there is, persistence of major depressive episode) to a minimum of three appropriate depression treatments of at least three different treatment categories (SSRIs, TCAs, other antidepressants, addition of lithium , irreversible MAO inhibitors); adequacy of treatments defined by a score of at least 4 according to the ATHF criteria in the current episode: documented resistance to ECT (at least six sessions [there is, a minimum score of 3 according to the ATHF criteria]) or <6 treatments if there is clear evidence of inability to tolerate more, or treatment refused; Global Assessment of Functioning with Score <50; Modified Mini-Mental State Examination score ≥27; on a current stable medication regimen or free of antidepressant medication ≥4 weeks. The surgery was performed by stereotactic technique, with insertion of the bilateral electrodes in the cingulate subcallosal gyrus (SCG). The stimulation parameters were chosen based on previous experience and on patients' responses to stimulation over a period of 1-2 weeks. HRSD-17 was the primary outcome, and the response was defined as a minimum 50% reduction in baseline HRSD-17 score (RESP50). The HRSD-17 score was applied at baseline and at three, six and 12 months after DBS. The proportion of patients in the RESP50 group was 57% at one month, 48% at six months and 29% at 12 months. The mean decline in the HRSD-17 score was: at two months, there was a reduction of 40.3%±29.8%. At six months, the drop was 43.3%±31.3%, and at 12 months, it was 41.4%±23.0%. Reductions in depressive symptomatology were associated with improvements in disease severity and overall improvements in patients. Suicide was the most serious adverse event not related to DBS. Nausea and vomiting occurred in 35% of patients[12](B).

Deep brain stimulation, although not yet approved by the FDA, is a reversible invasive technique involving the stereotactic implantation of electrodes powered by a pulse generator for specific dysfunctional brain regions implicated in mood disorders, Parkinson's disease, Alzheimer's disease, movement disorders and other neuropsychiatric disorders. The implant, in patients with depression of DBS electrodes in the Nucleus accumbens (NAC), determines in 12 months, in 50% of the cases, 50% reduction in the HDRS score, with a significant increase in leisure activities. However, the small sample size limits the interpretation of the results and surveys, and larger sample sizes are required. It was found that patients treated with DBS in subcallosal cingulate gyrus leads to variable response over time: 57% at one month, 48% at six months and 29% at 12 months. The response rate after 12 months of DBS increased to 62% when redefined as a reduction in the HRSD reference level of 40% or greater. In addition, the reduction in depressive symptoms was associated with an improvement in the severity of the disease in patients who responded to surgery[13](B).

The knowledge that patients with severe depression may benefit from injury neurosurgery has led to the adoption of DBS as a reversible and adaptive form of treatment. Based on the presence of neuronal dysregulation in limbic circuits and lesion positive effects, different target areas for DBS in depressive disorders have been discussed: ventral nucleus striatum accumbens; subgenual cingulate; internal globus pallidus; inferior thalamic peduncle; rostral cingulate cortex and lateral habenula. Epidemiological studies have evaluated the use of DBS in the ventral nucleus striatum accumbens and the subgenual cingulate, but only case reports are available for the inferior thalamic peduncle and the internal globus pallidus. Stimulation in the subgenual cingulate in 65% of patients with refractory depression results in symptom improvement after six months. There is an average 71% reduction in the Hamilton Depression Rating Scale score (HAM-D). No cognitive impairment detected after 12 months; and memory functions, sometimes negatively impacted by ECT, remained unchanged. After six months, there was a reduction of at least 50% on the HAM-D scale in 60% of the patients, and 35% of the patients met the criteria for remission (HAM-D-score <7). None of the patients had cognitive dysfunction. The nucleus accumbens constitutes a centre of interface between the neuronal circuits emotional, limbic and motor, being crucial in the experience of reward to hedonistic stimuli. This information stimulated the use of DBS in the nucleus with spontaneous positive effects, and within a

week the HAM-D score decreased by an average of 42%. When the stimulus was discontinued under double-blind conditions, 75% of cases deteriorated, with discontinuation of procedures. The correlation between stimulation and depression (HAM-D score) was significant ($p<0.01$), demonstrating the efficacy of stimulation in the nucleus accumbens. All patients responded to treatment without serious adverse effects. In addition to a 50% reduction in HAM-D score in 50% of the patients, there was distinct anxiolysis (measured by the Hamilton Anxiety Scale) within one year of observation. There is a report of DBS treatment in depressed patients, with target area of the internal ventral capsule/ventral striatum, obtaining a reduction in symptoms over the six-month observation period: the HAM-D score dropped by 42%[3]**(B)**.

What is the efficacy of DBS as an acute antidepressant therapy? In the largest open study reported so far, 20 patients with treatment-resistant depression were followed up for one year after surgery. Six months after surgery, 60% of the patients met the response criteria and 35% achieved remission. Improvements in depressive symptomatology remained stable for the remainder of the 12-month period, with 55% of patients meeting the response criteria. Similar results observed a response rate of 50%[14]**(B)**.

What is the efficacy of DBS as a relapse prevention therapy? Patients who had early response with DBS in the subcallosal cingulate gyrus (SCG) were more likely to maintain their response, although late responders (response after six months of DBS) were also observed. There are currently no relapse prevention studies, but anecdotal case reports suggest relapse when the device was inadvertently turned off or the battery failed, with a return to symptom improvement when the device is reactivated[14]**(B)**.

What are the adverse effects associated with DBS? Post-operative: pain or discomfort, intracranial or subcutaneous haemorrhage and infection in the intracranial or subclavian site. Emerging symptoms of hypomania have been reported in a limited number of patients, including those with and without a history of bipolar disorder. Follow-up of patients with neuropsychological tests did not reveal any evidence of cognitive impairment after 12 months of DBS in SCG. Adverse events associated with DBS for bipolar disorder, essential tremor and dystonia were reported in 10 years of experience, concluding that the prevalence of depression was lower (2% to 4%) than in patients with bipolar disorder who did not receive DBS, but whose suicide rate appears to be high compared to the general population and patients who did not receive DBS[14]**(B)**.

Can obsessive-compulsive disorder patients benefit from deep brain stimulation?

Patients (n: 4) with diagnosis of obsessive-compulsive disorder; Yale-Brown Obsessive Compulsive Scale (Y-Bocs) with a score of >25; Global Assessment of Functioning (GAF) score <44; and several failed attempts at treatment with anti-obsessive-compulsive medication at appropriate dosage and duration were subjected to deep brain stimulation (DBS). All patients had received at least four drugs with proven efficacy in the treatment of OCD (three selective serotonin reuptake inhibitors [SSRIs] and clomipramine hydrochloride). All patients received treatments lasting >12 weeks of maximum tolerated or approved doses, and all had been exposed to combinations of medications (for example, in addition to clomipramine hydrochloride or SSRI, serotonergic agent plus antipsychotic). All subjects received at least 12 weeks of cognitive-behavioural therapy (CBT) for OCD (exposure with response prevention) with no significant benefit. The primary outcomes were the Y-Bocs scale and 17 items of the Hamilton Depression Rating Scale (HAM-D). The stereotactic placement of the electrodes was at the base of the inner capsule, at its junction with the nucleus accumbens, followed by the connection to implantable pulse generators. The use of DBS was performed in three stages: 1) exploratory: stimulation combinations, establishing parameters over three to eight days, to determine the tolerability and to evaluate the acute effects; 2) double-blind controlled: 12 weeks with evaluation of stimulation effects using an on-off design; 3) open stimulation, seeking to optimize the results, adjusting the stimulation to conditions, pharmacotherapy and behavioural therapy. The main objective was to detect any evidence of potential efficacy, and whether DBS could specifically be performed compared to traditional anterior capsulotomy, for which it is a potential substitute treatment. The literature indicates that anterior capsulotomy produces a 35% improvement in OCD symptoms, and in about 45% of the patients receiving the surgery. The primary outcome used was the percentage of improvement in relation to the onset of OCD symptoms, as measured by the Y-Bocs scale, and the percentage of patients who achieved an improvement of 35% in this mea-

sure was calculated. In the exploratory phase, the side effects were more prominent in high amplitudes and monopolar configurations. Acute symptom responses were observed in 25% of the cases, with expressive high mood episode, increased activity and reduction in OCD symptoms. The elevation of mood decreased when the stimulators were turned off and returned when they were reconnected. The HAM-D score was 21 at the beginning of the study, 10 after the first day of acute testing, and 5 and 3 at the end of the next two days, when the most intense mood changes occurred. In the double-blind phase, the Y-Bocs scores at the beginning and throughout the four on-off periods demonstrate a significant clinical response in 50% of the cases. There was a clinically detectable and significant decline in OCD symptoms during the initial phase, in the ON blind period (17% improvement in Y-Bocs, with a decline of 36-30) and a clear worsening of symptoms (Y-Bocs increased to 32, HAM-D increased from 24 to 29, subjectively worse than at baseline), when moved to the subsequent OFF period. The Y-Bocs decreased more with ON stimulators (19.8%±29.8%) than with OFF (10.5%±17.8%). The HAM-D also decreased more with ON stimulation (22.5%±37.8%) than with them OFF (6.8%±16.5%). During follow-up in the open stimulation phase, 25% of the patients presented, over a period of seven months, a reduction of 36% in the Y-Bocs score (at 23), and then at 20 (44% improvement in relation to the beginning) and HAM-D decreased by 58% (to 10). The remaining patients developed discontinuity, mainly due to the association with depression, including suicide episode. Despite the concomitance with depression, there were patients with a Y-Bocs score reduced by 73%[15](B).

Diagnosis in patients (n: 10) with OCD was performed using the Structured Clinical Interview for DSM-IV, with a minimum level of severity [measured by the Yale-Brown Obsessive Compulsive (Y-Bocs) scale] of score 28. Resistance to treatment was defined as the inability to achieve significant improvement in OCD after pharmacotherapy, including adequate regimens (with equal doses or, if tolerated, beyond the maximum recommended dose) of at least three serotonin reuptake inhibitors (SRI), one of which had to be clomipramine hydrochloride. Associated SRI, neuroleptic and benzodiazepine combination treatments were required, as were a minimum of 20 behavioural therapy sessions (exposure and response prevention). All patients had chronic OCD, ranging from 11 to 39 years in duration. The initial pre-surgical severity on the Y-Bocs scale was 32 to 38. There was 80% follow-up for 36 months, and 10% of cases for 24 months, with discontinuation of stimulation in 20% of cases due to lack of appropriate therapeutic effects. The surgical target was the anterior limb of the internal capsule immediately anterior to the rostral border of the anterior commissure in the coronal plane. On the same day of the stereotactic implant, the neurostimulators were connected to the electrodes, with intraoperative DBS of 130 Hz for pulse widths of 90 and 210 μs, and to 2-6 V. The most common effects were improvement in mood and anxiety, spontaneity, expressiveness, verbal and facial fluency, along with increased alertness and heart rate. The evaluations were performed after about three weeks of postoperative recovery and then with 1, 3, 6, 16, 18, 24, 30, and 36 months of DBS. The primary outcome was the Y-Bocs. As clinical experience indicates that symptoms of depression and anxiety are associated with intractable forms of OCD that present for surgery, the Hamilton Depression Rating (HDRS)-24 scale and the Hamilton Anxiety (Hars) scale were used as secondary instruments. Overall functional status was assessed with the Global Assessment of Functioning (GAF). The mean Y-Bocs score, at the pre-implantation baseline, was 3,460, indicating severe disease. At three weeks after surgery, shortly before the start of pacing, the scores were 3,337, indicating that there is no effect of implant insertion alone. Y-Bocs scores decreased during DBS, reaching 2,237 in 36 months, with an average of 2,500±1,600 in three months. Stratifying patients by level of reduction in relation to the baseline pre-surgery Y-Bocs value (<25%, between 25% and 35%, and ≥35%), the following results were obtained: the number of responders' ≥35% Y-Bocs increased from 10% in one month to 50% in 36 months. With regard to comorbid depression and anxiety symptoms (24-item HDRS-24 and Hars) during DBS, the mean pre-surgical baseline HDRS-24 was 2,117, at three weeks post-implantation, but prior to stimulation, the scores were 1,997. The depression scores decreased to 1,477 for three months, after which it remained essentially stable. At 36 months, the HDRS-24 score was 1,547. Anxiety measured by Hars also improved over the long period of DBS. Hars scores were 1,827 at the pre-surgical baseline, decreasing to 1,317, three weeks after implantation (before the beginning of DBS). After three months of DBS, the Hars score

was 907, and at 36 months, 807. Regarding overall functioning, GAF scores improved significantly over time during DBS, from 3,667 at the pre-surgical baseline to 5,387 at 36 months. Potential complications of DBS can be separated into those related to surgical implantation, device failure and stimulation itself. Regarding the adverse effects of implantation, 10% of asymptomatic intracerebral haemorrhage, 10% of single generalized intraoperative tonic-clonic seizure after implant, and 10% of surface surgical wound infection after implantation. Regarding the adverse effects of the stimulation, transient sadness, anxiety and euphoria or vertigo. Patients also had motor effects (contralateral unilateral smile and muscular rigidity in the mandible with dysarthria). Olfactory and taste sensations, described as "chemical" or "metallic". All these adverse effects were reversed, usually within seconds and always within minutes, usually when DBS was discontinued or when parameters were changed, but sometimes spontaneously. There was no hypomania. Effects of DBS discontinuation include more depressed mood, acute worsening in OCD symptoms, with HDRS score increasing from 1,274 to 22,771 with discontinuation of DBS. Patients were monitored for suicide risk. No patient became acutely suicidal when DBS was discontinued. There were no significant declines in performance at the cognitive level of the group[16](B).

Patients (n: 5), with a mean age of 38 years old, underwent DBS placement in the anterior limb of the internal capsule and the region of the nucleus accumbens for OCD I refractory to treatment (pharmacological and cognitive behavioural). The mean duration of the disease was 17±4.1 years. The DBS electrode was placed by stereotactic in the region of the inner capsule. At about 30 days post-surgery, patients were randomized to a staged DBS activation (one month or two months). At follow-up, patients received simulated stimulation or active stimulation of DBS. Each patient was studied in two sessions (one simulated/one active or two active), and during programming sessions. The stimulation frequency was maintained constant at 135 Hz. Specific definitions for placebo, active and simulated DBS were established. Simulated and placebo responses were grouped for an analysis when comparing with active DBS. Active DBS analysis compared with simulated/placebo showed that active stimulation was significantly associated with response in all measured outcomes (p=0.001)[17](B).

Patients (n: 18) with refractory OCD were included, aged between 18 and 60 years, defined according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria, with a duration of disease of over 5 years, a Yale-Brown Obsessive Compulsive Scale (Y-Bocs) score >25 (on a scale of 0 to 40, with lower values indicating less severe symptoms), or a score >15 (on a scale of 0 to 20) with a Global Assessment of Functioning (GAF) score of <40 (on a scale of 1 to 90, with the highest scores indicating higher levels of function), and a disease severity score on Impression Clinical Global (CGI), a scale of more than 4 (on a scale of 1 to 7, with higher scores indicating greater disease severity). Additional inclusion criteria were the lack of response to drug therapy after adequate administration of at least three medications (defined as more than 12 weeks of the maximum tolerated dose): serotonin, serotonin reuptake inhibitor, clomipramine hydrochloride, increased of a period of at least one month with risperidone or pimozide and one of the following: lithium, clonazepam, buspirone hydrochloride or pindolol, lack of response to cognitive-behavioural therapy (exposure and response prevention technique) over a year of therapy, or after 20 sessions with at least two therapists; normal cognitive status (score >130 on the Mattis Dementia Rating Scale, ranging from 0 to 144, with lower scores indicating more severe dementia); normal findings in the MRI of the brain. The study had a randomized, double-blind, crossover design. Patients were divided into one of two groups: one group underwent active stimulation followed by a simulated stimulation period (the on-off group) and the other was submitted to simulated stimulation followed by an active stimulation period (the off-on group). An adverse event was classified as severe if the patient was hospitalized, if sequelae were present or if the event was considered serious. The subthalamic nucleus was the preoperative target through stereotaxia. The frequency and duration of the stimulation pulse were 130 Hz and 60 msec, respectively, with the voltage set for the individual patient. The primary outcome was the change in the Y-Bocs score at the end of each period. The Y-Bocs score was significantly lower at the end of the active stimulation (on stimulation period) than at the end of the simulated stimulation (off-stimulation period), with a mean score of 19±8 vs 28±7, P=0.01. The GAF score (where higher scores indicated higher levels of functioning) was significantly higher after active stimulation than after placebo stimulation (mean score at

the end of active stimulation, 56±14 vs 43±8, P=0.005). The CGI score (where the lowest scores indicate lower disease severity) was significantly lower at the end of the active stimulation than at the end of the stimulation simulation (P=0.008), with higher improvement during active stimulation observed in the on-off group than in the off-on group (P=0.03 for the period effect). MADRS scores, the Brief Scale for Anxiety, and the Sheehan Disability Scale at the end of active stimulation did not differ significantly from the score at the end of "simulated" stimulation. At the end of the first phase (three months after randomization), 75% of the patients had a response as measured by the Y-Bocs index and 100% showed a response after active stimulation (as measured by GAF). In addition, 62% of the patients presented an increase in the GAF score to 51 after active stimulation, compared to 12% after the simulated stimulation. Fifteen serious adverse events, of which four were related to surgery, were reported in 60% of patients. The most serious event was a cerebral parenchyma haemorrhage, resulting in permanent paralysis of a patient's finger. Seven transient motor events and psychiatric symptoms induced by stimulation occurred within the first month of stimulation, spontaneously or rapidly after adjustment of the setting. During the active stimulation period, behavioural adverse events were reported in 30% of patients[18]**(B)**.

Deep brain stimulation was used in the treatment of patients (n: 5) with a mean age of 36.8 years, mean Yale-Brown Obsessive Compulsive Scale (Y-Bocs) score of 35, mean of 17.4 years history of OCD and Global Assessment of Functioning (GAF) score between 10 and 30, diagnosed through a structured psychiatric interview according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR). In addition, the patient must have a history of OCD for more than five years and a Y-Bocs score greater than 23, which represents severe or extreme conditions. Two or more pharmacological treatments, including serotonin reuptake inhibitors, neuroleptics, anticonvulsants, benzodiazepines and cognitive-behavioural therapy, for a period of more than six months for each trial had been attempted. Despite this treatment, the reduction of scoring symptoms was less than 30%, according to Y-Bocs. Stereotactic electrodes were placed on the inferior thalamic peduncle. With the neurostimulator (DBS), ideal parameters were established, avoiding uncomfortable effects, with subjective reduction of OCD symptoms. After implantation, all patients were kept out of stimulation for one month during a period of surgical recovery. Then the stimulators were switched on for one year. Parameters were fixed at 5.0 V, 130 Hz and 450 microseconds. Outcomes were measured by the Y-Bocs scale, GAF scale and a neuropsychological evaluation, every three months in the stimulation period. Significant changes were observed in the Y-Bocs scores of the Friedman test. Improvement in GAF scores correlated with improvement in family and social relationships (confinement was discontinued and 60% of patients returned to work). The Y-Bocs score decreased from severe to mild symptoms (P=0.001). The GAF score increased from 20% to 70% (P=0.0001). This represents a shift from almost total family and social dependence to almost normal independence in daily life activities. Initially, patients had severe impairments in communication and social relationships, including those at work or school. For 12 months, this condition improved from moderate to mild disturbance in social relations[19]**(B)**.

Patients aged 18-65 years old who were diagnosed as having primary OCD according to DSM-IV may need DBS treatment. Only patients with a score of at least 28 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), measured twice for at least two weeks apart, should be included. Patients must have at least five years of OCD, experience significant functional impairment according to DSM-IV criterion C and a global assessment of functioning of ≤45. Treatment refractoriness was defined as any response or insufficient response following at least two treatments with a selective serotonin-reuptake inhibitor at the maximum dosage for at least 12 weeks plus one treatment with clomipramine hydrochloride for at least 12 weeks, and at least one treatment with an atypical antipsychotic for eight weeks in combination with a selective serotonin reuptake inhibitor and at least one treatment with CBT for a minimum of 16 sessions. After electrode implantation, patients entered an open phase of eight months, during which they were evaluated every two weeks for the severity of the symptoms and the optimal stimulation parameters. Once the initial and substantial decrease (an average of 6 points) in the Y-Bocs score had been obtained, usually after eight weeks of stimulation, a standardized CBT program was added (individual weekly sessions of 60 minutes for 24 weeks). After this phase, patients entered a double-blind, placebo-controlled phase. Patients were randomly assigned to two periods of two weeks with the stimulators blinded (active stimulation) at one time, and

switched off (stimulus simulation) at another time. Patients were assessed three times (baseline, after a two-week period of active or simulated stimulation, and after a second two-week period of active reverse or placebo stimulation). Treatment with CBT was continued during the crossover period. Electrode implantation was performed using a stereotactic technique targeting the nucleus accumbens. The stimulation parameters were standardized for a frequency of 130 Hz, a pulse width of 90 microseconds and a voltage of 5.0 V. Obsessive-compulsive symptoms were measured using the Y-Bocs, with scores ranging from 0 to 40; higher scores indicate more severe symptoms. Patients were defined as responders if they had a score reduction of at least 35% (Y-Bocs). Depression was classified using the Hamilton Rating Scale for Depression with 17-items (HAM-D) and anxiety was assessed using the Hamilton Anxiety Rating Scale (Hama). The Sheehan Disability scale was used to assess general symptomatic and functional deterioration, and consists of three separate classifications that assess the effect of symptoms at work, social life and family life. Open-phase stimulation resulted in a decrease in the mean Y-Bocs score of 15.7±10.8 points (46%) (P=0.001). The analysis revealed that 60% of patients had a 35% Y-Bocs score decrease, with a mean increase of 23.7±7.0 points (72%) compared with a mean decrease of 5.4±3.1 points (24%) in the group of non-responders. In the open phase, 30% of the patients reached a final Y-Bocs score below 10 (mean reduction of 81%), 20% of patients with final Y-Bocs scores between 10 and 20 (mean reduction of 51%), 20% of patients achieved a final Y-Bocs score between 20 and 30 (mean reduction of 22%) and 30% of patients achieved a final Y-Bocs score of over 30 (mean reduction of 10%). No patient worsened under stimulation. Patients with obsessive-compulsive symptoms, such as perfectionism, need for symmetry and quest for tranquillity, had an average decrease of 10% on the Y-Bocs. A significant reduction was observed in all outcome measures. In the double-blind phase, the mean Y-Bocs score difference between active and "simulated" stimulation throughout the sample was 8.8±9.1 points (P=0.003). The mean difference in Hama score between active and "simulated" stimulation was 12.1±9.1 (P=0.01), and the mean difference in Hama score between active and placebo stimulation was 11.3±7.2 (P=0.01). The improvement observed in the open phase was maintained over 12 months, in which all measures of results showed a statistically significant mean reduction between post-stimulation and baseline preoperative values. The most prominent adverse transient event related to stimulation was elevated mood or hypomania. Elevated mood was reported frequently in reactivation of stimulation after a period of no stimulation. Other adverse events were altered libido and mild forgetfulness[20](B).

All subjects were adults meeting the DSM-IV criteria for OCD, with a minimum score of 28 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs). They should have a history of five years of symptoms, refractory to treatment of OCD, with functional impact on the patient. In the 30-day postoperative period, patients were randomized to active DBS stimulation, targeting the ventral capsule/ventral striatum, or placebo stimulation. The result was measured by the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), the response being defined as a percentage change, to 35% and an effective score of ≤16 in the evaluation. It was found that there were significant reductions in the Y-Bocs score over time (p=0.0392), with a decrease of 15.67±11.60 after 12 months of activation. The categorical response and number of patients who achieved a Y-Bocs score ≤16 for the 12 months of DBS activation was 67% of patients met the criteria for response (Y-Bocs change ≥35% baseline and Y-Bocs ≤16). Within two months with configuration changes, the Y-Bocs score decreased by 33% (in ten months) and this improvement was sustained. Based on the Hamilton Depression Scale, scores significantly decreased for the whole group (p=0.0249), during the 12-month DBS. SF-36-V (vitality) increased significantly (p=0.0079). There were no serious adverse events, such as seizures or cerebral haemorrhages. All adverse events associated with implantation/anaesthesia were anticipated and limited in time. These were discomfort in the surgical site, pain in the incision, tingling, headache, nausea or numbness and sore throat. Adverse effects of stimulation, unwanted or unusual emotional effects, perceptual or somatic experiences. All these effects occur within seconds or minutes of DBS and can be reversed, usually within seconds, and always within minutes, by altering the stimulation parameters. Transient emotional effects, including euphoria, dizziness, anxiety, panic attacks or sadness may also occur. A contralateral smile accompanied by joy can be induced intraoperatively. Hypomania was observed at some point during chronic DBS. None of the participants gave a history of bipolar disorder. Difficulty

falling asleep was a common complaint that was addressed by adding required hypnotic sedatives or by adjusting the device. The clinical effects and effects of the time course of DBS discontinuation were similar, with worsening of mood or increased anxiety, signs of depression such as decreased energy or interest, and also emerged within days of device discontinuation, exacerbation of symptoms of OCD, but no intention of suicide expressed. In all cases, DBS recovery led to the reversal of transient clinical deterioration. The results indicate that the clinical efficacy of DBS in adolescents was achieved without significant neuropsychological morbidity. At 6 months post-DBS, only 2.1% of the patients showed a decline among the responders, while only 7.1% showed a decline in non-responders. In one year, 5.4% of respondents showed a decline, found in 10.7% of non-responders[21](B).

Patients (n: 10) aged 21-65 years, chronic, severe, treatment-resistant OCD (diagnosis by DSM-IV) underwent DBS. Patients score ≥25 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), more than five years of disease, and are resistant to treatment, defined as less than 35% improvement in Y-Bocs after four different treatment regimens: (1) the use of a serotonin reuptake inhibitor (SSRI) at a sufficient dosage over a period of at least ten weeks, (2) the use of another SSRI or clomipramine hydrochloride (300 mg/d) for at least ten weeks, (3) association with lithium, buspirone hydrochloride or an antipsychotic for 10 weeks, and (4) complete cognitive-behavioural psychotherapy for a minimum of 20 sessions with documented inefficiencies. All patients underwent psychiatric examination at the beginning (preoperative), in the first week and 3, 6, 9 and 12 months after the implant. The primary outcome was the reduction of symptoms according to Y-Bocs. The following instruments were used to measure secondary outcomes: the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HDRS), the State-Trait Anxiety Inventory (STAI), the Hamilton Anxiety Rating Scale (Hars), Symptom Checklist 90 (SCL-90-R), Global Assessment of Functioning (GAF) and Modular System for Quality of Life (MSQL). Cognitive function was assessed by Verbal Fluency Exam (VFE). Executive performance was measured with Tower of London (TOL) test. Sustained and selective attention was measured with the Continuous Performance Test (CPT). Under local or general anaesthesia, the quadripolar electrodes were implanted stereotactically in the nucleus accumbens. The stimulation procedure was divided into three phases. In the operating room, the test stimulus was initiated, and patients were asked to report changes in mood, anxiety, alertness or body sensations. The double-blind phase began after the neurostimulator was implanted. During this time, the stimulator was turned on or off during the first three months. The patient was then migrated to the condition of another stimulus for the next three months. During stimulation, the parameters were set at 145 Hz, 90 μS and 4.5 V. After six months, stimulation was continuous in all patients, without blinding, with the option of changing the parameters every three months. In the stimulation test, anxiety, agitation, drowsiness, smell of bitter almonds and a sense of comfort were reported. All these events disappeared by changing parameters, with the exception of a patient whose anxiety lasted a few hours. Of the patients who received first stimulation and then no stimulation, 40% showed a decrease during the three months. Both deteriorated again in the following off-stimulation period. Of the patients who received no stimulation at first, then stimulation, 40% remained stable in their baseline Y-Bocs score up to the end of the three-month "off period". Patients showed substantial improvement over the six-month follow-up. Overall, mean total Y-Bocs scores of patients differed significantly between the beginning (32.2±4.0) and in the "on" stimulation period (27.9±6.4, p=0.033), but not between "off" stimulation (31.1±5.0) and "on" stimulation (27.9±6.4, p=0.205). Only 10% of the patients had a "complete response" after one year, defined as a reduction in the Y-Bocs score of more than 35%; 40% of patients achieved a "partial response", defined as a reduction of 25%-35% of the initial Y-Bocs score. The remaining patients did not improve, at least 25%, after one year. The mean Y-Bocs score decreased significantly, from 32.2 (±4.0) at baseline to 25.4 (±6.7) after 12 months (p=0.012). BDI significantly decreased from the mean 22.7 (±10.1) at baseline to 15.9 (±9.5) after 12 months (p=0.033). In addition, the mean HDRS score showed a significant decrease from 21.6 (±5.9) to 16.6 (±8.2) within one year after implantation (p=0.012). The STAI for anxiety symptoms did not improve significantly (from 56.4±13.6 to 50.7±15.3, p=0.139). The Hars score for anxiety symptoms also did not decrease significantly (from 21.2±6.7 to 15±8.5, p=0.066). The overall psychological symptom, measured by SCL-90-R, "Global Severity Index (GSI)", remained stable (from 1.3±0.7 to 1.2±0.8 at 12 months, p=0.575). In contrast, global functioning (GAF) improved significantly from 36.6 (±3.0) to 53.1 (±9.3) (p=0.012), and quality of life (MSQL) improved significantly from 41.3 (±15.8) to 53.2 (±19.8) (p=0.038). No adverse events occurred during the sur-

gical procedure. After implantation of the neurostimulator, one patient reported dysesthesia in the subclavian region, which lasted several weeks. Four patients experienced transient agitation and anxiety for several days after an increase in voltage. These effects were reversed after the reduced voltage. Two of the patients developed a hypomanic state that lasted several days and reverted spontaneously. Another patient reported difficulty concentrating and failing memory, but these side effects disappeared after the pacing parameters were altered. One patient developed suicidal thoughts after six months, being hospitalized. One patient reported an increase in the frequency of headache during the year after the implant. Another reported a shorter sleep duration and a slight increase in internal tension[22](B).

Several evaluations of obsessive-compulsive disorder patients treated with DBS have been identified. For the stimulation of the area of the nucleus accumbens/caudate nucleus, the adjacent inner capsule and the subthalamic nucleus, good effects were obtained, despite the divergent positioning of the electrodes. In all the research groups, at least 50% of the patients exhibited previously refractory improvements within one year in terms of partial response (≥25% improvement in the Yale-Brown Obsessive Compulsive Scale [Y-Bocs]). Long-term observation has shown improvements in both the degree of symptom reduction and the proportion of patients with obsessive-compulsive disorder who benefit from stimulation[3](B).

Patients (n: 6) with severe OCD were submitted to electrode implantation in the anterior limb of the internal capsule (AL/IC). After 21 months, 50% of the cases had changes in the regional activity, measured by functional magnetic resonance imaging (fMRI) and tomography by emission of tomography (PET). Another group of patients (n: 3) with severe OCD was treated with DBS for the anterior limbs of the internal capsules, with a 65% response and little adverse effect. Patients (n: 4) resistant to the treatment of OCD with severe anxiety disorder received DBS for the nucleus accumbens, with 75% of total remissions over 24 to 30 months. Patients with chronic intractable OCD were treated with DBS and electrodes placed bilaterally in the anterior limbs of the anterior capsules, with improvement in 50% of the cases. Treatment resistant severe OCD (n: 10) was treated with implanted electrodes extending into the ventral capsule and ventral commissure. The patients were followed up for 36 months. Of the patients, 40% had an improvement over 34% based on the Yale-Brown Obsessive Compulsive Scale; 20% had reductions between 25% and 35%. There was incidental improvement of depression. Side effects included asymptomatic haemorrhage, convulsion, superficial infection, worsening of symptoms when DBS stopped due to battery failure and transient hypomanic symptoms. Patient with depression and patient with obsessive-compulsive disorder had the stereotactic implant of electrodes in the thalamic inferior peduncle. Using the GAF scale, both cases showed improvement. In a multicentre study of severe OCD (n: 16) with subthalamic DBS, there was significant improvement in OCD with active stimulation, but there were 15 severe adverse events (including a cerebral haemorrhage) and 23 minor adverse events. Of the patients, 25% were recovered, using a Y-Bocs of 6 or less as an indicator of recovery. It was noted that there was no improvement in depression, and hypomania was one of the adverse events[23](B).

DISCUSSION

Due to the number of cases studied, despite the significant differences obtained with the various outcomes and measurement instruments, the results of the studies assessing DBS in the treatment of depression or OCD lack power (type II error). However, the published effects of treatment of refractory psychiatric conditions with DBS should be considered since, in the majority of cases, there has been a clear improvement in the psychiatric status of these severely ill and previously intractable patients. The various case series have been replaced by an increasing number of randomized, double-blind, phase II clinical trials comparing patients with and without use of DBS. Similarly, the adverse effects of DBS use in such patients are reduced, often reversible, spontaneously, by adjustment of treatment parameters, or are well tolerated by patients.

At present, deep brain stimulation seems to provide new options for the treatment of refractory psychiatric illnesses, including depression and OCD, but in decision making there must be rigor in the selection of refractory patients, especially in relation to severity and lack of options and the potential benefits faced with the risks involved in the procedure should be considered.

It should also be taken into account, within the injury psychosurgery, as form of treatment of refractory severe patients, as depression and obsessive-com-

pulsive disorder (OCD), ethical issues arising from the increased application of deep brain stimulation (DBS). As efforts have been made in clinical research and medical care, evaluating the role of DBS in the treatment of these patients, ethical norms should accompany this process (especially in the care setting), issues of explanation and informed consent to patient, study designs used and the explicit definition of which level of severity should be included in this therapeutic modality.

RECOMMENDATION:

Benefit

Patients with depression or OCD refractory to all appropriate forms of treatment today are candidates for treatment with deep brain stimulation.

Harm

There is an increase in the occurrence of adverse effects, mainly related to the intervention or the stimulation, being usually reversible with the change in the parameters used.

ANNEX I

Clinical question

Can patients with depression or obsessive-compulsive disorder benefit from deep brain stimulation?

Structured question

P	Patients with depression or obsessive-compulsive disorder
I	Deep brain stimulation
C	Simulation of deep brain stimulation (simulated), clinical treatment or after deep brain stimulation
O	Non-intermediary clinical outcomes

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

Evidence search strategy

PubMed-Medline

#1: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND Random* = **426** recovered

#2: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND Prognosis/narrow[filter] = **63** recovered

#3: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND (Therapy/broad[filter] OR Epidemiologic methods) = **1,877** recovered

1st RECOVERY: #1 OR #2 OR #3 = 1,893 recovered

Embase

electric AND ('stimulation'/exp/mj OR stimulation) AND ('therapy'/exp/mj OR therapy) OR deep AND ('brain'/exp/mj OR brain) AND ('stimulation'/exp/mj OR stimulation) OR DBS AND (temporal AND lobe OR 'hippocampus'/exp/mj OR hippocampus OR 'thalamus'/exp/mj OR thalamus OR nucleus AND accumbens OR globus AND pallidus OR anterior AND thalamic AND nuclei OR subthalamic AND nucleus OR corpus AND callosum OR prefrontal AND cortex OR cerebral AND cortex OR posterior AND thalamic AND nuclei OR depressive AND disorder, AND major OR depressive AND ('disorder'/exp/mj OR disorder) OR depressive AND disorder, AND 'treatment resistant' OR 'obsessive compulsive' AND ('disorder'/exp/mj OR disorder) OR bipolar AND ('disorder'/exp/mj OR disorder) OR 'depression'/exp/mj OR depression) AND [randomized controlled trial]/lim AND [embase]/lim

2nd RECOVERY = **53** recovered

Cochrane

#1 – 'deep brain stimulation

#2 – (Depressive Disorder OR Obsessive Compulsive Disorder)

3rd RECOVERY = #1 AND #2 = **25** recovered

Papers recovered

Obtaining the evidence to be used to analyse the clinical question followed the steps of: elaboration of the clinical question, structuring the question, searching for the evidence, critical evaluation and selection of the evidence, exposure of the results and recommendations.

The primary databases of scientific information consulted were Medline via PubMed and Embase; and secondary, the Cochrane Library. A manual search was carried out based on references of revisions (narratives or systematic), as well as the selected papers.

Of 21 papers (11 on depression and 10 on obsessive-compulsive disorder) considered for critical evaluation, none were excluded because of full text unavailability. After evaluation of the titles and abstracts and from the inclusion and exclusion criteria, all were used to support the synthesis of the evidence.

INCLUSION AND EXCLUSION CRITERIA OF THE PAPERS

Studies within the limits of PICO were included.

All papers recovered in the primary and secondary information bases were evaluated. In the manual search, no papers were selected.

The papers included in the evaluation are from the period between 2005 and 2013.

The main reasons for exclusion were: patient does not fit the description, performance evaluation of healthcare professionals, pilot study, post-hoc analysis, intermediate outcome, subgroup evaluation, letter, case-control design, case report, comparison between application techniques and cost.

According to the study designs

Only studies with epidemiological study design (Clinical Trial [Randomized or not], Observational Cohort or Before and After Study) and systematic reviews of epidemiological studies were included.

A critical reading was made of each of the studies to look for biases that could compromise the internal validity of the studies. In the absence of serious biases that invalidated the studies, these were included in the review.

Only studies that evaluated at least one clinical or clinically relevant outcome were included. When there was more than one publication of the same study, only the one whose clinical outcome was considered relevant and had the longest follow-up was evaluated.

When subgroup analysis was performed, which increases the possibility of random associations, the power of the study was calculated to detect the difference of the results, being considered relevant if greater than 80%.

5.2 Language

Studies available in Portuguese, English or Spanish were included.

5.3 According to the publication

Only papers whose complete texts were available were considered for critical evaluation.

METHOD OF CRITICAL EVALUATION

When, after applying the inclusion and exclusion criteria, the evidence selected in the search was defined as a cross-sectional study or randomized controlled clinical trial (RCT), it was submitted to an appropriate checklist (Table 1) for critical evaluation

TABLE 1 - CRITICAL EVALUATION SCRIPT OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Study data – Reference, study design, Jadad, strength of evidence	**Sample calculation** – Estimated differences, power, level of significance, total patients
Patients selection – Inclusion and exclusion criteria	**Patients** – Recruited, randomized, prognostic differences
Randomization – Blinded description and allocation	**Patients follow-up** – Time, losses, migration
Treatment Protocol – Intervention, control and blinding	**Analysis** – Treatment intention, analysed, intervention and control
Outcomes considered – Primary, secondary, measurement instrument of outcome of interest	**Result** – Benefit or harm in absolute data, benefit or harm in mean

TABLE 2 - CRITICAL EVALUATION SCRIPT OF COHORT STUDIES

Representativeness of exposed and selection of 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 on the basis of design or analysis (max 2 points)	Evaluation of the outcome (max 1 point)	Appropriate follow-up time (max 2 points)	Score and level of evidence

(Quadas[24] or Consort[25]). The controlled clinical trials were evaluated according to the Jadad[26] score and/or the Grade[27] score.

The critical evaluation of the included studies makes it possible to classify them by the Oxford scale[28] as evidence strength 1b or 2b, and corresponding degree of recommendation A or B, respectively. Systematic reviews were classified on the strength of evidence 1a or 2a, and degrees of recommendation A or B, respectively.

The selected evidence defined as a comparative study (observational cohorts or non-randomized clinical trial) was submitted to an appropriate critical evaluation checklist (Table 2), allowing the classification of the study according to the Newcastle-Ottawa Scale score[29], considering the consistent cohort studies with score ≥6 and inconsistent <6.

EXPOSURE OF RESULTS

For results with available evidence, the population, intervention, outcomes, presence or absence of benefit and/or harm and controversies will be defined in a specific way, whenever possible.

The results will be preferably exposed in absolute data, absolute risk, number needed to treat (NNT) or number needed to harm (NNH) and possibly in mean and standard deviation (Table 3).

TABLE 3 - WORKSHEET USED TO DESCRIBE AND PRESENT THE RESULTS OF EACH STUDY.

Evidence included
Study Design
Population selected
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ration, mean

RECOMMENDATIONS

The recommendations will be prepared by the authors of the review, with the initial characteristic of synthesis of the evidence, being submitted to the validation by all the authors participating in the preparation of the guideline.

The degree of recommendation to be used stems directly from the available strength of the studies included according to Oxford[28] and the use of the Grade[27] system.

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Atypical presentation of metastasized renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC) is a heterogeneous family of neoplasias. Currently it corresponds to 90% of all renal malignancies and is the most lethal of urological tumors.[1] Now, with the increased frequency of imaging exams in the general population, many of these tumors are detected coincidentally; two-thirds of them occur in men.[1,2]

Clinical manifestations of RCC include hematuria (60%), back pain (40%), and palpable flank mass (30–40%).[1,2] The most common histological types are clear cell, papillary, and chromophobe carcinomas. About 25–59% of patients with RCC present with distant metastasis at the time of diagnosis.[3]

Clear cell carcinoma is the most common histological subtype of RCC, representing 70–75% of cases.[1,2] It occurs typically around the age of 50 years. The most frequent locations are the lungs (50%), bones (33%), lymph nodes (15%), skin (11%), liver (8%), and brain (3%).[1] Adrenal gland metastases are rare, occurring in less than 10% of patients, and they are generally silent. Imaging techniques such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) play an important diagnostic role in RCC; they enable early detection and are essential for therapeutic staging and planning. Chest x-ray and urine cytology are also used in the diagnosis of this disease. Complete surgical resection continues to be the only curative treatment for RCC.

CASE

A male patient aged 59 years and residing in São Paulo, Brazil, with systemic arterial hypertension and type 2 diabetes, and no previous history of surgery was admitted to the emergency room with a history of vertigo and two episodes of fainting in the two pre-

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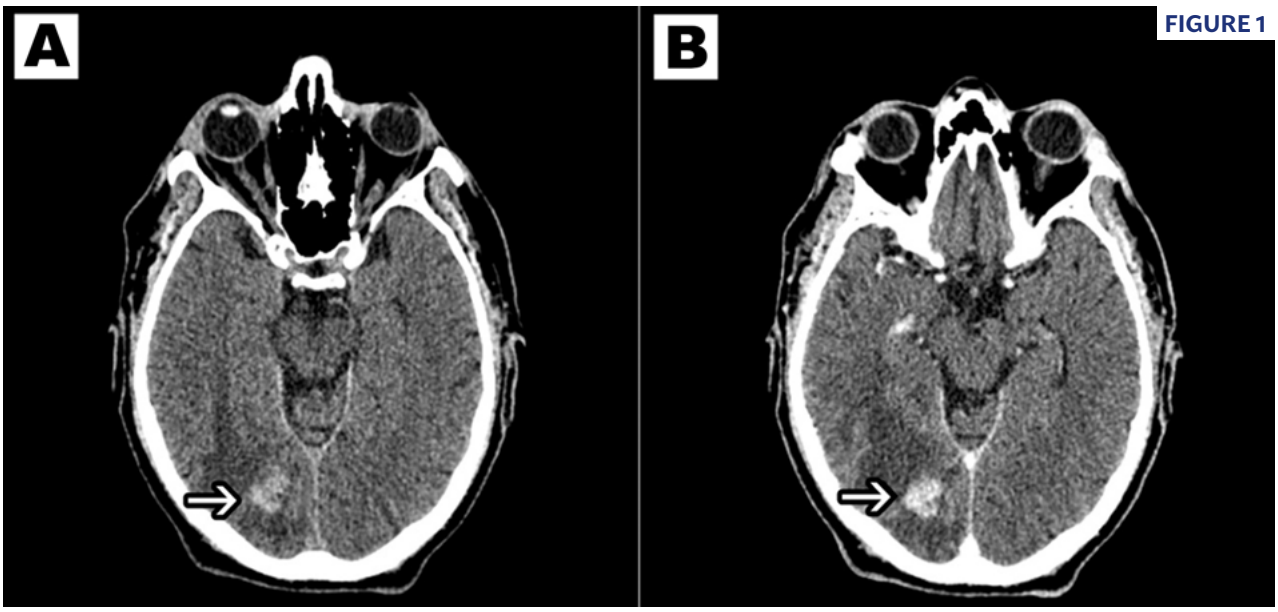

FIGURE 1

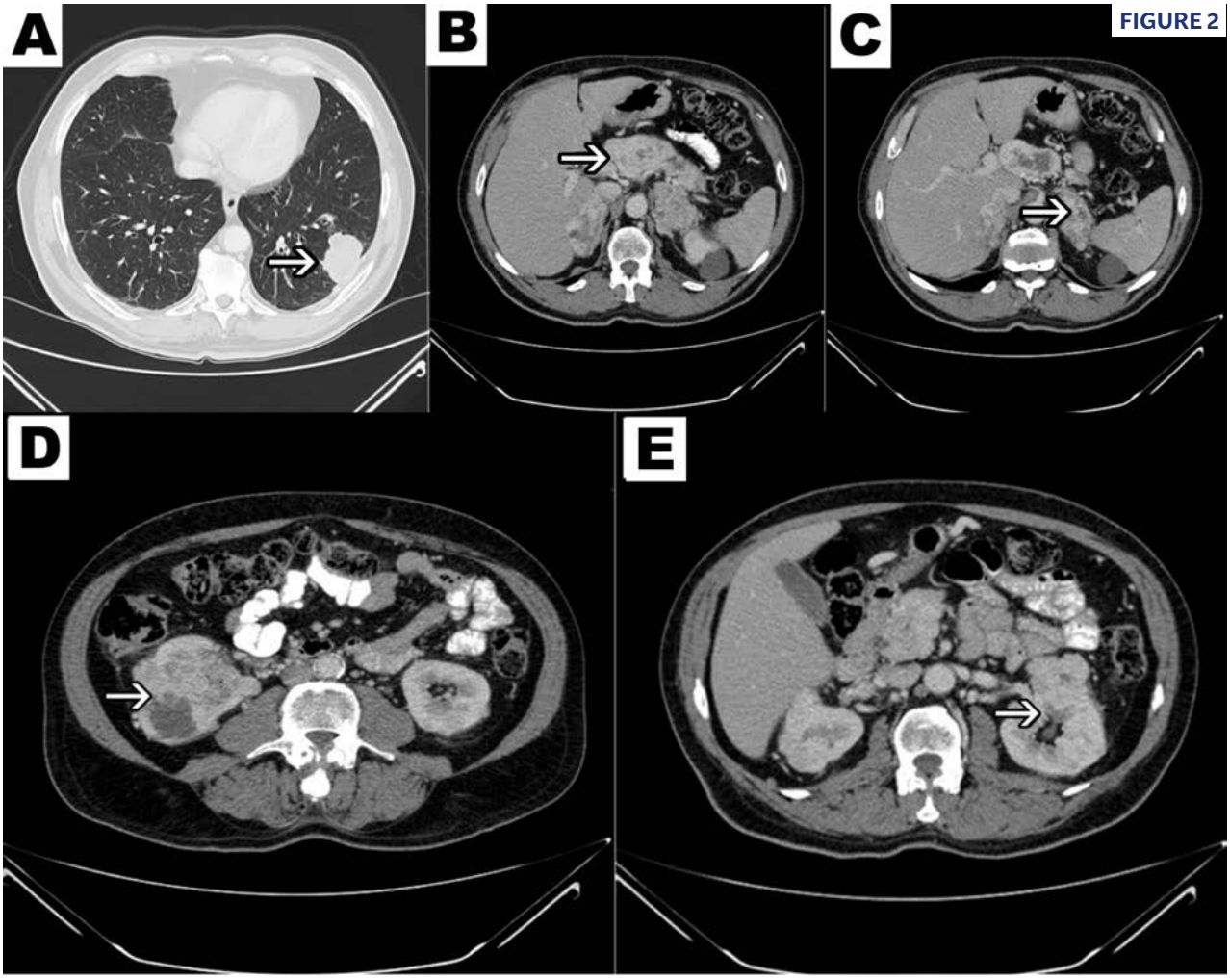

FIGURE 2

vious months. The findings of physical, neurological, and laboratory tests were not remarkable. Due to limited clinical open neurological status, we started a CT scan of the skull and found a series of brain metastases (Figure 1). As a result of the presence of encephalic nodules with the appearance of metastases, a search was made for the most frequent tumors in the male sex: lung, colorectal, and prostate. However, physical

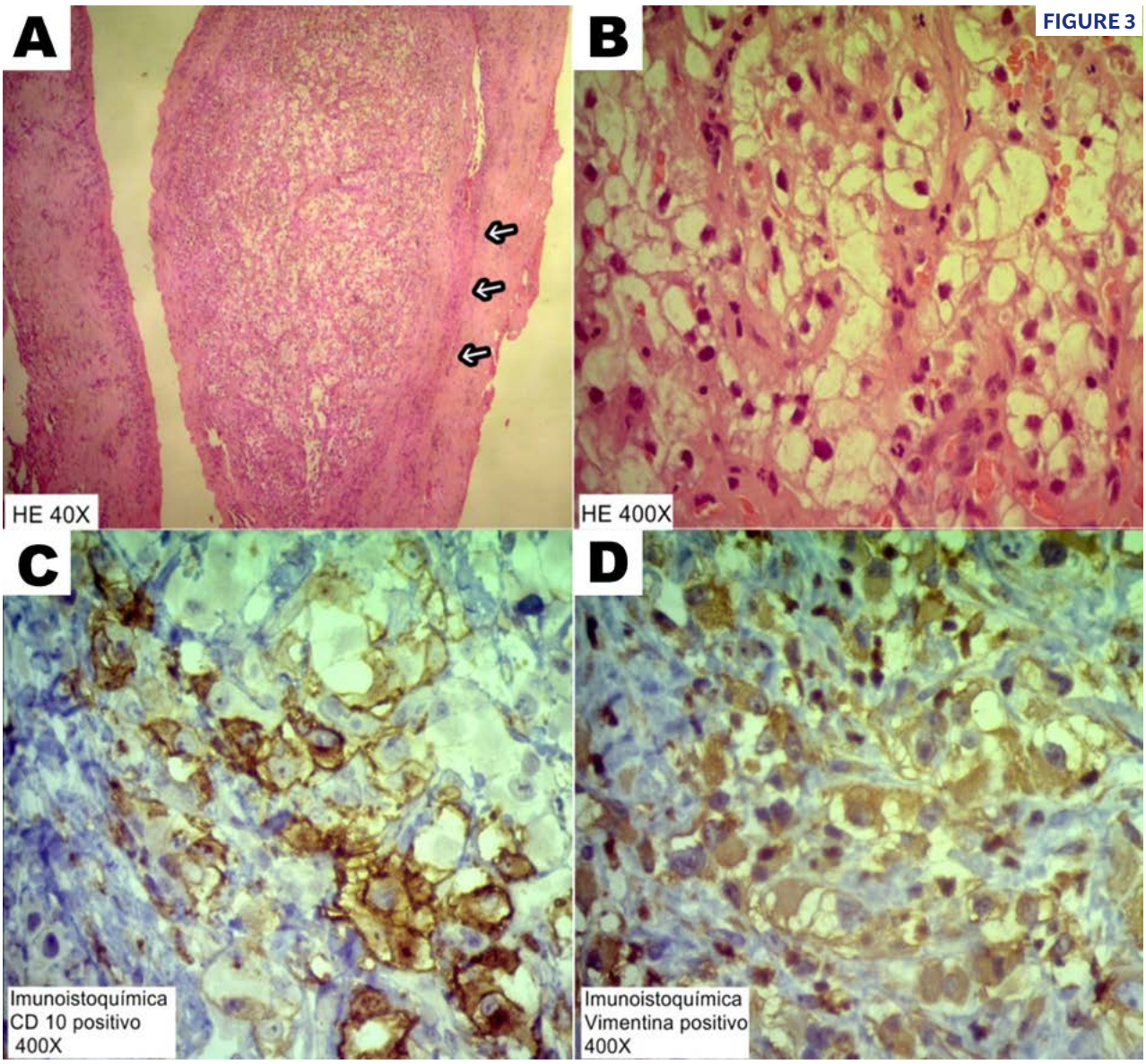

FIGURE 3

examination revealed no abnormalities, thus restricting the diagnosis for some subtypes of tumors such as lung, melanoma, kidney, and gastrointestinal neuroendocrine tumors. CT of the thorax, abdomen and pelvis revealed a sizeable continuous mass of 5.9 × 5.5 × 5.4 cm and solid pulmonary nodules (Figure 2A), as well as hypervascular masses in the pancreas (6.2 × 5.9 × 4.6 cm) (Figure 2B), kidneys and bilateral adrenal glands (7.4 × 6.8 x 6.4 cm) (Figure 2C). Based on the hypervascular appearance of multiple lesions, a primary tumor of the kidney was suspected. This diagnosis was confirmed by a biopsy of one of the abdominal masses that proved to be a clear cell tumor of the kidney. The patient started treatment with systemic chemotherapy and developed febrile neutropenia. As a result of this latter condition, chemotherapy was discontinued at the end of the first cycle. Thirty days later, because of septic shock, he died of multiple organ failure.

DISCUSSION

This report, duly consented to by the study patient, demonstrates a case of multiple hematogenic metastases of renal clear cell carcinoma to various organs including the pancreas, adrenal glands, and kidney (Figure 2D, 2E). Clear cell carcinoma represents 80% of metastatic cases, and metastasis sites are often multiple[2] (Figure 3).

Lung metastases are responsible for 14% of all metastatic RCCs, thus representing the most common anatomical site of dissemination. They are asymptomatic in 90% of cases. The lesions are usually well circumscribed, rounded, and subpleural. Pancreatic metastases originating from any tumor are exceptionally rare. Pancreatic involvement in RCC metastasis accounts for only 0.25% to 3% of cases.[4] The diagnostic sensitivity

of US and CT for renal cell carcinoma is 79% and 94%.[1]

CT and MRI are essential in the monitoring of these patients. Imaging tests are crucial for the early diagnosis of metastasis.[5] The histological diagnosis of carcinomas is also of critical importance, as the histological subtype has significant prognostic and therapeutic implications.

CONCLUSION

Radiologists must be familiar with atypical presentations of metastatic renal tumors and include a differential diagnosis for renal cell carcinoma when imaging examinations reveal multiple chest and abdominal hypervascular lesions.

Conflict of interest: None.

Palavras-chave: Carcinoma de células renais. Metástase neoplásica. Diagnóstico tardio. Tomografia computadorizada por raios X. Histologia. Neoplasias de células epitelioides perivasculares.

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Blunt thoracic trauma with the formation of pseudoaneurysm with the junction of the right subclavian artery

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KEYWORDS: *Thoracic injuries. Subclavian artery, non-penetrating wounds.*

INTRODUCTION

A male, 27-year-old ambulating patient, assisted in the Emergency Medical Unit, complaining about pains in the anterior region of the cervicothoracic transition a few minutes ago. He reported that crashed into a car door when it was opened while riding a bicycle, causing an impact on right hemothorax, and falling to the ground. He denied prior comorbidities. At physical examination, it was noted a heart rate of 135 beats per minute, arterial pressure of 92/56 mmHg and respiratory frequency of 22 per minute; no hematoma, abrasions or puncturing and cutting wounds.

The Computed Tomography (CT) of the thorax was carried out, showing in the precontrast phase: mediastinal formation with soft tissue density and central region discreetly hyperdense with the junction of the right subclavian artery, discrete areas of ground-glass attenuations in both lungs, massive right hemothorax with passive pulmonary atelectasis partially ipsilateral (figures 1A and 1B). When administering the intravenous contrast media, the formation showed a filling-up, confirming a pseudoaneurysm of the right subclavian artery (figures 2A, 2B and 3A). No injuries were found.

During the assessments, the patients presented dyspnea and signs of hemodynamic instability. It was chosen the emergency surgical approach, evolving to a recent postoperative death.

Diagnosis: Blunt thoracic trauma with a mediastinal injury of great artery.

DISCUSSION

In traumas, the thorax is the third topography frequently affected (fatal at 20%), and it is secondary es-

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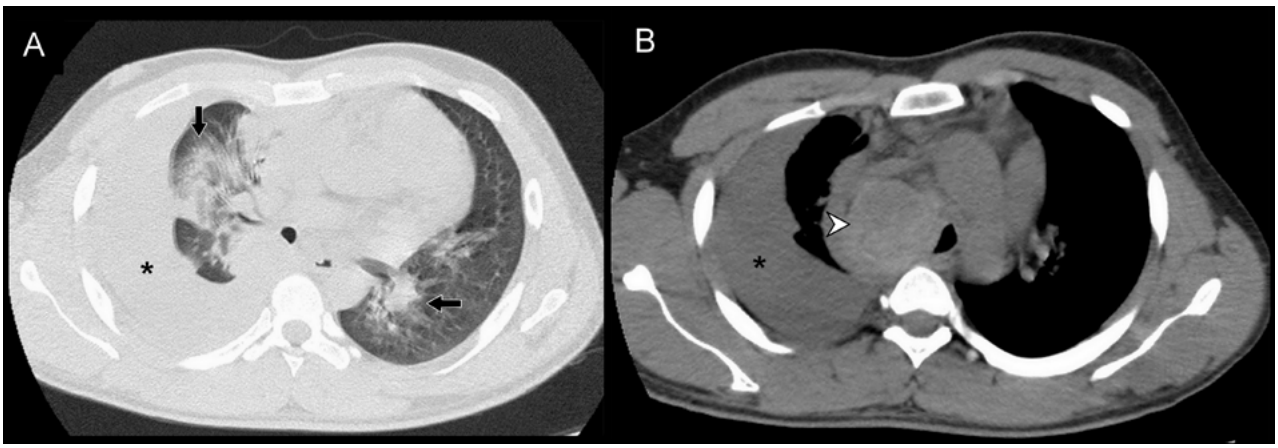

FIGURE 1. (A) High resolution axial tomographic section of the chest, pulmonary window showing discrete areas of ground-glass attenuation in both lungs (black arrows), massive right pleural effusion (*) with ipsilateral partial passive pulmonary atelectasis. (B) Axial tomographic section without venous contrast showing evidence of mediastinal formation with soft tissue density and central region discretely hyperdense (white arrowhead), measuring approximately 7.7 x 6.9 x 4.1 cm, determining contralateral mediastinal deviation and massive right pleural effusion (*).

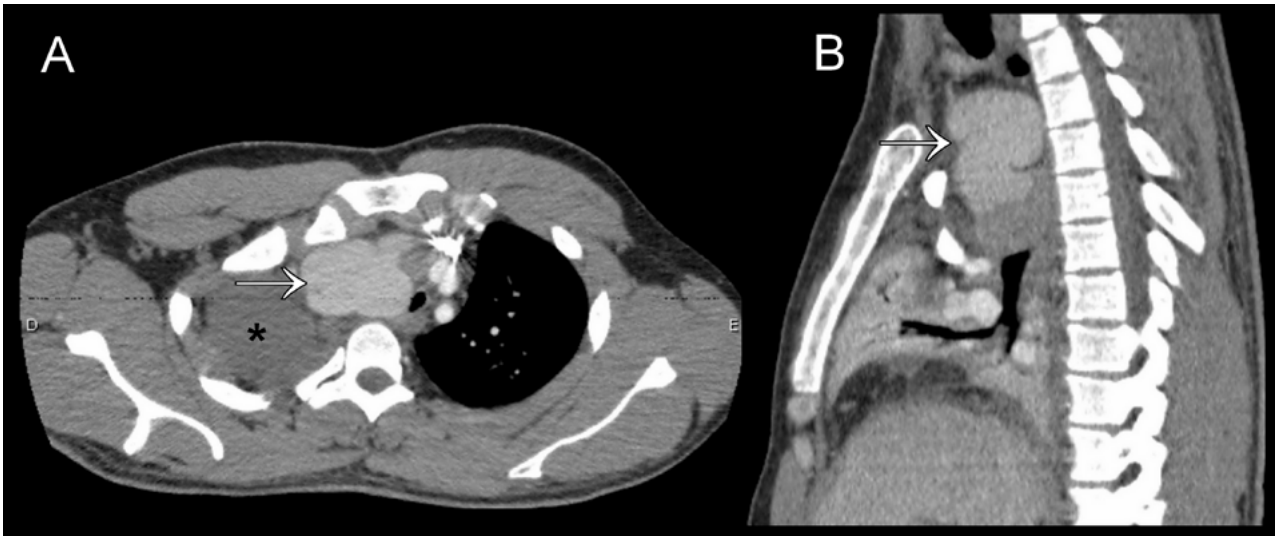

FIGURE 2. (C, D, E) Computed tomography imaging, axial (A) and sagittal (B) plans, demonstrating the filling of the formation by contrast after its intravenous administration (thin white arrow).

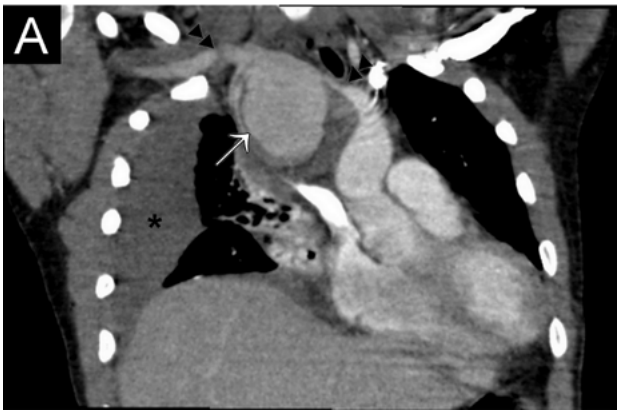

FIGURE 3. (A) Coronal tomographic reconstruction discretely oblique demonstrating the pseudoaneurysm filled by contrast after its intravenous administration (thin white arrow) and its intimate contact with the right subclavian artery (double black arrowhead).

pecially to automobile accidents (66%-85%), in which young men [1-4] are the victims

Classified in "penetrating" or "blunt", with a slight predominance of this second type. Some frequent changes: hemothorax, pneumothorax, pulmonary laceration-contusions injuries, herniations, tracheobronchial and diaphragmatic ruptures, esophageal and cardiac injuries, hematomas, pseudoaneurysms, ruptures and vascular dissections, fractures mainly of costal arches (if present in two or more sites of at least three ribs, it may be considered an "unstable thorax")[1,5,6].

In general, traumas involving aorta and great mediastinal vessels add approximately 5% of incidents; however, there is a high rate of mortality representing up to 15% of deaths in the automobile collisions. About 4/5 of patients with aortic injuries die before intra-hospital care with a rate of up to

90% of death after 14 days of those who survive[1-3].

The mechanisms of aortic injury and the junction of supra-aortic vessels involve pinchcock between the anterior thoracic wall and column; extension of neck and shoulder traction, respectively, with the action of sudden deceleration, traction, torsion, and hydrostatic forces[1,7].

The ascending aorta is rarely affected (5%) due to its anchorage, where the arterial ligament[1,2].

Pseudoaneurysms are very common in vascular wounds in this scope, characterized by hematic overflow by rupture of the layers in the arterial walls, organizing a hematoma in contact with the lumen, contained by adjacent and scar tissues[7,8].

The radiography has a sensitivity of 90% and specificity of 10% for vascular injuries in this context, highlighting the signs: enlargement of mediastinum, blurring of aortic contours, paratracheal thickening[1,4-6].

The angiography and CT are the best methods of assessment. CT has a predictive negative value of 100%, with the advantage of not being so invasive, direct view of injuries and other non-vascular injuries; however, the use of intravenous contrast injection is very important in detecting vessels injuries[1-5].

PALAVRAS-CHAVE: *Traumatismos torácicos. Artéria subclávia. Ferimentos não penetrantes.*

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How is cell proprioception related to cell growth and differentiation? Strong scientific evidence for future clinical activities

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INTRODUCTION

Why do cells care about physical stimuli?

Tissues are continuously subjected to the effects of different physical stimuli, with profound importance at clinical activities, and the interactions of these stimuli might affect cell development. We can observe different examples in the physical effects on cell growth, the results of gravitational force on the mineral status of bones, and the deficits in the mineral deposition in bones when the effects of gravity are absent. For example, astronauts can get osteoporosis after long periods in space, and the direct application of UVA improves skin healing in patients with psoriasis.

The spatial and temporal responses to physical phenomena are being investigated in detail to obtain in-depth knowledge of these responses and increase our understanding of the cellular nature and use of these physical elements to increase physiological responses, prevent pathological effects on the cell components and improve clinical activities in nursing, podiatry, physical therapy, and medicine among others [1].

How do cells respond to physical stimuli?

At the basic level, the cell occupies a known and limited volume and might receive physical stimuli anywhere in it. Knowledge of biology, chemistry, and physics indicates that physical stimuli can assist in the growth, differentiation, and proliferation of cells and aid our understanding of the mechanisms by which these cells die.

This idea can serve as a strong starting point but must then be transferred to the next level of organi-

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zation, which will promote the maintenance of tissue balance via physical stimuli to increase the health of tissues and organs and serve as a reliable tool for preventing pathology [2]. This concept will promote an exciting perspective for clinical professionals about these factors.

Similarly, when patients suffer an injury to an active tissue, such as a muscle-tendon unit or an articulation (e.g., an ankle sprain), one of the most important and useful techniques for promoting healing is known as perturbation training or proprioception. Proprioception is the process by which the body responds to incoming information about external forces by utilizing receptors and integrators to promote healing. These stimuli indicate that mechanoreceptors sense, integrate, and promote healing, and different responses are present in the muscle-tendon unit. We can translate this idea to the cellular level to observe how a cell responds via the strong actions of integrin to transfer physical stimuli and act as a local integrator that can generate different responses that develop into real cell proprioception that promotes healing and homeostasis at the cellular level. We propose that this complex mechanism should be defined as cell proprioception.

Moreover, the study of the relationship between the complex extracellular cell matrix (ECM) and stimuli is essential. An integrin-mediated mechanism can modify many cellular activities, such as cell-cell and cell-matrix interactions. There are other mechanosensors known to be important, such as GJS, cilium, and hemichannels.

Regarding integrins, these crucial elements can transfer mechanical stimuli from the matrix to the cytoskeleton through the formation of adhesion complexes. These complexes can redirect signal transductions (for example, via kinases) that influence the cytoskeleton and promote matrix remodelling[4]. This clinical approach is very interesting to handle clinical activities in all aggressive chemical and pharmacological cancer treatment approaches.

When we observe the action of the cytoskeleton, we can affirm that the behavior of the cytoskeleton is a crucial integrator[5]. This integration is mediated by the cytoskeleton tensegrity, which is led by two principal ideas. The first is structural self-remodeling. The second is the equilibrium between tensile and compressive forces (internal and external) that leads to the dynamic equilibrium that is so important for molecular changes[4-6]. The modification of passive cells and their neighbors by external stimuli alters cell-cell adhesion complexes [7]. Through such complexes, cells are joined to each other and the matrix to generate a dynamic system that is modified by stimuli at the cell level. We can understand the matrix as a controller of dynamic cell functions and behaviors and not only as the place where cells can be found.

Cells also use the physical characteristics of the ECM microenvironment to develop a traction-activated system that can influence both the cell and the ECM[8]. Therefore, we can appreciate the dynamic mechanical equilibrium between traction forces on the cell and the resistance points in the ECM, which generates a reciprocal isometric system of force [9].

Many studies have provided strong evidence about how the interactions and modifications of this dynamic equilibrium can promote tissue regeneration. First, ECM elasticity can lead pluripotential cells to different evolutions within the same basal conditions, and in such situations, the only differences are related to the biophysical characteristics of the ECM and its geometric development[10,11]. Homeostasis can be properly handled by clinicians to promote a better development of this cell interactions.

The difference in stiffness across different ECMs can be associated with the loss of filaments or actin microtubules[12]. This biophysical model suggests that the cytoskeleton is an essential target of stimulation factors. Therefore, influences on the cytoskeleton can affect and modify the geometry of cell distributions via influences on cell development. Recent studies have shown that modified cell geometries can alter cell signaling and function[13] and that modification to the cytoskeleton force can modify cell proliferation[14]. Therefore, distortions of cell shapes can lead to stem cell evolution: Human MSCs are differently regulated if they promote or restrict[15]. It is important to remember that integrin acts as an essential mechanosensor that is helped by other known mechanosensors, such as CJS or hemichannels[16].

Mechanotherapy that guides mechanotransduction signaling developments can be primarily targeted to control the following four processes [17]: (a) the mechano-coupling phase, the external physical stimuli is transformed into a mechanical signal; (b) biochemical coupling, in which the local signal is transduced into a biochemical signal; (c) signal transmission in which the signal is then passed from the signal biochemistry receptor cells to the effector

cells; and (d) the response of the effector cells. A recent study has reported on the control of the union of the external forces, and biochemical signaling networks spatial-mechanical regulation controls cell; the simple mechanical restriction of motion surface molecules can alter cell behavior.

Distinguishing the mechanisms of physical stimuli, gravitational force, and electromagnetic force

Multiple physical stimuli can work in a combined or straightforward manner on the cell interactions. It is important to know both the most profound nature of the cell and its characteristics and the most profound nature of the stimuli with which the cell interacts. By analyzing the different forces that can influence a cell, we can observe, at the most fundamental level, what appears to be the so-called fundamental forces – those forces are the forces of the universe that cannot be explained like other more basic forces. There are four of these fundamental forces: gravitational, electromagnetic, strong nuclear and weak nuclear. Clinicians can frequently use gravitational and electromagnetic forces to improve healing levels in patients The gravitational force is the attraction that is exerted on the subject matter and affects all bodies. Gravity is feeble and is a one-way force but is of infinite extent. At the cellular level, we can understand the force of gravity as existing between all cells; we could understand the gravitational force as externally inducing the active system of ECM-cell or cells. The electromagnetic force affects electrically charged bodies, and this force is involved in the physical and chemical transformations of the atoms and molecules. Molecules are located at the cell level before the organizational level. This force is much stronger than the gravitational force and has two meanings (positive and negative), with infinite range. Moreover, we can externally induce an electromagnetic field to influence the cell and the ECM-cell system. These physical effects are deeply known by clinicians, podiatry doctors, or physiotherapist.

The nuclear force or strong interaction is the component that holds atomic nuclei and acts interchangeably between any two nucleons, protons or neutrons. The scope of this force is on the order of nuclear dimensions, but it is stronger than the electromagnetic force.

The nuclear force or weak interaction is responsible for the beta decay of neutrons; neutrinos are only sensitive to this type of interaction. The intensity of this force is lower than that of the electromagnetic force, and its range is even smaller than the strong nuclear interaction. Everything that happens in the universe and therefore in the cell is due to the action of one or more of these forces, whether alone or combined, and these forces differ from each other in that each involves the exchange of different particle types. These particle exchanges are denominated or intermediary. All exchanged particles are bosons, while the interaction source particles are fermions. Currently, scientists are attempting to prove that all of these apparently different fundamental forces are manifestations of a single mode of interaction in different circumstances. There are various theories. The term "unified field theory" encompasses new theories in which two or more of the four fundamental forces appear as if they are basically identical. The theory of everything is another unified field theory that aims to provide a unified description of the four fundamental forces. Currently, the best candidate to become a theory of everything is superstring theory.

Physical stimuli might promote important cell effects; therefore, we can transfer it to clinical fields to influence and change the associated biological processes. Physical stimuli are essential for obtaining tissue homeostasis and common clinical treatments. It can lead to and help the cells to check and modify their behavior for a new relationship with new and altered environmental conditions. Consequently, a strong candidate for inducing optimal regeneration, promoting homeostasis and promoting the cell repair process is the contribution of physical stimuli in a controlled and correct manner. The most essential elementary forces studied enable us to externally induce cell and ECM-cell complexes regarding gravitational and electromagnetic forces, which we will describe below. These physical effects are deeply known by clinicians, podiatry doctors or physiotherapist.

GRAVITATIONAL FORCE

The influence of gravity as a direct mechanical vector in leading cell processes has a crucial historical antecedent. Galileo studied how bone modification is associated with vector components and their influences. The papers of Rubin and Ingber are strongly knowledgeable [18-20]. Cells are subject to the effects of several physical stimuli that are caused by among

other things, gait, posture, and respiration, and generate different possibilities. It has been shown that changes in standard components can modify cell complexes in important manners. Cells can receive stimuli that are moved through membrane receptors and are transferred to the cell cytoskeleton to the ECM and other cells. These factors modify the ECM mechanistic behavior and cell shape [20]. The extracellular matrix is an essential elastic structure that is continuously renewed, particularly concerning the cell environment. The ECM is associated with cells that offer relevant information and physical stimuli factor into the structural and external forces [21]. Stimulus factors change ECM homeostasis; e.g., physical stimuli help to control the production of ECM components through, for example, the activation of intracellular signaling pathways [22].

The in vitro test of different cells with different physical stimuli, such as mechanical stretch, simulate the mechanical action of heart cells, which exhibit morphological activations that are similar to those that occur during heart growth [15,23]. It is important to remember that internal and external stimuli can influence cell shape and that recent trials have demonstrated that cell shape can lead to apoptosis and different cell actions such as gene expression and protein synthesis [24]. Simulations of the effects of gravity, pairs of real gravity and modeling of gravity with random positioning machines (RPMs) could be difficult for the cellular organization and ECM creation in immature cartilage[25]. Different studies have shown how gravitational effects, after 72 h of microgravity exposure, result in cytoskeletal reorganization, and the important osteoclastic markers of nuclear factor kappa-B and receptor activator of nuclear factor kappa-B ligand are solidly augmented to affect the ability of bone reabsorption[26]. These studies, in concordance with other authors [27,28], promote the notion that mechanical or gravitational stimuli influence osteoblastic differentiation.

In contrast, gravitational effects and decreases in mechanical stimuli cause osteoclastogenesis and bone tissue resorption or modifications of laminin and fibronectin production by fibroblasts [29]. These modifications of fibronectin might be the cause of altered wound-healing responses [30,31]

In contrast, following controlled hypergravity exposure (10x*g*), we did not find significant changes in cell metabolism or cell anatomy. Findings have been published that state that hypergravity effects maintain endothelial cell survival and the actions of the activation of adaptive characters [32].

For example, in 1997, Chen *et al.* [33] developed a trial using mechanical stimuli and obtained significant improvements and differentiation of human endothelial cells. Later, Chiquet *et al.* [34] used mechanical stress mediated by stretching with 5 to 15% elongation and a frequency of 0,3 a 1 Hz and observed an increase in extracellular matrix components (mainly tenascin C). In 2006, Park *et al.* [35] also used stretching as mechanical stimuli with a frequency of 0,5 Hz and 8% intensity in fibroblasts and found that obtaining a cell growth and proliferation as well as collagen. In 2007, Vatsa *et al.* [36] developed mechanical stress microneedles into osteocytes by increasing the regulation of NO-stimulated cell growth. In 2008, Monici *et al.* [37] developed a stress stimulus with hypergravity and generated 10 min cycles of 10 g with 10 min of recovery at 1 g in human mesenchymal cells and obtained an overexpression of genes related to osteoblastogenesis. In 2011, Chan *et al.* [38] conducted a study on the compressive mechanical effects ranging from 5 to 20% with a frequency of 0.15 at 1 Hz and a duration of 1-12 h/day at a hydrostatic pressure of 0, 1 to 10 MPa and held on intervertebral discs and stem cells. These authors found that phenotypic therein affects discogenic differentiation. Grad *et al.* [39] developed a mechanical stimulus with uniaxial and multiaxial loadings of 7 to 10 MPa of stress in chondrogenic cells and observed that a regulation of the chondrogenic patterns. In 2011, Maul *et al.* [40] performed mesenchymal stem cell stimulation via mechanical stretch stimuli at 5% with a frequency of 1 Hz and increased the expression of the same.

Electromagnetic force

In the ancient times of the first century AD, we found proof of the use of electric fish to treat a headache. In the 15th century AD, Paracelsus studied the medical use of electricity, and later Digby described the use of the magnetic field in wound treatment. Then, Galvani led the ideas for actual research lines related to physiological electromagnetic fields and their effects.

In the last four decades, in-depth knowledge has been acquired related to the understanding of bioelectricity effects; changes in electrical membrane potentials of the living have been shown to result in modifications of potential gradients that have been associated with morphogenetic changes[41]. Thus, many physiological events have been localized to the

critical tool-signals for processes in development[42].

An in-depth and consistent analysis of the electrical and magnetic implications of cell biology is shown in a paper written by Funk *et al.* [43]. This paper demonstrated the association between physical stimuli and cell biology integration processes. EMFs can influence the polarization of bound charges, the orientation of dipoles, the diffusion of charges, ion-channel and receptor modifications, conformational modifications of voltage-sensitive enzymes and essential modifications of membrane phospholipids with different activation kinetics of the ion channels[43].

The modifications of EMFs created by living tissues are generated by different physiological activities; for example, muscle contraction is known for the existence of vibrations of muscles that promote direct mechanical strain and currents via both posture (5–30 Hz) and gait (<10 Hz) and have been studied [44]. Muscle contractions generate bone tissue EMFs, which are essential for maintaining bone homeostasis. Bone cells are particularly sensitive to low frequencies (in the range of 15 to 30 Hz). In this range, electromagnetic fields of 0.01 mV/cm aid bone remodeling[18,19]. It has been found that the EM activation produced by mechanical loading (1 Hz during walking) in bone promotes the range of 0.1–1.0 mA/cm2[45]. In general terms, physiologically endogenous EMFs are characterized by low frequencies (ELF) from 0 to 300 Hz and low intensity.

EMFs field interventions are frequently used in the treatment of musculoskeletal disorders, and many studies have indicated that the most effective applications are associated with pulsed EMFs in the range of 1 to 100 Hz; this range promotes EF on the order of μV/cm[46]. Thus, physiological benefits may be induced by low-frequencies and -amplitude EMFs (range 8-60 Hz) [44]. It has been shown that pulsed EMFs can stimulate osteoblastic differentiation and proliferation or inhibit osteoclastogenesis, and both of these bone processes are important to bone homeostasis [47,48].

Recent trials have shown the possibility of applying EMFs to promote ligament healing processes and repair and aiding ligament homeostasis after a pulsed EMF stimulates fibroblasts to improve migration speed and enhance collagen I expression. Ligaments and tendons are similar in their healing processes, and tendon can be favored by pulsed EMFs.

Conversely, static EMFs slow the wound healing process. In contrast, pulsed EMFs can improve this process[49]. We affirm that EMFs modulate cell proliferation, and both of the EMF components of intensity and frequency are fundamental in the final effect. Regarding magnetism, Kwee *et al.*[50] showed an increase in human fibroblast proliferation following exposure to 0.08 mT. Kula *et al.*[51] demonstrated an inhibition of cell growth in fibroblasts exposed to 20 mT. Different trials that have been performed by exposing different cultures have shown different effects (i.e., increases, decreases or no effect) that are intensity-dependent[52].

Regarding frequency, many authors have shown significant increases in the proliferation of different cell types at a rate of 50 Hz[53]. Several trials have designated the interaction between EMFs and calcium fluxes because calcium is an essential regulator of many cellular processes and leads to the activation of the cyclic AMP, which is a crucial trigger molecule in intracellular metabolic processes. It has been shown that EMFs can modify calcium concentrations in different ways that depend on cell type and field intensity[54].

The effects of EMFs on cell differentiation have also been intensely studied. A progressive inhibition of enzyme activity and differentiation in osteoblasts that follows exposure to 30 Hz EMF was described by McLeod and Collazo[55]. In cultures exposed to EMFs during chondrogenic differentiation, it has been observed that collagen II and glycosaminoglycan increase[48]. Therefore, EMFs might be a way to promote and maintain chondrogenesis and to illustrate new steps in regenerative treatment for cartilage.

Preliminary experiments have shown the effect of pulsed EMFs on the role of fibroblasts in wound healing and aligned with other authors[57]. EMFs can influence the acceleration or slowing of the migration of fibroblasts, depending on the properties of the applied field. The possibility of modulating fibroblast migration during wound healing could be very interesting. Indeed, this possibility might be useful for enhancing the migration of fibroblasts to promote wound healing in chronic ulcers and general cases in which healing is slow. Inhibiting migration would be beneficial for preventing the formation of dysfunctional scars.

In 1993, McLeod and Rubin[45] assessed the effects of pulses of 15 to 30 Hz with a characteristic of 0.01 mV/cm on bone cells with the goal of improving remodeling activity. In 1995, Kwee & Raskmark [50] con-

ducted a study of human fibroblast proliferation in an electromagnetic field of 50 Hz with an intensity of 25-180 microtesla and found an increase in cell proliferation. In 2002, Harting *et al.* [47] conducted a study of an electric field of 100 v to 16 Hz in osteoblastic cells and found proliferation, increased expression of alkaline phosphatase and an improvement in the production of extracellular matrix synthesis. In 2004, Chang *et al.*[48] appreciated the effects of an electromagnetic field with a frequency of 15 Hz and an intensity of 0.1 mT on osteoblastic populations and found an increase in osteoblast proliferation. In 2010, Mayer-Wagner *et al.* [56] studied the effect of electromagnetic fields with frequencies of 15 Hz and intensities of 5 MT on mesenchymal cells and found an increased production of type II collagen and glycosaminoglycans during chondrogenic differentiation.

CONCLUDING THOUGHTS

Interaction of cell-physical stimuli

The cell continuously receives physical stimuli, and these stimuli can directly influence the future evolution of the cell. Different characteristics of the physical quantities are of great interest in defining and meeting their influence on cells.

1. The theory of the right stimulus. The first principle of cell proprioception.

a) The quality of the nature of the physical stimuli, either scalar or vector, must be appropriate for each cell type and each time in different cell cycles in which it is to generate a favorable effect on the development and/or cell differentiation thereof if no adequate quality can have a negative impact on their differentiation and/or development or have a neutral effect.

b) The amount of the physical stimuli, either scalar or vector, must be appropriate for each cell type and for each different cell cycle in which it is to generate a beneficial effect on the development and/or differentiation time if no adequate quality can have a negative impact on their differentiation and/or development or have a neutral effect.

c) The temporal components of physical stimuli, such as frequency and duration that interact with the cell must be appropriate for each cell type and for each different cell cycle in which it is to generate a beneficial effect on the development and/or differentiation time. If the temporal component is not adequate, it might have a negative effect on their differentiation and/or development or have a neutral effect.

d) The spatial components of the physical stimuli that interact with the cell and the cellular environment must be appropriate for each cell type and for each different cell cycle in which it is to generate a beneficial effect on the development and/or differentiation, if the spatial component is not adequate may have a negative effect on their differentiation and/or development or have a neutral effect,

2. The theory of right equivalent stimulus. The second principle of cell proprioception.

a. Two physical stimuli generating an effect equivalent to a third stimulus effect are equivalent among themselves.

b. If the sum of the effects of physical stimuli that interact are equal to the sum of other different physical stimuli that interact with one another, the resulting stimulus is equivalent to both interactions.

c. If two physical stimuli of different natures produce the same effect; they are equivalent.

d. The sum of the effects of different physical stimuli is different from the sum of the separate parts due to the interference of the same.

PALAVRAS CHAVE: *Biofísica. Estresse mecânico. Biologia celular. Saúde.*

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Use of probiotics in atopic dermatitis

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SUMMARY

Atopic dermatitis is a common skin disease. Its increased incidence has changed the focus of research on atopic dermatitis toward epidemiology, prevention, and treatment. Evidence suggests that intestinal microbiota plays an important role in the pathogenesis of atopic dermatitis inducing immunosuppression, but its exact mechanism is still unclear. Probiotics have been widely reported to act on the immune system. They are living microorganisms with immunomodulatory effects that stimulate Th1 cytokines and suppress the Th2 response, which are being researched for the treatment of several diseases. Probiotics most commonly used are part of the intestinal microflora like lactobacilli, bifidobacteria, and enterococci. We describe here a case of evident response to the use of probiotics in a girl with severe atopic dermatitis, with a significant change in severity scores of atopic dermatitis (BSA/SCORAD/FDLQI). Modulation of the intestinal microbiota with probiotics may offer a way to prevent or treat allergic diseases, including atopic dermatitis.

KEYWORDS: *Allerg. Atopic dermatitis. Inflammation. Intestinal microbiota. Probiotics.*

INTRODUCTION

About a century ago, Metchnikoff first hypothesized that some intestinal bacteria "produce compounds useful against premature aging". Since then, studies progressed, leading to a remarkable improvement of the knowledge about the role of intestinal micro-organisms[1], in several areas of medicine. Many studies on the pathogenesis of allergy continue to show the importance of commensal gastrointestinal tract bacteria in the stimulation and targeting of the immune system[2].

The gut of newborns is sterile and is gradually colonized by environmental bacteria. There is a known difference between children born of vaginal delivery and cesarean section. In the cesarean section, there is a delay in the colonization of *bifidobacteria, lactobacilli*, and *bacterioids* in the gut. After this initial colonization phase, the type of feeding will influence the maintenance of the flora, so breastfed children will have higher growth and activity of *bifidobacteria* and *lactobacillus* than those fed with formula[2].

There is an increasing number of children with allergies; in 1950 the prevalence of allergic symptoms in developed countries was 5% and now is about 40%[2]. Epidemiological studies show that a higher incidence of gastrointestinal tract infections is associated with a lower prevalence of allergies[2]. A defect in the early stimulation of TH1 cells is related to the development of allergic diseases[2].

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, and its prevalence is also growing[3-5].

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There is a known genetic cause for AD, but it alone does not explain this increasing prevalence[5]. So, AD is considered a multifactorial disease with genetic, epigenetic, developmental and environmental factors associated with its presentation[5].

A mechanism involved in the pathogenesis of AD is the decrease in regulatory T cells (Treg), which are crucial regulators of the immune response[6]. It is already known that an imbalance in the activation of TH1/TH2 cytokines is implicated in the development of AD[6] and, increasing evidence suggests that intestinal microbiota play an important role in immune system regulation[7]. Pathogenesis of AD is complex and microbial exposures early in life proved to be protective against it[5]. Knowing that differences in intestinal microbiota composition have been found in AD and have been implicated in its triggering[4].

Another mechanism involved in AD is dysfunction in the skin barrier. Barrier defects in AD also seem to affect the intestinal mucosa, also the composition of the intestinal microflora is different in AD patients. In AD the barrier is impaired, not only in the skin but also in the intestinal mucosa, causing the transfer of exogenous antigens. In this matter, *Lactobacillus paracasei* was found to speed barrier function recovery[6].

The use of probiotics has been researched for the treatment of several diseases, including in dermatology. However, the results of the studies have been controversial[8].

Probiotics are live microorganisms with immunomodulatory effects and have a beneficial action on the hosts' health by changing immune response, competing with harmful gut flora, toxins, and host products, thus improving gut barrier function[5].

The most commonly used organisms are *lactobacill*us *bifidobacterium* and *enterococci*[6], and it is known that each strain has a specific immunomodulatory function, producing pro and anti-inflammatory cytokines[5].

Probiotics mimic Th1 cytokines and suppress the Th2 response[8]. They also act on Tregs, which regulates the immune response, showing an inversely correlated level with immunoglobulin E (IgE), eosinophilia, and interferon-gamma (IFN-γ)[6], so Tregs diminishes the inflammatory pathway. Also, some of them demonstrated the ability to accelerate the recovery of the skin barrier function[6].

What is expected is that if the colonies of probiotics administered successfully colonize the gut, the flora change could modulate the immune response both locally and systemically[5].

We report the use of probiotics in a patient with severe AD with excellent response.

CASE

Female patient, phototype two, 18 months of age, brought by the father, who related a previous history of classic atopic dermatitis with occasional cheilitis. Also referred episodes of wheezing and rhinorrhea started 8 months before, after hospitalization for adenovirus-related bronchiolitis.

She had already consulted with several dermatologists, had been using emollient after bath and mometasone cream two times a day on the lesions.

Physical examination showed xerosis, Dennie-Morgan double fold and areas of erythema and lichenification in the antecubital fossae (Figure 1), abdomen (Figure 2) and legs. Scoring atopic dermatitis index (SCORAD) was 60.15[3], Body surface area (BSA) with lesions was 60% and Family Dermatology Life Quality Index (FDLQI) was 18. IgE was 140 kU/L (normal <60 kU/L).

Treatment with probiotics (*Bifidobacterium lactis* HN019, *Lactobacillus acidophilus* NCFM, *Lactobacillus rhamnosus* HN001, *Lactobacillus paracasei* LPC-37) once a day was started with the maintenance of mometasone once a day and moisturizer after the bath. The patient returned after 2 weeks with significant improvement of the lesions (Figure 3). Physical exam showed no areas of erythema and complete resolution of the lesions. SCORAD was 4.95, BSA was 5%, and FDLQI was 8. The girl remains in follow-up, using probiotics for 12 months, maintaining the clinical improvement.

DISCUSSION

Atopic dermatitis is an immune disorder that is becoming increasingly prevalent throughout the world[3,4]. It is a common, chronic, and refractory skin disease that manifests as eczema and pruritus with repeated exacerbations and regressions. The exact etiology of this disease remains unknown, and a cure is not currently available[3,4]. A lot has been said now about the hygiene hypothesis in the origin of DA and allergic diseases[5].

Healthy gut flora includes more than 400 species[5], and various non-pathogenic microorganisms

FIGURE 1: LICHENIFIED PLAQUES WHIT ERYTHEMA IN THE ANTECUBITAL FOSSAE

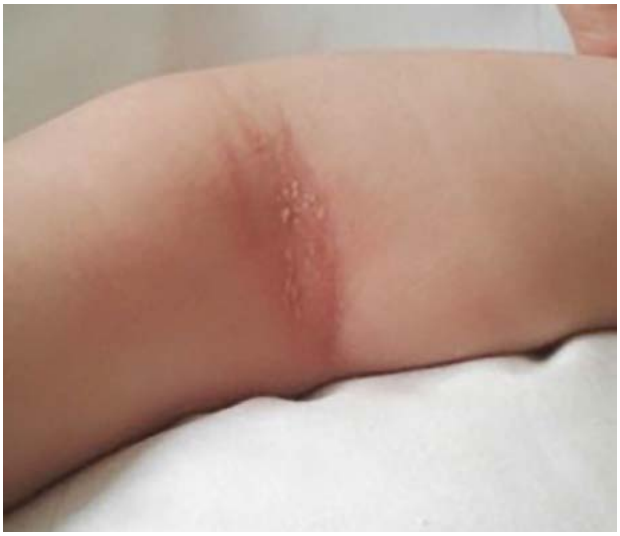


FIGURE 2: ERYTHEMATOUS PLAQUES IN THE ABDOMEN

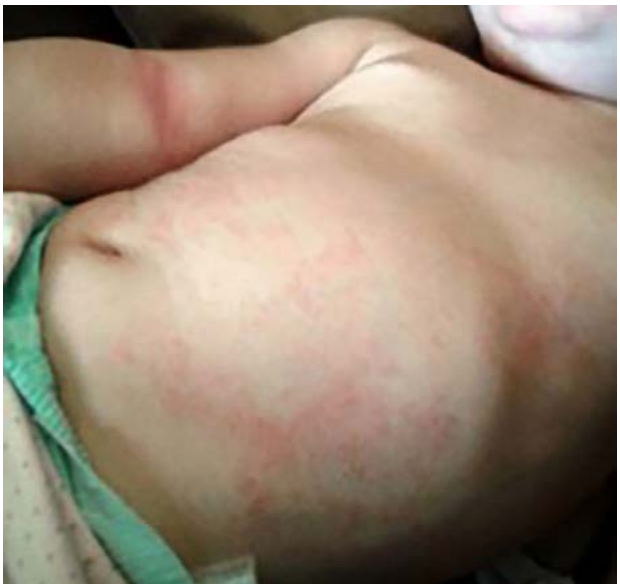
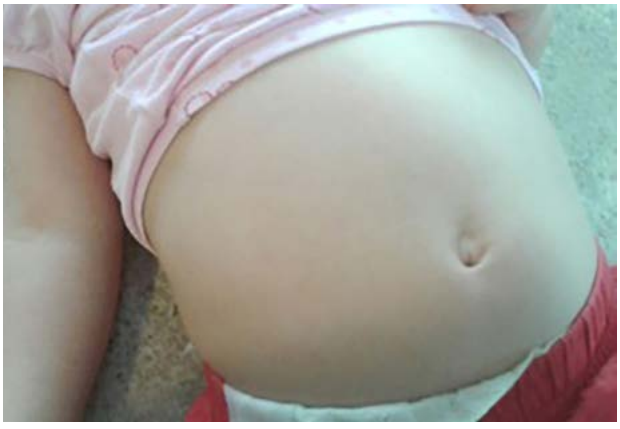


FIGURE 3: SKIN AFTER TREATMENT



lead to the establishment of protective immunity against allergic disorders as the intestinal immune system comprises the most substantial portion of the overall immune system and remains exposed to intestinal bacteria[8].

The stimulation by commensal bacteria of the gut during the early life is essential for the targeting of regulatory cells[2]. Infants with AD or other allergic diseases show less frequent intestinal colonization by *Lactobacillus* or *Bifidobacterium*, which is expected in healthy individuals, and more by *Clostridium* or *Staphylococcus* when compared to non-allergic infants[5].

The use of substances that acts in this path of the immune system is of great interest. Pro and prebiotics do this.

Prebiotics are non-digestible substances that benefit the host by selectively stimulating the growth or activity of a specific group of intestinal bacteria[2].

Probiotics are defined as non-digestible oligosaccharides, live microbial food supplements that provide benefits when administered in adequate way[8]. They selectively stimulate the growth of certain bacteria in the large intestine, thus producing a probiotic effect[6].

Probiotics are useful in balancing gut microecology, restoring intestinal permeability, improving immunological gut barrier function and diminishing pro-inflammatory cytokines production[8]. They selectively stimulate the growth of certain bacteria in the large intestine, improving the bioavailability of calcium, reducing the development of precancerous lesions in the colon and inflammation of the mucosa in various gastrointestinal disorders[8].

Probiotics have been used for centuries and have demonstrated a very safe profile as they are widely used in premature infants to prevent necrotizing enterocolitis and in immunosuppressed patients and patients undergoing chemotherapy or radiation to prevent and treat diarrhea[8].

Individual response to probiotics is determined by the probiotic strain and dose, by the person's genetic background, lifestyle, diet, and resident microbiota[4]. Also, different strains of probiotics act in different inflammatory mediators paths.

The use of probiotics in dermatology is still incipient. Its applicability in AD is an open topic with controversial results[9]. It is already known that exposure to certain microbes early in life may influence the development of atopy[9], as exposure and lack of exposure to certain microorganisms during early childhood alter the immune status toward the develop-

ment of allergic diseases[10]. Also, it has been observed that the gut microflora of atopic children presents a reduced neonatal *bifidobacteria* to *clostridia ratio*[8].

Probiotics have already been used in several dermatological diseases[8], including acne and AD, however, whether probiotics have a therapeutic effect on AD is still in question[4] as studies on the use of probiotics on AD are small and heterogeneous[6].

Lee *et al.*[11] say that there is good evidence for the use of probiotics in prevention but not yet in the treatment of AD. Pre and postnatal use may reduce up to 61% the development of pediatric atopic dermatitis (PAD).

Wang and Wang[4] found that exposure to these organisms is an effective intervention to reduce the severity of AD and improve quality of life of patients, with an implication in measures of some serum cytokine levels, urine oxidative stress biomarker, and fecal microbiota. They found that probiotics suppresses the Th2 response and IL-4, IL-5, and IL-13 cytokines production, and increase IL-10 and TGF-b levels by inducing Treg cells function[4]. Also, the reaction to probiotics has been found in IgE-associated and non-IgE-associated AD[4]. It is known that these bacteria and their function persist at least 6 months after cessation of supplementation[5].

Yang *et al.*[5] made a double-blind, randomized trial with 100 children and found no statistical difference between the group who used probiotics and placebo. The study showed that there was intestinal colonization but not a different immune modulation between cases and controls. These authors say that studies do not reflect the real world exposure to probiotics species, the action of combined species and the effect of one probiotic over another[5].

Research of Pandurur *et al.*[12] found that probiotics seem to have a protective role in AD prevention if administered in pre and postnatal period in both general and allergic risk population. Administration of probiotics in early life may have a role in the prevention of atopic sensitization[12], even though it seems to be more effective in severe cases of AD[13].

The cutoff point suggested for evaluation of treatment efficacy is 15 Scorad change, since 11 is considered a normal range fluctuation in AD [11]. Also, treatment studies should take into account the sensitization of the host, for example to milk allergy [11].

The group also suggests the identification of PAD as dependent or independent IgE beyond the definition of severity. Probiotics must meet the criteria of the European Union for research: Human origin; Non-pathogenic behavior even in immunocompromised patients; Resistant to technological processes; Resistant to gastric acid and bile; Adherent to the intestinal epithelium and persistent for some period in gut; Able to produce antimicrobial substances and modulate immune system; Able to influence on metabolic activities[11].

Other confounding factors in probiotics researches are the use of topical corticosteroids, elimination diets, and antibiotic use concomitantly. So a two-week washout period is suggested[11]. Yang *et al.*[5] say that fermented foods should also be excluded from studies to avoid confounding factors. Betsi *et al.*[14] indicate SCORAD should be assessed by two physicians independently to reduce bias.

CONCLUSIONS

We describe here a case of evident response to the use of probiotics in a girl with severe AD, with significant change in severity scores of atopic dermatitis (BSA/SCORAD/FDLQI).

AD has a complex multifactorial pathogenesis pathway. Modulation of the intestinal microbiota with probiotics may offer a way to prevent or treat allergic diseases such as AD.

We have the informed consent of the parents.

RESUMO

A dermatite atópica é uma doença de pele comum. O aumento da incidência mudou o foco da pesquisa em dermatite atópica para epidemiologia, prevenção e tratamento. Evidências sugerem que a microbiota intestinal desempenha um papel importante na patogênese da dermatite atópica, induzindo imunossupressão, mas o mecanismo exato ainda não está claro. Os probióticos foram amplamente divulgados para atuar no sistema imunológico. Eles são microrganismos vivos com efeitos imunomoduladores que estimulam as citocinas Th1 e suprimem a resposta Th2 que vem sendo pesquisada para o tratamento de diversas doenças. Probióticos mais comumente usados são parte da microflora intestinal como lactobacilos, bifidobactérias e enterococos. Descrevemos um caso de resposta evidente ao uso de probióticos em uma menina com dermatite atópica grave, com grande alteração nos escores de gravidade da dermatite atópica (BSA/Scorad/FDLQI). A modulação da microbiota intestinal com probióticos pode oferecer uma maneira de prevenir ou tratar doenças alérgicas, incluindo a dermatite atópica.

PALAVRAS-CHAVE: *Alergia. Dermatite atópica. Inflamação. Microbiota intestinal. Probióticos.*

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ORIGINAL ARTICLE

Endoscopic full-thickness resection for gastric gastrointestinal stromal tumor originating from the muscularis propria

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SUMMARY

OBJECTIVE: *This study retrospectively reviewed 46 cases of gastric gastrointestinal stromal tumors treated by endoluminal endoscopic full-thickness resection (EFR) microsurgery in our gastrointestinal endoscopy center. We aimed to evaluate the EFR for the treatment of gastric gastrointestinal stromal tumors originating from the muscularis propria.*

METHODS: *A total of 46 patients with gastric gastrointestinal stromal tumors originated from the muscularis propria layer from January 2012 to June 2015 were treated with EFR. The patients were followed up with gastroscope and computed tomography (CT) for evaluation of therapeutic effect and safety.*

RESULTS: *EFR was successfully accomplished to remove all tumors in 46 patients. The mean procedure time was 82.5±39.8min (56-188min). Except in 3 leiomyomas, pathological examination confirmed gastrointestinal stromal tumor (GIST) in 43 cases. None of the patients had occurred bleeding, peritonitis and other complications after EFR. Thereafter, all patients were followed up with gastroscope after 1, 6, 12 months.*

CONCLUSIONS: *EFR is effective and safe for patients with gastric gastrointestinal stromal tumors originated from muscularis propria layer and has the advantage of less invasive treatment and higher tumor resection rate. It should be considered for further application.*

KEYWORDS: *Gastrointestinal neoplasms. Gastrointestinal stromal tumors. Neoplasms, connective tissue. Stromal cells. Gastrectomy. Gastroscopy. Laparoscopy.*

INTRODUCTION

The gastric submucosal tumor less than 3cm in most benign tumors, but gastrointestinal stromal tumor (GIST) currently regarded as a potentially malignant tumor. Stromal tumors arising from the muscularis propria are located in deeper layers, especially those that do not grow within cavities[1]. The main treatment is complete tumor resection[1-3]. Recently, endoscopic full-thickness resection (EFR) has been applied as a treatment for gastrointestinal submucosal tumors (SMTs).

We used EFR for complete resection of gastric gastrointestinal stromal tumors from the muscularis propria and have summarized the effect of treatment.

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MATERIAL AND METHODS

Patients

From January 2012 to June 2015, 46 cases of gastric gastrointestinal stromal tumors, originating from the muscularis propria layer, were confirmed by endoscopic ultrasound (EUS) and computed tomography (CT) at The Affiliated Yantai Yuhuangding Hospital of Qingdao University. No metastasis of gastric gastrointestinal stromal tumors was found. The patients consisted of 21 males and 25 females at ages 23–65 years (median age 47.6±13.2 years). All the cases were single occurrences. The tumors were 1.2–4.5cm in size and located in the fundus (n = 36), the gastric corpus (n = 9), the gastric antrum (n = 1). Each patient's written informed consent was obtained. This retrospective study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University.

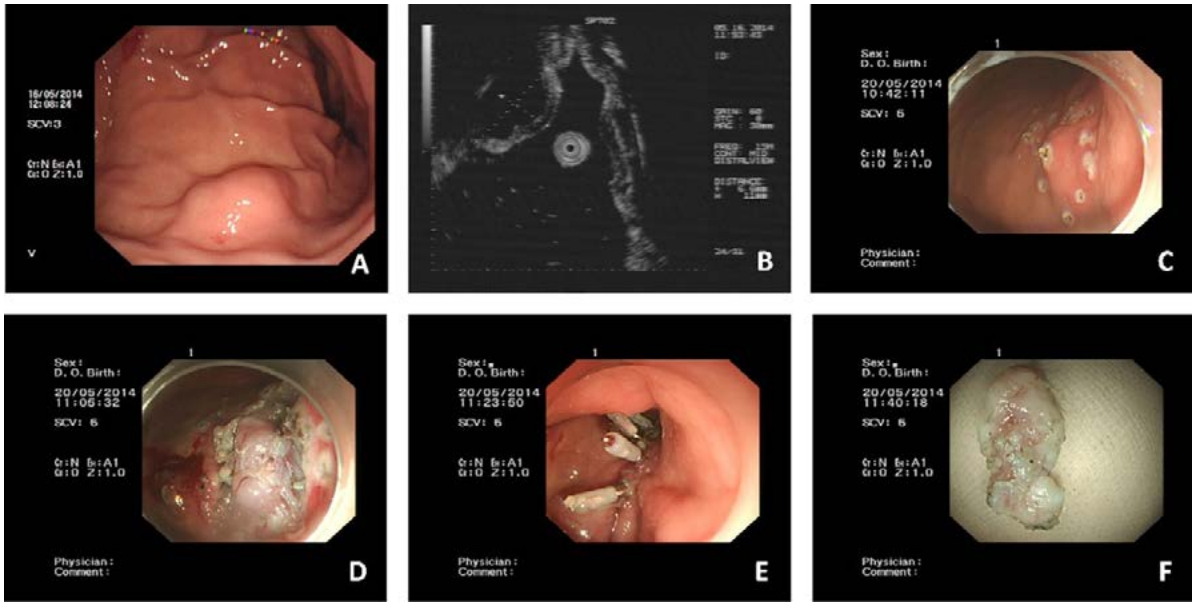
Instruments

We selected these instruments to extend our previous study[4,5]. The following instruments were used: Electronic gastroscope (Olympus GIF-Q260J, Olympus company, Japan), hyaline cap (D-201-11304, Olympus company, Japan), spiculiform cutting knife (KD-1 L-1, Olympus company, Japan), IT knife (KD-611 L, Olympus company, Japan), hook knife (KD-620 LR, Olympus company, Japan), injection needle (NM-200 L-0525, Olympus company, Japan), snare (AS-1-S, ASJ-1-S, COOK company, United States), hot biopsy forceps (FD-410 LR, Olympus company, Japan), hemostatic clip (HX-610-90, Olympus company, Japan; HX-600-135, Olympus company, Japan; Boston Resolution™, Boston company, United States), high frequency electric knife (ERBE VIO 200S, ERBE company, Germany) and, Argon Plasma Coagulation instrument (ERBE APC2, ERBE company, Germany).

EFR Method

EFR method was done as previously described[4,5]. Pneumoperitoneum will happen inevitably as gas will spill into the abdominal cavity in the process of tumor resection and suture of gastric defects in if EFR full-thickness resection of gastrointestinal mucosa lead to gastric perforation, the used of CO2 in solution in water can reduce postoperative abdominal distension. The key to successful treatment of EFR is the endoscopic therapeutic perforation occurred as a mend. Under endoscopic guidance, the incisions on the gastric body from the two ends to the middle were fully closed with titanium clips, and the gastric wound was sealed. For wounds that were too large to seal directly, negative pressure was applied to suck the omentum into the gastric cavity, and the titanium clips were used to seal the wound by clipping the omentum to the gastric mucosa (Figure 1). When the serosa was cut all

FIGURE 1: PROCESSES OF EFR FOR GIST ORIGINATED FROM MUSCULARIS PROPRIA.



(A) Protruding submucosal lesion in the gastric body. **(B)** Endoscopic ultrasound showing that the lesion arose from the muscularis propria. **(C)** Endoscopic view of the submucosal tumor and labeling margins with argon plasma coagulation. **(D)** Application of the IT knife to isolate the stromal tumor along its periphery. **(E)** Sealing of a perforation with multiple titanium clips. **(F)** Resected tumor with the mucosa removed

around the GIST tumor, the lesion can fall within the peritoneal cavity. For tumors larger than 4 cm, we use double-channel gastroscope to avoid that.

Sample processing

Post-EFR pathological diagnosis was made by focusing on cell types. The immunohistochemical tests for CD34, CD117, Dog-1, S-100, and SMA. Mitotic counts per 50 highpower fields were evaluated in GISTs.

Postoperative treatment

After EFR surgery, a gastrointestinal decompression drainage tube was placed. Postoperative medication included nothing perorally, gastrointestinal decompression drainage for 24 hours, and drug therapy, such as a proton pump inhibitor and broad-spectrum antibiotic intravenous administration, for 3 days. Patients were discharged with proton pump inhibitor therapy for 2 months.

Statistical analysis

Statistical analysis was performed with SPSS for Windows Version 17.0 software (SPSS Inc., Chicago, IL, USA). Data were analyzed using the two-tailed Student's *t* test. $P < 0.05$ was considered significant. Data are expressed as mean ± standard error of the mean (SEM).

RESULTS

Clinicopathological characteristics and outcomes of EFR are summarized in Table I. Among all enrolled patients, 46 tumors were located in the gastric fundus with 36 cases, 9 cases were in the gastric corpus, and 1 case was in the gastric antrum. All lesions were confirmed as originating from the muscularis propria or close to the serosa by endoscopic ultrasonography examination.

The EFR success rate was 100%. The median operation time was 82.5 minutes (range, 56-188minutes; SD, 39.8minutes). Mean size (the maximum diameter) of resected tumors was 2.6 (range, 1.2–4.5) cm. Pathological diagnosis showed 43 GISTs, 3 leiomyomas. Among the 43 GISTs, 33 cases were benign, 8 cases were a very low risk of malignancy, and 2 were at low risk of malignancy (Mitotic counts per 50 highpower fields≤5). All specimens were border-free.

Effects of tumor sizes affecting the entire EFR process were then assessed by subgroup analysis (Table II). EFR for GISTs larger than 2 cm took longer times.

No procedure-related death was found. No single case had severe complications, such as GI bleeding, peritonitis, or abdominal abscess. The length of hospital stay in the EFR ranged from 4 to 11 d, with a mean of 5.5 ± 1.6 d. The mean follow-up time was 1,6,12 months. No tumor residual or recurrence has been found yet.

DISCUSSION

Most GISTs, including GISTs, grow intraluminally and rarely metastasize to local lymph nodes. Laparoscopic wedge resection with a linear stapler is the mainstay to manage those GISTs[6,7].

In recent years, based on endoscopic submucosal dissection and endoscopic submucosal excavation and due to improvements in the application of titanium clips under endoscopy, EFR treatment of gastrointestinal tumors arising from the muscularis propria has become possible. The key to EFR procedure is the successful closure of wall defect after resection to prevent peritonitis and surgical intervention.

In the present study, we retrospectively reviewed those cases of gastric gastrointestinal stromal tumors treated by EFR therapy in our center.

Successful treatment using EFR required successful repair of the perforation, thus avoiding the need for additional surgical repair and postoperative peritonitis(8-10). The most common method for re-

TABLE 1: CLINICOPATHOLOGICAL CHARACTERISTICS AND OUTCOMES OF EFR

Characteristic	Value
Patients (n)	46
Gender (male/female)	21/25
Age (years)	47.6±13.2 (23–65)
Gastric fundus	36
Gastric corpus	9
Gastric antrum	1
Size (cm)	1.2–4.5
Mean operation time (minutes)	82.5±39.8min(56–188min)
Titanium clips (n)	7.1±4.0 (3–18)
GISTs, malignancy (n)	43
Benign	33
Very low risk	8
Low risk	2
Mild risk	0
High risk	0
Leiomyoma (n)	3

TABLE 2: EFFECTS OF TUMOR SIZES AFFECTING THE ENTIRE EFR PROCESS

	Tumor size (cm)				
	< 1.0	1.0-2.0	2.0-3.0	> 3.0	P value
Number	21	18	5	2	
Gender (male/female)	10/11	7/11	4/1	0/2	.580
Location					.785
Gastric fundus	17	15	3	1	
Gastric corpus	3	3	2	1	
Gastric antrum	1	0	0	0	
Operation time (minutes)	40.9 ± 20.9	49.3 ± 20.1	96.0 ± 36.3	137.50 ± 46.1	.000
Titanium clips (n)	6.9 ± 3.8	7.1 ± 4.1	9.9 ± 4.3	16.0 ± 6.5	.361
GISTs					.001
Benign	20	16	5	2	
Risk of malignancy	15	14	4	0	
Very low	5	1	1	1	
Low	0	1	0	1	
Mild	0	0	0	0	
High	0	0	0	0	

pairing perforations was titanium clip repair. Several clips can close small defects [11,12].

Immediate closure of the gastric wall defects using metallic clips was performed in all 46 patients who received EFR. Consistent with the reports of Liu et al. [13] gastric muscularis propria originating GISTs were mostly found at the gastric fundus. Also consistent with had been previously presented[4]. In addition, a novel over-the-scope clip (OTSC) system may be suitable for closure of various GI perforations[14]. OTSCs are increasingly used in the treatment of acute gastrointestinal perforations and fistulas[15,16]. Furthermore, OTSCs are also used in submucosal tunneling endoscopy for resection of SMT in recent series[17].

According to our experience, a too big GIST is not suitable for EFR. Incision of large lesions is associated with the potential high risk of suturing difficulty, long operative times, and complications during and after surgery. Preoperative computed tomography is very important, especially in patients with large lesions. In one patient with a partly nonintracavity GIST of 3.8 cm, EFR was successfully carried out in 138minutes; however, the tumor body was retrieved in a piecemeal manner. Outcomes of our study demonstrated that GISTs are most common in GISTs, which is similar to previous studies[18,19].

We found that the complete resection rate in our EFR group was 100%, with a 0% recurrence rate. Lying in a semi-reclining position, administration of antibiotics and proton-pump inhibitors and nasogastric decompression can prevent peritoneal infection effectively[20]. In the present study, none of the patients in our EFR group experienced peritonitis or intra-abdominal abscess. Our outcomes of EFR for gastric GISTs are encouraging, because of active perforation being performed and GISTs being successfully resected, as well as observing no severe post-EFR complications in all 46 patients.

Our study was limited by the Short-term follow-up. Because of the biological characteristics of GISTs, the follow-up period was relatively shorter in our study. Long-term follow-up is essential to assess complete removal and recurrence of GISTs.

CONCLUSION

In conclusion, we consider that in the treatment of the gastric gastrointestinal stromal tumor, full-thickness endoscopic resection is safe. We suggest that this technique can replace some surgical and it should be applied more widely in clinical practice to convey advantages.

Acknowledgments

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Disclosure Statement: The authors declare to have no conflicts of interest.

RESUMO

OBJETIVO: *Este estudo revisou retrospectivamente 46 casos de tumores gástricos estromáticos gastrointestinais tratados por microcirurgia endoluminal endoscópica de ressecção completa (EFR) em nosso centro de endoscopia gastrointestinal. Pretendemos avaliar a EFR para o tratamento de tumores gastrointestinais estromáticos originários da muscularis própria.*

MÉTODOS: *Um total de 46 pacientes com tumores gástricos estromáticos gastrointestinais originários da camada muscular própria, de janeiro de 2012 a junho de 2015, foi tratado com EFR. Os pacientes foram acompanhados com gastroscópio e tomografia computadorizada (TC) para avaliação de efeitos terapêuticos e segurança.*

RESULTADOS: *A EFR foi realizada com sucesso para remover todos os tumores em 46 pacientes. O tempo médio de procedimento foi de 82,5±39,8 min (56-188 min). Exceto em três leiomiomas, exame patológico confirmou tumor estromal gastrointestinal (Gist) em 43 casos. Em nenhum paciente ocorreu sangramento, peritonite e outras complicações após EFR. Posteriormente, todos os pacientes foram acompanhados com gastroscópio após um, seis e 12 meses.*

CONCLUSÕES: *A EFR é eficaz e segura para pacientes com tumores gastrointestinais originários da camada muscular própria e tem a vantagem de ser um tratamento menos invasivo e com maior taxa de ressecção tumoral. Deve ser considerada para posterior aplicação.*

PALAVRAS-CHAVE: *Neoplasias gastrointestinais. Tumores do estroma gastrointestinal. Neoplasias de tecido conjuntivo. Células estromais. Gastrectomia. Gastroscopia. Laparoscopia.*

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ORIGINAL ARTICLE

The measurement of dorsal radial tilt by x-ray and computed tomography

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SUMMARY

OBJECTIVE: *We conducted this study to define and measure the dorsal radial tilt, and to guide the reduction of distal radius fractures and the pre-bending of steel plates used in surgery.*

METHODS: *The dorsal radial tilt was measured using both computed tomography (CT) and x-ray from both left and right side. The differences and correlations of the data measured by those two methods and from two sides were analyzed.*

RESULTS: *The tilts measured by x-ray were significantly bigger than those measured by CT from the left side ($t=55.51$, $p < 0.01$) and from the right side ($t=49.81$, $p < 0.01$). The tilts measured by those two methods from the left and right sides were correlated ($r=0.85$, $p < 0.01$; $r=0.81$, $p < 0.01$). The dorsal radial tilts measured from the left side were not significantly different from those measured from the right side by CT ($t=1.49$, $p > 0.05$) and by x-ray ($t=1.51$, $p > 0.05$). The dorsal radial tilts measured from the left side by CT were significantly different from those measured from the right side by x-ray ($t=43.07$, $p < 0.01$), and these two sets of data were correlated ($r=0.71$, $p < 0.01$). The dorsal radial tilts measured from the left side by x-ray was significantly different from that measured from right side by CT ($t=40.43$, $p < 0.01$), and those two sets of data were also correlated ($r=0.75$, $p < 0.01$).*

Conclusions: The dorsal radial tilts measured from one side by one method can be used to estimate the tilts measured from the other side / the same side by the same method / the other method.

KEYWORDS: *Radius fractures. Tomography, X-ray computed. X-Rays.*

INTRODUCTION

The forearm contains two bones of different sizes and the radius is the larger one.[1] The distal end is the end that towards the wrist. The distal radius fracture is the fracture that happens at the region of the radius near the wrist.[2] Distal radius fracture can happen in many different ways, but almost all the cases happened at the area about 1 inch from the end of the bone. Distal radius fracture, which is a common type of fracture, accounts for about 17% of all the cases of emergency fracture.[3] The occurrence of distal radius fracture is usually followed by the displacement and deformity healing, which in turn affect the wrist function.[4] In addition, distal radius fracture can cause the emergence of pain, limited rotation capacity, lower grip strength and other complications, which will reduce patients' quality of life. The dorsal radial tilt is one of the important factors that affect the prognosis of the fracture.[5] However, no study on the measurement of dorsal radial tilt has been reported.

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X-ray and CT are two imaging systems that are widely used in medical diagnosis. [6, 7] The wavelength of x-ray ranges from 0.01 to 10 nanometers. X-ray imaging is based on the phenomena of the attenuation of the x-ray beam. That is, an x-ray can go through the body with part of the energy absorbed by the body, and this energy absorption can be detected by a detector on the opposite side of the body, resulting in clinical images.[8] Conventional x-ray imaging can only produce a 2D image. While computed tomography, which is also called CT scanning, can produce 3D images by combing many images obtained from x-ray imaging taken in different directions,[9] resulting in images with more information and information that is more accurate. In our study, the dorsal radial tilts of 50 healthy volunteers were measured using both CT and x-ray from both the left side and right side. The measured date from different sides and by different methods was analyzed and compared. We found that the tilts measured by x-ray were bigger than those measured by CT. There was no significant difference in tilts measured by the same method from the different side, indicating the symmetric development of distal radius. In addition, the tilts of the distal radius measured by CT from one side were significantly different from the tilts measured by x-ray from the other side, and the two sets of data were correlated. Therefore, an x-ray can be used to measure the tilts of the distal radius and to estimate the tilts measured by CT, which can be used to provide an individualized treatment method for the patients with distal radius fractures.

OBJECTS AND METHODS

Grouping and processing of experimental objects

We discussed the research background, purpose, procedures, risks and benefits of this clinical trial in detail with the volunteers in this study and gave them sufficient time to consider carefully. All the patients signed the informed consent. The ethics committee of Yantaishan Hospital approved this study. This study was carried out from January 2016 to April 2016 at the Yantaishan Hospital.

50 cases of healthy adult volunteers were involved. The dorsal radial tilts of the 50 volunteers were measured both left side (50 cases) and right side (50 cases). The definition of dorsal radial tilts: the surface of the distal radius bone forms curve towards palm, and the angle formed by the distal and proximal bone is the dorsal radial tilt. The distal radius bone was scanned by both x-ray and CT to measure the dorsal radial tilt.

Specimen data collection and processing

The dorsal radial tilt was measured by both x-ray and CT.

CT measurement. Philips Ingenuity 128-layer CT (CTMR room, Yantaishan Hospital) was used to perform sagittal tomography along the long axis of the bony outgrowths of the distal radius. CT imaging system measured the angle formed by the distal and proximal bone of the curve at the surface of the distal radius bone.

X-ray measurement. Philips multi-function digital photography system (department of radiology, Yantaishan Hospital) was used to take photos on specimen wrist with standard side position, and this system was also used to measure the angle formed by the distal and proximal bone of the curve at the surface of the distal radius bone.

The dorsal radial tilt measured from the same side by x-ray and CT was statistically analyzed. The dorsal radial tilts measured by x-ray and CT from different sides were also statistically analyzed. In addition, the dorsal radial tilts measured from one side by CT was used to compare with the tilts measured from the other side by CT.

Statistical analyses

SPSS13.0 statistical software was used to analyze the measured data. The results of each group were expressed as the mean ± standard deviation ($\overline{x} \pm SD$). The statistical analysis of the measurement results was carried out by the paired t-test and the correlation analysis of two variables.

RESULTS

Dorsal radial tilts measured by x-ray and CT from two sides

The mean value of the dorsal radial tilt measured by CT was 29.12 ± 1.95° from the left side and 29.46 ± 2.18° from the right side, and the tilt measured by x-ray was 38.65 ± 2.31° from the left side and 38.96 ± 2.23° from the right side. The tilts measured by x-ray were significantly bigger than those measured by CT from the left side ($t=55.51$, $p < 0.01$), and the tilts measured by those two methods from the left side were correlated ($r=0.85$, $p < 0.01$). The 95% confidence interval of angle difference is (9.19 °, 9.88 °). The tilts mea-

sured by x-ray were significantly bigger than those measured by CT from the right side (t=49.81, $p < 0.01$), and the tilts measured by those two methods from the right side were correlated (r=0.81, $p < 0.01$). The 95% confidence interval of angle difference is (9.12 º, 9.89 º) (Table 1). These data suggest that the tilt measured by these two methods are different but correlated.

The comparison of tilts of dorsal radial tilt measured by x-ray from different sides and by CT from the different sides

There was no significant difference in the dorsal radial tilts measured by CT from different sides (t=1.49, $p > 0.05$), in addition, no significant difference in the tilts of distal radius measured by x-ray from different sides was found (t=1.51, $p > 0.05$) (Table 2).

The comparison between the dorsal radial tilt measured by CT from one side and the tilt measured by x-ray from the other side

The dorsal radial tilts measured from the left side by CT were significantly different from those measured from the right side by x-ray (t=43.07, $p < 0.01$), and the 95% confidence interval of angle difference is (9.38º, 10.30º). The dorsal radial tilts measured from the left side by x-ray were significantly different from those measured from the right by CT (t=40.43, $p < 0.01$), and the 95% confidence interval of angle difference is (8.74º, 9.65º) (Table 3). These data suggest that the tilt measured by one method from one side is different from the tilt measured by the other method from the other side.

The comparison between the dorsal radial tilt measured by CT from the left side and the tilts measured by x-ray from the right side aa: $p < 0.01$; the comparison between the dorsal radial tilts measured by CT from the right side and the tilts measured by x-ray from the left side aa: $p < 0.01$.

The dorsal radial tilts measured from the left side by CT were correlated with the data measured from the right side by x-ray (r=0.71, $p < 0.01$), and the dorsal radial tilts measure from the left side by x-ray were also correlated with those measured from right by CT (r=0.75, $p < 0.01$) (Table 4). These data suggest that the tilt measured by one method from one side is correlated with the tilt measured by the other method from the other side.

The correlation between the dorsal radial tilts measured by CT from the left side and the tilts measured by x-ray from the right side aa: $p < 0.01$; the correlation between the dorsal radial tilts measured by CT from the right side and the tilts measured by x-ray from the left side aa: $p < 0.01$.

DISCUSSION

Distal radius fracture is a common type of fracture, accounting for about 17% of all the cases of emergency fracture.[3] Distal radius fracture usually brings pain, limited rotation capacity, lower grip strength and other complications to the patients, which can affect the wrist function, reduce the patients' quality of life and bring heavy economic and psychological burdens to the patients and their fam-

TABLE 1 - THE COMPARISON TILTS OF DISTAL RADIUS MEASURED BY X-RAY AND CT FROM THE SAME SIDE

Groups	Tilts measured by CT (°)	Tilts measured by x-ray (°)
Left group	29.12 ± 1.95 †	38.65 ± 2.31 †
Right group	29.46 ± 2.18 ‡	38.96 ± 2.23 ‡

Left group †: $p < 0.01$; right group ‡: $p < 0.01$

TABLE 2 - THE COMPARISON OF DORSAL RADIAL TILTS MEASURED BY X-RAY FROM DIFFERENT SIDES AND BY CT FROM THE DIFFERENT SIDES

Groups	Tilts measured by CT (°)	Tilts measured by x-ray (°)
Left group	29.12 ± 1.95 §	38.65 ± 2.31 ¶
Right group	29.46 ± 2.18 §	38.96 ± 2.23 ¶

Comparison of the tilts measured by CT from different sides §: $p > 0.05$; comparison of the tilts measured by x-ray from different sides ¶: $p > 0.05$

TABLE 3 - THE COMPARISON BETWEEN THE TILTS OF THE DISTAL RADIUS MEASURED BY CT FROM ONE SIDE AND THE TILTS MEASURED BY X-RAY FROM THE OTHER SIDE

Groups	Tilts measured by CT (°)	Tilts measured by x-ray (°)
Left group	29.12 ± 1.95 †	38.65 ± 2.31 ‡
Right group	29.46 ± 2.18 ‡	38.96 ± 2.23 †

TABLE 4 - THE CORRELATION BETWEEN THE DORSAL RADIAL TILTS MEASURED BY CT FROM ONE SIDE AND THE TILTS MEASURED BY X-RAY FROM THE OTHER SIDE

Groups	Tilts measured by CT (°)	Tilts measured by x-ray (°)
Left group	29.12 ± 1.95 †	38.65 ± 2.31 ‡
Right group	29.46 ± 2.18 ‡	38.96 ± 2.23 †

ily.[10,11] The dorsal radial tilt, which is formed by the distal and proximal bone of the curve at the surface of the distal radius bone, is one of the important factors that affect the treatment as well as prognosis of patients with the fracture.[5] Based on our knowledge, no study on the measurement of dorsal radial tilt has been reported. Therefore, this study was carried out to define and measure the dorsal radial tilt for purposes of providing a reference for the treatment. In our study, the dorsal radial tilts of 50 healthy volunteers were measured by both CT and x-ray from both the left side and right side. We found that the mean value of the dorsal radial tilt measured by CT was 29.12 ± 1.95º from the left side and 29.46 ± 2.18º from the right side, and the tilt measured by x-ray from was 38.65 ± 2.31º from the left side and 38.96 ± 2.23º from the right side. The dorsal radial tilts measured by x-ray were significantly bigger than those measured by CT from the left side (t=55.51, $p < 0.01$), indicating that the outcomes of dorsal radial tilt measurement were different from different measurement methods. In addition, we also found that the tilts measured by those two different methods were different from each other but also correlated each other (Table 1). So the data measured by one method can be used to estimate the data measured by the other method.

In our study, no significant difference was found in the dorsal radial tilts measured from different side by CT (t=1.49, $p > 0.05$) and by x-ray (t=1.51, $p > 0.05$) (Table 2), indicating the symmetric development of distal radius, so the dorsal radial tilt measured from either side can be used for clinical diagnosis. In addition, the dorsal radial tilts measured by CT from one side were used to compare the dorsal radial tilts measured by x-ray from the other side, and the results showed that the dorsal radial tilts measured from the left side by CT were significantly different from those measured from right by x-ray (t=43.07, $p < 0.01$). In addition, the dorsal radial tilts measured from the left side by x-ray were also significantly different from those measured from the right by CT (t=40.43, $p < 0.01$) (Table 2). However, further analyses found that the dorsal radial tilts measured from the left side by CT was correlated with the data measured from right by x-ray (r=0.71, $p < 0.01$), and the dorsal radial tilts measured from the left side by x-ray were also correlated with those measured from right by CT (r=0.75, $p < 0.01$) (Table 4). Our data suggested that the dorsal radial tilts measured from one side by one method was significantly different from those measured from the other side by the other method, but they are still closely correlated with each other. Therefore, we think, in clinical practice, the dorsal radial tilts measured from one side by one method can be used to estimate the tilts measured from the other side/the same side by the same method/the other method. These findings in our study will facilitate the clinical measurement of dorsal radial tilts and the treatment and prognosis of patients with distal radius fractures, and it should be popularized in clinical practice.

CONCLUSION

In conclusion, the dorsal radial tilts measured by x-ray were found to be bigger than those measured by CT from both sides. No significant difference was found in dorsal radial tilts measured by the same method from different sides, indicating the symmetric development of distal radius. The dorsal radial tilts measured by CT from one side were significantly different from the tilts measured by x-ray from the other side, and the two sets of data were correlated. Therefore, an x-ray can be used to measure the dorsal radial tilt, and the data got from x-ray can be used to estimate the tilts measured by CT, which will provide the basis for the individualized treatment of distal radius fractures.

RESUMO

OBJETIVO: *Realizamos este estudo para definir e medir a inclinação radial dorsal, e para orientar a redução das fraturas do raio distal e a pré-flexão das chapas de aço utilizadas na cirurgia.*

MÉTODOS: *A inclinação radial dorsal foi medida usando tomografia computadorizada (TC) e raios X dos lados esquerdo e direito. As diferenças e correlações dos dados medidos por esses dois métodos e de dois lados foram analisadas.*

RESULTADOS: *As inclinações medidas por raios X foram significativamente maiores que as medidas pela TC do lado esquerdo (t=55,51, p<0,01) e do lado direito (t=49,81, p<0,01). As inclinações medidas por esses dois métodos dos lados esquerdo e direito foram correlacionadas (r=0,85, p<0,01; r=0,81, p<0,01). As inclinações radiais dorsais medidas a partir do lado esquerdo não foram significativamente diferentes das medidas do lado direito por CT (t=1,49, p>0,05) e por raios X (t=1,51, p>0,05). As inclinações radiais dorsais medidas a partir do lado esquerdo por TC foram significativamente diferentes das medidas a partir do lado direito por raios X (t=43,07, p<0,01), e*

esses dois conjuntos de dados foram correlacionados (r=0,71, p<0,01). As inclinações radiais dorsais medidas a partir do lado esquerdo por raios X foram significativamente diferentes das medidas do lado direito por CT (t=40,43, p<0,01), e esses dois conjuntos de dados também foram correlacionados (r=0,75, p<0,01).

CONCLUSÕES: *As inclinações radiais dorsais medidas de um lado por um método podem ser usadas para estimar as inclinações medidas do outro lado/o mesmo lado pelo mesmo método/o outro método.*

PALAVRAS-CHAVE: *Fraturas do rádio. Tomografia computadorizada por raios X. Raios X.*

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ORIGINAL ARTICLE

Clinical Observation of the Efficacy of Endoscopic Retrograde Cholangiopancreatography on Elder Choledocholithiasis and Its Effects on the Levels of TNF-α, IL-1, and IL-6

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SUMMARY

OBJECTIVE: *We conducted this study to investigate the clinical efficacy of endoscopic retrograde cholangiopancreatography (ERCP) on elder choledocholithiasis and its effects on the levels of TNF-α, IL-1, and IL-6.*

METHODS: *Elder patients with choledocholithiasis were enrolled in this study, and according to the surgical methods, they were divided into the ERCP group and the surgical group. After treatment, we compared the efficacy of these two methods on patients, inflammatory responses indicated by the levels of TNF-α, IL-1, and IL-6, and the complications.*

RESULTS: *No statistical significance was identified in the difference of the success rate in removal between the two groups (98% vs. 94%), but indicators of the ERCP group, including the surgical duration (28.5±12.8) min, remission duration of abdominal pain (1.2±0.2) d, recession time of jaundice (2.0±0.3) d, postoperative bedridden time (1.4±0.2) d, treatment time of the anti-infection (1.5±0.2) d, length of stay in hospital (6.5±0.3) d, levels of TNF-α (2.1±0.2) μg/L, IL-1 (6.3±0.8) μg/L, IL-6 (2.8±0.3) μg/L, and the incidence rate of complications (1.8%), were all significantly lower than those in the surgical group ($p<0.05$).*

CONCLUSION: *In the treatment of choledocholithiasis, ERCP is excellent in controlling the trauma, accelerating the recovery duration, reducing the occurrence of complications and ameliorating the inflammatory responses. Thus, it is an ideal choice for choledocholithiasis.*

KEYWORDS: *Choledocholithiasis. Cholangiopancreatography, endoscopic retrograde. Tumor necrosis factor-alpha. Interleukin-1. Interleukin-6.*

INTRODUCTION

As a common disease in the biliary system, choledocholithiasis usually leaves severe trauma even the obstruction can be resolved effectively through choledocholithotomy, resulting in a poor tolerance for elder patients. Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) are the major methods with minimal invasions for treatment of choledocholithiasis and

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have shown a variety of advantages, like a high efficiency in removal of calculus, minimal trauma, a low incidence of complications and short length of stay in hospital [1,2]. In this article, we investigated the clinical efficacy and safety of endoscopic retrograde cholangiopancreatography in the treatment of elder choledocholithiasis, and the detailed information is reported as follow:

1 DATA AND METHODS

1.1 Clinical data

A total of 100 elder patients who were diagnosed as choledocholithiasis in this hospital between May 2016 and May 2017 and had the surgical indications were enrolled in this study. Among these patients, there were 73 males and 27 females aged between 61 and 78 years old with an average of (68.1±8.6) years old. After admission, they underwent CT or MRCP, through which they were diagnosed as choledocholithiasis, and the diagnoses were all confirmed by the ERCP. According to the surgical methods, they were divided into the ERCP group and the surgical group, and the differences in the demographic data, complications, and type, diameter and number of calculus showed no statistical significance ($p>0.05$; Table 1).

1.2 Treatment

1.2.1 ERCP group

Under non-intratracheal intubation anesthesia, duodenoscope was inserted through the mouth, stomach to get into the duodenum, where the major papilla was found in the descending segment. Guided by the guiding wire, sphincterotome was used for biliary cannulation, and then the contrast agent was injected to clarify the size, position, and quantity of choledocholithiasis. Papillotomy was performed according to the position of uplift of the papilla and the size of calculus, and the basket was placed to retrieve the calculus under the monitoring of radioactive rays; otherwise, calculus was destroyed mechanically or retrieved after dilation by balloon. For small calculus, balloon was recommended to drag the calculus out. For patients that had too many calculi to remove all at once, it was suggested to repeat the steps above to remove all calculi. After surgery, nasobiliary drainage was placed routinely, and diet was forbidden for 24 h. In addition, patients were monitored closely for 24 to 48 h [3].

1.2.2 Surgical group

After general anesthesia and pneumoperitoneum, Trocar was inserted appropriately, and the surgical vision of common bile duct was exposed sufficiently using an electrocautery or elastic separating plier. Then, the duct was confirmed to be the bile duct through puncture-aspiration of the bile duct and was cut for calculus removal using lithotomy forceps or choledochoscope. A T tube was inserted into the bile duct that was later sutured. In the Winslons hole, a drainage tube was inserted. After surgery, the routine anti-infection procedure was performed with fluid infusion and hemostasis treatment, and patients were required to undergo routine examinations of blood and liver functions.

1.3 Observation

1.3.1 Treatment

Treatment was observed through following indicators: success rate of calculus removal, surgical duration, postoperative bedridden time, remission time of abdominal pains, recession time of jaundice, duration of anti-infection treatment, length of stay in hospital and complications; we also compared those indicators between two groups.

1.3.2 Stress responses

During the surgery, peripheral blood was collected to detect the levels of TNF-α, IL-1, and IL-6 of patients in two groups through ELISA.

TABLE 1 COMPARISON OF THE GENERAL DATA BETWEEN TWO GROUPS ()

Group	Case	Gender (M/F)	Age (years)	Type of calculus		Number of choledocholithiasis	Diameter	Complications	
				Gall bladder and common bile duct	Bile duct			Diabetes mellitus	Hypertension
ERCP group	50	37/13	68.7±9.1	33	17	2.5±0.3	2.2±0.1	17	21
Surgical group	50	36/14	67.1±8.7	32	18	2.5±0.6	2.1±0.2	18	20

1.3.3 Complications

After surgery, cases of ERCP-associated complications, effusion surrounding the incision, residue of calculi, infection and fever in two groups were recorded.

1.4 Statistical analysis

Statistical analysis was carried out with SPSS 18.0. Measurement data were presented as mean ± standard deviation (), and t test was applied in comparison. For comparison of the enumeration data, chi-the square test was adopted. α=0.05 was set as the inspection level.

2 RESULTS

2.1 Treatment

In the ERCP group, the surgical duration, remission time of abdominal pains, recession of jaundice, postoperative bedridden time, anti-infection treatment duration and length of stay in hospital were all significantly shorter than those in the surgical group ($p<0.05$; Table 2).

2.2 Levels of TNF-α, IL-1, and IL-6

During the surgery, the levels of TNF-α, IL-1, and IL-6 in the ERCP group were significantly lower than those in the surgery group ($p<0.05$; Table 3).

2.3 Comparison of the success rate of calculus removal and complications

In the ERCP group, the success rate of calculus removal was 98%, while the first-time and second-time success rates were 92% (46/50) and 6% (3/50) with no failure in calculus removal; there was one patient with mild pancreatitis that was recovered after 3 days of symptomatic treatment; no ERCP-related complications, like bleeding or perforation events, were observed. In the surgery group, there were 6 patients with fever caused by postoperative infection, 7 patients with effusion surrounding the puncture site of the abdominal wall, and 12 with abdominal pain or dull pain. Comparison of the success rate of calculus removal showed that the difference had no statistical significance ($p>0.05$), while the incidence rate of the complications in the ERCP group (2%) was significantly lower than that in the surgical group ($p<0.01$; Table 4).

TABLE 2 COMPARISON OF THE EFFICACY BETWEEN TWO GROUP ()

Group	Surgical duration (min)	Recession of jaundice (d)	Remission time of abdominal pains (d)	Anti-infection treatment duration (d)	Postoperative bedridden time (d)	length of stay in hospital (d)
ERCP group	28.5±12.8	2.0±0.3	1.2±0.2	1.5±0.2	1.4±0.2	6.5±0.3
Surgical group	103.0±38.3	4.2±0.4	2.3±0.4	3.1±0.4	3.7±0.6	12.6±3.4
t	11.583	11.269	10.493	11.476	18.736	10.843
p	<0.01	<0.05	<0.05	<0.05	<0.05	<0.01

TABLE 3 COMPARISON OF THE INFLAMMATORY RESPONSES BETWEEN THE TWO GROUP ()

Group	Case	TNF-α (μg/L)	IL-1(μg/L)	IL-6(μg/L)
ERCP group	50	2.1±0.2	6.3±0.8	2.8±0.3
Surgical group	50	5.3±0.7	28.0±4.7	15.1±2.3
t		12.753	24.692	29.486
p		<0.05	<0.05	<0.05

TABLE 4 COMPARISON OF THE SUCCESS RATE OF CALCULUS REMOVAL AND COMPLICATIONS BETWEEN TWO GROUPS

Group	Case	Success rate	Complications			Total
			Residual calculus	Effusion	Infection and fever	
ERCP group	50	49 (98%)	1 (2%)			1 (2%)
Surgical group	50	47 (94%)	5 (10%)	7 (14%)	6 (12%)	18 (36%)
t		0.483				13.274
p		>0.05				<0.01

3 - DISCUSSION

As a common disease in biliary system, choledocholithiasis usually leads to incomplete obstruction in the bile duct, which, with the variations in position, contraction, and movement of the common bile duct, can migrate inside the biliary system, thus giving rise to the intermittent attack[4]. According to its pathogenesis, choledocholithiasis is divided into two types, i.e. the secondary and primary choledocholithiasis: Secondary choledocholithiasis is generated from the gall bladder in a small volume, and quite susceptible to be stuck in ampullar region, thus resulting in acute clinical symptoms; primary choledocholithiasis originates in local part, but the compensate dilation of common bile duct usually curbs its adverse effect, which can prevent the symptoms of acute obstruction[5]. For cases without obstruction in common bile duct, patients present only mild abdominal discomfort or pains; for cases with obstruction, patients may complain about acute angina, or even jaundice in some severe cases; once the disease advances into this stage, clinical symptoms can be alleviated through spasmolysis or anti-infection treatment. For recurrent symptoms or purulency in common bile duct, surgical treatment should be considered[6].

In clinical practice, sphincterotomy is usually considered for treatment of choledocholithiasis, in which an incision is made on the bile duct to remove the calculus, and obstruction is resolved through drainage by T tube [7]. Nowadays, sphincterotomy has been adopted by many hospitals in China for its advantages like a small invasion. However, suture of the incision in the bile duct is one of the problems to be solved. Besides, sphincterotomy also causes severe trauma to patients, leaving scars or stenosis, and for these cases, patients usually face a bigger risk if they have the recurrence of choledocholithiasis [8], and the symptoms like abdominal pains, fever or jaundice may require the surgical treatment again [9]. Thus, indications should be fully confirmed before sphincterotomy.

In recent years, many clinical researchers have made a tremendous effort in searching for a new method for treatment of choledocholithiasis with small invasions, so as to avoid the trauma caused by surgery, and benefit the prognosis of patients [10]. ERCP can get into the bile duct through the papillary of the duodenum, where an incision can be made against the size of choledocholithiasis to remove the calculus, thereby resolve the obstruction; thus, ERCP is excellent in mini-invasion and efficiency, and patients can rapidly recover after operation [11]. Through comparison between the two groups, we found that the success rate of the calculus removal in the ERCP group was significantly higher than that in the surgical group, and the surgical duration, postoperative bedridden time, remission time of abdominal pain, recession time of jaundice, duration of anti-infection treatment, and length of stay in hospital were all significantly shorter than those in the surgical group, suggesting a positive value of ERCP in treatment of choledocholithiasis.

To further evaluate the safety of ERCP in the treatment of choledocholithiasis, we observed the inflammatory responses during the operation and the complications after operation. At the time of surgical injury, the release of inflammatory factors could be triggered in response to the tissue injuries. In this study, changing the level of TNF-α was the first to be observed after trauma, which could not only mediate the inflammatory responses, but also involve in the recruitment of the inflammatory mediators; IL-1 and IL-6 are the inflammatory factors directly involved in the injuries [12]. Through comparison of the indicators of inflammatory responses between the two groups, we noted that the levels of TNF-α, IL-1, and IL-6 in the ERCP group were significantly lower than those in the surgical group, reflecting that ERCP results in a milder inflammatory response. Besides, we also observed that the incidence rate of ERCP-associated complications in the ERCP group was lower than that in the surgical group, which showed that ERCP is the most ideal choice for the treatment of choledocholithiasis.

Successful intubation in bile duct is necessary for the ERCP, especially for incarcerated gallstones, giant calculus or complications of acute cholangitis, for which pre-cut sphincterotomy should be considered [13]. Moreover, how to remove the giant calculus confuses the physicians. In this study, endoscopic sphincterotomy was made at the papillary for mechanical lithotripsy, dilation by balloon or direct removal by lithotomy balloon; analysis of the efficacy showed that dilation by balloon following the endoscopic sphincterotomy can significantly increase the efficiency in calculus removal, shorten the removal time and decrease the risk of complications, which, however, also requires abundant clinical experience of the endoscopist [14]. Nevertheless, for elder choledocholithiasis, ERCP is conducive to the control of trauma, recovery, alleviation of inflammatory responses and reduction of the complications, and, thus, it is an ideal treatment method for choledocholithiasis.

RESUMO

OBJETIVO: *Realizamos este estudo para investigar a eficácia clínica da colangiopancreatografia retrógrada endoscópica (ERCP) na coledocolitíase idosa e seus efeitos nos níveis de TNF-α, IL-1 e IL-6.*

MÉTODOS: *Pacientes idosos com coledocolitíase foram matriculados neste estudo. De acordo com os métodos cirúrgicos, eles foram divididos em grupo ERCP e grupo cirúrgico. Após o tratamento, comparamos a eficácia desses dois métodos em pacientes, respostas inflamatórias indicadas pelos níveis de TNF-α, IL-1 e IL-6 e as complicações.*

RESULTADOS: *Não houve significância estatística na diferença da taxa de sucesso na remoção entre os dois grupos (98%* versus *94%), mas indicadores do grupo ERCP, incluindo a duração cirúrgica (28,5 ± 12,8) min, duração da remissão da dor abdominal (1,2 ± 0,2) d, tempo de recessão de icterícia (2,0 ± 0,3) d, tempo pós-operatório (1,4 ± 0,2) d, tempo de tratamento da infecção (1,5 ± 0,2) d, duração da internação (6,5 ± 0,3) d, níveis de TNF-α (2,1 ± 0,2) μg / L, IL-1 (6,3 ± 0,8) μg / L, IL-6 (2,8 ± 0,3) μg / L e a taxa de incidência de complicações (1,8 %) foram todos significativamente inferiores aos do grupo cirúrgico (p<0,05).*

CONCLUSÃO: *No tratamento da coledocolitíase, a ERCP é excelente no controle do trauma, acelerando a duração da recuperação, reduzindo a ocorrência de complicações e melhorando as respostas inflamatórias. Assim, é uma escolha ideal para a coledocolitíase.*

PALAVRAS-CHAVE: *Coledocolitíase. Colangiopancreatografia retrógrada endoscópica. Fator de necrose tumoral alfa. Interleucina-1. Interleucina-6.*

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ORIGINAL ARTICLE

Polycystic ovarian syndrome: rs1799752 polymorphism of *ACE* gene

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SUMMARY

PURPOSE: *To investigate the contribution of the deletion polymorphism and insertion (rs1799752) of the angiotensin converting enzyme (ACE) gene in the aetiology of Polycystic Ovarian Syndrome (PCOS).*

METHODOLOGY: *97 women diagnosed with PCOS who received care at the Gynaecology and Obstetrics clinic of the Hospital das Clínicas of UFTM, participated in this study. The control group consisted of 94 women. All participants were submitted to the collection of 10 mL of whole blood and the genomic DNA was obtained by the saline extraction method. The genotyping of the samples was performed by means of the Polymerase Chain Reaction (PCR). The statistics analyses were performed by descriptive analysis, univariate analysis and logistic regression model. The results were presented in odds ratio (OR) and confidence interval of 95% (CI-95%), with a significance level of 5% ($p \leq 0.05$).*

RESULTS: *There were no statistical differences between patients and controls for the genotypic ($\chi 2 = 1.52$, $p = 0.47$) and allelic frequencies ($\chi 2 = 0.21$, $p = 0.76$). The distribution of the genotypic frequency is not in HWE for patients ($\chi 2 = 18.80$, $p < 0.05$) and for controls ($\chi 2 = 6.85$, $p < 0.05$). In relation to the risk factors for the syndrome, the history of familial PCOS is more frequent between women with the syndrome.*

CONCLUSION: *In the study population, there was no association between I/D polymorphism of the ACE gene and PCOS.*

KEYWORDS: *Polycystic ovary syndrome. Ovarian cysts. Polymorphism, genetic. Angiotensin.*

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women's reproductive age and it is the most frequent cause of chronic anovulation and infertility[1]. The criteria for the diagnosis of PCOS include at least two of the following manifestations: oligovulation or chronic anovulation, clinical and/or laboratory aspects of hyperandrogenism and presence of ovarian cysts visualized by ultrasound examination.[2]

Although the aetiology of PCOS remains undeter-

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mined, it is considered a multifactorial disease, with several metabolic, endocrine, environmental and genetic alterations.[3]

Among the metabolic alterations present, insulin resistance and hyperinsulinemia are evident in the majority of those affected. PCOS increases the risk for type II diabetes mellitus, gestational diabetes and other complications related to pregnancy, venous thromboembolism, cerebrovascular and cardiovascular events, and endometrial cancer.[4] Among the environmental risk factors, smoking and alcohol habits are related to increased risk for reduced fertility, complications during pregnancy, miscarriages, cardiovascular disease, and insulin resistance in PCOS.[5] The prevalence of PCOS is higher among first degree relatives, thus indicating that the interaction between multiple genes and environmental factors is probably necessary for the development of PCOS. This hypothesis has given rise to a large number of studies aimed at investigating the role that genetic mechanisms play in the aetiology of the syndrome.[6]

Among the metabolic pathways, the ovarian renin-angiotensin system acts on follicle development/atresia and ovulation and in secretion of steroid hormones. The proper functioning of this system is necessary for normal reproduction, and its activity is regulated by gonadotrophins and it depends on the activation of proteases in the area of follicle growth. Angiotensin and its receptors are distributed in the ovarian follicles, in the preovulatory teak, in the granulosa cells and in the cells of the post-ovulatory granulosa layer and they regulate steroid production. Abnormal function of this system may be associated with infertility and PCOS.[7]

Angiotensin-converting enzyme (*ACE*), a key enzyme in the renin-angiotensin system (RAS), can convert angiotensin I to angiotensin II, which is the main effector peptide of this system. The angiotensin converting enzyme gene is located on chromosome 17 (17q23.3) and has more than 160 polymorphisms described. Individual variations in *ACE* concentration are associated with an insertion (I)/deletion (D) polymorphism of 287 bp at intron 16 of the gene (rs1799752). The DD genotype is associated with high plasma levels of the protein, the DI genotype at intermediate levels and II at low plasma protein levels, evidencing that this polymorphism may influence the renin-angiotensin system and its abnormal function may be associated with PCOS.[7-9] This polymorphism has already been associated with some clinical consequences of PCOS, such as hypertension[10,11], diabetes[10] and metabolic syndrome.[12]

Despite the importance of the *ACE* gene in ovarian physiology, studies published on polymorphisms in this gene and its susceptibility to PCOS are scarce and have shown controversial results. A meta-analysis involving six studies with 1,451 patients and 773 controls suggested that the polymorphism is associated with the risk of developing PCOS in Caucasian women.[13] In addition, there are no studies on this polymorphism and PCOS in Brazilian women. In view of the above, this study aimed to determine the frequency of the insertion (I)/deletion (D) polymorphism of the *ACE* gene (rs1799752) in patients with PCOS and to compare it with a control population in order to verify the association of this polymorphism with the syndrome.

METHODS

This case control study was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro, protocol 1796, and all the participants signed the Free and Informed Consent Term. The sample consisted of 191 women (97 women of reproductive age with no history of hyperandrogenism, menstrual dysfunction, infertility or sonographic signal of PCOS, who constituted the control group and 94 women diagnosed with PCOS). The Rotterdam criteria for the diagnosis of PCOS were used.[14]

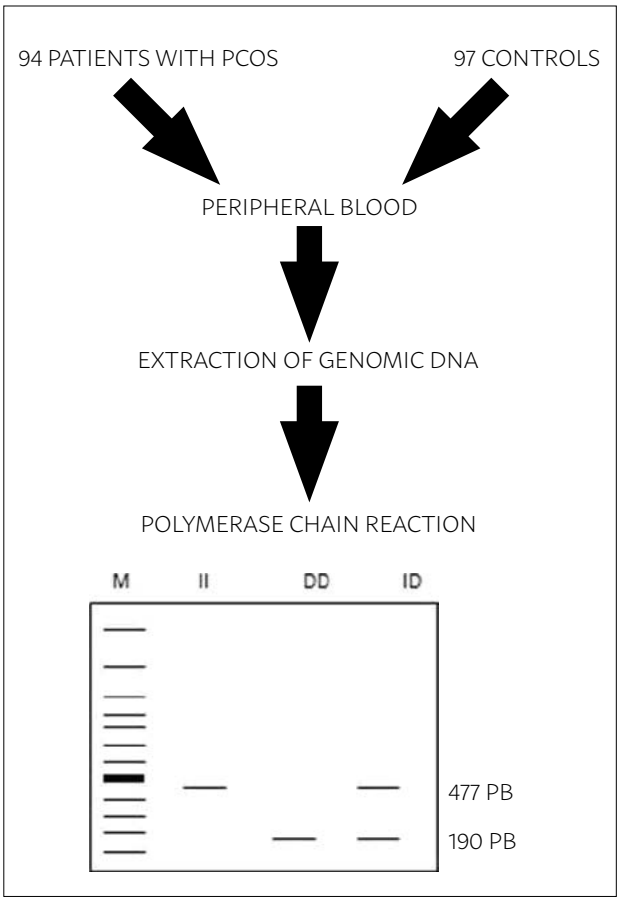
Women with Cushing's Syndrome, 21-hydroxyalase deficiency, thyroid dysfunction, hyperprolactinemia, diabetes, androgen-secreting tumours, and current or six-month use of oral contraceptives, antiandrogens, statins, glucocorticoids or infertility medications were excluded from this study. All participants in the study answered a questionnaire for the collection of sociodemographic and clinical data. The sociodemographic data collected were age, smoking habits and alcohol consumption. Clinical data included Absence of Pregnancy, Abortion, Association of Infertility Factors (AIF), Body Mass Index (BMI), Acne, Oiliness, Hirsutism, Hair Loss, History of Polycystic Ovarian Syndrome in the Family (HPCOSF), Use of Hormonal Medication (UHM) and Cardiovascular Diseases (CD).

The genomic DNA was extracted by means of the saline extraction technique,[15] from 5mL of peripheral blood. The Polymerase Chain Reaction (PCR) was performed for analysis of the insertion/deletion polymorphism of the *ACE* gene (rs1799752), with a final volume of 30 µL containing 100 ng genomic DNA, 1X

PCR buffer, 1.5 mM MgCl2 , 2 uM of dNTP, 20 pmol of each primer and 1 U of Taq DNA polymerase. The sequences of the primers used were sense: 5' CTG GAG ACC ACT CCC ATC CTT TCT 3' and antisense: 5' GAT GTG GCC ATC ACA TTC GTC AGA T 3'. Amplification conditions were 95°C for 10 minutes and 35 cycles of 95°C for 45 seconds for denaturation, 63°C for 45 seconds for annealing of the primers and 72°C for 30 seconds for extension, followed by a final extension at 72°C for 10 minutes. PCR products were visualized on 2% agarose gel coloured with GelRed®. The 477 bp products corresponded to the insert (I) and the 190 bp products to the deletion (D) (Figure 1)

In the statistical analysis, the chi-square test was used to analyse the genotypic and allelic distribution of the polymorphisms, as well as to test the Hardy-Weinberg Equilibrium (HWE). The multiple logistic regression model was used to determine the effect of risk factors on PCOS (family history of PCOS, smoking, alcoholism and the presence of polymorphism) and was analysed in 94 patients and 83 controls who had all these data. Multiple logistic regression was performed only for the patients and the model included the clinical consequences of PCOS and the polymorphism studied. Multiple logistic regression was also performed in patients in the model that included the biochemical data and the presence of the polymorphism. The results were presented in odds ratio (OR) and 95% confidence interval (CI - 95%). The level of significance for the analyses was set at 5% (p = 0.05). The statistical power of the sample was 96.8%.

FIGURE 1: SCHEMATIC REPRESENTATION OF THE METHODOLOGY USED DURING MOLECULAR ANALYSIS.



M: represents the 100 pb marker of molecular weight; II: the homozygous genotype for insertion; DD: homozygous genotype for the deletion; ID: heterozygous genotype for insertion/deletion.

RESULTS

In the control group (n = 94), 14.9% (14/94) had genotype II, 30.8% (29/94) had ID genotype and 54.3% (51/94) presented the DD genotype. In the patient group, the genotype frequencies were 20.6% (20/97); 24.7% (24/97) and 54.7% (53/97), and exhibited genotypes II, ID and DD, respectively. No statistical differences were observed between patients and controls for genotype frequencies ($\chi 2=1.52$; p=0.47). Allelic frequencies were 0.33 and 0.67 for alleles I and D in patients, and 0.30 and 0.70 in controls, for the same alleles. There were also no differences between allele frequencies ($\chi 2=0.21$, p=0.76). The distribution of the genotypic frequency was not in HWE for patients ($\chi 2=18.80$, $p<0.05$) and for controls ($\chi 2=6.85$, $p<0.05$).

Table 1 shows the multiple logistic regression model of risk factors (family history of PCOS, smoking and alcoholism) and the I/D polymorphism of the *ACE* gene in patients with PCOS and controls. It was evidenced that the family history was more frequent in patients with PCOS (OR=2.56, 95% CI: 1.26-5.20, $p <0.05$), smoking was more frequent in controls (OR=0.18; 95% CI: 0.07-0.46, $p<0.05$) and there were no differences in alcohol consumption (OR=0.97, 95% CI: 0.48-1.96, p=0.93) and in the distribution of polymorphism (OR=0.67, 95% CI: 0.30-1.51, p= 0.33).

Table 2 shows the multiple logistic regression model in patients with PCOS and the clinical consequences of the syndrome. There were no differences between the patients with the presence of the polymorphism and the clinical consequences of the disease.

In relation to the biochemical analyses and the presence of polymorphism, no differences were found between the following changes in hormones related to the reproductive cycle - Luteinizing Hormone - LH (OR=0.51, 95% CI: 0.07-3.55, p=0.50);

TABLE 1: DISTRIBUTION OF POLYMORPHISM OF THE *ACE* GENE AND RISK FACTORS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS) AND CONTROLS.

VARIABLE ANALYZED	PCOS n (%)	Controls n (%)	OR (95% CI)	p
Smoker				<0.05
Yes	07 (7.53)	25 (28.09)	0.18 (0.07-0.46)	
No	86 (92.47)	64 (71.91)		
Alcohol consumption				0.93
Yes	23 (24.73)	28 (31.46)	0.97 (0.48-1.96)	
No	70 (75.24)	61 (68.54)		
PCOS Family History			2.56 (1.26-5.20)	<0.05
Yes	35 (37.63)	19 (21.35)		
No	58 (62.37)	70 (78.65)		
Polymorphism of the *ACE* gene			2.56 (1.26-5.20)	0.33
Yes	19 (20.43)	46 (54.76)		
No	74 (79.57)	38 (45.24)		

TABLE 2: DISTRIBUTION OF POLYMORPHISM OF THE *ACE* GENE AND CLINICAL OUTCOMES IN PATIENTS WITH GENOTYPE ID OR DD .

VARIABLE ANALYZED	Patients with genotype II n (%)	Patients with genotypes ID or DD n (%)	O.R (95% CI)	p
Absence of Pregnancy			2.61 (0.42-16.19)	
Yes	06 (31.6)	14 (18.9)		0.30
No	13 (68.4)	60 (81.1)		
Abortion			0.23 (0.02-2.63)	
Yes	03 (15.8)	03 (4.1)		0.24
No	16 (84.2)	71 (95.9)		
Menstrual Irregularity			1.04 (0.18-6.01)	0.96
Yes	14 (73.7)	42 (56.8)		
No	05 (26.3)	32 (43.2)		
Factors Associated with Infertility			4.40 (0.38-51.08)	0.24
Yes	01 (5.3)	11 (14.9)		
No	18 (94.7)	63 (85.1)		
Use of Hormone Medication			1.19 (0.25-5.59)	0.83
Yes	09 (47.4)	43 (58.1)		
No	10 (52.6)	31 (41.9)		
Hirsutism			014 (0.02-1.11)	0.06
Yes	14 (73.7)	37 (50)		
No	05 (26.3)	37 (50)		
Acne			1.33 (0.23-7.85)	0.75
Yes	11 (57.9)	48 (64.9)		
No	08 (42.1)	26 (35.1)		
Oiliness			0.77 (0.12-5.09)	0.79
Yes	15 (78.9)	57 (77.0)		
No	04 (21.1)	17 (23.0)		
Hair Loss			2.82 (0.62-12.83)	0.18
Yes	11 (57.9)	46 (62.2)		
No	08 (42.1)	28 (37.8)		

Follicle stimulating hormone - FSH (OR=2.78, 95% CI: 0.20-38.2, p=0.44); Inverted LH/FSH function (OR=0.52, 95% CI: 0.05-5.14, p=0.58) and testosterone (OR=1.05, 95% CI: 0.23-4.87, p=0.95) and presence of the polymorphism.

DISCUSSION

It is known that the *ACE* enzyme plays an important role in the renin-angiotensin system that regulates blood pressure, as well as participate in the angiogenesis of the ovarian epithelium, follicular

growth, steroidogenesis and inflammation.[7] The *ACE* gene insertion/deletion polymorphism is associated with changes in plasma protein concentration. The presence of the D allele results in high plasma levels of the protein, which subsequently leads to an elevation of angiotensin II levels and alterations in the synthesis of steroid hormones.[8]

In the present study, the univariate analysis found no association between polymorphism and PCOS, which is in agreement with the study by Sun et al.[16] in 2010, which evaluated 142 patients and 100 controls and did not observe differences between the groups. However, a study in the Turkish population that analysed 100 patients with PCOS and 100 controls, and a Polish study with 138 patients and 110 controls showed differences between the groups using the same analysis, indicating that the deletion may be a risk factor for PCOS.[17,18]

Our results are according to a study in South India with 582 women of reproductive age (346 with PCOS and 236 controls) who found no association between the I/D polymorphism in the *ACE* and PCOS, but the multiple logistic regression analysis found an association of the deletion polymorphism with age of onset of disease and acanthosis.[19] In our study multiple logistic regression analysis was performed and no differences were detected between the clinical consequences of PCOS analysed (clinical hyperandrogenism, pregnancy-related problems), and presence of the polymorphism. However, the age at onset of the disease and the presence of acanthosis were not analysed as in the work performed in South India.

Regarding the genotypic distribution, the sample studied was not in Hardy-Weiberng equilibrium (HWE). One of the possible explanations is that this result can be due to the random selection of the studied individuals, inheritance model of the adopted disease and random changes in the genotype frequencies due to sample errors or sample size (genetic drift).[20-22]

In the present study, the multiple logistic regression model evidenced an increased frequency of smoking in the control group, which is not in agreement with a study that evaluated the effect of smoking in women with PCOS and concluded that they are at increased risk for developing endocrine dysfunctions and other diseases associated with the syndrome when smokers.[16] Our study also showed an increased frequency of family recurrence of PCOS in the study group, which is in agreement with the literature that shows that PCOS is a multifactorial disease with genetic factors in its aetiology. Studies with twins have shown that a mother or sister with PCOS favours a 30% -50% risk of developing PCOS.[4]

The work of Sun et al.[16] of 2010 did not show an association of the I/D polymorphism in the *ACE* gene with PCOS, however, differences in testosterone concentration among the three genotypes were observed in patients and controls. In our study, no association was found between the presence of the polymorphisms and the biochemical test data analysed.

A study of 801 patients with PCOS subdivided into three groups (A: patients with biochemical hyperandrogenism and other diagnostic criteria for PCOS; B: patients with clinical hyperandrogenism and other characteristics and C: group with anovulation and presence of cysts without manifestations of hyperandrogenism) showed differences between groups A and B in the distribution of the polymorphism compared to the control group. The group without manifestations of hyperandrogenism (group C) did not present any difference when compared to the control group. Genotype II was also positively correlated with Homa-IR (Homeostasis model assessment, calculated by Glycaemia (mMol) x Insulin (uU/mL) ÷ 22.5) and Quicki (Quantitative insulin sensitivity check index, by 1 ÷ (Log insulin + Log glycaemia).[23] A study carried out in the Turkish population showed an association of the DD genotype with the plasma insulin concentration and the Homa-IR index.[24] Our patients were not divided according to the diagnostic criteria and insulin was not measured in all patients for the calculation of Homa-IR and Quicki indexes, which is one of the limitations of our study.

The meta-analysis performed by Jia et al.[13] in 2013 showed no association of polymorphisms with PCOS in the general population. Only after stratification in ethnicities, it was concluded that the polymorphism is associated with the disease in Caucasian women, but it is not related in Asian women.[10] Our study did not perform the categorized assessment by ethnic groups due to the fact that the Brazilian population has a genomic heterogeneity due to process of miscegenation since the discovery of the country. The study by Pena et al.[25], conducted in 2011, analysed 934 Brazilian women categorized with white, brown and black skin colour in a panel containing 40 insertion and deletion polymorphisms. The researchers concluded that the Brazilian population of different regions is more uniform than expected.

CONCLUSION

In conclusion, in the sample studied there is no association of the I/D polymorphism of the *ACE* gene and PCOS. Acknowledgments: This work was supported by the Fapemig - (Process APQ 01608-14) and CNPq (Process 476423/2013-9). The authors also thanks to Evaldo Maia to collected of blood samples

RESUMO

OBJETIVO: *Investigar a contribuição do polimorfismo de deleção e inserção (rs1799752) do gene enzima conversora de angiotensina (ECA) na etiologia da Síndrome dos Ovários Policísticos (SOP).*

MÉTODOS: *Participaram deste estudo 97 mulheres diagnosticadas com SOP, atendidas no ambulatório de Ginecologia e Obstetrícia do Hospital de Clínicas da UFTM. O grupo controle foi constituído por 94 mulheres. Todas as participantes foram submetidas à coleta de 10 mL de sangue total e o DNA genômico foi obtido pelo método de extração salina. A genotipagem das amostras foi realizada por meio da Reação da Cadeia da Polimerase (PCR). A análise estatística foi realizada por análises descritivas, análise univariada e modelo de regressão logística. Os resultados foram apresentados em odds ratio (OR) e intervalo de confiança de 95% (IC – 95%). Foi considerado o nível de significância de 5% (p≤0,05).*

RESULTADOS: *Não foram observadas diferenças estatísticas entre pacientes e controles para as frequências genotípicas ($\chi 2=1,52$; $p=0,47$) e alélicas ($\chi 2=0,21$; $p=0,76$). A distribuição da frequência genotípica não está em equilíbrio de HWE para as pacientes ($\chi^2=18,80$; $p<0,05$) e para controles ($\chi^2=6,85$; $p<0,05$). Em relação aos fatores de risco para a síndrome, a história familial de SOP é mais frequente entre as pacientes.*

CONCLUSÃO: *Na casuística estudada não há associação do polimorfismo I/D do gene ACE e SOP.*

PALAVRAS-CHAVE: *Síndrome do ovário policístico. Cistos ovarianos. Polimorfismo genético. Angiotensinas.*

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ORIGINAL ARTICLE

Cosmesis in patients with breast neoplasia submitted to the hypofractionated radiotherapy with of intensity-modulated beam

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SUMMARY

OBJECTIVE: *To assess the cosmetic satisfaction of patients diagnosed with breast cancer submitted to the hypofractionated radiotherapy with IMRT (hIMRT) technique and its correlation with dosimetric data of the radiotherapy planning.*

MATERIALS AND METHODS: *The retrospective cohort study that assessed women with a diagnosis of malignant breast neoplasia submitted to the conservative treatment or radical mastectomy and treated with hIMRT. In the period between August 2007 to December 2014, in a philanthropic / private institution, 170 records were selected. The cosmetic assessment was carried out by means of the Harvard/RTOG/NSABP scale with one-year minimum range after treatment. The collected dosimetric data were: breast / chest wall volume, volume that received 95% (V95%) and 107% (V107%) of the prescribed dose.*

RESULTS: *The volume of the treated breasts ranged from 169 to 2.103 ml (median = 702; IQR: 535 to 914 ml). Median V95% was 86.7% (54.6-96.6%; IQR: 80.0% to 90.6%); eight (5.7%) patients had V95% higher than 95%. Median V107% was 0% (0%-16.3%; IQR: 0.0% to 0.3% and 13); 9.3% patients had V107% higher than 2%. One hundred and thirty-three (78.2%) patients responded to the cosmetic assessment: 99 (74.4%) considered the cosmetic results excellent. Significant associations between cosmetic assessment and breast volume (p=0.875), V95% (p=0.294) e V107% (p=0.301) were not found.*

CONCLUSION: *The cosmetic results showed favorable when using hIMRT, and the lack of correlation with usual the dosimetric data illustrates the capacity of hIMRT to minimize the heterogeneity of the dose in this endpoint, even in voluminous breasts.*

KEYWORDS: *Hypofractionation. Breast neoplasia. Radiotherapy.*

INTRODUCTION

The breast cancer is a malignant neoplasia more commonly in women. It is known that radiotherapy (RT) is an integral part of the adjuvant treatment for the most patients, regardless of the type of surgery that is carried out, producing benefits in local control and survival[1].

Significant breakthroughs were made in RT, including modernization of imaging techniques, equip-

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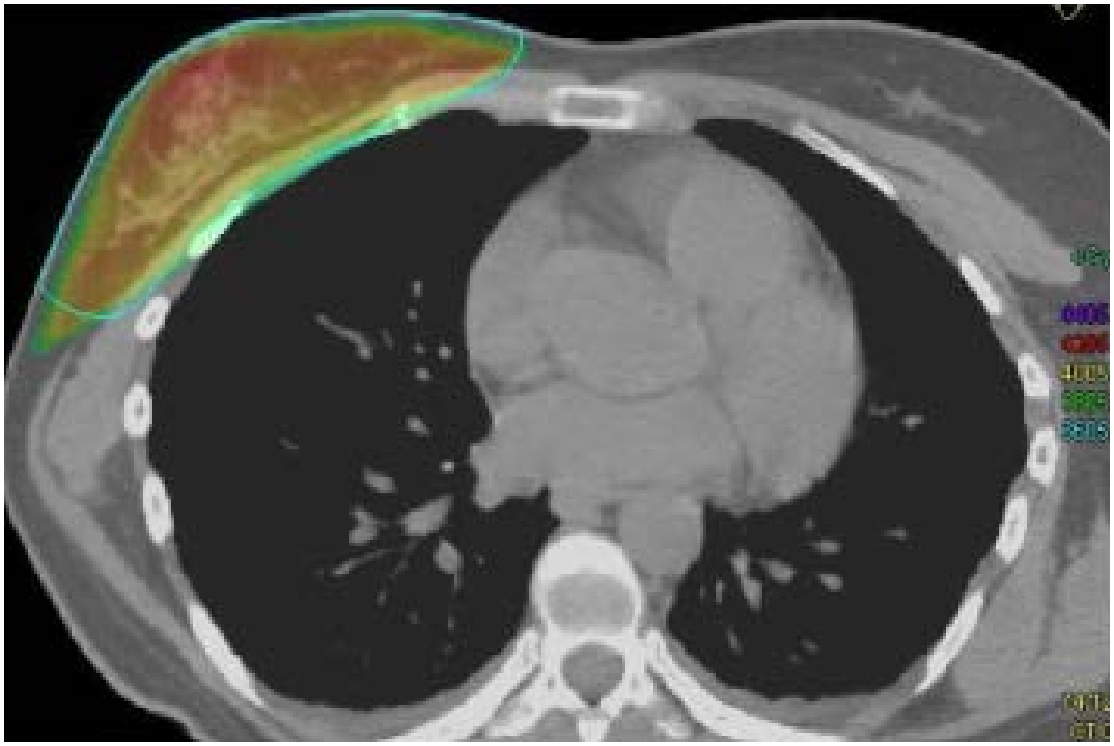
ment, and planning systems, allowing better accuracy in defining the target volume of treatment and more conformal plannings[2]. The latest techniques of treatment, including conformal three-dimensional RT (RT3DC) and intensity modulated RT (IMRT), allow a greater preservation of adjuvant bodies[3,4].

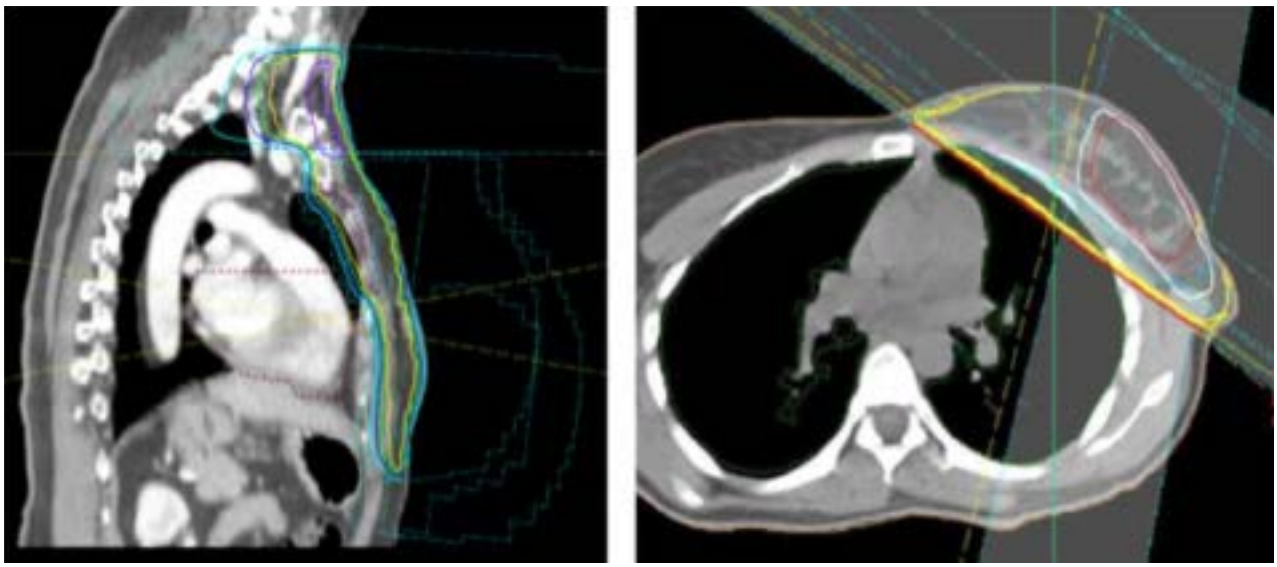
Field-in-field technique may be carried out with opposed tangential fields and it is considered a simple way of IMRT (*forward-planned* IMRT), without the need for a reverse planning system or other more complex technologies. Smaller fields are added to the main field in order to achieve a homogenization of the dose by handling the collimator blades. This technique may be easily implanted and the treatment period is similar to the conventional techniques[5,6] (Figure 1).

The conventional treatments use profiles from five to six weeks of duration, total dose of 50 Gy. Therefore, for patients selected, the hypofractionated regimes (shorter period of treatment with a higher dose per fraction), such as 42.5 Gy in 16 fractions or 40 Gy in 15 fractions are equally efficient, besides

FIGURE 1: FIELD-IN-FIELD TECHNIQUE X 3D



Field-in-field technique – Defined as the standard modality of IMRT for breast cancer with a homogeneous distribution of doses.



3D Technique

producing cosmetic results similar or better than the conventional profile[7,8].

This study aims to assess the cosmetic satisfaction of patients diagnosed with breast cancer submitted to hypofractionated RT with IMRT technique (hIMRT), and its correlation with dosimetric data of the radiotherapy planning.

PATIENTS AND METHODS

This is a retrospective uni-institutional cohort study that assessed women with diagnosis of non-metastatic breast malignant neoplasia submitted to conservative treatment or radical mastectomy, whether or not followed by immediate reconstruction, provided that no prosthesis, and submitted to the adjuvant irradiation of breast or chest wall (which corresponds to the surgical bed after mastectomy), with or without inclusion of classical lymph node sites with the hIMRT technique. The patients were assessed between August 2007 and December 2014. All included patients shall be a minimum follow-up of one year to assess the cosmesis.

The adopted exclusion criteria were: patients who did not complete the proposed RT, the presence of other neoplasia, except for non-melanoma skin or *in situ* carcinoma of cervix uteri, as well as information on insufficient follow-up for analysis.

The cosmetic assessment was made by the Harvard/RTOG/NSABP[9] scale by simple questions and comparison with the non-treated side (Table 1), from one year after treatment. The data were collected by researches by review of records, phone interview, and satisfaction questionnaire.

TABLE 1 - ASSESSMENT OF COSMESIS

Characteristic	% Patients
Stage	
0	20.2
IA	63.2
IB	0.6
IIA	12.3
IIB	2.5
III	1.2
Histological Grade	
Invasive ductal carcinoma	72.1
Others	27.9
Histological grade	
I	20.6
II	35.3
III	17.6
NA	26.5

Demographic data and aspects involved in the tumor were collected, such as histological type, staging, surgical extension, presence and type of breast reconstruction and additional treatments. In addition, dosimetric data was also collected: prescribed dose, volume of breast / chest wall (Clinic Target Volume, CTV), volumes that received 95% (V95%) and 107% (V107%) of the prescribed dose corresponding respectively to the coverage of target volume and volume of "hot spots", that is, it is assessed the homogeneity for distribution of dose. The planning system used was *Oncentra Masterplan (Nucletron)*®.

The descriptive analysis was carried out by calculating the frequencies, mean and standard deviation (dp) or median and interquartile range (IQR). The assessment of association between cosmetic satisfaction and dosimetric data was carried out when using Kruskal-Wallis test. It was admitted the level of statistical significance $p<0.05$. The statistical analysis was carried out using the Stata™ program (version 11.2).

RESULTS

170 patients with a median age of 65.8 years (31 to 95 years, dp=3 years) were included. Among them, the majority (63.2%) presented neoplasias in IA stage, 33 (20.2%) in 0 stage and the other IB to III. The more frequent histological type was the invasive carcinoma with a special type (72.1%). Thirty-four (20%) patients carried out adjuvant chemotherapy and 135 (79.4%) were submitted to anti-hormone therapy. One hundred and nine (64%) patients were submitted to the conservative surgery and 61 (36%) to modified radical mastectomy (Table 2).

The adopted hypofractionated profile was 40.05 Gy in 15 fractions to 43.5% of patients and 42.4 Gy in 16 fractions in 56.5% of cases assessed. Twelve patients (7.0%) received irradiation of lymph node drainages and 28 (16.3%) received a booster dose in the operative bed with a dose of 10 Gy in five fractions.

The volume of breasts treated ranged from 169 to 2.103 ml (median = 702 ml; IQR: 535 to 914 ml), in which in 20%, the volume was higher than 1.000 ml (Chart 1). Median V95% was 86.7% (54.6%-96,6%; IQR: 80.0% to 90.6%); eight (5.7%) patients had V95%

TABLE 2 - PATIENTS CHARACTERISTICS

Nuclear Grade	
I	14.1
II	45.3
III	24.7
NA	15.9
Adjuvant Chemotherapy	
Yes	20
No	80
Anti-Hormonal Treatment	
Yes	79.4
No	20.6
Surgery	
Conservative	64
Radical mastectomy	36
Reconstruction (without implants)	15.9
hIMRT scheme	
15 fractions of 2.67Gy (40.05Gy)	43.5
16 fractions of 2.65Gy (42.40Gy)	56.5
RT of LM drainage	
Yes	7
No	93
Boost use during surgery	
Yes	16.3
No	83.7
Cosmetic Assessment	
Excellent	74.4
Good	24.1
Regular	1.5
Bad	0

Excellent: Little or no difference in size, symmetry or shape
Good: Slight asymmetry in size or shape
Regular: Obvious differences in size and/or shape
Bad: Marked change in appearance, involving more than 14 of the breast

higher than 95%. Median V107% was 0% (0%-16.3%; IQR: 0.0% to 0.3% and 13); 9.3% patients had V107% higher than 2%. 133 patients (78.2%) responded to the questionnaire of cosmetic assessment. Among them, 99 (74.4%) considered cosmetic results excellent, 32 (24.1%) considered good, and two (1,5%) considered reasonable (Table 2). Significant associations between cosmetic assessment and the breast volume were not found (p=0.875), V95% (p=0.294) and V107% (p=0.301).

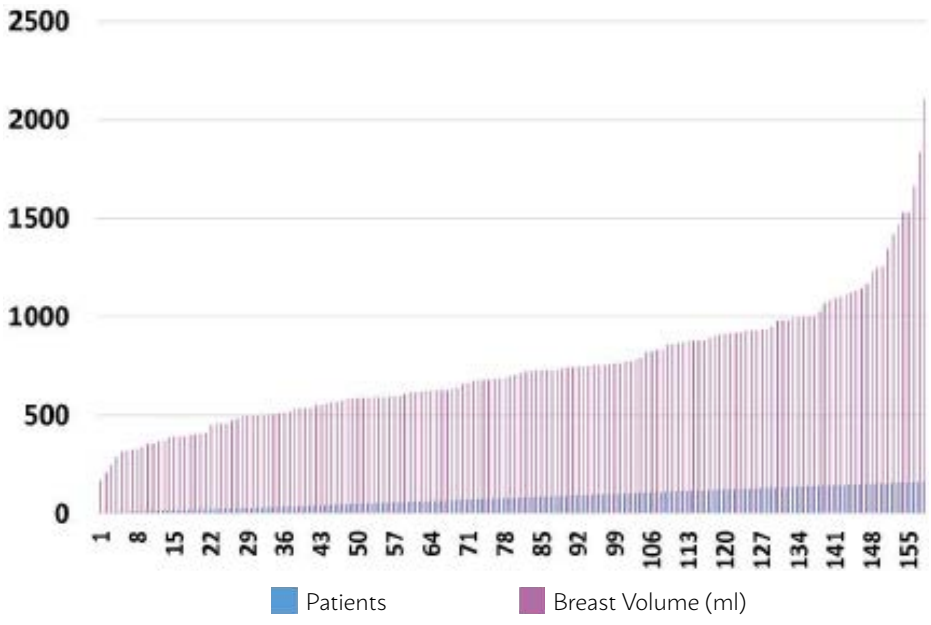
DISCUSSION

Two decades ago, the first studies were designed, suggesting a hypofractionated treatment profile. It was sought an optimization of the dose-time relation to keep a maximum tumor response with rates of acceptable toxicity. Moreover, a shorter treatment profile would offer an advantage of a more efficient and productive use of the funds from RT department[10].

The safety and efficacy, besides better cosmetic results compared to the conventional treatment, were shown in four randomized trials, involving 5.685 patients treated with hypofractionated profile[11].

The Canadian study randomized 1.234 women among the doses of 42.5 Gy in 16 fractions or 50 Gy in 25 fractions. After a median follow-up of 69 months, there was no difference in relation to the free survival of local relapse and global survivals and

CHART 1 – BREAST VOLUME



free disease, with 77% of excellent or good cosmetic results in both arms[12,13].

The Britain clinical trials *Standardization of Breast Radiotherapy Trial*, divided into (Start) A and B, sought to define the ideal fractionation, finding results similar to the prior studies[14]. With a mean follow-up of five years, Start A included 2.236 operated patients with breast neoplasia (T1-T3, N0-N1), without immediate reconstruction. The patients were treated with 50 Gy in 25 fractions, 41.6 Gy in 13 fractions or 39 Gy in 13 fractions. In the results, the local failure was similar to the groups of 50 Gy and 41.6 Gy, showing an equivalence among the profiles. Start B assessed 2.215 patients treated with 50 Gy in 25 fractions and 40 Gy in 15 fractions. After a mean follow-up of six years, the local failure was similar in both groups. Moreover, the dose of 40 Gy offered results of the local and esthetic control as good as the profile of 50 Gy[15].

When the first works of hypofractionation started, the concern about increasing the breast fibrosis and the worsening of cosmetic results increased, especially because of patients with voluminous breasts, there was a greater trend to a worst cosmetic result already showed in the results of works with conventional fractionation. In this way, many of these studies excluded women with voluminous breasts – in the Canadian studies, the patients were simply excluded if they had the distance between mean line and mean axillary line, measured in the breast center higher than 25 cm – and the trials that included these patients did not provide clear information about the impact on breast volume related to the toxicity and cosmesis, especially by the fact of using conventional radiotherapy[16].

In the Canadian trials and Start, the toxicities were not worse when compared with patients who received the standard fractionation up to now (50 Gy in 25 daily fractions), in view of the study used as a radiobiological substrate for the equivalence of different treatments, the linear-quadratic model[17]. Even though, the selection criteria of patients in these studies involved patients who did not receive prior chemotherapy, and in which there was no indication of irradiation of lymph nodes drainage nor immediate plastic reconstruction or voluminous breasts[18]. The latest works published tried to assess the relation between cosmesis and dosimetry of the planning of these patients, who were submitted to breast hypofractionated RT because, besides radiobiological implications, it is important to consider the practical advantages of hypofractionation, such as its convenience in terms of costs both for patients and health service, and also patient's compliance to the treatment[19].

It is known the importance of the correlation between toxicity and cosmetic results with patients' characteristics (age, comorbidities, body mass index) and medical treatments (neoadjuvant / adjuvant chemotherapy, hormonal deprivation, other concomitant drugs). Therefore, besides these factors being assessed, the impact of the CTV volume must be analyzed (representing the breast volume) and dosimetric data, especially focused on maximum dose and homogeneity of the planning (absolute volumes of breast tissues exposed to ≥107% of the dose prescribed). In this way, patients with postoperative complications or voluminous breasts for which a maximum dose <107% is not reachable, or patients with implants for the increase or breast reconstruction would have an increased risk of late fibrosis or cosmetic deterioration after RT[20].

Recently, a Chinese clinic study[21], published only in a summary format, studied over 800 patients with post-mastectomy breast cancer and showed benefits of hypofractionated RT in the advanced disease with 43.5 Gy delivered over three weeks. After a five-year follow-up, the rates of tumor recurrence were not lower than standard RT with conventional fractionation. The rates of locoregional recurrence were 8.3% for hypofractionated RT and 8.1% in the standard treatment (HR=1.10, IC 95%:0.67-1.83), with difference of 0.2% (IC 95% = –4.1 to 4.5). The rates of free survival of disease were from 74.6% to hypofractionation arm and 70.7% for the standard treatment arm (HR=0.88, IC 95%:0.67-1.16). The rates of global survival (GS) in five years were 83.2% after hypofractionation and 85.6% with standard treatment (HR=1.13, IC 95%:0.78-1.62). In addition, fewer side effects were evidenced in patients of hypofractionation, indicating that hypofractionated RT after mastectomy is a safe and efficient option for the locally advanced disease[21].

The guidelines of American Society of Therapeutic Radiology and Oncology (Astro), initially located in 2010, recommended the breast hypofractionation for patients in initial stages, age above 50 years, treated with conservation surgery, without chemotherapy or indication of lymph nodes irradiation, and with dosimetric parameters minimally acceptable, according to the techniques of conventional treatment[22]. These recommendations were based on the consensus of an

expert panel, and not in formal contraindication. In this year of 2018[23], the same society joined again and the panel updated the recommendations to a wider group of situations, such as the inclusion of systemic treatments, patients with advanced stages and without definitive age.

The breast volume as a relevant fact related to the skin toxicity is a contradictory topic in the pertinent literature. Many authors reported a close correlation between the breast size and intensity of acute effects[24]. It is up to us a questioning in relation to the criteria used for the definition of voluminous breast. Vicini et al. verified that patients with breast volume >1.600 cm^3 presented higher acute toxicity in the skin[25]. On the other hand, Harsolia et al. did not show level 3 acute toxicity with breast volume <975 cm^3 [26]. An interesting note of Moody et al. was the evidence of the relation between the breast size and cosmesis associated with distributions of dose in its planning, finding a significant correlation between the breast size and the non-homogeneity of dose[27].

This could explain the cosmetic changes in the appearance of the voluminous breasts, once great volumes are frequently associated with the non- homogeneity of the dose and maximum doses higher than 107% of the prescribed dose[20]. In addition to the acute toxicity, a higher breast volume may be correlated to an increased risk of late effects[28]. In this sense, IMRT could ensure higher homogeneity in the planning with great breast volumes. Many works that used hIMRT and allowed any breast sizes found lack of acute toxicity in the skin and presented dose of homogeneity lower than 7%[29], data also showed in our study, with lack of significant correlation between the cosmesis and the breast volume, most likely in terms of homogenous terms with median V107% of 0% (0%-16.3%; IQR: 0.0% to 0.3% and 13).

This study showed that breast volume did not have a correlation with prejudice to the cosmesis in the patients assessed, probably due to the benefit obtained with intensity-modulated planning. These findings allowed us to think about using hIMRT could expand the indications of hypofractionated RT for patients with voluminous breasts.

The more common changes in the appearance of the breast after RT are retraction, edema, and telangiectasia. These effects, in long-term, damage the cosmesis and are the results of the breast atrophy, and fibrosis. There are specific responses of fibrosis to the irradiation that may increase the proliferation of these cells and change and reabsorption of collagen[30].

The late adverse effects usually show up after a mean follow-up ranging from five to ten years. The great critics to be carried out is if the cosmetic changes, in relation to the fractionation presented when was made the notes, are representing those that will develop over the patients' lives[31].

Curran et al. showed in their studies that the cosmesis after breast hypofractionated RT was the worst in the patients followed by five years more[32]. In contrast, an English study did not show a significant difference in toxicity after RT between five and ten years of assessment[33]. Based on these considerations and uncertainties, currently, we cannot consider the follow-up as a factor that restricts the interpretation of the hypofractionated studies[34].

It is important to highlight, as a counterpoint to the study, the times of different follow-up, once it is about a retrospective cohort. Many patients did not complete the estimating period from five to ten years of follow-up for the appearance of adverse effects, despite the initially established objective has been defined with at least one-year follow-up.

In addition, another point of difficult interpretation would be to know if the dissatisfaction in relation to the cosmesis happened after surgery or after radiotherapy since the patients were not assessed soon after the surgical procedure and the criteria were the comparison with contralateral breast. Moreover, it is currently hard to think about in patients with breast cancer treated with conservative surgery without adjuvant irradiation.

Despite these variables, 98.5% of patients considered the cosmetic results from good to excellent, with the lack of significant correlation between cosmesis and breast volume. This result highlights the importance and the potential impact of the lack of homogeneity, areas of dose >107%, of a planning with short fractionation.

Offering a shorter treatment is more convenient and preferred for patients when compared to the treatment from five to seven weeks, and was associated with quicker recovery. However, the hypofractionated breast treatment had its use limited due to the fear that it might increase fibrosis and worsen cosmetic results. The fact of this work is consistent with great randomized clinical trials support the indication as for the new standard since initially criteria should be respected as homogeneity and lack of reconstruction surgery with a prosthesis.

CONCLUSION

The cosmetic results of the hIMRT for patients with breast cancer showed to be consistent with what is noted in the current literature, which is favorable to the use of hIMRT. The lack of correlation of the results with dosimetric data suggests that hIMRT may minimize the heterogeneity of the dose and ensure this benefit even in voluminous breasts.

Prospective studies and with longer time of follow-up will be necessary to support the findings of this study.

RESUMO

OBJETIVO: *Avaliar a satisfação cosmética de pacientes diagnosticadas com câncer de mama submetidas à radioterapia hipofracionada com técnica IMRT (hIMRT) e sua correlação com dados dosimétricos do planejamento radioterápico.*

MATERIAIS E MÉTODOS: *Estudo de coorte retrospectivo que avaliou mulheres com diagnóstico de neoplasia maligna de mama submetidas a tratamento conservador ou mastectomia radical e tratadas com hIMRT. No período de agosto de 2007 a dezembro de 2014, em uma instituição filantrópica/particular, foram selecionados 170 prontuários. A avaliação cosmética foi feita por meio da escala de Harvard/RTOG/NSABP com um intervalo mínimo de um ano após o tratamento. Dados dosimétricos coletados foram: volume da mama/plastrão, volume que recebeu 95% (V95%) e 107% (V107%) da dose prescrita.*

RESULTADOS: *O volume das mamas tratadas variou de 169 a 2.103 ml (mediana = 702; IQR: 535 a 914 ml). O V95% mediano foi 86,7% (54,6-96,6%; IQR: 80,0% a 90,6%); oito (5,7%) pacientes tiveram o V95% superior a 95%. O V107% mediano foi 0% (0%-16,3%; IQR: 0,0% a 0,3% e 13); 9,3% pacientes tiveram o V107% superior a 2%. Cento e trinta e três (78,2%) pacientes responderam à avaliação cosmética: 99 (74,4%) consideraram o resultado cosmético excelente. Não foram encontradas associações significativas entre a avaliação cosmética e o volume da mama (p=0,875), V95% (p=0,294) e V107% (p=0,301).*

CONCLUSÕES: *Os resultados cosméticos mostraram-se favoráveis com o uso de hIMRT, e a ausência de correlação com os dados dosimétricos usuais ilustra a capacidade do hIMRT em minimizar a heterogeneidade da dose neste desfecho, mesmo em mamas volumosas.*

PALAVRAS-CHAVE: *Hipofracionamento. Neoplasia de mama. Radioterapia.*

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COMMENT

Comment: "Cosmesis in patients with breast neoplasia submitted to the hypofractionated radiotherapy with of intensity-modulated beam"

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The retrospective cohort study "Cosmesis in patients with breast neoplasia submitted to the hypofractionated radiotherapy with intensity-modulated beam"[1], conducted by Dr. Fabiana Miranda at Hospital Sírio-Libanês, in São Paulo, shows the feasibility and the importance of maintaining radiation dose homogeneity delivered to breast cancer patients.

It is known that there is a greater probability of toxicities and complications for breast tissues that receive daily higher radiation doses due to heterogeneity, with the differences for biological effects being called "Double-Trouble" or "Triple-Trouble" effects[2]. For patients irradiated with hypofractionated schemes, dose coverage and dose homogeneity are even more important, as even small differences in radiation dose distribution may lead to great differences in the biological effect.

As far as I know, this is the first Brazilian publication about dose homogeneity that can be reached with the use of "Forward Planning" Intensity Modulated Radiation Therapy in the context of breast cancer, serving as basis and an example of care that must be used in order to reach not only good results in the tumor control, but also in breast cosmesis.

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ORIGINAL ARTICLE

The role of neonatal screening in nutritional evolution in the first 12 months after diagnosis of cystic fibrosis

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SUMMARY

OBJECTIVE: *to assess the progression of pediatric cystic fibrosis (CF) patients' nutritional status during the first 12 months after diagnosis and to establish its association with neonatal screening and clinical variables. Patients were recruited from two reference centers in Southern Brazil.*

METHODS: *Retrospective cohort study was carried out with all the patients diagnosed between 2009 and 2014. Anthropometric, clinic and neonatal screening were collected from medical files. Analysis of anthropometric markers over time was performed by generalized estimating equations. A multivariate regression analysis model to predict the Δ percentile body mass index (BMI) (BMI percentile difference between one year after the treatment and BMI percentile at diagnosis) was done.*

RESULTS: *Forty-seven patients were included in the study. Analysis of nutritional data over the period between six months and one year after diagnosis showed significant improvement of BMI, weight/age and weight/height percentiles and Z scores. The neonatal screening was associated with a significant increase of 31.2 points in ΔBMI percentile at the one-year evaluation ($p<0.05$). On the other hand, a one-point increase of initial BMI percentile was associated with a reduction of 0.6 points in ΔBMI percentile.*

CONCLUSION: *This study demonstrated the role of neonatal screening in the nutritional status of patients diagnosed with CF in the first year after diagnosis. Early diagnosis can significantly contribute to the achievement of appropriate anthropometric indicators and important nutritional recovery of CF patients.*

KEYWORDS: *Cystic fibrosis. Neonatal screening. Nutritional assessment. Anthropometry.*

INTRODUCTION

Cystic Fibrosis (CF) is accompanied by chronic obstructive pulmonary disease, pancreatic insufficiency with poor digestion and poor absorption of nutrients, leading to the worsening of the nutritional status[1]. The prognosis and the life expectation increased in virtue of progress that offered an intense and proper nutritional follow-up from the diagnosis[2].

The neonatal screening for CF with early treatment and identification of the pancreatic disease and proper nutritional management has been associated with the reduction of nutritional deficits and improvement of growth parameters over the years[2,3]. Despite an existing gap of evidence about the advantage of neonatal screening in relation to the progres-

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sion of the pulmonary disease and survival, the studies show an advantage in the pulmonary function up to at least 8 to 10 years old[4]. Besides that, the strong association of the nutritional status and pulmonary function[5,6] and the increase of survival[7] indicate a possible improvement of morbimortality in the patients diagnosed by neonatal screening.

In Brazil, neonatal screening for CF in the Brazilian Unified Health System (SUS – *Sistema Único de Saúde*) was implemented with the publication in the *Official Federal Gazette* on 06/06/2001, Ordinance 822[8], that governs the rules for its performance. However, Rio Grande do Sul started the neonatal screening for CF by SUS in 2012 only. Nowadays, the neonatal screening represents an important tool, which is responsible for almost 70% of diagnosis carried out in 2014, in Brazil. In any case, the median age of patients diagnosed by the symptoms in Brazil is still high (3.82 years), particularly when compared to the patients diagnosed by neonatal screening (0.14 year)[9].

The nutritional status in the diagnosis is directly associated with age that is carried out and at the beginning of the treatment. On the other hand, the evolution of the nutritional state in the first year after diagnosis has been poorly studied in Brazil. The objective of this study was to assess the evolution of the nutritional status of pediatric patients with CF from two reference centers of Rio Grande do Sul during the first 12 months after diagnosis and to establish an association with neonatal screening and clinical variables.

METHODS

Retrospective cohort study carried out with all patients with CF diagnosed between 2009 and 2014, assisted in the outpatient clinic of Pediatric Pulmonology of Hospital de Clínicas de Porto Alegre (HCPA) and outpatient CF clinic of Hospital São Lucas (HSL) of Pontifícia Universidade Católica do Rio Grande do Sul. These hospitals are reference centers with a multidisciplinary team in the treatment of patients with CF in Rio Grande do Sul, representing 75% of the service to these patients.

The diagnosis of CF was confirmed by two doses of electrolytes in sweat by the method of pilocarpine iontophoresis or the presence of two mutations known to be originating agents of the disease.

The collection period was from January to August of 2015. The patients' details with a diagnosis of CF in nutritional and clinical follow-up in the outpatient department of HCPA and HSL were collected from its electronic records. A structured data sheet was used containing date of birth, sex, date of diagnosis, neonatal screening held, genetic identification and pancreatic insufficiency. The genetic identification was carried out by the method of polymerase chain reaction (PCR). The pancreatic insufficiency was established by clinical diagnosis and dose of fecal elastase in cases that were not clinically evident, such as malformed stools and inappropriate weight gain. In the diagnosis, after 6 and 12 months, the following data were collected: presence and type of bacteria colonization, number of usage days of antibiotics in the period, serum albumin (verified only at the diagnosis and after one year), anthropometric measurements and respiratory systems (cough, increased sputum, etc.). The bacteria colonization was proven by sputum culture, when available, or culture of an oropharyngeal swab in other cases. The dose of serum albumin was carried out by the bromocresol green colorimetric method. The collected anthropometric measures were the weight and height; the body mass index (BMI), percentile and Z score of BMI by age (BMI/A), weight by age (W/A), weight by height (W/H) and height by age (H/A) were calculated, according to the curves of World Health Organization (WHO)[10]. The nutritional diagnosis was carried out in accordance with the recommended criteria for CF that establish cutoff points of BMI/A above 50 percentile[5]. Nutritional risk corresponds to the BMI/A between 10 and 50 percentiles. The poor nutrition is classified when BMI/A is below 10 percentile[11,12]. The BMI/A percentile values above 85 were classified as overweight and above 97 percentile as obesity[13].

The data analysis was carried out with the assistance of the SPSS program, version 18.0. The continuous variables were described by average and standard deviation or median and interquartile range. The categorical variables were described using absolute and relative frequencies. For analysis of anthropometric indicators and other variables in the study, the generalized estimating equations (GEE) were used, with analysis of the significant difference between the times by the Wald chi-square test and Bonferroni test. The evolution of the anthropometric variables was controlled for pancreatic insufficiency, the presence of homozygous F508 del, neonatal screening, bacteria colonization and age of diagnosis.

The multivariate regression framework was used

to predict the ΔBMI/A percentile (difference between BMI/A percentile, one year after the treatment and ΔBMI/A percentile at the time of diagnosis). The level of significance established was 5%.

This project was approved by the Research Ethics Committee of HCPA under the opinion number 967.715, Project number 150.293 and Ethics Committee of Hospital São Lucas under the opinion number 1.294.834.

RESULTS

All patients (n=47) diagnosed with CF between the years 2009 and 2014, in which 30 of HCPA and 17 of HSL, participated in the study. There were no losses by discontinuity of follow-up or death in the period assessed. Sample characterization is presented in Table 1. The age of diagnosis ranged from 2 months to 10 years and 2 months years old, in which the median is equal to 3.2 months. The neonatal screening was carried out in 30 (63.8%) patients, 19 (40.4%) patients were homozygous for F508del mutation and 45 (95.7%) showed pancreatic insufficiency.

In relation to the nutritional status, at that time of diagnosis, 28 patients (60%) were classified with poor nutrition, 12 (25%) with nutritional risk, six (13%) eutrophic and one (2%) with overweight. After one year of follow-up, six patients (13%) remained with poor nutrition, 15 (32%) with nutritional risk, 16 (34%) eutrophic, seven (15%) with overweight and three (6%) with obesity. Graph 1 shows the evolution of nutritional variables during 12 months of follow-up.

The analysis of nutritional data over a period of six months and one year after the diagnosis showed a significant improvement in the parameters of percentile and Z score of BMI, W/A, and W/H in each period analyzed. In relation to the H/A index, the increase of percentile and Z score was significant after six months and one year when compared to the diagnosis, but between the periods of six months and one year, there was no significant difference statistically. The albumin showed a significant improvement after one year of follow-up when compared to the diagnosis (Table 2).

In relation to the bacteria colonization, it was noted in the diagnosis that 17% of patients already presented *Pseudomonas aeruginosa*, and one year later, this number increased to 30 %; however, this difference was not significant between the times assessed. It was noted a significant difference between diagnosis colonization and after 12 months (p=0.02), with an increase of bacteria colonization over time, but no significant difference between bacteria analyzed (*Staphylococcus aureus,* Methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa mucoide, Burkholderia cepacia,* and other bacteria). The use of antimicrobial treatment did not present significant difference between the periods analyzed, although it has increased the medium number of usage days of medications. There was also no statistically significant difference in respiratory symptoms during periods.

The improvement of the nutritional status in patients with CF noted over time by BMI/A percentile was statistically different at the diagnosis at six months and after one year of follow-up, even when controlled to pancreatic insufficiency, presence of homozygous F508 del, neonatal screening, bacterial colonization and age of diagnosis.

After analyzing individual variables over the time, a model was built to predict the BMI/A percentile Δ,

TABLE 1. CHARACTERIZATION OF THE SAMPLE OF PEDIATRIC PATIENTS WITH CYSTIC FIBROSIS DIAGNOSIS FROM 2009-2014 IN HOSPITAL DE CLÍNICAS DE PORTO ALEGRE AND HOSPITAL SÃO LUCAS

Variables	n = 47
Sex – n (%) Male	 24 (51.1)
Age at diagnosis (years) - Median (p25-75)	0.27 (0.15-1.33)
Neonatal screening – (%) Genetics – n (%)	30 (63.8) 38 (80.9)
ΔF508 Heterozygote ΔF508 Homozygote Others Unidentified Mutation Pancreatic insufficiency – n (%)	13 (27.7) 19 (40.42) 1 (2.1) 5 (10.6) 45 (95.7)

N = number of sample; F = Phenylalanine

TABLE 2. ANALYSIS OF THE MEAN OF THE NUTRITIONAL PARAMETERS IN THE THREE DIFFERENT MOMENTS OF THE STUDY: AT THE DIAGNOSIS, AFTER 6 MONTHS, AND AFTER 12 MONTHS

Variable	Diagnosis (n=47)	6 months (n=47)	12 months (n=47)	P value
Albumin	3.50± 0.15[a]	-	4.34±0.04[c]	<0.001
BMI (percentile)	21.64± 3,77[a]	42.63±4.46[b]	55.11±4.18[c]	<0.001
W/A (percentile)	15.49± 3,45[a]	33.91±4.45[b]	44.30±4.34[c]	<0.001
W/H (percentile)	26.68± 4,21[a]	40.57±4.93[b]	53.57±4.46[c]	<0.001
H/A (percentile)	18.02± 3,79[a]	27.99±3.88[b]	31.85±4.14[b]	0.005

n = number of sample; BMI = Body Mass Index; W/A= weight for age; W/H = weight for height; H/A= height for age. Different letters represent significant differences (p<0.05) between the situations

described in Table 3. The screening and BMI/A percentile of diagnosis were significant to define this percentile difference before and after the treatment. The neonatal screening was associated with a significant increase of 31.2 points in the BMI/A percentile Δ during one year. On the other hand, one point more of initial BMI/A percentile was associated with a reduction of 0.6 point in BMI/A percentile Δ during the period analyzed.

TABLE 3. MULTIPLE LINEAR REGRESSION INCLUDING NEONATAL SCREENING AND PERCENTILE OF BMI AT THE DIAGNOSIS AND OUTCOME ΔBMI PERCENTILE

Variables	β	CI 95%	P value
Neonatal screening	31.2	(5.73/ 49.07)	<0.05
BMI percentile at the diagnosis	-0.60	(-0.94/ -0.27)	<0.01

Δ Percentile of BMI = Delta percentile of BMI; BMI = Body Mass Index; CI = Confidence interval.

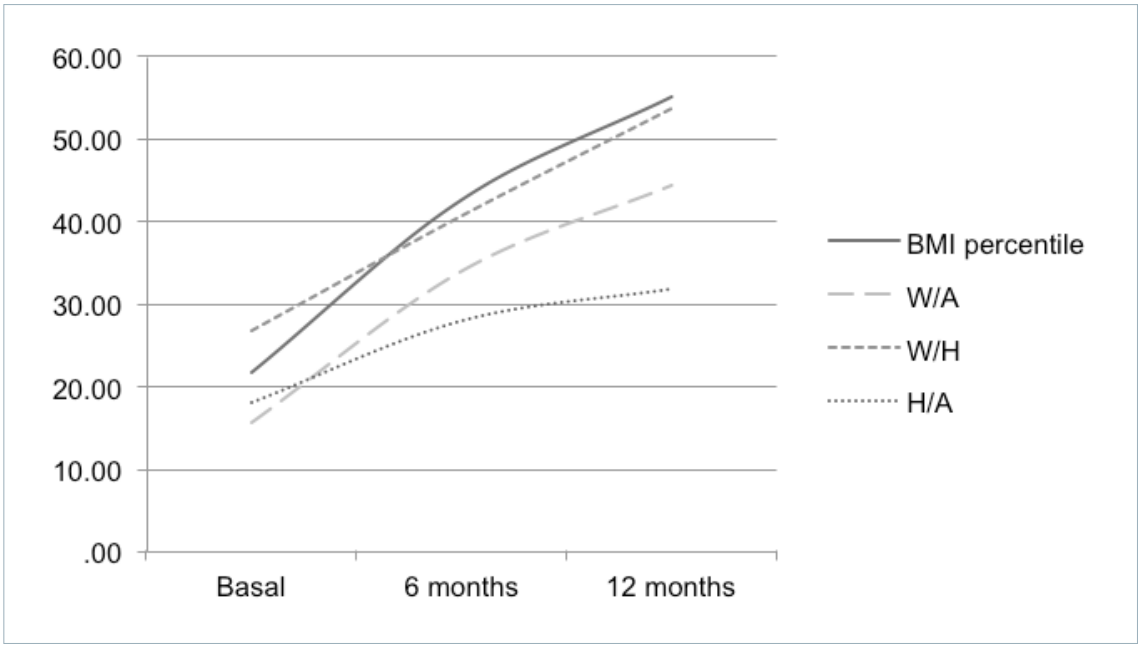
DISCUSSION

It was noted significant improvement in the nutritional status of patients with CF after one year of follow-up, showing the importance of the nutritional treatment to these patients. In addition, the neonatal screening was associated with a higher substantially increase of BMI/A percentile, highlighting the importance of early treatment and diagnosis.

The follow-up and early nutritional intervention offered the evolution of the nutritional status, with a decrease of approximately four times in the number of patients with poor nutrition and increase of three times in the number of patients with the good nutritional state when compared to the period in relation to this diagnosis. The nutritional evolution was evidenced by the significant difference between the variation of three times analyzed in relation to the anthropometric parameters of W/A and BMI/A. H/A percentile showed a significant difference at the diagnosis with after one year of follow-up, showing a higher increase in the first six months and a stabilization of the period between six months to one year. Ranganathan et al.[14], analyzing 42 patients with CF at the diagnosis and after three years of follow-up, found similar results.

The average BMI/I and P/E percentiles after one year of diagnosis achieved the average for age and target established for CF, reinforcing the envisioned provisions in the literature, whose assessment of the nutritional status and dietary advice must be instant as soon as the diagnosis was established, with the purpose of reaching the target established and slow the progression of the disease[15,16]. On the other hand, the H/A indicators, despite remaining below the av-

CHART 1. EVOLUTION OF THE NUTRITIONAL STATUS OF THE DIAGNOSIS (BASELINE), AFTER SIX MONTHS, AND AFTER 12 MONTHS, THROUGH THE BMI PERCENTILE, W/A, W/H, AND H/A (N=47)



BMIP=Body Mass Index percentile. WAP= Weight for age percentile. WHP= Weight for height percentile. HAP= Height for age percentile

erage of age, showed an increase of approximately 14 points. The height is one of the best indicators of the child's health status, once it is currently influenced by environmental, emotional and socio-economic factors, and ethnic factors [17]. In CF, the height is an important nutritional indicator in view of its association to the survival of these patients[18].

The neonatal screening was the main gaining predictor of BMI/I percentile in the period of one year after the diagnosis. Nowadays, only 15 Brazilian states are qualified to perform the screening for CF in Brazil and, among the difficulties mentioned, there are high cost for screening, false positives, and false negatives, as well as the lack of qualified teams to assist these patients. Despite little evidence in relation to the difference in the evolution of the disease, among patients diagnosed by neonatal screening and those who had their diagnosis after the beginning of symptoms, in relation to the nutritional status, studies have proven that patients diagnosed by neonatal screening have better nutritional parameters, especially during the first childhood[2,19,20]. *Wisconsin Cystic Fibrosis Neonatal Screening Projetc*[3] also evidenced that patients diagnosed by neonatal screening persevered with better parameters of weight and height in a segment for 16 years. Zhang et al.[21] showed that in adult life, the screening patients reached a height higher than those diagnosed by symptoms.

Another marker used in this study was the analysis of albumin, which is also a marker of nutritional status, in the CF, is also studied by its property as a pulmonary antioxidant, preventing pulmonary damage[22]. This study showed a significant increase in the plasmatic levels of albumin between the diagnosis and after 12 months, from the limit to the diagnosis of poor nutrition and reaching mean values of 4.34 mg/dL. Simon et al.[23] reported an association of albumin above 4.1 mg/dL with better pulmonary function.

In relation to the pulmonary infection, despite not being noted the significant difference between bacteria analyzed in the beginning and the finishing of the study, it is highlighted the high prevalence of colonization by *Pseudomonas aeruginosa* in the diagnosis and its increase after one year, achieving 30% of the sample. This infection is a determining factor for worsening of pulmonary disease in patients with CF, consequently, with reduction of survival[24,25]. Lim et al.[26], monitoring 104 patients after neonatal screening in London, noted that 47% of them already showed *Pseudomonas aeruginosa* at 2 years old.

The limitation of the study is related to the sample size and the fact of being a retrospective study, in which there is no control of standard assessments carried out. Another limitation was the lack of social and economic data, as well as the treatment compliance, which did not appear on the patients' records. However, the relevance of this study is due to the fact that data of two reference centers in Southern Brazil support the findings of international literature and reinforce the importance of early diagnosis and the institution of treatment for a better prognostic also in our country.

CONCLUSION

This study proves the important role of neonatal screening in the nutritional evolution of patients diagnosed with CF in Brazil in the first year after diagnosis. Therefore, the early diagnosis, combined with treatment of multiprofissional teams in Reference Centers, may significantly contribute to the nutritional recovery of patients with CF.

Acknowledgments

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RESUMO

OBJETIVO: *Avaliar a evolução do estado nutricional de pacientes pediátricos com fibrose cística (FC), provenientes de dois centros de referência do sul do Brasil, durante os 12 primeiros meses após o diagnóstico e estabelecer associação com a triagem neonatal e com variáveis clínicas.*

MÉTODOS: *Estudo de coorte retrospectivo realizado com todos os pacientes diagnosticados entre 2009 e 2014. Foram coletados dados antropométricos, clínicos e de realização da triagem neonatal a partir dos prontuários dos pacientes. A análise dos indicadores antropométricos ao longo do tempo foi realizada por equações de estimativas generalizadas. Utilizou-se o modelo de análise de regressão multivariada para predizer o D percentil índice de massa corporal - IMC/I (diferença entre percentil de IMC/I um ano após o tratamento e percentil de IMC/I no momento do diagnóstico).*

RESULTADOS: *Participaram do estudo 47 pacientes. A análise dos dados antropométricos ao longo do período de seis meses e um ano*

após o diagnóstico demonstrou melhora significativa dos parâmetros de percentil e escore Z de IMC/I, peso/idade e peso/estatura em cada período analisado. A realização da triagem neonatal foi associada com um aumento significativo de 31,2 pontos no Δ percentil de IMC/I durante o período de um ano (p<0,05). Por outro lado, um ponto a mais de percentil de IMC/I inicial foi associado com uma redução de 0,6 ponto no Δ percentil de IMC/I (p<0,01).

CONCLUSÃO: *O presente estudo evidencia o papel da triagem neonatal na evolução antropométrica de pacientes com FC no primeiro ano após o diagnóstico. O diagnóstico precoce pode contribuir significativamente para a recuperação nutricional desses pacientes.*

PALAVRAS-CHAVE: *Fibrose cística. Triagem neonatal. Avaliação nutricional. Antropometria.*

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ORIGINAL ARTICLE

Health-related quality of life in a cohort of youths with type 1 diabetes

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SUMMARY

Health-related quality of life (HRQOL) in type 1 diabetes mellitus (T1DM) has been widely studied. The objectives of this study were to evaluate and identify the factors influencing the HRQOL of children and adolescents with T1DM.

MATERIAL AND METHODS: *In total, 59 patients (9–16 years, T1DM for ≥1 year) responded to a version of the Diabetes Quality of Life Instrument for Youth (DQOLY) adapted to adapted to Brazilian patients, the Instrumento de Qualidade de Vida para Jovens com Diabetes (IQVJD). This instrument comprises 50 items (domains satisfaction, impact, and concerns, with the lowest scores corresponding to better HRQOL) and a questionnaire gathering social, demographic, and clinical parameters.*

RESULTS: *The mean age of the patients was 13.6 years, and 57.6% were girls. The median age at diagnosis was 7.16 years, 63% presented diabetic ketoacidosis (DKA) at diagnosis and 29% during follow-up. Mean glycated hemoglobin (HbA1c) in the previous year was 10%. All patients administered multiple insulin doses (mean 4.2 applications/day), 74.5% used rapid-acting and intermediate-acting insulin analogs, and 67.8% used pens for insulin application. The results of the DQOLY were within the cutoff limit for better HRQOL. An isolated analysis of each domain and the questionnaire results showed that the following factors were associated with better HRQOL: height Z-score, lower HbA1c, practice of physical activity, use of pen, fewer hospitalizations, and residence in a rural area. There was a high DKA rate at diagnosis, and the metabolic control was inappropriate in most patients. Despite coming from low-income households, most patients had access to the recommended treatment.*

CONCLUSION: *Among T1DM patients, 71% had IQVJD scores compatible with better HRQOL.*

KEYWORDS: *Quality of life. Child. Adolescent. Diabetes mellitus, type 1.*

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the third most prevalent chronic disease in childhood and the most frequent type of diabetes in children [1]. The incidence of T1DM in this population has been increasing worldwide since 1960 at an approximate 3–5% yearly rate [2]. The causes of this epidemic are not well known, but studies suggest the participation of multiple factors, including autoimmunity, genetic predisposition, diet, weight gain, viral infections, and early introduction of solid foods and cow's milk to infants [3-5]. Approximately 80,000 children below the age of 15 years are estimated to develop T1DM annually across the world [6].

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Management of T1DM requires intensive treatment and adequate medical advice. Results from the Diabetes Control and Complications Trial (DCCT), the largest study conducted in T1DM patients, have shown that intensive treatment can prevent or delay the development of acute and chronic complications, and reduce the morbidity and mortality associated with the disease [7].

For a long time, the mortality rate was a key determinant of the impact of a particular disease on public health. More recently, researchers have turned towards other determinants not confined to the medical dimension of a disease to include also subjective aspects related to health, such as health-related quality of life (HRQOL)[8]. Assessment of an individual's HRQOL offers a clear and objective analysis of the global impact that chronic diseases have on a patient's life since it encompasses several areas with potential health impact – physical, psychological, socioeconomic, and cultural satisfaction and well-being. Several studies have been relying on HRQOL as an indicator of treatment efficiency and as a basic parameter to understand an individual's perception of their condition and the impact of the disease on his health[9].

Diabetes is often associated with substantial HRQOL impairment, imposing functional limitations, social and financial stress, emotional discomfort, and major depression. The reduction in HRQOL in patients with diabetes may result from complications associated with the disease and poor glycemic control, which is directly influenced by the patient's psychological profile and degree of acceptance of the disease [7].

Considering the increasing incidence of diabetes in childhood and the lack of studies assessing HRQOL in this population, we conducted this study to evaluate and identify the factors that influence the HRQOL evaluated with the Instrumento de Qualidade de Vida para Jovens com Diabetes (IQVJD) in a group of children and adolescents with T1DM attending a reference center for diabetes in Curitiba (Brazil).

MATERIALS AND METHODS

This cross-sectional study was carried out between March and May 2013, at the outpatient diabetes clinic of *Unidade de Endocrinologia Pediátrica* (UEP) at *Hospital de Clínicas, Universidade Federal do Paraná* (UFPR). A total of 195 patients with diabetes (~95% of whom had T1DM) were seen at the clinic during this period. We excluded patients younger than 9 years or older than 16 years of age, those diagnosed with diabetes for less than 1 year, with comorbidities that could interfere with their HRQOL (such as severe asthma or heart disease, blindness, and with genetic syndromes), with type 2 diabetes or with diabetes secondary to other diseases (cystic fibrosis or Fanconi anemia), illiterate, with cognitive disorders, or who refused to participate in the study. We selected by convenience 59 patients out of 79 who met the inclusion criteria.

We used the IQVJD to assess the HRQOL in our cohort. This adapted instrument maintained the three domains of the original Diabetes Quality of Life for Youth (DQOLY): satisfaction (17 items assessing patient's satisfaction with treatment and personal matters, such as family and friends), impact (22 items evaluating the impact of the diabetes on the patient's life), and worries (11 items assessing the patient's concerns with the diabetes and the future). The questions are presented on a Likert scale with five response options ranging from "very satisfied" to "very dissatisfied" in the satisfaction domain, and from "never" to "always" in the impact and concern domains. Scores are added to each domain, and the total scores are calculated by adding the scores in each domain, in which a lower score indicates a better HRQOL. It is worth noting that although this instrument has no cutoff values [10], we adopted those values described in the study by Novato *et al.*[10], which was performed in a similar geographical area as ours, characterizing as "worse" when the HRQOL was above the 75th percentile. The IQVJD is composed of 50 objective questions completed by the patient and an interview conducted by the researcher to gather sociodemographic data (gender, race, age, marital status, nationality, hometown location, who the patient lives with, and household income) and clinical data (age at diagnosis, disease duration, type of insulin administered, device used for insulin application, identification of the person in charge of the insulin administration, number of insulin applications per day, number of measurements of capillary glucose a day, associated diseases, occurrence of diabetic ketoacidosis [DKA] at diagnosis and during the course of the disease, number of hospital admissions during the treatment, physical activity, weight, height, body mass index [BMI, calculated with the formula weight/height^2], pubertal stage according to the Tanner criteria, current glycosylated hemoglobin [HbA1c] level, and mean HbA1c level in the previous year). The same

researcher administered all questionnaires. Each patient completed the IQVJD individually in a room to prevent the caretaker from interfering with the answers. The researcher interviewed the caretakers and the patients to collect sociodemographic data.

For analysis purpose, we converted the weight, height, and BMI into z-scores using the software WHO AnthroPlus, version 10.4 [11]. Levels of HbA1c were measured by a turbidimetric method, and clinical data were collected from medical records.

For statistical analysis, we used the software Statistica (Statsoft®). To estimate the differences between continuous variables, we used the Student's *t* test, and for asymmetric variables, we used the Mann-Whitney test. The association between categorical variables was analyzed with Fisher's exact and Pearson's chi-square tests. A stepwise forward logistic regression model was applied to identify the key variables associated with HRQOL. We estimated the sample size considering a type I error fixed at 5%, type II error at 10%, and effect size of 30%, with a test power of 90%. We considered for all tests a significance level of 5% and a confidence interval of 95%.

The Ethics and Research Committee at Hospital de Clínicas, UFPR, approved the study. All patients and their caretakers signed a free and informed consent form.

RESULTS

The study included 59 patients with an average age of 13.6 years, of which 34 (57.6%) were girls (Table 1). The median age at T1DM diagnosis was 7.16 years, and the median duration of the disease was 6.5 years. Most patients (66.1%) lived with both parents. The household *per capita* income was less than half of the minimum wage in 44.0% of the patients, between half and the minimum wage in 44.0%, and between one and two times the minimum wage in only 12.0% of the cohort. Overall, 37.0% of the parents had not completed the elementary education, and only 10.2% of the fathers and 8.5% of the mothers had a university degree. With regard to the degree of education of the patients, 43 were in elementary school, and 16 were in middle school. Twenty-four patients (40.7%) had experienced a school failure.

TABLE 1 – PATIENTS' CHARACTERISTICS (N = 59).

Characteristics	n (%), mean, median
Gender	
Male	25 (42.4%)
Female	34 (57.6%)
Ethnicity	
White	43 (72.8%)
Mixed (Black/White)	16 (27.2%)
Origin	
Curitiba	24 (40.6%)
Metropolitan region of Curitiba	21 (35.6%)
Other regions in Paraná	14 (23.8%)
Level of education	
Elementary school	43 (72.8%)
Middle school	16 (27.2%)
Age	
Current	13.6 ± 1.5 years
At diagnosis	7.16 years (0.66 – 13.5)
Disease duration	6.5 years (1.3 – 14.5)
Clinical information	
Height z-scores	-0.35 (-2.12 – 2.04)
BMI z-scores	0.52 (-1.69 – 2.66)
Pubertal stage	
Pre-pubescent	08 (13.6%)
Pubescent	51 (86.4%)
Metabolic control	
HbA1c - latest assessment	10.2 ± 2.6%
HbA1c - average in the previous year	10.0 ± 1.6%

TABLE 2 - IQVJD RESULTS (N = 59).

Domain / Cutoff value for improved HRQOL	Mean ± SD
Satisfaction Improved HRQOL <41	34.9 ± 8.7
Impact Improved HRQOL <56	54.4 ± 10.6
Worries Improved HRQOL <28	25.3 ± 6.9
Overall sum of the domains Improved HRQOL <128	114.6 ± 22.0

IQVJD: Instrumento de Qualidade de Vida para Jovens com Diabetes; HRQOL: Health-related quality of life.

TABLE 3 - ASSOCIATION BETWEEN THE DOMAINS AND VARIABLES FOR IMPROVED QOL.

Domain	Variables associated with improved QOL	p
Satisfaction	Height z-score HbA1c Use of pen Practice of physical activity	0.02 (1) 0.03 (2) 0.04 (3) 0.01 (3)
Impact	Use of pen Practice of physical activity Lower number of hospital admissions	0.04 (3) 0.04 (3) 0.007 (3)
Worries	Height z-score HbA1c Hometown location (rural)	0.02 (1) 0.03 (2) 0.04 (3)

QOL: quality of life. (1) Mann-Whitney test; (2) Student's t test; (3) Fisher exact test.

In all, 54 patients performed some type of physical activity at an average of 3.2 times/week. DKA was present at the time of T1DM diagnosis in 63.0% of the patients and during the course of the disease in 29.0% of them. The mean number of hospital admissions in the course of the disease was 1.5 (range 0–6). The average HbA1c in the last assessment was 10.2% and the mean HbA1c in the previous year was 10.0%.

All patients were on a regimen of multiple insulin applications, ranging between 3 and 6 applications a day, with an average of 4.2. As for the type of insulin, 74.5% used a basal insulin analog (glargine) and a fast-acting insulin (lispro or aspart), 22.0% used an NPH and a regular insulin, and 3.5% used an NPH and a fast-acting insulin. To administer the insulin, 67.8% of the patients used insulin pens, 18.6% used syringes, and 13.6% used both pens and syringes. The persons in charge of administering the insulin were both the patient and caretaker in 45.7%, only the patient in 37.2%, only the caretaker in 11.8%, and another family member in 5.3% of the cases. The average number of capillary glucose measurements a day was 3.9 times, ranging from 2 to 10 measurements.

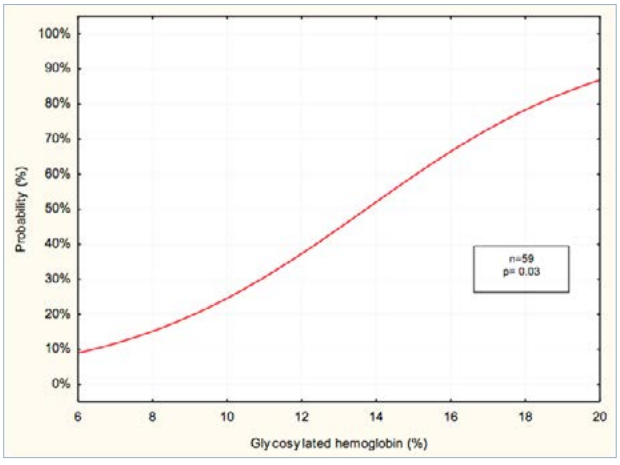
Chronic diabetes complications were absent in 93.0% of the participants, whereas 3.5% had nephropathy, and 3.5% had dyslipidemia. A total of 24.0% of the patients had Hashimoto's thyroiditis, 7.0% had celiac disease, and 5.0% had other diseases (rhinitis, congenital glaucoma, and psoriasis).

Table 2 presents the results of the IQVJD according to the different domains. The mean values in the overall cohort for the domains satisfaction, impact, worries, and overall sum of the scores were above the cutoff limit that characterizes the HRQOL as "better".

When we analyzed each domain separately considering the clinical and sociodemographic data, we observed that 43 patients scored above the cutoff limit in the satisfaction domain, whereas 16 patients scored below the limit in this domain. Compared with patients with lower scores, those with better scores showed higher height z-scores (-0.63 [range -1.56 to -0.06] versus -0.25 [range -2.12 to 2.04]; p = 0.04) and lower HbA1c levels (11.3% versus 9.7%, respectively; p = 0.02). On univariate logistic regression analysis, we observed that the higher the HbA1c, the higher was the likelihood of a worse score in the satisfaction domain (p = 0.03) (Figure 1). Patients who performed physical activity and used a pen to administer insulin were more likely to have a higher score in this domain (p = 0.01 and p = 0.04, respectively). The use of a syringe and more than one hospital admission increased by 5 times and 4.4 times, respectively, the chance of a patient having worse scores in the satisfaction domain, whereas those without DKA on diagnosis had a 75.0% higher chance of having better scores in this domain.

In the satisfaction and impact domains, patients rated their own health answering the question "When compared with other adolescents of your age, would you say your health is". A total of 17% of the participants evaluated their lives as excellent, 49% as good, 24% as satisfactory, and 10% as poor. In 51% of the patients, the scores were below the cutoff limit in the impact domain. The use of insulin pen and practice of physical activity and a lower number of hospitalizations were indicative of a better score in the impact domain (p = 0.04, p = 0.04, and p = 0.007, respectively). The use of syringes increased by 7.5 times the chance of a worse score in the impact domain, while the presentation of DKA at diagnosis and after the diagnosis increased by 6 times and 15 times, respectively, the chance of a worse score in this domain. A total of 57.0% of the patients had a mean score above the cutoff level for better HRQOL in the worries domain. Compared with patients with worse HRQOL, those with better HRQOL presented higher height z-scores (-0.67 [range -0.92 to -0.41] versus -0.26 [range -0.4 to 0.24], respectively; p = 0.02) and lower HbA1c (10.6% versus 9.7%, respectively; p = 0.03), and lived in regions of Paraná other than Curitiba or its metropolitan region (p = 0.04) (Table 3). Other analyzed sociodemographic factors showed no association. In multivariate logistic regression in-

FIGURE 1 - RELATIONSHIP BETWEEN CURRENT HBA1C LEVEL AND WORSE SCORE IN THE SATISFACTION DOMAIN (UNIVARIATE LOGISTIC REGRESSION ANALYSIS).



cluding selected variables with significant p values, we found that no other variable was strongly associated with the quality of life domains, reflected by odds ratios close to 1 and unimpressive confidence intervals containing values of or close to 1.

DISCUSSION

Patients with T1DM included in this study showed an overall good HRQOL assessed with the IQVJD, a version of the DQOLY adapted to the Brazilian population. The mean scores in the satisfaction and worries domains were above the cutoff limit characterizing "better" HRQOL. In contrast, slightly more than half of the patients scored below the limit in the impact domain, reflecting a substantial impact of diabetes on these youths' lives. Patients with a better HRQOL in this study were generally more likely to have higher height z-scores and lower HbA1c levels, a finding that corroborates the importance of the HRQOL as a determinant of health in diabetes.

Novato *et al.* applied the IQVJD to evaluate the HRQOL in a Brazilian cohort of 245 T1DM children and adolescents aged 10 to 19 years. The authors found average scores of 37.5 ± 9.8 in the satisfaction domain, 23.7 ± 7.9 in the concerns domain, and 110.3 ± 24.4 in the overall sum of the domains. These results are generally similar to those found in our study (Table 2), except in the impact domain in which the scores found by Novato *et al.*[10] were lower (49.0 ± 11.3) than ours. This suggests that our cohort had a better HRQOL in the impact domain despite the fact that our study included patients of a lower social stratum. Since studies conducted in other countries use reduced versions of the DQOLY questionnaire, we were unable to compare our results with those of these studies.

Although most of the patients evaluated in our study belong to low-income households, all patients received the recommended treatment with multiple doses of insulin, conducted frequent self-monitoring, and had access to devices and insulin analogs when recommended. It would be valuable to compare our data with those of patients followed at a private setting in the same geographical area, but this was not possible. The frequency of patients with DKA at diagnosis was high, and the metabolic control was inadequate in most patients. The analysis of the HRQOL showed that 71% of the patients had scores compatible with better HRQOL, which was associated with a lower frequency of DKA at diagnosis and during the course of the disease, better metabolic control, use of a pen to apply insulin, practice of physical activities, residence in rural areas of the state, and higher height z-scores.

The median age at T1DM diagnosis in our patients (7.16 years) was below that reported in the national [12,13] and international [14] literature (generally between the ages of 8 and 10 years). The prevalence of T1DM is currently higher in younger children, as evidenced in this study and in other Brazilian studies carried out in São Paulo (6.8 years) and Bahia (7.7 years) [15,16].

Overall, 80% of the patients reported a monthly household *per capita* income below the minimum wage. This information contrasts with the average family income in the state of Paraná, where only 44.7% of the families have incomes below the minimum wage. This may be explained by the fact that the study was carried out in a center that provides care exclusively for patients covered by the Brazilian Unified Health System (*Sistema* Único *de Saúde*, SUS)[17]. However, familial income was not associated with better or worse quality of life.

We found a high school failure rate when we compared our cohort with another with similar age range [18], but the rate in our cohort was even higher than that reported by Alves *et al.* [16] (25.8%) in patients with T1DM in northeast Brazil. There is growing evidence that children with T1DM have a higher risk of developing cognitive problems than children of similar age without diabetes. A history of an early T1DM diagnosis (below the age of 7 years), longer diabetes duration, recurrent hypoglycemia, and poor glycemic control are associated with cognitive impairment that adversely affects school performance and educational achievements[19,20]. In addition, children with a history of severe hypoglycemia have reduced verbal and language functioning[21]. A recent study has shown that children with T1DM show slower growth of both white and gray matter when compared with controls without diabetes. This observation was associated with prolonged hyperglycemia and variability in blood glucose levels, but not with hypoglycemia [22]. Tolu-Kendir *et al.* [23] assessed the neurocognitive function of 60 T1DM patients between the ages of 6 and 12 years and 40 nondiabetic, age-matched controls. They applied specific questionnaires to assess several cognitive areas and observed that the group with T1DM had lower scores in tests evaluating information, arithmetic, and comprehension. The scores were even lower in children with earlier onset of the disease.

The frequency of patients with DKA at diagnosis was high in the present study (63%) but was similar to that reported in a study conducted in the southeast region of Brazil (66%)[1]. Usher-Smith *et al.*[24] studied the frequency of DKA at diagnosis in 31 countries and observed a variation between 12.8% and 80.0%, with higher frequencies in the United Arab Emirates, Saudi Arabia, and Romania, and lower frequencies in Sweden, the Slovak Republic, and Canada. The frequency of DKA was inversely associated with the gross domestic product, latitude of the country, and incidence of T1DM. Other studies have also shown a great variability in the incidence of DKA in Europe and in the United States (15 to 70%) which is due in part to the different degrees of awareness of the disease and provision of health care [24,25]. This reflects an urge in reducing the incidence of DKA. Vanelli *et al.* [26] showed that this is possible to achieve with an informative program. The authors implemented a program that presented signs and symptoms of childhood diabetes to children in public and private schools in Parma (Italy). The program successfully reduced the incidence of DKA at diagnosis from 78% (1987-1991, a period prior to the study) to 12.5% (1991-1997, the study period).

The average level of HbA1c in the patients evaluated in our study was above that recommended by both the ADA[27] and the ISPAD [28]. Brazilian studies[10] with patients of similar age groups showed similar HbA1c values (around 10%), while a multicenter study with children and adults with T1DM in several Brazilian areas showed a mean HbA1c of 9.4%, with only 12.2% of the patients achieving the goal of metabolic control [29]. A Norwegian study showed that only 30% of the adolescents with T1DM had achieved the HbA1c goal, showing that the challenge in controlling blood glucose levels, particularly in adolescents, is common in different countries [30].

The frequency of each insulin regimen in our study differed from that in the study by Gomes *et al.* [29] in which 47% of the diabetics used NPH plus regular insulin and 22% used basal analog plus fast-acting insulin. The frequency was also different from that in a study carried out in Salvador [16], in which 91.5% of the patients used NPH insulin and 89.4% used regular insulin. This difference may be due to the fact that the state of Paraná is one of the few states in Brazil with a program in which the government (SUS) has been offering insulin analog to eligible patients since 2006 [31].

The method of insulin application in our study differed from that described in a study by Alves *et al.* [16], in which 78.9% of the patients applied insulin using only syringe, 11.3% used only pen, and 9.9% used pen and syringe.

The average frequency of capillary glucose tests performed by our patients was within that recommended by the ADA of at least four measurements a day [27] and superior to that reported in the study conducted in Salvador, which was 2.1 times/day [16].

The prevalence of diseases associated with T1DM in our study was similar to rates found in the literature. Kordonouri *et al.* [32] reported a prevalence of Hashimoto thyroiditis between 3 and 8% and celiac disease between 1 and 10% in a population with T1DM, while Whitacker *et al.* [33] found in the southeastern region of Brazil a prevalence of celiac disease of 4% in children with T1DM. The prevalence of complications was low in our population. This is probably due to the short duration of diabetes in our patients (median 6.5 years) in contrast to the disease stage in which the complications of the disease usually develop (15 to 20 years) [19].

CONCLUSION

The findings of our study corroborate the importance of assessing the HRQOL in children and adolescents with T1DM, supporting efforts to improve the care of the disease by approaching the patient and his health in more comprehensive ways, rather than from a medical perspective only. Similar studies should be conducted in patients with diabetes with higher socioeconomic levels in Brazil to assess the impact of HRQOL on disease control and care.

RESUMO

A qualidade de vida relacionada à saúde (HRQOL) no diabetes mellitus tipo 1 (T1DM) tem sido amplamente estudada. Os objetivos deste estudo foram avaliar e identificar os fatores que influenciam a HRQOL de crianças e adolescentes com T1DM.

MATERIAL E MÉTODOS: *No total, 59 pacientes (9-16 anos, T1DM por ≥1 ano) responderam a uma versão do Instrumento de Qualidade de Vida para Jovens com Diabetes (DQOLY) adaptada aos pacientes brasileiros (IQVJD). Esse instrumento compreende satisfação, impacto e preocupações de domínios, com os menores índices correspondentes a uma melhor HRQOL, e um questionário que reúne parâmetros sociais, demográficos e clínicos.*

RESULTADOS: *A idade média foi de 13,6 anos e 57,6% eram meninas. A idade mediana no diagnóstico foi de 7,16 anos, 63% apresentaram cetoacidose diabética (DKA) no diagnóstico e 29% durante o seguimento. A hemoglobina glicada média (HbA1c) no ano ante-*

rior foi de 10%. Todos os pacientes receberam doses múltiplas de insulina (média de 4,2 aplicações/ dia), 74,5% utilizavam análogos de insulina de ação rápida e de ação intermediária e 67,8% usavam canetas para aplicação de insulina. Os resultados do DQOLY estavam dentro do limite de corte para melhor HRQOL. Uma análise isolada de cada domínio e os resultados do questionário mostraram que os seguintes fatores estavam associados a uma maior HRQOL: score z de altura, HbA1c menor, prática de atividade física, uso de caneta, menos hospitalizações e residência em uma área rural. Houve uma alta taxa de cetoacidose diabética no diagnóstico, e o controle metabólico foi inadequado na maioria dos pacientes. Apesar de serem provenientes de famílias de baixa renda, a maioria dos pacientes teve acesso ao tratamento recomendado.

CONCLUSÃO: *Entre pacientes com T1DM, 71% tinham escores IQVJD compatíveis com melhor HRQOL.*

PALAVRAS-CHAVE: *Qualidade de vida. Criança. Adolescente. Diabetes mellitus tipo 1.*

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ORIGINAL ARTICLE

Normal delivery and cesarean section: cost per brazilian regions, 2015

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SUMMARY

OBJECTIVE: *To describe the number of funds made by the Brazilian National Health System to normal delivery and cesarean procedures, according to the Brazilian regions in 2015, and estimate the cost cutting if the recommendation concerning the prevalence of cesarean deliveries by the World Health Organization (10 to 15%) were respected.*

METHODS: *Secondary analysis of data from the Hospital Information System of the Brazilian National Health System. The variables considered were the type of delivery (cesarean section and normal), geographic region of admission, length of stay and amount paid for admission in 2015.*

RESULTS: *In the year 2015, there were 984,307 admissions to perform labor in the five Brazilian regions, of which 36.2% were cesarean section. The Northeast and Southeast regions were the two regions that had the highest number of normal deliveries and cesarean sections. The overall average hospital stay for delivery was 3.2 days. About R$ 650 million (US$ 208,5 million) were paid, 45% of the total in cesarean deliveries. If the maximum prevalence proposed by the World Health Organization (WHO) were considered, there would be a potential reduction in spending in the order of R$ 57.7 million (US$ 18,5 million).*

CONCLUSIONS: *Cesarean sections are above the parameter recommended by the WHO in all Brazilian regions. The Northeast and Southeast had the highest total number of normal and cesarean deliveries and thus the greatest potential reduction in estimated costs (69.6% of all considered reduction).*

KEYWORDS: *Health Policy, Planning and Management. Public Health Policy. Health economics. Natural childbirth. Cesarean section.*

INTRODUCTION

Cesarean sections have become increasingly common in industrialized and developing countries. Faúndes and Cecatti[1] warned about of the increased incidence of cesarean sections in Brazil in the early 1990s: from 14.6% in 1970 to 31% in the 1980s. At that time, they showed to be a phenomenon common to almost all countries of the world, but in no other country the increasing curve was so accentuated and the rates had reached levels as high as in Brazil. Two decades after, the surgical practice (cesarean section) reached 85% of births in private hospitals and 40% in the public health system[2].

Some factors contributed to the increase in these taxes, such as the evolution of surgical and anesthetic techniques, the risk of immediate postoperative complications reduction, defensive obstetric practice, health system characteristics, and remuneration, as well as the patients' demand[3]. As regards the demand of patients, Resolution 2.144 / 2016 of the Federal Council of Medicine[4] states that "It is ethical the

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doctor to meet the will of the pregnant woman to perform cesarean section, guaranteed the autonomy of the physician, the patient and the safety of the mother and neonate", but only after 39 weeks of pregnancy.

An indicator used to evaluate the delivery care model is the cesarean section rate. According to the normative standard of the World Health Organization (WHO), this rate should not exceed 15%, a level lower than the Brazilian. The high prevalence of cesarean sections in Brazil does not seem related to changes in obstetric risk but to socioeconomic and cultural factors, especially the controversial phenomenon of "culture of cesarean section"[5].

Faúndes and Cecatti[1] point out that "in developed countries, 1% increase in cesarean section rates is an extra expense of US$ 9,5 million" [6]. It was estimated for Brazil in 2006, for an amount of 560,000 cesarean sections performed without a real need per year, an equivalent to R$ 84 million (US$ 38,7 million).

Several actions have been taken by the Ministry of Health, in partnership with the National Regulatory Agency for Private Health Insurance and Plans (ANS) in order to sustain normal birth and reduce cesarean sections in public and private service. Below, there are examples of these actions, among others: (a) Delivery Suitable Pilot Project, for the purpose of changing the delivery care model, promoting normal birth, calling assistance services during labor, delivery and postpartum, favoring the reduction of unnecessary cesareans and possible adverse events resulting from an inadequate delivery[7]; (b) Normative Resolution No. 368, with measures to ensure the beneficiaries of health plans the percentage of cesarean surgery standards and pregnant card[8]; and (c), the Pregnancy Care Guidelines Protocol: a cesarean section in order to guide women, health professionals and managers on issues related to the delivery routes, their statements and conducts, based on the best available scientific evidence[2].

In 2015, there were 2,211,997 hospitalizations for pregnancy, childbirth and postpartum in women between 10 and 59 years in Brazil, representing 51.2% of total admissions. Out of these, 984,307 corresponded to vaginal delivery or cesarean section[9]. In this context, the aim of this article is to describe the number of funds paid by Brazilian National Health System (SUS, in Portuguese) to normal delivery and cesarean procedures, according to the five geographical regions in 2015; and to estimate the cost cutting if the WHO recommendation regarding the prevalence of cesarean sections were considered.

METHODS

This study is a descriptive and quantitative approach and using secondary data of all hospitalizations in the country, available in the Hospital Information System of the Brazilian National Health System (SIH /SUS). The five geographic regions considered in the study were North, Northeast, Midwest, Southeast, and South. The variables considered for 2015 were: Type of delivery (cesarean section and normal birth), geographic region, days of hospital stay and the amount paid by the SUS.

The tool "Tabnet", provided by the Ministry of Health, was used for data collection of hospital procedures and place of occurrence, in the year 2015. The following hospital procedures were selected: "cesarean delivery", "cesarean delivery in high-risk pregnancy" and "cesarean section with tubal sterilization"; "normal delivery", "normal delivery in high-risk pregnancy" and "normal delivery in normal delivery center". Cesarean delivery was defined as the surgical procedure that includes abdominal incision for extracting the fetus from the maternal womb, during labor[10]. Normal labor starts spontaneously, remaining thus throughout the process, until birth. The baby is born spontaneously in head position, between 37 and 42 completed weeks of gestation[11].

Values in R$ were converted to US$ by the rate of the annual mid-point (the exchange value of July 1st of the respective year).

The management of data used descriptive statistics (frequency and average).

By employing secondary data from public domain databases, there was no need for referral to the Ethics Committee.

RESULTS

In 2015, 984,307 hospitalizations for delivery were recorded in the five Brazilian regions. Of this total, 63.8% were normal deliveries and 36.2% cesarean births (Table 1). The Northeast and Southeast regions were the ones that showed the highest percentage of normal deliveries in 2015, with 37% and 33% of the total, respectively. Regarding the total number of cesarean deliveries, the scene is the same: the Northeast and Southeast regions were the regions with the highest quantity of cesarean deliveries (36% and 30% of the total, respectively). However, when comparing the percentage of cesarean deliveries, regions Mid-

west and South have the highest levels (43% and 39%, respectively).

The average hospital stay for delivery in 2015 ranged from 1.6 days (northern region) and 3.1 days (Southeast) for normal deliveries and 3.1 days (Southeast) to 4.0 days (Midwest) for cesarean births, with an overall average of 3.2 days for the country.

In 2015, SUS spent R$ 650,2 million (US$ 208.5 million) in hospitalizations for childbirth. Of the total amount spent in the five Brazilian regions, 54.9% was allocated to admissions for deliveries of the normal type and 45.1% for deliveries of cesarean section type (Table 2).

To obtain an estimate of costs, respecting the levels recommended by WHO for cesarean sections, the number of cesarean sections surplus to 15% by geographic region was obtained and increased to the normal delivery. The resulting calculation, as a means of payments made for each type of delivery (normal and cesarean section) and the difference between the values defined the estimated reduction of spending.

In Table 3, it is possible to identify the value of reduced spending in cesarean sections considering the WHO recommendation. The largest reduction occurred in the two regions with the largest numbers of cesarean sections (Northeast and Southeast), resulting in 69.6% of all considered reduction.

DISCUSSION

The data above confirm a study by Faúndes and Cecatti[1], which pointed to a progressive increase in the rate of cesarean sections since the 1970s. As pointed out in the analysis of the health situation in Brazil[12] in the year 2013, there was an increasing

TABLE 1: NUMBER OF VAGINAL DELIVERIES AND CESAREAN SECTIONS PER BRAZILIAN GEOGRAPHIC REGION, IN 2015.

Type of Delivery	South	Southeast	Midwest	Northeast	North	Total
Vaginal delivery	44,163	190,973	42,648	208,492	90,722	576,998
Vaginal delivery in high-risk pregnancy	3,074	17,327	1,603	23,983	4,171	50,158
Vaginal delivery in delivery center	0	688	0	0	0	688
Total - normal delivery	**47,237**	**208,988**	**44,251**	**232,475**	**94,893**	**627,844**
cesarean section	25,061	74,375	27,906	95,123	45,505	267,970
cesarean section in high-risk pregnancy	4,394	25,500	3,352	31,259	8,713	73,218
cesarean section with tubal sterilization	1,358	6,834	1,531	3,708	1,844	15,275
Total - cesarean sections	**30,813**	**106,709**	**32,789**	**130,090**	**56,062**	**356,463**
Overall Total	**78,050**	**315,697**	**77,040**	**362,565**	**150,955**	**984,307**

Source: Ministry of Health – Hospital Information System of the Brazilian National Health System (SIH /SUS).

TABLE 2: TOTAL AMOUNT PAID (US$) IN HOSPITALIZATIONS FOR VAGINAL DELIVERIES AND CESAREAN SECTIONS PER BRAZILIAN REGION, IN 2015

Type of Delivery	South	Southeast	Midwest	Northeast	North	Total
Vaginal delivery	8,205,333.36	35,066,895.28	7,507,523.50	34,878,025.90	15,787,196.78	101,444,974.81
Vaginal delivery in high-risk pregnancy	783,368.19	4,424,807.85	410,715.36	6,054,130.01	1,147,514.39	12,820,535.81
Vaginal delivery in delivery center	0.00	126,930.93	0.00	0.00	0.00	126,930.93
Total – Vaginal deliveries	**8,988,701.55**	**39,618,634.06**	**7,918,238.86**	**40,932,155.90**	**16,934,711.17**	**114,392,441.54**
Cesarean section	5,978,276.50	17,439,262.47	6,314,945.44	21,174,633.28	10,339,933.49	61,247,051.18
Cesarean section in high-risk pregnancy	1,678,339.84	9,771,917.40	1,367,210.33	12,348,651.57	3,359,536.80	28,525,655.95
Cesarean section with tubal sterilization	382,998.92	1,950,694.52	399,963.64	1,110,063.16	460,208.23	4,303,928.47
Total – Cesarean sections	**8,039,615.25**	**29,161,874.39**	**8,082,119.42**	**34,633,348.01**	**14,159,678.52**	**94,076,635.59**
Overall Total	**17,028,316.80**	**68,780,508.45**	**16,000,358.28**	**75,565,503.92**	**31,094,389.69**	**208,469,077.14**

Source: Ministry of Health – Hospital Information System of the Brazilian National Health System (SIH /SUS).

TABLE 3: ESTIMATED COST REDUCTION (US$) PER BRAZILIAN REGION, IN 2015

	South	Southeast	Midwest	Northeast	North	Total
% Surplus of cesarean sections	24	19	28	21	22	
Excess number of cesarean births	18,732	59,982	21,571	76,139	33,210	209,634
Excess amount paid (US$)	5,635,474.75	18,057,292.83	6,438,394.49	23,273,415.95	9,546,506.29	62,951,084.30
Value to be added to vaginal delivery (US$)	4,126,973.51	12,466,099.33	4,662,106.81	15,978,595.59	7,200,579.15	44,434,354.39
Reduction (US$)	1,508,501.23	5,591,193.50	1,776,287.68	7,294,820.36	2,345,927.14	18,516,729.91

Source: Estimates calculated by the authors, 2016.

trend of cesarean sections in all regions of the country between 2000 and 2012, especially in the Northeast region.

Of the total number of cesarean deliveries, 15.275 (4.3%) involved tubal ligation. It should be noted that surgical sterilization as a contraceptive method is only permitted if proven necessary by successive previous cesarean sections, according to the Law 2,263 of January 12, 1996[13].

Faúndes and Cecatti[1] pointed to the use of cesarean deliveries as a form of tubal ligation in 1991, at a time when surgical sterilization was not formally prohibited in Brazil. A study conducted in the Metropolitan Region of Campinas, São Paulo, between October 2004 and February 2005, pointed out that, even after surgical sterilization was regulated in 1996, the majority of the cases remained in the delivery, involving a cesarean section[14].

The Northeast and Southeast regions were the ones that performed the most normal deliveries, with the lowest mean AIH values for the procedures. At the same time, they also performed the highest number of cesareans, with the highest mean AIH values. The Northeastern region presented the highest variation among the means of payment of AIH, with a difference of R$ 298.84 (US$ 95.81), while the North region had the lowest average variation, with only R$ 220.33 (US$ 70.64).

Usual risk pregnancies accounted for 860,931 (87.5%) of all deliveries in 2015, while high-risk pregnancies accounted for 123,376 (12.5%) deliveries. Of these, 50,158 (5.1%) normal high-risk deliveries and 73,218 (7.4%) high-risk cesarean deliveries. High-risk pregnancies were responsible for the highest average AIH paid in all Brazilian regions, despite the disparities in values.

These data are consistent with Zorzetto[6], who estimated in 2006 that approximately 560,000 unnecessary cesareans were performed in Brazil, consuming almost R$ 84 million (US$ 38,7 million). Faúndes and Cecatti[1] stated that the cost of a surgical delivery was easier to identify when compared to a vaginal delivery due to the longer stay and the use of drugs and other consumables, in addition to numerous cases of iatrogenic prematurity. Finally, WHO states that (unnecessary) cesarean sections generate significant additional expenditure for already overburdened health systems[15].

CONCLUSION

The findings indicate that cesarean sections are above average recommended in all regions, particularly the Northeast and Southeast regions, as they represent the largest reduction in estimated costs. As would be expected, it was obtained a positive relationship between the length of stay in hospital basis and the amount reimbursed by SUS: the longer the stay, the greater the final amount paid.

When it is accepted the birth cesarean section levels recommended by the WHO, there would be a potential reduction of $ 57,7 million Brazilian currency (or US$ 18,5 million).

A limiting factor to this research was not to have found similar studies to compare with our data. However, regardless of this fact, the value found could be allocated to improve access to maternal and child care, as well as improve hospital structures and create new normal delivery centers in order to encourage natural / normal delivery in all regions of Brazil.

In summary, there is a need for change, restructuring the pattern of births in Brazil. The situation was already pointed out in previous studies and full of knowledge of agencies such as the Ministry of Health and the National Regulatory Agency for Private Health Insurance and Plans.

RESUMO

OBJETIVO: *Descrever o montante de recursos pagos pelo Sistema Único de Saúde por procedimentos de parto normal e cesárea, segundo as regiões brasileiras, em 2015, estimando a redução de gastos caso a recomendação da Organização Mundial da Saúde quanto à prevalência de partos cesáreas (10% a 15%) fosse seguida.*

MÉTODOS: *Emprego de dados secundários presentes no Sistema de Informações Hospitalares do Sistema Único de Saúde. As variáveis consideradas foram: tipo de parto (cesárea e normal), região geográfica de ocorrência, tempo de permanência hospitalar e valor da Autorização de Internação Hospitalar paga, em 2015.*

RESULTADOS: *No ano de 2015 ocorreram 984.307 internações para realização de parto nas cinco regiões brasileiras, sendo 36,2% de partos por cesárea. Nordeste e Sudeste foram as duas regiões que se destacaram, com os maiores números de partos normais e cesáreas. A média geral em dias de internação para parto nas cinco regiões foi de 3,2 dias. Foram pagos aproximadamente R$ 650 milhões (US$ 208,5 milhões), 45% desse total em partos cesáreas. Caso o parâmetro máximo proposto pela Organização Mundial da Saúde fosse considerado, haveria uma redução potencial de gastos na ordem de R$ 57,7 milhões (US$ 18,5 milhões).*

CONCLUSÕES: *Os partos cesáreas estão acima do parâmetro recomendado em todas as regiões brasileiras. As regiões Nordeste e Sudeste se destacaram por representar potencialmente a maior redução na estimativa de gastos (69,6% de toda a redução considerada).*

PALAVRAS-CHAVE: *Políticas, Planejamento e Administração em Saúde. Políticas Públicas de Saúde. Economia da saúde. Parto normal. Cesárea.*

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REVIEW ARTICLE

Mapping the scientific research on the negative aspects of the medical school learning environment

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SUMMARY

Objective: We sought to understand the landscape of published articles regarding medical schools' learning environments (LE) worldwide, with an explicit focus on potentially negative aspects of the LE as an effort to identify areas specifically in need of remediation or intervention that could prevent future unprofessional behaviours, burnout, violence and mistreatment among students and physicians. Methods: A bibliometric analysis was conducted in six electronic databases (PubMed/Medline, Web of Science, Cochrane Library, SCOPUS, ERIC-ProQuest and PsycINFO) through December 31, 2016, including 12 themes: learning environment – general, hidden curriculum (negative), unethical behaviours, bullying/hazing, violence, sexual discrimination, homophobia, racism, social discrimination, minorities' discrimination, professional misconduct, and "other" negative aspects. Results: Of 9,338 articles found, 710 met the inclusion criteria. The most common themes were general LE (233 articles), unprofessional behaviours (91 articles), and sexual discrimination (80 articles). Approximately 80% of articles were published in the 21st century. Conclusion: There is a clear increase in scientific articles on negative aspects of the medical school LE in high-quality journals, especially in the 21st century. However, more studies are needed to investigate negative LE aspects with greater attention paid to experimental, longitudinal, and cross-cultural study designs.

KEYWORDS: *Learning Environment, Medical Education, Medical Students, Ethics, Professionalism.*

INTRODUCTION

Environment can be defined as "the surroundings or conditions in which a person, animal, or plant lives or operates".[1] This concept, derived from the biological sciences, has increasingly been the subject of study in medical sciences and educational research. Specifically for medical schools, a student's "surroundings or conditions" encompass physical, social, and psychological influences and must be conducive to developing the knowledge, attitudes, skills, and behaviours students will need to practice as physicians. The terminology used to describe this environment varies, and has included educational environment,[2] teaching environment,[3] and, most commonly, the learning environment.[4]

The first study that focused on studying learning environments (LE) in higher education dates back to 1958.[5] Concerning medical schools' LEs, Hutchins (in 1961)[6] developed the first questionnaire and the first attempt to understand quantitatively how the environment might impact students' attitudes, values,

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and behaviours. Since then, many tools have been developed to assess medical students' perceptions of their LE,[7] showing the growing importance of this subject to medical researchers. According to Cohen,[8] if medical schools intend to deal with the erosion of professionalism during the course of medical training, "purging their own learning environments of unprofessional practices" (p. 610) is a key endeavour.

Much research now supports Cohen's[8] idea that this purging of negative aspects of the LE is critical for developing a professional physician. Much of this focuses on the cognitive/curricular or social aspects of the LE and was derived from small populations of students.[9] Reported perceptions of poor LE have already been correlated with high levels of student burnout and worse perception of quality of life,[10] decreased personal growth,[11] worse academic performance on the United States Medical Licensing Examination Step 1,[12] and also less time spent by students on activities involving direct patient contact.[13]

However, many LE general instruments used in research might not encompass all aspects of the LE that influence students' lives. Specifically, it may be especially important to consider the negative aspects of the LE because these are likely to have ensuing negative effects on medical students, as has been demonstrated for unprofessional/unethical behaviours, violence, and harassment, and their impact on students' professionalism and quality of life.[14-18]

Mapping the research on the negative aspects of the LE will help to identify areas that are already well explored, areas where more work needs to be done, how interests have trended over time among researchers, and the geographic and cultural areas where interest in these topics is greatest. Thus, the purpose of this study was to build on our current understanding of LEs through a comprehensive bibliometric analysis that develops a broader framework for LEs and their negative aspects, which can guide further investigation about each specific topic (such as original studies and systematic reviews) and medical curricula interventions.

METHODS

From September 2016 to January 2017, we carried out a bibliometric analysis to evaluate all original articles related to medical schools' LE up to December 31st, 2016. This bibliometric approach is defined as "a tool by which the state of science and technology can be observed through the overall production of scientific literature"[19] (p. 6) and is used to map a field of research, providing a statistical description of this (recent and/or historical) data.[19-21]

Since this is a review of literature, ethical approval is not required for this project. The sequence of the main phases is described below.

KEYWORDS SELECTION

Initially, three authors (R.F.D., A.O.C., J.G.O.) reviewed a sample of LE articles and independently generated a list of keywords focusing on capturing all potentially negative aspects of medical school LEs. After each list was created, four authors (R.F.D., A.O.C., J.G.O., G.L.) examined the list to eliminate redundancies and add new words to the list. Then, each independent researcher (R.F.D., A.O.C., J.G.O.) created a list of themes (clusters) made up of related keywords and compared them with the Learning Environment literature to check for alignment with the current scientific data. For this initial stage of development of themes, we examined systematic reviews and the most prominent articles published in high tier journals.

One author (R.F.D.), in collaboration with the institution librarian, was responsible for comparing each list of themes, merging similar ones and removing duplicates. A discussion among all authors brought a consensus of twelve thematic clusters, including the "general LE" and eleven negative aspects of medical schools' LE: hidden curriculum (negative), unethical behaviours, bullying/hazing, violence, sexual discrimination, homophobia, racism, social discrimination, minorities discrimination, professional misconduct, and other negative aspects. These clusters were arbitrarily defined by the authors of this paper. The general theme was based on articles with a focus on the Learning Environment, usually containing "Learning Environment" in the title and using LE measurement instruments. However, the negative aspects included research that did not always define the negative aspect as a component of the LE. Figure 1 summarizes the conceptual framework of the LE used by this manuscript.

ELIGIBILITY CRITERIA

Inclusion criteria were: original studies (longitudinal studies - cohort and case-control, cross-sectional studies, case reports, experience reports and

TABLE 1. CHARACTERISTICS OF STUDIES ON MEDICAL SCHOOLS' LEARNING ENVIRONMENT

All Studies (N = 710)	
Characteristics	**No. Studies**
Publication year	
Until 1980	15 (2.1%)
1981-1990	32 (4.4%)
1991-2000	97 (13.7%)
2001-2010	236 (33.2%)
2011-2016	330 (46.5%)
Study Design	
Cross-Sectional	551 (77.6%)
Longitudinal	75 (10.6%)
Experimental	41 (5.8%)
Experience Report	39 (5.5%)
Case Report	4 (0.6%)
Measurement Methods (only if cross-sectional or longitudinal)	
Quantitative	422 (67.4%)
Qualitative	160 (25.6%)
Qualitative / Quantitative	44 (7.0%)
Journals	
Academic Medicine	126 (18.4%)
Medical Education	67 (9.8%)
Medical Teacher	48 (7.0%)
BMC Medical Education	29 (4.2%)
Teaching and Learning in Medicine	17 (2.5%)
Impact factor journals (WoS)	
No impact factor	188 (26.5%)
0.000 - 1.00	65 (9.2%)
1.01 - 3.00	219 (30.8%)
> 3.00	237 (33.4%)
Countries (by author's affiliation)	
United States	309 (43.5%)
United Kingdom	61 (8.6%)
Canada	39 (5.5%)
Australia	32 (4.5%)
Netherlands	23 (3.2%)

experimental studies) carried out with medical students and related to their LE. Studies considered out of area (not related to LE) and out of population (not with medical students) were excluded. Furthermore, as our focus was on original studies, reviews, replications, theoretical pieces, articles without abstracts (because we needed the abstracts in order to review the paper), and book chapters were not included. No language limit was applied.

Databases search

We conducted a search in six electronic databases (PubMed/Medline, Web of Science, Cochrane Library, ERIC-ProQuest, SCOPUS, and PsycINFO) including all studies published up to December 31, 2016. A variety of Boolean expressions based on the twelve thematic clusters were created to guide the search in these databases (see Supplemental Material 1), and then each database outcome was exported to Mendeley Desktop version 1.17.6 (a free reference management program - ELSEVIER®) and sorted alphabetically in order to facilitate the review process. A hand search of references from the oldest articles identified one additional article[6] that was included in our analysis.

Data collection

Three reviewers (R.F.D., A.O.C., J.G.O.) independently screened the title, authors, and abstracts to determine if they met inclusion and exclusion criteria. If excluded, the reason for exclusion as described in the previous section was noted, and if included, the classification into one of the twelve clusters as defined above was noted. Papers that mentioned more than one theme mentioned above were discussed by all authors, who came to consensus on the most relevant finding of the article. Any discrepancies were resolved by a discussion among the reviewers in a follow-up meeting. The intra-class correlation between reviewers was assessed for the first 100 studies, based on the choice of inclusion/exclusion criteria, and we found an intra-class correlation coefficient of 0.915, showing excellent reliability between the three reviewers.

Bibliometric analysis

All included articles were exported to Excel for Mac version 14.7.2 (Microsoft®), and then each article was classified according to its characteristics: title, authors' name, journal title, journal's impact factor (by Web of Science, 2015), study design, year of publication, article's number of citations (by Web of Science and Google Scholar), and country of origin (of the corresponding author). Then descriptive statistics of all variables were analysed.

RESULTS

We found 9,337 articles across 6 databases and 1 article via hand search, resulting in a total of 9,338 articles (see Supplemental Material 2). After dropping duplicates (using the automatic Mendeley function), 5,155 articles remained. Based on our eligibility criteria, 4,445 articles were withdrawn due to one

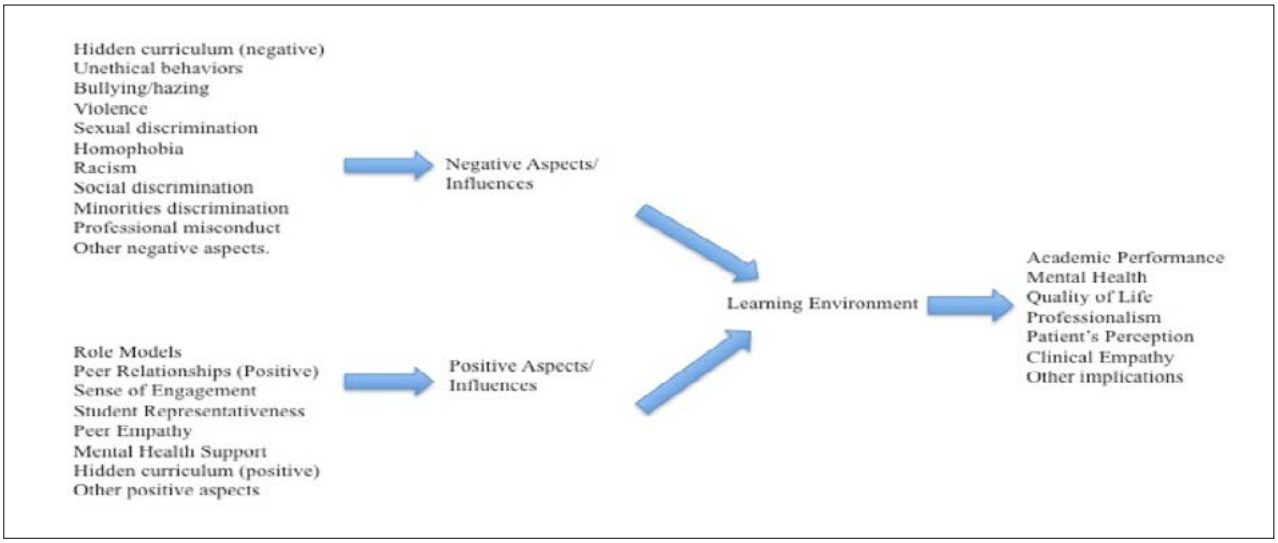
TABLE 2. MOST CITED ARTICLES ON MEDICAL SCHOOLS' LEARNING ENVIRONMENT

Rank	Article	No. WoS Citations	No. Google Scholar Citations	Average Citations/ Year - WoS
1	Lempp H, Seale C. The hidden curriculum in undergraduate medical education: qualitative study of medical students' perceptions of teaching. BMJ. 2004;329(7469):770-3.	190	471	15.8
2	Sheehan KH, Sheehan DV, White K, Leibowitz A, Baldwin DC Jr. A pilot study of medical student 'abuse'. Student perceptions of mistreatment and misconduct in medical school. JAMA. 1990;263(4):533-7.	190	311	7.3
3	Papadakis MA, Hodgson CS, Teherani A, Kohatsu ND. Unprofessional behavior in medical school is associated with subsequent disciplinary action by a state medical board. Acad Med. 2004;79(3):244-9.	189	358	15.7
4	Christakis DA, Feudtner C. Ethics in a short white coat: the ethical dilemmas that medical students confront. Acad Med. 1993;68(4):249-54.	151	248	6.6
5	Dyrbye LN, Massie FS Jr, Eacker A, Harper W, Power D, Durning SJ, Thomas MR, Moutier C, Satele D, Sloan J, Shanafelt TD. Relationship between burnout and professional conduct and attitudes among US medical students. JAMA. 2010;304(11):1173-80.	149	318	24.8
6	Richman JA, Flaherty JA, Rospenda KM, Christensen ML. Mental health consequences and correlates of reported medical student abuse. JAMA. 1992;267(5):692-4.	122	236	5.1
7	Kassebaum DG, Cutler ER. On the culture of student abuse in medical school. Acad Med. 1998;73(11):1149-58.	97	205	5.4
8	Moffat KJ, McConnachie A, Ross S, Morrison JM. First-year medical student stress and coping in a problem-based learning medical curriculum. Med Educ. 2004;38(5):482-91.	95	298	7.9
9	Karnieli-Miller O, Vu TR, Holtman MC, Clyman SG, Inui TS. Medical students' professionalism narratives: a window on the informal and hidden curriculum. Acad Med. 2010;85(1):124-33.	90	154	15
10	Baxter N, Cohen R, McLeod R. The impact of gender on the choice of surgery as a career. Am J Surg. 1996;172(4):373-6.	87	136	4.3
11	Madigosky WS, Headrick LA, Nelson K, Cox KR, Anderson T. Changing and sustaining medical students' knowledge, skills, and attitudes about patient safety and medical fallibility. Acad Med. 2006;81(1):94-101.	85	167	8.5
12	Papadakis MA, Osborn EH, Cooke M, Healy K. A strategy for the detection and evaluation of unprofessional behavior in medical students. University of California, San Francisco School of Medicine Clinical Clerkships Operation Committee. Acad Med. 1999;74(9):980-90.	85	127	5
13	Patenaude J, Niyonsenga T, Fafard D. Changes in students' moral development during medical school: a cohort study. CMAJ. 2003; 168(7): 840–844.	83	223	6.4
14	Hicks LK, Lin Y, Robertson DW, Robinson DL, Woodrow SI. Understanding the clinical dilemmas that shape medical students' ethical development: questionnaire survey and focus group study. BMJ. 2001; 322(7288): 709–710.	76	207	5.1
15	Roberts LW, Warner TD, Lyketsos C, Frank E, Ganzini L, Carter D. Perceptions of academic vulnerability associated with personal illness: a study of 1,027 students at nine medical schools. Collaborative Research Group on Medical Student Health. Compr Psychiatry. 2001;42(1):1-15.	74	135	4.9
16	Dyrbye LN, Thomas MR, Harper W, Massie FS Jr, Power DV, Eacker A, Szydlo DW, Novotny PJ, Sloan JA, Shanafelt TD. The learning environment and medical student burnout: a multicentre study. Med Educ. 2009;43(3):274-82.	70	153	10
17	Edwards MT, Zimet CN. Problems and concerns among medical students--1975. J Med Educ. 1976;51(8):619-25.	68	98	1.7
18	Stern DT, Frohna AZ, Gruppen LD. The prediction of professional behaviour. Med Educ. 2005;39(1):75-82.	66	130	6
19	Frank E, Carrera JS, Stratton T, Bickel J, Nora LM. Experiences of belittlement and harassment and their correlates among medical students in the United States: longitudinal survey. BMJ. 2006;333(7570):682.	64	162	6.4
20	Wolf TM, Randall HM, von Almen K, Tynes LL. Perceived mistreatment and attitude change by graduating medical students: a retrospective study. Med Educ. 1991;25(3):182-90.	63	116	2.5

of the following reasons: no abstract (416 articles); book chapter (20 articles); duplicate (missed by Mendeley; 376 articles); review (123 articles); theoretical articles (467 articles); out of population (not on medical students; 567 articles); and out of area (not on LE; 2,476 articles).

Finally, 710 articles were included in this bibliometric analysis. Each article was classified into one of the twelve themes, resulting in a final distribution as follows: learning environment – general (233 articles – 32.8%); unprofessional behaviours (91 articles – 12.8%); sexual discrimination (80 articles – 11.3%); minorities discrimination (76 articles – 10.7%); violence (65 articles – 9.1%); hidden curriculum (52 articles –

FIGURE 1. CONCEPTUAL FRAMEWORK OF LE USED IN THIS ARTICLE.



7.3%); unethical behaviours (49 articles – 6.9%); racism (16 articles – 2.2%); homophobia (13 articles – 1.8%); bullying/hazing (7 articles – 1.0%); social discrimination (5 articles – 0.7%); and other (23 articles – 3.2%).

Supplemental Material 3 shows the distribution of publications of all articles related to medical schools' LE included in this manuscript. The first such publication dates back to 1961;[6] publications remained relatively stable and infrequent until the 21st century, when there was a notable increase in manuscripts related to medical schools' LE. In fact, 80% of all articles related to medical schools' LE were published after 1999. Notably, a large spike occurs at approximately 2006; almost 70% of all articles were published from 2006 through 2016.

The characteristics of these studies are shown in Table 1. Most of them (77.6%) are cross-sectional and quantitative studies (67.4%). We found only 41 (5.8%) experimental studies and 75 (10.5%) longitudinal studies. Almost two-thirds of the articles were published in journals with an impact factor (IF) greater than 1.00, with one third published in journals with IF greater than 3.00. Academic Medicine (IF 4.194), *Medical Education* (IF 3.369), *Medical Teacher* (IF 2.355), *BMC Medical Education* (IF 1.312) and *Teaching and Learning in Medicine* (IF 1.159) represent five leading journals in this area. Most articles on this topic had corresponding authors who resided in the United States (43.5%), followed by the United Kingdom (8.6%) and Canada (5.5%).

Finally, Table 2 presents the 20 most-cited articles in the area of medical schools' LE. The number of citations for these articles is quite high, with 6 articles having more than 100 citations in Web of Science (WoS) and 10 articles having more than 200 citations in Google Scholar.

Supplemental Materials 4-7 present the characteristics of each of the 12 themes defined by this article. The journal *Academic Medicine* has published the most articles on medical students' LE across most of the dimensions we examined. Whereas researchers from the United States published most of the papers in this field, Pakistan published the most in bullying/hazing. Finally, some areas are quite new in the scientific literature, and until the 1980s there were no published articles on the following areas: unprofessional behaviours, violence, hidden curriculum (negative), unethical behaviour, racism, homophobia, and bullying/hazing.

In relation to the instruments used to measure the LE, we found high use of the following tools: the Dundee Ready Education Environment Measure (DREEM),[2] the Medical Student Learning Environment Scale (MSLES),[22,23] and the most recent Johns Hopkins Learning Environment Scale (JHLES).[4] Comparing articles using these tools (cluster: learning environment – general) with all articles, we found an even higher proportion of manuscripts published between 2011-2016 (53%) that used these popular measurement tools.

DISCUSSION

This study represents the first comprehensive bibliometric description for learning environment (LE) research in medical schools with a focus on negative aspects. We identify here the relatively recent rapid increase in interest in LE globally, demonstrating in-

creased awareness of the importance of this topic, and also the recent attempts to improve LE research study designs. For educators, this is an important call to increase our attention to the importance of the medical school LE as well as to explore in greater depth the potentially negative aspects of medical school LEs.

To facilitate our understanding about the conceptual framework of the LE area, we developed a concept map (Figure 1) based on the authors' own experience and the most prominent studies reviewed by this manuscript. First, our understanding is that both positive and negative aspects might influence students' perception of their LE. In this article, we decided to focus more on the negative ones. We have identified ten main negative areas that might impact students' perception of their LE (in parentheses the most cited on each area): unprofessional behaviors;[17] sexual discrimination;[24] minorities discrimination;[25] violence;[26] hidden curriculum (negative);[27] unethical behaviors;[28] racism;[28] homophobia;[30] bullying/hazing;[31] and social discrimination.[32] These negative themes may be concomitantly the source and the consequence of a "bad" LE; that is, these negative environments may create a poor perception that creates a positive feedback on these unacceptable behaviours. Educators should be aware of this, attempting to prevent a state where the "mean" turns inherent and cannot be seen, such as in the famous study of the Stanford prison experiment.[33]

Noteworthy is that while there has been an increasing number of articles published in medical education in general, not all content areas receive the same attention.[34] In our study, we found a recent and rapidly growing interest in medical school LE research, with the great majority (approx. 70%) of studies having been published from 2006 onward and in journals with an IF greater than 1.00, further indicating interest in this field among medical education researchers. What may be driving this interest in the medical school? First, our data suggest that the availability of LE measurement instruments may facilitate research. Over half of the published articles that utilized the most frequently used measures were published since 2011. Second, interest is likely being driven by greater concern for the potential negative impact of poor learning environments in medical schools, particularly student mistreatment and overwork, as these impact trainees' empathy and well-being.[10,34-36] For example, in the U.S., the American Medical Association, driven by these concerns, began supporting a longitudinal study of medical students at 28 medical schools in 2010 that has already led to several publications.[37,38] Third, medical school accreditation standards may play a role, as the creation of a new Liaison Committee on Medical Education[39] (LCME) standard related to LE quality coincides with the rapid increase in LE studies.

The United States has by far the most LE research identified in this study, followed by the United Kingdom, Canada, Australia, and the Netherlands. These findings are similar to analyses of all medical education articles[40,41] and global scientific production as a whole. Given that medical education research on the learning environment is dominated by several countries that do not represent most of the world's medical schools, educators and investigators must be cautious to ensure that they focus on local needs and do not seek to overgeneralize their results. For example, in the field of empathy research, a decline in student empathy during medical schools seems to have been largely driven by several studies from the U.S., and they were not corroborated by the bulk of international studies.[42] At the same time, when reviewing the top countries by topic, we saw that some developing countries had the greatest number of publications for certain clusters. For example, Pakistan had the most publications on bullying/hazing and Nigeria had the third most in violence. Future studies should explore whether these findings reflect the initiative of individuals or research teams or a larger trend in negative LE aspects. Considering that, like most medical education research, cross-sectional and single site studies comprised the majority of LE research, future work should use multiple methods across cultures to better understand the complex interactions between students and their LEs.

Our findings have implications for health managers and medical educators, providing further evidence that the LE could have a positive but also a negative influence on medical students. Educators must promote appropriate infrastructure, active learning strategies, good clinical scenarios, high- and low-fidelity labs, formative feedback, valuable educational content, and consistent theoretical and practical assessments. Yet, on the other hand, educators must be aware that unethical behaviours, bullying, violence, sexual discrimination, professional misconduct, and the hidden curriculum could impair medical students' academic performance and mental health. Thus, they must become aware of these possible be-

haviours occurring in their curricula. The early identification of these negative aspects of the LE and the implementation of educational and preventive interventions should serve to minimize medical training distress and future unprofessional behaviours.

This research has several limitations. First, we focused only on original studies to characterize the current evidence base related to negative aspects of the LE, which meant that we excluded many other highly cited reviews and theoretical studies that may be influential in this field. Second, we may not have identified every relevant original research article, as no database has every paper and no search strategy can find every paper. However, we did not limit by language, so this is truly an international search. Third, the databases that we searched tended to be more focused on American and European journals, possibly excluding important contributions from the southern hemisphere. Fourth, this is a novel operationalization of the learning environment and has limitations and potential biases; however, it is important to initiate a discussion about all these possible important aspects of the LE. Fifth, many of the articles included more than one of the negative areas identified in this study. However, we tried to isolate the most important subject of each manuscript in order to facilitate our understanding. Finally, we focused more on negative aspects of the learning environment. Positive aspects, such as role models, peer relationships, and sense of engagement, clearly are important in understanding medical students' LE. However, we concentrated on negative aspects because the focus of this paper was to identify research that is related to negative outcomes for medical students and that has potential for remediation. In the future, it will be important to incorporate both negative and positive aspects of the medical school LE that contribute to changes in students' empathy and well-being.

CONCLUSION

Our analysis identifies the most important areas that articles, authors, and countries have studied or reported on in terms of negative aspects of the learning environment in medical schools. We demonstrated an important growth of scientific production in high-quality journals, especially in the 21st century. However, more studies are needed that investigate the negative aspects of medical students' LE, with particular attention to experimental and cross-cultural/multi-school studies. Heightened awareness of negative aspects of the medical student LE should be useful in empowering medical professionals to make changes in the LE that will, in turn, improve student professionalism.

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Declarations of Interest

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RESUMO

OBJETIVO: *Buscou-se entender o panorama dos artigos publicados sobre os ambientes de aprendizagem (AA) das escolas médicas em todo o mundo, com um foco explícito nos aspectos potencialmente negativos do AA como um esforço para identificar áreas especificamente necessitadas de remediação ou intervenção que poderiam evitar futuros comportamentos não profissionais, violência e maus-tratos entre estudantes e médicos. Métodos: Foi realizada uma análise bibliométrica em seis bases de dados eletrônicas (PubMed/Medline, Web of Science, Biblioteca Cochrane, Scopus, Eric-ProQuest e PsycInfo) até 31 de dezembro de 2016, incluindo 12 temas: ambiente de aprendizagem - geral, currículo oculto (negativo), comportamentos antiéticos, bullying/trote, violência, discriminação sexual, homofobia, racismo, discriminação social, discriminação de minorias, má conduta profissional e "outros" aspectos negativos. Resultados: Dos 9.338 artigos encontrados, 710 preencheram os critérios de inclusão. Os temas mais comuns foram LE geral (233 artigos), comportamentos não profissionais (91 artigos) e discriminação sexual (80 artigos). Aproximadamente 80% dos artigos foram publicados no século XXI. Conclusão: Há um claro aumento em artigos científicos sobre aspectos negativos da escola de medicina LE em periódicos de alta qualidade, especialmente no século XXI. No entanto, mais estudos são necessários para investigar aspectos negativos do LE com maior atenção aos desenhos de estudos experimentais, longitudinais e transculturais.*

PALAVRAS-CHAVE: *Ambiente de aprendizagem. Educação médica. Estudantes de medicina. Ética. Profissionalismo.*

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