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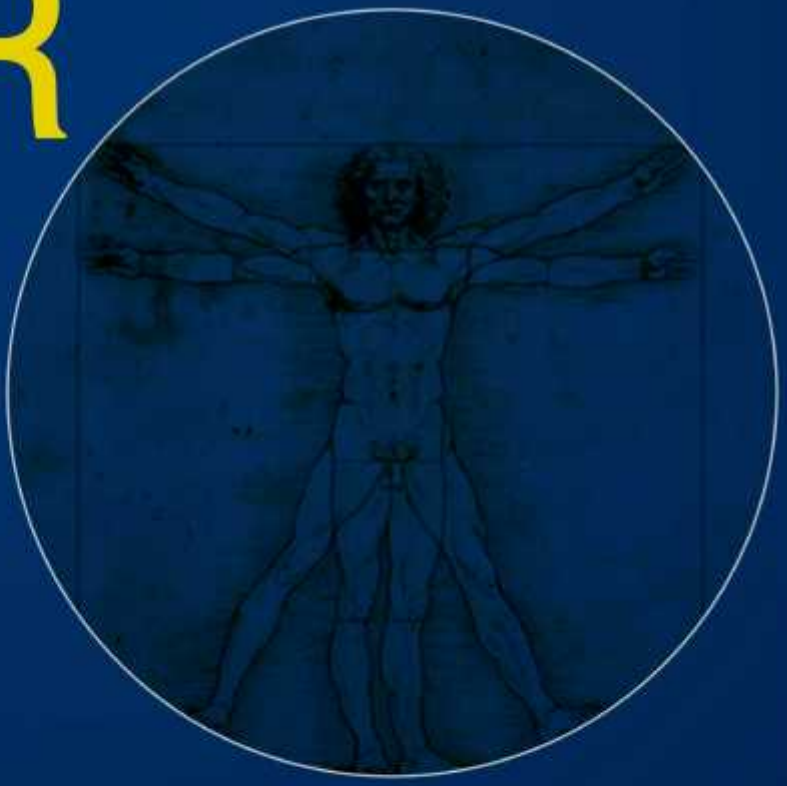

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Editorial

Prezado leitor,

Disponibilizamos a oitava edição, volume um, do periódico ***Brazilian Journal of Surgery and Clinical Research – BJSCR****.*

A ***Master Editora*** *e o* ***BJSCR*** *agradecem aos Autores que abrilhantam esta edição pela confiança depositada em nosso periódico. O* ***BJSCR*** *é um dos primeiros "Open Access Journal" do Brasil, representando a materialização dos elevados ideais da* ***Master Editora*** *acerca da divulgação ampla e irrestrita do conhecimento científico produzido pelas Ciências da Saúde e Biológicas.*

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Our eighth edition, volume two, will be available in October, 2014!

Happy reading!

Mário dos Anjos Neto Filho
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Sumário summary

Original

Case Report

Literature Review

SOCIODEMOGRAPHIC AND EPIDEMIOLOGICAL CHARACTERISTICS OF PROSTATECTOMIZED PATIENTS AT THE HOSPITAL AMARAL CARVALHO OF JAÚ

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ABSTRACT

Prostate cancer (PCa) is one of the types of disease that come with aging, due the increasing life expectancy, becoming a public health problem. PCa is one of the types of disease that come with aging, due the increasing life expectancy, becoming a public health problem. The present study study aimed to identify the characteristics sociodemographic, epidemiological and the level of information related to signs and symptoms in men with PCa undergoing radical prostatovesiculectomy at the Hospital Amaral Carvalho of Jau. A clinical, prospective and quantitative study was conducted in 42 patients with PCa, attended at Department of Urology, Hospital Amaral Carvalho of Jau. It was observed that this clientele is mostly elderly, predominantly Caucasian, the majority in overweight condition, married with low schooling, predominantly presented some type of chronic disease other than cancer and family history of oncologic disease. PCa, more than any other type, is considered a cancer of the third age, but that has now been diagnosed with precocity in its asymptomatic early stage, due to the development of health programs geared to human health and political prevention; additionally, breaking a cultural taboo of man in relation to care of your health.

KEYWORDS: Prostate cancer, prostatovesiculectomy, cancer, prostate, nursing.

1. INTRODUCTION

Prostate cancer (PCa) has become a public health problem. It is one of the types of diseases that come with aging due the increased life expectancy. However, through screening programs its disease can be detected and treated early. The PCa is an important cause of death among men in Brazil, with a strong socioeconomic impact on the population[1].

The worldwide incidence of PCa is about 20% and 4.3% of all cancer diagnoses in developed and developing countries respectively, and PCa is more prevalent than other types of cancer in men. Its considered a carcinoma of elderly, with 75% of cases occurring after 65 years old[2].

This type of visceral neoplasia represents more than 40% of tumors affecting men older than 50 years and its incidence varies with ethnicity and nationality. Countries where the disease occurs more frequently are Brazil and the United States, while Eastern countries have lower incidence. According to the Brazilian Society of Urology, it was estimated that in 2010 there would be about 234,460 new cases/ year and 27,350 deaths/ year in the United States[3]. In Brazil, its incidence rate is six times larger than other countries, with 52/100.000 cases per year, ranking second among the most common cancers among men[4]. The annual incidence rates of PCa point to Goiania, Aracaju, Belo Horizonte and Porto Alegre cities[5].

The increased incidence is related to better identification of subclinical cases, facilitated by expanding the use of prostate specific antigen (PSA) test. However, the increase in the mortality rate suggests that the increased incidence can not be completely explained due to the induction of increased proportion of new cases diagnosed at earlier stage[6].

According Rodhen & Averbeck (2010)[7], the process of care for patients with PCa should be individual, considering characteristics such as life expectancy, therapeutic results throughout the duration of treatment and its consequences, and to observe such aspects as sexual function, urinary incontinence and other side effects. Thus, knowledge of the profile of patients is important for the scientific improvement, knowledge of existing

techniques for diagnostic study and reduced mortality from this cancer.

This study aimed to identify the characteristics socio-odemographic, epidemiological and the level of information related to signs and symptoms in men with PCa undergoing radical prostatovesiculectomy at the Hospital Amaral Carvalho of Jau.

2. MATERIAL AND MÉTHODS

It is about a clinical study, qualitative and prospective character, including 42 patients with PCa undergoing radical prostatovesiculectomy by the Urology Service of the Hospital Amaral Carvalho of Jau, attended by the state-owned Unified Health System (UHS), the period from March 29 to May 27, 2011..

The data collection was conducted through direct questionnaires, after signing the consent form, observing education, place, use of tobacco and alcohol, marital status, age, date of diagnosis and date of surgery , symptomatology, Gleason score, family history of cancer among others.

Semi-structured interviews were conducted on the eve of the proposed surgery or during the postoperative period, that last four days, performed at the urology ward in a single encounter, lasting on average 30 minutes. In this type of collection, we tried to establish a conversation with the interviewees addressed around themes that formed the object of research. In the case of this part of the research were focused issues related to the care of human health, symptoms, history of cancer in the family and sexual power condition. The completion of the data and test results was taken by medical records.

The research project which incorporates this work was reviewed by the Ethics Committee on Human Research of the Hospital Amaral Carvalho of Jau, Protocol 015/11, in compliance with the standards of the National Board of Health.

3. RESULTS

Relating to the personal characteristics of the clientele at the Department of Urology, Hospital Amaral Carvalho of Jau, 14.2% of respondents were 44-55 years old, from 56 to 65 years 38.2% and 66-75 years is 47.6 %, mean age 63.0 years; 92.8% belong to the white race; only 21.4% were eutrophic and 78.6% are obese; 11.9% were smokers and 42.8% consumed alcohol; 73.8% did not complete primary school and 2.4% are illiterate; 80.8% are married and 95.2% from the State of São Paulo (Table 1).

About the pathological characteristics of the clientele at the Department of Urology, Hospital Amaral Carvalho of Jau, 62.0% had a chronic disease; 64.3% reported family history of cancer; 73.8% had PSA levels below 10 ug / l; 52.3% have prostate weight estimated by ultrasound between 14 to 30g and 47.7% have prostates weighing more than 30g.

Table 1. Personal characteristics of the clientele at the Department of Urology, Hospital Amaral Carvalho of Jau.

Characteristics	n	%
Age (years)		
44 – 55	6	14,2
56 – 65	16	38,2
66 – 75	20	47,6
Raçe		
Caucasian	39	92,9
Blacks	3	7,1
BMI*		
Eutrophic	9	21,5
Overweight	25	59,5
Obesity I	7	16,7
Obesity II	1	2,3
Tobacco use		
Yes	5	11,9
No	35	83,3
Ex	2	4,7
Alcoholic		
Yes	18	42,8
No	24	57,1
Educational level		
Illiterate	1	2,3
1st Grade Complete	5	11,9
1st Grade Incomplete	31	73,8
2nd Grade Complete	3	7,1
2nd Grade Incomplete	1	2,3
3rd Grade Complete	1	2,3
Marital status		
Single	2	4,7
Married	34	80,9
Separated/ divorced	3	7,1
Widower	3	7,1
Home State		
São Paulo	40	95,2
Minas Gerais	2	4,7
Total	**42**	**100**

* Body Mass Index

On the pathological characteristics of the clientele at the Department of Urology, Hospital Amaral Carvalho of Jau, 62.0% had a chronic disease; 64.3% reported family history of cancer; 73.8% had PSA levels below 10 ug / l; 52.3% have prostate weight estimated by ultrasound between 14 to 30g and 47.7% have prostates weighing more than 30g. In the population studied, 2.4% had Gleason score with value = 4; 69.0% Gleason score = 6; 26.2% Gleason score = 7; 2.3% Gleason score = 9; Approximately 88.0% of the surgeries were performed via

the perineal access; 4.8% by the perineal route associated with pelvic lymphadenectomy and 7.2% by retro via pubic; 45.2% reported unsatisfactory penile erection before surgery (Table 2).

Table 2. Pathological characteristics of the clientele at the Department of Urology, Hospital Amaral Carvalho of Jau.

Characteristics	n	%
Chronic disease		
Hypertension	18	42,8
Diabetes	3	7,1
Vasculopathy	1	2,3
Others	4	9,5
No	14	33,3
Family history of cancer		
Yes	27	64,2
No	15	35,7
PSA (ug/l)		
< 10	31	73,8
> 10	11	26,1
Prostatic weight (g)		
14 – 20	13	30,9
21 – 30	9	21,4
31 – 40	12	28,5
41 – 50	1	2,3
51 – 60	3	7,1
61 – 70	2	4,7
71 – 80	0	0
81 – 90	1	2,3
91 – 100	0	0
> 100	1	2,3
Gleason´s score		
4	1	2,3
6	29	69,0
7	11	26,1
9	1	2,3
Surgery		
Retropubic	3	7,1
Perineal + Linf. pelvic	2	4,7
Perineal	37	88,1
Erectile function		
Satisfactory	23	54,7
Unsatisfactory	19	45,2
Total	**42**	**100**

4. DISCUSSION

In this study there was a higher concentration of patients in the range 66-75 years. It is hereby confirmed, therefore the data published studies, where according to the National Cancer Institute[5], PCa is considered a cancer of old age, because most cases in the world occur from 65 years and up obtained in this study 47.6% were aged over 65 years. The mean of age of this population was 63.0 years. There was also diagnosed with PCa in patients aged less than 65 years. It is believed that this result may reflect the development of health programs geared to health of man and policies for prevention and early diagnosis, this adds up to a cultural break taboo of man in relation to care of their health, with the possible detect cancer at an early, asymptomatic stage. In a study conducted by Dini & Koff (2006)[1] for a period of five years, with 3,056 volunteers aged from 40 years, with a prevalence of PCa in 80 (10.1%) of them. Men diagnosed with PCa were: more younger than 60 years (21.2%), between 60-69 years (46.3%) and 70 (32.5%). The mean age was 65.8 years. Results that are consistent with the literature and our study. Gonçalves *et al.* (2008)[8], in a study of 78 medical records of patients observed higher concentrations in the range 69-73 years, representing 45% of the sample and 23.57% 63-68 years of age. The remaining amount to 13.95%, with 79 to 84 years; 20% 74-78 years 7.09% 59-63 years 2.37% 54-58 years and 3.57% 49-53 years old.

The predominance of Caucasian patients was evident, representing almost the entire sample. Race / ethnicity is considered a risk factor for the onset of cancer. The bands are classified as high risk (African-Americans), intermediate (white) and low (Japanese)[9]. Srougi (2007)[10] points out that PCa in U.S. is 10 times more common than in Japanese residents in Japan However, the rates are equal when the Japanese began to reside in the U.S., stressing that are environmental or dietary factors, not heredity, responsible for the occurrence of the disease.

About BMI, was found in the studied population, a higher concentration of patients classified as overweight, representing 59.5% of the sample; class I obesity totaled 16.7% and 2.4% was classified as obesity class II. Adopting a healthy lifestyle is important for the prevention of PCa and involve eating foods rich in fiber, fruits, vegetables, grains; low intake of saturated fat, especially animal fat; control of sugar, salt, tobacco and alcohol, associated with the practice of daily physical exercises that help in reducing the body weight[11].

Has been found that a small percentage of the sample was tobacco use and 4.8% reported having already made use of tobacco, he left the smoking habit. Regarding the use of alcoholic drinks nearly half of them reported having used any type of alcoholic beverage regularly. The INCA[12] states that, so far, are not known specific forms for the prevention of PCa, however, notes that a healthy lifestyle and quality can prevent the onset of diseases, including cancer.

Among those surveyed, the majority stated that there is 1 not completed elementary school. Low levels of education are associated with lack of information on the prevention or treatment of PCa[11]. Lucumí-Cuesta &

Cabrera Arana (2005)[13], argue that the lack of information is a characteristic of the male population with lower education levels and lower socioeconomic status. Gomes *et al.*(2008)[11] note that the information does not always result in prevention. However, research conducted by Miranda *et al.* (2004)[6], with teachers, doctors at a university, concluded that 20.7% of them even having easy access to information and diagnostic services, never made to prevent PCa. Therefore, access to information can be a preventive way to practice, but that does not mean it will go through.

Most men in this study were married, followed by separated and/ or divorced, widowed and single. In the study conducted by Gonçalves *et al.* (2008)[8], 80% of men evaluated were married, 8.23% widowed, 4.7% were single, 4.7% and 2.37% consensually united divorced. There were similarities between the results of the two studies. It is believed that a stable life, the support of a partner is very healthy for the recovery of patients with PCa.

Among the patients, almost all were stemmed city of São Paulo, while only a small percentage came from cities in the state of Minas Gerais. The fact that the geographical situation of Hospital Amaral Carvalho of Jau should, because people who have the disease seek treatment closer to the region where they live, as a state to another everything becomes more difficult and tiring for the distance to be traveled.

In respect to the pathology associated, most respondents claimed to be the bearer of any chronic disease, including, hypertension, diabetes mellitus, vascular disease, epilepsy or hemorrhoids. Note that some patients had more than one chronic disease concurrently. Generally chronic diseases affect adults around 40 years old, has cancer, often appears later in older age.

About the family history of cancer, the largest number of patients reported having other close family member diagnosed with cancer. According Srougi10 in relation to family history as a risk factor when a close relative, parent or sibling is affected by the disease, it increases the risk 2.2 times, however when two 1st degree relatives are carriers of tumor soar to 4.9 times, and is even more serious when three 1st degree relatives have the disease, the rates are 10.9 times. In such cases it is recommended to achieve the preventive examinations from the age of 40.

PCa second blood PSA level, the study showed that most patients had PSA results with values less than 10 g/L in a lower portion of the figures were above 10 g /L. According to Study Dini & Koff (2006)[1], 80 patients with CaP, the results were 6.3% PSA <4 ng/mL, 53.8% 4-10 ng/mL and 40.0%> 10 ng/mL. This study compared with the other, the data are similar, and show a positive prognosis for patients with PCa.

According with prostatic weight, the results showed that only a portion of the sample had prostate weight estimated by transrectal ultrasonography, 52.3% from 14 to 30g, followed by 28.5% from 31 to 40g, 2.4 to 41% 50 and 7.2% 51-60. Only 2.4% of the sample had prostate weight of 81 will more than 90g and 100g. To Crippa *et al.* (2009)[14] frames benign hyperplasia are associated with elevated levels of serum PSA. The maximum value of PSA compatible with benign growth equivalent to 1/10 of the weight or volume of the prostate, that is, a man with a serum PSA equal to seven or eight probably do not have cancer of the prostate gland is a weighing 80 g, but if your prostate weigh 30 g it may carry local neoplasia.

Regarding the Gleason score, it was found that all patients had Gleason score 4-9. According Crippa *et al.* (2009)[14], the expectation of patients with normal prostatic touch manifest PCa is 22% to 27% when the values of serum PSA levels ranging between 2.5 and 4 ng/mL. The diagnosis of the risk of PCa when PSA levels are between 4 and 10ng/ml of 25% and 75% of these patients have negative biopsies routine. The chance of a PCa is 55% when the PSA levels are above 10 ng/mL, in which case a local biopsy is indicated. Additional reviews have been performed in these patients to reduce the use of biopsy in high-risk cases, avoid discomfort and possible complications caused by the procedure.

Evaluating on the type of surgery, we observed a higher frequency by the perineal route. According to the Brazilian Society of Urologia (2006)[15], radical prostatectomy can be performed by retropubic, perineal and laparoscopic. There is no evidence in the literature concerning the good quality and a technique to differentiate from each other in relation to disease control. The retropubic classical pathway is the most used by surgeons due to the ease with access road, the opportunity to perform lymphadenectomy simultaneously exempts the use of specific instruments and also because it requires only basic knowledge to perform the technique.

When evaluated on the issue of erectile function, more than half of men have declared satisfactory erection prior to surgery, while others stated already present unsatisfactory erection prior to surgery. According to Srougi (2007)[10] there adverse factors related to radical surgery, despite its relevance in therapy, can cause sexual impotence and urinary incontinence. The rates of impotence are related to patients' age and affects 95% of operated above 70 years of age, approximately 60% of patients 55-65 years and in 15% to 20% of those who have less than 55 years. The risk of impotence cases are much smaller tumor hidden, i.e. not palpable on digital touch, but diagnosed by the surgeon's experience. A moderate or severe urinary incontinence affects only 1% to 2% of patients who undergo the procedure in specialized clinics, however, affects 20% to 40% of patients seen by physicians not enabled.

5. CONCLUSION

The results indicate that sociodemographic and epidemiological patients with PCa undergoing radical prostatovesiculectomy, characteristics analyzed in this study showed no significant difference in relation to literature.

Although PCa is considered a cancer of old age, this study showed the importance of early diagnosis in its early, asymptomatic stage. This is due to the development of health programs in human health and prevention policies, adds to this a cultural break taboo of man in relation to care of their health. The variability of populations in Brazil and worldwide, regarding race, ethnicity, culture and others, indicate the need and the importance of increasingly seek to characterize the profile of the disease in each region and thus evaluate the effectiveness of programs public health for the management of PCa.

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MANDIBULAR AMELOBLASTOMA RECURRENCE: RADICAL APPROACH WITH IMMEDIATE RECONSTRUCTION

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ABSTRACT

Ameloblatoma is a benign odontogenic tumor of epithelial origin, with specific clinical features as cortical expansion, painless, associated with tooth displacement and root resorption. Ameloblastoma treatment is controversial. There are conservative and aggressive treatment options, ranging from a simple enucleation associated or not with curettage to a complete mandibular resection with secure margins. This paper aims to expose a clinical case of a 60 years old patient, male, who presented with an ameloblastoma in right mandibular body 15 years ago treated by a conservative way. Treatment failed and tumor recurred 2 years ago when radical treatment option based on mandibular resection and immediate reconstruction with anterior iliac crest graft was chosen. Then, resection of ameloblastoma and immediate reconstruction proved to be a secure and effective option, providing satisfactory functional and aesthetic results as facial symmetry and later dental rehabilitation.

KEYWORDS: Ameloblastoma, reconstruction, oral pathology.

1. INTRODUCTION

The ameloblastoma is a benign odontogenic tumor of epithelial origin, derived from odontogenic epithelium or the basal cell layer of the epithelium lining the maxilares[1,2], locally invasive and rarely undergo malignant transformation[3]. On the list of benign facial tumors, it is considered one of the most aggressive, with a high recurrence rate.

These tumors represent about 1% of all tumors of the oral cavity[4]. Regarding the location, can occur in any region of the maxilla and mandible, while 99.1% of tumors are more prevalent in the mandible[5]. Like clinical characteristics, presentation is usually painless with cortical bone expansion, associated or not with tooth displacement.

The imaginological characteristics of ameloblastoma resemble other odontogenic or non-odontogenic mandibular pathologies. Although the definitive diagnosis is made by histopathological analysis, clinical and imaging findings through panoramic radiographs and computed tomography (CT) suggest some important features for the differential diagnosis[6].

Thus, ameloblastoma is classified according to clinical and radiographic findings in three main types[1]: a) peripheral ameloblastoma: cannot be diagnosed radiographically; b) multicystic ameloblastoma: evidenced radiographically as radiolucent multilocular described as "soap bubbles", characterized by aggressive behavior; c) unicystic ameloblastoma: its radiographic appearance of a radiolucent area is rounded and well defined[7].

About the treatment, there are currents of differing thoughts, making it a controversial discussion. Although some authors recommend less aggressive intervention, such as enucleation with or without other adjunctive method (curettage, ostectomy, cryotherapy, Carnoy's solution), other studies indicate a radical approach by marginal resection, segmental resection or even total mandibulectomy, in cases of mandibular ameloblastomas of considerable dimensions. Thus, the election of the best therapeutic option for each case is based on factors such as location, size and the clinical type of lesion[7]. The removal of the lesion should be performed aiming to cure the patient and maintain stomatognathic function and facial aesthetic.

This article aims to report a clinical case of recurrent ameloblastoma, previously submitted to a flawed con-

servative therapy and, after recurrence, treated with mandibular resection and immediate reconstruction with autologous anterior iliac crest graft.

2. CASE REPORT

Patient with 60 years old, male, was referred to the Oral and Maxillofacial Surgery Service, Caruaru – PE, via Regional Hospital of the Agreste. He complained of swelling in the body of the jaw, right side, without painful symptoms and associated with a history of previous treatment for an injury to the same location for approximately 15 years ago.

Figure 1. Extra oral preoperative appearance. Notice slight volume increase in the right mandibular body.

Physical examination revealed an increase in volume of painless region of the right mandibular body, lack of mobility or tooth displacement (Figure 1). Panoramic radiographs showed multilocular radiolucent area suggestive of osteolysis in the right mandibular body extending to the basal cortex of the mandible. Erosive aspect and mandibular expansion of the cortical bone were noted on the same location, seen on computed tomography (3D reconstruction) (Figure 2, A and B).

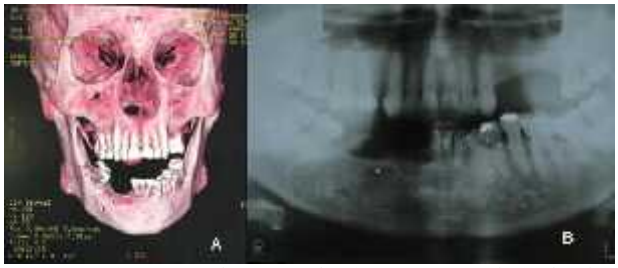

Figure 2. A) Computed tomography (3D Reconstruction) showing superficial erosion on the right mandibular body; B) A panoramic radiograph. Note region of osteolysis.

In an outpatient setting, incisional biopsy of the lesion presented ameloblastoma as pathological result. Established the definitive diagnosis and knowing about lesion's recurrence after conservative treatment, we chose radical approach with mandibular resection and reconstruction with anterior iliac crest graft, to be performed in a hospital setting.

After assessment of patient's general health condition, it was led to the operating room for the surgery, under general anesthesia and local infiltration of 2% lidocaine and epinephrine 1:100,000, submandibular incision combined with intra oral vestibule fund access, exposure of the lesion and subsequent complete resection using reciprocating saw, with 1.5 cm of safety margins. (Figure 3).

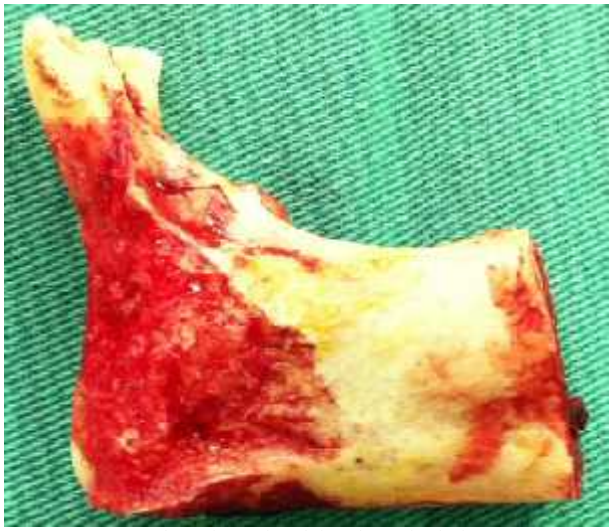

Figure 3. Resected specimen, involving the entire lesion.

Subsequently, anterior iliac crest graft was removed and modeled to the surgical receiver site, based on the size of the mandibular defect (Figure 4A). The graft was perfectly adapted to the recipient site and fixed by using a reconstruction 2.4mm plate and bicortical screws (2.4 mm x 12 mm) (Figure 4-B). The accessions were sutured in layers.

Figure 4. A) Anterior iliac crest graft; B) Correct adjustment of the graft in the defect region; C and D) Appearance of intra oral and extra oral postoperative aspect, 30 days after intervention.

The patient recovered uneventfully without immediate or late postoperative complications (Figure 4 - C and D). The patient keeps on outpatient follow-up from about one year and six months, with no signs of recurrence and adequate aesthetic and functional restoration,

with satisfactory results.

3. DISCUSSION

According to the literature regarding the clinical behavior of ameloblastoma, pathological injury that affected mandibular body of the patient on this case corroborates the general findings, which are: painless evolution, slow expansive growth but locally invasive and the pathognomonic finding of radiolucency in "soap bubbles" or "honeycomb"[5,6].

Due to the locally invasive potential and high recurrence rates reported, the best treatment option remains controversial[5]. Although some studies employ conservative treatment for treating these injuries, ambulatory monitoring showed clinical and radiographic signs of recurrence eight years after conservative treatment, requiring radical treatment to be employed[7]. These findings are similar to the case reported, where it was found to recurrence 15 years after conservative treatment.

Radical approachs as mandibular resection has some disadvantages, including morbidity of the surgical procedure and the deformity with aesthetic and functional losses that would arise, which is bypassed with immediate reconstructive procedures[8]. The selection of the appropriate type of reconstruction to be used depends mainly on the extent of the remaining defect, the surgeon's experience and the general health of the patient[8,9].

An important question concerning the mandibular reconstruction after resection of lesions corresponds to the possibility of preservation of cortical basal jaw, which provides higher quality and predictability for repair of bone defects[2]. Nevertheless, as in our case there was basilar involvement and then impossibility to maintain this bone bridge, it was necessary to complete mandibular resection.

It is imperative that, in addition to the complete removal of the lesion, it is possible to perform immediate reconstruction of bone structure lost by resection, ensuring aesthetic and functional rehabilitation in a single surgery. Immediate reconstruction has the advantages of preserving the jaw line, maintenance of facial symmetry, mucosal integrity and proper occlusion[8].

In this case, we opted for anterior iliac crest graft by several factors, such as: assessing the extent of the defect, the greater availability of bone volume, ease of removal, less interference in patient's ambulate comparing to posterior iliac crest graft removal[10]. This type of graft has shown good results in relation to integration and compatibility with dental implants for future rehabilitation[9].

4. CONCLUSION

While it is still controversial, the ideal treatment for ameloblastoma should be analyzed case by case. However, in cases of extensive lesions and/ or in cases in which relapses are observed, mandibular resection associated with immediate reconstruction is the best option because it allows adequate removal of the lesion with safety margins and immediate reconstruction, restoring aesthetics and function.

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PHARMACOLOGICAL CONTROL OF OBESITY: A ADJUNCTIVE TOOL IN THE PROCESS OF RESTRUCTURING OF HABITS OF PATIENT IN STATE OF OVERWEIGHT AND/ OR OBESITY

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ABSTRACT

Obesity is a heterogeneous group of conditions with multiple causes that ultimately reflect the obese phenotype. The positive energy balance, which occurs when the calorie intake is higher than the expense, is very important to the development of obesity since it promotes an increase in stocks of energy and body weight. The beginning of maintaining a positive caloric balance on the needs of the body, may be the result of an increase in caloric intake, as the reduction in total caloric expenditure, or both factors combined. However, it should be emphasized that the positive caloric balance is not always function as it acquires the diet. Moreover, the feeding behavior is a complex phenomenon that goes beyond the act of eating and may be related to internal and external stimuli, whereas organic factors, psychological and social. For these and many other reasons, including bringing the motivation of the patient, the use of drugs that promise to reduce weight without much effort, seems simple and a shortcut to reach the patient. But, the drugs used in weight loss should be considered as a therapy assistant, with precise indications. The limited effect of these drugs requires that patients maintain the same effort on a diet with low calories, permanent changes in diet and a program of activities and physical preparation. However, the anorexigenic are also indicated for overweight patients who are unable to lose weight without medical support and to have comorbidities such as hypertension, diabetes and dyslipidemia, with disease associated with weight gain. In such cases, as the reduction in weight may represent a better control of comorbidities, the risks of the use of these drugs are at least mitigated. Thus, the objective of this study is to suggest that drugs that promote weight reduction be used as adjuvants in weight management of obese individuals, for a limited time, so that a balanced diet and regular physical activity incorporated the daily life of the patient.

KEYWORDS: obesity, drugs, food education.

1. INTRODUCTION

The obesity is not a single disease but a heterogeneous group of conditions with multiple causes that ultimately reflect in the obese phenotype. The positive energy balance, which occurs when the ingested calorie value is higher than the expenditure, is an important contributor to the development of this disease, since it promotes an increase in the energy stores and body weight. The onset of maintaining a positive caloric balance on the body's needs, can be a consequence of increased caloric intake, as the reduction in total energy expenditure, or both factors combined[1,2].

The obese subject, besides being the target of diseases caused by excess weight, is often excluded from society worshiper of the body, where there is a default "standard of beauty", predominantly thin. Thus, the feeling of discomfort with the appearance of the body, even in non-obese or overweight subjects, is observed due to the requirements imposed by the media, especially cultists "lean beauty"[3]. Thus, given the importance of image and appearance is noticeable nowadays. Increasingly a model of beauty is gaining strength despite the real needs and possibilities of the vast majority of people; the ideal of a thin or well-designed body, which is not always achieved, providing discomfort to the individual who seeks him. In contrast, overweight is increasing alarmingly, including among children and adolescents, presenting itself as a public health problem in Brazil[3].

Given this context of increasing overweight, it is necessary to spread the basic knowledge about what is the "calorie balance" of an individual. When the subject can estimate indirectly, by calculating the BMI (Body Mass Index), which has a positive caloric balance, ie, that the intake of calories in the diet is greater than your daily requirement, and that this actually promotes weight gain, they gain the ability to awaken this individual the need to reeducate themselves about their eating habits. The BMI is calculated by dividing body mass (kg - kg) by the square of height (meters - m²). So, have befitting BMI and stature, people with less than 24.9 kg / m² BMI.

The subject are considered overweight individuals who have BMI between 25.0Kg / m² and 29.9 kg / m². Subjects who have already exceeding 30.0Kg/ m² BMI are considered obese. Within the group considered obese, the subdivision is possible in moderate obesity (30.0 – 34.9Kg / m²), severe obesity (35.0 – 39.9Kg / m²) and very severe obesity (above 40.0 Kg/ m²)[4].

It should be noted that the positive caloric balance of a person is not always a function of which is acquired through diet. Incidentally, eating behavior is a complex phenomenon that goes beyond the act of eating. Castillo *et al.* (1990)[5] also relate food intake to internal and external stimuli, whereas organic, psychological and social factors. Thus, the act of eating transcends the nutritional value and sensory characteristics of food, possessing ulterior motives related to the psychological and emotional needs and conflicting experiences that are independent of hunger[6,7].

For these and numerous other reasons, including passing the patient's motivation, the use of drugs that promise weight loss without much effort seems a simple butcher and within reach of the patient. However, the drugs available to help lose weight should be considered as an auxiliary therapeutic measure, with precise indications[8]. There is no particular strategy or medication that should be recommended for routine use there. Thus, the obese subject should be thoroughly evaluated as to errors in dietary habits and physical activity, depressive symptoms, complications or diseases associated with obesity and the possibility of developing side effects[9].

The Pharmaceutical products used in weight loss, with anorectic characteristics should be used for a limited time only with the goal of helping the patient to increase adherence to diet, with nutritional and behavioral changes as well as the introduction of a physical activity program, whose purpose would be the fitness and energy expenditure. This is because, the anorectic drugs, decrease the patient's perception in terms of difficulty of maintaining a new, more regulated than the eating routine that led to overweight or obesity[9].

The objective of this study is to suggest that drugs that promote weight reduction be used as adjuvants in weight management of obese individuals, for a limited time, so that a balanced diet and regular physical activity incorporated the daily life of the patient.

2. MATERIAL AND METHODS

For the development of this integrative review we chose the proposal of Ganong (1987)[10], according to the following steps: 1) identification of the research question, followed by a search of the descriptors or keywords; 2) determining the criteria for inclusion or exclusion of research in online databases; 3) categorization of studies, summarizing and organizing relevant information; 4) assessment of studies for critical analysis of the extracted data; 5) discussion and interpretation of the examination results, contextualizing theoretical knowledge and evaluating their applicability as; 6) presentation of the integrative review and synthesis of knowledge of each article reviewed briefly and systematic way.

In the present study the guiding question of the integrative review was: to review the literature for evidence that the anorectic drugs, thermogenic or fat absorption inhibitors should be used as aids in weight control in obese subjects, for a limited time, until the diet balanced and incorporated into the daily practice of regular physical activity of the patient.

Bases (Latin American and Caribbean Literature on Health Sciences) LILACS, SciELO (Scientific Electronic Library on Line) and PubMed (- NCBI US National Library of Medicine National Center for Biotechnology Information) were consulted. Studies that have addressed the thematic, published from 1987 to 2011, regardless of the languages of publication were included. The following controlled for the search and also used as keywords descriptors were used: obesity, anorexigens, food reeducation.

3. LITERATURE REVIEW

Obesity as a disease

As survival requires a continuous supply of energy to the maintenance of homeostasis, even when dietary supplementation is discontinuous in evolution provide a mechanism to retain adipose tissue excess latent energy from food. An example are triglycerides rich in energy, which can easily be deployed when food is absent or is less abundant. However, the combination of a sedentary lifestyle, genetic susceptibility, cultural influences and unrestricted access to an ample supply of high-calorie foods, is leading to a global obesity epidemic[11]. According Vries (2007)[12], one in five children is overweight or obese in the United States and Europe. For this reason, every year, the number of reports and studies on obesity is rising, especially in developed countries[13].

The high prevalence of overweight and obesity in children and how quickly these numbers increase every year, cause concern. Although there is little scientific evidence linking excess body fat with damage to the health of children, alarming data about the risk of morbidities related to obesity in adults generate suspicions that children can present a serious risk of developing a range of diseases with obesity, such as occurs in the adult population. Some studies suggest that obese children has about 6-7 times more likely to become obese adults, depending on the age at which children become obese[14]. In this sense, the increase in cases of type II diabetes in children, seems to confirm these concerns[15].

The obesity is not a single condition, but rather a heterogeneous group of conditions with multiple causes that ultimately reflect in the obese phenotype. This disease should be considered the result of a complex set of behavioral choices related to decisions regarding nutrition and exercise. Increasingly, people are living in an environment called "obesogenic", where the intake of high calorie foods is associated with a time availability dwindling for physical activity, resulting in increased body mass[14]. Indeed, the positive energy balance, which occurs when the ingested calorie value is higher than the expenditure, is a major contributor to the development of body mass gain, since it promotes an increase in the energy stores and body weight. The onset of maintaining a positive caloric balance on the body's needs, can be a consequence of both increased caloric intake, as the reduction in total energy expenditure, or both factors combined[1,2].

In May 2004, the United States Department of Health determined that obesity were to become recognized as a disease[16], requiring, obesity, medical care[17] More specifically, obesity should be defined as a chronic disease[18], which can be assessed by systematic scanning of body weight gain. In this sense, an indirect way to assess whether body mass gain of an individual is positive, it is through BMI - Body Mass Index. With this index, it is possible to infer, for example, if caloric intake in the diet is greater than the daily requirement, promoting body weight gain.

Some studies show that perhaps there should be a direct relationship between increasing BMI and mortality. This is because, in relation to a person with a BMI around 24 kg / m², it is observed that overweight people seem to have less chances of reaching old age; The life time also appears to be greater for individuals with mild overweight compared with those moderately obese phenotypes (BMI 30.0 - 34,9Kg / m²). Interestingly, people underweight for their height (BMI <23 kg / m²) also have lower life expectancy[19]. It is even intriguing to note that the treatment of obesity through weight reduction can result in damage to the organs and tissues resulting in higher mortality when compared with the life expectancy of people who never tried to lose weight, although were obese[20]. Overweight people or obese who are relatively active, who do not diet to lose weight, and do not continue to increase the weight gradually seem to be as healthy in the long run, as those individuals who make attempts to lose weight[21].

There is strong scientific evidence that children are tending to obesity[22]. The high rates of childhood obesity care professionals in health and therefore related to prevention research, the causes and treatment of childhood obesity are being made[23]. An important issue for the collection of these data lies in the fact that in some countries, most notably in the Mediterranean countries, children with a BMI above the ideal weight for their height are normally considered healthy. In addition, it is precisely in those countries where the prevalence of childhood obesity is higher. In Italy, for example, more than a third of children are considered too heavy[24], although the prevalence of adult obesity in this country is very low compared to other European countries[25]. Away from indicating a contradiction, the observation made in Italy can illustrate the novelty of an epidemic of childhood obesity, which in the future could result in increasing obesity for adult population.

The obese subject

If obesity is a disease, the obese would be a patient, or someone who has a condition that predisposes other diseases triggered by obesity? To answer this question, it would be necessary to turn our attention to the study of childhood obesity[26].

The prevalence of childhood obesity is rapidly increasing in recent decades, and is characterized as a worldwide epidemic. The major concern generated by this fact should be the association of obesity with metabolic abnormalities such as dyslipidemia, hypertension and glucose intolerance, which are considered risk factors for diabetes mellitus type 2 [27,28,29,30]. The consequences of childhood obesity may be noted in both short and long term. In the short term, we have orthopedic disorders, respiratory disorders, diabetes, hypertension and dyslipidemia, in addition to psychosocial disorders. Already in long-term mortality have increased particularly from coronary heart disease in adults who were obese during childhood and adolescence[31].

In addition, the obese subject, besides being the target of secondary diseases caused by excess weight, is excluded from society, where the cult of the body beautiful and is predominant. This extreme valuation of thinness, which occurs mainly in women, is influenced by the requirements imposed by the media and contrary to the real nutritional needs of that individual[3,6,32]. Increasingly a model of beauty is gaining strength despite the real needs and possibilities of the population; the ideal of a thin or well-designed body, which is not always achieved, providing discomfort to the person who seeks Him. In contrast, overweight is increasing alarmingly, including among children and adolescents, presenting itself as a public health problem in Brazil[3]. For this reason, individuals are influenced to start diets and inadequate practices of weight control for a standard set by the media, which conveys images of success, control, acceptance, love and conquest of psychological stability, associated with thinness. In the event of failure to control weight gain, the person can be seen as incapable and lacking self control. Thus, obese or overweight subjects make use of inappropriate practices for reducing body

mass, such as smoking, self-induced vomiting, use of laxatives and / or weight-loss drugs[6].

It should be emphasized, however, that the positive caloric balance of a person is not always a function of what is acquired by diet. Incidentally, eating behavior is a complex phenomenon that goes beyond the act of eating. Castillo *et al.* (1990)[5] also relate food intake to internal and external stimuli, whereas organic, psychological and social factors. Thus, the act of eating transcends the nutritional value and sensory characteristics of food, possessing ulterior motives related to the psychological and emotional needs and conflicting experiences that are independent of hunger[6,7]. Considering these factors, appropriate treatment for obesity should aim at maintaining a healthy weight, prevention of weight gain and stabilization, management of comorbidities and weight loss[33].

Dietary reeducation for obese subjects

It is commonly believed that obesity is merely the result of poor diet, or the fact led to overeat purposely disease known as hyperphagia. In fact, the situation is much more complex because many people subject to the same choices in diets did not become obese, suggesting the presence of some intrinsic homeostatic system that works to keep certain predetermined weight. Furthermore, two-thirds of obese consume carbohydrates to combat stress, anxiety, depression, mental fatigue, and not only just to alleviate hunger[6,11,32].

The search for food, which arises from the need of the metabolic process, is determined by sensory processes associated with smell and taste[32] Other influences include the price and the prestige of food, religion, geography, and storage ability in the preparation of food, and personal preferences and intolerances, as well as affective factors, beliefs and values[34].

The possibility of controlling the problem depends mainly on the patient's motivation and efficiency of the treatment plan used and dedication, competence and experience of the professionals involved. This allows teaching and helping the patient to promote permanent changes in your lifestyle habits, especially in the way they eat and relate to food, with saciamento and satisfaction with less food intake and development of a plan of regular physical activity aiming to improve and maintain their fitness[35]. The rational goal of dietary intervention is the reduction of body fat so that there is an improvement in health status or reduce the risk of complications, to prevent or reduce the morbidity related to overweight[36].

Dietary habits are the result of experience gained throughout life. Thus, it is possible to reformulate these habits in order to correct possible nutritional disorders. For example, diets high in fiber can reduce the risk of cardiovascular disease due to a reduction of total and LDL serum cholesterol. Thus, it appears that the combination of an individualized diet and nutritional education in groups help to reduce the consumption of fats, cholesterol, and simple carbohydrates that impair the body's energy balance and its oxidative metabolism[37].

If we change habits such as balanced diet, regular practice of physical exercise, stress management and not use drugs to produce weight loss, the individual could live better with quality, preventing the onset of diseases. For this reason, work with power needs to take into account and respect the regional and personal peculiarities of the patient, whenever possible, in addition to assessing the risks and factors that contributed or predisposed the onset of disease[36], demystifying the idea of food as a only source of gratification. It is also seldom mentioned the possibility of relapse or how to address it in weight reduction programs, depriving individuals to develop skills to cope with these situations or minimize their damage. In this case, the nutritionist and the psychologist may be valuable[34,38].

Regular physical activity

Regarding proposals to control obesity, exercise, united to balance energy intake has been shown to be an important determinant in this process, since low levels of physical activity may be related to increased risk, especially cardiovascular[33]. The exercise probably early, aids in weight loss and long term has the advantage of contributing to the maintenance of weight, in addition to other health benefits[38]. However, most studies do not present a consensus on the types, duration and which are best suited to each individual exercise levels and diet, reinforcing the idea that the treatment of obesity should be a restructuring of the behavior of these individuals, seeking a healthy way of life[37,45]. According to Sousa Junior & Virtuoso (2005)[45], the most recommended exercises for fat loss are aerobic exercise and resistance against those. These have the function to keep the basal metabolism of the organism or increase energy expenditure in the body leading to a negative calorie imbalance that, in turn, contributes to the loss of body weight[45].

Emotional support

Since obesity is a difficult disease to control, with high percentage of therapeutic failures and relapses, the growing emergence of eating disorders, insecurity and dissatisfaction about the body, and may have serious organic and psychosocial effects, especially in the more severe forms[32,47].

The possibility of controlling the problem depends mainly on the patient's motivation and efficiency of the treatment plan used and the dedication, expertise and experience of professionals involved in teaching and helping the patient to promote permanent changes in

your lifestyle habits, especially in form eating and relating to food, with saciamento and satisfaction with less food intake and development of a plan of regular physical activity in order to improve and maintain their fitness[35].

To get motivated, emotional balance and ability to modify eating habits permanently, many patients need a psychotherapeutic approach. Cognitive-behavioral psychotherapy associated with guidance, counseling and rehabilitation may lead the patient to a process of nutritional, sensory, emotional and remodeling learn how to rebalance do with being, teaching him to "*deal with their feelings instead of eating them*"[35]. In this sense, the family has an important role in both nutritional as part in physical activities, participating together, encouraging, suggesting alternatives and pointing failures. As well as praising the advances achieved, providing support in times of difficulties and discouragement[35].

It is known that most obese individuals eat to solve problems or offset of which, at times, unaware. Obese comes to see food as a major source of pleasure, which, because of prejudice, therefore, restricts and further impoverishes their affective and social relations. Furthermore, depreciation of the physical picture itself leads to the inability to maintain the weight loss. The lack of confidence, feelings of isolation, and humiliation, to which obese individuals are subject, refer enormous psychological burden to them. This process leads to a progressive weight gain and increasing loneliness[32].

Pharmacological control of obesity

Currently, the vast majority of obese people, the rational use of drugs that induce weight loss is considered indispensable when there is a major health risk, although it should be seen as an adjuvant[39].

In the anxiety to reduce weight, they accept any kind of suggestion, especially when it comes to miraculous formulas with quick results, without taking into account the risks of a treatment without adequate guidance[40].

The addition of anorectic, thermogenic or inhibitory drugs absorption of fats to a program of weight reduction increases the ultimate weight loss after 6 months to 1 year of continuous treatment, on average, only 2-6 kg, although a significant financial cost, side effects and increased risk of rebound quickly regained weight[8]. However, the anorectic are also indicated for patients who are overweight who can not lose weight without medical support and to have comorbidities such as hypertension, diabetes and dyslipidemia, injury associated with weight gain. In these cases, such as weight reduction may represent an improvement possibility to control these comorbidities, the risks of using these drugs are mitigated by the benefits obtained with the control or elimination of health hazards produced by comorbidities[41,42].

The use of drugs that promise weight loss without much effort seems a simple shortcut to reach the patient, especially for those little incentive for a non-pharmacological treatment. However, medications are available to help you lose weight must be considered as an auxiliary therapeutic measure, with precise indications[8]. The limited effect of these drugs requires that the patient keep the same effort of low-calorie diet, permanent changes in eating habits and program Activity and Fitness.

However, the anorectic are also indicated for patients who are overweight who can not lose weight without medical support and to have comorbidities such as hypertension, diabetes and dyslipidemia, with aggravation associated with weight gain. In these cases, such as weight reduction may represent an improvement in the control of these comorbidities, the risks of using these drugs are at least mitigated[42,43]. Then it follows that pharmacotherapy should always be used in conjunction with a program of change in lifestyle, as an aid in changing eating habits and regular physical activity[39].

The drugs used in the pharmacological control of obesity can be divided into three different categories, the main drugs are cited: 1 lipase inhibitors (orlistat), 2 combined serotonergic and adrenergic receptors (Sibutramine) and 3-adrenergic agonists (diethylpropion, phentermine, and maindole fenproporex). Other drugs such as fluoxetine, sertraline, topiramate zonizamida and will not be discussed here because they are not considered as anti-obesity drugs. However, we emphasize that fluoxetine and sertraline are useful in the treatment of depressive states associated to obesity[39,43]. Also diuretics, chorionic gonadotropin, amphetamine, dexamphetamine and thyroxine are not considered suitable for the treatment of obesity drugs. The metformin and acarbose may be useful in the treatment of obese diabetic patients, but have proven to obese non-diabetic efficacy[39].

Moreover, the results so far the pharmacological treatment of obesity has been disappointing. Some drugs have been withdrawn from the market by exhibiting unfavorable risk-benefit relationship and the long-term effectiveness mainly of appetite suppressants, is questionable. While causes weight loss in the first week of treatment, such loss compared that achieved by diet and exercise, is often modest, but a partial weight recovery occurs when used for more than one year. Note also that in almost all cases, the weight loss achieved with appetite suppressants is reversed when the drug is discontinued. Thus, the association of this fact plus the fact that obesity is a chronic condition, it is likely that patients take these drugs for life[44].

Above all, the drugs should be used as a characteristic effect on adipose tissue and not on the water or on the body lean mass, should be tolerated in the short and long

term and should be theoretical and reputable scientific studies that permit the use[33].
It should be emphasized that the medicines should only be used under medical supervision and after a careful assessment of the risk-benefit ratio for each patient especificamente[39]. Other forms of treatment used, but which are not recommended by the lack of scientific evidence of effectiveness, are acupuncture, creams for cellulite and obesity, herbal medicine, mesotherapy, yoga, hypnotherapy, the masterful said natural formulas, diuretics and laxatives[39].

Perspectives of pharmacotherapy for obesity

Studies involving the discovery of leptin, produced by adipocytes and ghrelin, produced in the stomach, opening new fields of study for the control of obesity, especially in the areas of nutrition and metabolism[47].

The action of leptin in the central nervous system, the hypothalamus in mammals, promotes the reduction of food intake and increased energy expenditure, and neuroendocrine function and regulate the metabolism of glucose and fats[47]. The expression of leptin is controlled by various other substances, such as insulin, glucocorticoids, and pro-inflammatory cytokines. Infectious states and endotoxins can also increase plasma concentrations of leptin. Conversely, testosterone, exposure and catecholamines reduces the synthesis of leptin, as well as situations of stress imposed on the body, such as prolonged fasting and strenuous exercise[47].

This hyperleptinemia found in obese people, is attributed to changes in the leptin receptor or a deficiency in its transportation system in the blood-brain barrier, a phenomenon known as leptin resistance[47]. The therapeutic benefits of treatment with leptin, in obese subjects, are still controversial.

This observation is due to plasma leptin concentration be partly related to the size of adipose tissue mass in the body[47]. Leptin reduces appetite from inhibition of appetite related neuropeptides such as neuropeptide Y and also the increased expression of anorectic neuropeptides (a-melanocyte stimulating hormone (a-MSH), corticotropin releasing hormone (CRH) and substances synthesized in response to amphetamine and cocaine[48]. Thus, high levels of leptin reduces food intake while low levels induce hyperphagia. This is proven in obese lab animals have low levels of leptin deficiency or complete[47].

However, obese subjects have elevated plasma levels of leptin, about five times more than those found in lean subjects[47]. Following this line of thinking, Friedman & Hallaas (1998)[48] found that four weeks of administration of exogenous leptin in both normal individuals as obese experienced significant weight loss. However, the reduction was only observed when the subjects had no hyperleptinemia, because the administration of leptin in obese patients with hyperleptinemia (leptin resistance) did not cause any change in body weight of these subjects[47].

Recent studies in rodents suggest that the hormone ghrelin, administered peripherally or centrally decreases fat oxidation and increases food intake and adiposity[49]. As this hormone appears to be involved in stimulus to start a meal, your levels are influenced by acute changes and chronic nutritional status, lying in a state of high nervous anorexia and reduced in obesity[50]. Furthermore, ghrelin acts as releasing growth hormone (GH) by stimulating the secretion corticotrophic lactotrófica and coupled to the control of energy expenditure orexígena activity, controlling acid secretion and gastric motility, influencing pancreatic endocrine function and glucose metabolism and even cardiovascular actions and antiproliferative effects in neoplastic cells[50].

For all these regulatory functions ghrelin are directly involved in regulating short-term energy balance. Circulating ghrelin levels are increased during prolonged fasting and in states of hypoglycemia, while its concentration is decreased after the meal or intravenous glucose[50].

Previous studies involving release of this hormone in humans show that they are the types of nutrients in the meal, not its volume, those responsible for the increase or decrease in postprandial plasma ghrelin levels[50]. Thus, the plasma concentration is decreased ghrelin after meals rich in carbohydrates, concomitantly with the elevation of plasma insulin. Moreover, increased plasma ghrelin levels were found after meals rich in protein and animal lipids, associated with a small increase in plasma insulin[50].

4. CONCLUSION

The would recommend that everyone knew exactly what your ideal weight and make an effort to lose weight every time accumulates an excess of 3 or 4kg, even before it reaches the limits of the concept of overweight.

The education of eating habits depends on knowledge of the subject that is correct in his feeding, as well as the risks involved with the promotion of obesity. Thus, it is necessary to unrestricted use of information easily accessible and understandable by everyone using: public programs and collective control of obesity, based in health centers, schools, churches, clubs, and the use of material print, video, or available in digital media, conducting group meetings, explanatory talk with doctors, nutritionists, culinary expert, physical education teachers, psychologists.

The use of anorectic agents for medical indication or self-medication is rarely accompanied by nutritional education, resulting in regained weight after the drug treatment, and often emotional imbalances related to

dissatisfaction with physical appearance. As seen, the effect of drugs with reduced weight does not have significant efficacy per se, should be used as adjuvants in the treatment of this patient, the shortest time possible, but long enough for your everyday eating habits should be restructured definivamente time.

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METHYLPHENIDATE: THE OBEDIENCE'S DRUG USED TO TREAT ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD)

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ABSTRACT

The recently most largely prescribed drug to treat Attention Deficit and Hyperactivity Disorder (ADHD) is methylphenidate. Methylphenidate is a drug that works by stimulating the "Alfa" and "Beta" adrenoceptors, in direct and indirect ways, through the liberation of Dopamine and Noradrenalin, acting in similarity to the amphetamines, which stimulates the growth and concentration of Dopamine on the synapses process. There are serious controversies regarding the effects of this substance in a long term use, since it can cause physical and psychological dependency; it can also lead to other illicit drugs addiction and in some cases have driven people to commit suicide. Professional guidance to patients that are using or will be using methylphenidate is crucial, because several patients have died as consequence of its use. The methodology used in the development of this study, was based in bibliographical references with theoretical fundaments and above all, in books and electronic documents, referents to the contents related to the methylphenidate. The results of this research looks to contribute with technical information for health professionals, that can on other hand transmit this information to parents and professors and help them to make sure this substance will be used in a very careful an rational manner.

KEYWORDS: Methylphenidate, Attention Deficit, Hyperactivity Disorder.

1. INTRODUCTION

The methylphenidate is currently the most widely prescribed for the treatment of disorder and attention deficit hyperactivity disorder (ADHD) psychostimulant. The methylphenidate helps people with ADHD blocking reuptake of dopamine and thus increasing synaptic uptake of dopamine, possibly in critical regions of the brain related disorders[1]. It is well known that psychostimulant can cause neuro-chemical and behavioral changes, chronicling-mind when used. The mechanisms responsible for the therapeutic and adverse effects of this drug are still largely unknown. Studies have shown that methylphenidate alters brain metabolic activity. Most of the energy is obtained by oxidative phosphorylation in the mitochondrial respiratory chain. Tissues with high energy demand, such as the brain, have large amounts of mitochondria[2].

The mechanism of action may be through stimulation of alpha and beta adrenoceptors directly, or by the release of dopamine and noradrenaline from synaptic indirectly terminals. Its action occur about 30 minutes before administration; the peak of concentration occur at 1 - 2 h, and has a half-life of 2 – 3 h[1,3]. This transporter regulates dopamine concentration in the synaptic cleft, which is proportional to the magnitude and duration of nerve impulse transmission. The blockade of dopamine transporter (DAT) causes an increase in dopamine levels, amplifying the signal that arises in response to nerve transmission dopa and thereby the extracellular concentration remain active for longer, significantly increasing the density of these transmitters in the synaptic gap[4].

Some neuroimaging studies specifically evaluating the effect of methylphenidate on brain metabolism. In children with ADHD the methylphenidate is associated with an increase of perfusion in the frontal lobes in the thalamus and caudate[5].

The methylphenidate is widely used in the treatment of this disorder, and the use of this drug has increased dramatically in recent years, formed especially by children and teenagers[6]. The increase in the use of methylphenidate led to questions about the consequences, in the long term, the use of this drug in children with ADHD[7]; this medication indiscriminately and improperly takes the individual to a mental addiction and often looking for other illicit substances and even suicide.

The aim of this paper is to present the use of methylphenidate as medication for ADHD; its pharmacological characteristics, as well as its adverse effects. We intend to insert the pharmacist as an active and indispensable agent, since its role is related to provide optimal support for the patient, the community and the family, in order to ensure the best quality of life, ensur-

ing a correct and effective treatment. We know that education to patients is of paramount importance, since this drug may cause the patient to death.

2. MATERIAL AND METHODS

In the present study the guiding question of the integrative review was: contribute to technical information for professional health care in order that they may be passed on to parents, teachers and patients taking this measure displacement, or will make use of it, ensuring the rational use of methylphenidate.

Bases (Latin American and Caribbean Literature on Health Sciences) LILACS, SciELO (Scientific Electronic Library on Line) and PubMed (- NCBI US National Library of Medicine National Center for Biotechnology Information) were consulted. Studies that have addressed the thematic, published from 1987 to 2011, regardless of the languages of publication were included.

3. LITERATURE REVIEW

The ADHD is one of the most common disorders that occur in children. Currently, ADHD is described as a neurobehavioral syndrome. The hyperactivity of genetic origin is an uncontrolled severe motor, which causes the child has sudden and inappropriate movements, mood swings and emotional instability. ADHD is a set of symptoms, causes and personal and environmental factors that arise in child development and behavior as a whole[1,8].

The core features of the ADHD is a problem of inattention, hyperactivity, impulsivity, or a combination thereof. Affect the academic life, family and social relationships. In addition to these basic symptoms there is comorbidity with learning disabilities, mood disorders and anxiety, and abuse of drugs and alcohol. The presence of comorbidity often makes the prognosis, long time, even worse[9].

ADHD is a very common syndrome, identified the individual who does not arouse interest and concentration in its activities, as much as we strive always ends up diverting their attention. Due to these factors, one realizes that there is no single form of ADHD.

According with Amorim (2012)[10] there are three main types of ADHD, according to the current classification of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders): ADHD Inattentive Type, ADHD Hyperactive-Impulsive Type and ADHD Mixed Type. The ADHD can occur with or without hyperactivity.

In ADHD Inattentive Type the most common characteristics are: inattention, resistance to distraction, difficulty in sustaining the effort in more demanding activities and perception of time passing. In the ADHD Hyperactive-Impulsive Type the characteristics are: agitation, hyperactivity, impulsivity, are most striking. Hyperactivity may be a problem, since disturbs the environment around. The constant search for stimulation, impulsivity and difficulty thinking before acting can bring consequences, both children and adults. The ADHD mixed Type, simultaneously displays the characteristics of the types of ADHD inattentive and hyperactive-impulsive are presents. A complete diagnosis can only be performed by a specialist for detailed diagnosis[10].

Methylphenidate use for the treatment of ADHD

According Itaborahy & Ortega (2011)[11], the methylphenidate was synthesized in 1944 and patented in Switzerland in 1954. His first appointment was as mild psychostimulant, not requiring a prescription for purchase. Marketing in Brazil, according to National Health Surveillance Agency, began in 1998.

Methylphenidate is now the most consumed psychostimulant in the world, more than all the other added stimulants. According to the report of the United Nations on production of psychotropic drugs, its global production rose from 2.8 tons in 1990 to almost 38 tons in 2006. From 38 tons produced in 2006, 34.6 were produced by the USA, which are also the largest consumers of the stimulant. In 2011, global consumption of methylphenidate was 35.8 tons, 82.2% were consumed by the USA. According to the report, the large increase in the consumption of methylphenidate, mainly in the USA, is due to its connection to ADHD and the intense publicity the drug targeted directly to American consumers[11].

In 1970, about 150,000 American children used the drug. In 1987, this estimate increased to 750,000 schoolchildren. In 1995, this number reached more than 2.6 million. In Brazil, the consumption is also growing over the years. In 2000, domestic consumption of methylphenidate was 23 kg[6]. The Brazilian production increased from 40 kg in 2002 to 226 kg in 2006. Also in 2006, Brazil imported 91 kg of stimulant[11].

Some hypotheses for the growth of production and consumption of methylphenidate are presented. One, are the changes in diagnostic criteria that always tend to expand the group of people who fall within the diagnosis of ADHD, thus increasing potential users of stimulants. Moreover, the pressure on the children's performance would disproportionately increased social support given to them[11].

One of the most controversial points in relation to ADHD refers to treatment, and disturbing the overall growth of the use of psychostimulants, which appear in the literature as the drugs of first choice. Methylphenidate is the most used and object larger number of surveys prescribed in about 90% of cases[12].

Methylphenidate is widely used in the treatment of this disorder, and the use of this drug has increased dramatically in recent years, especially by trained child and adolescent public[6]. The increase in the use of

methylphenidate led to questions about the consequences, in long-term, chronic use of this drug in children with ADHD[7]. The drug is a psychostimulant prescribed mainly for the treatment of children diagnosed with ADHD. Being a stimulant related to amphetamines (like cocaine), if consumed in the right dosage, it is argued that would help the performance of students and academic tasks, it increases the activity of executive functions, increasing concentration, besides acting as attenuator the fatigue[13]. This medicine comes with a promise to calm the circle of impulsivity and restlessness, resulting in better concentration and motor coordination. For this reason is one of the most common alternatives prescribed to treat ADHD.

Pharmacological characteristics of methylphenidate

After oral administration, the active ingredient (methylphenidate hydrochloride) is rapidly and almost completely absorbed. Owing to extensive first pass metabolism, its systemic availability was only 30% (11-51 %) of the dose. Ingestion with food accelerates the absorption, but has no effect on the amount absorbed. Peak plasma concentrations of around 40 nmol/ L (11 ng/ mL) are obtained on average 2 h after administration of 0.30 mg/ kg. Peak plasma concentrations, however, vary markedly between patients. The area under the plasma concentration curve (AUC) and maximum plasma concentration is proportional to the dose[14].

In blood, methylphenidate and its metabolites are distributed between the plasma (57%) and erythrocytes (43%). The binding to plasma proteins of methylphenidate and its metabolites is low (10-33 %). The apparent volume of distribution is around 10 L/ kg[14].

The methylphenidate resides primarily in the D-enantiomer (based on desired therapeutic effect). D-methylphenidate binds to the DAT in the brain while the L-methylphenidate enantiomer does not bind (base desired therapeutic effect)[2].

The distribution of D-methylphenidate in the human brain is greater in the basal ganglia, while the enantiomer L-methylphenidate is distributed homogeneously throughout the brain. Both enantiomers have similar rates of uptake, with peak concentrations reached within 10 minutes after administration. However, the rate of clearance of D-enantiomer is significantly slower than that of L-enantiomer [2].

Biotransformation of methylphenidate is rapid and extensive. The predominant peak plasma concentrations of the diesterified metabolite, acetic-phenyl-2-piperidin acid are reached at about 2 h after administration of methylphenidate is 30 to 50 times higher than those of unchanged substance. The half-life of the acid-phenyl-2-pipe-ridine acetic is about twice that of methylphenidate and mean systemic clearance is 0.17 L/ h/ kg. Only small amounts of hydroxylated metabolites (eg.: hydroxymethylphenidate and hydroxyritalinic acid) are detectable. The therapeutic activity seems to be mainly due to the parent compound[14].

The methylphenidate has been considered a weak CNS stimulant because the recommended oral dose is metabolized rapidly into ritalinic acid. The metabolite formed has low affinity for DAT, indicating that this drug at therapeutic doses, blocks a large portion of the DAT[2, 15]. The apparent mean systemic clearance is 10 L/ h/ kg. After oral administration 78 - 97 % of the administered dose is excreted in the urine and 1 to 3% in the faeces as metabolites, in 48 to 96 hours. Only small amounts (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as acid-phenyl-2-pipe-ridine acetic (60-86%)[14].

There are no apparent differences in pharmacokinetic behavior of methylphenidate between hyperactive children and normal adults. The data show that elimination in patients with normal renal function, renal excretion of unchanged methylphenidate would be reduced only in the presence of decreased renal function. However, the renal excretion of acid metabolite-phenyl-2-piperidine acetic acid can be reduced[14].

The methylphenidate treatment leads to an amplification of the signal by blocking DAT, whereas the decreases in striatal dopamine neuron after release while the cortical-striatal signal are stronger in striatal cells. This increases the selective amplification signal in target neurons, which could lead to improved care and decreased distraction[2].

Thereby, it could be speculated that the improvement of the dopaminergic signal induced by methylphenidate causes an increase in the perception of the stimulus for achievement and motivation of the individual to engage in tasks with improved attention and performance. Little is known about the mechanisms that contribute to the effectiveness of stimulants or on neuroadaptacional possible consequence of methylphenidate on its long-term effects of chronic use, especially in children, and its effects on neurochemistry[2].

Methylphenidate acts as a potent agonist of the alpha and beta-adrenoceptors directly, or indirectly by the release of dopamine and norepinephrine, which is similar to the mechanism of action of amphetamines that stimulate increased concentration of dopamine in the synapses[3, 4,16].

The role of methylphenidate on prefrontal cortex is implicated in the development of locomotor sensitization and behavioral changes. Furthermore, there are studies indicating their association with certain aspects of drugs of abuse. Given the fact that there is great interest in finding out whether there are adverse effects of prolonged use of stimulants on learning and behavior, whereas in children, the CNS is under continuous development and maturation[2, 3].

Very little is known about the neurochemical changes induced by this drug and changes in cell signaling pathways or expression of immediate genes. It is crucial that these data come to know since this drug is widely used in children, period of diagnosis of ADHD, where the indi-vidual is in full neurobiological and psychological development[2].

Methylphenidate raises alert level in the central nervous system, causing increased production and recycling of neurotransmitters, resulting in improved concentration, coordination and impulse control in patients with ADHD. Some neuroimaging studies specifically evaluating the effect of methylphenidate on brain metabolism. In children with ADHD are methylphenidate associated with an increase of perfusion in the frontal lobes in the thalamus and caudate[5].

Its mechanism of action has not been completely understood and is still used to treat ADHD. The mechanism by which it exerts its mental and behavioral effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system. The L-enantiomer appears to be pharmacologically inactive[14,17].

Adverse effects of methylphenidate

The adverse short-term effects, we have to nervousness, decreased appetite and insomnia as major, occur early in treatment and is usually controlled by reducing dosage and omitting the dose in the afternoon or night. There is also less frequently, abdominal pain, headache, drowsiness, dizziness, proneness to crying, tics, nausea, nail biting, talking little, anxiety, indifference, euphoria, irritability, nightmares, sadness, "stopped looking" toxic psychosis sometimes with visual and tactile hallucinations, transient depressed mood, and even suicide wish. In the long term, there are three most important adverse effects: dependence, cardiovascular effects and possible decrease in height[15,16].

Other adverse effects of methylphenidate, already described, are visual disturbances, tingling sensations, increased willingness to cramps, to fits of epilepsy and damage to heart vessels, with isolated cases of death[18].

Effects that this substance causes the individuals are extremely worrying. The most talked reaction, and that just nicknaming of "obedience's drug" is the zombie effect that can cause a sort of apathy or lethargy[19].

In the gastrointestinal tract has been reported abdominal pain, nausea, vomiting, dry mouth, which according to literature usually occur early in treatment and may be alleviated by concomitant food intake. Occasionally, tachycardia, palpitations, arrhythmias, changes in blood pressure and heart rate and angina pectoris was rarely observed. May appear on the skin rash, pruritus, rash, fever, arthralgia, alopecia. Isolated cases of thrombocytopenic purpura, exfoliative dermatitis and erythema multiforme. Blood have been reported isolated cases of leukopenia, thrombocytopenia and anemia[14].

These reactions can cause great inconvenience to patients and their families, because in addition to the symptoms of ADHD, will acquire others through the use of the drug. We should take some precautions with treatment using methylphenidate.

> Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only after detailed survey of the history and evaluation of the child. The decision to prescribe methylphenidate should carry the specification of the severity of symptoms and their appropriateness to the age of the child, considering not only the presence of one or more abnormal behavior characteristics. In which these reactions are associated with symptoms of acute stress, treatment with methylphenidate is usually not indicated[14].

The use of the drug is an alternative that can bring some benefits. Remember that behavioral patterns, skills, abilities, are developed over the years, with practice and persistence. There is a saying: "*Pills do not teach skills*".

"The World Health Organization - WHO classifies Ritalin in the world as the most addictive drug which, due to its high potential for abuse."[18].

> [...] Excess methylphenidate may refer to marked tolerance and psychological dependence with varying degrees of behavioral changes. Episodes of frank psychosis may occur, especially with parenteral abuse. Clinical data indicate that children who received methylphenidate have no more possibility of drug dependence compared to teens and adults[14].

This medication indiscriminately and improperly takes the individual to a mental addiction and often the search for other substances such as alcohol, drugs and even suicide. As children clinical data says that the probability of dependency during childhood does not increase, even so be careful when administering methylphenidate in children is the duty of parents and physicians, especially in children under six years of age since the bull itself warns that "should not be used in children under six years of age, since safety and efficacy in this age group have not been established" [14].

The evidence suggests that methylphenidate should be indicated for children with ADHD over six years, behavioral therapies the treatment of choice until this age, and then six years of age enter as methylphenidate treatment. Even with so many evidences that indicate that methylphenidate for children under six years of age

should not be given doctors continue prescribing this medication, not caring about age. There are cases of children with three or four years old already taking this medication[20].

Among the reports listed as the misuse of methylphenidate in children under six years (age range for which the use is expressly contraindicated in bull) that can lead children to serious complications further aggravating the situation you are in because of the association between the drug and the onset of severe adverse reactions, especially cardiovascular events (37.8%) as tachycardia and hypertension, psychiatric disorders (36%) such as depression, psychosis and addiction, as well as the neurological system as dyskinesia, involuntary muscle contractions and spasms, among others[21].

Recently there have been several criticisms of the very high increase (more than 1,000% in Brazil) in prescribing medication for children, especially methylphenidate. Today, Brazil is the second country that consumes more methylphenidate in the world. In addition, consumption of non-ADHD patients, illegal Internet sales, abuse by young people in ballads or better results in tests or work already assumed frightening proportions and very similar to the other manifestations of drug trafficking[22].

The high increase in the prescription of methylphenidate makes Brazil the second largest consumer of this drug in the world, second only to the USA. This drug has been used improperly and incorrectly, both by prescription and illegally by students, businessmen, etc.

Pharmaceutical assistance to patients with ADHD using methylphenidate

Resolution 308 (May 2, 1997) defines the Pharmaceutical Assistance as "*the set of activities and services in order to ensure integrated care, promotion and restoration of health, in public and private establishments that perform project activities, research, handling, production, storage, dispensing, distribution, warranty and quality control, sanitary and epidemiological surveillance of medicinal and pharmaceutical products* "[23]. The Pharmaceutical Assistance encompasses a range of activities, from production to the use of medicines by patients[24].

A multidisciplinary team should be part of the monitoring of the patient with ADHD so that there is an complete evaluation and detailed individual from a wide range of factors, such as biological, psychological and educational, for this reason the presence of the pharmacist is essential that staff[24].

The pharmacist is essential in the treatment of ADHD, as their role is to provide optimal support for the patient, the community and the family, in order to ensure the best quality of life, ensuring a correct and effective treatment. Having duty to direct patients to the importance of treatment adherence, explaining about the correct antihypertensive medication use, the purpose, dosage, how to act, and their side effects, drug interactions, such as methylphenidate, the same decreases the effectiveness of the medication used to treat hypertension. The combination with alcohol may intensify adverse effects of the drug in the CNS and clarify the contraindications how to make use of the methylphenidate when patients have the following conditions: hyperthyroidism, cardiac arrhythmia, glaucoma, individuals with bouts of anxiety, tension and agitation, among other cases[24].

The methylphenidate hydrochloride is a stimulant drug of the CNS, belongs to the class of amphetamines, a psychotropic substance (narcotic) international control of notifiable prescription type - A3, issued in the form of yellow color. The yellow color indicates the narcotic substance as "*a substance that can result in physical or psychological dependence*"[25]. The pharmacist acts still stressing the importance of the rational use of medicines, helping to prevent the misuse of drugs used in the treatment of ADHD, which drugs are stimulants, often misused by students seeking better performance in their school and academic activities.

The pharmacist seeks an interaction with the patient, aimed at logic pharmacotherapy, with excellent results-improving the quality of life of patients.

4. CONCLUSION

Would be recommend everyone to know exactly what the indiscriminate use of methylphenidate hydrochloride has been performed frequently by many people, especially in children can lead to serious complications further aggravating the situation you are in because of the association between the drug and the onset of severe adverse reactions, especially cardiovascular events such as tachycardia and hypertension, psychiatric disorders such as depression, psychosis and addiction, as well as the neurological system as dyskinesia, involuntary muscle contractions and spasms, among others; including mostly the people who are not suffering from any disorder use as a device to remain awake, to focus beyond the usual or even lose weight. This practice is not recommended because it is dangerous and can cause serious problems to the usurer medicine. The methylphenidate hydrochloride should be prescribed by a doctor, only with notification recipe yellow A3 list. The increase of indiscriminate use of methylphenidate is associated with immediate effect as a stimulant of the central nervous system, but what most people do not know are the adverse effects caused by this drug. The pharmacist as a health professional should guide users of methylphenidate and enlighten the public that the abuse of this drug

causes adverse reactions from, cardiovascular, central nervous system digestive, psychosis, hallucinations, seizures, drowsiness, anxiety and even desire suicide.

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HORMONE REPLACEMENT THERAPY IN MENOPAUSE

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ABSTRACT

The menopause is understood like a menstruation cease, because of sudden fall in hormone production. Generally, the symptoms at this stage are heat waves, lack of vaginal lubrication, loss of skin elasticity, hormonal changes, intensification of bone decalcification and reduction of libido. In order to alleviate these symptoms there are Hormone Replacement Therapies (HRT) that use synthetic drugs as estrogen and progesterone and/ or phytoestrogens as isoflavones. However, must be analyzed each person and the purpose of treatment. The prescription medications should be made based on the risks and benefits for the patient, aiming to improve the quality of life and relief of discomforts caused by hormonal lack.

KEYWORDS: Menopause, hormone replacement therapies, estrogen, progesterone, isoflavone.

1. INTRODUCTION

Throughout the life cycle, women are faced with a series of hormonal changes, with menarche, first period, the representative mark of the beginning of the reproductive period and menopause, with the stop of menstruation, the end of this period. Menopause is the result of disruption of production of ovarian follicles as a result of a sharp decline in the production of female hormones, which takes place between 40 and 50 years[1,2].

Regarding to their origin, menopause may occur in two forms: natural menopause divided into early and late and the artificial divided into surgical and radiotherapy chemotherapy[3].

Twelve months prior to the experiment are referred to as perimenopause, which is the period of change between reproductive and non-reproductive phase. This period is the first of three phases of menopause, also called premenopausal or perimenopausal then has properly menopause, and then, post-menopausal[4,5].

The lack hormonal featuring menopause induces prevalence of symptoms such as hot flashes, decreased vaginal lubrication, reduction in the elasticity and stiffness of the skin, changes in mood, loss enhancement of bone calcification as well as reduction of libido[6].

In order to alleviate these symptoms, there Hormone Replacement Therapies (HRT), using synthetic drugs such as estrogen and progesterone and/ or phytohormones such as isoflavones. To do so, each agency and the purpose of treatment should be considered[6].

The inclusion of healthy habits in everyday life through physical exercise, balanced diet and entertainment with activities that enhance the quality of life are also important points that may reflect on healthy aging and possibly in a less discomfort with menopause[7].

Therefore, this study aimed to address the hormone replacement therapies that make use of synthetic hormones and phytoestrogens aimed at mitigating the symptoms of the menopause, it was necessary to distinguish the phases that compose it, set the menopause and its types and present prominent symptoms.

MATERIAL AND METHODS

This study was based on a literature review, through the survey and consultations on scientific sites like: liberary Scientific Electronic Online (SciELO) and Latin American and Caribbean Literature on Health Sciences (LILACS), using keywords like: menopause, hormone replacement therapy, estrogen, progesterone and isoflavones.

In search of material were taken into considering the articles that contained a broad approach to the use of hormone replacement therapy in menopause, as well as the definition of the symptoms and stages of their.

2. LITERAURE REVIEW

Menopause is composed of three stages: perimenopause, menopause and postmenopause.

Menopause, also known as perimeno-break or pre-menopause is diagnosed by menstrual irregularity present in the 12 months leading up to menopause[5].

It is characterized as a period in which a decrease occurs in the production of hormones, estrogen and progesterone, due to the decreased ovarian activity. Rocha (2010)[8] stated that with the disappearance of ovulation and corpus luteum formation in the uterus, thereby re-

ducing the reservoir of follicles in the ovaries occur making the body unable to developing embryo in its early stages, marking the transition from premenopausal for senescence[9].

Menopause is considered as the period perimenopause (two to five years before the last menstrual period) until one year after the end of menstrual cycles[9]. This stage can be characterized by hypoestrogenism, leading to prevalence of symptoms such as hot heat, irritability, sweating, headache, decreased sexual desire, anxiety, night sweats and other[10].

Already menopause itself is understood as the cessation of menstruation. Results from a series of changes that occur in the ovary, since the decline of gonadal function to the depletion of follicles, leading to a disturbance in the synthesis of estrogen and progesterone, characterizing the end of the reproductive period of woman. Generally, this phase takes place at around 45 to 55 years of age[5,11], followed by one year of amenorrhea[11]. Menopause can, in some cases, be diagnosed as menstrual or even as an exacerbation of vaginal blood flow and may lead to irregularities frames hemorrhage[9].

Finally, we have the post-menopause, which covers the period of one year after amenorrhea, and in some cases, prevails in later years. The same can be divided into early post-menopausal corresponding to the first five years of menopause and late post-menopausal women who are following the end of the recent post-menopausal ten years. At this stage the woman should be aware of the changes that may occur in your body, being the common prevalence of osteoporosis due to extremely low levels of estrogen, as well as the onset of heart disease[3,12,13].

Types of menopause

Regarding its origin, menopause may be natural or artificial factors of current[3].

Natural menopause occurs spontaneously according to the female physiology, without interference from extrinsic factors, may present early or late way[3].

Early menopause can occur around 40 years old going on due to the increase of the hormones FSH and LH, and autoimmune processes that would completely inhibit the functioning of the cells of the ovary. Thus, there is an early ovarian failure, and hence the depletion of ovarian follicles, leading the last menstruation. During this period the increase in LDL can occur, as well as the onset of osteoporosis and insomnia[3].

There are reports that smoking is seen as a factor that favors the anticipation of menopause, due to hypoestrogenism caused by the same. Beyond the early menopause, tobacco use may enhance the development of osteoporosis and the onset of cardiovascular disease[14].

On the other hand, late menopause is taken as a rare and occurs when the last menstruation occurs at about age 55, in which case the probability of diagnosis of breast cancer and endometrial is increased due to prolonged hormonal stimulation[4].

Artificial menopause as their name suggests, are cases which is caused by menopause artificial factors, namely the female body is subjected to changes that induce menopause. There are several reasons that lead to this event and can be divided into surgical, chemotherapy, radiotherapy and transient[3].

Surgical menopause is caused by performance of an oophorectomy, consisting of the removal of the ovaries or a hysterectomy, the uterus is removed, the extinction occurring in the production of sex hormones and consequently making menopausal women[3].

Regarding chemotherapy menopause, it is acquired as a result of exposure to substances used in chemotherapy[3].

Already radiotherapy menopause is caused by exposure to radiation due to neoplastic treatments arising from the use of synthetic hormones [4].

Finally, the temporary menopause from the use of medications for treatment of fibroids and endometriosis, that interfere with the natural physiology, thereby inhibiting the action of GnRH hormone producing the FSH and LH, and as a result of cessation of hormone production[3,15].

Hormone Replacement Therapy (HRT)

As a consequence of hormonal changes from the female physiology, all women at some point in their life cycle through menopause will thus suffer from the discomforts arising from same.

Whereas life expectancy in Brazil has increased from 70 years in 2000 to 74 years in 2013, according to IBGE, it is estimated that Brazilian women spend more than a third of his life in postmenopausal consequently will have a period of hormonal shortage prolonged. Thus, there is need to use treatments that aim to provide better quality of life by relieving the discomforts caused by this hormone lag[16, 17].

To assist in alleviating the symptoms, there HRT composed of synthetic hormones and/ or phytoestrogens.

HRT makes use of synthetic hormones like estrogen and progesterone, has been an increasingly acceptable alternative among women. The use of estrogen during this period will lessen vasomotor discomforts and act in controlling bone density. On the other hand, progesterone associated with estrogen may contribute to the protection of the uterine lining, preventing the prevalence of endometrial carcinogenesis. However, it should be considered the treatment time and the characteristics of each patient. According to the Pan American Health Organization (PAHO) should opt for a quick therapy does not ex-ceding five years and preferably at low doses[18].

As with any other drug treatment, the patient will be

subject to the incidence of side effects. Clinical studies conducted by the Women's Health Initiative (WHI) show that the use of synthetic-based estrogen and progesterone increase the possibility of breast cancer and thromboembolic diseases[19].

There are controversies regarding the use of this type of treatment because of side effects previously mentioned above, with this many patients end up anticipating the end of treatment, or adhering to therapy that uses phytoestrogens such as isoflavones, since they have similar effects to estradiol. However, if treatment is appropriate taking into account factors such as the route of administration, the genetics and physiology of each organism always happen through medical care, the benefits may outweigh the risks[21].

Synthetic hormones

Hormones are substances essential for the regulation and operation of all human physiology processes are involved in the growth, reproduction, and metabolism. Over the years, the female body naturally undergoes wear, occurring some transformations such as hormone deficiency when entering menopause. To overcome this lack, HRT has been widely used. The same is the use of synthetic hormones, or artificially synthesized substances, which are aimed at replacing natural hormones and reduction of climacteric discomfort arising as vasomotor symptoms, vaginal dryness, osteoporosis and other[22, 23]. Among the synthetic hormones most used, highlight the estrogen, progesterone, and tibolone.

About the estrogen synthesis in human body is controlled by means of stimulation of the hypothalamic/ pituitary axis. Initially the hypothalamus will stimulate the pituitary to release FSH in the blood stream, in turn, FSH contact promotes ovarian hormone release and circulating estrogen production when it reaches the appropriate level, there occurs the release of LH thus the formation of the corpus luteum and the synthesis of other hormones. However, over the years this cycle becomes irregular[20].

After the cessation of menstruation hypoestrogenism is inevitable because the synthesis of estrogen decreases gradually and one way to restore this deficiency is the use of synthetic hormones. Estrogen is present in the execution of many physiological processes. It is a substance of great importance in the treatment of menopause can act in mitigation of vasomotor symptoms and preventing bone loss through increased mineral absorption. Can still be used in cardiovascular problems, inhibiting platelet aggregation, acting in decreased glucose levels and promote increased vascularity and collagen synthesis in the skin, it is essential to restore strength, elasticity, decreasing the incidence of wrinkles. Its deficiency can cause urogenital system boards urinary incontinence[17, 10].

Therapies that use of estrogen and progestin are the most common. This because the use of estrogen alone can cause a number of severe side effects such as endometrial cancer[21]. Some randomized studies have shown that this type of cancer in the seventh place among the existing neoplasms, mainly in developed countries[24].

As early as concerns the tibolone, clinical studies showed that the same, in contact with the blood have the capability to provide estrogenic effects, with significant results in controlling hot flashes, skin elasticity, osteoporosis, and may act in reducing headache. Because of its androgenic property, has been an increase in testosterone resulting in improvements in the sexual realm, by controlling disturbances of libido and urogenital atrophy, and eventually his progestin therapy function provides protection by preventing possible uterine cancer[6].

Risks and benefits of HRT with synthetic hormones

Risks:

Prevalence of breast cancer: studies indicate that women who use HRT using estrogens have predisposition disorderly proliferation of cells due to the stimulation of mammary glands, which leads to the same, and consequently, development of tumors. This type of cancer is usually diagnosed in premenopausal, which occurs around the age of 50. Chemotherapy and surgical procedures are some of the alternative treatment in order to prevent an increase in neoplasia[25, 26].

Venous thromboembolic disease: the risk of venous thromboembolism is increased among HRT users, since the effects of estrogen in the clotting mechanism may contribute to or be responsible for a generalized hypercoagulable state. Oral estrogens affect the synthesis of clotting factors by a hepatic first pass. Studies indicate that use of estrogen for transdermal, may be associated with a lower risk for thromboembolic events compared with oral estrogen, since by not transdermal occurs first pass metabolism. However, randomized clinical trials are needed to better characterize the different effects of estrogens by mouth not in risk of events[26].

Endometrial cancer: the isolated use of estrogen can promote the emergence of endometrial cancer, so women who have or have a history of uterine endometrial carcinoma are prone to develop this disease, and should opt for the concomitant use of estrogen and progesterone, ie, the separate administration should be exclusive to patients hysterectomy[27,28].

Systemic lupus erythematosus: studies indicate that HRT with estrogen may contribute to the spread of this disease and aggravation of the case, so its use is contraindicated in patients with systemic lupus[21];

Ovarian cancer: it is considered the most common type of cancer among women and the difficulty of diagnosis, usually when discovered, is already at an ad-

vanced stage. Long-term use of estrogen leads to the formation of neoplasms, as well as their residual effects favor the propensity of the disease[27, 29].

Liver Disease: in patients with acute liver disease is contraindicated hormone therapy. Patients with chronic liver dysfunction also should not receive therapy is particularly orally. On the other hand, some studies using estrogen not orally showed no adverse effects in patients with primary biliary cirrhosis and chronic hepatitis cases of active[21].

Benefits:

Alleviation of hot flashes: coming from estrogen deficiency, heat waves are also intensified by extrinsic factors such as smoking, alcohol. Sa *et al.* (2006)[30] demonstrated that the upper body like the arms and face, are the hardest hit with hot flashes from that stage, so the hormone replacement therapy helps in easing this discomfort[31].

Control of drying of the vaginal mucosa: decline in estrogen leads to reduced synthesis of sebaceous glands, which are responsible for vaginal lubrication, thus, there is minimal discomfort and bleeding and trauma. Hormone reposition can normalize levels of this substance and restore the functioning[31].

Osteoporosis: hypoestrogenism resulting in decreased calcium absorption and in the synthesis of calcitonin, so the risk of fracture is enhanced during menopause. Certain studies highlight the efficacy of the HRT in relation to reduction of fractures due to osteoporosis because these therapies, whether used with or associated with estrogen-progesterone, can save for increasing intestinal calcium absorption or by increasing the renal conservation thereof. In addition, estrogen may have a direct effect on the function of osteoclasts, reduce bone loss and to a limited extent, reverse the onset of osteoporosis. However, studies indicate that the results are perceived only during treatment, and with the cessation of estrogen therapy, has the deficiency in calcium reabsorption again[17].

Skin changes: over the years, the skin undergoes some modifications. For stiffness and elasticity, the estrogen treatment provides significant results in the regeneration of the skin due to increase of tissue cells and collagen production, thus restoring the integrity and improved expression marks[32].

Phytoestrogens

In order to reduce the discomfort caused by menopause natural substances that contain phytoestrogens can be used[34].

Phytoestrogens are nonsteroidal diphenolic compounds, which are estrogen-like structure. Are capable of binding to the estrogen receptor ERα that can be found in the uterus, liver, kidney and breast tenderness and ERβ estrogen receptors present in prostate, ovary, testes and pituitary. Phytoestrogens are divided into three classes: lignans, isoflavones and the cumestanos, the latter being the most common phytoestrogen[34, 35].

Isoflavones are phenolic compounds whose biosynthesis of the phenylpropanoids pathway stems. Its molecule is similar to estrogen, however, their functionality is less intense. It is found in higher concentrations in the legumes especially soybean (Glycine max) which is connected to sugars and beta-glicosíderos. Soy is extremely important as active substances as genistein and daidzein, which are subtypes of isoflavones[36]. To that isoflavones are absorbed by the body must be in the form of aglycones, because only then managed to cross the plasma membrane and exert its effect. It is noteworthy that the absorption occurs in a dose-dependent, ie the concentration rises proportionally to the amount consumed. During its use is contraindicated antibiotics, as they can interfere with the absorption of the same[35].

Genistein is an isoflavone component, which alone or combined with daidzein may inhibit the growth of cancer cells. The daidzein exerts this effect only when combined with genistein, its mechanism of action includes the inhibition of enzymatic activity of thyroxine kinase, ribosomal kinase, DNA topoisomerase controlling the uncontrolled growth of cells. Genistein may also have vasodilating action, inhibit oncogenesis and angiogenesis and surveys indicate an improvement in lipid profile from genistein and daidzein binding in liver receptors favoring the catabolism of LDL cholesterol[20,36,37].

Recent studies regarding isoflavones results indicate, that many flavonoids exhibit inhibitory activity on P-glycoprotein-mediated transport. Among these flavonoids are included genistein. Knowing that the digoxin and quinidine are substrates of this protein, which has the same actions as limiting oral bioavailability, facilitating the biliary excretion and renal clearances of these drugs, we can conclude that the interaction between isoflavones and these drugs may induce cardiac a picture of intoxication increased serum concentration of the latter[36].

Isoflavones may also generally operate in the intensity of hot flushes resulting from estrogen decline, having antioxidant activity, for inhibiting free radicals, provide satisfactory results in bone formation preventing the onset of osteoporosis, and in order to have a vascular protective action[38].

It is recommended that the intake of 45 mg/ day, however studies indicate the use of up to 160 mg/ day without adverse effects[36].

Isoflavones are presented as an alternative between prescriptions where not exhibit higher probabilities of incidence of breast cancer due to decreased risks of this treatment provides, but the alleviation of menopausal

symptoms will occur in smaller proportions[27].

Besides soybean, plants may be other sources of phytoestrogens. Among them stand out the Primrose (*Oenethera biennis*), the Licorice (*Glycyrrhiza glabra*), the Cimicifuga (*Cimicífuga racemosa*), the Dong quai *(Angelica sinensis,* the Ginseng (*Panax ginseng*) *e o* Trefoil of the meadows (*Trifolium pratense*).

Regarding the Primrose, its seeds are rich in oils containing linolenic acid and linoleic acid. There is evidence that its oil reduces the incidence of hot flashes during the night in menopausal women, and increase calcium absorption by the intestine, thereby increasing bone deposition thus preventing osteoporosis. Its oil is also much used in cases of mastalgia and its use does not induce the formation of nodules. It can also be used to decrease the intensity of symptoms like hot flushes and in the control of LDL and HDL[36].

The Licorice (*Glycyrrhiza glabra*) has active substances in its composition as glycyrrhizic acid and some isoflavones. Its can act in reducing estrogen levels also have significant results in increased progesterone. The recommended daily dose is 380 mg and should be avoided by hypertensive, as it may contribute to increased blood pressure, as it has the ability to retain sodium. Hypokalemia can further increase, and therefore its use simultaneously with the digoxin and loratadine should be avoided due to the risks of intoxication by these drugs[36].

In the case of Cimicifuga (*Cimicífuga racemosa*) Sousa, *et al.* (2006)[36] has as main active substances the isoflavones, formononetin and triterpenic terpenoids. Emphasize its possible action on vaginal atrophy, besides relieving hot flashes and reduce the release of LH. The recommended daily intake is 20 mg daily. Their use should be avoided in combination with the use of anti-hypertensive agents, for Cimicifuga can cause a sudden fall in blood pressure[39].

Already *Angelica sinensis,* popularly known as Dong quai, participates in the regulation of the hormone estrogen, which may alleviate hot flashes and vaginal dryness. In addition, has anti-inflammatory action, prevent thrombus formation, improves blood flow contributing to a good cardiac function, and may serve as a hepatic protector. Moreover, it can also have power, antihypertensive, antispasmodic, antibiotic action to reduce dysmenorrhea, amenorrhea and hypermenorrhea. The recommended dose ranges from 300 to 500 mg once to five times a day, and should always be taken with food[36, 39,40].

The Ginseng (Panax ginseng) acts on the immune system providing greater resistance to external aggressors. Has stimulating action promoting increased physical and mental vigor. Also contributes to hormonal balance, thus there is a control on behavioral oscillations providing better interaction with the social circle. Can be effective in relieving vaginal dryness and pain during intercourse. Also has the effect, control the menstrual disorders. However, the appearance of estrogenic effects in women were reported in pre and postmenopausal inducing breast pain and metrorrhagia in the sequence of use of Ginseng. Should avoid their combined use warfarin because it can interfere with the action of this drug, thus decreasing the effect of inhibiting the formation of blood clots[36, 41];

The Trefoil of the meadows (*Trifolium pratense*) has as main active substances isoflavones and coumarin derivatives. Promotes relief of hot flushes, decreased vascular resistance, thereby lowering blood pressure. Studies report that can be an alternative for women who are prone to breast cancer, because it may decrease or stop the proliferation of breast tumor cells. Due to the presence of coumarin derivatives may decrease the blood coagulation time, so its use is contraindicated in patients who take anticoagulants and antiplatelet agents, it can cause increased bleeding time and consequently hemorrhaging. The maximum dose is 500 mg. Concurrent use with digoxin should be avoided as it may enhance its effects, increasing the risk of toxicity of this drug[36].

3. CONCLUSION

At some stage of a woman's life, as a result of natural aging, decreased production of hormones occurs, resulting in menopause.

The hormone replacement therapies, which use synthetic hormones, help to normalize hormone levels and to mitigate the perceived symptoms during menopause. However, you should take into account the characteristics of each patient, because of the risks and benefits that it can bring.

Another option are existing therapies that make use of phytoestrogens such as isoflavones. This therapy may provide relief of symptoms arising from the menopause, causing fewer side effects, among both its effect on the symptoms may be less than shown by the use of synthetic hormones.

Prescriptions should be made based on the risks and benefits for each patient, aiming to improve the quality of life for menopausal women, alleviating the discomforts caused by this hormone lag.

Physiological changes in the female body are inevitable and menopause consists of the phases to be lived according to human chronology, therefore, studies on the subject contribute to demystify and help in understanding the changes experienced.

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POTENTIAL RISKS TO PREGNANT DUE USE OF MEDICINAL PLANTS

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ABSTRACT

The use of medicinal plants with therapeutic purposes is an ancient practice spread throughout the population for healing and disease prevention. This practice has increased due to the belief that "natural" product is safe. From this mistaken idea, pregnant women often seek natural alternatives to treat symptoms resulting from pregnancy, believing that medicinal plants have no harmful effects on the fetus. However, numerous research show that medicinal plants are not without risks to health and may cause toxicity. Faced with this problem, this study aimed to describe the risks of indiscriminate use of medicinal plants, as a warning, not only for pregnant women, but also to healthcare professionals, so that they orient to the public on the safe use these products.

KEYWORDS: Medicinal plants, pregnancy, abortion.

1. INTRODUCTION

Pregnancy is an event full of changes. An experiment in which the mother is overwhelmed with intense feelings that can make room for unconscious contents of the mother. Pregnant women have sought ways to provide a safe and healthy pregnancy, seeking their welfare and the baby[1].

During pregnancy, the care in relation to health must be doubled, since the exposure of pregnant women to risks, environmental or biological factors can cause complications for both mother and the fetus[2].

The use of medicinal plants as a therapeutic resource for the prevention, treatment and cure of this disease is a practice since the dawn of humanity, seeking in nature, the cure for your ills[3].

Leite *et al*. (2008)[4], argue that the prevalence of medication use is considered high among all strata and for various classes of drugs. Mainly the drugs frequently used by pregnant women, children and the elderly, do not have sufficient toxicological studies to age and physiological condition. In many cases, the choice of drug to be used is made or repetition of an old or indication of lay people (neighbors, relatives, friends, clerks pharmacy) recipe, featuring self-medication.

In recent years have also seen a significant increase in products considered by natural population. The concept of natural is related to what is produced by nature, not featuring fireworks, mixture or composition, being something of vegetable origin. Thus, natural products are said to be synonyms of beneficial and safe products, following the popular saying "*natural product does no harm to health*". This synonym is inadequate, and an erroneous idea of the population, since the medicinal plants are considered xenobiotic agents, i.e. foreign compounds that the human body can indeed bring many complications if used improperly[5].

Pregnant women deserve a special focus overall population which encourages the use of medicinal plants, because they believe that will not cause harm to the fetus[6]. However, especially during the first trimester of pregnancy can occur from congenital malformations, even a spontaneous miscarriage[7].

Some medicinal plants have teratogenic and abortifacient potential and its systemic use is contraindicated in the first trimester of pregnancy, by being able to cross the placental barrier and may thus affect the fetus[8].

Many people use medicinal plants as an aid for health care practice[9]. This increase in consumption of medicinal plants, has happened for advertising and promotion in the media and the economic crisis affecting the country, related to the difficult access of the population to health care, ranging from hospital care until obtaining tests and drugs. It is also due to easy access to this type of product that has great marketing in public places such as health food stores and pharmacies[3].

Many plants are known to be teratogenic and abortifacient. However, lack of information and publicity can make use of a simple "*natural medicine*" a serious problem.

Therefore, this study aimed to establish the likelihood of the use of medicinal plants by pregnant women, presenting their potential teratogenic and abortifacient effects, in order to warn of the risks that they are exposing themselves doing the indiscriminate use or even routine these plants.

2. MATERIAL AND METHODS

This study was conducted through a literature review, through the electronic bibliographic databases Google Scholar, Medline and SciELO, using the following keyword combinations: medicinal plants; abortion; pregnancy.

3. LITERATURE REVIEW

During pregnancy, a series of physiological changes that are due to period and may cause unpleasant symptoms occurs to pregnant women. These changes occur due to hormonal factors that change the physiological patterns of functioning of a woman's body, in order to tailor it to the maternal-fetal complex own organic needs and childbirth[10].

Based on these changes, symptoms such as nausea, vomiting, constipation and urinary system disorders, with increased frequency of urination, are reasons that can often lead to pregnant women using drugs to relieve these symptoms, they may, be conventional or vegetable origin. It is noteworthy that before using any medication during pregnancy, a detailed analysis of each specific situation must be made, taking into account the risk-benefit[12].

The main guidance for pregnant women, it would be no use of any medicine, but there is no way to seal the risks of drug therapy in pregnant women, because like most of the population, the mother is also subject to variations requiring drug interventions[13].

Medicinal plants are significantly important for maintaining the health of the population. From various studies reported in the literature, there is proof of the therapeutic action of plants that are popularly used by a knowledge diffused over several generations[14].

According to WHO (World Health Organization) medicinal plant is "*any plant that has, in one or more organs, substances that can be used for therapeutic purposes or which are precursors of semisynthetic drugs*"[15].

The aid for research, technological development and innovation based on Brazilian biodiversity, according to the epidemiological needs of the population, provides an important challenge for the National Policy on Medicinal Plants and Herbal Medicines (NPMP). The NPMP was approved in 2006, encouraging the rational use of medicinal plants and herbal[16]. In Brazil, the National Agency for Sanitary Vigilance is the main organ responsible for the regulation of these products[17].

The therapy from medicinal plants have been used in various ways for treatment, prevention and cure of diseases. The most common form is tea, which can be prepared by extractive techniques such as infusion, decoction or maceration. Other homemade preparations like syrups, compresses, poultices, baths and potions can also be included as a treatment[18].

The correct identification of medicinal plants is of utmost importance, since many plants have similarities with each other, and are many popular names, making it difficult to choose[16]. So do not know the safety of its use when a mistaken identification of the plant, intentional or accidental tampering and other contaminants occurs[5].

In addition to checking the plant, there must be conditions for collection and proper storage, since the plant produces secondary metabolites that represent a chemical connection between medicinal plants and the environment around. Thus, the synthesis of plants can be sensitized by different environmental conditions, the main factors being the day/ night cycle, seasons, temperature, age and plant growth, water availability, ultraviolet radiation, nutrients, altitude and air pollution, can have lower or higher concentrations of its assets[20].

Medicinal plants when used during pregnancy have constituents that can cross the placenta, reach the fetus, and promote serious problems such as teratogenicity, embryo toxicity and even abortion[21].

Teratogens integrate environmental, physical, chemical and biological agents may cause congenital malformation[22]. Teratogenic effect on the fetus depends on what stage it is, the association between dose and effect, the maternal fetal genotype and specific pathogenic mechanisms of each agent[23]. Thus, the teratogenic effects of the drug for therapeutic purposes, can cross the placenta, reach the fetus, and lead to harmful effects[24].

Embryo toxicity it is a change in embryonic development, dependent doses that do not affect the maternal organism. The reaction of the embryo is related to exogenous agents, most often with the same genetic constitution[24].

Abortion is the termination of pregnancy, the death of the embryo or fetus, from a stimulation of uterine contraction. Among the most used means abortifacient, highlight the infusions and teas made from medicinal plants[25].

Accordingly, it can be seen that self-medication is indiscriminate alarming, since in most cases no knowledge of the toxicity of the plant. Thus, there may be health risks if there is no assurance that the expected pharmacological properties are obtained, without side effects or adverse[26].

In Brazil, the State of Rio de Janeiro is one of the few states that has a law that contraindicate the use of

herbal medicines by pregnant women. This state has a resolution-SES/ RJ No. 1757 of February 18, 2002, which still considers toxic, teratogenic and abortifacient the most varied species of plants with medicinal effects purpose[27].

According Mengue *et al.* (2001)[12], plants with reports of abortive action or any other suspected risk during pregnancy are: arruda, cinnamon, horsetail, bushing, Bilberry, purple ipe, herv of Saint Mary, jeriquiti spring mint, *Parthenium sp*, melon of Saint Caetano, pinion-to-purge, Hypericum, poeja, me-nobody-can, among other.

The use of laxatives, because of problems of constipation is very common in pregnant women. This problem is related to the physiological changes resulting from pregnancy, as the action of specific hormones on intestinal motility[28]. Plants that effect with stimulant laxative anthraquinones has in its composition, senna (*Senna alexandrina* Mill - Fabaceae) is the laxative antanoide most used worldwide. Anthraquinones induce uterine contractions[29], causing the increase in uterine blood flow, thereby enabling the risk of fetal loss. The same can also reach the breast milk and cause unwanted effects, such as diarrhea, the baby[30].

Regarding stimulants of the central nervous system, there is caffeine, which is present in coffee beans (*Coffea arábica*L. - Rubiaceae), yerba mate (*Ilex paraguariensis*St.-Hil - Aquifoliaceae family), tea- black and green tea (*Camellia sinensis*(L.) - Theaceae family), cola (*Cola nitida* (Vent) Schott & Endl -.. Sterculiaceae family) and guarana (*Paullinia cupana* Kunth - Sapindaceae family). Caffeine can cross the placental barrier, reducing blood flow to the placenta. Thus, their intake during pregnancy may be associated with fetal growth retardation, with a reduction in weight of newborn babies[31]. However, this fact is contradictory, according Clausson *et al.* (2002)[31] and Bracken *et al.* (2003)[32], this reduction can be confused with the effects of nicotine on the fetus, since smoking is related to the ingestion of large amounts of beverages containing caffeine.

Another species of medicinal plant with its action in the central nervous system is popularly cognized as hiperico or St. John's Wort (*Hypericum perforatum* L. –Guttiferae family) being used in the treatment of mild to moderate depression, having a profile superior to synthetic antidepressants reasonableness. There is disagreement among authors regarding the risks of using hiperico during pregnancy[33,34]. However, Gregoretti *et al.* (2004)[35] reported from experiments in animals receiving extracts of *H. perforatum* during pregnancy, their offspring had severe kidney and liver damage. These lesions were also seen in pups whose mothers received only extracts during breastfeeding. Other studies that examined changes in growth, development, physical maturation and cognitive capacity of animals that were exposed to extracts hiperico during the prenatal period, showed no differentiation with respect to the animals who received placebo in the same period[29]. However, studies to date are not sufficient to ensure the safe use of this plant during pregnancy.

According Tsui *et al*. (2001)[36], the main problem reported by pregnant women is sick. The ginger (*Zingiber officinale* Roscoe – Zingiberaceae family) is used to relieve morning sickness in pregnant women. In studies, it was administered ginger pregnancy in rats, it was observed that ginger above could cause loss of normal embryo, but also increase the weight of the remaining fetuses[29]. While studies of the toxic potential of ginger in pregnancy, some authors advocate its use. According to Amorim (2013)[37], ginger may be more effective in treating nausea and vomiting in pregnancy, when compared to placebo. Already Belew (1999)[38], said pregnant women in India make use of ginger in food; there are no reports of adverse effects, and the use of the same in Chinese medicine for nausea, no contraindication.

The *Ruta graveolens* L. – Rutaceae Family recommended in folk medicine, as the plant that "*force menstruation*", is one of the most used by women for contraception or induced abortion[39]. Contains toxic and photosensitive substances. Your handling can cause dermatitis if exposure to the sun, besides presenting abortive activity [40]. Starting at experiments in rats, anti-fertility and/ or contraceptive activity was observed when administered to an animal an extract of different plant parts. The ingestion of alcoholic extract, at high doses for rats during the pre-implantation period change caused cells from the blastocyst by reducing the number of cells and delaying embryonic development. It was also observed that when administered in the early organogenesis, the extract could cause fetal death[29]. Thus, if discouraging also been found that the use rue during pregnancy is extremely contraindicated its use in inducing abortion.

The *Peumus boldus* Molina - Monimiaceae family, known as bilberry-true, is originally from Chile and is commonly confused with the false Boldo (*Coleus barbatus* Benth Andrews - Lamiaceae), Brazil[19]. Bilberry is indicated as choleretic and cholagogue, being used in the treatment of hepatic disorders in general. In some experiments, in which the crude extract were administered the *Peumus boldus* to female rats from gestation was observed anatomical abnormalities in the fetus and in blastocysts[41]. Also was observed that the false-bilberry when administered to animals in the pre-implantation causes a large increase in embryonic loss. The false-bilberry presents a likely mechanism for the anti-implantation action with relaxing effect on tubal mobility, which interferes with the transport of the embryo to the uterus and its subsequent deployment[42].

The plant popularly known as bush “buchinha”, a lit-

tle bush (*Luffa operculata* (L.) Cogn. – família Cucurbitaceae), is distinguished among the ten most used plants as abortion in Brazil[39]. His dried fruit are indicated for rhinitis and sinusitis, being administered through inhalation and nasal drops solution, with recommendations for use that cause poisoning. Poisonings were recorded related to abortion attempts among women 19 to 26 years, and these records kept by the Toxicological Information Center of Santa Catarina State, between 1984 and 1997[43]. Recently, studies have shown that the result of decoction (decoction) of buchinha administered to female mice during the embryo implantation, the rate decreases denatalidade[29].

The *Symphytum officinale* L. – Boraginaceae family, known as consolide or confreié originally from Europe and Asia. In countries of origin, the roots were used consolidates with healing purpose in outdoor use. More known as comfrey was popularly used to treat asthma, hepatitis, diabetes, gastritis and rheumatism, in an internal use[40]. In Brazil, in 1992 after the Ministry of Health (Ordinance No. 19, 30/01/1992) has banned evidence of their toxicity, the internal use of comfrey, restricting the indication of its products to external use, topic application[44]. From studies in rats, the roots and leaves of comfrey, showed carcinogenic and hepatotoxic action when administered chronically. Its toxicity is attributed to the presence of pyrrolizidine alkaloids, compounds known for their carcinogenic activity, hepatotoxic, teratogenic and mutagenic[45].

The vine species known as "thousand-men" or vine "jarrinha" (*Aristolochia triangularis* Cham. – Aristolochiaceae family), is known for its wide variety of indications, such as stomach problems, fever, diarrhea, convulsions, anorexia and also has antiseptic and anti-inflammatory properties. Several authors of books on folk medicine attach to species of this genus, mutagenic, and carcinogenic effects abortifacients. After studies of the vine "thousand-men," noted the presence of toxic components, leading to banning the trade of products containing these components, even in highly diluted preparations used in homeopathy[12].

Melon of St. Caetano (*Momordica charantia* L. – Cucurbitaceae family) is known for his action emenagoga, anthelmintic and purgative[40]. Tests on mice have shown that from the administration of glycoproteins (alpha and beta momorcharina) isolated from the seeds, the induction of abortion and inhibitory action on cell proliferation of the endometrium occurs and myometrium. In the study, intraperitoneal administration of beta-momorcharina the fourth and sixth days of gestation caused an inhibition of pregnancy; disrupts the pre-implantation and embryonic development, by blocking the incubation of embryos through the pellucid zone, the decrease in the incidence of effective attachment of the blastocyst, reduced growth of the trophoblast and suspend the development of the inner cell mass[12].

The ginkgo biloba (*Ginkgo biloba* L. – Ginkgoaceae family) is indicated for cognitive disorders, recent memory loss, dizziness, headache, and emotional lability with anxiety, improving erectile dysfunction secondary to antidepressant treatments, increase peripheral blood flow in patients with diabetes mellitus, and improving the impaired hearing of patients by poor blood circulation in the ears. Can also decrease fertility between men and women. Thus, its use should be avoided by couples who want to have children. In turn, the adverse reactions related to pregnancy are hemorrhagic disorders, which can be result of chronic use of ginkgo as a result of increased hemorrhagic potential probably associated with the reduction of platelet aggregation by inhibiting the PAF (Platelet Aggregation factor) by "ginkgolides" components[46].

4. CONCLUSION

The easy acceptance by the population of medicinal plants has led to a potential danger of self-medication. The main problem is related to using the belief that plant products are free of toxicity and adverse reactions, as they are natural.

The consumption of homemade dressings using parts of plants from many plant species known and seemingly harmless can cause us serious of the health of the mother and fetus. Thus, there is need for further information to pregnant women about the harmfulness of some medicinal plants administered during pregnancy. It is up to health professionals such as physicians, pharmacists, nurses, among others, be prepared to provide such clarification to the population.

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VITAMIN D: A LITERATURE REVIEW ON ITS EFFECTS AND RELATION WITH THE USE OF SUNSCREEN PRODUCTS

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ABSTRACT

Vitamin D is crucial for homeostasis of calcium and phosphorus and for musculoskeletal and cardiovascular health and disease. Its deficiency may be related to several autoimmune diseases and some cancers. A major pathway of vitamin D synthesis occurs in skin, mediated by the sunlight, but it can also be obtained from the food or vitamin supplements. Ultraviolet B radiation is responsible for various effects on human health. Beneficial effects as the synthesis of vitamin D, but also detrimental ones, as the development of skin cancer. Concern about the risk of skin cancer led to the diffusion of large-scale photo protection. The purpose of this article is to make a detailed and updated review on vitamin D, its main sources, effects on the human organism and factors affecting its production. Problems associated with low vitamin D levels and the use of sunscreens are also discussed.

KEYWORDS: Vitamin D, ultraviolet B radiation, skin cancer, sunscreens.

1. INTRODUCTION

Vitamin D is a steroid hormone crucial for musculoskeletal and cardiovascular health as well as for the homeostasis of calcium and phosphorus. Its deficiency may be associated with some types of cancer and various diseases such as multiple sclerosis, diabetes mellitus types 1 and 2, systemic lupus erythematosus, inflammatory bowel disease, among other[1].

Lately, concern about the risk of skin cancer led to the diffusion of large-scale photoprotection and currently there are two divergent positions by physicians: on one hand the community of dermatologists and, more recently, the World Health Organization, guiding patients about the use of sunscreen to avoid any exposure to the sun. On the other hand are doctors who recommend the need for sun exposure to ensure a good level of vitamin D[2].

In a general way, vitamin D produced in the skin remains in the body up to two times more than vitamin D ingested in the diet. In addition, most humans must have only a few minutes of sun exposure daily to maintain healthy levels of vitamin D during the year[1]. However, the spectrum of UVB radiation required for the activation of vitamin D in the skin is a recognized carcinogen factor to keratinocytes[3].

Thus, this paper aims to review the literature on the importance of vitamin D for homeostasis and the consequences of the reduction of its synthesis by use of sunscreens.

2. MATERIAL AND METHODS

In the present study the guiding question of the integrative review was: contribute to technical information for professional health care.

Bases (Latin American and Caribbean Literature on Health Sciences) LILACS, SciELO (Scientific Electronic Library on Line) and PubMed (NCBI US National Library of Medicine National Center for Biotechnology Information) were consulted. Studies that have addressed the thematic, published from 1975 to 2014, regardless of the languages of publication were included.

3. LITERATURE REVIEW

Vitamin D consists in a group of lipophilic pre-hormones, which are converted in the body into several biologically active metabolites that function as hormones circulating in the blood and regulating the activities of several cell types[4].

This vitamin is a steroid wherein ring B of the nucleus of the molecule is replaced by non-saturated hydrocarbon bridge containing two double bonds. The cleavage of the C-C bond between C9 and C10 is essential to the change produced by the photochemical process [5].

The major source of vitamin D is the skin, stimulated by ultraviolet radiation; food sources contribute only with a small portion of the daily needs. Vitamin D3 or cholecalciferol is synthesized in human skin by the action of UVB radiation from 7-dehydrocholesterolas well as being found in foods such as fish oil and egg yolk[6]. Vitamin

D2 or ergocalciferol is formed from a fungal steroid ergosterol and are rarely supplied naturally in foodstuffs, but used as a food supplement[6].

Vitamins D2 and D3 differ in structure and metabolism, but their biological activities in humans are comparable. They are sterols with an open core, although they are thermostable, they are quickly degraded by light, oxygen and acid[5]. The chemical structures of vitamins D2 and D3 are shown in Figure 1.

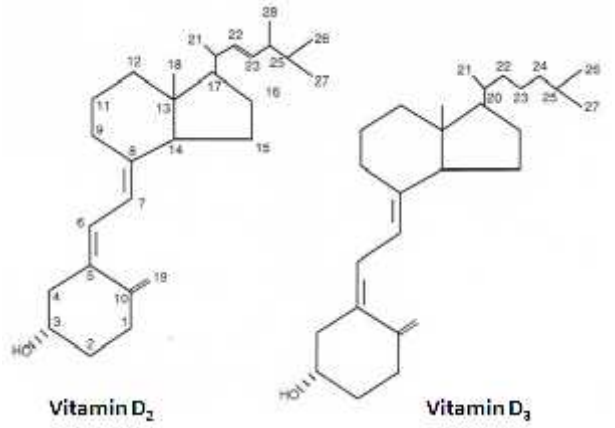

Figure 1. Chemical structure of vitamin D2 and D3. Aires [7]

One time ingested or synthesized in the skin, vitamin D is transported to the liver where it undergoes to first hydroxylation at carbon 25, converting to 25-hydroxy Vitamin D or 25(OH)VD. This is the main circulating form of VD, with a half-life of around two to three weeks[1]. In the kidney, 25(OH)VD undergoes a new hydroxylation with the production of the active form, 1,25-dihydroxy vitamin D or 1,25$(OH)_2$D. Although this is the active form, is not suitable to an estimate of the body´s stock of vitamin D, because it has a shorter half-life, around 6 to 8 hours[6].

In the blood, the transport of vitamin D is mainly made by vitamin D binding protein and to a lesser extent by albumin[8].

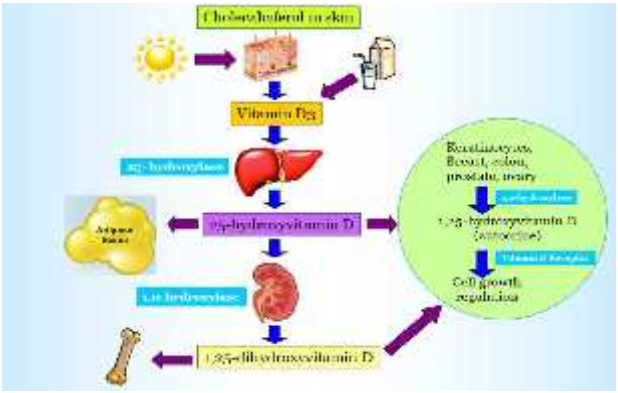

Figure 2. Synthesis of Vitamin D and effects on skeletal tissue and extra-skeletal tissues. Modified from Swati11[11]

Vitamin D exerts its biological functions through its binding to nuclear receptors, vitamin D receptors (VDR), which regulate the transcription of DNA into messenger RNA, similar to receptors for steroids, thyroid hormones and retinoids[9]. There receptors to vitamin D, virtually, in all tissues, such as brain, pancreatic islets, bone, skeletal muscle, kidney, intestine, skin, parathyroid, pituitary, breast, lymphocytes and monocytes[10].

2. Sources of Vitamin D

In humans, 90% of vitamin D comes from the skin by the sun-mediated synthesis. The remainder can be obtained from foods that contain vitamin D naturally in foods that have been fortified and the use of pharmaceutical products[12].

Natural sources are cod liver oil, tuna, salmon, egg yolks, swiss cheese, liver and sardines. Fortified foods include milk, juices, margarines, yoghurts and cereals. In pharmaceutical forms there are the vitamin D2 and D3 [12].

3. Effect of Vitamin D

Vitamin D exerts various effects on homeostasis, which are summarized below[2].

In bone, vitamin D prevents osteopenia, osteoporosis, osteomalacia, rickets and fractures. Vitamin D is required for maintenance of plasma calcium by increasing calcium absorption from the small intestine, mobilizing calcium from bone and reducing its renal clearance. Vitamin D plays important roles in the absorption and bone deposition. Low calcium absorption generates a number of physiological problems, since calcium is important for most metabolic functions, as well as the muscular activity[13,10]

In relation to cells, it has been shown that vitamin D may prevent certain types of cancer, such as prostate, pancreatic, breast, ovarian and colon cancer. Also prevents infectious diseases and infections of the upper airways, asthma and other respiratory illnesses. These effects occur because the genes regulated by vitamin D influence biological processes such as inhibition of cell proliferation, apoptosis and stimulate the production of bactericidal proteins[14].

Considering the immune system, adequate levels of Vitamin D appear to prevent multiple sclerosis, type 1 diabetes, Crohn's disease and rheumatoid arthritis. This occurs because the effect on the immune system of vitamin D translates into increased innate immune regulation associated with an acquired immunity. Vitamin D interacts with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages and Natural Killer cell, besides interfering in production of cytokines[8, 9].

3.1 Other effects of vitamin D recently described

Recently, many studies indexed in PubMed related to

vitamin D. Below are some conclusions of the various medical specialties.

3.1.1. Obstetrics and Gynecology

Low maternal vitamin D levels during pregnancy may be associated with a higher risk of pre-eclampsia, gestational diabetes, preterm birth or small for gestational age neonates[15]. In addition, a study demonstrated that supplementation of pregnant women with 50,000 IU of vitamin D every two weeks significantly improved the insulin resistance during pregnancy[16]. The data from randomized controlled studies indicated that 4,000 IU / day of vitamin D3 during pregnancy "normalize" the metabolism of vitamin D and improve birth outcomes, including the rate of primary cesarean delivery and comorbidities, without risk of side effects[17]. It has been further shown that low levels of vitamin D increase the risk of rickets in the offspring, which leads to the need for all women to be informed, at the time of the query, the importance of adequate vitamin D stores during pregnancy and breastfeeding[18]. Still, it is described that obese women transfer less 25(OH)D to the fetus than women of normal weight, even with similar serum levels[19].

A vitamin D deficiency may be more common in premenopausal women than previously thought, and may compromise the quality of life by increasing weakness, fatigue, and nonspecific pain[20].

Furthermore, treatment with vitamin D3 had beneficial effects on some risk factors of cardiovascular disease by reducing serum levels of total cholesterol, triglycerides and VLDL in patients with polycystic ovary syndrome and vitamin D deficiency[21].

3.1.2. Endocrinology

According to the work done in the Department of Exercise Nutrition and Physiology of the University of Missouri (USA), obese adolescents have a higher risk of vitamin D deficiency, because it is considered that vitamin D is sequestered by excess fatty tissue[22]. A BMI (body mass index) higher than the normal leads to lower levels of 25(OH)D, while possible effects of lower levels of 25(OH)D in the increase of the BMI are probably small[23].

Low levels of vitamin D were associated with a higher prevalence of metabolic syndrome, type 2 diabetes or both conditions in adults and adolescents[22].

It was described that replacement of vitamin D in mild primary hyperparathyroidism is safe, effective and does not increase calcium levels to dangerous levels[24].

3.1.3. Orthopedics

Hypovitaminosis D is common among children with fractures of the upper extremities[25]. A level of 25(OH)VD of 65 nmol/L is required to reduce the risk of non-vertebral fractures and 75 nmol/L may be necessary to reduce the risk of hip fractures[26]. Most patients of both genres, aged 18 or more and featuring hip fractures showed vitamin D insufficiency, and those with 71 years or older had significantly lower levels of 25(OH)D when compared to a control group submitted to total arthroplasty[27].

3.1.4. Pediatrics

Maternal vitamin D insufficiency during lactation, related to the lack of sun exposure and a minimal intake of vitamin D in the diet contributes to low vitamin D in breast milk and therefore to vitamin D deficiency in the baby[28]. As for school-age children, studies suggest that vitamin D deficiency is associated with an increased incidence of gastrointestinal infections and otitis[29].

3.1.5. Dermatology

The vitamin D levels in children are correlated with severity of atopic dermatitis, but only in patients with allergic sensitizations. It is believed that vitamin D affects the progression and severity of atopic dermatitis[30].

3.1.6. Cardiology

The deficiency of vitamin D has a positive correlation with blood pressure and hypertension may be related to the non-dipper type (without a nocturnal decrease). The measurement of vitamin D may be used to indicate a higher risk of adverse cardiovascular events related to hypertension[31]. Other clinical studies support the concept that vitamin D deficiency is involved in the pathogenesis of cardiovascular and renal disease through its association with diabetes, obesity and hypertension. This fact is particularly important for African Americans and women in postmenopause, that present an additional risk of cardiovascular disease. It is suggested that the adverse cardiovascular effects of low levels of vitamin D in postmenopausal women could be reduced by a combined therapy of vitamin D and sex steroids which act via endothelial dependent or independent mechanisms, resulting in the generation of nitric oxide and calcitonin gene related peptide[32].

It has been reported that vitamin D deficiency may influence the increase in blood pressure because the vitamin suppresses the biosynthesis of renin, which activates the renin-angiotensin-aldosterone, [14].

3.1.7. Central nervous system

The deficiency of vitamin D has been associated with a higher risk of depression and schizophrenia. Vitamin D affects the brain regardless of the hormonal pathways that regulate serum calcium. The non-significant difference in the serum level of vitamin D among schizophrenic and depressed patients suggests that the effect into the brain is a generalized one and not restricted to a specific region or via in the brain[33].

Finally, with respect to the central nervous system, vitamin D appears to prevent Alzheimer's disease and dementia. This occurs by immunomodulation, regulation of neuronal calcium, antioxidant mechanisms, increased neuronal conduction and detoxification mechanisms. As for the humor, it seems to prevent seasonal affective disorder, premenstrual syndrome and disorders of sleep, increasing the feeling of well being[2, 14].

4. Identification of body levels of vitamin D

The most reliable test for evaluating the level of vitamin D is the measurement of 25-hydroxy Vitamin D or 25(OH)VD in the serum. 25(OH)VD has a serum half-life of 2 to 3 weeks, and its measurement in serum is considered to be the ideal marker of vitamin D stores in the body[10].

The $1,25(OH)_2VD$, despite being the active form, is normally not measured, since the half life is short (about 6 hours). Furthermore, in the case of vitamin D deficiency, there is a compensatory increase in the secretion of parathyroid hormone (PTH), which stimulates the kidney to produce more $1,25(OH)_2VD$. Thus, when vitamin D deficiency occurs and there are a decrease in levels of 25(OH)VD, concentrations of $1,25(OH)_2VD$ remain within normal levels, and in some cases even higher levels are found[8].

The main vitamin D toxicity is hypercalcemia. Unlike vitamin D supplements, neither exposure to the sun nor artificial tanning cause intoxication, which is linked to several serious symptoms, including nausea, vomiting, loss of appetite, constipation, increased thirst, increased urination, depression, calcification of the kidneys and renal failure[2,5].

Table 1. Recommended intake of vitamin D, according to the different age groups.

Age	Estimated average needs (IU/day)	Daily dose Recommended (IU/day)	High dosage (IU/day)
0-6 months	0	0	1000
6-12 months	0	0	1500
1-3 years	400	600	2500
4-8 years	400	600	3000
9-70 years	400	600	4000
>71 years	400	800	4000
14-18 (pregnant and lactating)	400	600	4000
19-50 (pregnant and lactating)	400	600	4000

Source: Modified data from the Institute of Medicine (IOM) of the National Academy of Sciences of the United States, 2014 (in www.iom.edu).

Currently most authors adopt the following values for the levels of vitamin D in the human body: A) deficiency (<20 mg/ml), B) failure (21-29 mg/ml), C) normal reference range (30-100 mg/ml), D) Poisoning (> 150 mg/ml)[2]. The daily intake of VD recommended by the Institute of Medicine of the National Academy of Sciences of the United States, in different age groups is shown in Table 1.

5. Factors which affect the Vitamin D' production

There are endogenous and exogenous factors that affect the production of vitamin D[14]. These factors are described below.

5.1 Endogenous factors

5.1.1 Pigmentation

Black and white people have the same ability to produce vitamin D. The difference lies in the amount of melanin, because melanin is a natural sunscreen. Studies show that the epidermal conversion of 7-dehydrocholesterol to pre-vitamin D in the skin phototype II (fair-skinned Caucasians) is 5-10 times more efficient than a phototype V (Hindu or Asian with dark brown) skin. Dark-skinned individuals synthesize less VD when exposed to the same amount of radiation[14].

5.1.2. Age

The physiological changes associated with aging are related to low levels of vitamin D in the elderly because there is reduced capacity to generate its precursor in the skin, 7-dehydrocholesterol which turns into vitamin D3 by the action of UVB rays. Such effects arise by daily use of sunscreen, change of lifestyle and reduced physical activity outdoors. The vitamin D production is affected as the skin thins with age[1].

Regarding young people, the childhood and adolescence are considered critical periods of vulnerability to the effects of sun exposure. The skin photoaging is started early in childhood with inadequate sunlight exposure. Besides, excessive sun exposure in this age group is a particularly significant factor in the future risk of developing skin cancer. About 25% of sun exposure of an individual's life occurs before 18 years of age[34].

Moreover, in the elderly the probability of death due to fractures (especially hip) caused by osteoporosis and other causes related to vitamin D deficiency is much higher than death from skin cancer[1, 2].

5.1.3. Body mass index:

Patients with higher body weight have lower vitamin D levels than people with normal weight. This is because the vitamin D excess accumulates in the fat, so that it cannot be properly used in the absorption and deposition in bone[1].

5.1.4. Liver and kidney diseases

The kidneys and liver are two key organs for the production of vitamin D. All patients with kidney or liver disease will likely have problems with the production of VD and therefore should receive vitamin D supplements[2].

5.1.5. Drugs which interfere in metabolism of VD

Some drugs like antifungals, anticonvulsants, antiretrovirals, corticosteroids and St. John herb, among others increase the destruction of vitamin D in the body [2].

5.2. Exogenous factors

5.2.1. Altitude above sea level

Ultraviolet radiation is more intense at higher altitudes because there is a smaller amount of air for its absorption. In the higher altitudes the probability of overexposure is greater [1].

5.2.2. Latitude

The solar radiation is more intense at the equator, where the sun shines directly and the route of its radiation through the ozone layer is the lowest of all. At the equator, a larger volume of ultraviolet radiation reaches the soil surface[1, 2].

5.2.3. Pollution

Pollution can filter out UV radiation and, therefore, a smaller volume of UV reaches the ground[2].

5.2.4. Season

The angle of the sun changes according to the seasons of the year. This causes variation in the intensity of ultraviolet radiation, which is greater during the summer months[1].

5.2.5. Clothing

People that use clothing from head to toe, for example, in some cultures, may have vitamin D deficiency by not exposing the body to the sun[1].

5.2.6. Sunscreen usage

Sun exposure produces some adverse health effects. The use of sunscreen prevents almost completely, the production of vitamin D in the body, as it blocks UVB radiation [10].

6. Reactivity to sunlight and skin types

In dermatology, the best classification for the types of skin is proposed by Fitzpatrick[35] that classifies the individual according to your skin type[34]. This classification is shown in Table 2.

Table 2. Types of skin reactivity in relation to the sun.

Type	Skin color	Performance of the skin to the sun
I	Very fair skin Caucasians	They burn easily and never tan.
II	Fair-skinned Caucasians	They burn easily and tan slowly and with difficulty.
III	Caucasian skin lightly brunette	They rarely burn and tan relatively easy (light brown).
IV	Caucasians slightly dark skin	They virtually never burn out or tan readily with little burn (moderate brown color). Some individuals with Mediterranean origin or ancestry.
V	Asian or Hindu	Rarely burn and deeeply tan (dark Brown color)
VI	African Caribbean or Black people	They never burn and are intensely pigmented.

Source: Modified from Criado[34]

7. Photoprotection X Vitamin D

The sun is the main source of heat and ultraviolet radiation to the earth, and is the major source of vitamin D in human [36]. Ultraviolet radiation is non-ionizing electromagnetic wave composed of three ranges: UVC (100 to 280 nm), UVB (280 at 320 nm) and UVA (320 to 400 nm)[36]. In general, the UV does not reach the ground and UVA radiation penetrates deeper into the skin than UVB radiation[36].

Ultraviolet radiation from the sun that reaches the earth's surface is made up of 95% UVA and 5% by UVB[36]. UVB radiation is the ultraviolet spectrum responsible for cleaving the provitamin D (7-dehydrocholesterol) to pre-vitamin D in the skin. On the other hand, it is also the most biologically active factor in skin carcinogenesis[36].

The skin has two layers, the outer, called epidermis and the inner called the dermis. The dermis contains blood vessels, lymph ducts, fibers, nerve endings and hair follicles. The epidermis is thinner than the dermis and is made of squamous cells (keratinocytes). Under these squamous cells, there are cells with more rounded shape, termed basal cell. The basal cells constantly divide to rejuvenate the skin. They are positioned at the top of the epidermis, where they are programmed to die and form the outer layer of dead skin (stratum corneum). The stratum corneum acts as a mirror that reflects both UVA and UVB radiation from the sun, away from the skin. Interspersed in the basal cells are melanocytes. The melanocytes produce melanin that protects the skin cells against sunburn, because they absorb ultraviolet radiation[2].

There is a dose-dependent relationship between solar exposure (cumulative) and the development of cutaneous carcinomas - squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), jointly referred to as non-melanoma skin cancer (NMSC) - and also a marked relationship between intermittent sunburn and the development of malignant melanoma (MM)[34].

The NMSC is the most common skin cancer and accounts for 25% of all malignant tumors registered in Brazil. From these, basal cell carcinoma accounts for 70% of diagnoses. It shows high cure rates if detected

early. It is more common in people over 40 years and it is relatively rare in children and blacks, except those already suffering from previous skin diseases. The main victims are people with light skin, sensitive to the action of sunlight or previous skin diseases [37].

The MM is less common and accounts for 4% of malignant tumors registered in Brazil. It is a type of skin cancer that originates in melanocytes, has predominance in white adults and is more severe due to high possibility of metastasis[37].

According to INCA and the Ministry of Health (2014), estimates are that the non-melanoma skin cancer is the most frequent, with a forecast of 182 000 new cases[37].

The risk of skin cancer have led dermatologists to prescribe sunscreens to the population, indicating to them to avoid exposure to the sun and replenish the sunscreen whenever necessary[3]. The existing sunscreens are products that have in their composition, substances called solar filters. These, in turn can be divided into organic and inorganic ones. Organic chemical filters absorb UV radiation, reducing its effect on the human body. Inorganic physical filters offer protection by reflection of the incident radiation[3]. When the sunscreen is topically applied properly (2 mg/cm^2), there is a reduction of approximately 95% in the production of vitamin D_3[1].

Sun exposure produces adverse effects on the health of the skin and is the main trigger factor for skin cancer and for this reason there are campaigns that recommend avoiding sun exposure and encourage the use of sunscreens. However, currently this position is controversial, since the same ultraviolet rays that are necessary for the production of vitamin D, with all its benefits, are blocked by the use of sunscreens[3].

Moreover, it is estimated that in terms of time of sun exposure, approximately 20% of the body surface (arms and/ or legs), for 5 to 15 minutes between 10 and 15 hours 2 to 3 times per week for summer, spring and autumn is a sufficient amount of sun exposure to increase levels of vitamin D. After this time one should use sunscreen with a protection factor appropriate to the skin type[1].

4. CONCLUSION

Vitamin D is very important for the health of the human being, and maintaining adequate levels of vitamin D not only brings benefits as it prevents a number of diseases. However, the data are contradictory and there is no consensus within the medical society both with respect to the existence of a sufficient and safe level of sun exposure in order to maintain an optimal level of vitamin D, as well as what would be the amount of vitamin D that should be administered in patients with deficiency/ insufficiency. There are uncertainties also concerning its usage for specific pathological conditions, time of treatment and the maintenance dose.

Anyway, one should avoid radical guidelines, such as avoiding the sun at any time and continuously use sunscreen during the day in all age groups, because there is no general rule. The physician should be alert, before prescribing the best treatment, to some issues such as the disease the patient presents. There are some groups of people to which sun exposure is contraindicated as transplant patients, individuals with lupus, those with a predisposition to develop cancer skin, or in use of immunosuppressive drugs, among others. There are other groups of patients who have risk factors for vitamin D deficiency, but that can sunbathe, such as patients with lactose intolerance, intestinal malabsorption, renal failure, cystic fibrosis, liver disease. Also, there is another group of people who use some medications that decrease the level of vitamin D as antifungal drugs, anticonvulsants, antiretrovirals, and glucocorticoids. Thus, the best treatment should be the one in which the doctor examines the patient and all his medical history and, based on the risk-benefit, prescribes what is most appropriate for the patient in that circumstance.

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