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VITAMIN D AND INFLAMMATORY MARKERS IN OBESE WOMEN

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ABSTRACT

Introduction: Currently, some nutrients have been the target of science due to the relationship they can establish with many chronic diseases, especially obesity. Vitamin D, with prominence, has received great attention for its role in maintaining glucose homeostasis and in regulating the inflammatory pathways characteristic of obese individuals. **Objective:** This study aimed to associate vitamin D concentrations with inflammatory markers in obese women. **Methods:** Case-control study involving 76 women (20 to 50 years old), categorized according to the BMI and with similar demographic and socioeconomic characteristics. For the analysis of vitamin D, high performance liquid chromatography (HPLC) associated with mass spectrophotometry was used.For serum levels of TNF-α, IL-1β, IL-6 and IL-10, blood serum was used, adopting the flow cytometry technique using a commercial human kit BD ™ Cytometric Bead Array (CBA) Human. Pearson and Chi-square tests were applied and the degree of association was tested using Cramer's coefficient. The p value <0.05 was adopted, and a 95% confidence interval. The project was approved by the Ethics Committee of the Federal University of Piaui (number1872442). **Results:** Vitamin D concentrations showed that 52.6% and 31.6% of obese women had deficiency and insufficiency, in that order. Obese women had high concentrations of TNF-α (p=0.04). **Conclusion:** There was an association between significantly reduced concentrations of vitamin D and high serum levels of TNF-α in the sample.

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INTRODUCTION

Obesity is still a serious public health problem, with an endemic character and prevalence rates that are increasing worldwide. In the last decade, the morbidity and mortality of many countries have been impacted by about 4 million deaths worldwide (1), in addition to the percentages that point to the incidence of overweight in 30% of the population global, of which more than 600,000 are obese, according to epidemiological data (2). Currently, some nutrients have been the target of science due to the relationship they can establish with many chronic diseases, especially obesity. Vitamin D, with prominence, has received great attention for its role in maintaining glucose homeostasis and in regulating the inflammatory pathways characteristic of obese individuals (3).

Based on this assumption, it has been observed that vitamin D deficiency represents a potential risk factor for obesity. According to studies, more than one billion people worldwide are already vitamin D deficient (4-5). The causes that possibly justify this scenario are mainly related to behavioral aspects and inherent to the modern lifestyle, such as a sedentary lifestyle, low exposure to sunlight, unbalanced diet, excess body fat and abuse of topical or oral medications, which can interfere with the absorption or metabolism of this nutrient (6). The study by Stokic et al. (7) demonstrated that obese individuals are more likely to have a low vitamin D status, given that the accumulation of adipose tissue reduces its availability, due to the disruption of adipocytes. Fat cells act as a large capacity tank for the storage and release of vitamin D, vitamin accumulated in proportion to its concentration in the serum, and releasing it much more slowly. Such a mechanism

may affect the bioavailability of 25OHD impair its biological activity (8), the hypothalamus trigger a cascade of reactions that leads to increased hunger and decreased energy expenditure. Among these reactions are increasing levels of parathyroid hormone (PTH), promoting lipogenesis and can modulate adipogenesis by suppressing the vitamin D receptor (9). The role of vitamin D in the inflammation of obesity comes from its effect on immunity, expression of NF-kβ, an important transcription factor that induces expression of TNF-α, IL-6, C-Reactive Protein (CRP) and fibrinogen (10-13), so that vitamin D deficiency intensifies inflammation. Obesity due to its proinflammatory pathways support the production of inflammatory markers (TNF-α, IL-6, CRP, MCP-1) adipocytes, as well as the production and release of these markers by other organs such as liver and immune cells. In this sense, this article aims to illustrate the immunomodulatory effect of vitamin D, its potential role in the development and perpetuation of systemic diseases, as well as its respective therapeutic contribution. Therefore, it seeks to associate concentrations of vitamin D and inflammatory markers in obese women, in order to contribute to a better understanding of the role of this vitamin in the inflammation-obesity axis.

MATERIALS AND METHODS

Study Characterization and Experimental Protocol: This is a case-control study, involving 76 women aged 20 to 50, equally divided into two groups. The study group was composed of 38 women with a BMI> 30 kg/m²and the case group, 38 women with a BMI between 18.5 and 24.9 kg/m², both with similar demographic and socioeconomic characteristics. The sample was defined based on the number of obese individuals, in a total of 1256, treated at Hospital Getúlio Vargas in 2016. The calculation was performed by the Raosoft program, applying a 10% margin of error for losses and refusals. The women in the case group were recruited by a non-probabilistic convenience technique, in the integrated ambulatory Dirceu Mendes Arcoverde of Hospital Getúlio Vargas in the city of Teresina-PI, Brazil, and the participants in the control group, through public calls, on digital media. Data were collected by researchers from the Nutrition course atFederal University of Piaui (UFPI), including undergraduate students, undergraduate and master's students, defining the collection period between the months of January to August 2017.

The eligibility criteria for the study group were: Signature of the Free and Informed Consent Form (ICF); not being pregnant or breastfeeding; not participating in another clinical study; not having a diagnosis of diabetes mellitus, chronic kidney disease, cancer, liver disease and/or inflammatory bowel disease; absence of the use of mineral vitamin supplements and/or medications that interfere with the nutritional status related to vitamin D. All participants were approached and selected through interviews, and the signature of the informed consent form, which legitimized voluntary acceptance to compose the study. Soon thereafter, forms for registering the participants and a socio-demographic and anthropometric questionnaire were delivered, followed by the application of the 24-hour recall (R24h) method, and finally, setting or scheduling dates for blood collection and filling in the second R24h, three months after the first.

Anthropometric Characterization of Nutritional Status: Nutritional status was classified by anthropometric measurements (weight, height, waist circumference), according to the methodology described by the Ministry of Health (14), and calculation of the Body Mass Index (BMI). Body weight and height were determined, respectively, using a Filizola® digital scale (São Paulo, Brazil), with a maximum capacity of 180 kg, graduated in 100 grams, and a Seca® stadiometer, graduated in centimeters and with a vertical bar fixed for positioning above the head. At the time of the assessment, participants were wearing light clothing, bare feet, feet together, standing and looking at the horizon. Each parameter wasmeasured in triplicate, obtaining the average (14, 15). The values were applied in Equation 1 below, which relates weight (kg) and height squared (m²), to obtain BMI (16), and classification of nutritional status, according to cut points established by the World Health Organization (Board 1).

Equation 1. BMI calculation

$$BMI = \frac{Weight\ (kg)}{Statute\ (m^2)}$$

Board 1.Classification of nutritional status by BMI (Kg/m²) for adults, of both sexes

BMI (Kg/m²)	Classification
< 16	Grade III thinness
16 - 16,9	Grade II thinness
17 - 18,4	Grade I thinness
18,5 - 24,9	Eutrophy
25 - 29,9	Pre-Obesity
30 - 34,9	Grade I obesity
35 - 39,9	Grade II obesity
> 40	Grade III obesity

Source: WHO (16).

To measure waist circumference, a non-extensible Seca® tape measure (São Paulo, Brazil) was used, with 0.1 cm precision, which was positioned at the midpoint between the last rib and the iliac crest. The participants were in an upright position, with a relaxed abdomen, arms extended along the body and feet apart. According to World Health Organization (16), borderline waist circumference values associated with the development of obesity-related metabolic complications for women are ≥ 80 cm for high risk and ≥ 88 cm for very high risk.

Biological Material Collection: Samples containing 18 mL of blood were collected between 7 and 9 am, using disposable and sterile syringes and plastic needles. Participants were fasting for at least 12 hours. The collected content was distributed in separate tubes: (1) vacuum tube with clot activator for serum and analysis of inflammatory cytokines and (2) vacuum tube with EDTA to determine vitamin D. The separation of blood components for analysis of vitamin D and cytokines required control of the mineral contamination of the polypropylene cups used in the preparation of the reagents. Therefore, the glass material was demineralized before use, by immersion in a 10% nitric acid solution, for a minimum period of 12 hours. Subsequently, all the glass material needed for the analyzes was washed in deionized water, at least 10 times, dried in an oven and kept in closed deposits previously demineralized, until the moment of use. All reagents used were of analytical purity (P.A). All aqueous solutions and dilutions

were prepared with ultrapure water, obtained using a Milli-Q system (Millipore®, United States). For analysis of vitamin D and serum inflammatory cytokines, plasma and serum were separated from whole blood by centrifugation (CIENTEC® 4K15, São Paulo, Brazil) at 1831xg for 15 minutes at 4ºC. The serum was placed in a tube with clot activator, from where it was aspirated with an automatic pipette and stored in polypropylene microtubes, as well as plasma, both later stored at - 80°C.

Determination of vitamin D: The diagnostic marker for determining vitamin D levels was the concentration of 25-hydroxyvitamin D (25(OH)D), with its D2 (25(OH)D2) and D3 (25(OH)D3) fractions. The analyzes were performed in the Microscopy laboratory at USP in São Paulo, by determining the calcidiol. Calcidiol was calculated by adding the concentrations of 25(OH)D2 and 25(OH)D3, which were determined by high performance liquid chromatography (HPLC) associated with mass spectrophotometry. Calcidiol concentrations ≥30ng/ml, between 20 and 29ng/ml and <20ng/ml were classified, respectively, with vitamin D sufficiency, insufficiency and deficiency as recommended by the United States Endocrinology Society (17).

Determination of Serum Cytokines: For the determination of serum concentrations of TNF-α, IL-1β, IL-6 and IL-10, blood serum was used, adopting the flow cytometry technique using a commercial BD ™ Cytometric Bead Array (CBA) kit with human respective cytokines, from BD Bioscience, following the manufacturer's instructions, at the Nathan Portella Tropical Diseases Institute. The same procedure was used to prepare the standard curve. In the same sample, four populations of *beads* with different fluorescence intensities were conjugated with a specific capture antibody for each cytokine, forming the *beads* curves and then read on the FACSCantoll flow cytometer.

Statistical analysis

The results of the study were exported to the SPSS program (for Windows® version 20.0) in which the statistical treatment was performed. The Kolmogorov-Smirnov test was applied to verify the normality of the data. Then, for the purpose of comparison between the groups studied, the *Student t* test was used for variables with normal distribution and the *Mann Whitney* test for those with nonparametric distribution. A test was carried out to compare the average vitamin D concentrations between the two groups, distributed according to the body mass index. Pearson's linear correlation coefficient was used to study the correlations of the data with the normal distribution. Associations between variables were verified using the chi-square test and the degree of association was tested using Cramer's coefficient. Values of $p < 0.05$ were considered significant, adopting a 95% confidence interval.

Ethical aspects: The project was approved by the Research Ethics Committee of the University Federal do Piauí, under opinion number 1.872.442, as provided for in Resolution 466/12 of the National Health Council (CNS) (18). All participants signed the Free and Informed Consent Form (ICF), prepared in accordance with the "Declaration of Helsinki III", chapter 50, paragraphs 50.20/27, which deals with the protection of participants and guides the procedures related to the research that needs of experience with humans. Subsequently, a registration form was completed, after receiving detailed information about the research in the appropriate language, as established in Resolution 466/12 of the National Health Council (18).

RESULTS AND DISCUSSION

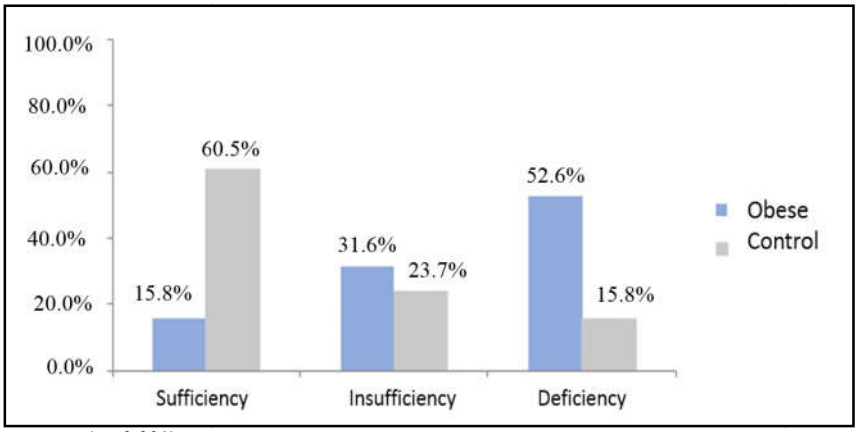
The high prevalence of vitamin D deficiency, routine screening for the absence of risk groups such as obese, and the potential association between vitamin D deficiency and obesity motivated the present study. Research evaluating associations between low 25(OH)D concentrations and inflammatory markers in the general population, especially in obese women, and serum vitamin D concentrations for health in obese people is scarce. However, it should not be overlooked that low concentrations of 25(OH)D represent a health problem resulting from inflammatory processes (19) The obese women in this study showed reduced concentrations of vitamin D in relation to the normal parameters proposed by Holick (20), when compared to the control group (Table 1). These results are aligned with the Al Haj Ahmad and Al Domi (21), Esteghamati et al. (22), and Ilincic et al. (23) and. For Schmidt (24), vitamin D plays a role in the regulation of lipolysis and its active form could regulate adipocyte death and decreased fat mass.

Table 1. Mean and standard deviation values of anthropometric parameters obese and control group patients. Teresina-PI, Brazil, in 2018

Parameters	Obese (N = 38) Mean ± SD	Control (N = 38) Mean ± SD	*p*
Age years)	31.53 ± 6.19	28.79 ± 6.25	0.059
Body weight (kg)	86.77 ± 11.14 *	58.38 ± 6.37	<0.001
Height (m)	1.60 ± 0.06	1.62 ± 0.06	0.164
BMI (kg / m2) to	32.90 (30.10 to 42.00) *	22.50 (18.70 to 24.90)	<0.001
DC (cm)	95.95 ± 7.90 *	71.36 ± 5.34	<0.001

*Significantly different values between obese patients and control group, *Student's t-test* or *Mann-Whitney* test ($p < 0.05$). [a]Represented as median, minimum and maximum values. BMI = Body Mass Index.

Among the mechanisms that can explain these findings, there is that vitamin D in the presence of excess fat, seems to suffer imprisonment in this tissue. Due to its fat-soluble characteristic, leading to a deficiency in circulation.Moreover, with chronic low-grade inflammation, present in obesity, may be increased nutrient demands that the site of inflammation due role anti-inflammatory and antioxidant, which contributes to the reduction of their concentration in plasma (8, 25-26). In agreement with this finding, Domingues (27) found 93.6% of the sample with the vitamin D levels below 30 ng/ml. Karlsson et al. (28) found half of obese pregnant women with vitamin D status below the ideal in early pregnancy, compared with normal-weight women, suggesting increased demand for this nutrient in obese pregnant women. The possible reasons that justify this finding are related to lifestyle characteristics. For example, the sample consisted predominantly of women who worked indoors and exercised little, avoiding the key factor in the production of vitamin D, which is exposure to the sun. In addition, 71.4% and 65.4% of the participants who presented situations of vitamin D insufficiency and deficiency, respectively, used sunscreen. The vitamin D status in these women showed that 52.6% and 31.6% of them were deficient and insufficient, respectively (Figure 1), which corroborates the complex interaction of vitamin D in obesity. As reported by Rocha et al. (29), vitamin D deficiency leads to metabolic changes and increased body fat, waist circumference and BMI.



Chi-square test (p <0.001).

Figure 1. Percentage distribution of obese participants and control group, according to the reference values of vitamin D. Teresina-PI, Brazil, 2018

Table 2. Median, minimum and maximum values of serum cytokines in obese and control group patients. Teresina-PI, Brazil, in 2018

Parameters	Obese (N = 38) Med (Min - Max)	Control (N = 38) Med (Min - Max)	*p*
TNF-α (pg / ml)	0.03 (0.00 to 6.97) *	0.00 (0.00 to 5.04)	0.044
IL-6 (pg / ml)	1.14 (0.09 to 13.38)	1.07 (0.26 to 12.75)	0.266
IL-1β (pg / ml)	0.00 (0.00 to 0.83)	0.00 (0.00 to 0.57)	0.728
IL-10 (pg / ml)	0.10 (0.00 to 1.18)	0.12 (0.00 to 3.68)	0.892

* Values significantly different among obese patients and a control group, Mann-Whitney test (p <0.05). TNF-α: tumor necrosis factor; IL-6: interleukin 6; IL-1β: interleukin 1β and IL-10: interleukin-10.

Table 3. Simple linear correlation analysis between the concentrations of vitamin D, dietary vitamin D and serum cytokines in obese patients and the control group. Teresina-PI, Brazil, 2018

	Obese disabled and insufficient (n = 32)				Sufficient controls (n = 23)			
Parameters	Dietary Vit D		Vit D		Dietary Vit D		Vit D	
	r	*p*	r	*p*	r	*p*	r	*p*
TNF-α	-0.108	0.557	-0.395*	0.025 *	0.242	0.265	0.042	0.850
IL-6	-0.122	0,505	-0.075	0.685	0.397	0.061	0.141	0.521
IL-1β	-0.188	0.303	-0.064	0.727	-0.077	0.728	-0.106	0.632
IL-10	-0.253	0.163	-0.149	0.415	-0.203	0.353	0.188	0.390

* Significant correlation, Pearson correlation coefficient (p <0.05)

The obese women had elevated TNF-α concentrations (p = 0.04) (Table 2) compared to the control group, aligning the Al-Sharif (30) and Bellia et al. (31). Obese patients exhibit increased activation of kinases like c-Jun N-terminal kinase and the kinase inhibitor-k, which are capable of inducing the expression of inflammatory cytokines. These kinases regulate transcriptional programs through transcription factors protein-1, κβ nuclear factor and interferon regulatory factor, inducing the deregulation of gene expression of inflammatory mediator. The increase of cytokine receptor activation exacerbates establishing a positive feedback inflammation inhibitory signaling and metabolic pathways (32-34). In this study, there was a concentration grade I obese (30; 78.9%), which suggests that increasing TNF-αexpression may be a limiting factor for further expansion of adipose tissue by inducing insulin resistance in adipocytes which may influence the activity of lipoprotein lipase (LPL) and thus avoid the excessive growth of adipose tissue according Popko et al. (35). In view of achieving better understanding of the contribution of vitamin D and its role of inflammation in obesity was conducted correlation analysis between concentrations of vitamin D and inflammation parameters. Initially, no significantly different concentrations of cytokines were observed between the two groups studied. This encouraged a new stratification of the initial grouping according to the concentrations of vitamin D in: not deficient, deficient and insufficient. The result in Table 3 showed a moderate, negative and significant correlation between vitamin D and TNFα in obese women with vitamin D deficiency and insufficiency, that is, the lower the concentration of vitamin D, the greater the expression of TNFα. Based on the results, vitamin D plays a crucial role in controlling concentrations of anti-inflammatory and pro-inflammatory cytokines. It is believed that TNFα concentrations may contribute to a decrease of 25(OH)D, impairing its production or accelerating its catabolism, although further investigation is needed to confirm this hypothesis.In addition, the pro-inflammatory effect of hypovitaminosis D conditions induces inflammatory events that include positive regulation of NF-Kβ and expression of genes encoding TNF-α. These processes narrow the link between the degree of inflammation and vitamin D deficiency in obese people (36, 37). Dickie et al. (38) and Haque et al. (39) confirmed inverse relationships between plasma concentrations of 25 (OH) D and pro-inflammatory cytokines such as: CRP, IL-6, IL-23 and TNF-α, observed in obese, type 2 diabetic and vitamin D deficient individuals. Likewise, Adela et al. (40) reported the inverse relationship between metabolic and inflammatory cytokines of vitamin D in pregnant women with pre-eclampsia.In this context, it is worth mentioning that the increase in inflammatory markers may reflect the effects of different factors, such as the disease itself, adiposity or vitamin D deficiency. In this study, obese participants showed no preexisting disease and stratifying them according to the degree of obesity, BMI rated by

criterion, there was a concentration degree obese I (30; 78.9%), which stresses the state of mild chronic inflammation in this segment, which leads to an immediate increase in TNF-α levels, and subsequent increase of other cytokines (41-43). In this view, it is possible to explain the absence of a negative correlation between the concentrations of vitamin D and IL-6 in obese individuals. (44).

Despite the small sample, there was evidence of the hypothesis raised. In addition, the protocols were standardized and the performance of all exams with trained examiners and certified laboratories guaranteed the quality of the data. However, some limitations of the present study need to be considered. First, as it is a cross-sectional study, it is not possible to establish cause and effect relationships, and the results may not necessarily be valid in non-obese individuals. The main biases of this type of study are: selection bias and classification error as a result of the retrospective aspect, absence of more specific markers, such as CRP, MCP-1, to assess inflammation and even adiponectin, which can also contribute to limit the discussion such results.Cytokines have a very short half-life in the blood and should ideally be measured "locally". Therefore, in tissues, the analysis of inflammatory markers was performed in a single moment and may not have adequately represented the inflammatory condition of obese women.The serum concentration of a cytokine, being an isolated factor, can overestimate or underestimate the result and even reflect a systemic change. It would be of great interest to conduct similar new studies in patients with other chronic diseases and inflammatory conditions, with larger samples that included the evaluation of other inflammatory markers. New proposals may contribute to a better understanding of the metabolic behavior of vitamin D in the pathogenesis of inflammation of obesity and other diseases, enabling the application of interventions that can control or minimize metabolic disorders.

CONCLUSION

Obese women had significantly reduced concentrations of vitamin D and high serum concentrations of TNF-α. Vitamin D deficiency and insufficiency correlated negatively with TNFα concentrations. The results of this study contribute to the evidence supporting the role of vitamin D in inflammatory processes.

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