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Association between serum vitamin d levels and cardiometabolic alterations

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ABSTRACT

Introduction: Hypovitaminosis D has been described as an epidemic in the recent years and its association with cardiometabolic alterations such as arterial hypertension, diabetes *mellitus*, dyslipidemia, obesity and Metabolic Syndrome have been studied.

Objectives: To evaluate the association between serum levels of vitamin D and cardiometabolic alterations.

Methods: A cross-sectional study involving patients seen outpatient in a public hospital service, reference in cardiology in Recife-PE, Brazil. Serum levels of 25 hydroxyvitamin D were measured and assessed for their relations with cardiovascular and metabolic risk parameters.

Results: 90 individuals were evaluated with a mean age of 57.0 ± 11.9 years, predominantly female (75.6%). Vitamin D deficiency (levels < 20 ng/ml) was observed in 12.2% of the subjects and an insufficiency (levels 20-29 ng/ml) in 35.6%. Serum vitamin D levels were higher in males (p<0,001), in subjects with normal waist circumference (WC) (p=0,008), and in those with elevated glycated hemoglobin (HbA1c) (p=0,006). Inverse correlation was observed between serum levels of vitamin D and total cholesterol (TC) (r=-0,214; p=0,045) and LDL-c (r=-0,227; p=0,033) and direct correlation with HbA1c(r=0,211; p=0,048). In the adjusted analysis, it was observed that patients that had central obesity had a 2.8 (IC95%: 1,1–7,7; p=0,048) higher chance of having vitamin D deficiency when compared to patients with normal WC. It was verified that patients with high triglycerides levels had protection for vitamin D deficiency (OR=0,3; $IC_{95\%}$: 0,1–0,8; p=0,023).

Conclusions: Hypovitaminosis D was highly prevalent in the studied population. Low levels of vitamin D correlated with elevated levels of TC and LDL-c and central adiposity.

KEYWORDS

Vitamin D; Vitamin D Deficiency; Risk Factors.

LIST OF ABBREVIATIONS

ADA: American Diabetes Association.

BARC: Brazilian Association of Anthropology and Brazilian Association of Research Companies.

BMI: Body Mass Index.

DM: Diabetes Mellitus.

HbA1c: Glycosylated Haemoglobin.

MS: Metabolic Syndrome.

NCEP: National Cholesterol Education Program's Adult Treatment Panel III Report NHANES: Third National Health and Nutrition Examination Survey.

PTH: Parathyroid Hormone.

TC: Total Cholesterol.

TG: Triglycerides.

WC: Waist Circumference.

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INTRODUCTION

The classic role of Vitamin D is the regulation of calcium and phosphorus metabolism by controlling intestinal absorption and tubular reabsorption of those ions, keeping them in appropriate serum levels to secure an adequate growth and bone mineralization in infants and adolescents and global bone health[1]. It is well described the role of Vitamin D in different cellular processes, such as: regulation of cellular proliferation and differentiation, regulation of hormone secretion and regulation of immune function[2].

Hypovitaminosis D is the status of insufficiency or deficiency of Vitamin D, defined, according to the *Endocrine Society*, as serum levels of 25 hydroxyvitamin D [25(OH)D] between 20 and 30 ng/mL and < 20ng/mL, respectively[3]. This condition has been described as an epidemic in the recent years and its consequences beyond bone health have been studied. A limited number of studies has described the prevalence of hypovitaminosis D in Brazil, the majority included mainly the elderly and post-menopausal women which are the populations at risk for osteoporosis[4,5]. However, studies held between 2005 and 2013, involving individuals of different age groups, showed a prevalence of Hypovitaminosis D between 33 and 90.6%[3].

The discovery of receptors of Vitamin D in various tissues unrelated with the bone metabolism e the identification of the enzyme 1-α-hydroxylase in non-kidney tissues has suggested the possibility of extraskeletal effects of vitamin D[6] and in the last decades has been described its association with cardiometabolic alterations such as arterial hypertension, diabetes *mellitus* (DM), dyslipidemia, obesity and Metabolic Syndrome (MS)[7]. Thus the aim of this study is to evaluate the association between serum levels of vitamin D and cardiometabolic alterations.

METHODS

This was a cross-sectional study, which involved patients evaluated on the outpatient of Nutrition in universitary public hospital reference in Cardiology in Notheast Brazil, between 2013 and 2015. The following inclusion criterion was applied: individuals of both sexes, aged ≥ 20 years old that agreed to join the study. The exclusion criteria adopted were as follows: individuals with hepatomegaly; kidney disease; ascites; recent abdominal surgery; pregnant women and women that had had children until six months before the screening of the research; pacientes with edema, that would prevent the analysis of anthropometric measurements and those on Vitamin D replacement therapy.

The study protocol was approved by the Ethics Committee of University of Pernambuco.

Casuistry

Considering an α error of 5%, a β error of 20%, an estimated mean correlation between 25 (OH) D serum levels and the glycolipid profile of 0.5 (obtained from a pilot study) and one variability of 0.15 (d^2), a minimum sample size of 88 individuals was obtained. To correct any losses, this number was increased by 10%, totaling a sample n of 97.

Biochemical Analysis

Were conducted on the laboratory of clinical analysis in the hospital. Serum levels of 25(OH)D were evaluated by Chemiluminescence Immunoassay, using a Diasorin Analyzer LIAISON (Turin, Italy), with coefficient inter and intra variation test of 8% to 15% and 8% to 13%, respectively, and a detection limit of 2ng/ml. Vitamin D status were defined considering deficient values <20ng/ml, insufficient when values were between 20-29ng/ml and sufficient when ≥30 ng/ml[5].

For the analysis of cardiometabolic alterations, were evaluated the following parameters: fasting glucose and glycosylated haemoglobin (HbA1c), considering the reference values recommended by the American Diabetes Association (ADA)[8], and blood lipid concentrations (Triglycerides (TG), total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol and TG/HDL ratio), considering standard the values on the V Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis[9].

Fasting glucose and lipid profile were analyzed by the enymatic method, and HbA1c by turbidimetry. Clinical analysis were made using Cobas Íntegra 400 (Roche Diagnostics) analyzer. The non-HDL cholesterol was used as an estimate of the total number of aterogenic particles on plasma (VLDL + IDL + LDL). Non-HDL cholesterol was calculated by the subtraction of HDL-c to TC: non-HDL cholesterol = CT - HDL-c. For all samples, it was considered a fasting of 12 hours and preparation protocol, according to the recommended by the V Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis[9].

Anthropometric evaluation

The parameters waist circumference (WC) and body mass index (BMI) were evaluated. All measurements were collected in duplicates by a single observer and repeated when the gauging error between them was greater than 0.1 cm or 0.1 kg. The final measure considered was the average between the two closest values. The BMI was obtained by the equation: Weight/Height^2, being the nutritional status of the adults classified according to the World Health Organization proposal[10], and the elderly, according to the classification proposed by Lipschit[11]. Weight and height were measured according to recommended techniques, using an electronic scale (Welmy®, Santa Bárbara d'Oeste, São Paulo, Brazil), capacity 150kg with 100g division, and Tonelli® stadiometer (Criciúma, SC, Brazil), with precision in millimeters.

Socioeconomic and demographic variables

Among socioeconomic and demographic variables, informations on age, sex, race, schooling and socioeconomic le-

vel were collected. The race was self-defined by the interviewee, considering white, black, brown or other. The schooling was obtained in years of study, considering the categories: ≤ 9 years and > 9 years of study. In the determination of the socioeconomic level, the "Brazilian Classification Criteria", established by the Brazilian Association of Anthropology and Brazilian Association of Research Companies (BARC), were used to classify the population in economic classes A1, A2, B1, B2, C1, C2, D and E, in descending order, respectively initiated by the one with the best purchasing power. After classifying, the economy class was recategorized in subclasses: high economic class (categories A1, A2 and B1) and low economic class (categories B2, C1, C2, D and E).

Clinical variables

The presence of comorbidities: hypertension, DM and dyslipidemia, were considered when the patient reported a previous diagnosis emitted by the physician; used antihypertensive, hypoglycemic or lipid-lowering drugs, respectively; and/or it was reported on the medical record.

For the diagnosis of MS, the criteria proposed by the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP / ATP III), which defines the diagnosis by the presence of three or more of the following components: abdominal obesity, defined by the measurement of the waist circumference (WC) >102cm for men and >88cm for women; triglycerides >150mg/dL; HDL-c <40mg/dL for men and <50mg/dL for women; blood pressure ≥130mmHg or ≤85mmHg and fasting blood glucose ≥100mg / dL.

Statistical analysis

The data were analyzed with the aid of the Statistical Package for Social Sciences - SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Continuous variables were tested for normality of distribution by the Kolmogorov Smirnov test. Data with normal distribution were described as mean and standard deviation and those with non-normal distribution were described as median and interquartile range. Linear correlation of Pearson or Spearman was used to evaluate the association of 25 (OH) D levels with biochemical parameters.

The association between the categorical variables was analyzed through the Pearson Chi-square test. Subsequently, a multivariate analysis was performed using the logistic regression method, and all the variables associated with vitamin D deficiency were included in the univariate analysis with statistical significance of up to 20%. For acceptance of the associations investigated in the final model, the value of p <0.05 was adopted.

RESULTS

97 eligible individuals were evaluated, of which 7 were not considered for the analysis due to inconsistency or refusal to take part on the study. The final sample was 90 patients, mean age of 57,0±11.9 years, majority of women (75.6%) and low social class patients (93.2%).

The Prevalence of arterial hypertension and DM were 64.4% and 32.2%, respectively. MS was present in 50% of the patients, 65.2% of the population studied was overweight and abdominal obesity was observed in 65.9%. 7.2% of the subjects were smokers.

Hypovitaminosis D was identified in 47.8% of the patients (35.6% with insufficiency status and 12.2% with deficiency status). Serum levels of Vitamin D were higher among men (p<0.001), individuals with normal WC (p=0.008) and those with high levels of HbA1c (p=0.006) (Table 1).

There was an inverse correlation between serum levels of Vitamin D and TC (r=-0.214; p=0.045) and LDL-c (r=-0.227; p=0,033) and direct correlation with HbA1c (r=0.211; p=0.048) (Table 2).

On the adjusted analysis, it was observed that obese patients had 2.8 (IC95%: 1.1-7.7; p=0.048) higher chance of show deficiency on Vitamin D compared to those with normal WC. It was also verified that patients with high levels of TG showed protection to deficiency of Vitamin D (OR=0.3; IC95%0.1-0.8; p=0.023) (Table 3).

DISCUSSION

Cardiovascular diseases are the main cause of death worldwide. Over recent decades, Brazil has witnessed a decline in mortality rates due to coronary heart disease and stroke. However, in 2012, these diseases were the first and the third commonest causes of premature death nationwide, respectively[12].

Concomitant to this decline in mortality rates, it has been shown that hypovitaminosis D represents a major health issue worldwide[13]. It has also been described its role with cardiovascular alterations that predisposes cardiovascular diseases[7].

Investigations on this topic are recent in Brazil, more studies are necessary to report the prevalence of hypovitaminosis D and its association with cardiometabolic risk factors. The prevalence found on this study (47.8%, being 35.6% with insufficiency status and 12.2% with deficiency) was close to the one described by Silva *et al.*[14], that showed a prevalence of 43.8% in a sample of 132 individuals in Belo Horizonte (MG) with similar characteristics to the present study: patients is currently undergoing outpatient follow-up, with median age of 58.9 years and predominance of female individuals.

However, Gondim *et al.*[15] found a higher prevalence of Vitamin D deficiency (33%) in a sample of 100 patients, with median age of 57.63±11 years, in a coronary care facility on

Table 1. Mean and standard deviation of serum levels of 25 (OH)D according to sociodemographic, clinics and anthropometric variables in patients followed on the ambulatory of a hospital (n=90) in the Brazilian Northeast between 2013 and 2015.

Variable	n	Mean	SD	p-value*
Sex				
Male	22	40.1	13.4	<0.001
Female	68	30.1	9.8	
Age				
<60 years	49	32.7	10.7	0.888
≥60 years	41	32.4	12.7	
Education (Years of study)				
≤9 years	42	31.5	10.2	0.314
>9 years	46	33.9	12.7	
BARC Classification				
High	6	29.6	7.9	0.539
Low	82	32.7	11.8	
Diabetes *Mellitus*				
No	61	31.5	10.8	0.198
Yes	29	34.8	12.8	
Nutritional Status				
No Weight Excess	31	35.4	13.4	0.092
Weight Excess	58	31.1	10.4	
Waist Circumference				
Normal	30	37.0	12.2	0.008
Elevated	58	30.2	10.5	
Fasting Glucose				
<100 mg/dl	46	31.6	11.3	0.350
≥ 100 mg/dl	41	33.9	11.9	
HbA1c				
<6%	18	28.3	5.2	0.006
≥6%	70	33.8	12.5	

BARC - Brazilian Association of Research Companies; SD – Standard Desviation; NCEP III– National Cholesterol Education Program's Adult Treatment Panel III Report. * Student "t" Teste.

Table 1 continuación. Mean and standard deviation of serum levels of 25 (OH)D according to sociodemographic, clinics and anthropometric variables in patients followed on the ambulatory of a hospital (n=90) in the Brazilian Northeast between 2013 and 2015.

Variable	n	Mean	SD	p-value*
Total cholesterol				
<200 mg/dl	49	33.9	10.4	0.221
>= 200 mg/dl	39	30.8	13.0	
Triglycerides				
<150 mg/dl	53	32.8	11.5	0.796
≥ 150 mg/dl	35	32.1	12.1	
LDL-c				
<100 mg/dl	28	34.8	11.8	0.212
≥100 mg/dl	60	31.4	11.6	
HDL-c				
Low	39	31.9	11.4	0.678
Normal	49	33.0	12.0	
TG/HDL				
<4.0	61	32.3	11.7	0.785
≥4.0	27	33.0	11.9	
Non HDL-c				
<130 mg/dl	29	34.0	12.2	0.396
≥130 mg/dl	59	31.8	11.5	

BARC - Brazilian Association of Research Companies; SD – Standard Desviation; NCEP III– National Cholesterol Education Program's Adult Treatment Panel III Report. * Student "t" Teste.

a hospital in Recife Metropolitan Area. The authors point out the elevated prevalence of Vitamin D deficiency, although the individuals live in the tropics with average high sunny index and with average to three hour daily exposure solar light.

The studies mentioned above, as ours, were conducted in states where incidence of direct solar light is elevated in most parts of the year, even though hypovitaminosis D was reported in 50% of the patients.

It is noteworthy that in our population there were prevalences of females (75.6%), black or mixed race individuals (63.3%) and overweight individuals (63.3%), characteristics often associated to lower levels of Vitamin D[13,16].

Serum levels of Vitamin D are influenced by many factors, such as sex and age. IIt is common to find lower serum levels of Vitamin D in elderly people[3], however, in our sample, there was not a significant difference between serum levels of Vitamin D in adults and elderly individuals, corroborating with the study by Giorelli *et al.*[17], that evaluated 53 individuals, with median age of 65.3±10.3 years, and also did not find differences between age brackets. Lower levels of Vitamin D in the elderly can be explained by the physiological decrease in levels of 7-dehydrocholesterol (7-DHC), precursor for the cutaneous synthesis of vitamin D, therefore, the elderly have a reduced capacity of producing this vitamin and are susceptible to hypovitaminosis D[18].

Lower Serum Levels of 25(OH)D in women, as found in the present study, were also described by Yetley[19], in a investigation involving participants of the *Third National Health and*

Table 2. Correlation (r) between 25(OH)D and age, anthropometry and biochemical parameters in patients followed on the ambulatory of a hospital (n=90) in the Brazilian Northeast between 2013 and 2015.

Variable	r	p-value
Age	-0.106*	0,321
Body Mass Index	- 0,098*	0,363
Waist Circumference	- 0,084*	0,436
Total Cholesterol	- 0,214*	0,045
HDL-c	- 0,092*	0,394
LDL-c	- 0,227*	0,033
Triglycerides	- 0,020†	0,851
Triglycerides/HDL-c	0,044†	0,684
Non HDL Cholesterol	- 0,194*	0,070
Fasting GLucose	0,149*	0,168
HbA1c	0,211*	0,048

* Pearson Correlation; †Spearman Correlation.

Nutrition Examination Survey (NHANES) that showed that women had a higher prevalence of low levels of 25(OH)D when compared to men in all age brackets, with exception of children aged between 1 and 5 years old. This difference is associated, mainly, to the direct relation between vitamin D and testosterone, therefore it is expected to find higher levels of vitamin D in men due to their higher serum levels of testosterone[20].

Our study did not find differences in serum levels of vitamin D in patients with high or not blood pressure, tough this relation is described in the literature[7,21]. The main mechanism to explain the relation between hypovitaminosis D and high blood pressure is the elevation on the levels of parathyroid hormone (PTH) due to the chronic deficiency of Vitamin D[22].

Low levels of vitamin D cause a reduced intestinal absorption of calcium and the lower serum calcium concentration causes an increase of PTH secretion on the try to regulate vitamin D levels. By this mechanism serum 1,25-(OH)2D is kept at (nearly) normal levels at the expense of a higher serum PTH concentration, which is referred to as secondary hyperparathyroidism[22]. Secondary hyperparathyroidism is related to the activation of the renin-angiotensin system. inhibition of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] synthesis also led to an increase in renin expression, whereas 1,25(OH)2D3 injection led to renin suppression.

Table 3. Logistic regression of factors associated to the deficiency of 25(OH)D in patients followed on the ambulatory of a hospital (n=90) in the Brazilian Northeast between 2013 and 2015.

Variable	OR	($CI_{95\%}$)	p-value
Waist Circumference			
Normal	1.0	-	0.048
Elevated	2.8	(1.1 - 7.7)	
Triglycerides			
Normal	1.0	-	0.023
Elevated	0.3	(0.1 - 0.8)	

OR: Odds Ratio; CI: Confidence Interval of 95%.

We did not observe lower serum levels of vitamin D in individuals that have DM, and HbA1c was directly correlated to 25(OH)D levels, though a weak correlation, this result does not reproduce previously published data and indicates that patients with high levels of fasting glucose or HbA1c are more susceptible to have lower levels of vitamin D[7].

The relationship between hypovitaminosis D and DM is associated to the PTH elevation, that involves an elevation of insulin resistance and dysfunction of pancreatic beta cells. The action of 25(OH)D in insulin resistance happens through direct effects, stimulating insulin receptor expression and insulin responsiveness for glucose transport[24], or indirect, through its role on the regulation of extracellular calcium ensuring the normal influx of calcium through the cell membranes and adequate pool of intracellular calcium, because this ion is essential to intracellular processes mediated by insulin on the insulin responsive tissues[25]. High levels of calcium in insulin target cells may induce insulin resistance by insulin signal transduction impaired leading to the diminution activity of GLUT-4[26].

Vitamin D can also have an affect on insulin answer to glucose stimulation directly or indirectly. The direct effect may be mediated by the bond of its circulating levels, $1,25(OH_2)D$ to the vitamin D receptor in beta cells. Alternatively, vitamin D activation may also occur in beta cells by the enzyme 1alpha-hydroxylase, that has been recently shown to be expressed in those cells[27]. Indirect effects of vitamin D may be mediated by its role on the regulation of extracellular calcium and of the flow of calcium through the beta cell. Insulin secretion is a calcium dependent process, therefore, alterations on this flow may have adverse effects on the secretory function of beta cells[28].

Corroborating with the literature[21], in our sample we found inverse correlation between 25(OH)D and alterations in lipid profile like elevation of TC and LDL-c. However, it is not fully elucidated in literature the mechanisms that connect vitamin

D deficiency to the increase of blood lipid concentrations (TC and LDL-c).

On the adjusted analysis, we verified that patients with elevated TG presented protection to hypovitaminosis D, what is different of the literature that associates low levels of Vitamin D to hypertriglyceridemia[29].

Two mechanisms have been proposed to explain the association between hypovitaminosis and hypertriglyceridemia. In first place, vitamin D may reduce serum TG by reducing its hepatic synthesis and secretion mediated by its effect on the calcium hepatocellular. In second place, elevated levels of PTH are followed by lipolitc activity reduction, whilst the reduction of serum PTH may decrease TG levels by elevation on its peripheral clearance[31].

Although the relation between hypovitaminosis D and BMI be well described in literature[16], we did not find this result in our study. However, serum levels of 25(OH)D were lower in patients with elevated WC, as was established on the adjusted analysis almost three times higher the chance of having vitamin D deficiency in abdominal obese patients, when compared to patients with normal WC.

Evidences support that obesity may initiate a condition of deficiency of vitamin D and vitamin D may be a risk factor for obesity, being suggested that the excess of body fat retains metabolites of vitamin D and that cholecalciferol produced by the skin of acquired on the diet may be partially kidnapped by body fat and transported to the liver to the first hydroxylation[32]. Additionally, the significant level of o1-α-hydroxylase in fat cells of obese individuals would explain the larger local use of 25(OH)D[33].

Some experimental data indicate that vitamin D deficiency may favor adiposity by the elevation of PTH levels, which causes a larger influx of calcium in the adipocytes, increasing lipogenesis[34]. Other evidences also suggest that 1,25(OH_2)D inhibits adipogenesis through actions modulated by vitamin D dependent receptors. So, vitamin D depletion may lead to an excessive differentiation of pre-adipocytes and adipocytes[35].

CONCLUSION

The results of the present study indicate that hypovitaminosis D was highly prevalent even though it is a population living in a sunny region. Low levels of vitamin D correlated with elevated levels of TC and LDL and elevated abdominal adiposity.

Hypovitaminosis D topic still represents a gap in our national literature. Therefore, it is important to highlight the need for further studies on the subject that may better clarify this high prevalence of hypovitaminosis D in our population and evaluate new results with analysis of other variables such as food consumption and time of sun exposure, not performed in this study.

REFERENCES

1. Castro LCG. The vitamin D endocrine system. Arq Bras Endocrinol Metab. 2011; 55(8):566-575.
2. Bikle D. Non classic Actions of Vitamin D. Arq Bras Endocrinol Metab. 2009; 94(1):26–34.
3. Maeda SS, Borba VZC, Camargo MBR, Silva DMW, Borges JLC, Bandeira F, et al. Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D. Arq Bras Endocrinol Metab.2014; 58(5):411-433.
4. Maeda SS, Saraiva GL, Kunii IS, Hayashi LF, Cendoroglo MS, Ramos LR, et al. Factors affecting vitamin D status in different populations in the city of São Paulo, Brazil: the São Paulo Vitamin D Evaluation Study (SPADES). BMC Endocr Disord. 2013; 13(14):1-8.
5. Bandeira F, Griz L, Freese E, Lima DC, Thé AC, Diniz ET, et al. Vitamin D deficiency and its relationship with bone mineral density among postmenopausal women living in the tropics. Arq Bras EndocrinolMetabol. 2010; 54(2):227-232.
6. Christakos S, DeLuca H. Minireview: vitamin D: is there a role in-extraskeletal health? Endocrinology. 2011; 152(8):2930-2936.
7. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007; 167(11):1159-1165.
8. American Diabetes Association. Comprehensive medical evaluation and assessment of comorbidities. Sec. 3. In Standards of Medical Care in Diabetes—2017. Diabetes Care. 2016; 39(Suppl. 1):1-119.
9. Brazilian Society of Cardiology. V Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis. Arq Bras Cardiol. 2013; 101(4):1-22L.
10. World Health Organization. Obesity: Preventing and managing the global epidemic. Reportof a WHO Consultatio non Obesity. Geneva; 1998.
11. Lipschitz DA. Screening for nutritional status in the elderly. Primary Care, 1994, 21(1):55-67.
12. Lotufo AP. Cardiovascular diseases in Brazil: premature mortality, risk factors and priorities for action. Comments on the preliminary results from the Brazilian National Health Survey (PNS), 2013.São Paulo Med J. 2015; 133(2):69-72.
13. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009; 20(11):1087-1820.
14. Silva BCC, Camargos BM, Fujii JB, Dias EP, Soares MMSPrevalence of Vitamin D Deficiency and its Correlation with PTH, Biochemical Bone Turnover Markers and Bone Mineral Density, Among Patients from Ambulatories. Arq Bras Endocrinol Metab. 2008; 52(3):482-488.

15. Gondim F, Caribé A, Vasconcelos KF, Segundo AD, Bandeira F. Vitamin D Deficiency Is Associated with Severity of Acute Coronary Syndrome in Patients with Type 2 Diabetes and High Rates of Sun Exposure. Clin Med Insights Endocrinol Diabetes. 2016; 9:37–41.

16. Guasch A, Bulló M, Rabassa A, Bonada A, Del Castillo D, Sabench F, et al. Plasma vitamin D and parathormone are associated with obesity and atherogenic dyslipidemia: a cross-sectional study. Cardiovasc Diabetol.2012; 11(149):1-11.

17. Giorelli GV, Matos LN, Saado A, Soibelman VL, Dias CB. No association between 25-hydroxyvitamin D levels and prediabetes in Brazilian patients. A cross-sectional study. São Paulo Med J. 2015; 133(2):73-77.

18. Holick MF, Matsuok LY, Wortsman J. Age, vitamin D, and solar ultraviolet.Lancet. 1989; 2:1104 –1105.

19. Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr. 2008; 88(2):558S-64S.

20. Chang EM, Kim YS, Won HJ, Yoon TK, Lee WS. Association Between Sex Steroids, Ovarian Reserve, and Vitamin D Levels in Healthy Nonobese Women. J Clin Endoc Metab. 2010; 99(7): 2526–32.

21. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010;106(7):963-8.

22. Lips p. Vitamin D Deficiency and Secondary Hyperparathyroidism in the Elderly: Consequences for Bone Loss and Fractures and Therapeutic Implications. Endocr. Rev. 2001; 22(4):477–501.

23. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002; 110(2):229–232.

24. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J. 2000; 47(4):383–391.

25. Williams PF, Caterson ID, Cooney GJ, Zilkens RR, Turtle JR. High affinity insulin binding and insulin receptor-effector coupling: modulation by Ca2+. Cell Calcium. 1990; 11(8):547–556.

26. Begum N, Leitner W, Reusch JE, Sussman KE, Draznin B. GLUT-4 phosphorylation and its intrinsic activity. Mechanism of Ca(2+)-induced inhibition of insulin-stimulated glucose transport. J Biol Chem. 1993; 268(5):3352–3356.

27. Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M. Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. J Steroid Biochem Mol Biol. 2004; 89–90(1-5):121–125.

28. Milner RD, Hales CN. The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro. Diabetologia. 1967; 3(1):47–49.

29. Chaudhuri JR, Mridula KR, Anamika A, Boddu DB, Misra PK, Lingaiah A, et al. Deficiency of 25-Hydroxyvitamin D and Dyslipidemia in Indian Subjects. J Lipids. 2013; 2013:1-7.

30. Cho HJ, Kang HC, Choi SA, Ju YC, Lee HS, Park HJ. The possible role of Ca21 on the activation of microsomal triglyceride transfer protein in rat hepatocytes. Biol Pharm Bull. 2005; 28(8):1418-1423.

31. Lacour B, Basile C, Drüeke T, Funck-Brentano JL. Parathyroid function and lipid metabolism in the rat. Miner Electrolyte Metab. 1982; 7(3):157-165.

32. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000; 72(3):690–693.

33. Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. Diabetes Care. 59(1):242–248.

34. Hjelmesaeth J, Hofsø D, Aasheim ET, Jenssen T, Moan J, Hager H, et al. Parathyroid hormone, but not vitamin D, is associated with the metabolic syndrome in morbidly obese women and men: a cross-sectional study. Cardiovasc Diabetol. 2009; 8(7):1-7.

35. Wood RJ. Vitamin D and adipogenesis: new molecular insights. Nutr Rev.2008; 66(1):40–46.