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Hypovitaminosis D is Associated with the Components of Metabolic Syndrome in Brazilian Women

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Abstract

Low vitamin D status and oxidative/nitrosative stress have been recognized as risk factor for chronic diseases such as metabolic syndrome (MetS). The objective of this study was to evaluate the metabolic and oxidative/nitrosative markers for association with hypovitaminoses D in Brazilian women with MetS. The following included 88 women with MetS and evaluated metabolic biomarkers (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, uric acid, plasma glucose, insulin), and oxidative/nitrosative stress biomarkers (hidroperoxides-CL-LOOH, carbonyl protein, nitric oxide metabolites-NOx, sulfhydryl groups-SH of proteins, total radical-trapping antioxidant parameter-TRAP, total serum activity of PON1). The homeostasis model assessment (HOMA-IR) was calculated. Vitamin D was determined as 25(OH) D and categorized as hipovitaminosis (MetSHD) and suficient vitamin D (MetSD). Levels of vitamin D were lower in the MetSHD ($p < 0.0001$). MetSHD group showed increase in fasting glucose ($p = 0.03$), TG ($p = 0.04$), HOMA-IR ($p = 0.03$), CT/HDL ($p = 0.04$), LDL/HDL ($p = 0.03$), non-HDL ($p = 0.04$). There were increased levels of AOPP ($p = 0.03$) and NOx ($p = 0.04$) levels in MetSHD group. In MetSHD, the SH group were negatively correlated with TC ($r = -0.36$, $p < 0.05$) and LDL-C ($r = -0.347$, $p < 0.05$) whereas AOPP was negatively correlated with HDL ($r = -0.37$, $p < 0.05$), and positively correlated with fasting glucose ($r = 0.32$, $p < 0.05$), TG ($r = 0.66$, $p < 0.0001$) insulin levels ($r = 0.50$, $p < 0.001$) and HOMA-IR ($r = 0.54$, $p < 0.001$). NOx was positively correlated with HOMA-IR ($r = 0.34$, $p < 0.05$) and TRAP/uric acid was negatively correlated with BMI, WC, and insulin levels ($r = -0.33, -0.34, -0.366$; $p < 0.05$), respectively. In conclusion, the present study showed that hypovitaminosis D in women with MetS is associated metabolic and oxidative/nitrosativo biomarkers, which are important factors for cardiovascular risk.

Keywords

Hypovitaminosis D, Oxidative stress, Metabolic syndrome, Nitrosativo stress, Metabolic markers

Introduction

Metabolic syndrome (MetS) is a complex disease characterized by a distinct process and cardiovascular risks factors that could culminate in cardiovascular disease and type 2 diabetes (D2M) [1].

Vitamin D has a pleiotropic action and can affect multiples organs and metabolic processes, including the cardiovascular, renal and immune systems [2]. Some studies showed that hypovitaminosis D is associated with several risk components of MetS, individually. The abdominal obesity, characteristic of individuals with MetS, is associated with lower levels of vitamin D [1,3,4]. MetS affects approximately 50% of the female and is associated with a threefold increase in morbidity and mortality due to cardiovascular disease [5-8]. A transversal study showed that hypovitaminosis D is associated with cardiovascular disease independently of the degree obesity [1]. Another study showed that individuals with low levels of vitamin D presented higher risks of cardiovascular diseases after 10-15 years of segment [9].

An imbalance between reactive oxygen/nitrogen species (ROS/RNS) production and antioxidant substances is main

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characteristic of oxidative stress [10-12]. Inflammation and oxidative stress occurs when the energy supply begins to exceed the storage capacity of the adipocytes and, as result, hypertrophy occurs. This hypertrophy leads to a higher release of adipokines as proinflammatory cytokines, resulting in low-grade inflammation, which begins in the adipose tissue and eventually reaches the circulation system and other organs [10-12].

Additionally, paraoxonase (PON) is a family of Ca^{++} dependent enzymes, namely PON1, PON2 and PON3 [13,14]. Paraoxonase1 (PON1) is exclusively associated with HDLc and is a genetically polymorphic enzyme. It plays a vital role in the prevention of microvascular complications due to oxidative stress and against various toxic chemicals. HDL oxidation is stopped by PON1-mediated hydrolysis of lipid peroxides [15].

Oxidative stress plays an important role in the pathogenesis of insulin resistance by disrupting the release of adipokines by adipose tissue that can trigger inflammation. Thus, it seems that MetS is a factor associated with inflammation and oxidative stress. The possible importance of vitamin D status as a novel risk factor for various chronic diseases has gained more interest. In addition, one area of recent study has been the investigation of the association between vitamin D status and MetS. However, despite evidence of the association of the serum vitamin D and MetS in women, some studies have demonstrated contradictory results. More clinical studies are needed to confirm the association between Vitamin D and women with MetS. Thus, in this context, the aim of the present study was to evaluate the oxidative and nitrosative markers, and the association with hypovitaminosis D in Brazilian women with MetS.

Materials and Methods

Participants

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the Ethical Committee of the University of Londrina, Paraná, Brazil (CAAE 41718014.9.0000.5231). Written informed consent was obtained from all patients. This study included 88 women with MetS from the ambulatory centre of the University Hospital of Londrina, Parana, Brazil. Patient motivation was related to the intake of a nonpharmacologic therapy that was practically without side effects. The exclusion criteria were cardiovascular disease (CVDs) (except hypertension); thyroid, renal, hepatic, gastrointestinal, and oncologic diseases; or acute infection and utilization of lipid lowering drugs, estrogens replacement therapy, drugs for hyperglycaemia; and antioxidant supplements. Patients who were taking antihypertensive drugs were not excluded and were allowed to continue taking their prescribed dosage. None of the participants followed a specific diet before the start of the study. The patients were instructed not to change their usual diets, alcohol intake, level of physical activity, or other lifestyle factors throughout the study.

Anthropometric Measurements

MetS was defined following the Adult Treatment Panel III criteria [16]. When three of the following five of the characteristics were verified, a diagnosis of MetS was given: 1. Abdominal obesity: Waist circumference > 88 cm in women; 2. Hypertriglyceridemia ≥ 150 mg/dL (1.695 mmol/L); 3. Low levels of HDL-C: ≤ 50 mg/dL (1.295 mmol/L) in women; 4. High blood pressure: ≥ 130/85 mm Hg; and 5. High fasting glucose: ≥ 100 mg/dL (5.5 mmol/L). Height and weight were measured in the morning with participants wearing light clothing, but no shoes. After 20 min of rest, each participant had her blood pressure measured on the left arm while in a sitting position. We considered the current use of antihypertensive medication as an indication of high blood pressure. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Waist circumference was measured at the umbilical level with the participants standing after normal expiration and the hip girth was measured at the widest part of the hip and, the waist-to-hip ratio was calculated.

Blood sample

Peripheral blood samples were collected from each participant with EDTA as anticoagulant and without anticoagulant. All samples were immediately centrifuged at 3,000 rpm for 15 minutes and plasma, serum, and buffy coat aliquots were stored at freezer -80°C until use. The samples were identified consecutively by number to guarantee the confidentiality.

Metabolic markers

The 25 hidroxi (OH) were determined using a quimioluminescence assay (CMIA) (Architech™, Abbott Laboratory, Abbott Park, IL, USA) and the results were expressed as ng/mL. The MetS patients were categorized as Vitamin D levels < 30 ng/mL (MetSHD) and ≥ 30 ng/mL (MetSD).*T*he metabolic biomarkers were evaluated by serum levels of lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), uric acid and by plasma glucose using Dade Behring™ reagents in a biochemical autoanalyser (Dimension™ Dade AR Dade Behring, Deerfield, IL, USA). Plasma insulin levels were determined by chemiluminescence microparticle immunoassay (Architech™, Abbott Laboratory, Abbott Park, IL, USA). The homeostasis model assessment (HOMA-IR) was used as a surrogate measurement of insulin sensitivity [17]. The homeostasis model of assessment in insulin resistance (HOMA-IR) was used as a surrogate measure of insulin sensitivity using HOMA-IR = insulin (mU/mL) × glucose (nmol/L/22.5) (HAFFNER, 2003).

Oxidative Stress Biomarkers

Tert-butyl hydroperoxide-initiated chemiluminescence (CL-LOOH) was evaluated as described previously by Gonzalez-Flecha [18] and the results were expressed in counts per minute (cpm). Carbonyl protein content was measured as an estimate of protein oxidative injury as described by Reznick and Packer [19]. Nitric oxide metabolites (NOx) were assessed by nitrite (NO_2^-) and nitrate (NO_3^-) concentration according to the Griess reaction supplemented by the reduction of nitrate

to nitrite with cadmium [20] and the results were expressed in µM. The sulfhydryl group of proteins was evaluated in the plasma by a spectrophotometric assay based on 5,5-dithiobisnitrobenzoic acid (DTNB) as reported previously [21] and the results were expressed in µM. Total radical-trapping antioxidant parameter (TRAP) was determined as reported previously [22]. This method detects hydrosoluble and/or liposoluble plasma antioxidants by measuring the chemiluminescence inhibition time induced by 2,2-azobis (2-amidinopropane). The system was calibrated with the vitamin E analogue Trolox and TRAP values were expressed in the equivalent of µM Trolox and the results were expressed as TRAP/AU. Total serum activity of PON1 was determined by the method described by Richter, Jarvik, and Furlong [23]. The rate of hydrolysis of phenyl acetate was determined in a microplate reader EnSpire, Perkin Elmer® (Walthman, MA, USA) at 270 nm and the temperature was maintained at 25 °C. Measures were recorded for 4 min each 15 s. The activity was expressed in U/mL on the phenyl acetate molar extinction coefficient of 1.31 mMol/L cm^{-1}.

Statistical analysis

The data were evaluated by the statistical analysis program GraphpadStatemate 2.0 (GrahpPad Software, San Diego, CA)**.** Continuous variables were evaluated using the Mann-Whitney test and data were expressed as the median and interquartile range (25%-75%). Correlations were evaluated by Spearman's rank correlation. All the results were considered significant when $p < 0.05$.

Results

Clinical, anthropometric and metabolic parameters in women categorizes as MetSHD and MetSD are shown in Table 1. The mean age o MetSHD group was 50.61 ± 7.65 years and MetSD group was 53.7 ± 4.35 years. According to BMI, the MetSHD and MetSD group presented 33.5 (25.3-61.0) Kg/m^2 and 30.6 (24.0-39.0) Kg/m^2, respectively. MetSHD group presented WC and AC as 95.0 (81.0-140.0) cm and 103.5 (89.0-170.0) cm, respectively, while MetSD group presented 95.0 (67.0-115.0) cm and 96.2 (90-127.0) cm, respectively. No differences about age, BMI, WC, and AC were found between the groups. MetSHD group showed a statistically significant increases in fasting glucose ($p = 0.03$), TG ($p = 0.04$), HOMA-IR ($p = 0.03$), CT/HDL ($p = 0.04$), LDL/HDL ($p = 0.03$), non-HDL ($p = 0.05$) when compared with MetSD. As expected, levels of vitamin D were lower in the group women with MetSHD compared with those with MetSD ($p < 0.0001$).

Oxidative stress markers in MetSHD and MetSD groups were described in Table 2. There was a significant increase in AOPP ($p = 0.03$) and NOx ($p = 0.04$) levels in MetSHD group when compared to MetSD. No difference was found in the SH group, hydroperoxides (CL-LOOH), TRAP/uric acid, and AOPP/TRAP ($p < 0.05$). Additionally, there was a tendency to higher levels of PON in the MetSHD group ($p = 0.06$).

A correlation rank between clinical, metabolic, and oxidative stress parameters in women with MetS and D hypovitaminosis was performed and the results were described in Table 3. The SH group was negatively correlated with TC ($r = -0.36$, $p < 0.05$) and LDL-C ($r = -0.35$, $p < 0.05$)

Table 1: Clinical, anthropometric and metabolic parameters in women with metabolic syndrome with or without D hypovitaminosis.

	MetSHD (n = 63)	MetSD (n = 25)	p value
Age (years)	50.61 ± 7.65	53.7 ± 4.35	0.85
BMI (Kg/m^2)	33.5 (25.3-61.0)	30.6 (24.0-39.0)	0.06
WC (cm)	95.0 (81.0-140.0)	95.0 (67.0-115.0)	0.93
AC (cm)	103.5 (89.0-170.0)	96.2 (90.0-127.0	0.51
SBP (mmHg)	130 (110-190)	125 (110-145)	0.61
DBP (mmHg)	85 (78-120)	85 (70-100)	0.94
Fasting glucose (mg/dL)	113 (84-389)	99 (91-150)	**0.03**
Insulin (mU/mL)	13.9 (3.4-35.6)	10.6 (4.8-28.8)	0.07
HOMA-IR	3.49 (1.4-25.3)	2.6 (1.1-7.9)	**0.04**
TC (mg/dL)	200.0 (130.0-301.0)	181.0 (138.0-298.0)	0.07
HDL (mg/dL)	42.0 (23.0-80.0)	49.0 (28.0-73.0)	0.31
LDL (mg/dL)	130.0 (57.0-229.0)	107.9 (76.2-228)	0.21
TG (mg/dL)	130.0 (47.0-298.0)	108.0 (54.0-296.0)	**0.05**
Uric acid (mg/dL)	4.4 (2.7-8.1)	4.6 (3.0-6.9)	0.42
CT/ HDL	4.7 (2.2-8.6)	3.5 (2.4-8.5)	**0.03**
LDL/HDL	2.8 (1.0-5.8)	2.1 (1.2-6.5)	**0.05**
Non-HDL (mg/dL)	153.5 (73.0-254.0)	129.5 (93.0-263.0)	**0.05**
CT/TG	1.4 (0.6-4.4)	1.6 (0.7-3.0)	0.14
LDL/TG	0.8 (0.2-3.3)	1.0 (0.4-2.0)	0.12
Vitamin D (ng/mL)	20.2 (8.1-29.5)	32.5 (30.0-45.8)	**< 0.0001**

MetSHD: metabolic syndrome with hypovitaminosis D (Vitamin D < 30 ng/mL); MetSD: metabolic syndrome with sufficient vitamin D (D Vitamin ≥ 30 ng/mL); BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure; WC: waist circumference, AC: abdominal circumference, TC: Total cholesterol, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglycerides, HOMA-IR: Insulin Resistance Homeostasis Model Assesment.

The results were expressed as median, interquartile range (25%-75%). Differences were assessed by Mann Whitney test ($p < 0.05$). NS: not significant

Table 2: Oxidative stress parameters in women with metabolic syndrome with or without D hypovitaminosis.

	MetSHD (n = 63)	**MetSD (n = 25)**	**p value**
SH	304.3 (192.9-488.5)	413.0 (199.0-471.5)	0.38
AOPP (uMol/ L of chloramine-T-equivalent)	84.9 (39.9-206.2)	67.5 (39.2-241.75)	**0.03**
NOx (uM)	7.02 (3.7-16.7)	5.0 (3.1-20.5)	**0.05**
CL-LOOH (cpm)	930265 (103887-3363230)	1142567 (409383-4730787)	0.12
TRAP/Uric acid	220.4 (121.4-406.8)	221.1 (145.7-332.7)	0.84
AOPP/TRAP	0.34 (0.1-1.3)	0.3 (0.2-1.3)	0.72
PON (mMol/Lcm-1)	428.1 (133.8-744.7)	289.3 (160.6-583.2)	0.06

MetSHD: Metabolic syndrome with hypovitaminosis D (Vitamin D < 30 ng/mL); MetSD: Metabolic syndrome with sufficient vitamin D (D Vitamin ≥ 30 ng/mL); SH: Sulphydril group; AOPP: Advanced oxidation products protein; NOx: Nitric oxide products; CL-LOOH: Terc-butil hydroperoxide-9-initiated chemiluminescence; TRAP: Total radical trapping antioxidant parameter; PON: Paraoxonase,

The results were expressed as median, interquartile range (25%-75%). Differences were assessed by Mann Whitney test ($p < 0.05$).

Table 3: Correlation between anthropometric and metabolic with oxidative stress parameters in women with hypovitaminosis D.

	SH	**AOPP**	**NOx**	**PON**	**CL-LOOH**	**TRAP/Uric acid**
BMI (Kg/m^2)	0.04	011	0.21	-0.168	0.09	**-0.33***
AC (cm)	0.02	0.21	0.15	-0.146	0.18	**-0.344***
SBP (mmHg)	-0.186	0.163	0.27	-0.315	0.133	0.119
DBP (mmHg)	-0.03	0.144	0.05	-0.139	-0.02	-0.129
Fasting glucose (mg/dL)	-0.09	0.32	0.315	0.04	0.09	0.09
TC (mg/dL)	**-0.359***	0.218	0.06	0.203	0.146	0.24
HDL (mg/dL)	-0.07	**-0.365***	-0.282	0.13	-0.06	-0.002
LDL (mg/dL)	**-0.347***	0.122	0.11	0.122	0.101	0.263
TG (mg/dL)	0.103	**0.655**$^{\square}$	0.009	-0.013	0.006	-0.203
Insulin (mU/mL)	0.07	**0.501****	0.217	0.228	-0.026	**-0.366***
HOMA-IR	-0.016	**0.541****	**0.343***	0.213	0.05	-0.099
D vitamin (ng/mL)	0.023	0.009	-0.04	0.019	-0.09	-0.124

SH: Sulphydril group; AOPP: Advanced oxidation products protein, NOx: Nitric oxide products; CL-LOOH: terc-butil hydroperoxide-9-initiated chemiluminescence, TRAP: Total radical trapping antioxidant parameter, PON: Paraoxonase; BMI: Body mass index; AC: Abdominal circumference; SBP: Systolic blood pressure, DBP: Diastolic blood pressure; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides; HOMA-IR: Insulin Resistance Homeostasis Model Assesment.
Spearman Correlation, $^{*}p < 0.05$; $^{**}p < 0.001$; $^{\square}p < 0.0001$.

whereas AOPP was negatively correlated with HDL (r = -0.37, $p < 0.05$), and positively correlated with fasting glucose (r = 0.32, $p < 0.05$), TG (r = 0.66, $p < 0.0001$), insulin levels (r = 0.50, $p < 0.001$) and HOMA-IR (r = 0.54, $p < 0.001$). NOx was positively correlated with HOMA-IR (r = 0.34, $p < 0.05$) and TRAP/uric acid was negatively correlated with BMI, WC, and insulin levels (r = -0.33, -0.34, -0.37, $p < 0.05$), respectively [24-26].

Discussion

The main finding of this study was that women with MetSHD presented higher levels of fasting glucose, HOMA-IR, triglycerides, and biomarkers of oxidative stress than did women without hypovitaminosis D. In addition, it seems that hypovitaminosis D is a determinant factor for cardiovascular risk and oxidative stress, once all women presenting MetS were assessed.

Our results agree with previous research's involving hypovitaminosis D and disturbance in metabolic and oxidative stress markers, showing that serum vitamin D levels seems to be inversely correlated with measures of obesity, BMI, fat mass and WC [4,27-34].

There is an inverse correlation between serum 25(OH) D levels and cardiovascular disease, MetS and their complications, such as glucose intolerance, obesity, hypertension, insulin resistance, ischaemic heart disease, and stroke [35,36]. Schimitt, et al. [37] showed that women postmenopausal with vitamin D deficiency had a higher risk of developing MetS, hypertriglyceridemia and low HDL levels than did women with adequate levels of vitamin D ($p < 0.05$).

In this study, women with MetSHD presented higher levels of fasting glucose and HOMA-IR, and these results agree with previous studies [37-40]. The most plausible explanation is that vitamin D influences insulin secretion and sensitivity, which plays a major role in MetS. The vitamin D receptor is expressed in insulin-secreting pancreatic beta cells and in peripheral target tissues such as skeletal muscles and adipose tissue. Vitamin D can compromise the capacity of beta cells to convert pro-insulin in insulin [41,42]. Vitamin D indirectly affects insulin sensitivity in skeletal muscles and adipose tissue by regulating the levels of extracellular calcium, which is essential for insulin-mediated intracellular processes [41].

A study showed that vitamin D stimulated the expression of insulin receptor and low vitamin D levels were associated

with beta-cell dysfunction. Vitamin D deficiency was independently associated with insulin resistance and beta-cell function in patients at risk for diabetes [43-46]. Individuals with lower levels of vitamin D presented a higher incidence of type 2 diabetes due to insulin secretion and sensibility. *In vitro* studies showed that 1,25(OH)-vitamin could stimulate insulin secretion directly by enhancing calcio levels due to adequate vitamin D levels [44,47].

Vitamin D also has an immunomodulation effect than can protect against type 1 diabetes [48]. In addition, studies support a direct correlation between vitamin D and insulin resistance [44]. The relationship between hypovitaminosis D and hypertension is clear, and the mechanism of this association is due to the interaction of Vitamin D with the renin-angiotensin-aldosterone system, the immune inflammation in MetS and the effects of vitamin D in the vascular endothelium and smooth muscle [49].

Diabetes is not only about the body's inability to handle glucose properly but is also an inflammatory disease. Because vitamin D has anti-inflammatory effects, it is not surprising that it has beneficial effects on improving islet cell functions, insulin release, ad decreasing insulin resistance [38,50-55].

Our results showed that women with MetSHD presented higher triglycerides levels. The relationship between vitamin D deficiency and dyslipidaemia may be due, in part, to vitamin D's effects on hepatic lipid metabolism. Vitamin D promotes intestinal calcium absorption, and calcium may bind to fatty acids to form insoluble complexes that inhibit lipid absorption. Thus, vitamin D deficiency may lead to abnormal processing of lipids due to calcium available [56]. Linear regression analysis demonstrated a significant inverse association between vitamin D and LDL-cholesterol, and TG. In addition, vitamin D was independently associated with greater odds of hyperlipidaemia [43]. Schimitt, et al. [37] found that women with vitamin D deficiency had a higher risk of hypertriglyceridemia and low HDL. Other review study also showed that subjects with high serum levels of vitamin D had a more favorable lipid profile than those with vitamin D deficiency [57]. A longitudinal study demonstrated that an increased in serum 25(OH)D levels was associated with a significant reduction of triglycerides levels and that the mechanism underlying the inverse association is a reduction in the intestinal absorption and synthesis of lipid, as well as decreased in lipolysis with increasing vitamin D concentrations [34,58].

The inflammatory process seems to be responsible for oxidative stress generation and may induce gene expression related with inflammatory cytokines [59]. On the other hand, vitamin D has a potent immunoregulatory action, such as inhibiting the production of interleukin-6, interleukin-8, interferon-γ by peripheral blood mononuclear cells in autoimmune disease [60]. Reported results support the concept that increased oxidative stress may play an important role in MetS [61,62].

In our study, women with MetS and hypovitaminoses D presented higher levels of AOPP. In addition, a significantly and positive correlation between AOPP and triglycerides, fasting glucose, insulin and HOMA-IR values were found. We also showed a negative correlation between AOPP and HDL-cholesterol. Korkmaz, et al. [27], showed that AOPP values are higher in MetS patients group when compared with control group and found a positive correlation between AOPP levels and glucose, triglycerides, insulin levels, and HOMA-IR values ($p < 0.0001$). Cakatay [63] reported that patients with type 2 diabetes exhibit elevated protein oxidation, indicated by elevated plasma protein carbonyl and AOPP levels, this can be correlated glycemia and with glycemic control. Another study permed a multiple regression analysis and revealed that AOPP levels are the most important independent determinants of the MetS. This finding confirms that high AOPP levels are indicative of an increase in oxidative stress and can cause direct oxidative damage in proteins in MetS patients [63-65]. Our group of research demonstrated a positive correlation between AOPPs and waist circumference ($p < 0.01$), fasting glucose ($p < 0.05$), homeostasis model assessment insulin resistance ($p < 0.001$), triacylglycerol ($p < 0.0001$), and uric acid ($p < 0.01$), whereas there was an inverse correlation with high-density lipoprotein cholesterol ($p < 0.001$) [66].

Women with MetSHD presented higher levels NOx compared with those with MetSD. In addition, NOx metabolites were positively associated with HOMA-IR in women with MetS and lower levels of vitamin D. The role of insulin resistance at the level of the endothelial cell in vascular pathophysiology is unclear. Several studies in humans and gene-modified mice have demonstrated a close association between insulin resistance and nitric oxide bioactivity [67]. Endothelial dysfunction and vascular insulin resistance usually coexist, and chronic inflammation engenders both. Growing evidence from both clinical and animal studies has suggested that endothelial dysfunction and vascular insulin resistance coexist in obesity and diabetes and they may play a causative role in the development of metabolic insulin resistance [68-71].

Choi, et al. [72], concluded that uric acid induced endothelial dysfunction by contributing to vascular insulin resistance in terms of insulin-induced NO production, potentially leading to the development of hypertension. Montagnani, et al. [73] dissected the pathway by which insulin stimulate the NO release from endothelial tissue *in vitro*. In addition, Kuboki, et al. [74] demonstrated that insulin regulates the eNOS transcription in the endothelium.

MetSHD group showed a negative correlation between SH groups and TC, and HDL. Several oxidative modifications of proteins may be introduced by ROS-RNS. The thiol (-SH) group of cysteine residues is a particularly sensitive target of oxidant species, forming sulfenic acid, mixed disulfide, S-glutathiolated derivatives, as well as sulfinic and sulfonic acid [75]. Cysteine-bound thiol may also be nitrosylated through the addition of a NO group. Such S-nitrosylation is a reversible modification playing essential roles in modulating the function of a great number of cellular proteins [76,77]. Tyrosine residues may be affected by peroxynitrite-mediated nitration, that is, the addition of an NO_2 group to the phenolic ring of tyrosine [78].

Oxidized proteins may be subject to accelerated degradation and loss of function, with potentially significant cytotoxic consequences [79]. A study showed suggest AOPP as the most appropriate parameter for determination of oxidative stress by the action of the chloraminated oxidants, mainly by the action of chloramines, produced by myeloperoxidase un activated neutrophils. They also determined that group with more MetS components (with 5 components) presented higher AOPP an lower TRAP when compared with another group of MetS with less components (4 components) [80]. Taken together, MetSHD group presented higher AOPP levels when compared with MetSD group, which are in agreement with previous results.

Studies have found decreases in individual antioxidants, such carotenoids, vitamin C, and vitamin E, as well as TRAP in MetS subjects [81,82]. A study showed lower TRAP concentration compared with control group [82]. Althought no difference was found between TRAP concentrations in MetSHD and MetSD groups, MetSHD group showed a negative correlation between TRAP/uric acid and BMI, AC, and insulin.

Our research group showed that hypertriacyglycerolemia, hyperglycemia, hypertension, and lower HDL-cholesterol values are important factors in increasing oxidative stress, which leads to increase production of superoxide anion via the nicotinamide adenosine phosphate oxidase pathway. This anion reacts rapidly with NO to form peroxynitrite, thus inactivating NO and leading to endothelial disfunction. Thus, the individuals with MetSHD of our study showed a similar metabolic profile of the previous cited study, and also increased levels oxidative markers such AOPP, NOx, and a tendency to increased antioxidant defense evaluated by PON activity [82].

Conclusions

In conclusion, hypovitaminoses D in women with MetS is associated with elevated levels of fasting glucose, HOMA-IR, triglycerides, and biomarkers of oxidative stress than women with MetSD. These are important factors for cardiovascular risk.

Conflict of Interest

The authors declare none conflict of interest.

Authorship

The authors' responsibilities were as follows: M.C.S., A.M.O. collected the data, designed the study, interpreted the results, wrote the manuscript, D.V. performed the statistical analysis. R.D.B.M, F.K.G, A.C.F.M., A.K.M, B.S.A. performed the oxidative stress parameters. D.V and D.S.B developed the hypothesis tested in the study, designed the study, interpreted the results, and wrote the manuscript.

References

1. Miñambres I, Sánchez-Herández J, Sánchez-Quesada JL, et al. (2012) The association of hypovitaminosis D with the metabolic syndrome is independently of the degree of obesity. ISRN Endocrinol 2012: 691803.
2. Ding C, Gao D, Wilding J, et al. (2012) Vitamin D signaling in adipose tissue. Br J Nutr 108: 1915-1923.
3. Maki KC, Fulgoni VL, Keast DR, et al. (2012) Vitamin D intake and status are associated with lower prevalence of metabolic syndrome in U.S. adults: National Health and Nutrition Examination Surveys 2003-2006. Metab Syndr Relat Disord 10: 363-372.
4. Cheng S, Massaro JN, Fox CS, et al. (2010) Adiposity, cardiometabolic risk, an vitamin D status: The Framingham Heart Study. Diabetes 59: 242-248.
5. Mottillo S, Filion KB, Genest J, et al. (2010) The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 56: 1113-1132.
6. Nahas EAP, Padoani NP, Nahas-Neto J, et al. (2009) Metabolic syndrome and its associated risk factors in Brazilian postmenopausal women. Climacteric 12: 431-438.
7. Gurka MJ, Vishnu A Santen RJ, et al. (2016) Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc 5: e003609
8. Wang TJ, Pencina MJ, Booth SL, et al. (2008) Vitamin D deficiency and risk of cardiovascular disease. Am J Med Sci 117: 503-511.
9. Khan H, Hunutsor S, Franco OH (2013) Vitamin D, type 2 diabetes and other metabolic diseases: A systematic review and meta-analysis of prospective studies. Proc Nutr Soc 72: 89-97.
10. Skurk T, Alberti-Huber C, Herder C, et al. (2007) Relationshipo between adipocytes size and adipokine expression and secretion. J Clin Endocrinol Metab 92: 1023-1033.
11. Klöting N, Blüher M (2014) Adipocyte dysfunction, inflammation and metabolic syndrome. Rev Endocr Metab Disord 15: 277-287.
12. Cotillard A, Poitou C, Torcivia A, et al. (2014) Adipocyte size threshold matters: Link with risk of type 2 diabetes and improved insulin resistance after gastric bypass. J Clin Endocrinol Metab 99: E1466-E1470.
13. Primo-Parmo SL, Sorenson RC, Teiber J, et al. (1996) The human serum paraoxonase/arylesterase gene (PON1) is one member of a multigene family. Genomics 33: 498-507.
14. Mackness B, Durrington PN, Mackness MI (1998) Human serum paraoxonase. Gen Pharmacol 31: 329-336.
15. Rosenblat M, Karry R, Aviram M (2006) Paraoxonase 1 (PON1) is a more potent antioxidant and stimulant of macrophage cholesterol efflux, when present in HDL than in lipoprotein-deficient serum: relevance to diabetes. Atherosclerosis 187: 74-81.
16. Grundy SM, Cleeman JI, Daniels SR et al. (2005) Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112: 2735-52.
17. Haffner SM (2013) Insulin resistance, inflammation and the prediabetic state. Am J Cardiol 92: 18J-26J.
18. Gonzalez-Flecha BG, Llesuy S, Boveris A (1991) Hydroperoxide-initiated chemiluminescence: An assay for oxidative stress in biopsies of heart, liver and muscle. Free Radic Biol Med 10: 93-100.
19. Reznick AZ, Paccker L (1994) Oxidative damage to protein: Spectrophometric method for carbonyl assay. Methods Enzymol 233: 357-363.

20. Panis C, Mazzuco T, Costa CZF, et al. (2011) Trypanossomacruzi: Effects of the absence of 5-lipoxygenase (5-LO)-derived leukotrienes on levels of cytokines, nitric oxide and iNOS expression in cardiac tissue in the acute phase of infection in mice. Exp Parasitol 127: 58-65.
21. Hu ML (1994) Measurement of protein thiol groups and glutathione in plasma. In: Abelson JN, Simon MI, Methods in Enzymology. Academic Press, California, 380-382.
22. Repetto M, Reides C, Carretero MLG, et al. (1996) Oxidative stress in blood of HIV infected patients. Clin Chim Acta 255: 107-117.
23. Richter RJ, Jarvik GP, Furlong CE (2008) Determination of paraoxonase 1 status without the use of toxic organophosphate substrates. Circ Cardiovasc Genet 1: 147-152.
24. Gorter PM, Olijhoek JK, Van Der Graaf Y, et al. (2004) Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis 173: 363-369.
25. Trevisan M, Liu J, Bahsas Fb, et al. (1998) Syndrome X and mortality: A population-based study. Risk Factor and Life Expectancy Research Group. Am J Epidemiol 148: 958-966.
26. Ford ES, Giles WH, Dietz WH (2002) Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. J Am Med Assoc 287: 356-359.
27. Korkmaz GG, Altinoglu E, Sabiha Civelek, et al. (2013) The association of oxidative stress markers with conventional risk factors in the metabolic syndrome. Metabolism 62: 828-835.
28. Wortsman, J, Matsuoka, Ly, Chen, Tc, et al. (2000) Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 72: 690-693.
29. Parikh SJ, Edelman M, Uwaifo GI, et al. (2004) The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 89: 1196-1199.
30. Snijder MB, Van Dam RM, Visser M, et al. (2005) Adiposity in relation to vitamin D status and parathyroid hormone levels: A population-based study in older men and women. J Clin Endocrinol Metab 90: 4119-4123.
31. Botella-Carretero, JI, Alvarez-Blasco F, Villafruela JJ, et al. (2007) Vitamin D deficiency is associated with the metabolic syndrome in morbid obesity. Clin Nutr 26: 573-580.
32. Ford ES, Ajani Ua, Mcguire LC, et al. (2005) Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. Diabetes Care 28: 1228-1230.
33. Konradsen S, Ag H, Lindberg F, et al. (2008) Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. Eur J Nutr 47: 87-91.
34. Jorde R, Grimnes G (2011) Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. Prog Lipid Res 50: 303-312.
35. Ford ES, Zhao G, Tsai J (2011) Associations between concentrations of vitamin D and concentrations of insulin, glucose, and HbA1c among adolescents in the United States. Diabete Care 34: 646-648.
36. Majumdar V, Nagaraja, D, Christopher R (2011) Vitamin D status and metabolic syndrome in Asian Indians. Int J Obes (Lond.) 35: 1131-1134.
37. Schmitt EB, Nahas-Neto J, Bueloni-Dias F, et al. (2018) Vitamin D deficiency is associated with metabolic syndrome in postmenipausal women. Maturitas 107: 97-102.
38. Wimalawansa SJ (2018) Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J Steroid Biochem Mol Biol 175: 177-189.
39. Ju SY, Jeong HS, Kim H (2014) Blood vitamin D status and metabolic syndrome in the general adult population: a dose-response meta-analysis. J Clin Endocrinol Metab 99: 1053-1063.
40. Vitezova A, Zillikens AC, Van Herpt TW, et al. (2015) Vitamin D status and metabolic syndrome in the elderly: The Rotterdam Study. Eur J Endocrinol 172: 327-335.
41. Oh JY, Barrett-Connor E (2002) Association between vitamin D receptor polymorphism and type 2 diabetes or metabolic syndrome in community-dwelling older adults: The Rancho Bernardo Study. Metabolism 51: 356-359.
42. Bland R, Markovic D, Hills CE, et al. (2004) Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. J Steroid Biochem Mol Biol 89-90: 121-125.
43. Baker F, Mehta NN, Baker DG, et al. (2012) Vitamin D, metabolic dyslipidemia, and metabolic syndrome in rheumatoid arthritis. Am J Med 125: 1036e9-1-36e15.
44. Pittas AG, Lau J, Hu FB, (2007) The role of vitamin D end calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 92: 2017-2029.
45. Chiu KC, Chu A, GO VL, et al. (2004) Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 79: 820-825.
46. Kayaniyil S, Vieth R, Retnakaran R, et al. (2010) Association of vitamin D with insulin resistance and beta-cell dysfunction in subjects at risk for type 2 diabetes. Diabetes Care 33: 1379-1381.
47. Mathieu C, Gisemans C, Giulietti A, et al. (2005) Vitamin D and diabetes. Diabetologia 48: 1247-1257.
48. Hyppönen E (2010) Vitamin D and increasing incidence of type 1 diabetes evidence for an association? Diabetes Obes Metab 33: 1379-1381.
49. Wang L, Song Y, Manson JE, et al. (2012) Circulating 25-hydroxi-vitamin d and risk cardiovascular disease: A meta-analysis of prospectives studies. Circ Cardiovasc Qual Outcomes 5: 819-829.
50. Moyad MA (2003) The potential benefits of dietary and/or supplemental calcium and vitamin D. Urol Oncol 21: 384-391.
51. Dandona P, Aljada A, Bandyopadhyay A (2004) Inflammation: The link between insulin resistance, obesity and diabetes. Trends Immunol 25: 4-7.
52. Sung CC, Liao MT, Lu KC, et al. (2012) Role of vitamin D in insulin resistance. J Biomed Biotechnol 2012: 634195.
53. Pilz S, Kienreich K, Rutters F, et al. (2013) Role of vitamin D in the development of insulin resistance and type 2 diabetes. Curr Diab Rep 13: 261-270.
54. Krishnan AV, Feldman D (2011) Mechanisms of the anti-cancer and antiinflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol 51: 311-336.
55. Chagas CE, Borges MC, Martini LA, et al. (2012) Focus on vitamin D, inflammation and type 2 diabetes. Nutrients 4: 52-67.

56. Vaskonen T, Mervaala E, Sumuvuori V, et al. (2002) Effects of calcium and plant sterols on serum lipids in obese Zucker rats on a low-fat diet. Br J Nutr 87: 239-245.

57. Challoumas D (2014) Vitamin D supplementation and lipid profile: What does the best available evidence show? Atherosclerosis 235: 130-139.

58. Jorde R, Sneve M, Emaus N, et al. (2010) Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: TheTromso study. Eur J Nutr 49: 401-407.

59. Ridker PM, Buring JE, Cook NR et al. (2003) C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. An 8-year follow-up of 14 719 initially healthy American women. Circulation 107: 391-397.

60. Inoue M, Matsui T, Nishibu A, et al. (1998) Regulatory effects of 1alpha, 25-dihydroxyvitamin D3 on inflammatory responses in psoriasis. Eur J Dermatol 8: 16-20.

61. Ceriello A, Motz E (2004) Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 24: 816-823.

62. Roberts CK, Sindhu S (2009) Oxidative stress and metabolic syndrome. Life Sci 84: 705-712.

63. Cakatay U (2005) Protein oxidation parameters in type 2 diabetic patients with good and poor glycaemic control. Diabetes Metab 31: 551-557.

64. Meaney E, Vela A, Samaniego V, et al. (2008) Metformin, arterial function, intima-media thickness and nitroxidation in metabolic syndrome: The Mefisto study. Clin Exp Pharmacol Physiol 35: 895-903.

65. Sebeková K, Boor P, Valachovicová M, et al. (2006) Association of metabolic syndrome risk factors with selected markers of oxidative status and microinflammation in healthy omnivores and vegetarians. Mol Nutr Food Res 50: 858-868.

66. Venturini D, Simão ANC, Dichi I (2015) Advanced oxidation protein products are more related to metabolic syndrome components than biomarkers of lipid peroxidation. Nutrition research 35: 759-765.

67. Kearney MT, Duncan ER, Kahn M, et al. (2008) Insulin resistance and endothelial cell dysfunction: studies in mammalian models. Exp Physiol 93: 58-63.

68. Jonk AM, Houben AJ, De Jongh RT, et al. (2007) Microvascular dysfunction in obesity: A potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology 22: 252-260.

69. Kim F, Pham M, Maloney E, et al. (2008) Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance. Arterioscler Thromb Vasc Biol 28: 1982-1988.

70. Caballero AE, Bousquet-Santos K, Robles-Osorio L, et al. (2008) Overweight Latino children and adolescents have marked endothelial dysfunction and subclinical vascular inflammation in association with excess body fat and insulin resistance. Diabetes Care 31: 576-582.

71. Muris DM, Houben AJ, Schram MT, et al. (2013) Microvascular dysfunction: An emerging pathway in the pathogenesis of obesity-related insulin resistance. Rev Endocr Metab Disord 14: 29-38.

72. Choi YJ, Yoon Y, Hien TT, et al. (2014) Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. FASEB J 28: 3197-3204.

73. Montagnani M, Ravichandran LV, Chen H, et al. (2002) Insulin receptor substrate-1 and phosphoinositide-dependent kinase-1 are required for insulin-stimulated production of nitric oxide in endotelial cells. Mol Endocrinol 16: 1931-1942.

74. Kuboki K, Jiang ZY, Takahara N (2000) Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo: A specificvascular action of insulin. Circulation 101: 676-681.

75. Shao D, Oka S, Brady CD, et al. (2012) Redox modification of cell signaling in the cardiovascular system. J Mol Cell Cardiol 52: 550-558.

76. Murray CI, Van Eyk JE (2012) Chasing cysteine oxidative modifications: Proteomic tools for characterizing cysteine redox status. Circulation Cardiovasc Genet 5: 591.

77. Haldar, SM, Stamler JS (2013) S-nitrosylation: Integrator of cardiovascular performance and oxygen delivery. J Clin Invest 123: 101-110.

78. Castro L, Demicheli V, Tortora, V, et al. (2011) Mitochondrial protein tyrosine nitration. Free Radic Res 45: 37-52.

79. Dalle-Donne I, Giustarini D, Colombo R, et al. (2003) Protein carbonylation in human diseases. Trends Mol Med 9: 169-176.

80. Venturini D, Rampazzo CH, De Souza SAF, et al. (2015) Increased oxidative stress according to number of risk factors in metabolic syndrome patients. Diabetology & Metabolic Syndrome 7: A134.

81. Piwowar A, Knapik-Kordecka M, Warmas M (2007) AOPP and its relation with selected markers of oxidative/antioxidative system in type 2 diabetes mellitus. Diabetes Res Clin Pract 77: 188-192.

82. Venturini D, Simão ANC, Scripes N, et al. (2012) Evaluation of oxidative stress in overweight subjects with or without metabolic syndrome. Obesity 20: 2361-2366.

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