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Methodology

Is the association between vitamin D, adiponectin, and insulin resistance present in normal weight or obese? A pilot study

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SUMMARY

Objective: Obesity is classically associated with vitamin D deficiency. The aim of this study was to investigate the association of vitamin D with serum adiponectin concentration and insulin resistance in normal weight and obese individuals.
Research methods and procedures: Cross-sectional analysis was performed in 76 participants without diabetes (40 obese and 36 normal weight) from a convenience sample of a health counseling center in Belo Horizonte, MG, Brazil. All participants self-reported their skin color as white. Body weight and height were used to calculate body mass index (BMI). Serum insulin, glycemia, vitamin D (25OHD), and adiponectin were evaluated after 12 h fasting. Body fat percentage by electric bioimpedance and waist circumference were analyzed. Pearson's or Spearman's correlation coefficients were calculated. Age- and gender-adjusted associations by multivariate logistic regression were used. Multiplicative interaction terms between 25OHD/adiponectin and BMI were calculated.
Results: Participant's mean age was 35 ± 9.5 years; 75% were female, and 65.8% were vitamin D insufficient (25OHD < 20 ng/mL). The mean of 25OHD was 28.4 ± 8.6 ng/mL, median of adiponectin was 204 ng/L, and the median of *Homeostatic Model Assessment for Insulin Resistance* (HOMA-IR) was 2.2. There was no association

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between 25OHD status, adiponectin, and HOMA-IR in total sample or among obese or normal weight individuals. After adjustments, there was an association between 25OHD insufficiency and body fat percentage (odds ratio = 0.94; confidence interval 95% = 0.88 to 0.99, p = 0.04) in the total sample. BMI did not influence the association between 25OHD and adiponectin.

Conclusion: There was a negative association between fat percentage and 25OHD status, but there were no associations between 25OHD, adiponectin, and insulin resistance in this sample. Further studies are needed to understand these associations in other populations.

1. Introduction

Obesity is a worldwide health problem that affects more than 500 million people, and its incidence has been increasing in recent decades. Approximately 3 million deaths per year worldwide can be attributed to overweight and obesity [1]. According to the Brazilian Institute of Geography and Statistics, in 2015, 59% of the Brazilian population are overweight and 20.8% are obese [2].

Adipose tissue acts as a reservoir of energy and produces biologically active substances, and it can be considered an endocrine organ. It is also involved in insulin resistance [3] mediated by macrophage inflammation [4]. The adipokines, produced by the adipose tissue, can participate in insulin sensitivity and in many inflammatory and anti-inflammatory processes [5–7]. Obesity, as a state of low-grade inflammation, could contribute to insulin resistance. Adiponectin levels can negatively correlate with obesity and insulin resistance and positively with vitamin D (25OHD) levels [8]. Adiponectin contributes to increasing muscle glucose uptake and oxidation induction of fatty acids in muscle and fat cells [9]. In the liver, adiponectin stimulates the β-oxidation, suppresses neoglycogenesis and the uptake of fatty acids, and lipogenesis. In the pancreas, 25OHD reduces apoptosis and contributes to the synthesis of insulin [10]. Therefore, it could help minimize the insulin-resistance mechanisms. However, the association between 25OHD and adiponectin is controversial [11]. In overweight Brazilians, a negative correlation of adiponectin and 25OHD was found [12]. Other researchers found a positive [8,13] or no association [11] between these parameters.

Like obesity, 25OHD insufficiency is pandemic [14]. 25OHD receptors are present in the membrane of the adipocytes and can be involved in adipogenesis [15]. Evidence exists of a negative association between 25OHD levels, insulin resistance, and body mass index (BMI) [16]. Vitamin D mediates the influx of calcium in pancreatic β-cell and can be involved in the regulation of insulin secretion, contributing to reduce insulin resistance [17]. The mechanisms of the association between obesity and 25OHD insufficiency are not well elucidated. There are inconsistencies in weight loss leading to higher levels of 25OHD [18]. While some studies show that polymorphisms of the Vitamin D receptor (VDR) could be associated with obesity and inflammatory profile [5], and 25OHD could contribute to fat cell apoptosis, others deny the genetic association between 25OHD and obesity [19,20].

The pathophysiologic mechanisms of the association between hypovitaminosis D, obesity, and insulin resistance are unknown. Adiponectin could be a link between them. Walker et al. showed a negative association of adiponectin in children with obesity and 25OHD insufficiency and a positive feedback of adiponectin levels after 1 year of vitamin D supplementation [21]. Others show no effect on adiponectin levels after vitamin D therapy [22].

Considering the controversial results of the studies that investigate the connections between 25OHD, obesity, insulin resistance, and adiponectin [8,13], this study aimed to verify these associations

in a Brazilian sample, among normal weight and obese people. Our hypothesis is that 25OHD insufficiency is associated with insulin resistance and lower adiponectin levels.

2. Material and methods

2.1. Design and subjects

This is a cross-sectional study of the association of 25OHD status with levels of adiponectin and insulin resistance, in the total sample and among two groups (obese and non-obese weight patients). A convenience sample was recruited from adult patients between 18 and 60 years old, of both sexes, who attended medical appointments in a private nutrition advice center, in Belo Horizonte-MG, Brazil, between July 2015 and February 2017. A well-trained single researcher (MCR) collected all data. After the sample size calculation (using PASS NCSS software, version 11, USA), 38 subjects were included in each group to obtain a power of 81%. The bilateral z test was used (significance level of 0.05).

Inclusion criteria were non-obese weight or obese individuals, according to BMI, and self-reporting their skin color as white.

We excluded patients who did not sign the informed consent, with any auto-referred skin color different from white, who were overweight, with renal insufficiency (defined as serum creatinine $\geq$2.0 mg/dl), type 1 and 2 diabetes mellitus, chronic liver disease, cancer (except nonmelanoma skin cancer), cardiovascular diseases, intestinal malabsorption syndrome, or after bariatric surgery. We also excluded people who used drugs that could alter serum insulin or adiponectin concentrations (such as theophylline, phenytoin, beta blockers, diuretics, inhibitors of renin-angiotensin system) or medications for weight loss, lipid-lowering drugs, diabetes, or insulin resistance or vitamin D supplementation for the last 6 months; pregnant women; and patients who refused to collect blood samples for the research. The menopausal state was not considered.

2.2. Ethical aspects

All participants were volunteers and signed the informed consent form. The research was approved by the Research Ethics Committee of the Federal University of Minas Gerais – COEP-CAAE 42364915.0.0000.5149.

2.3. Sociodemographic and anthropometric data

Clinical data (sociodemographic, hours of sun exposure, use of sunscreen, and physical activity [Portuguese validated version of the International Physical Activity Questionnaire – IPAQ short version]) [23] were assessed by a self-reported questionnaire.

Participants were weighed without shoes and wearing light clothes using a Tristar® Platform scale (capacity up to 200 kg, model WG2420, the Netherlands). The height was measured with patients standing barefoot, with feet parallel, and trunk and head touching the stadiometer (accuracy of 0.5 cm). BMI was calculated from height and weight (BMI = weight [kg]/height^2[m^2]) [24]. We used World Health Organization criteria to stratify BMI into normal-weight ($\geq$18.5–24.9 kg/m^2) or obese ($\geq$30 kg/m^2). Waist circumference (WC) was measured using inelastic tapes (cm) at the midpoint between the lowest rib and iliac crest [25].

Body fat percentage was assessed by bioelectric impedance (Tristar WG2422). Patients were afebrile, fasting 2 h before the exam, without alcohol or excess of caffeine consumptions and without intense physical activity the day before the exam. The female patients were not menstruating. Personal metal objects were removed before bioelectric impedance.

2.4. Biochemical analysis

Peripheral blood samples were collected in tubes containing EDTA (1 mg/mL of blood) after 12 h of fasting and abstaining from alcoholic beverages for at least 72 h. Fasting glucose (hexokinase method,

enzymatic colorimetric) and creatinine (Jaffe's Method) were determined by automated methods (Advia 2400, Siemens, Japan). Insulin and 25OHD were determined by immunoassay using direct chemiluminescence (ADVIA Centaur XP, Siemens, Ireland).

Only for adiponectin measurement were serum samples frozen to −20 °C, stored for up to 12 months (in accordance with MyBiosource®'s manual, San Diego, CA, USA), and total adiponectin was determined by ELISA (MyBiosource), made in duplicate. The mean of those two adiponectin values was considered for analysis. The analytical sensibility, intra e inter-assay precision of adiponectin were, respectively, of 0.78 ng/mL, CV% < 8%, and CV% < 10%.25OHD was categorized as normal (≥20 ng/mL) or insufficient (<20 ng/mL), according to the Brazilian Society of Endocrinology and Metabolism [26]. We also categorized vitamin D status according to the cut-off of < or ≥30 ng/mL 25OHD was analyzed as a categorical variable (normal or insufficient) and classified according to the season in which they were collected.

Insulin resistance was evaluated by the *Homeostatic Model Assessment for Insulin Resistance* (HOMA-IR) calculated by the formula: insulin (mUI/mL) × fasting glucose (mg/dL) × 0.05551/22.5 [27,28].

2.5. Other variables

Solar exposition was categorized as often (one or more times/day) or rare (eventually), and use of sunscreen as daily or rare. Physical activity was categorized as low, moderate, or vigorous according to the IPAQ [23].

2.6. Statistical analysis

Normality of data distribution was assessed by histograms and Shapiro–Wilk test. According to normality of the data or otherwise, Pearson's or Spearman's correlation coefficients were used to evaluate the correlations between the variables. Descriptive and univariate analyses (Pearson Chi-square test, Mann–Whitney, and Student t-test) were used to compare clinical and biochemical data between 25OHD status (normal or insufficient) groups. Logistic regression analysis was performed to estimate the relationships among 25OHD status (normal or deficient), adiponectin (continuous), and insulin resistance (HOMA-IR-continuous), after adjustments (for age, sex, fat percentage or WC [separate models]) (Table 3). Sensitivity analyses with the vitamin D reference levels < or ≥30 ng/dL were also performed, and the results were the same.

We also analyzed the association of 25OHD status and adiponectin and HOMA-IR among each BMI group (normal weight or with obesity). We subsequently added multiplicative interaction terms between 25OHD/adiponectin and BMI.

We used SPSS software (IBM, version 19, USA) and STATA™ version 14.

3. Results

Ninety-eight adults were selected for this study, but only 76 were in the final analysis according to the forward flowchart (Fig. 1). Participants' mean age was 35.5 ± 9.6 years, with 75% women (n = 57), and 14.5% had 25OHD insufficiency. Regarding the cut-off < or ≥30 ng/mL, we had 65.8% of vitamin D insufficiency. Mean of 25OHD was 28.4 ± 8.6 ng/mL, median of adiponectin was 209.7 ng/L(136.8–296.2), and median of HOMA-IR was 2.18(1.55–4.13). The median BMI was 30.2 (23.5–33.2), and WC was 96.5 (87.0–110.5). Forty participants were classified as obese and 36 as normal-weight. The mean creatinine was 0.74 (±0.14). Their main characteristics are displayed in Tables 1 and 2.

We found no difference across the 25OH groups regarding age, sex, adiponectin levels, HOMA-IR (Tables 1 and 2), or other laboratory tests. Regarding the whole sample (normal weight and obese patients), there was no association between 25OHD status and adiponectin, nor with HOMA-IR (Table 3). There was an association between 25OHD insufficiency and fat percentage, which remained significant after adjustments by age and sex, but lost significance after adjustment by waist or BMI (separate models). The association between 25OHD and adiponectin was not influenced by BMI (OR by the product of the interaction term = 0.00; 95% CI = −0.004 to 0.003, p = 0.69).

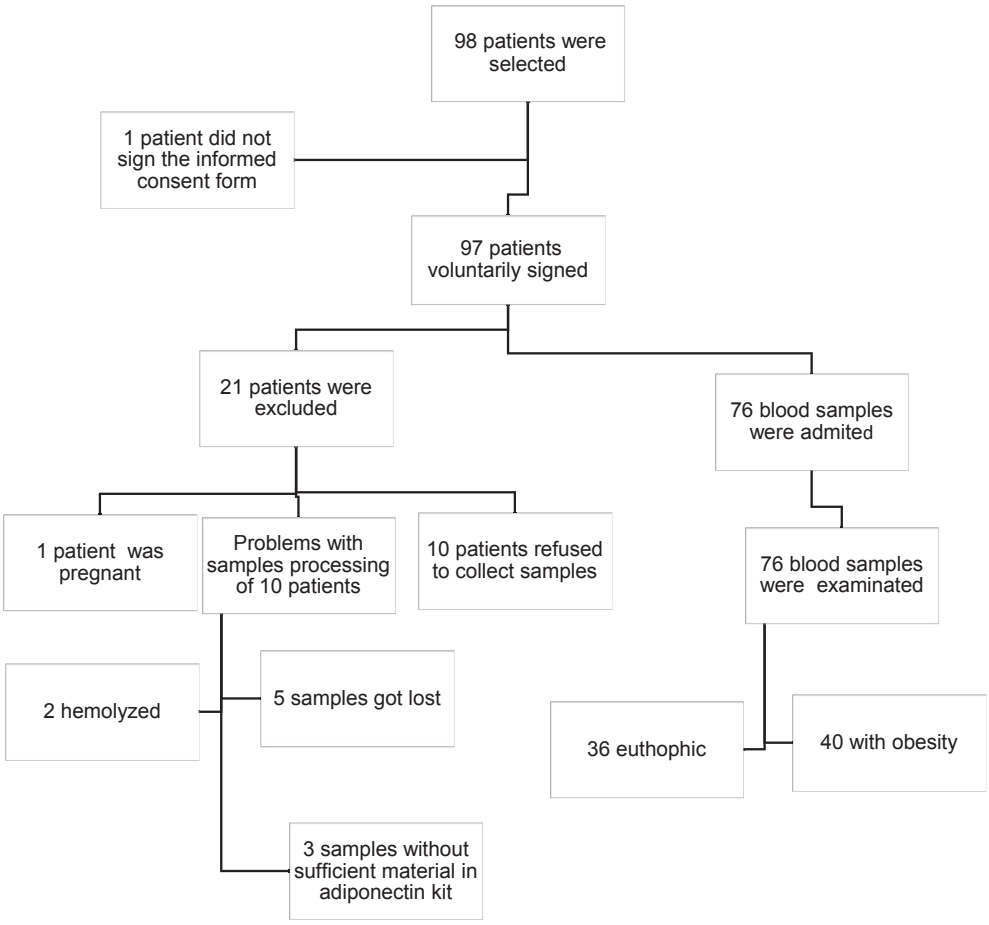

Fig. 1. Inclusion criteria.

The analysis by BMI groups showed that there was no association between 25OHD status and adiponectin among the normal-weight or obese group (Table 3). An association between 25OHD status and HOMA-IR was detected only among the normal-weight group, but lost significance after age and sex ($p = 0.15$), and after waist ($p = 0.21$) or fat percentage ($p = 0.23$) adjustments.

4. Discussion

We found no association among normal-weight and obese individuals between 25OHD levels, insulin resistance, and adiponectin in this sample with almost 15.0% of 25OHD insufficiency. Those results are similar to the results found by other authors [11,29,30], where positive associations between 25OHD and insulin sensitivity were no longer valid after adjusting for BMI [31] or physical activity [32]. Wright et al. showed no association in a population with obesity but no diabetes between 25OHD and insulin sensitivity or adiponectin [33]. Vilarrasa et al. found no correlations between 25OHD and adiponectin or with HOMA-IR in morbidly obese or normal-weight groups [11]. In the present study, we did not evaluate patients with class III obesity. Two studies with patients without diabetes found a positive correlation between 25OHD and adiponectin that disappeared after adjusting for BMI [16,34]. In a study with individuals with morbid obesity, no differences in insulin resistance were found

Table 1
Main characteristics of the study population, according to vitamin D status among adults (n = 76), Belo Horizonte, Brazil.

Variable	25OHD normal (n = 65)		25OHD insufficient (n = 11)		*p* value
	N	%	N	%	
Age (years)[a]	35.6	±9.9	34.9	±7.6	0.83
Scholarship (years)[a]	15.8	±3.3	16.4	±3.0	0.61
Female population	48	(73.8%)	9	81.8%	0.57
Obese population	31	(47.7%)	9	81.8%	0.61
Sunscreen use					
Daily	32	49.2%	8	72.7%	0.15
Rare	33	50.8%	3	27.3%	
Sun exposure					
Often	57	87.7%	11	100.0%	0.22
Rare	8	12.3%	0	0%	
Season of data collection					
Summer	19	29.2%	1	9.1%	0.43
Spring	15	23.1%	2	18.1%	
Autumn	13	20.0%	3	27.3%	
Winter	18	27.7%	5	45.5%	

[a] Age and Scholarship are presented as media and SD 25OHD – 25-Hydroxivitamin vitamin D; 25OHD normal – 25OH vitamin D ≥ 20 ng/mL; 25OHD insufficient – 25OH vitamin D < 20 ng/mL.

Table 2
Distribution of clinical characteristics according to vitamin D status among adults (n = 76), Belo Horizonte, Brazil.

Variable	25OHD normal (n = 65)		25OHD insufficient (n = 11)		*p* value
	Mean	SD	Mean	SD	
BMI (kg/m^2)	28.5	±6.9	31.9	±5.6	0.12
WC (cm)	94.5	(87; 108)	107	(96; 117)	0.09
Adipo (ng/mL)[a]	209.7	(136.8; 296.2)	208.9	(179.2; 251.4)	0.72
HOMA-IR[a]	2.07	(1.39; 3.81)	2.92	(2.18; 4.58)	0.08
Fat %	34.5	±11.4	42.7	±13.3	0.03
IPAQ (METS) [a]	990	(450; 1878)	400	(160; 990)	0.13
Glycemia (mg/dL)	83.5	±7.9	84.0	±6.9	0.84

[a] Values presented as median and interquartile range. 25OHD – 25-Hydroxivitamin vitamin D; 25OHD normal – 25OH vitamin D ≥ 20 ng/mL; 25OHD insufficient – 25OH vitamin D < 20 ng/mL; BMI – body mass index, WC – waist circumference, Adipo – Adiponectin, HOMA-IR – Homeostasis model assessment of insulin resistance, Fat % – Fat percentage, IPAQ – International Physical Activity Questionnaire.

Table 3
Not adjusted Logistic regression between vitamin D status (normal or insufficient) and adiponectin, and insulin resistance.

	Total sample	Normal weight	Obese
	OR [95% CI] (p value)	OR [95% CI] (p value)	OR [95% CI] (p value)
Adiponectin	1.00 [0.99–1.00] (0.68)	1.01 [0.99–1.03] (0.22)	1.00 [0.99–1.01] (0.97)
HOMA-IR	0.92 [0.72–1.18] (0.55)	0.29 [0.09–0.88] (0.03)	1.26 [0.84–1.89] (0.26)

Normal Vitamin D – Vitamin D ≥ 20 ng/mL; Insufficient Vitamin D – Vitamin D < 20 ng/mL.
HOMA-IR – Homeostatic Model Assessment for Insulin Resistance; OR – Odds ratio; 95% CI – Confidence interval; Normal weight – Body mass index < 30 kg/m^2; Obese – Body mass index ≥ 30 kg/m^2.

between participants with and without 25OHD insufficiency [35]. In contrast, others observed a negative association between 25OHD and insulin resistance [36–39] or a positive association between 25OHD and adiponectin in patients with obesity [8,40,41] or even positive association between high fat

percentage and adiponectin levels only in men, without differences in 25OHD levels [42], showing that this topic remains controversial.

The association between 25OHD and insulin resistance observed by some authors could be explained by some mechanisms. In vitro, there was an improvement in insulin sensitivity after vitamin D stimulus of VDR [43], which could, in peripheral tissue, facilitate the transport of glucose mediated by insulin, thereby improving insulin resistance. Vitamin D also participates in the mechanism of insulin secretion [44–46], interfering in its biosynthesis and accelerating the conversion of proinsulin in insulin [47,48]. An association was observed between 25OHD insufficiency and reduced insulin secretion [46,49]. However, other mechanisms that linked vitamin D and insulin resistance, such as gene polymorphisms of VDR [50], could be a plausible hypothesis for our discrepant findings because of the potential genetic variation in a Brazilian population. Polymorphisms of VDR and genetic variations could alter this relationship [19,50]. The genetic metabolic phenotype may also influence the relationship between 25OHD and adiponectin levels [51]. Until now, few genetic studies with VDR polymorphisms in Brazilian people have been investigated. A study with Brazilian children in Amazonas showed that a polymorphism in VDR was positively associated to HOMA-IR [52]. Further researchers may be able to answer why these associations are not the same in all people and characterize individuals to enhance the mechanistic understanding of the relationship between 25OHD, adiponectin, insulin resistance, and obesity.

Ethnic aspects in a country with a lot of miscegenation, such as Brazil, should be considered. The META-health study showed that the association between 25OHD, adiponectin, and insulin resistance (by HOMA-IR) could differ depending on race, gender, and BMI category [53]. This could be one of the reasons for our findings but also for the controversy in the literature.

In our study, the association between 25OHD insufficiency and fat percentage, was lost after adiposity markers adjustments. Vilarrasa et al. found inverse association of vitamin D levels and fat percentage only in the healthy group, and there was no association between vitamin D and adiponectin or insulin resistance neither in the obese, nor in the healthy group [11]. Cediel et al. showed an inverse association between 25OHD and fat percentage in children [54]. Al-Daghri et al. found that serum 25OHD was associated inversely with hip circumference ($r = -0.195$, $p = 0.047$), BMI ($r = -0.190$, $p = 0.026$) and HOMA-IR ($r = -0.304$, $p = 0.001$) in people with and without diabetes [55]. The reasons for that association between fat percentage and serum 25OHD could be explained by the sequestration or hyper-dilution of 25OHD in the extensive reservoir of adipose tissue in people with a high percentage of fat mass, less sun exposure, and fewer physical activities outdoors. Individuals with percentage of fat mass have a lower conversion rate of the vitamin to 25hydroxivitamin D, due to negative feedback by elevation of 1.25Dihydroxivitamin D and parathormone, and by lower expression of the enzymes that activate 25OHD (25-hydroxylase and 1α-hydroxylase) [56]. Finally, the increased 24-hydroxylase enzyme activity related to the high-fat percentage is responsible for the degradation of the active form of vitamin D, thus leading to its greater catabolism [57].

Our study has limitations in its sample size and that we chose a convenience sample, with white self-reported skin color. However, this population was chosen to standardize skin color, minimizing the possible biases. HOMA-IR was used to characterize insulin resistance. Although the hyperinsulinemic-euglycemic clamp is the gold standard for evaluating insulin resistance, such testing is not feasible in clinical studies because of the procedure's complexity.

Our study's strengths were that we included the internal validity concerning accuracy and standardization of measurements, the duplicity of adiponectin samples, and the fact that no previous studies have investigated the association between 25OHD, adiponectin, and insulin resistance in an obese, normal-weight Brazilian population.

5. Conclusion

Except for a negative association between 25OHD status and fat percentage, there was no association between 25OHD, adiponectin, and insulin resistance in that population. Future studies with larger samples are needed, mainly from developing countries, which may have diverse sociodemographic and genetic characteristics.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yclnex.2018.10.004.

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