Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 258–263

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Association between vitamin D deficiency and insulin resistance markers in euthyroid non-diabetic individuals

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ARTICLE INFO

Article history:
Received 5 August 2018
Accepted 7 September 2018

Keywords:
Vitamin D deficiency
Insulin resistance
Glucose tolerance test
Diabetes mellitus
Euthyroid

ABSTRACT

Aim: To evaluate the association between vitamin D deficiency and insulin resistance (IR) or hyperinsulinemia after oral glucose tolerance test (OGTT) in euthyroid non-diabetic individuals.
Materials and methods: We carried out an analytical cross-sectional study in euthyroid non-diabetic adults of both sexes, who attended the outpatient service of a private clinic in Lima-Peru during the 2012–2016 period. Participants were categorized in two groups according to their serum vitamin D levels: normal vitamin D levels (serum vitamin D values ≥ 20 ng/dL) and vitamin D deficiency (serum vitamin D values < 20 ng/dL). IR was defined as a Homeostasis Model Assessment (HOMA-IR) value ≥ 3.8 and hyperinsulinemia after OGTT was defined as a serum insulin value ≥ 80μU/mL after 120 min of 75-g glucose intake. We elaborated crude and adjusted Poisson regression models to assess the association between serum vitamin D levels and IR or hyperinsulinemia after OGTT. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI).
Results: We analyzed 204 participants, the average age was 38.5 ± 10.6 (SD) years, 40 (19.6%) were males and the vitamin D median was 25.0 (IQR: 19.0–33.3) ng/dL. The prevalence of vitamin D deficiency, IR and hyperinsulinemia after OGTT was 29.4% (n = 60), 29.9% (n = 61) and 25.0% (n = 51). In the adjusted Poisson regression models, the prevalence of hyperinsulinemia after OGTT was higher among the vitamin D deficient group (aPR=1.75; 95%CI: 1.06–2.90); however, we did not find statistically significant association between vitamin D deficiency and IR (aPR=0.99; 95%CI: 0.61–1.63).
Conclusions: We found an association between vitamin D deficiency and hyperinsulinemia after OGTT in euthyroid people with no T2DM.Our findings are consistent with previous reports; providing evidence that serum vitamin D deficiency could be an IR marker.

1. Introduction

Insulin resistance (IR) is defined as the decrease in the ability of insulin to exert its biological actions in tissues such as skeletal muscle, liver or adipose tissue, and is considered an indicator in the pathogenesis of type 2 diabetes mellitus (T2DM) [1,2]. In 2014, the World Health Organization (WHO) reported that the global prevalence of T2DM was 9% in people over 18 years of age [3]. T2DM represents a public health problem, especially in low-income countries where 80% of the deaths caused by this condition occur [3].

IR has been associated with pathologies such as breast, endometrial and colon cancer; and polycystic ovarian syndrome [4–6]. Additionally, a meta-analysis described the relationship between the presence of insulin-like growth factor 1 (IGF-1) and IGF-binding proteins (IGFBP) with the development of IR and ovarian cancer [7]. Furthermore, it has also been reported that the presence or progression of renal failure is associated with IR [8]. Therefore, IR does not only represent a risk factor for the development of metabolic

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https://doi.org/10.1016/j.dsx.2018.09.008
1871-4021/

diseases.

Previous studies report that vitamin D deficiency has been associated with cardiovascular diseases, T2DM and cancer [9]. In addition, some studies have described the possible influence of vitamin D supplementation on glucose homeostasis, however, no consensus has yet been reached [10,11].

Despite the importance of the prevention of metabolic disorders and complications caused by IR, we do not find many studies in Latin America about vitamin D deficiency and its association with IR or hyperinsulinemia after oral glucose tolerance test (OGTT) in the non-diabetic adult euthyroid population. As well, there is no clear consensus regarding the role of vitamin D supplementation in the pathogenesis of IR. Therefore, the objective of the present study was to evaluate the association between vitamin D deficiency and IR or hyperinsulinemia after OGTT in a population of adults with no medical history of endocrine or metabolic disorders in a private clinic in Lima, Peru.

2. Methods

2.1. Study design and population

Analytical cross-sectional study, carried out in euthyroid adults of both sexes with no medical history of type 2 diabetes mellitus (T2DM), who attended the outpatient service of a private clinic in Lima-Peru during 2012–2016.

2.2. Sample type and analysis unit

A non-probabilistic sampling was performed; the sample consisted of all patients who attended the outpatient service of the private clinic between January 2012 and December 2016 and met the eligibility criteria of the study. The statistical power calculated for the associations among vitamin D deficiency and IR was 87%.

2.3. Procedures

We reviewed the medical records of the patients treated during the study period and collected all the data of interest. The laboratory values were only collected if the patient laboratory tests were performed with a maximum of 30 days after they were attended in the outpatient service of the private clinic. All participants had a minimum fasting period of eight hours for laboratory tests, according to the protocols established by the individual medical centre.

2.4. Eligibility criteria

Participants included were aged ≥18 with no medical background of T2DM, hypothyroidism, subclinical hypothyroidism, hyperthyroidism or metabolic syndrome.

We excluded participants aged ≥60, patients with fasting glucose values ≥ 126 mg/dL, OGTT ≥200 mg/dL, with thyroid hormones values outside the following ranges: free triiodothyronine (FT3): 2.3–4.2 pg/mL, free thyroxine (FT4): 0.89–1.76 ng/dL, thyroid stimulating hormone (TSH): 0.40–5.0 μU/mL [12]; and pregnant women.

2.5. Variables definition

2.5.1. Exposure

Participants who met the eligibility criteria were categorized in two groups according to their serum vitamin D levels: normal vitamin D levels (serum vitamin D values ≥ 20 ng/dL) and vitamin D deficiency (serum vitamin D values < 20 ng/dL) [13].

2.5.2. Outcomes: IR and hyperinsulinemia after OGTT

IR was defined as a Homeostasis Model Assessment (HOMA-IR) value ≥ 3.8 [14]. Mathews et al. proposed HOMA-IR in 1985 in a mathematical model to assess hyperinsulinemia. The gold standard to assess IR is the hyperinsulinemic euglycemic clamp, however HOMA-IR is well correlated with it. HOMA-IR was calculated using the formula: fasting glucose (mg/dL) x fasting insulin (μU/mL)/405 [15].

Hyperinsulinemia after OGTT was defined as a serum insulin value ≥ 80 μU/mL after 120 min of 75-g glucose intake [16]. Participants were divided in two groups according to this criterion.

2.5.3. Other variables

The following variables were also included in the analysis: age (years), sex, body mass index (BMI), fasting glucose, postprandial blood glucose, fasting insulin, FT3, FT4 and TSH.

2.6. Statistical analysis

We used STATA v14.0 (StataCorp, TX, USA) for our analysis. Descriptive results for numeric variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR), depending on their distributions; otherwise, we expressed the qualitative variables as numbers with percentages. The study population characteristics according to the serum vitamin D levels, IR or hyperinsulinemia after OGTT were compared using the student T test or the Wilcoxon rank sum test as appropriate for continuous variables and using the Chi-square test for categorical variables.

Four generalized linear models (1 crude and 3 adjusted) from Poisson family with robust standard errors were constructed to assess the association between serum vitamin D levels and IR or hyperinsulinemia after OGTT. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI). The first adjusted model to evaluate the association between serum vitamin D levels and IR or hyperinsulinemia after OGTT included the following confounding variables: age (years) and sex. The second adjusted model included the first model confounding variables and added FT3 and TSH [17]. Finally, the third adjusted model included the second model confounding variables and BMI [18]. The reported association measure for the adjusted models was the adjusted prevalence ratio (aPR) with their respective 95%CI.

2.7. Ethical considerations

The data was collected by two researchers from the private clinic to study epidemiological surveillance. For this study, participant information was delivered in a Microsoft Excel 2010 file with no biological identifiers, maintaining the confidentiality of the information.

3. Results

In total, we enrolled 1817 patients during the study period; we excluded 373 participants because they were 60 or older. Besides, 636 patients were withdrawn due to hyperthyroidism, hypothyroidism, subclinical hypothyroidism or T2DM and 604 because they did not have the variables of interest. Finally, 204 participants were analyzed.

3.1. Characteristics of the study population

The average age of the participants was 38.5 ± 10.6 (SD) years, 40 (19.6%) were males and the median BMI was 27.3 (IQR:

Table 1
Characteristics of the study population by vitamin D levels (N = 204).

Variables	N = 204	Normal (n = 144)	Deficiency (n = 60)	P value
Age (years)	38.5 ± 10.6	38.9 ± 11.0	37.6 ± 9.7	0.434
Male	40 (19.6)	35 (24.3)	5 (8.3)	0.009
BMI (kg/m^2)	27.3 (23.4–30.5)	27.3 (23.4–30.6)	27.7 (23.9–30.5)	0.630
Fasting glucose (mg/dL)	89.0 ± 9.3	89.7 ± 9.8	87.3 ± 7.9	0.093
Postprandial glucose (mg/dL)	94 (78.5–107)	93 (77–107)	97.5 (79–106)	0.458
Fasting insulin (μU/mL)	10.8 (7.4–17.9)	10.5 (6.9–17.9)	12.2 (8.4–18.4)	0.163
Serum insulin after OGTT (μU/mL)	47.7 (28.1–81.3)	45.1 (27.1–71.0)	57.5 (30.2–100.5)	0.148
Glycated haemoglobin A1c (%)	5.45 ± 0.3	5.5 ± 0.3	5.4 ± 0.3	0.048
HOMA-IR	2.4 (1.5–4.1)	2.3 (1.5–4.1)	2.5 (1.7–4.2)	0.313
Vitamin D (ng/mL)	25.0 (19.0–33.3)	29.8 (23.9–37.1)	16.1 (14.2–18.7)	<0.001
FT3 (pg/mL)	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.4	0.364
FT4 (ng/dL)	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	0.053
TSH (μU/mL)	2.1 (1.6–3.2)	2.1 (1.6–2.9)	2.5 (1.8–3.9)	0.022

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

23.4–30.5) kg/m^2. The prevalence of vitamin D deficiency was 29.4% (n = 60) and the vitamin D median was 25.0 (IQR: 19.0–33.3) ng/dL. The IR prevalence was 29.9% (n = 61) whereas the prevalence of hyperinsulinemia after OGTT was 25.0% (n = 51). Additionally, the FT3, FT4 and TSH, mean or median levels were 3.2 ± 0.4 pg/mL, 1.2 ± 0.2 ng/dL and 2.1 (IQR: 1.6–3.2) μU/mL respectively. Furthermore, the fasting glucose, HOMA-IR and fasting insulin, mean or median levels were 89.0 ± 9.3 mg/dL, 2.4 (IQR: 1.5–4.1) and 10.8 (IQR: 7.4–17.9) μU/mL respectively. The group with normal serum vitamin D levels had a median of 29.8 (IQR: 23.9–37.1) ng/mL, while the deficient group had a median of 16.1 (IQR: 14.2–18.7) ng/mL, with statistically significant differences (Table 1).

3.2. Characteristics of the study population by vitamin D levels

We observed a lower proportion of male participants (12.5 vs. 33.5%; p = 0.009), a lower mean of glycated haemoglobin A1c (5.4 vs. 5.5; p = 0.048) and a higher median of TSH (2.5 vs. 2.1; p = 0.022) in participants with vitamin D deficiency compared with the normal serum vitamin D levels group. There were no statistical differences in age (years), BMI, fasting glucose, postprandial glucose, fasting insulin, HOMA-IR, FT3 and FT4 levels between exposure groups (Table 1).

3.3. Characteristics of the study population based on IR

We found a higher BMI median (30.7 vs. 25.7; p < 0.001), a higher fasting glucose mean (95.6 vs. 86.1; p < 0.001), higher medians of postprandial glucose (103 vs. 88; p < 0.001) and fasting insulin (23.3 vs. 8.8; p < 0.001) in participants with IR compared with the no IR group. Additionally, we observed a higher glycated haemoglobin A1c mean (5.6 vs. 5.4; p < 0.001), a higher HOMA-IR median (5.3 vs. 1.9; p < 0.001), a higher FT3 mean (3.3 vs. 3.1; p = 0.003) and a lower FT4 mean (1.2 vs. 1.3; p = 0.017) in participants with IR compared with the no IR group (Table 2).

3.4. Characteristics of the study population based on hyperinsulinemia after OGTT

Similarly, we found a higher BMI median (30.7 vs. 26.2; p < 0.001), a higher fasting glucose mean (92.4 vs. 87.9; p = 0.003), higher medians of postprandial glucose (114 vs. 86; p < 0.001) and fasting insulin (24.0 vs. 9.3; p < 0.001) in participants with hyperinsulinemia after OGTT compared with the group without this condition. As well, we observed a higher glycated haemoglobin A1c mean (5.6 vs. 5.4; p < 0.001), a higher HOMA-IR median (5.3 vs. 2.0; p < 0.001), a lower vitamin D median (23.0 vs. 26.4; p = 0.037) and a lower FT4 mean (1.2 vs. 1.3; p = 0.040) in participants with hyperinsulinemia after OGTT compared with the normal group (Table 3).

3.5. Generalized linear models from Poisson family to assess the association between vitamin D deficiency and IR or hyperinsulinemia after OGTT

In the crude Poisson regression model to assess the association between vitamin D deficiency and IR, compared with the normal

Table 2
Characteristics of the study population based on IR (N = 204).

Variables	No IR (n = 143)	IR (n = 61)	P value
Vitamin D deficiency	41 (68.3)	19 (31.7)	0.722
Age (years)	38.2 ± 10.3	39.2 ± 11.4	0.509
Male	23 (57.5)	17 (42.5)	0.052
BMI (kg/m^2)	25.7 (22.7–28.5)	30.7 (27.4–34.4)	<0.001
Fasting glucose (mg/dL)	86.1 ± 7.3	95.6 ± 10.3	<0.001
Postprandial glucose (mg/dL)	88 (75–102)	103 (93–129)	<0.001
Fasting insulin (μU/mL)	8.8 (6.3–11.3)	23.3 (18.8–30.4)	<0.001
Serum insulin after OGTT (μU/mL)	40.8 (23.7–58.0)	101.6 (61.9–153.1)	<0.001
Glycated haemoglobin A1c (%)	5.4 ± 0.3	5.6 ± 0.4	<0.001
HOMA-IR	1.9 (1.4–2.5)	5.3 (4.2–7.1)	<0.001
Vitamin D (ng/mL)	24.7 (19.2–33.9)	26.0 (18.6–32.0)	0.813
FT3 (pg/mL)	3.1 ± 0.4	3.3 ± 0.4	0.003
FT4 (ng/dL)	1.3 ± 0.2	1.2 ± 0.2	0.017
TSH (μU/mL)	2.3 (1.6–3.2)	2.1 (1.6–2.9)	0.632

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 3
Characteristics of the study population based on hyperinsulinemia after OGTT (N = 204).

Variables	No hyperinsulinemia after OGTT (n = 153)	Hyperinsulinemia after OGTT (n = 51)	P value
Vitamin D deficiency	38 (63.3)	22 (36.7)	0.013
Age (years)	38.1 ± 10.6	39.8 ± 10.8	0.317
Male	27 (67.5)	13 (32.5)	0.222
BMI (kg/m^2)	26.2 (23.0–29.0)	30.7 (26.2–34.2)	<0.001
Fasting glucose (mg/dL)	87.9 ± 8.8	92.4 ± 10.2	0.003
Postprandial glucose (mg/dL)	86 (75–101)	114 (100–136)	<0.001
Fasting insulin (μU/mL)	9.3 (6.4–14.3)	24.0 (16.9–31.2)	<0.001
Serum insulin after OGTT (μU/mL)	39.6 (23.4–55.0)	128.5 (101.4–173.4)	<0.001
Glycated haemoglobin A1c (%)	5.4 ± 0.3	5.6 ± 0.4	<0.001
HOMA-IR	2.0 (1.4–3.0)	5.3 (4.0–7.4)	<0.001
Vitamin D (ng/mL)	26.4 (20.0–33.9)	23.0 (15.9–31.7)	0.037
FT3 (pg/mL)	3.2 ± 0.4	3.2 ± 0.4	0.726
FT4 (ng/dL)	1.3 ± 0.2	1.2 ± 0.2	0.040
TSH (μU/mL)	2.2 (1.6–3.1)	2.1 (1.6–3.5)	0.728

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 4
Generalized linear models from Poisson family with robust standard errors to assess the association between vitamin D deficiency and IR or Hyperinsulinemia after OGTT.

Outcomes	Variables	Crude PR (95% CI)	P value	Adjusted PR (95% CI)[a]	P value	Adjusted PR (95% CI)[b]	P value	Adjusted PR (95% CI)[c]	P value
IR	Normal vitamin D levels (ng/mL)	Reference	–	Reference	–	Reference	–	Reference	–
	Vitamin D deficiency (ng/mL)	1.09 (0.69–1.71)	0.721	1.20 (0.76–1.91)	0.435	1.24 (0.77–1.97)	0.374	0.99 (0.61–1.63)	0.993
Hyperinsulinemia after OGTT	Normal vitamin D levels (ng/mL)	Reference	–	Reference	–	Reference	–	Reference	–
	Vitamin D deficiency (ng/mL)	1.82 (1.14–2.90)	0.012	2.05 (1.27–3.31)	0.003	2.04 (1.25–3.33)	0.004	1.75 (1.06–2.90)	0.029

[a] Adjusted by: age (years), sex.
[b] Adjusted by: age (years), sex, FT3 (pg/mL) and TSH (μU/mL).
[c] Adjusted by: age (years), sex, FT3 (pg/mL), TSH (μU/mL) and BMI (kg/m^2).

serum vitamin D levels group, the prevalence of IR was 9% higher (PR=1.09; 95%CI: 0.69–1.71), however, this association was not statistically significant. Equally, the association remained with no statistical significance in the adjusted model for age (years), sex, FT3, TSH and BMI (aPR=0.99; 95%CI: 0.61–1.63) (Table 4).

In the crude Poisson regression model to assess the association between vitamin D deficiency and hyperinsulinemia after OGTT, compared with the normal serum vitamin D levels group, the prevalence of hyperinsulinemia after OGTT was 82% higher (PR=1.82; 95%CI: 1.14–2.90). Finally, after adjusting for age (years), sex, FT3, TSH and BMI, the association remained significant (aPR=1.75; 95%CI: 1.06–2.90) (Table 4).

4. Discussion

In the present study, which included a population of euthyroid people with no T2DM, we found an association between vitamin D deficiency and hyperinsulinemia after OGTT. However, we found no association between vitamin D deficiency and IR defined by the HOMA-IR.

Some studies found association between low serum concentrations of vitamin D and IR assessed by HOMA-IR in adults with no history of T2DM [19–24]. Nevertheless, in a cohort conducted in 3854 Swiss adults, authors did not find association between the serum vitamin D values divided by quartiles and the incidence of IR. Even so, participants who developed IR had lower baseline serum vitamin D concentrations than those who did not develop this condition [18].

In our study, vitamin D deficiency showed association with hyperinsulinemia after OGTT but not with IR evaluated with HOMA-IR. It is important to specify that the participants included in this study were euthyroid and the relationship between vitamin D deficiency with Hashimoto's thyroiditis and Graves' disease has been described; also, it is known that thyroid hormones play a regulatory role in the IR [17,25]. Therefore, the euthyroid condition of our population is probably part of a compensatory mechanism of the IR in participants with vitamin D deficiency. Despite this, we showed that participants with vitamin D deficiency when subjected to an oral glucose overload, had high levels of serum insulin.

Other publications report that vitamin D could regulate IR through its effect on calcium metabolism, phosphorus and the regulation of the insulin receptor gene [26,27]. On the other hand, pancreatic β cells increase their activity to release more insulin and overcome IR. This hyperactivity causes that β cells experience an increase in Ca 2+, activate the signaling of the reactive oxygen species (ROS) and result in cell death [28]. Vitamin D deficiency would result in IR due to a decrease in insulin receptor expression, increasing Ca2 + concentration and decreasing the activity of glucose transporter type 4 (GLUT-4), which also contributes to IR [28].

Similarly, other articles try to explain the association between vitamin D deficiency and IR through inflammatory and immune system mechanisms. Some studies have shown that vitamin D acts by reducing the release of chemokines and cytokines that lead to inflammation and in this way, monocyte chemotaxis is reduced [29]. This inflammation would be responsible for the IR induction [30–32]. Vitamin D can also cause inflammation through the mediation of the Toll-like receptor (TLR), which is found in monocytes and macrophages [33,34].

Vitamin D receptors (VDR) are found in many tissues, including pancreatic β cells [18]. Vitamin D, in addition to its effect on inflammation and the immune system, could also directly influence

insulin sensitivity through interaction with VDRs located in the skeletal muscles; which would stimulate the expression of insulin receptors in the target tissues and finally, across activation of the peroxisome proliferator activator δ receptor (PPARδ) [35]. Besides, polymorphisms in the VDR gene have been associated with IR, suggesting that vitamin D probably contributes to glucose metabolism. Though, some studies show that these results are contradictory [36–39]. Another mechanism proposed to increase insulin sensitivity is the inhibition of the renin-angiotensin-aldosterone system (RAAS), which could improve the transport of glucose across the cell membrane through the recruitment of the GLUT-4 [40,41].

Some studies have described an improvement of IR due to vitamin D supplementation in diabetic and non-diabetic patients [11,42,43]. However, two meta-analysis of randomized clinical trials (RCTs) concluded that there is currently not enough evidence to suggest vitamin D supplementation to improve glycemic metabolism and prevent T2DM, even in individuals with high levels of postprandial or fasting glucose [39,44]. Despite this, we consider that patients deficient in vitamin D at risk of developing T2DM are those in whom we should prioritize supplementation, obviously with a complete periodically evaluation of metabolic and cardiovascular parameters. It is necessary to develop RCTs with a great number of participants, to determine if there is a direct association between serum vitamin D levels and IR or T2DM in Latin American populations [45].

Our study has limitations: 1) the cross-sectional design does not allow us to determine causality among the evaluated variables, however, we can assess the strength the associations; 2) we used information collected from medical records, which could have presented errors at the time of being filled; nevertheless, we have made a rigorous evaluation of the data quality in order to reduce the possibility of information bias; 3) we conducted the study in a single private medical centre, so our results can not be generalized to the Hispanic population; however, given the consistency of our findings with those described in other evaluated populations, we believe that they could be extrapolated to Hispanic euthyroid populations with no T2DM.

In conclusion, we found an association between vitamin D deficiency and hyperinsulinemia after OGTT in euthyroid people with no T2DM. Our findings are consistent with previous reports; providing evidence that serum vitamin D deficiency could be an IR marker.

Funding

Self-funded.

Conflicts of interest

The authors disclose no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.09.008.

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