

Lipid Accumulation Product and 25-OH-Vitamin D Deficiency in Type 2 Diabetes

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Abstract

BACKGROUND: Emerging data suggest a link between vitamin D (25(OH)D) deficiency, type 2 diabetes (T2D), and visceral adiposity. The lipid accumulation product (LAP), strictly correlated with abdominal fat depots, is proposed as marker of dysfunctional adiposity. **AIM:** To verify the association between 25(OH)D levels and LAP in T2D. **METHODS:** Body mass index (BMI), waist circumference (WC), glucose, HbA1c, lipids, and 25(OH)D were assessed in 420 T2D outpatients and in 150 non-diabetic obese with similar anthropometric characteristics. LAP was computed as the product of sex-specific enlarged WC and triglycerides (TG). **RESULTS:** In T2D patients, 63.0% showed 25(OH)D deficiency (<20 ng/ml) vs. 71.3% in the obese control group. Overweight males showed a higher prevalence of 25(OH)D deficiency (60.3%) than women (48.8%, $p < 0.001$), while in obese patients this prevalence was not significant. In both

genders, 25(OH)D was not significantly associated with HbA1c and fasting glucose. Age-adjusted 25(OH)D levels were inversely correlated with BMI ($p < 0.001$), WC ($p < 0.001$), and LAP ($p < 0.001$) in both genders. Metabolic syndrome presented an odds ratio (OR) for 25(OH)D deficiency of 1.6 (1.1-2.5, $p = 0.048$) in females and 1.7 (1.2-2.7, $p = 0.016$) in males, while the highest quartile of LAP showed an OR of 2.1 (1.2-3.6, $p = 0.019$) in females and 3.2 (1.6-6.5, $p = 0.02$) in males. A similar trend was observed in the obese control group. **CONCLUSIONS:** In the presence of excess weight, subjects with and without T2D frequently feature low 25(OH)D levels. Subjects with higher LAP exhibit a high risk of 25(OH)D deficiency, suggesting that dysfunctional adiposity is a worsening factor for vitamin D hypovitaminosis.

Keywords: type 2 diabetes · vitamin D · hypertriglyceridemia · lipid accumulation · insulin resistance · visceral fat

Introduction

Low circulating vitamin D level, expressed as 25-hydroxyvitamin D (25(OH)D) concentration, is an important risk factor for osteoporosis, frequently observed in different populations. In recent years, several papers have highlighted the association between reduced 25(OH)D levels in both type 1 [1] and type 2 diabetes (T2D), as well as in insulin resistance (IR), obesity, and metabolic syndrome (MetS) [2, 3], although the association between IR and low 25(OH)D has recently been

questioned [4]. It is known that IR is associated with a specific lipid pattern, the so-called “lipid triad”, characterized by increased levels of triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and increased small dense low-density lipoprotein cholesterol (LDL-C), which is associated with increased atherogenic risk [5]. Vitamin D deficiency is associated with this lipid pattern [6]. This link could be mediated by IR; alternatively, it is possible that vitamin D directly affects lipid metabolism by interfering with the activity of different enzymes, as suggested by some

observations *in vitro* [7]. To date, a direct effect of vitamin D deficiency on atherogenic dyslipidemia is still debated, being supported by some studies [8, 9], but only modestly confirmed by other authors [10].

In epidemiological studies, overweight and obesity led to alterations in the lipid profile [5, 11], and weight loss brought about an improvement in circulating lipids [12]. This association could be mediated by IR, which is also associated with obesity, or by other mechanisms, considering the relevant role of the adipose tissue in lipid metabolism. Notably, the degree of IR and the extent to which the lipid profile is altered are widely variable among obese subjects. In other words, among those with a similar body mass index (BMI), some are relatively healthy, whereas others show remarkable metabolic disturbances [13]. This means that the functionality of the adipose tissue is relevant, besides its mere mass. In fact, two markers of dysfunctional adiposity have been proposed:

1. The triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), which is considered as a surrogate marker for insulin resistance [14]
2. The lipid accumulation product (LAP), a novel index of central lipid accumulation, expressed by the association of pathological waist circumference and hypertriglyceridemia.

The LAP index has proved to be an easy and essential parameter for the calculation of dysfunctional adiposity, and it is proposed as a powerful marker of MetS and IR [15]. However, the relationship of dysfunctional adiposity expressed by LAP index with vitamin D deficiency has not been thoroughly explored so far. Therefore, the aim of this study was to explore the complex relationships of vitamin D levels with LAP index in T2D outpatients.

Subjects and methods

Subjects and measurements

A consecutive series of 420 T2D outpatients (55% females) and a control group of 150 obese subjects (49% females) were studied between October 1, 2011 and March 31, 2012, when the vitamin D synthesis produced by seasonal UV exposure is minimal. Patients with a history of alcohol abuse, hepatic or severe chronic renal failure, and those treated with vitamin D were excluded. Only

Abbreviations:

25(OH)D - 25-hydroxyvitamin D
ALT - alanine aminotransferase
ASA - acetylsalicylic acid
AST - aspartate aminotransferase
BMI - body mass index
BP - blood pressure
HbA1c - glycated hemoglobin
HDL-C - high-density lipoprotein cholesterol
HPLC - high-pressure liquid chromatography
IR - insulin resistance
LAP - lipid accumulation product
LDL-C - low-density lipoprotein cholesterol
MetS - metabolic syndrome
NHANES III - 3rd National Health and Nutrition Examination Survey
NCEP ATP - National Cholesterol Education Program Adult Treatment Panel
OR - odds ratio
SD - standard deviation
SPSS - statistical package for social sciences
T2D - type 2 diabetes
TC - total cholesterol
TG - triglycerides
UV - ultra violet
WC - waist circumference

5% of males and 3% of females were currently smokers. All participants provided their informed, signed consent before study participation, which was approved by the University of Florence Medical Ethical Committee. Only 2% of patients screened declined to participate to the study.

Seated blood pressure levels (mean of three measurements) were recorded, along with height and weight for calculation of BMI and waist circumference (WC). WC was measured by a soft tape on standing subjects midway between the lowest rib and the iliac crest and considered the mean of two measures from the same operator. After overnight fasting (>8 hr), blood samples for glucose, glycated hemoglobin (HbA1c), serum creatinine, 25(OH)D levels, and a standard lipid profile with total cholesterol (TC), HDL-C, and TG were collected. Plasma glucose and lipids were automatically measured in our central laboratory (Beckman Instruments, Brea, USA). HbA1c was measured by high-pressure liquid chromatography (HPLC, Menarini Diagnostics, Italy). Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula [16]. Vitamin D status, specifically 25(OH)D, was measured in serum using the DiaSorin vitamin D TOTAL competitive chemiluminescent immunoassay on an automated LIAISON analyzer (Stillwater, MN). This assay had a detection limit of 10 nM with intra- and inter-assay coefficients of variation of 6.7% and 11.6%, respectively.

Metabolic syndrome (MetS) was diagnosed according to the revised NCEP-ATP III criteria [17]. The TG/HDL-C ratio was calculated as a marker of dyslipidemia and IR [18]. The LAP index was calculated as follows:

1. $(WC \text{ (cm)} - 65) \times (TG \text{ concentration (mmol/l)})$ for men
2. $(WC \text{ (cm)} - 58) \times (TG \text{ levels (mmol/l)})$ for women [14].

The LAP index was created to describe the metabolic interplay between accumulated visceral fat and impaired triglyceride metabolism. The formula includes the minimum WC values used to define sex-specific origin points (65 and 58 cm for men and women, respectively) in the Third National Health and Nutrition Examination Survey (NHANES III).

Table 1. Clinical and biochemical characteristics of type 2 diabetes patients

Characteristic	Men (n = 189)	Women (n = 231)	p
Age (yr)	61.5 ± 13.0	56.8 ± 16.0	< 0.001
Diabetes duration (yr)	6.0 ± 1.4	5.4 ± 1.3	0.041
BMI (kg/m ²)	30.2 ± 6.9	34.0 ± 8.0	< 0.001
Waist circumference (cm)	107.4 ± 14.8	108.6 ± 15.6	NS
Systolic BP (mmHg)	135.5 ± 17.0	128.7 ± 17.5	< 0.001
Diastolic BP (mmHg)	77.6 ± 11.7	75.1 ± 9.8	0.034
Fasting glucose (mg/dl)	124.1 ± 30.7	114.9 ± 35.8	0.006
HbA1c (%)	6.4 ± 0.9	6.4 ± 1.0	NS
TC (mg/dl)	178.2 ± 40.0	192.2 ± 43.7	< 0.001
HDL-C (mg/dl)	44.3 ± 12.2	52.7 ± 14.0	< 0.001
LDL-C (mg/dl)	103.2 ± 35.4	112.2 ± 38.3	0.016
Triglycerides (mg/dl)	142.1 ± 90.0	129.2 ± 61.8	0.089
AST (U/I)	24.1 ± 12.0	22.4 ± 10.1	NS
ALT (U/I)	27.8 ± 17.4	25.6 ± 14.1	NS
TG/HDL-C	3.6 ± 2.8	2.7 ± 1.7	< 0.001
Creatinine (mg/dl)	0.9 ± 0.2	0.8 ± 0.2	< 0.001
25 (OH)D (ng/ml)	18.2 ± 9.3	17.7 ± 9.2	NS
LAP index	74.0 ± 42.7	70.0 ± 52.3	NS

Legend: Data are means ± SD. **Abbreviations:** 25(OH)D- 25-hydroxyvitamin D; ALT: -alanine aminotransferase; AST - aspartate aminotransferase; BMI - body mass index; BP- blood pressure; HbA1c - glycated hemoglobin; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LAP - lipid accumulation product; TC - total cholesterol; TG - triglycerides.

Statistical analysis

Data are expressed as mean ± SD. All statistical analyses were performed separately in both T2D and obese female and male subjects since LAP index is a sex-specific measure. Group differences for continuous variables were examined using unpaired Student *t*-tests. Fasting triglyceride levels were log-transformed because values were not normally distributed. In all analyses, a p-value of <0.05 was considered as statistically significant.

Univariate linear regression analysis was performed to evaluate the association between serum 25(OH)D levels and BMI, waist circumference, and LAP, adjusted for confounding factors. A logistic regression analysis, adjusted for age, BMI, waist circumference, and smoking habit as covariates was performed to assess the risk of vitamin D deficiency (<20 ng/ml) and diagnosis of MetS or the higher quartile of LAP, considered as a dichotomous variable. All statistical analyses were performed using SPSS 19.0.

Results

Of the 420 T2D patients enrolled (55% females), 48% were treated with hypertensive drugs, 23% with acetylsalicylic acid (ASA) and 33% with lipid-lowering drugs. The patients received the following anti-diabetic therapy:

1. Non-insulin hypoglycemic agents only (84.8%)
2. Insulin only (2.0%)
3. Combination of insulin and other drugs (13.2%)

Of the patients studied, 85.5% were overweight/obese (88.2% females and 82.2% males) and 64.0% were diagnosed with MetS (64.4% females and 63.7% males). Considering data from the obese group, we found that 40.6% had MetS (40% of women and 42.4% of men), 10% took hypertensive and 4.0% lipid drugs.

Tables 1 and 2 summarize the anthropometrical and biochemical parameters of the T2D and obese non-diabetic control subjects, respectively. In **Table 1**, women had higher BMI, total cholesterol, HDL and LDL cholesterol, and a significantly lower age. We also found that women had lower duration of diabetes ($p < 0.05$), blood pressure, fasting glucose, serum creatinine, and TG/HDL-C ratio ($p < 0.001$). Conversely, no significant differences were found in WC, TG concentrations, transaminases, and LAP levels between men and

Table 2. Clinical and biochemical characteristics of obese non-diabetic subjects

Characteristic	Men (n = 76)	Women (n = 74)	p
Age (yr)	49.4 ± 14.1	46.0 ± 14.0	0.056
Diabetes duration (yr)	-	-	
BMI (kg/m ²)	31.0 ± 4.3	34.2 ± 3.6	0.043
Waist circumference (cm)	110.2 ± 7.6	108.4 ± 8.5	NS
Systolic BP (mmHg)	133.2 ± 16.2	119.6 ± 13.8	0.02
Diastolic BP (mmHg)	78.6 ± 13.3	72.4 ± 9.2	0.044
Fasting glucose (mg/dl)	96.2 ± 11.3	93.4 ± 12.4	NS
HbA1c (%)	-	-	
TC (mg/dl)	203.0 ± 43.5	206.1 ± 45.5	NS
HDL-C (mg/dl)	39.9 ± 7.6	52.7 ± 14.3	< 0.001
LDL-C (mg/dl)	118.3 ± 51.7	125.2 ± 39.3	NS
Triglycerides (mg/dl)	180.9 ± 61.6	132.3 ± 68.7	0.038
AST (U/I)	22.3 ± 7.7	22.9 ± 12.9	NS
ALT (U/I)	30.0 ± 18.0	27.0 ± 17.5	NS
TG/HDL-C	4.8 ± 4.6	2.8 ± 1.9	0.005
Creatinine (mg/dl)	1.0 ± 0.2	0.8 ± 0.2	0.001
25 (OH)D (ng/ml)	16.0 ± 8.3	18.1 ± 8.5	0.041
LAP index	106.8 ± 91.1	76.3 ± 39.7	0.027

Legend: Data are means ± SD. **Abbreviations:** 25(OH)D- 25-hydroxyvitamin D; ALT- alanine aminotransferase; AST - aspartate aminotransferase; BMI - body mass index; BP- blood pressure; HbA1c - glycated hemoglobin; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LAP - lipid accumulation product; TC - total cholesterol; TG - triglycerides.

women. With respect to vitamin D levels, no significant differences were found between the two sexes.

Table 2 shows that there were significant gender differences in BMI, blood pressure, HDL-C, TG, alanine aminotransferase (ALT), TG/HDL-C, and creatinine. Vitamin D was significantly higher ($p < 0.05$) in females, while LAP levels were higher in men ($p < 0.05$). We divided the 25(OH)D concentrations into three classes:

1. Normal levels (>30 ng/ml)
2. Mild deficiency (20-30 ng/ml)
3. Moderate-to-severe deficiency (<20 ng/ml)

According to these three classes, we found a moderate-to-severe vitamin D deficiency in 63.0% and a mild deficiency in 27.3% of the T2D patients. In the obese control group, we observed a moder-

ate-to-severe vitamin D deficiency in 71.3% and a mild deficiency in 18.0%. In 9.7% of T2D and 10.7% obese subjects the levels of 25(OH)D were normal.

Dividing for gender, a mild vitamin D deficiency was statistically significant between females and males in the T2D and obesity group (25.5% vs. 29.0%, $p < 0.05$ and 8.8% vs. 16.2%, $p < 0.001$, respectively). In the other two classes of 25(OH)D, no differences were observed in T2D patients (64.5% vs. 62.3%, and 10.0% vs. 8.7%). In obese control subjects, the moderate-to-severe deficiency was detected in 72.6% of women vs. 67.6% of men, $p < 0.05$. It was noteworthy that a severe deficiency of vitamin D (<10 ng/ml) was registered in 17.4% of T2D and 26.0% of obese patients. In T2D, Pearson correlations of 25(OH)D showed a significant ($p < 0.05$) inverse correlation with BMI ($r = -0.36$), WC ($r = -0.38$), LAP index ($r = -0.28$), triglyceride ($r = -0.136$), and TG/HDL-C ($r = -0.14$) in women. In men, vitamin D also showed a significant ($p < 0.05$) inverse correlation with BMI ($r = -0.29$), WC ($r = -0.32$), LAP index ($r = -0.28$), triglycerides ($r = -0.20$), and TG/HDL-C ($r = -0.20$). In the obese control group, we found significant Pearson correlations ($p < 0.05$) between vitamin D and BMI ($r = -0.33$), WC ($r = -0.38$), creatinine ($r = 0.26$), and LAP ($r = 0.26$) in women. In men, significant correlations were found only for WC ($r = -0.45$), HDL-C ($r = 0.56$), and LAP ($r = -0.40$). Moreover, no significant correlations were found between vitamin D and glucose levels in both obese controls and obese T2D patients.

In T2D patients, 25(OH)D levels were significantly reduced in overweight and obese individuals, compared with normal-weight patients. We found a higher prevalence of 25(OH)D deficiency in men (60.3%) than in women (48.8%, $p < 0.001$) in overweight subjects only. However, in women, obesity (BMI > 30 kg/m²) was associated with a further reduction in vitamin D levels with respect to overweight (BMI 25-30 kg/m²). In contrast, 25(OH)D levels in obese men were not different from those observed in patients with BMI 25-30 kg/m² (**Figure 1**).

After adjustment for age, vitamin D levels were inversely significant related to BMI (**Figure 2**, panel A), WC (panel B), and LAP (panel C) in both genders of T2D patients. The same trend was observed in the obese control group, where vitamin D levels were inversely correlated with BMI ($r = 0.42$, $p < 0.001$ in women and $r = 0.56$, $p < 0.05$ in men), WC ($r = 0.42$, $p < 0.05$ in women and $r = 0.57$, $p < 0.05$ in men), and LAP index ($r = 0.36$, $p < 0.05$ in women and $r = 0.38$, $p < 0.05$ in men).

When used as covariates in the same linear regression model together with age, BMI, WC, LAP, and TG/HDL-C, vitamin D levels were significantly correlated with BMI, WC, and LAP in both genders in the T2D (**Table 3**) and obese control group (**Table 4**). In contrast, TG/HDL-C was correlated with vitamin D levels ($p < 0.05$) in obese men and women, but in male T2D subjects only. Taken together, these data suggest that in both T2D and obese subjects, total fat mass and visceral obesity are critical conditions for low vitamin D levels. Dysfunctional adiposity also plays a pivotal role, since the LAP index is inversely correlated with 25(OH)D deficiency.

A logistic regression analysis was performed to explore the risk (OR with 95% confidence interval) of vitamin D deficiency (<20 ng/ml) associated with the diagnosis of MetS and the higher quartile of LAP (>100.9 and >91.0 in women and men, respectively). In T2D patients, MetS was associated with a risk of vitamin D deficiency of 1.6 (1.1-2.5, $p = 0.048$) and 1.7 (1.2-2.7, $p = 0.016$) in women and men, respectively, whereas corresponding data for the highest quartile of LAP were 2.1 (1.2-3.6, $p = 0.019$) and 3.2 (1.6-6.5, $p = 0.02$). In obese control subjects, the same trend was observed in the MetS subgroup where the OR was 1.3 (1.1-2.2, $p = 0.043$) for women and 1.6 (1.1-2.5, $p = 0.022$) for men, while the analysis of the highest quartile of the LAP index (>106.6 in women and >115.4 in men) showed that the OR was 2.2 (1.2-3.7, $p = 0.018$) in women and 3.3 (1.7-6.7, $p = 0.01$) in men.

Discussion

The proportion of diabetic subjects with vitamin D deficiency in the present study was quite remarkable. Similar patterns were provided by other studies involving samples with T2D patients [19]. The association of T2D with lower vitamin D levels has been described previously [20]. This phenomenon does not seem to be a consequence of hyperglycemia. In contrast, no correlation was observed in the present study between glycated hemoglobin and vitamin D levels. In accordance with this result, no correlation between fasting glycemia and

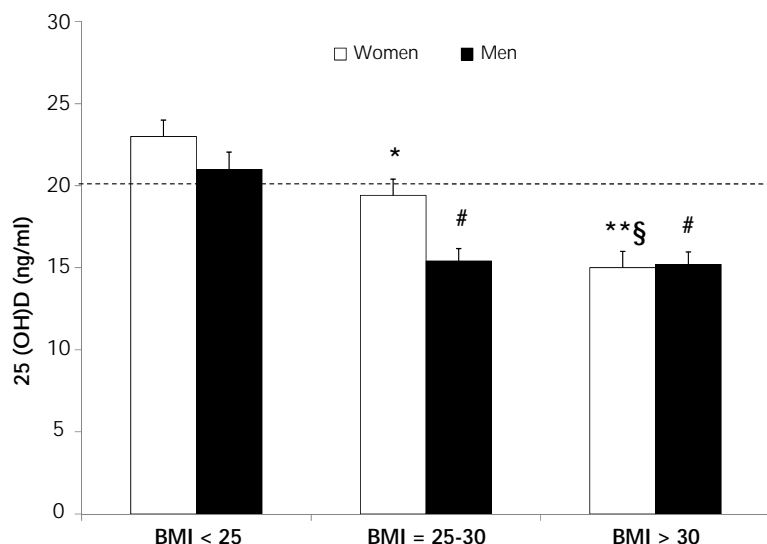


Figure 1. Vitamin D concentrations in men and women and different body mass index levels. The dotted line represents the threshold for 25(OH)D deficiency. Data are expressed as means \pm SD. Abbreviations: 25(OH)D - 25-hydroxyvitamin D, BMI - body mass index. * $p < 0.05$. ** $p < 0.001$ vs. BMI < 25. # $p < 0.05$ vs. BMI < 25. § $p < 0.05$ vs. BMI 25-30 (males).

vitamin D was found in non-diabetic obese control subjects.

The present study confirms the well-known association of obesity with vitamin D deficiency [21]. In addition, lower levels of vitamin D were observed in patients with higher WC and with MetS, again confirming the previous observations [22]. Interestingly, these associations could even be found in a specific population, such as T2D patients, who are characterized by elevated levels of visceral fat accumulation and who are frequently affected by MetS.

The fact that circulating vitamin D levels are lower in obese subjects is not surprising. In fact, liposoluble vitamins, such as vitamin D, are accumulated mainly in adipose tissue, so that an increase in adipose mass determines a relevant augmentation of the distribution volume. However, visceral fat seems to have a much greater impact on vitamin D levels than subcutaneous fat [23]. In the present study, elevated WC was associated with vitamin D deficiency even after adjustment for BMI. It is important to bear in mind that BMI is only an indirect index of overall fat mass; it is also influenced by other components, such as muscle and bone mass. We should also recall that WC is only a surrogate index of visceral fat mass. Despite these limitations, the present re-

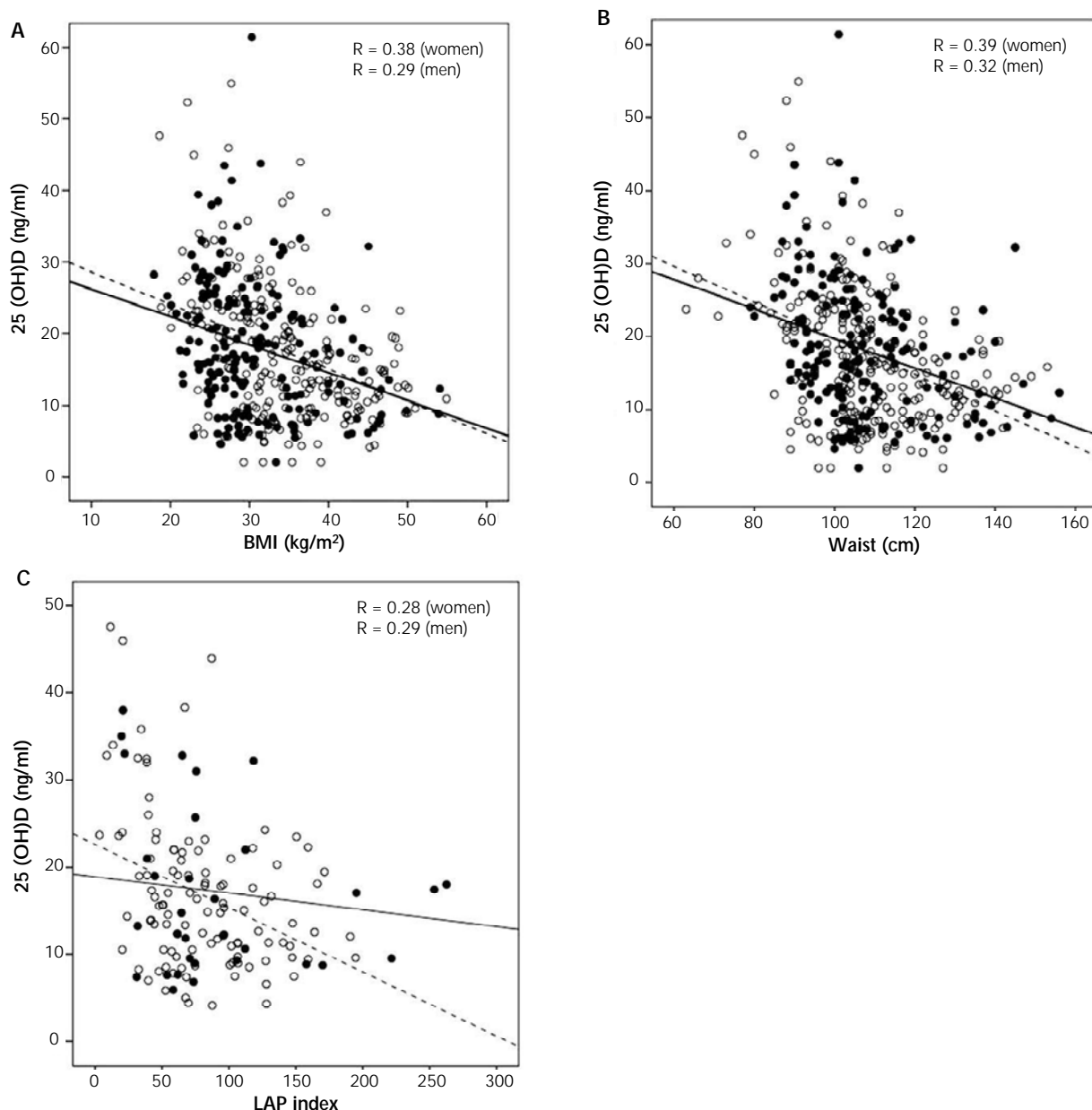


Figure 2. Linear regression plot for the relation of 25-hydroxy-vitamin D levels to body mass index (panel A), waist circumference (panel B), and lipid accumulation product (panel C) in women (open circles and dotted lines) and men (black circles and continuous lines). *Abbreviations:* 25(OH)D - 25-hydroxyvitamin D, BMI - body mass index, LAP - lipid accumulation product.

sults strongly suggest a specific role of visceral fat in the regulation of circulating vitamin D levels in diabetic patients.

Interestingly, we showed that vitamin D deficiency in T2D overweight individuals (BMI 25-30 kg/m²) occurs to a greater extent in men than in women. It can be speculated that, in this BMI

range, the accumulation of visceral fat is, on average, greater in the male gender with a significant higher prevalence of pathological WC (54.8% vs. 44.2%). These data have been convincingly demonstrated by Cheng and colleagues in the Framingham cohort, where vitamin D deficiency was highly correlated with adiposity measures as

Table 3. Linear regression coefficients between vitamin D levels and age, BMI, waist, TG/HDL-C, and LAP in type 2 diabetes subjects

Characteristic	Men		Women	
	Beta	p	Beta	p
Age	-0.095	NS	-0.9	NS
BMI	-0.29	< 0.001**	-0.39	< 0.001**
Waist	-0.33	< 0.001**	-0.25	< 0.001**
TG/HDL-C	-0.23	0.005*	-0.16	0.064
LAP index	-0.18	0.032*	-0.15	0.035*

Legend: BMI - body mass index; LAP - lipid accumulation product; TG - triglycerides; HDL-C - high-density lipoprotein cholesterol.

Table 4. Linear regression coefficients between vitamin D levels and age, BMI, waist circumference, TG/HDL-C, and LAP in obese control subjects

Characteristic	Men		Women	
	Beta	p	Beta	p
Age	-0.24	NS	-0.092	NS
BMI	-0.38	< 0.039*	-0.33	< 0.041*
Waist	-0.45	< 0.026*	-0.38	< 0.001**
TG/HDL-C	-0.14	0.047*	-0.17	0.044*
LAP index	-0.28	0.031*	-0.26	0.027*

Legend: BMI - body mass index; LAP - lipid accumulation product; TG - triglycerides; HDL-C - high-density lipoprotein cholesterol.

sessed by computed tomography and more prevalent in subjects with high visceral and low subcutaneous fat, although no analysis of gender differences has been reported [23].

In the last years, a connection has been established between the simple term “visceral obesity” and the concept of “dysfunctional adiposity”, which includes the idea that abdominal fat depots are frequently associated with impaired lipid/glucose metabolism. The LAP index is a simple, inexpensive, and easy to compute measure; it can be a useful estimator of individuals with dysfunctional adiposity at high risk for cardiovascular disease [24]. A strong association between LAP index, MetS, and IR has been reported in both healthy and T2D subjects [25]. However, in this study, we are the first to describe that the LAP index is more strongly associated with low vitamin D levels than with MetS both in T2D and obese non-diabetic subjects. These data suggest that the LAP index could be a more sensitive measure to identify indi-

viduals with dysfunctional adiposity and at high risk for vitamin D hypovitaminosis.

Interestingly, the LAP index also shows a significant negative association with vitamin D levels after adjustment for BMI and WC. Considering that insulin-resistant subjects have higher LAP levels, lower vitamin D concentrations could either account for an effect of vitamin D on insulin sensitivity [26] or an action of insulin on vitamin D metabolism in these patients [27]. It is also possible that low vitamin D levels in insulin-resistant subjects are due to a reduction in vitamin D-binding protein, which has been previously described in subjects with impaired insulin sensitivity [28]. A limitation of this study is thus the unavailability of measurements for vitamin D-binding protein and IR.

Some authors have suggested a possible beneficial effect of vitamin D supplementation on IR or other parameters of glucose metabolism [29, 30], although others disagree [31-34]. It is also possible that other metabolic pathways [35], independent of insulin action, link visceral adipose tissue and lipid profile with 25(OH)vitamin D. Therefore, it has been suggested that the hypertriglyceridemia associated with vitamin D deficiency may be a consequence of a direct effect of vitamin D itself on lipoprotein-lipase activity [7]. Thus, it can be speculated that the association of increased abdominal fat mass and high triglycerides could be synergic, which would explain the low circulating levels observed in these patients.

This study has several limitations. Firstly, the study lacks specific IR data. Secondly, visceral and subcutaneous fat have not been quantified using specific methods. Thirdly, the determination of one triglyceride may be an insufficient basis for calculating the LAP index. It should also be taken into account that lipid-lowering drug treatments may have affected the calculation of the LAP index. Also, vitamin D levels were measured with immunoassay instead of the more reliable methods of mass spectrometry. Finally, several lifestyle factors which are difficult to assess, but relevant for vitamin D metabolism (e.g., eating habits, physical activity, time spent outside) have not been measured in the present study. Although all overweight and obese patients were recommended to restrict food intake and increase physical activity, preferentially outdoors, those factors could have acted as confounders.

In conclusion, in patients with T2D, vitamin D deficiency occurs frequently and is highly associated with dysfunctional adiposity. Patients with higher LAP levels have a high risk of 25(OH)D de-

ficiency, suggesting that this dysfunctional adiposity, readily identifiable by the LAP index, is a worsening factor for vitamin D hypovitaminosis.

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