Journal of Diabetes and Treatment
Ly-Liu D, et al. J Diabetes Treat 6: 1093.
www.doi.org/10.29011/2574-7568.001093
www.gavinpublishers.com

Research Article

Prevalence of Low Vitamin D Levels and Metabolic Syndrome in Patients Attending Consultation at a Tertiary Level Hospital

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Citation: Ly-Liu D, Becerra-Fernández A, Aguilar-Vilas MV, Pérez-López G, Ly-Pen D (2021) Prevalence of Low Vitamin D Levels and Metabolic Syndrome in Patients Attending Consultation at a Tertiary Level Hospital. J Diabetes Treat 6: 1093. DOI: 10.29011/2574-7568.001093

Received Date: 22 November, 2021; **Accepted Date:** 26 November, 2021; **Published Date:** 29 November, 2021

Abstract

Background and Aim: Vitamin D is involved in multiple metabolic alterations that affect adiposity, glycemic control and cardiovascular risk factors. Cardiovascular Diseases (CVD) are the leading cause of global mortality. The aim of the study is to investigate the prevalence of low levels of vitamin D and Metabolic Syndrome (MS) in our population, and which cardiovascular markers and diseases are related to vitamin D deficiency.

Methods and Results: Descriptive cross-sectional study of patients attending endocrinology consultations at Ramón y Cajal Hospital, from March 2015 to May 2017. A total of 234 patients were included, 49.1% had vitamin D deficiency and 53.8% had MS. Increased waist circumference was the factor with the highest prevalence (61.74%) in individuals with vitamin D levels <20 ng/ml compared to the rest of the groups ($p<0.05$). The decrease in HDL cholesterol, glycated hemoglobin and insulin resistance were the cardiovascular markers related to vitamin D deficiency ($p <0.05$). The CVD associated with low levels of vitamin D were type 2 diabetes mellitus (T2DM) ($p<0.02$), acute myocardial failure ($p<0.01$) and coronary revascularization ($p<0.005$). All these conditions were associated with men ($p<0.05$).

Conclusions: Patients with MS had significantly lower vitamin D values than those without MS. Vitamin D deficiency is related to the development of major cardiovascular events in relation to T2DM pathogenesis, from microvascular alterations to the latter macro vascular processes. The therapeutic and nutritional approach to central obesity, HDL-cholesterol levels and diabetes metabolism markers, with an elevation of vitamin D, would decrease the prevalence of MS and CVD.

Keywords: Prevalence; Vitamin D deficiency; Metabolic syndrome; Type 2 diabetes mellitus; Cardiovascular diseases; Cardiovascular markers; Metabolism markers; Waist circumference; HDL cholesterol; Glycated hemoglobin; Insulin resistance; Acute myocardial failure; Coronary revascularization

Introduction

The main function of vitamin D is to maintain calcium and phosphorus levels within physiological levels that allow metabolism, neuromuscular transmission and bone mineralization

[1]. Vitamin D is gaining mounting importance in the physiopathogenesis of metabolic alterations that affect adiposity and the imbalance of glycemic control and Cardiovascular Risk Factors (CVRF). Therefore, low levels of vitamin D could be related to an increase in the prevalence of the Metabolic Syndrome (MS) and the presence of Cardiovascular Diseases (CVD).

The term MS is the most accepted term to describe the set of CVRF that are related to metabolic alterations, identifying those people with a higher risk of developing CVD or T2DM [2]. This concept is useful to carry out an integrative management, diagnosis and treatment of a group of diseases (such as obesity, carbohydrate intolerance, T2DM, dyslipidemia and hypertension) that may develop based on genetic susceptibility combined with overeating and physical inactivity. Some research implicates a vitamin D deficiency in the cause and phenotype of MS. There is not a clear statement about the association between vitamin D and MS, their components, CVD and mortality. The mechanism of hypovitaminosis D as a risk factor for the MS and their consequences remain unclear. However, the nature of this relationship in the different subgroups is not elucidated [3-5].

Taking into account that CVDs are the main cause of death, according to the World Health Organization [6], it would be of vital importance to detect the population most susceptible to developing these diseases in order to carry out prevention and treatment measures if necessary. In addition, vitamin D levels are influenced by different factors such as seasonality and nutritional status. We will study if these situations are related with vitamin D levels, and the effects of vitamin D supplementation. The aim of this study was to stablish the relationship between low vitamin D levels with MS and CVDs, in patients who went for medical consultation in a tertiary hospital in Madrid.

Methods

Study design: It is a descriptive cross-sectional study. The inclusion period was from March 2015 to May 2017. Inclusion criteria were patients above 18 years old who attended the general endocrinology department consultations at Ramón y Cajal University Hospital. Exclusion criteria was age under 18 years. A total of 234 patients were recruited. Authorization was obtained from the Ethics and Research Committee at University of Alcalá.

Studied variables: Demographic variables were studied, including the sex of the patient and their age in years. We also recorded the different anthropometric measurements reflected in the patient's medical history at the time of the analytical extraction: weight (kg), height (m), Body Mass Index (BMI), waist and hip circumference (cm). To define the obesity degree according to the BMI in adults, the SEEDO (Spanish Society for the Study of Obesity) criteria have been followed [7]. Other diseases and habits recorded in the patient's medical history were considered, including: history of tobacco and/or alcohol consumption, hypertension, T2DM, dyslipidemia, obstructive sleep apnea syndrome, previous coronary infarction, episodes of angina, congestive heart failure (CHF), coronary revascularization, presence of cerebrovascular disease and osteoporosis.

Vitamin D levels were categorized as follows [8]: deficiency (values below 20 ng/ml or 50 nmol/l); insufficient (levels between 20 to 30 ng/ml or 50 to 75 nmol/l); optimal (above 30 ng/ml or 75 nmol/l). Intoxication limits are considered above 150 ng/ml or 375 nmol/l. In addition to vitamin D levels, we also collected data on different biochemical variables that could be related to the different CVRF, liver, kidney, hormonal, metabolic, inflammatory, and hemostatic profile. Regarding the treatment with vitamin D supplements, the dosage and treatment duration with ergocalciferol/cholecalciferol were recorded. These data were extracted retrospectively according to the evolution of the patient's medical history during the control visits to the consultation. Malnutrition status was determined using the CONUT screening tool ("Nutritional Control Index") [9], which is a simple and automated method, based on three analytical parameters: albumin, total lymphocytes and total cholesterol.

For the diagnosis of MS, we used the criteria of the unified definition by the IDF (International Diabetes Federation) and the AHA/NHLBI ATP-III [10]. The presence of 3 of the 5 criteria listed below defines a diagnosis of MS: a) waist circumference greater than 102 cm in men, and in women > 88 cm; b) TG elevation or pharmacological treatment for TG elevation ≥ 150 mg/dl (1.7 mmol/l); c) decrease in HDL-C or pharmacological treatment to increase HDL-C concentrations in men <40 mg/dl (0.9 mmol/l) and in women <50 mg/dl (1.1 mmol/l); d) elevation of blood pressure (systolic ≥ 130 mmHg and / or diastolic ≥ 85 mmHg) or pharmacological treatment for HT; and e) fasting blood glucose or pharmacological treatment for hyperglycemia ≥ 100 mg/dl.

Statistical analysis

A sample size estimation was performed. According to the literature [11], it is assumed that the prevalence of vitamin D deficiency in the study population will be 55%. Therefore, accepting an α risk of .05 and a β risk of .2 in a bilateral contrast, 123 subjects are required in the group of patients with deficits and 100 in the group of patients with no deficits, to detect the difference between the deficit as statistically significant. The proportion of cases with MS is expected to be 44% for the deficit group and 26% for the non-deficit group.

For the descriptive analysis, frequencies and percentages were used for the qualitative variables, as well as the mean and Standard Deviation (SD) or the median and the interquartile range for the quantitative variables.

To analyze the association between qualitative variables, the χ^2 test or Fisher's exact test was used. To study the relationship between quantitative variables and dichotomous qualitative variables, the t-test or Wilcoxon's non-parametric test have been used, and to analyze the relationship between quantitative variables with polytomous qualitative variable, the analysis of variance with multiple comparisons of Scheffe, or the non-parametric Kruskal-Wallis test.

Factors associated with low levels of vitamin D have been studied, both considering levels <20 vs. ≥20, as levels ≤30 vs. > 30, using the logistic regression model. Firstly, univariate analyzes were carried out to verify the individual association of each of the factors with low levels of vitamin D. Secondly, multivariate analyzes were proposed, considering as possible independent variables of the model those with $p < 0.10$ in the univariate analyses. In the final multivariate model, only those who achieved a $p < 0.05$ were maintained. The data are presented using odds ratio (OR) with the 95% confidence interval. The predictive capacity of the model has been evaluated using the area under the ROC curve (AUC) [12].

A significant result has been considered for $p < 0.05$. All analyzes were performed using the SAS System for Windows program, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Two hundred and thirty-four patients were recruited, 124 were women (53%) and 110 men (47%). The mean age was 58.7 years, with a SD ± 13.3. Vitamin D deficiency levels (less than 20 ng/ml) are present in 115 patients (49.1%). Insufficient levels of vitamin D (between 20 and 30 ng/ml) in 73 patients (31.2%). Finally, 46 patients (19.6%) achieved optimal levels of vitamin D.

Of our 234 patients included, 126 met the MS criteria, representing 53.8% of our sample. Patients without MS were 108, the 46.1% of them. There was a statistically difference in males regarding vitamin D deficiency and MS prevalence ($p < 0.05$).

Considering vitamin D as a continuous variable, the mean value of vitamin D is higher among individuals without MS than in those diagnosed with MS (24.3 ng/ml vs. 20.6 ng/ml), these differences were statistically significant ($p = 0.0310$) (Table 1). Regarding the results of the logistic regression, it is observed that whenever the vitamin D level increases, the probability of MS decreases significantly (OR = 0.98; $p = 0.0319$). Regarding the results of categorized vitamin D, the percentage of MS increases as the level of vitamin D decreases. In relation to the results of the logistic regression, it is also observed how the risk of MS increases as the levels of vitamin D decrease, reaching significance when vitamin D < 20 ng/ml with respect to those of > 30 ng/ml (OR = 2.06; $p = 0.0420$).

	No SM	SM	p	OR (CI 95%)	p
Vit.D, mean (SD)	24.35 (13.93)	20.62 (11.91)	0.0310	0.98 (0.96 – 0.99)	0.0319
Vit. D groups			0.1219		
n (%)					
< 20 ng/ml	47 (40.87)	68 (59.13)		2.06 (1.03 – 4.12)	0.0420
20 – 30 ng/ml	34 (46.58)	39 (53.42)		1.63 (0.77 – 3.44)	0.1990
>30 ng/ml	27 (58.70)	19 (41.30)		Ref.	
SD = Standard deviation; OR = Odds ratio; CI = Confidence interval; Ref. = Reference group.					

Table 1: Relationship between vitamin D serum levels and MS.

The relationship between vitamin D groups and sex was studied for treatment with vitamin D supplements. For vitamin D levels < 20 ng/ml, there is a higher percentage of women in treatment. In addition, the largest number of patients with vitamin D levels < 20 ng/ml have received higher doses with statistical difference ($p = 0.0195$), being 28.3% of women with the highest doses compared to 7.2 % (Table 2). There is also a higher prevalence of patients receiving high doses of vitamin D among those with adequate levels of vitamin D, being 46.15% women, and 20% men, although no statistical difference ($p = 0.0526$) was found in this case.

Vit. D groups	< 20 ng/ml			20-30 ng/ml			30-150 ng/ml		
Sex n (%)	Doses UI/d								
	400	800	1066	400	800	1066	400	800	1066
Female	1 (1.57)	1 (1.57)	17 (28.33)	1 (2.63)	0	5 (13.16)	2 (7.69)	0	12 (46.15)
Male	0	2 (3.64)	4 (7.27)	0	0	1 (2.86)	0	0	4 (20)
p	0.0195			0.1645			0.0526		

Table 2: Comparative analysis between vitamin D groups and sex, related to vitamin D supplements.

To assess the prevalence of the different levels of vitamin D in relation to the seasonality, the different months of the year were divided into quarters (Table 3). In the data analyzed, the lowest levels of vitamin D are detected during the months from December to May. As the months go by, the proportion of subjects with levels > 30 ng/ml increases, reaching the maximum difference from September to November, finding statistically significant differences (p > 0.001).

Months	December - February	March - May	June - August	September - November	p
Vit. D groups, n (%)					<0.001
< 20 ng/ml	25 (71.43)	48 (73.85)	22 (37.29)	20 (26.67)	
20 – 30 ng/ml	9 (25.71)	10 (15.38)	26 (44.07)	28 (37.33)	
> 30 ng/ml	1 (2.86)	7 (10.77)	11 (18.64)	27 (36)	

Table 3: Vitamin D levels throughout the months.

It was possible to assess the nutritional status in 78 patients according to the CONUT criteria. Among these patients, 44 (56.4%) had vitamin D levels <20 ng/ml. Mild malnutrition was detected in 16 patients (20.5%), half of them had vitamin D levels <20 ng/ml. It was detected only one case with moderate malnutrition, presenting vitamin D levels <20 ng/ml. However, no relationship was found between vitamin D levels and malnutrition (p = 0.8165).

Elevated waist circumference was the most prevalent MS criteria in vitamin D deficiency, statistically significant difference (p <0.001) was found between the group with the highest and lowest vitamin D levels (Table 4). There were no differences in the rest of the criteria, but a tendency of higher prevalence of presenting them was found as vitamin D levels decreased.

Vitamin D levels (ng/ml)	< 20[a]	20-30[b]	>30[c]	p
MS Criteria n (%)				
1. Elevated waist circumference	71 (61.74)[c]	35 (47.95)[c]	11 (23.91)[a,b]	<0.001
2. Elevated TG or drug treatment for elevated TG	66 (57.39)	39 (53.42)	22 (47.83)	0.5374
3. Reduced HDL-C or drug treatment for reduced HDL-C	76 (66.09)	44 (60.27)	23 (50)	0.1645
4. Elevated blood pressure or drug treatment for hypertension	46 (40.00)	26 (35.62)	16 (34.78)	0.7557
5. Elevated fasting glucose or drug treatment for elevated fasting glucose	65 (56.52)	48 (65.75)	21 (45.65)	0.0949
[abc]Indicate multiple Scheffe comparisons among groups.				

Table 4: Relationship between MS criteria and categorized vitamin D levels.

Reduced HDL cholesterol (HDL-C) was the overall most prevalent MS criteria (61.11%), following hyperglycemia (57.6%), hypertriglyceridemia (54.27%), increased waist circumference (50%) and hypertension (37.61%).

When comparing CVRF markers in relation with the different vitamin D groups, statistically significant differences (p <0.05) were found between low levels of vitamin D groups and adequate vitamin D level group. These CVRF markers are: HDL-cholesterol (HDL-C), Glycated hemoglobin (HbA1c) and Insulin Resistance (IR) measured by HOMA (Table 5). Thus, lower levels of vitamin D are associated with lower levels of HDL-C, higher levels of HbA1c and greater values of IR. No statistically significant differences were found between vitamin D levels and calcium or parathyroid hormone (p >0.05).

Vitamin D groups	**<20 ng/ml [a]** (n = 115)		**20-30 ng/ml [b]** (n = 73)		**>30 ng/ml [c]** (n = 46)		
Quantitative variables	Mean	SD	Mean	SD	Mean	SD	p
HDL cholesterol (mg/dl)	50.75[c]	12.56	51.39[c]	21.3	60.75[a,b]	29.02	0.0209
LDL cholesterol (mg/dl)	108.74	31.36	112.44	28.20	116.18	37.54	0.6801
Triglyceride (mg/dl)	125.65	77.46	130.03	73.7	116.38	65.49	0.5124
Glycated hemoglobin (%)	6.48[c]	1.55	6.54[c]	1.50	5.95[a,b]	1.18	0.0260
HOMA-Insuline resistance	2.62	1.47	4.30[c]	3.09	2.35[b]	1.74	0.0396
Calcium (mg/dl)	9.40	0.78	9.45	0.48	9.62	0.54	0.1511
Parathyroid hormone (pg/ml)	74.94	37.29	69.37	33.46	70.08	43.02	0.3867
[abc]Indicate multiple Scheffe comparisons among groups.							

Table 5: Comparison of quantitative variables between Vitamin D groups.

Regarding the relationship of vitamin D levels with CVD (Table 6), the percentage of individuals with T2DM increases in those with low vitamin D levels. Furthermore, vitamin D levels <20 ng/ml showed a greater prevalence (10.4%) of suffering from acute myocardial infarction (AMI) and coronary revascularization. No statistically significant differences were found between the different levels of vitamin D and the presence of the rest of studied diseases. There was a statistically difference in males regarding increased waist circumference, reduced HDL-C, higher levels of HbA1, greater values of IR, T2DM, AMI and coronary revascularization (p<0.05).

Vit. D groups (ng/ml)	**< 20[a]**	**20-30[b]**	**>30[c]**	**p**
Disease, n (%)	**(n=115)**	**(n=73)**	**(n=46)**	
Hypertension	44 (38.60)	24 (32.88)	17 (36.96)	0.7284
T2DM	43 (37.39)	34 (46.58)[c]	10 (21.74)[b]	0.0240
Dyslipidemia	57 (49.57)	33 (45.21)	18 (39.13)	0.4776
AMI	12 (10.43)[b]	1 (1.37)[a]	1 (2.17)	0.0183
Angina	10 (8.70)	3 (4.11)	2 (4.35)	0.3732
Revascularization	12 (10.43)[b,c]	1 (1.37)[a]	0 (0)[a]	0.0056
Heart failure	5 (4.35)	4 (5.48)	2 (4.35)	0.9307
Cerebrovascular disease	9 (7.83)	2 (2.74)	0 (0)	0.0671
[abc] indicate multiple Scheffe comparisons among groups.				

Table 6: Frequency of cardiovascular diseases in relation to the different levels of vitamin D.

A multivariate analysis was carried out to study the combination of factors that could be associated with low levels of vitamin D. In the first multivariate analysis, the variables associated with vitamin D levels <20 ng/ml were coronary revascularization and the presence of cerebrovascular disease (CEVD). Patients who underwent for coronary revascularization are 13.6 times more likely to have serum vitamin D content <20 ng/ml than those without revascularization (OR = 13.699; CI 95%= 1.743-107.649; p = 0.0128). Regarding the history of CEVD, these patients are 4.9 times more likely to present vitamin D levels <20 ng/ml than those without CEVD (OR = 4.940; 95% CI= 1.028-23.735; p = 0.0461). From this analysis, it is worth highlighting as a limitation to the few cases that exist, the wide confidence interval for the OR, probably due to the few cases registered (13 in the case of revascularized patients (5.5%) and 11 in those with CEVD). In the multivariate analysis for vitamin D levels ≤ 30 ng/ml, the presence of DM and obesity are associated with these levels ($p < 0.05$). T2DM increases the risk of vitamin D levels ≤ 30 ng/ml (OR = 2.74; 95% CI = 1.005-4.705), and obese patients had 2.6 times the probability of presenting these low levels of vitamin D (OR = 2.679; 95% CI = 1.171-6.130). In the analysis of BMI and vitamin D, according to the SEEDO classification, no statistically significant differences were found (p = 0.0513).

Discussion

The prevalence of vitamin D deficiency was 49.1% in this study. The global rate of vitamin D <20 ng/ml in Europe is 40.4% [13]. Despite an apparently sunny weather in Spain, Spanish levels of vitamin D are similar to the European ones. This can be explained by the fact that endogenous synthesis is not capable of compensating the low dietary intake (most of Spain is above the parallel 35ºN (Madrid at 40.41ºN), where the skin's production capacity of vitamin D in non-sunning months is scarce [14]. The prevalence of MS was 53.8%. This percentage is higher than other studies in Madrid (36.1%), in patients who attended a health center [15] and the Spanish general prevalence, which according to different studies is between 31% and 22.7% [16,17]. This difference may be explained because the patients came from a specific endocrinology consultation, and not from the general population. The relationship between low levels of vitamin D and MS found in our study, follows the tendency of other studies [11,18,19].

According to vitamin D supplementation, the highest supplementation rates were observed in patients with serum concentrations lower than 20 ng/ml and a higher proportion of women taking supplementation was detected (28.3% women versus 7.27% men; p = 0.01). It is of interest that this coincides with a higher prevalence of MS in men with vitamin D deficiency. Thus, an adequate supplementation with vitamin D would improve the prevalence of MS. In patients with supplemented vitamin D levels > 30 ng/ml, 46.1% were women and 20% of men (p = 0.05) who received the same doses as in the previous group (1066 IU per day). The explanation of the different levels of vitamin achieved for the same dosage is the treatment duration, being 360 days for the former group and 180 for the latter. Monitoring vitamin levels should be followed during supplementation in order to avoid toxicity and adequate treatment. Although the exact dose of vitamin D required has not been established, there is evidence that its supplementation coincides with increases in vitamin D levels [20]. Therefore, in the sample studied it could be an indicator of insufficient supplementation and the need for a higher vitamin intake [21-23].

Winter months had the maximum prevalence of vitamin D levels < 20 ng/ml (71.4%). In summer months, this proportion lowers to 37.2%, with a statistically significant decrease. This trend coincides with European [13] and Spanish [24] data. The relationship between categorized vitamin D levels and months was analyzed, controlling whether or not vitamin D supplements were received. In both cases, there is still a relationship between vitamin D levels and seasonality. In other words, although no treatment with vitamin D supplements was taken, the relationship between these levels and months remains statistically significant. The factors that would have contributed to this decline have been attributed to changes in BMI, dairy intake, and sun protection [25].

Nutrition status could only be studied in 78 patients. No statistically significant differences were found between vitamin D levels and malnutrition, probably due to the low number of patients analyzed, a greater sample might be necessary to find this relationship. The inclusion of objective parameters such as CONUT are useful as screening tools, although such data are not always available. There is no single nutritional marker that can predict or diagnose malnutrition, but other conditions such as health, social and clinical status, anthropometry, eating habits and biochemical analyzes must be taken into account [26]. Therefore, it is advisable to adapt the different tools available for malnutrition screening with the specific condition of each patient [27]. These findings suggest that these patients could benefit from a serum vitamin D level screening and supplementation if deficient.

Waist circumference was the most prevalent MS criteria (61.7%) associated to vitamin D deficiency. This data has ben also found in other studies, where there is an inverse correlation between waist circumference and vitamin D levels [28]. The prevalence of MS according to the different components varies according to the different countries and sex [16,29]. In Spain, the most common combination includes changes in blood glucose, elevated blood pressure, and abdominal circumference. In the DARIOS study [16], the abdominal obesity and a decrease in HDL-C were the most frequent factors in women, while an increase in blood glucose and TG predominated among men. On the other hand, in a recent study that analyzed the population aged 60 years or older, vitamin D deficiency was more frequent in women and they presented an increase in BMI, abdominal circumference, triglycerides, insulin resistance, and TNF-α [18]. This difference could be attributed to a decrease in estrogen and its effects on glucose and lipid metabolism, as well as fat distribution. Another reason could be the different models of the studied phenotype compared to those of other studies.

Lower HDL-C levels was the most prevalent MS overall criteria (61.1%) in our study. Non-HDL cholesterol has been studied to be a better predictor of CVD than just LDL-C, HDL-C, or total cholesterol, regardless of vitamin D levels [30]. Inadequate intake of vitamin D and its high prevalence have been related to low levels of HDL-C and vitamin D deficiency and insufficiency [31], for which it would be necessary to develop specific nutritional measures as well as education programs to stimulate and facilitate the access to food sources with vitamin D, such as dairy products and fish. A systematic review [32] supported the hypothesis of a causal effect in which high levels of vitamin D favor a better lipid profile and a lower incidence of MS. Nonetheless, more studies are necessary to establish an appropriate causal relationship.

When comparing the different cardiovascular markers among different levels of vitamin D, a statistically difference was found (p=0.02) between low HDL-C levels and vitamin D deficiency. It is also remarkable that higher values of HbA1c (p=0.02) and IR measured by HOMA (p=0.03) were associated with low levels of vitamin D. The CVDs associated with vitamin D deficiency were DM, AMI and coronary revascularization. From these results, it can be found a strong relationship between low levels of vitamin D and its implication and pathogenesis of T2DM, from its early stages at a microvascular level (alterations in IR and HbA1c) until the establishment of T2DM and a further progression of the disease, developing macrovascular alterations that can be traduced in AMI and coronary revascularization events. This theory reinforces the importance of the role of vitamin D in developing T2DM and as a cardiovascular marker of T2DM, insulin resistance and HbA1c. Ganji, et al. [19], reported the importance of vitamin D levels as a factor that enhances IR showing that vitamin D levels > 30 ng/ml are associated with a decrease in biomarkers of cardiometabolic diseases. Therefore, vitamin D levels above 30 ng/ml may be related to a lower incidence of MS and DM. However, there has been an unresolved issue about vitamin D status and the risk of developing T2DM [33]. In our study, it has been possible to clarify this topic. Not only has a relationship between vitamin D and T2DM in its early stages been found, but also of its macrovascular complications in the development of CVD, such as coronary revascularization and CEVD. This hypothesis is also reinforced in the multi variant analysis. Factors associated with vitamin D levels ≤30 ng/ml were T2DM and obesity. Obesity itself was not statistically significant in our study, but when associated to T2DM, it reaches this significance $p < 0.05$. Thus, depicting the importance and relationship between vitamin D levels and T2DM.

There is some controversy whether low vitamin D levels are a cause related to the development of CVD and to what extent it is related to mortality from CVD. Our study does not allow establishing a causal relationship between mortality due to CVD and vitamin D. Based on the literature [32,34,35], vitamin D levels could be a marker of cardiovascular risk, integrated within the context of MS such as lipid profile, central obesity and IR; although hardly modifiable, since a part of the vitamin D mechanism of action, would be dependent on genetic polymorphisms.

Based on these findings, it could be considered that CVD occurs in response to an underlying condition that is worsened by vitamin D deficiency, especially due to the lack of its ability to counteract oxidative stress. There is strong evidence supporting obesity as a possible underlying confounding factor due to its high prevalence and its deleterious effect on both vitamin D levels and cardiovascular mortality [36]. Our study has its limitations, and one of them is the confounding factors. Another limitation is that it has not been possible to collect the physical activity or the dietary behavior of the population, as they were not included in the medical records as common components in patient reviews. These items should be considered in the study of CVRF [37].

Highlights

Patients with MS had significantly lower mean vitamin D values than those without MS. Vitamin D deficiency is related to the development of major cardiovascular events in relation to T2DM pathogenesis, from microvascular alterations to the latter macro vascular processes. The therapeutic and nutritional approach to central obesity, HDL-cholesterol levels and diabetes metabolism markers, together with an elevation of vitamin D would decrease the prevalence of MS and CVD.

Conflicts of Interest: The authors declare no competing interests.

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