Vitamin D Status and Parathyroid Hormone Levels in Patients with Obstructive Sleep Apnea

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Key Words

Vitamin D · Parathyroid hormone · Metabolic syndrome

Abstract

Background: Vitamin D insufficiency and high levels of parathyroid hormone (PTH) appear to be emerging risk factors for metabolic syndrome (MS), diabetes and cardiovascular disease, conditions that occur frequently in patients with obstructive sleep apnea syndrome (OSAS). **Objectives:** This study examined whether serum concentrations of 25-hydroxyvitamin D [25(OH)D] and PTH were associated with the presence of MS, diabetes and hypertension among an OSAS population. **Methods:** A total of 826 patients (635 men and 191 women) with newly diagnosed OSAS were studied. The occurrence of the MS was analyzed according to the National Cholesterol Education Program Adult Treatment Panel III clinical criteria. Serum levels of 25(OH)D, PTH, glucose, triglycerides, cholesterol, HDL cholesterol, creatinine and uric acid were determined. **Results:** In 55.3% of the men and in 63.2% of the women, the serum 25(OH)D level was less than 30 ng/ml (insufficient status). After adjusting

for age, sex and seasonality, there was a significant trend of decreasing odds for diabetes [odds ratio (OR) 0.55, 95% confidence interval (CI) 0.33–0.94, $p_{\text{trend}} = 0.038$] and MS (OR 0.34, 95% CI 0.21–0.56, $p_{\text{trend}} < 0.001$) with increasing vitamin D levels. Higher PTH levels were associated with a higher prevalence of obesity (OR 2.05, 95% CI 1.06–3.09, $p_{\text{trend}} < 0.001$) and hypertension (OR 1.83, 95% CI 1.01–3.05, $p_{\text{trend}} = 0.049$). **Conclusions:** These data suggest an inverse association of 25(OH)D with diabetes and MS and a positive association of PTH with obesity and hypertension among patients with OSAS. Based on our observational study, the causative nature of the associations cannot be established. These findings require further examination in prospective studies including clinical trials.

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder defined by the occurrence of repeated episodes of upper airway obstruction and airflow cessation

(apneas) that normally lead to arterial hypoxemia and sleep disruption [1, 2]. A number of clinical features, such as obesity, metabolic syndrome (MS) and cardiovascular disease are often present in these patients [3–5].

The recognition of the presence of widespread low vitamin D status is increasing [6–9]. The consequences of this growing epidemic of vitamin D insufficiency are still not well understood [9–11]. Vitamin D and parathyroid hormone (PTH) participate in bone metabolism and calcium homeostasis. In addition, in recent years it has become clear that vitamin D has pleiotropic effects and plays an important role in a broad range of organ functions [6]. A growing body of evidence suggests that low levels of 25-hydroxyvitamin D [25(OH)D] may be inversely associated with obesity, glucose intolerance, MS and cardiovascular disease [8, 12–15]. Vitamin D concentrations are inversely associated with surrogate measures of insulin resistance and it has been reported that administration of vitamin D improves insulin secretion. Furthermore, based on blood pressure reduction with vitamin D supplementation in patients with hypertension, levels of this vitamin have been suspected to be involved in the regulation of blood pressure [16]. Elevated PTH secondary to a low level of vitamin D may also increase the risk of developing components of MS, including hypertension, diabetes and obesity [17, 13].

In this study, we hypothesized that vitamin D status may be associated with metabolic and cardiovascular complications in patients with sleep apnea.

To test this hypothesis we evaluated the associations of 25(OH)D status and PTH concentrations with the prevalence of diabetes, hypertension and MS among an OSAS population.

Methods

Subjects and Ethics

Our study sample comprised patients newly diagnosed with OSAS consecutively admitted to the sleep unit of our institution (Hospital Universitari Son Espases, Palma de Mallorca, Spain) between January 2008 and December 2010. During an interview conducted by physicians in the sleep medicine center, information was elicited about the patient's medical history, medication and lifestyle. No participant reported taking calcium or multivitamin supplements. No participant suffered from any other chronic disease (chronic obstructive pulmonary disease, liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, osteoporosis, chronic renal failure and/or psychiatric disorders). The study was approved by the ethics committee of our institution, and all participants signed their consent after being fully informed of the goal and characteristics of the study.

Measurements and Definitions

The diagnosis of OSAS was established by full polysomnography (E-Series Compumedics, Abbotsford, Australia) that included the recording of oronasal flow, thoracoabdominal movements, electrocardiography, submental and pretibial electromyography, electrooculography, electroencephalography and the transcutaneous measurement of arterial oxygen saturation. Apnea was defined as the absence of airflow for more than 10 s. Hypopnea was defined as any airflow reduction that lasted more than 10 s and resulted in arousal or oxygen desaturation. A decrease in SaO₂ greater than 3% was considered to represent an oxygen desaturation. The apnea-hypopnea index (AHI) was defined as the sum of the number of apneas plus hypopneas per hour of sleep. Patients were classified into 2 groups according to their AHI as mild-to-moderate OSAS (AHI <30, n = 280) and severe OSAS (AHI ≥30, n = 546).

Excessive daytime sleepiness was quantified subjectively by the Epworth sleepiness scale.

The occurrence of the MS was analyzed according to the National Cholesterol Education Program Adult Treatment Panel III clinical criteria [18]: (1) waist circumference ≥102 cm in men and ≥88 cm in women, (2) fasting glucose ≥100 mg/dl, (3) triglycerides ≥150 mg/dl, (4) HDL cholesterol (HDLc) <40 mg/dl in men and <50 mg/dl in women, and (5) systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg or a patient being on specific drug treatment. The MS was diagnosed if 3 of these 5 factors were present. Diabetes was defined by use of diabetes medications or a fasting glucose of ≥126 mg/ml. Hypertension was diagnosed if SBP was ≥140 mm Hg and/or DBP was ≥90 mm Hg or the individual was on specific treatment. Participants were considered obese when their body mass index (BMI) was higher than 30.

After fasting overnight, venous blood samples were obtained between 8 and 10 a.m. Blood was centrifuged and serum was immediately separated in aliquots and stored at –80°C until analysis.

Glucose, triglycerides, total cholesterol, HDLc, creatinine and uric acid were determined by standard enzymatic methods on a Hitachi Modular analyzer (Roche Diagnostics, Ind., USA). 25(OH)D levels were quantified in duplicate using a commercial enzyme immunosorbent assay kit (IDS, Boldon, UK) with a coefficient of variation of less than 10%. The lower limit of detection was 2 ng/ml. Vitamin D was stratified into 3 categories: normal >30 ng/ml, low (insufficient) 16–30 ng/ml and very low (deficient) ≤15 ng/ml. The PTH assay was performed using a chemiluminescence assay for the measurement of intact PTH on an Advia-Centaur analyzer (Siemens Medical Solutions Diagnostics, N.Y., USA).

Statistical Analysis

Results are presented as percentages, mean ± standard deviations (SD) or median (interquartile range). Skewed variables were logarithmically transformed before analysis. Patient characteristics were compared using independent sample Student t tests for continuous measures or repeated measures ANOVA when appropriate. Categorical variables were compared using the χ^2 or Fisher tests.

Correlations between the subjects' characteristics and vitamin D and PTH levels were explored using the Spearman rank test. Multiple regression analyses were used to confirm the significant

Table 1. Characteristics of the study sample grouped according to vitamin D status

	Categories of 25(OH)D, ng/ml			P _{trend}
	≤15 (n = 105)	16–30 (n = 377)	>30 (n = 344)	
Age, years ^b	54.0 ± 12.8	53.0 ± 12.4	50.9 ± 12.4	0.008
BMI ^b	31.9 ± 5.6	32.0 ± 6.7	30.4 ± 5.5	0.002
Waist circumference, cm ^b	109.6 ± 13.4	108.4 ± 14.5	106.3 ± 13.2	0.043
AHI, h ^{-1b}	50.6 ± 30.4	47.3 ± 25.7	45.7 ± 24.4	0.092
Arousal index, h ^{-1b}	56.6 ± 27.5	54.7 ± 22.4	52.2 ± 21.4	0.056
Mean SaO ₂ , % ^b	90.4 ± 4.9	91.8 ± 4.6	92.4 ± 3.9	<0.001
Minimal SaO ₂ , % ^b	77.9 ± 10.2	79.7 ± 9.6	80.6 ± 8.7	0.013
Epworth sleepiness scale ^b	9.8 ± 5.1	10.0 ± 5.1	10.2 ± 5.3	0.462
Current smoker, n (%) ^a	32 (30.5)	93 (24.7)	91 (26.5)	0.233
SBP, mm Hg ^b	130.6 ± 19.0	132.3 ± 18.3	131.0 ± 16.4	0.777
DBP, mm Hg ^b	81.6 ± 14.0	80.3 ± 12.6	80.2 ± 12.6	0.339
Hypertension, n (%) ^a	17 (16.2)	67 (17.7)	52 (15.5)	0.118
Obesity, n (%) ^a	63 (60.4)	221 (58.9)	167 (48.5)	0.006
Diabetes, n (%) ^a	29 (27.6)	63 (16.7)	54 (15.7)	0.026
MS, n (%) ^a	56 (53.8)	139 (37.3)	112 (32.7)	0.025
MS criteria, n ^a	2.8 ± 1.2	2.2 ± 1.2	2.1 ± 1.2	<0.001

^a χ^2 linear trend test; ^b ANOVA linear trend test.

Table 2. Biochemical parameters of the study sample, grouped according to vitamin D status

	Categories of 25(OH)D, ng/ml			P _{trend}
	≤15 (n = 105)	16–30 (n = 377)	>30 (n = 344)	
Glucose, mg/dl ^a	116.4 ± 39.1	105.6 ± 24.4)	104.9 ± 21.8	0.002
Triglycerides, mg/dl ^b	214 (176–253)	157 (147–168)	147 ± (139–156)	<0.001
Cholesterol, mg/dl ^a	218 ± 52	205 ± 38	201 ± 38	0.001
HDLc, mg/dl ^a	50.7 ± 14.9	54.0 ± 18.8	53.6 ± 18.4	0.316
Creatinine, mg/dl ^a	0.89 ± 0.26	1.06 ± 0.2	0.95 ± 0.2	0.760
Uric acid, mg/dl ^a	6.2 ± 1.4	6.3 ± 3.1	6.5 ± 3.0	0.351
PTH ^{a, b}	60.9 (45.3–86.9)	53.0 (39.7–69.8)	47.8 (37.8–64.5)	<0.001

^a ANOVA linear trend test; ^b logarithmically transformed for statistics.

associations detected with adjustment for age, gender, BMI, waist circumference and MS.

Logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for obesity, diabetes, hypertension and MS across categories of 25(OH)D and tertiles of PTH after adjusting for age, sex and season of data collection: Winter (January–March), Spring (April–June), Summer (July–September) and Autumn (October–December). Models of MS components were also adjusted for the other components. The lowest group of either 25(OH)D or PTH served as the referent group.

A p value lower than 0.05 was considered significant.

Results

We studied 826 patients (635 men and 191 women) with newly diagnosed OSAS. The main clinical and biochemical characteristics are shown in tables 1 and 2.

Vitamin D levels were lower in the severe OSAS group (27.2 ± 15.6 ng/ml) than in the mild-to-moderate group (30.7 ± 14.2 ng/ml), but the difference did not reach statistical significance (p = 0.06). PTH levels were significantly higher in the severe OSAS group than in the mild-to-moderate group (58.5 ± 28.1 vs. 53.1 ± 23.6 pg/ml, p = 0.004).

Table 3. Adjusted OR and 95% CI for diabetes, obesity, hypertension and components of MS by categories of 25(OH)D among OSAS patients

	25(OH)D, ng/ml			P _{trend}
	≤15 (n = 105)	16–30 (n = 377)	>30 (n = 344)	
Diabetes ^a	1.00 (referent)	0.64 (0.37–1.01)	0.55 (0.33–0.94)	0.038
Obesity ^a	1.00 (referent)	1.24 (0.75–2.03)	0.92 (0.55–1.51)	0.314
Hypertension ^a	1.00 (referent)	1.03 (0.53–1.98)	0.87 (0.44–1.71)	0.630
MS ^a	1.00 (referent)	0.44 (0.27–0.67)	0.34 (0.21–0.56)	<0.001
High waist circumference ^b	1.00 (referent)	0.57 (0.31–1.06)	0.48 (0.25–0.89)	0.02
Hyperglycemia ^b	1.00 (referent)	0.74 (0.42–1.30)	0.75 (0.42–1.34)	0.324
Hypertriglyceridemia ^b	1.00 (referent)	0.38 (0.21–0.69)	0.37 (0.20–0.67)	<0.001
Low HDLc ^b	1.00 (referent)	0.62 (0.34–1.14)	0.47 (0.25–0.87)	0.018
High blood pressure ^b	1.00 (referent)	0.97 (0.51–1.85)	0.76 (0.39–1.49)	0.901

^a Adjusted for age, season and sex; ^b adjusted for all variables in model 1 plus other components of MS.

Table 4. Adjusted OR and 95% CI for diabetes, obesity, hypertension and components of MS by tertiles of PTH among OSAS patients

	PTH, pg/ml			P _{trend}
	≤42.7 (n = 272)	42.8–62.5 (n = 275)	≥62.6 (n = 274)	
Diabetes ^a	1.00 (referent)	1.28 (0.87–1.86)	1.23 (0.83–1.81)	0.592
Obesity ^a	1.00 (referent)	1.62 (1.12–2.32)	2.05 (1.06–3.09)	<0.001
Hypertension ^a	1.00 (referent)	1.68 (1.02–2.78)	1.83 (1.01–3.05)	0.049
MS ^a	1.00 (referent)	0.94 (0.66–1.36)	1.30 (0.92–1.98)	0.136
High waist circumference ^b	1.00 (referent)	1.84 (1.21–2.80)	1.30 (0.84–1.99)	0.238
Hyperglycemia ^b	1.00 (referent)	1.26 (0.83–1.89)	1.27 (0.83–1.95)	0.218
Hypertriglyceridemia ^b	1.00 (referent)	0.85 (0.56–1.28)	0.88 (0.57–1.37)	0.599
Low HDLc ^b	1.00 (referent)	1.25 (0.80–1.81)	0.99 (0.97–1.01)	0.556
High blood pressure ^b	1.00 (referent)	1.26 (0.83–1.91)	1.91 (1.26–2.80)	0.002

^a Adjusted for age, season and sex; ^b adjusted for all variables in model 1 plus other components of MS.

Spearman's correlation analysis showed that PTH levels correlated positively with AHI ($r = 0.210$, $p = 0.002$) and negatively with the mean and minimal nocturnal oxygenation saturation ($r = -0.378$, $p < 0.001$ and $r = -0.312$, $p < 0.001$). Significant associations between PTH levels and indices of nocturnal hypoxia were attenuated but not eliminated after adjustment for other variables in multivariate analysis (mean oxygenation saturation $p = 0.035$ and minimal oxygenation saturation $p = 0.043$).

Patients were divided into 3 categories based on their 25(OH)D levels. The median (range) 25(OH)D level was 27.8 (20.1–38.7) ng/ml. The prevalence of vitamin D insufficiency (vitamin D ≤ 30 ng/ml) was 58.3%. Although

common, regardless of the season, vitamin D insufficiency was more prevalent during winter months (January–March 68.1%, April–June 63.3%, July–September 42.5% and October–December 59%; $p < 0.01$).

In 55.3% of the men and in 63.2% of the women, the serum 25(OH)D level was less than 30 ng/ml (insufficient status), and 10.5% of the men and 18.6% of the women had serum 25(OH)D levels below 15 ng/ml (very low status).

Patients with low 25(OH)D levels were older and had higher values of BMI, waist circumference, glucose, triglycerides, cholesterol and PTH than patients with sufficient 25(OH)D levels. Mean HDLc concentrations were

lower among those patients with low 25(OH)D levels (tables 1, 2).

After adjusting for age, sex and seasonality, there was a significant trend of decreasing odds for diabetes (OR 0.55, 95% CI 0.33–0.94, $p_{\text{trend}} = 0.038$) and MS (OR 0.34, 95% CI 0.21–0.56, $p_{\text{trend}} < 0.001$) with increasing vitamin D levels. Similarly, after additional adjustment for the other components of MS, there were inverse associations between 25(OH)D status and waist circumference (OR 0.48, 95% CI 0.25–0.89, $p_{\text{trend}} = 0.02$) hypertriglyceridemia (OR 0.37, 95% CI 0.20–0.67, $p_{\text{trend}} < 0.001$) and low HDLc (OR 0.47, 95% CI 0.25–0.87, $p_{\text{trend}} = 0.018$) (table 3). We also found no apparent modification of these relations according to smoking status (data not shown).

Table 4 displays metabolic variables according to tertiles of PTH levels. After adjusting for age, sex and seasonality, higher PTH levels were associated with a higher prevalence of obesity (OR 2.05, 95% CI 1.06–3.09, $p_{\text{trend}} < 0.001$) and hypertension (OR 1.83, 95% CI 1.01–3.05, $p_{\text{trend}} = 0.049$). In addition, there was an association between PTH and high blood pressure after adjusting for the other components of MS (OR 1.91, 95% CI 1.26–2.80, $p_{\text{trend}} = 0.002$).

Discussion

This study shows a high prevalence of low vitamin D levels among patients with OSAS. Low levels of 25(OH)D were associated with the presence of MS and diabetes. These associations were not explained by age, sex or season. We also found an increased prevalence of abdominal obesity, higher serum triglycerides and lower HDLc among those patients with lower 25(OH)D concentrations after adjustment for other components of MS. In addition, the odds for obesity and hypertension increased with increasing PTH levels. Furthermore, PTH levels were higher in patients with severe OSAS than in patients with mild-to-moderate OSAS, suggesting a potential role of OSAS in the metabolic and cardiovascular complications promoted by hypovitaminosis D.

Poor vitamin D status has been associated with the presence of MS and diabetes mellitus, suggesting that vitamin D could be an emerging association for these disorders [14, 19, 20]. A recent study reported an association of 25(OH)D concentrations with insulin resistance and β -cell dysfunction in subjects at risk for type 2 diabetes [20]. Our findings of an inverse association between 25(OH)D and diabetes among these patients suggest that lower concentrations of 25(OH)D may be a predictor of

an increased likelihood of diabetes in patients with OSAS. On the other hand, Bozkurt et al. [21] showed that subjects with more severe OSAS indices tended to present lower vitamin D levels correlated to an increased prevalence of insulin resistance, prediabetes and diabetes. Nevertheless, compared with this previous study, the advantage of our study was that we were able to adjust for potential confounders for the analyses.

The search for additional factors that may contribute to a better understanding of the links between OSAS and the MS is highly desirable [22]. Evidence from clinical and experimental studies support an inverse relationship between 25(OH)D and components of the MS, including elevated blood pressure, dyslipidemia, high blood glucose concentrations and abdominal obesity [15, 23]. Several mechanisms have been proposed to explain these relations: (1) vitamin D has been independently associated with insulin sensitivity and β -cell function, (2) vitamin D negatively regulates the renin-angiotensin system to lower blood pressure, (3) vitamin D deficiency may cause an abnormal lipid profile by increasing peripheral insulin resistance [20, 24, 25].

Our findings that serum levels of 25(OH)D are inversely associated with triglyceride levels and positively associated with HDLc levels are in accordance with previous epidemiological studies [13, 26]. The role of vitamin D in lipid metabolism is currently unclear. Experimental evidence suggests that vitamin D deficiency may cause an abnormal lipid profile by increasing peripheral insulin resistance and contributing to MS [9]. Recently, Oh et al. [27] reported that 1,25(OH)₂ vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes, suggesting another mechanism of risk of vitamin D deficiency. Furthermore, it is possible that vitamin D can protect against cardiovascular risk by promoting formation of large HDL particles, affecting reverse cholesterol transport [28].

Obesity has been associated with vitamin D deficiency [29, 30]. Increased storage of 25(OH)D in adipose tissue is a plausible explanation for increased rates of vitamin D deficiency in obese individuals [31]. Alternatively, obesity may also be the consequence of low vitamin D levels [30]. Elevated PTH secondary to low vitamin D may promote fat accumulation and obesity through increases of calcium influx into adipocytes, which enhances lipogenesis and inhibits lipolysis [32]. In our study, patients with low levels of vitamin D were more obese than patients with sufficient levels. The high prevalence of vitamin D insufficiency in OSAS patients raises the possibility that low vitamin D status could promote weight gain and mag-

nify the adverse effects of obesity on metabolic variables and the cardiovascular system.

In this study, higher PTH levels were associated with a higher prevalence of obesity and hypertension. There was no evidence of associations of PTH with MS except for a positive association with high blood pressure after adjusting for the other components of MS. Previous studies found positive associations of PTH with SBP and DBP independent of 25(OH)D and potential confounding factors [13, 33]. It has been suggested that PTH affects blood pressure through a proliferate effect on vascular smooth-muscle cells, which may contribute to vessel-wall-thickening and consequently to higher blood pressure [34].

Taken together, our findings suggest that the associations of vitamin D and PTH with MS represent different underlying associations with individual components, with vitamin D likely acting through pathways involving glucose and lipid metabolism and PTH having a more important effect via blood pressure.

The main mechanisms of vascular damage in OSAS are intermittent hypoxia, intrathoracic pressure changes and arousals [5, 35]. On the other hand, OSAS is tightly linked with and may aggravate each component of MS [36]. In this study, PTH levels were higher in patients with severe OSAS and were independently associated with indices of nocturnal hypoxia, suggesting a possible additional mechanism by which OSAS may influence these levels. In addition, because PTH levels are partly dependent on vitamin D status, our results suggest that the common association of OSAS and low levels of vitamin D may have additive effects on metabolic and cardiovascular complications. Considering the high prevalence of a low vitamin D level among patients with OSAS and the possible role of vitamin D and PTH in the development of diabetes, MS and hypertension, it may be relevant to take these parameters into account when assessing metabolic and cardiovascular disorders in patients with OSAS. Continuous positive airway pressure treatment has been associated with improvements in vascular abnormalities, but alternative treatments are needed. Future prospective studies and randomized clinical trials are required to determine possible mechanisms of any preventive effect via vitamin D supplementation against metabolic and cardiovascular diseases in these patients.

This study has some limitations. The causative nature of the observed associations could not be established. Our observational design could not demonstrate the temporal relationship between low vitamin D status and risk of MS. Vitamin D levels may be a surrogate marker for healthy nutrition. In a recent cohort study carried out in

a representative Spanish population, it was observed that one third (33.9%) of this population may be at risk of vitamin D deficiency [37]. In this sense, our study shows a high prevalence of low vitamin D levels among patients with OSAS (58.3%). In addition, OSAS patients may have reduced vitamin D production resulting from restricted mobility or lifestyle habits. An alternative explanation is that low vitamin D status is an indicator of chronic non-specific illness rather than a direct contributor. Low levels of vitamin D may promote the acute-phase response and vitamin D analogs have been shown to inhibit the production of several proinflammatory cytokines [38]. Other potential confounding factors, such as the interaction between genetic variants, were not taken into account in our analysis.

Conclusions

This study shows that lower plasma 25(OH)D levels were associated with higher levels of glucose and a higher prevalence of MS. In addition, elevated PTH levels were associated with an increased prevalence of obesity and hypertension and were higher in patients with severe OSAS and independently associated with indices of nocturnal hypoxia, suggesting a possible additional mechanism by which OSAS may influence PTH levels.

These findings warrant further examination in prospective studies which should include clinical trials.

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Financial Disclosure and Conflicts of Interest

All authors confirm that they have no conflicts of interest.

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