25-Hydroxyvitamin D Concentration Correlates With Insulin-Sensitivity and BMI in Obesity

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The prevalence of hypovitaminosis D is high among obese subjects. Further, low 25-hydroxyvitamin D (25(OH)D) concentration has been postulated to be a risk factor for type 2 diabetes, although its relation with insulin-sensitivity is not well investigated. Thus, we aimed to investigate the relationship between 25(OH)D concentration and insulin-sensitivity, using the glucose clamp technique. In total, 39 subjects with no known history of diabetes mellitus were recruited. The association of 25(OH)D concentration with insulin-sensitivity was evaluated by hyperinsulinemic euglycemic clamp. Subjects with low 25(OH)D (<50 nmol/l) had higher BMI ($P = 0.048$), parathyroid hormone (PTH) ($P = 0.040$), total cholesterol ($P = 0.012$), low-density lipoprotein (LDL) cholesterol ($P = 0.044$), triglycerides ($P = 0.048$), and lower insulin-sensitivity as evaluated by clamp study ($P = 0.047$). There was significant correlation between 25(OH)D and BMI ($r = -0.58$; $P = 0.01$), PTH ($r = -0.44$; $P < 0.01$), insulin-sensitivity ($r = 0.43$; $P < 0.01$), total ($r = -0.34$; $P = 0.030$) and LDL ($r = -0.40$; $P = 0.023$) (but not high-density lipoprotein (HDL)) cholesterol, and triglycerides ($r = 0.45$; $P = 0.01$). Multivariate analysis using 25(OH)D concentration, BMI, insulin-sensitivity, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides, as the cofactors was performed. BMI was found to be the most powerful predictor of 25(OH)D concentration ($r = -0.52$; $P < 0.01$), whereas insulin-sensitivity was not significant. Our study suggested that there is no cause–effect relationship between vitamin D and insulin-sensitivity. In obesity, both low 25(OH)D concentration and insulin-resistance appear to be dependent on the increased body size.

INTRODUCTION

25-Hydroxyvitamin D (25(OH)D) is well known for its role in regulating calcium absorption and bone metabolism. There are accumulating data suggesting its pleiotropic effects and possible involvement in the pathogenesis of cardiovascular diseases (1) and metabolic syndrome (2). Metabolic syndrome with low 25(OH)D concentration has been reported to be highly prevalent among severely obese patients (3–5). Obesity is therefore considered to be a risk factor for hypovitaminosis D. The cause of low 25(OH)D concentration in obese individuals is still under debate, where enhanced uptake by adipose tissue (4), sunlight underexposure (6), or low dairy consumption of calcium and vitamin D (7) are the most plausible explanations. Interestingly, although high parathyroid hormone (PTH) is usually viewed as a compensatory mechanism for low 25(OH) vitamin D, PTH has also been reported as an independent risk factor for diabetes (8,9). On the contrary, there is evidence to suggest that the association between 25(OH)D and impairments in glucose metabolism may be independent of PTH concentration, supporting a direct role for 25(OH)D in pancreatic β-cell function and insulin-sensitivity (10). Further, low 25(OH)D concentration has been found to be associated with reduced glucose tolerance (11,12), dyslipidemia (13,14), hypertension (15,16), and obesity (3–5), strengthening the hypothesis that vitamin D may play a role in the etiology of "metabolic syndrome" either via an association with individual components of metabolic syndrome or via insulin-resistance. Several studies examined the vitamin D status and insulin-resistance, with conflicting results (17–19). Such controversy is most probably due to variability of the method used. It is recognized that indirect indexes of insulin-resistance derived from fasting values of insulin and glucose mostly reflect hepatic insulin-sensitivity, whereas post-oral glucose tolerance test indexes do not take into account all variables influencing the results, including insulin secretion. Thus, the present study was designed to examine the relationship of 25(OH)D with insulin-sensitivity, as evaluated by hyperinsulinemic euglycemic clamp, the gold-standard method for measuring insulin-sensitivity independently from insulin secretion and obesity.

METHODS AND PROCEDURES

Thirty-nine subjects who attended our division were considered for inclusion (18 males and 21 females, aged 41.4 ± 12.4 years, BMI 30.1 ± 5.4 kg/m²) after approved consent. None of the study participants had relevant endocrine or nonendocrine diseases, including diabetes mellitus.

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All participants had normal liver, cardiopulmonary, and kidney functions as determined by medical history, physical examination, electrocardiogram, urinalysis, and screening blood tests as blood urea nytrogen, creatinine, uric acid, albumin, aspartate aminotransferase, and alanine aminotransferase measured by autoanaliser (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland). They were not taking any antidiabetic medications neither calcium or vitamin D supplementation.

The subjects consumed a weight-maintaining diet that contained 200–250 g carbohydrate per day for at least 3 days before the study. Body weight was stable in all of the subjects for at least 3 months before the study. Height and weight were measured wearing light clothing and no shoes; BMI was calculated as weight in kg divided by the square of height in meters (kg/m^2). The study protocol was approved by the ethical committee. All patients had blood samples taken for hormones assessment (insulin, PTH, 25(OH)D), electrolytes and serum lipid assay (total cholesterol, high and low-density lipoprotein (HDL and LDL cholesterol). All patients underwent an oral glucose tolerance test, and, 1 week after, insulin-sensitivity was tested with an hyperinsulinemic euglycemic clamp. The clamp test was performed after a 12-h overnight fast, as described by DeFronzo and colleagues (20). Before the start of the insulin clamp, a catheter was placed into an antecubital vein for the infusion of all test substances. A second catheter was inserted retrogradely into a vein on the dorsum of the hand. A primed constant infusion of insulin was given (Actrapid HM, 40 mIU/m^2·min; Novo Nordisk, Copenhagen, Denmark). The constant velocity for the insulin infusion was reached within 10 min to achieve steady-state insulin levels; in the mean time a variable infusion of 20% glucose was begun via separate infusion pump, and the rate was adjusted, on the basis of plasma glucose samples drawn every 5 min, to maintain the plasma glucose concentration at each participant's fasting plasma glucose level (±5%). During the last 30 min of the basal equilibration period, plasma samples were taken at 5–10 min intervals for determination of plasma glucose and insulin concentrations. Whole-body peripheral glucose utilization was calculated during the last 30-min period of the steady-state insulin infusion and was measured as M value, i.e., the mean glucose infusion rate (as mg/kg/min) during the second hour of the euglycemic clamp. Additionally, we calculated another marker of insulin-resistance in the form of the homeostasis model assessment of insulin resistance as follows: fasting insulin·fasting glucose/22.5 (21).

Blood measurements were done in the morning after an 8-h overnight fast. Hormones were all assayed in duplicate. Insulin and PTH were measured using an enzyme chemiluminescence immunoassay (Roche Products, Modular E, Penzberg, Germany, intra-assay and interassays coefficient of variations were, respectively, 4.5–7.2 and 3.2–6.0%). Serum levels of 25(OH)D were determined by chemiluminescence immunoassay radioimmunoassay (Liaison; Diasorin, Saluggia, Italy) (intra- and interassays coefficient of variations were 5.8 and 7.8%, respectively).

Patients were stratified into two groups according their vitamin D status: we selected 50 nmol/l as cutoff of low 25(OH)D, because it is closest to median value of our population (22).

Plasma glucose concentrations were determined by the glucose oxidase technique, using a glucose analyzer (Beckman Instruments, Palo Alto, CA). Plasma cholesterol concentrations were measured using commercially available kits. Calcium and other electrolytes were determined by colour photometric assay (Olympus AU 5400; Olympus, Tokyo, Japan).

Statistical analysis
Statistical analysis was carried out using BIOSTAT 2008 5.4.0.0 (Vancouver, British Columbia, Canada). Data are expressed as mean ± s.d. After checking whether the variables were normally distributed, two-tail Student's t-test was used to determine statistical differences in continuous variables between groups categorized on the basis of 25(OH)D concentration with a cutoff value of <50 nmol/l used to define low 25(OH)D concentration.

In the entire cohort of patients, linear associations between variables were described using Pearson correlation coefficients. Multivariate regression analysis was used to investigate the relationship of the anthropometric and metabolic parameters with 25(OH)D.

RESULTS
Selecting 50 nmol/l as cutoff point, low 25(OH)D was detected in 54% of all patients. **Table 1** summarizes the clinical and biochemical characteristics of the entire patient cohort.

The two groups were similar for age, proportion of male/female subjects, and serum calcium concentration although subjects in the low 25(OH)D group had higher BMI ($P = 0.048$) and PTH concentration ($P = 0.040$). Type 2 diabetes was diagnosed in one patient by oral glucose tolerance test; impaired glucose tolerance was found in seven patients (six obese and one normal patient). Taking into account the metabolic status, the low 25(OH)D group had lower M value ($P = 0.047$), total cholesterol ($P = 0.012$), LDL cholesterol concentration ($P = 0.044$), and triglycerides ($P = 0.048$) than the normal group. Homeostasis model assessment of insulin resistance resulted higher but did not reach statistical significance ($P = 0.053$), HDL cholesterol concentrations were similar.

Pearson coefficient analyses revealed a correlation between 25(OH)D and BMI ($r = -0.58$; $P = 0.01$) (**Figure 1b**), PTH ($r = -0.44$; $P < 0.01$), M value ($r = 0.43$; $P \leq 0.01$) (**Figure 1a**), homeostasis model assessment of insulin resistance ($r = -0.34$; $P = 0.055$), total cholesterol ($r = -0.34$; $P = 0.030$), LDL cholesterol ($r = -0.40$; $P = 0.023$), and triglycerides ($r = -0.45$; $P < 0.01$). 25(OH)D concentration was not associated with HDL cholesterol and serum calcium. The serum concentration of PTH and serum calcium were not associated with anthropometric and metabolic variables. Multivariate regression analysis ($P < 0.01$) was performed in a model including 25(OH)D concentration, BMI, M value, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. The most powerful predictor of 25(OH)D concentration was BMI ($r = -0.52$; $P < 0.01$), whereas M value, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides were not (**Figure 2**).

In order to determine whether variations in 25(OH)D concentration were due to body size or insulin-resistance, we restricted our analyses to moderately obese subjects. We therefore selected subjects with BMI >30 kg/m^2, but <35 kg/m^2. This population was then divided into two groups: insulin-resistant (M value ≤5 mg/kg/min) and insulin-sensitive (M value >5). By definition, M value was highly statistically different (2.8 ± 0.7 vs. 5.3 ± 0.8 mg/kg/min) between the two groups, whereas we did not find any statistical difference in 25(OH)D concentration (insulin-resistant: 34.7 ± 12.4 nmol/l vs. insulin-sensitive: 36.6 ± 13.2, respectively; P = NS) and BMI (insulin-resistant: 32.1 ± 2.3 kg/m^2 vs. insulin-sensitive: 31.6 ± 1.23, respectively; P = NS).

DISCUSSION
Low 25(OH)D concentration has been reported to be associated with decreased insulin-sensitivity, particularly among the obese population (5,17). The role of 25(OH)D in causing insulin-resistance is not yet clarified. Some studies suggested

Table 1 Clinical and biochemical characteristics of subjects in the entire cohort and based on 25(OH)D concentration (cutoff value: 50 nmol/l)

Parameters	All	Normal 25(OH)D (>50 nmol/l)	Low 25(OH)D (<50 nmol/l)	P
n (%)	39 (100)	18 (46)	21 (54)	—
Age (years)	41.4 ± 12.4	42.3 ± 12.6	39.6 ± 12.1	NS
Sex (% female)	21 (54)	10 (56)	11 (52)	NS
BMI (kg/m^2)	30.1 ± 5.4	26.6 ± 2.7	31.7 ± 6.0	0.048
25(OH)D (nnmol/l)	40.4 ± 18.3	63.68 ± 11.0	30.16 ± 9.1	—
PTH (pg/ml)	46.1 ± 16.0	38.3 ± 10.4	49.6 ± 16.8	0.04
Serum calcium (mg/dl)	9.8 ± 1.5	9.6 ± 0.46	9.8 ± 1.8	NS
Fasting glucose (mg/dl)	90.0 ± 9.0	84.3 ± 7.6	92.1 ± 8.8	0.02
Fasting insulin (μU/ml)	11.7 ± 6	10.6 ± 5.0	12.2 ± 6.5	NS
AUC$_{glycemia\ 0-120'}$ (mg/dl·min·10^6)	22.3 ± 12.4	17.8 ± 9.7	24.1 ± 13.1	NS
AUC$_{insulin\ 0-120'}$ (μU/ml·min·10^6)	8.7 ± 1.4	8.0 ± 1.0	8.9 ± 1.5	NS
M value (mg/kg/min)	5.2 ± 2.6	6.5 ± 2.5	4.7 ± 2.5	0.047
HOMA$_{IR}$	2.59 ± 1.44	1.76 ± 0.07	3.19 ± 0.29	0.053
Total cholesterol (mg/dl)	189.0 ± 49.0	160.1 ± 45.3	201.8 ± 45.6	0.012
LDL cholesterol (mg/dl)	111.4 ± 44.1	90.3 ± 36.6	120.8 ± 44.5	0.044
HDL cholesterol (mg/dl)	55.2 ± 13.8	52.7 ± 12.5	56.3 ± 14.5	NS
Triglycerides (mg/dl)	91.5 ± 43.2	71.1 ± 26.3	100.5 ± 46.5	0.048

Data are expressed as mean ± s.d.

AUC, area under the curve; HDL, high-density lipoprotein; HOMA$_{IR}$, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; 25(OH)D, low 25-hydroxyvitamin D; PTH, parathyroid hormone.

that 25(OH)D may have a beneficial effect on insulin responsiveness by either stimulating the expression of insulin receptors (23) or regulating the homeostasis of calcium, which is essential for insulin-mediated intracellular processes (24,25). On the contrary, considering that adipose tissue is a prevalent 25(OH)D storage site (3) and that obesity is the most common cause of insulin-resistance (26), the association of 25(OH)D and insulin-resistance might be simply the result of increased body size. Most previous studies have investigated the link between the 25(OH)D concentration and insulin-sensitivity in obese subjects using indirect methods of measuring insulin-sensitivity (5,17–19), or estimating it from studies performed for other purposes (27,28). In this study, the relationship of low 25(OH)D concentration and insulin-resistance was evaluated by the hyperinsulinemic euglycemic clamp, the gold standard to directly measure insulin-sensitivity. Although the measurement of insulin-sensitivity with the hyperinsulinemic clamp ensures clear results, the actual definition of normal 25(OH)D levels is still unsolved. A number of different 25(OH)D thresholds have been proposed for the definition of hypovitaminosis D (29–31). These differences mainly depend on latitude that determines the available sunlight exposure which in turn affects 25(OH)D concentration (32). We chose 50 nmol/l as cutoff of low 25 (OH) vitamin D, because it was closest to median value of Italian population (22,33).

Here, we confirm previous reports finding a direct correlation of 25(OH)D concentration with insulin-sensitivity: the
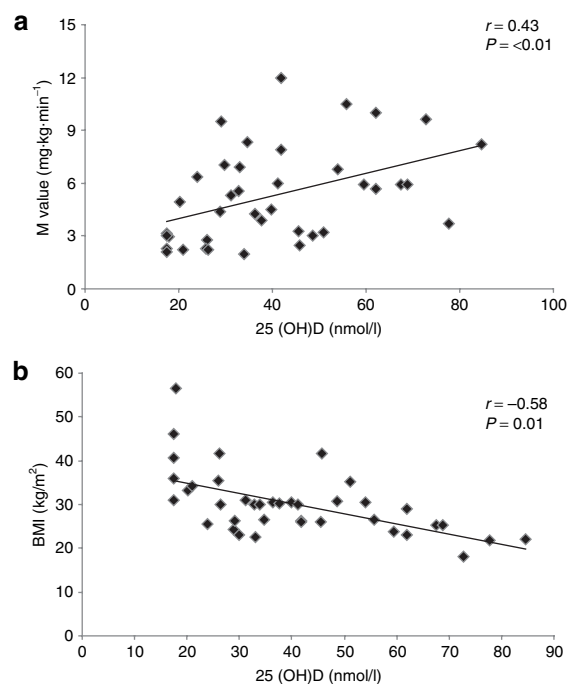

Figure 1 Correlation between 25(OH)D concentration and BMI (**b**) and insulin-sensitivity (**a**). 25(OH)D, 25-hydroxyvitamin D.

subjects with the lowest concentration of 25(OH)D were the most insulin-resistant, with the remaining population having 25(OH)D concentration within the normal range.
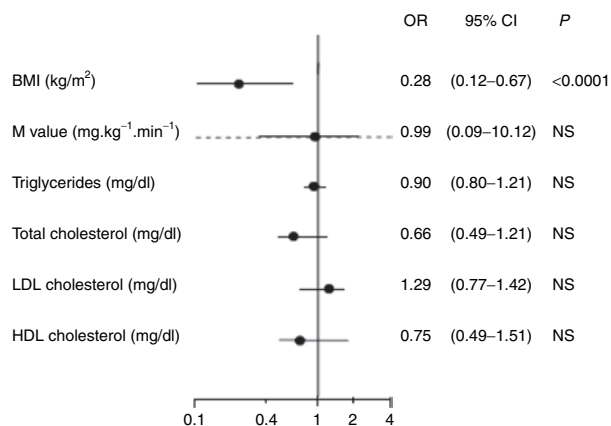
	OR	95% CI	P
BMI (kg/m²)	0.28	(0.12–0.67)	<0.0001
M value (mg.kg⁻¹.min⁻¹)	0.99	(0.09–10.12)	NS
Triglycerides (mg/dl)	0.90	(0.80–1.21)	NS
Total cholesterol (mg/dl)	0.66	(0.49–1.21)	NS
LDL cholesterol (mg/dl)	1.29	(0.77–1.42)	NS
HDL cholesterol (mg/dl)	0.75	(0.49–1.51)	NS

0.1   0.4   1   2   4

Figure 2 Multivariate regression analysis expressed as odds ratio for metabolic and anthropometric parameters predicting 25(OH)D levels <50 nmol/l. The only significant parameter was BMI. HDL, high-density lipoprotein; LDL, low-density lipoprotein; 25(OH)D, 25-hydroxyvitamin D.

It is recognized that many different factors contribute to the development of insulin-resistance, in particular obesity (26). We therefore aimed to clarify whether low 25(OH)D concentration has a direct link with the pathogenesis of insulin-resistance or whether this association is dependent on body size. Because in our population the low 25(OH)D subjects had higher BMI and lower M value than subjects with normal value of 25(OH)D, multivariate regression analysis was performed in a model including 25(OH)D concentration, BMI, insulin-sensitivity, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. We found that the powerful predictor of low 25(OH)D concentration was the BMI ($r = -0.52$; $P < 0.01$) whereas all other metabolic parameters lost their statistical significance, including insulin-sensitivity. Similar results, although not statistically significant, were obtained using homeostasis model assessment of insulin resistance as an estimation parameter of insulin-resistance.

Therefore, our results seem to suggest that obesity is responsible, in our population, for both insulin-resistance and low 25(OH)D. Obesity, however, is not invariably associated with insulin-resistance (34), as normal insulin-sensitivity can be present in some obese subjects as well. Therefore, to further test the hypothesis that insulin-resistance could be dependent to hypovitaminosis (or vice versa) and not to obesity per se, we divided the obese population into two subgroups, according to their insulin-sensitivity (low and high). The two groups resulted similar for BMI, age, and sex (data not shown), but did not show any difference in 25(OH)D concentration, thus confirming the hypothesis that the most determinant of hypovitaminosis D is the adipose tissue, as prior studies asserted (3,4). As already reported, fat mass acts as a reservoir of 25(OH)D and its metabolites (3,4), and obese people have been reported to have a lower intake of vitamin D (7) or less exposure to sunlight because of lower exercise and less mobility (6). A similar result was obtained by Blum et al. who measured 25(OH)D concentration in serum and subcutaneous adipose tissue collected from obese subjects undergoing gastric bypass surgery, showing an inverse association of 25(OH)D with body weight and adiposity (3). Attempting to explain the mechanism for the subnormal concentration of 25(OH)D in the obesity, Wortsman et al. assessed whether obesity could alter the cutaneous production of vitamin D or intestinal absorption. Both processes were similar to lean subjects, confirming that low 25(OH)D concentration is due to its increased sequestration in the enlarged pool of subcutaneous fat tissue (4).

Manco et al. evaluated the relationship of 25(OH)D concentration with insulin-sensitivity before and after bariatric surgery. They found an increase in insulin-sensitivity after the surgery while 25(OH)D remained low (35). This finding is in agreement with our data, indeed, comparing obese subjects matched for BMI but with different insulin-sensitivity, the 25(OH)D concentration did not differ between the two groups. Besides this, if 25(OH)D was involved in the pathogenesis of insulin-resistance, it could be expected that a supplementation of calcitriol or its analogues might lower insulin-resistance. This was not the case either in insulin-resistant diabetic patients (36), or in healthy subjects (37). Our findings, however, do not confirm previously reported observations (27,28) in which a correlation between hypovitaminosis D with β-cell dysfunction and insulin-resistance was found. In their works, the authors accurately measured insulin secretion with the hyperglycemic clamp, whereas insulin-resistance was only estimated as the ratio between glucose infusion and insulin concentration during the same hyperglycemic clamp. In these previous works, however, the large variability obtained in insulin secretion certainly highly influenced data estimating insulin-resistance.

Other studies (8,9) have reported that the compensatory increase in PTH concentration may be responsible of insulin-resistance associated with low 25(OH)D concentration. It has been hypothesized that PTH might blunt the lipolytic response to catecholamines by activating phosphodiesterase 3B, the same enzyme that mediates the antilipolytic effect of insulin, damaging the effect of insulin-mediated glucose uptake (38). In our cohort, we found a significant difference in PTH concentration between the normal 25(OH)D group and low 25(OH)D group, but we could not demonstrate any correlation between PTH and M value or lipid profile. Our data cannot exclude a role of PTH as a determinant of insulin-resistance; if this is the case, PTH, while compensating for the low vitamin D concentration associated with obesity, could play a role in worsening insulin-resistance. Prior studies suggesting a cause–effect relation between the vitamin D status and insulin-sensitivity used indexes of insulin-resistance calculated from fasting or postchallenge values, showing conflicting results. Our data do not seem to support this hypothesis. Although this study is limited by the relatively small sample size, the reliability of the glucose clamp strengthens our result of an absent cause–effect relation between vitamin D and insulin-sensitivity. Obese subjects, however, had both reduced 25(OH)D and insulin-sensitivity. Instead of hypothesizing a cause–effect of these two variables, we believe that both are an effect of increased body size.

In conclusion, our data showed that 25(OH)D status does not affect the development of insulin-resistance, therefore suggesting that the administration of vitamin D should not affect insulin-resistance. Only a reduction in fat mass, as a result of weight loss, will decrease the storage site of 25(OH)D and its metabolites, restoring normal values of 25(OH)D concentration and reversing insulin-resistance.

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