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Serum 25-hydroxyvitamin D Concentrations and Metabolic Syndrome in Egyptian Men

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Aim of the study is to investigate the correlations between serum concentrations of 25-hydroxyvitamin [25(OH)D] and components of metabolic syndrome in Egyptian men. Ninety-three Egyptian men with metabolic syndrome and seventy age matched healthy males were included in this study. Metabolic syndrome was diagnosed based on modified International Diabetes Federation worldwide definition of the metabolic syndrome (MetS), using Body Mass Index (BMI) instead of waist circumference. We found that serum 25(OH) D levels were significantly lower in the MetS patients than control subjects. In MetS patients, serum 25(OH)D levels were significantly correlated with BMI, insulin, HOMA, HDL and PTH. After splitting of the serum 25(OH)D into 4 quartiles, with lowest one <25 nmol L^{-1} (presumed hypovitaminosis D as the new reference category). In the first quartile, we found that 25(OH)D levels were significantly correlated with BMI, SBP, DBP, FBS, insulin, HOMA, TG and HDL. In the 2nd quartile, 25(OH)D levels were significantly correlated with BMI, insulin, HOMA and HDL. While in the third and fourth quartiles, 25(OH)D levels were significantly correlated with only HDL component of metabolic syndrome. So the patients with the lowest serum 25(OH)D levels have the more significant correlation with the MetS components as well as insulin levels and HOMA. In addition, the 25(OH)D levels were correlated significantly with serum PTH levels all through in the 4 quartiles. In conclusion, our study showed a correlation between low serum vitamin D and different components of metabolic syndrome in Egyptian men. Hypovitaminosis D should be considered as a risk factor for the metabolic syndrome.

Key words: Metabolic syndrome, serum 25-hydroxyvitamin D

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INTRODUCTION

Metabolic syndrome is a clustering of cardiovascular risk factors. Its definition is the presence of any 3 of the following: obesity, hypertriglyceridemia, low high-density lipoprotein, hypertension and impaired fasting glucose (Bhatheja and Bhatt, 2006).

Vitamin D has been recognized to have numerous non-calcemic functions (Holick, 2005). In addition to its traditional calcium-related effects on the skeleton, hypovitaminosis D has been now recognized to exert nonskeletal adverse effects on several other organ systems. Specifically, there is increasing evidence that vitamin D metabolism affects the risk of Insulin Resistance (IR), diabetes and of the metabolic syndrome (Scragg *et al.*, 2004).

The postulated relation between low serum 25(OH)D and reduced insulin sensitivity is a noteworthy hypothesis, which would imply that vitamin D supplementation in obese and diabetic patients might be extremely useful in reducing insulin resistance, in lowering the incidence of the metabolic syndrome and in reverting or reducing glucose intolerance and type 2 diabetes (Chiu *et al.*, 2004). Accumulating research suggests that low 25-hydroxyvitamin D3 [25(OH)D] concentrations may be inversely associated with type 2 diabetes and metabolic syndrome (Ford *et al.*, 2005).

Although the underlying molecular mechanism of this association remains to be elucidated. Much remains to be learned, however, about the relationship between vitamin D status and metabolic syndrome. Aim of the study is to investigate the correlations between serum concentrations of 25-hydroxyvitaminD [25(OH) D] and components of metabolic syndrome in Egyptian men.

MATERIALS AND METHODS

Ninety-three Egyptian men with metabolic syndrome and seventy ages matched healthy males were included in this study. The patients were selected in summer (2005 and 2006) from medical and endocrine out-patient clinics of Al-Zahraa University Hospital Cairo, Egypt. The patients gave informed voluntary consent to participate in the study according to the protocol approved by the local ethics committee and in accordance with the ethical standards of the Helsinki declaration. Those with recent history of acute illness or advanced chronic liver or renal disease and those who were taking any medications known to affect vitamin D metabolism and insulin resistance were excluded.

Metabolic syndrome was diagnosed based on modified International Diabetes Federation worldwide definition of the metabolic syndrome (Alberti *et al.*, 2005)

using Body Mass Index (BMI) instead of waist circumference. The diagnosis of metabolic syndrome was made if BMI >25.0 kg m^{-2} and at least two of the following factors were present: (1) Fasting glucose $\geq$ 5.6 mmol L^{-1} or being treated for diabetes mellitus (DM); (2) Hypertension: Systolic Blood Pressure (SBP) $\geq$130 mmHg, or and Diastolic Blood Pressure (DBP) $\geq$ 85 mm Hg or use of antihypertensive drug therapy; (3) Triglycerides (TG)$\geq$ 1.70 mmol L^{-1} ; (4) High density lipoprotein cholesterol (HDL-c) <1.03 mmol L^{-1} in male.

In MetS patients, serum 25(OH) D levels were splitting into four quartiles. The 1st quartile subgroup has <25 nmol L^{-1} (<25 nmol L^{-1}, presumed hypovitaminosis as the new reference category[1]), the second quartile with 25.1-35.3 nmol L^{-1}, the third quartile with 35.4-48.2 nmol L^{-1}, while in the fourth one with >48.2 nmol L^{-1}.

Fasting venous samples were collected for estimation of blood sugar, insulin levels, lipid profiles, 25 OH Vit D and intact PTH. Glucose was analyzed using a glucose oxidase electrode (Syncron CX7, Beckman, Brea, CA), insulin was measured by a solid phase I^{125} radioimmunoassay using the COAT-A-Count insulin kit from DPC (Diagnostic Products Corporation, Los Angeles, CA90045-5597 USA). Homeostasis Model Assessment (HOMA) was estimated using the formula: FBG (mmol L^{-1}) X fasting insulin level (uU mL^{-1})/22.5 (Matthews *et al.*, 1985).

Lipid profile analyzed for fasting plasma serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), on an automated analyzer (Hitachi 911 analyzer; Roche, Basle, Switzerland) with dedicated reagents supplied by Roche.

Intact PTH was assayed by a solid phase two site chemiluminescent enzyme -labelled immunometric assay (DPC, 5700 West 96 street, los Angeles, CA 90045 5597, USA). 25 (OH)D was assayed by liquid phase RIA after extraction by NaOH and acetonitrite using IDS gamma-beta 25 OH vit.D kit (IDS Inc.,17029, Fountain Hills, A285268, USA).

Statistical analysis: We used SPSS version 12 for data processing. Quantitative data were presented as mean and standard deviation for comparison of means, the Student t-test was used. Correlation between variables was done and Pearson correlation coefficient was calculated. All tests were 2-tailed and considered statistically significant at p<0.05.

RESULTS

We found that serum 25(OH)D levels were significantly lower in the MetS patients than control

Table 1: Baseline characteristics of MetS patients and controls

Parameters	Patients N = 93	Control group N = 70
Age (years)	45.2±2.6	47.1±3.1
S.25(OH)D (nmol L⁻¹)	40.5± 11.3**	61.4±11.2
BMI	31.8±3.8**	23.7±0.8
SBP (mmHg)	147.9±7.2*	120.8±3.1
DBP (mmHg)	90.1± 4.2**	77.0±3.2
FBS (mmol L⁻¹)	7.0±3.7*	5.9±0.3
S. insulin (uU mL⁻¹)	26.3± 5.2**	19.9±7.7
HOMA	8.3±2.3**	5.1±1.9
TG (mmol L⁻¹)	2.9±0.8*	1.4±0.2
HDL (mmol L⁻¹)	0.8±0.3**	1.2±0.8
PTH (pmol L⁻¹)	17.5±3.7**	4.4±0.5

*Significant $p<0.01$, **Highly significant $p<0.001$, BMI: Body Mass Index, SBP and DBP: Systolic and Diastolic blood pressure, FBS: Fasting Blood Sugar, HOMA: Homeostasis Model Assessment, TG: Triglycerides, HDL: High Density Lipoprotein, PTH: Parathyroid Hormone

Table 2: Correlation between quartiles of serum vitamin D concentrations and biochemical data of MetS patients

Parameters	S.25(OH)D	1st quartile (<25 nmol L⁻¹)	2nd quartile (25.1-35.3 nmol L⁻¹)	3rd quartile (35.4-48.2 nmol L⁻¹)	4th quartile (>48.2 nmol L⁻¹)
BMI	r = -0.684**	r = -0.784**	r = -0.774**	r = -0.044	r = -0.139
SBP	r = -0.114	r = -0.838**	r = -0.038	r = -0.038	r = -0.085
DBP	r = -0.021	r = -0.456*	r = -0.296*	r = -0.096	r = -0.019
FBS	r = -0.085	r = -0.335**	r = -0.115	r = -0.025	r = -0.017
S. Insulin	r = -0.396*	r = -0.496*	r = -0.286*	r = -0.296*	r = -0.014
HOMA	r = -0.395**	r = -0.435**	r = -0.365**	r = -0.435**	r = -0.046
TG	r = -0.075	r = -0.335**	r = -0.125	r = -0.035	r = -0.074
HDL	r = 0.277*	r = 0.396*	r = 0.296*	r = 0.281*	r = 0.220*
PTH	r = -0.235*	r = -0.635**	r = -0.475*	r = -0.335*	r = -0.280*

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed)

subjects. Fasting blood sugar, TG were significantly higher and HDL levels were significantly lower in MetS lower in MetS patients than in control group. Also Serum PTH levels were significantly higher in the MetS patients than control subjects (Table 1).

In MetS patients, serum 25(OH) D levels were significantly correlated with BMI, insulin, HOMA, HDL and PTH. After splitting of the serum 25(OH)D into 4 quartiles, with lowest one <25 nmol L⁻¹(presumed hypovitaminosis D as the new reference category). In the first quartile, we found that 25(OH)D levels were significantly correlated with BMI, SBP, DBP, FBS, insulin, HOMA,TG and HDL. In the second quartile, 25(OH)D levels were significantly correlated with BMI, insulin, HOMA and HDL. While in the third quartile, 25(OH) D levels were significantly correlated with insulin, HOMA and HDL. However In the fourth one, 25(OH) D levels were significantly correlated only with HDL (Table 2). So the patients with the lowest serum 25(OH)D levels have the more significant correlation with the MetS components as well as insulin levels and HOMA. In addition, the 25(OH) D levels were correlated significantly with serum PTH levels all through in the 4 quartiles.

DISCUSSION

To our knowledge, the current study is the first to show the relation of 25(OH)D concentrations to insulin resistance and metabolic syndrome in Egyptian men. In our study, we found that serum 25(OH)D levels were significantly lower and serum PTH levels were significantly higher in the MetS patients than control subjects.

In MetS patients, serum 25(OH)D levels were significantly correlated with BMI, insulin HOMA, HDL and PTH. After splitting of the serum 25(OH)D into 4 quartiles, with lowest one <25 nmol L⁻¹ (presumed hypovitaminosis D as the new reference category). In the first quartile, we found that 25(OH)D levels were significantly correlated with BMI, SBP, DBP, FBS, insulin, HOMA, TG and HDL. In the second quartile, 25(OH)D levels were significantly correlated with BMI, insulin, HOMA and HDL. While in the third and fourth quartiles, 25(OH) D levels were significantly correlated with only HDL component of metabolic syndrome.

So the patients with the lowest serum 25(OH)D levels have the more significant correlation with the MetS components as well as insulin levels and HOMA. In addition, the 25(OH) D levels were correlated significantly with serum PTH levels all through in the 4 quartiles.

The results of the present study are in agreement with previous reports showing an inverse association between concentrations of vitamin D and insulin resistance(Boucher *et al.*, 2005). Chiu *et al.* (2004) studied 126 participants, they found those with hypovitaminosis D were nearly three times as likely to have the metabolic syndrome as participants with normal concentrations of vitamin D. They concluded that hypovitaminosis D is a

risk factor for the metabolic syndrome. Extrapolations from the observations in their study suggest that increasing 25(OH) D from 10 to 30 ng mL^{-1} can improve insulin sensitivity by 60%. This improvement in insulin resistance could potentially eliminate the burden on beta cells and reverse abnormal glucose tolerance. Furthermore, the 60% improvement in insulin sensitivity that results from vitamin D treatment indicates that treatment is more potent than either troglitazone or metformin treatment.

Also Wortsman *et al.* (2000) found negative correlation between serum 25-OH-vit D and BMI. Parikh *et al.* (2004) found lower 25-OH-vit D and 1, 25-vit D and higher PTH concentrations in obese adults, independent of age, sex, or race. As excess weight is a major component of the metabolic syndrome, they reported an association between concentrations of vitamin D and excess weight. Also, hypovitaminosis D is considered as a risk of Insulin Resistance (IR), diabetes and of the metabolic syndrome (Scragg *et al.*, 2004).

The question of how vitamin D affects the BMI remains to be solved; however several mechanisms may explain this link. Animal and human studies indicated that high vitamin D affects adipocyte metabolism by inhibiting lipogenesis and stimulating lipolysis (Zemel, 2002).

Wortsman *et al.* (2000) observed that blood vitamin D3 concentrations increased in both the obese and nonobese subjects after exposure to an identical amount of UV-B irradiation. Moreover, the obese subjects had a larger body surface area of exposure and therefore would be expected to produce more vitamin D3, resulting in higher blood vitamin D3 concentrations, than would the nonobese control subjects. However, the increase in blood vitamin D3 concentrations was 57% less in the obese than in the nonobese subjects 24 h after the exposure. The content of the vitamin D3 precursor 7- dehydrocholesterol in the skin was not significantly different between obese and nonobese subjects. Furthermore, the percentage conversion to previtamin D3 and vitamin D3 was similar in both groups. They reported that, obesity did not affect the capacity of the skin to produce vitamin D3, but may have altered the release of vitamin D3 from the skin into the circulation. They explained these results by more sequestration of the cutaneous synthesized vitamin D3 in the obese than in the nonobese subjects as there was more fat available for this process.

Present study showed inverse correlation between 25(OH)D and PTH as well as between 25(OH) D and BMI. Vitamin D deficiency results in hyperparathyroidism (Zitterman, 2003). A key question that arises from this study is the mechanism of the association between body weight and low 25-OH-vit D levels.

The cause and effect relationship could operate in either direction. In MetS patients, the inverse correlation between BMI and 25(OH) D could be explained by more sequestration of the cutaneous synthesized vitamin D3 in adipose tissues. In the other hand, low 25(OH) D is associated with high PTH. PTH itself might also be involved in the development of obesity. PTH has been shown to increase intracellular calcium concentrations indeed, intracellular calcium seems to promote triglyceride storage and inhibit lipolysis (McCarty and Thomas, 2003). It is also possible that PTH influences adipocyte differentiation, because adipocytes and osteoblasts share common precursor cells (Civitelli, 1992) and PTH acts directly on osteoblasts (Dorheim *et al.*, 1993).These observations imply that increased fat mass is the main contributor to the increased body weight, is a consequence of hyperparathyroidism, Thus, increased body weight may promote vitamin D deficiency, resulting in secondary hyperparathyroidism (Raisz and Kream, 1983; Bell *et al.*, 1985).

CONCLUSION

In conclusion, present study showed a correlation between low serum 25(OH)D and different components of metabolic syndrome in Egyptian men. Hypovitaminosis D should be considered as a risk factor for the metabolic syndrome. Further investigation into whether vitamin D may play a role in the prevention of metabolic syndrome and insulin resistance states appears warranted.

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