Evaluation of Serum Intercellular Adhesion Molecule 1 in Patient With Metabolic Syndrome and Vitamin D Deficiency

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Abstract—Metabolic syndrome is a condition characterized by central obesity, hypertension and disturbed glucose and insulin metabolism. All the components of the metabolic syndrome are associated with altered function of the endothelium, a dynamic organ that regulates vascular tone and the interaction of the vessel wall with circulating substances and blood cells. Accumulating research suggests that the low levels of vitamin D were associated with an increased risk of metabolic syndrome and chronic diseases, and hypovitaminosis D-associated with endothelial dysfunction may predispose to higher rates of cardiovascular diseases. The purpose of the present study was to evaluate the intercellular adhesion molecule 1 as marker of endothelial dysfunction in patients with metabolic syndrome with and without vitamin D deficiency or vitamin D insufficiency. We have selected 18 patients (10 women and 8 men) with metabolic syndrome and with vitamin D deficiency or vitamin D insufficiency from the “N. Paulescu” National Institute of Diabetes and Metabolic Diseases. Patients were screened initially with a questionnaire detailing medical history, concomitant medications, alcohol consumption. The subjects were between 34 and 66 years. The metabolic syndrome were defined according the International Diabetes Federation Criteria. Anthropometric and biochemical parameters were assessed. Blood pressure was recorded. The plasma glucose, serum triglycerides, serum HDL-cholesterol were measured enzymatically. The plasma 25-hydroxyvitamin D was assayed with a radioimmunoassay kit. The ICAM1 levels were assayed using an ELISA method from Immuno Biological Laboratories. Results were compared with measurements in 17 subjects with metabolic syndrome but without vitamin D deficiency or vitamin D insufficiency. There were statistically significant differences in the recorded parameters in patients with metabolic syndrome and with and without vitamin D deficiency or vitamin D insufficiency. Systolic blood pressure, diastolic blood pressure, serum triglycerides was similar in both but age, body mass index, waist circumference, fasting blood glucose, intercellular adhesion molecule 1 level were higher and serum HDL cholesterol was lower in patients with metabolic syndrome and with vitamin D deficiency or vitamin D insufficiency.

Keywords—Metabolic Syndrome, Intercellular Adhesion Molecule 1, Vitamin D Deficiency.

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I. INTRODUCTION

Metabolic syndrome is a condition characterized by central obesity, hypertension and disturbed glucose and insulin metabolism. According to the International Diabetes Federation definition, for a person to be defined as having the metabolic syndrome, they must have: central obesity, waist circumference ≥94 cm for europid men and 80 cm for europid women with ethnicity specific values for other groups, and at least two of the following criteria: serum tryglicerides ≥150 mg/dl or known treatment, HDL-C ≤40 mg/dl in men or 50 mg/dl in women or known treatment, blood pressure ≥130/85 mmHg or known treatment, fasting plasma glucose ≥100 mg/dl or previously diagnosed diabetes [1].

All the components of the metabolic syndrome are associated with altered function of the endothelium, a dynamic organ that regulates vascular tone and the interaction of the vessel wall with circulating substances and blood cells. Endotelial cells produce several mediators (among these nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor) that exerts several anti-atherogenic effects: reduction of vascular smooth muscle proliferation, platelet aggregation, expression of adhesion molecule and monocyte adhesion [2]. Cell adhesion molecules are protein located on the cell surface involved with the binding with other cells or with the extracellular matrix. Most of the cell adhesion molecules belong to 5 protein families: immunoglobulin superfamily, the integrins, the cadherins, the selectins and the lymphocyte homing receptors. Intercellular adhesion molecule 1 (ICAM-1) is a member of the immunoglobulin superfamily. Intercellular adhesion molecule 1 is known for its importance in stabilizing cell-cell interactions and facilitating leukocyte endothelial transmigration. Intercellular adhesion molecule 1 signaling seems to produce a recruitment of inflammatory immune cells such as macrophages and granulocytes [3].

Endothelial dysfunction and central obesity. The evidence implicating a potential influence of central obesity on endothelial glucose dysfunction include: reduced nitric oxide bioavailability determined by an increased production of reactive oxygen species, the increased vasoconstriction mediated by cyclo-oxygenase-dependent, endothelial formation of prostanoids (likely prostaglandin H2, a potent vasoconstrictor) [2].

Endothelial dysfunction and dyslipidemia. The dyslipidemia associated with metabolic syndrome is characterized by hypertriglyceridemia, increase in small dense.
low density lipoprotein (LDL) and a decrease in high density lipoprotein (HDL) cholesterol. Monocytes release significantly reactive oxygen species when exposed to plasma from hypertriglyceridaemic patients. Nitric oxide inactivation by the reactive oxygen species is an important determinant of endothelial dysfunction. Endothelial protection by HDL cholesterol is mediated by two intrinsic antioxidative enzyme systems: platelet activating factor acetylhydrolase and paraoxonase. HDL cholesterol cause stimulation of nitric oxide synthases and downregulating of tumor necrosis factor-alpha a cytokine involved in systemic inflammation [2].

**Endothelial dysfunction and hypertension.** In hypertension there is an activation of the renin-angiotensin system. Angiotensin II stimulate O2 generation, stimulate cell hypertrophy induced by angiotensin type 1 receptor [2].

**Endothelial dysfunction and hyperglycemia.** Hyperglycemia increase the production of oxygen-derived free radical (higher amounts of oxygen-derived free radical can cause deoxyribonucleic acid damage, significant toxicity or apoptosis), induce the activation of protein kinase C (protein kinase C mediates leukocyte adhesion to the vascular wall, increases fibrinogen binding, overexpression of the adhesion molecules). Hyperglycemia is associated with an enhanced production of advanced glycation end products of endogenous asmetrical dimethyl arginine (competitor for nitric oxide synthases) and vasocostricting prostaglandins [2].

Accumulating research suggests that the low levels of vitamin D were associated with an increased risk of metabolic syndrome and chronic diseases (cardiovascular disease, cancer, diabetes mellitus) [4, 5]. Vitamin D is produced in the skin after exposure to ultraviolet B light (290 to 320 nm), and occurs naturally in a small range of foods. Vitamin D is metabolized by the liver to 25(OH)D (25-hydroxyvitamin D), which is then converted by 1α-hydroxylase enzyme in kidneys to 1,25(D)D (1,25-dihydroxycholecalciferol), or active vitamin D hormone. Circulating 25-hydroxyvitamin D (25(OH)D) concentrations are considered an indicator of vitamin D status (6, 7). Much of the prior work documenting the impact of vitamin D deficiency on endothelial dysfunction. Vitamin D metabolites are important immunomodulatory hormones, which activate monocytes and suppress lymphocyte proliferation, immunoglobulin production, and cytokine synthesis. Vitamin D metabolites has been shown to act as both an up-regulating agent during natural immunity via the enhancement of phagocytosis by monocyte/macrophage populations and a down-regulator during acquired immune response via an inhibitory effect on major histocompatibility complex class II expression by professional antigen-presenting cells [8]. Data indicate that the modulation of 1,25(OH)2D3 by binding to nuclear vitamin D receptors up-regulates protective innate host responses, including the induction of nitric oxide synthase. Some investigators have reported that the human macrophage-like cell line acquires the ability to produce substantial amounts of nitric oxide on stimulation with 1,25(Oh)2D3. In addition to the nitric oxide production induced by 1,25(OH)2D3, this metabolite also up-regulates the expression of 1α-hydroxylase, the enzyme that metabolizes 25(OH)2D3 to 1,25(OH)2D3 due to ligation of Toll-like receptor in macrophages [9, 10, 11]. Replacement of vitamin D has favorable effects on endothelial function. Vitamin D deficiency can be seen as an independent risk factor of atherosclerosis. Hypovitaminosis D-associated with endothelial dysfunction may predispose to higher rates of cardiovascular diseases [12, 13].

The purpose of the present study was to evaluate the Intercellular adhesion molecule 1 in patients with metabolic syndrome with and without vitamin D deficiency or vitamin D insufficiency.

**II. MATERIALS AND METHODS**

We have selected 18 patients (10 women and 8 men) with metabolic syndrome and with vitamin D deficiency or vitamin D insufficiency from the “N Paulescu” National Institute of Diabetes and Metabolic Diseases. Patients were screened initially with a questionnaire detailing medical history, concomitant medications, alchool consumption. The subjects were between 34 and 66 years. The metabolic syndrome were defined according the International Diabetes Federation Criteria. Anthropometric and biochemical parameters were assessed. Blood pressure was recorded. The anthropometric measurement included waist circumference (WC) and body mass index (BMI). BMI was computed as a ratio of weight to the square of height (kg/m2). Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Blood pressure was measured with a mercury sphygmomanometer. The measurement protocol included three measurements: the mean of all 3 measurements was used as systolic and diastolic blood pressure. Subjects were asked to fast for 12 h before blood sampling, which was done between 8.00 and 9.00 a.m. The plasma glucose, serum triglycerides, serum HDL-cholesterol were measured enzymatically. The plasma 25-hydroxyvitamin D was assayed with a radioimmunoassay kit. Although a consensus regarding the optimal level of serum 25-hydroxyvitamin D has not yet been established, most experts define vitamin D deficiency as a 25-hydroxyvitamin D level<20 ng/ml and vitamin D insufficiency as 21 to 29 mg/ml. For all studied end points to date the optimal concentration of 25-hydroxyvitamine D is at least 30 ng/ml. The ICAM1 levels were assayed using an ELISA method from Immuno Biological Laboratories. Results were compared with measurements in 17 subjects with metabolic syndrome but without vitamin D deficiency or vitamin D insufficiency.
A. Statistical Analyses

Data are presented as mean±SD. Clinical characteristics were compared using the t Student test. Pearson’s moment-product correlation coefficients were calculated to evaluate relationships between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences software (SPSS) version 15.

III. RESULTS

There were statistically significant differences in the recorded parameters in patients with metabolic syndrome and with and without vitamin D deficiency or vitamin D insufficiency. Systolic blood pressure, diastolic blood pressure, serum triglycerides was similar in both but age, body mass index, waist circumference, fasting blood glucose, Inter cellular adhesion molecule 1 level were higher and serum HDL cholesterol was lower in patients with metabolic syndrome and with vitamin D deficiency or vitamin D insufficiency.

The main differences between patients with and without vitamin D deficiency or vitamin D insufficiency (expressed as mean ± standard deviation) are presented in Table 1:

IV. DISCUSSION

The correlation analysis of the data revealed a significant negative correlation between the ICAM1 level and the plasma 25-hydroxyvitamin D (r=-0.857, p<0.0001). Vitamin D deficiency can be seen as an independent risk factor of atherosclerosis. Prior studies have described that hypovitaminosis D-associated with endothelial dysfunction may predispose to higher rates of cardiovascular diseases [12, 13]. Experimental data suggest that the treatment with the vitamin D derivatives significantly decreases ICAM1 levels and vitamin D could and affect cell-cell interaction by regulating adhesion molecule levels [14, 15].

A highly significant correlate of ICAM-1 was age (r=0.536, p=0.022). Keaney and his colleagues have investigated the relations of ICAM-1 and age in 3,295 subjects from the Framingham Heart Study. The results showed a significant correlate of ICAM-1 and age. In age- and gender-adjusted regression models, increased ICAM-1 levels were positively associated with age, gender emerged, in the Keaney’s study, as a significant correlate with women averaging ICAM-1 levels that were 9-ng/ml higher than men [16].

We observed that serum glucose also was positively associated with ICAM-1 (r=0.478, p=0.045). Experimental results in human subjects offer les clear evidence for an effect of hyperglycemia on ICAM-1. Separate studies report that glucose challenge increases in circulating levels of other cell adhesion molecule but not of ICAM-1 [17].

Obesity, measured as body mass index or waist circumference also emerged as a strong positive correlate of ICAM-1 (r=0.701, p=0.001, r=0.506, p=0.032). In the Framingham Offspring Study, Keaney and his colleagues found that each 5 kg/m² increase was associated with a 5-ng/ml increase in ICAM-1 levels [16]. Adipose tissue is now recognized as a source of proinflammatory cytokines and may explain the relation of adiposity to ICAM-1 because human endothelial cells in culture release ICAM-1 in response to cytokines such as tumor necrosis factor-alpha and interleukin-1 [18, 19]. Another smaller studies have suggested that adhesion molecules are associated with obesity [20, 21].

We found no significant associations between ICAM-1 levels and systolic blood pressure and diastolic blood pressure. In a cross-sectional study involving 508 apparently healthy men Chae and his colleagues have investigated the association between blood pressure and baseline plasma concentrations of 2 inflammatory markers, Inter cellular adhesion molecule-1 (ICAM-1) and interleukin-6. Therefore, in apparently healthy men, we observed significant graded relationships between blood pressure and levels of ICAM-1 as well as interleukin-6. These data tend to suggest that the increased blood pressure may be a stimulus for inflammation and that this is a possible mechanism underlying the well-established role of hypertension as a risk factor for atherosclerotic disease [22].

We observed no relation between ICAM-1 levels and serum triglycerides or serum HDL cholesterol. Previous studies have shown that patients with severe elevations of plasma LDL-C or triglycerides have increased levels of cellular adhesion molecules [23, 24]. Calabresiand and his colleagues have investigated whether the expression of cellular adhesion molecules is enhanced in individuals with low HDL...
cholesterol. The results showed that a low HDL-C was the strongest predictor of higher ICAM-1. Total and LDL cholesterol were minor, independent predictors of plasma ICAM-1, respectively, with triglycerides never entering the model. These results support the concept that a low HDL cholesterol concentration is a key factor in determining elevated plasma cellular adhesion molecules concentrations [25].

V. CONCLUSION

There were statistically significant differences in the recorded parameters in patients with metabolic syndrome and with and without vitamin D deficiency or vitamin D insufficiency. Systolic blood pressure, diastolic blood pressure, serum triglycerides was similar in both but age, body mass index, waist circumference, fasting blood glucose, Intercellular adhesion molecule 1 level were higher and serum HDL cholesterol was lower in patients with metabolic syndrome and with vitamin D deficiency or vitamin D insufficiency.

Age was a highly significant correlate of ICAM-1. We observed that serum glucose also was positively associated with ICAM-1. Obesity, measured as body mass index or waist circumference also emerged as a strong positive correlate of ICAM-1 in patients with metabolic syndrome and vitamin D deficiency or vitamin D insufficiency.

We found no significant associations between ICAM-1 and systolic blood pressure and diastolic blood pressure. We observed no relation between ICAM-1 and serum triglycerides or serum HDL cholesterol in patients with metabolic syndrome and vitamin D deficiency or vitamin D insufficiency.

Because prior studies have described that hypovitaminosis D-associated with endothelial dysfunction may predispose to higher rates of cardiovascular diseases, patients with metabolic syndrome should be routinely screened of vitamin D deficiency and adequately treated.

REFERENCES


