Endothelial Activation Markers Soluble E-Selectin and von Willebrand Factor in Primary Hyperparathyroidism*

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Abstract. The aim of the study was to investigate the possible alteration of endothelial activity and its reversibility, by the measurement of von Willebrand factor (vWF) and soluble E-selectin (sES) in patients with primary hyperparathyroidism (PHPT), before and after successful parathyroidectomy. Twenty-two patients with confirmed PHPT were prospectively enrolled in the study. Sixteen sex- and age-matched healthy volunteers were used as the control group. The baseline levels of both vWF (146.1±29.1 vs. 118.2±26.3 U/dL, p=0.004) and sES (47.1±19.7 vs. 34.2±13.2 ng/mL, p=0.029) were higher in the patients with PHPT, while at the 6-month follow-up, vWF decreased significantly (120.4±27.3 U/dL, p=0.004) and sES was normal (41.2±21.1 ng/mL, p=NS). No correlation (p=NS) was found between any of the baseline biochemical parameters. In conclusion, some markers of endothelial activation may be higher in patients with PHPT with respect to controls and the decrease of vWF after parathyroidectomy should be considered as a biochemical parameter of improved endothelial function.

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease, with an estimated annual incidence of 20 per 100,000 and a prevalence higher than 2% in postmenopausal women (1, 2). The relationship between PHPT and an increased risk of mortality from cardiovascular (CV) disease has long been reported and in patients with normocalcemic PHPT, an atherogenic metabolic profile has also been observed (3-5). In patients with asymptomatic PHPT, the vasoactivity of endothelium is functionally modified and such alteration may increase the risk of CV diseases. Recent studies have shown that patients with PHPT exhibit similar high rates of traditional CV risk factors and no benefit was demonstrated after surgery in those with mild PHPT, measuring both parameters of inflammation and surrogate CV markers (6, 7). In patients with PHPT, endothelium-dependent vasodilation should be considered an early predictor of atherosclerotic damage and subsequent increased CV risk, and in this setting, several biochemical markers may be used (8, 9). Endothelial dysfunction is common in a wide variety of CV diseases and could be related to plasma indices of endothelial damage and/or dysfunction, such as soluble E-selectin (sES), von Willebrand factor (vWF), and soluble thrombomodulin (10).

The aim of the study was to investigate the possible alteration of endothelial activity, and its reversibility, by the measurement of vWF and sES in patients with PHPT, before and after successful parathyroidectomy (PTx).

Patients and Methods

Twenty-two patients (19 women and 3 men, mean age 62 years, range 35-79 years) with confirmed PHPT were prospectively enrolled in the study. Sixteen sex- and age-matched healthy volunteers were used as the control group. The duration of disease at surgery ranged between one month and 9 years.

Blood samples were obtained from all the participants after overnight fasting and were assayed in duplicate. Plasma vWF antigen was determined by using a two-site enzyme-linked immunosorbent assay (ELISA, monoclonal antibody), while for sES measurement, a colorimetric quantitative sandwich ELISA technique was employed, as previously described (11). Serum intact PTH was measured through chemiluminescent immunometric assay, using two goat monoclonal antibodies against human PTH, while both serum calcium and creatinine were


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measured spectrophotometrically, by standard laboratory methods (12). For each patient, the measurements were repeated one day after surgery and 6 months later.

The reported data are expressed as the mean±standard deviation (SD). Differences between means were tested by Student’s t-test. Pearson’s correlation coefficient (R) calculation was used to evaluate the linear relationship between pairs of variables. The differences were considered significant at a p-value <0.05.

Results

In the patients with PHPT, preoperative serum calcium, PTH and creatinine levels were 2.88±0.26 mmol/L, 193.5±52.1 ng/mL and 74.5±13.2 μmol/L, respectively. Table I reports the sES and vWF serum levels in cases (baseline and 6-month follow-up) and controls and the p-values.

The baseline levels of the biochemical markers of endothelial dysfunction were significantly higher in the patients with PHPT, while no difference was found between pre- and postoperative (one-day after surgery) levels of either vWF (146.1±29.1 vs. 161.2±28.3 U/dL, p=0.088) or sES (47.1±19.7 vs. 36.3±17.0 ng/mL, p=0.058). Six months after PTx, vWF decreased significantly, while the sES levels were normal.

There was no relationship between the age of the patients and vWF (R=0.41, p=0.065) or sES (R=−0.005, p=0.984), as shown in Figure 1. Moreover, no correlation was found between baseline vWF and sES, or between the markers of endothelial dysfunction and routine biochemical parameters (Table II).

Discussion

Studied in rats have shown a direct effect of increased PTH serum levels on the vascular endothelium, which does express PTH receptors (13, 14). Endothelial cell dysfunction is the initiating event in the development of atherosclerosis and the assessment of endothelial function by different methods has emerged as a tool for the detection of evidence of pre-clinical CV disease (8). It has been suggested that the endothelium, a recognized target for PTH, is the site through which chronically elevated PTH could induce arterial hypertension, and in patients with PHPT, the impaired endothelial function improves after successful PTx (6, 15, 16).

In patients with PHPT, although the endothelium function is affected, the intima-media thickness does not change after PTx and thus hypercalcemia does not represent a consistent risk of CV disease (17, 18). The role of elevated serum calcium and PTH in the pathophysioloogy of CV diseases and increased risk of death is still under discussion (19, 20). Both serum sES and vWF levels have been variably associated with a number of common diseases, including atherosclerosis, type 1 and 2 diabetes and PHPT (21). E-Selectin is a lectin-like adhesion molecule involved in the adherence of leukocytes to the endothelium and it has long been suggested that ES plays an important role in the pathogenesis of atherosclerosis (22). Its synthesis seems to be induced mainly when endothelial damage is the result of inflammatory agents and the soluble form of ES released in the blood is biologically active.

Von Willebrand factor is a glycoprotein that plays an essential role in homeostasis and mediates platelet adhesion to the vascular wall, platelet aggregation, serves as a carrier for factor VIII and is regarded as a more conventional marker of endothelial cell activation in various diseases affecting the vascular system (23). The process of atherosclerosis requires endothelial cell activation but not actual endothelial denudation, and is inhibited by the inactivation of vWF (24, 25).

In the present study, no relationship was found between the preoperative standard biochemical parameters, such as serum calcium, creatinine and PTH levels, and the markers of endothelial activation. However, 6 months after PTx, a
reduction of both vWF and sES was observed. Other studies have found improved endothelial function (measured by flow-mediated dilation of the brachial artery) after successful PTx, but not deleterious effects of conservative management of mild PHPT at 2-year follow-up (7, 16).

**Conclusion**

Some markers of endothelial activation may be higher in patients with PHPT in respect to controls and the decrease of vWF after PTx should be considered as a biochemical parameter of improved endothelial function.

**References**


