Osteoprotegerin: A Promising Biomarker in the Metabolic Syndrome - New Perspectives

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Abstract

The metabolic syndrome (MS) is a cluster of cardio-metabolic alterations that has been known to increase the cardiovascular risk in these patients. The pathophysiologial mechanisms underlying this observation remain unclear. In this context, osteoprotegerin (OPG) has emerged as a possible mechanism. The implication of OPG in cardiovascular disease and cardiovascular risk, the expression of this cytokine in different cells involved in the atheroma and the increased circulating concentration observed in these patients reinforce the hypothesis. In this manuscript, the clinical, the analytical and the cellular fields are studied in order to offer a wide perspective over the subject.

Keywords: Metabolic syndrome; Osteoprotegerin; Biomarker

Metabolic Syndrome - Definition and Pathophysiology

The metabolic syndrome (MS) is a cluster of cardiometabolic alterations that include the presence of arterial hypertension, insulin resistance, dyslipidemia and abdominal obesity [1]. Several organizations have proposed different definitions and the definition by the National Cholesterol Education Program’s Adult Treatment Panel III has emerged as the most widely used [2]. Nowadays, the prevalence of the MS is dramatically increasing with the substantial progression of obesity and DM [3] and this is the reason why this syndrome has received more attention lately.

Prospective observational studies generally show that individuals who meet the clinical criteria for MS are at increased risk of cardiovascular events and type 2 diabetes mellitus compared to individuals without the syndrome [4]. In addition, several published meta-analysis concluded that the MS nearly doubled the risk of CV events including stroke, cardiovascular disease, myocardial infarction and cardiovascular mortality [5,6]. It also associated with a 1.5 fold increase in risk of all-cause mortality [7,8].

The pathogenesis of the MS is complex and not clearly understood. Abnormal body fat distribution and insulin resistance have been pointed out as the main key factors implicated. Many different mechanisms are implicated in the process such as hyperinsulinemia, inflammation and coagulation alteration among others [9]. However, all these mechanisms cannot fully explain the increased cardiovascular risk observed in patients with the MS. Thus, extensive research is currently being performed evaluating other possible mechanisms. Osteoprotegerin (OPG) has emerged as a possible mechanism linking the MS and cardiovascular risk.

Osteoprotegerin (OPG)

OPG is a cytokine of the tumor necrosis factor (TNF) receptor superfamily that was first identified in 1997 [10,11]. OPG was initially described as an anti-resorptive cytokine by binding principally to receptor activator of nuclear factor (NF)-κB ligand (RANKL). OPG is part of the OPG/RANKL/receptor activator of NF-κB (RANK) pathway. Classically, this network is involved in bone remodelling, regulates the differentiation and activation of osteoclasts and hence the critical balance between bone formation and bone resorption. Initially, OPG acts as a soluble decoy receptor, negatively regulating the interaction between RANK and RANKL [12,13]. Although OPG was first described in bone remodelling, nowadays, there is emerging evidence of the role of OPG in the pathogenesis of atherosclerosis, calcification and cardiovascular disease [14-17].

Patho-physiological role of OPG in metabolic syndrome

To date, different data both from animal models (high-fat diet fed C57BL6 mice) [18] as well as from humans [19-21] show the relationship between OPG and MS. Furthermore, higher OPG levels are associated with risk of MS. Even, after adjusting for age, gender, ethnicity, glucose and microvascular complications, OPG remained an independent predictor of MS [21].

In these studies, OPG circulating concentration is shown to be increased in MS patients as compared to controls. Besides, OPG is expressed in adipose tissue and this expression is upregulated in patients suffering from the MS [19]. These findings highlight the positive relationship between OPG and the MS drawing attention to adipose tissue and proinflammatory changes associated with the metabolic abnormalities. OPG, increased in MS patients may trigger adipose tissue proinflammatory changes in MS and high fat diet induced obesity.

The fact that OPG is expressed in adipose tissue and that its expression is upregulated in MS patients opens up the possibility that patients with increased circulating OPG may benefit from a dietary intervention combined with exercise focused on reducing fat. Further investigation is required to confirm the usefulness of OPG as a potential target of future therapies in the cardiovascular field. Furthermore, different common treatments in these patients have
shown to have an effect on OPG levels [22]. In this regard, selection of the therapy may be based on the modulation of OPG levels in order to implement the effects.

On the other hand, OPG positively associates with intima media thickness, coronary arterial calcium and cardiovascular risk factors [22]. Patients with elevated OPG circulating levels exhibit increased intima media thickness, presence of plaques or coronary arterial calcium [19]. OPG may add incremental information in addition to traditional risk factors and in combination with other cardiovascular risk markers. However, more studies in larger cohorts are needed to fully confirm the usefulness of OPG as a cardiovascular marker in atherosclerotic burden in MS patients.

Furthermore, the in vitro mechanism by which OPG is involved in the atherogenic and calcification process would be also worth exploring due to the relationship between MS and increased cardiovascular risk. In addition, OPG has been suggested to play a role in atherosclerosis being expressed by different cells involved in the atherogenic process. OPG seems to participate in vascular physiology and pathology in unique ways to promote endothelial cell survival, angiogenesis, monocyte or endothelial cell recruitment, and smooth muscle cell osteogenesis and calcification [23].

This molecule mediates different processes in cells known to be implicated in the atherogenic process such as endothelial cells or smooth muscle cells among others. OPG stimulates expression of several adhesion molecules as well as monocyte binding to endothelial cells [24]. Moreover, a proinflammatory milieu that characterizes MS, leads to secretion of OPG by endothelial cells [25]. When exposed to stimuli known to be upregulated in the MS, endothelial cells express and release OPG. OPG expression is increased under hyperglycemia and hyperinsulinemia and its release upregulated by inflammatory stimuli (OPG is expressed on endothelial cells and modulated by IL-1β, insulin, and glucose, by Pérez de Ciriza et al).

Besides, in vascular smooth muscle cells, recombinant OPG promotes proliferation [26]. This evidence suggests that OPG may be released from damaged endothelial cells in response to the proinflammatory state that characterizes MS. The finding that OPG promotes the release of proinflammatory molecules on endothelial cells, suggests that OPG is not only a marker but also a mediator in atherogenesis. More studies need to be carried out to clarify the link between elevated OPG and the clinical consequences in patients with the MS.

The discovery of the expression and regulation of OPG in these cells as well as in adipose tissue may have a tremendous impact for the control of the disease. These findings will lead to a potential therapeutic target in patients with increased OPG, to reduce the deleterious effects observed in these patients.

**OPG as a potential biomarker**

The enthusiasm raised by OPG as a potential biomarker in metabolic syndrome patients is hampered when looking at the different published studies in detail. Interpretation and comparison of the results from different studies is complicated due to the different samples, ELISA kits and the lack of an international standard that lead to wide differences in OPG levels across studies [27,28].

Several studies [29-31] focused on establishing the adequate pre-analytical and analytical conditions necessary to improve OPG measurement. In order to implement OPG determination in the clinical laboratory setting, it is vital to better control all the possible sources of variability and to allow comparison among studies.

Differences in concentration between serum and plasma (EDTA, heparin and citrate) specimens were reported. Serum samples yield lower OPG concentration when compared to plasma [29]. As a result, each laboratory should determine its own reference values and the specimen for collection due to the differences observed. Furthermore, comparison of results obtained in different specimens should be avoided.

The potential sources of circulating OPG as well as the pre-analytical and analytical factors in OPG measurement studied [29] set a stone to the future development and implementation of OPG determination in clinical practice. This knowledge will allow the transfer from the research laboratory towards the clinical setting and the implementation of OPG use as a cardiovascular biomarker.

Taken all these data together, determination of OPG in MS shows promising in helping the clinician better stratify the patients at higher risk of cardiovascular disease in combination with other traditional markers. However, further studies are necessary in order to better clarify and understand the role of OPG in MS patients as well as its potential implication as a therapeutic target.

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