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Osteoprotegerin (OPG) as Significant Biomarker of Cardiovascular Disease

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Abstract

Osteoprotegerin (OPG) is a soluble glycoprotein, which is primarily involved in bone metabolism and is also part of the superfamily tumor factor necrosis receptor TNF. Earlier studies showed that OPG levels of plasma are an independent cardiovascular risk factor. In combination with vascular calcification, myocardial infarction, and stroke, OPG levels in the blood also increase. Previous studies indicate an increase in the levels of OPG in diabetic patients who die of cardiovascular disease. OPG is deposited at the sites of damage to the inner artery wall and merges with fatty deposits that harden in the form of plates and eventually cause a blockage in the blood vessels and occurrence of atherosclerosis, thus caused myocardial infarction or heart attacks. Moreover, patients with diabetes develop intra-endothelial dysfunction in addition to the patient's CV risk factors such as hypertension, obesity, and dyslipidemia. Given the importance of the OPG in cardiovascular diseases, including atherosclerotic diseases, as a biomarker. Since OPG's function remains obscure, evidence of positive association with cardiovascular disease and diabetes-related cardiovascular disease has been presented from previous studies. Therefore, the purpose of the article was to provide an overview of the main aspects of OPG in cardio-vascular and heart diseases associated with diabetes in physiological and pathophysiological terms.

INTRODUCTION

Osteoprotegerin (OPG) is a soluble glycoprotein, which is primarily involved in bone metabolism and is also part of the superfamily tumor factor necrosis receptor TNF [1]. OPG is known to inhibit osteoclastogenesis as a soluble receptor for the NF-kappaB ligand-receptor activator (RANKL) [2]. OPG is secreted by osteoblasts, stromal cells in the bone marrow, fibroblasts, T-lymphocytes and is a major regulator for bone osteoclastic resorption [3]. It is also present in many other tissues, including vascular endothelium smooth muscle cells. OPG can cause many infections and diseases, including diabetes, silent ischemia of the myocardial cavity, acute cardiac infarction, and associated ventricular dysfunction [4]. OPG is also highly expressed in the heart, lung, kidney, liver, and other different tissues bone marrow [5].

The Human OPG gene consists of five exons of more than 29 kilobytes and is clustered on chromosome 8 (8q24), Exon 5 contains the translation termination codon [6]. In addition, three structural fields influence the biological function to constitute the OPG molecule. The N-terminal part is a cysteine-rich field that is important for osteoclastogenesis, while the C-terminal contains a heparin-binding domain and a death domain. The latter is able to interact with various proteoglycans including heparan sulfate and heparin [7]. Hematopoietic cells and osteoblasts stromal cells have demonstrated the principal biological activity of OPG and prevented the development of active osteoclasts, even in the presence of stimuli such as 125(OH)2 vitamin D3, parathyroid hormone, prostaglandin E2 (PGE2), and interleukin (IL)-11. Moreover, the increase in bone mass was reported with the prevention of bone loss in estrogen-deficient animals [8], when purified OPG was administered to mice, So the name 'Bone Protector' meaning has been coined [9]. This review is aimed at focusing on the participation of OPG in diabetes and cardiovascular diseases related to diabetes, like metabolism, endothelial dysfunction, diabetic nephropathic and atherosclerosis, and heart failure. Determining the mechanism of the potential role of OPG in diabetes and diabetes-related cardiovascular disease.

METHODS

Search Strategy

The search strategy was based on published articles and literature focusing on links between increased OPG levels and CVD severity. Several investigations have shown that increased OPG levels are related to a higher risk of cardiovascular disease and diabetes-related cardiovascular disease. The authors read many articles in-depth and extracted arti-

cles pertinent to the topic. In a final analysis, a total of eight articles were eligible. In many ways, the studies found were heterogeneous, including in the population investigated, and the findings parameter is summarized in Table 1. The search period ended in March 2021.

Table 1: Studies that evaluate the association of OPG levels with cardiovascular disease and cardiovascular disease associated with diabetes.

Study	Population	Findings	Ref
Browner et al. 2001	Diabetes mellitus	OPG is associated with cardiovascular mortality.	[10]
Dhore et al. 2001	Vascular surgery	OPG levels are positively associated with atherosclerotic calcification.	[11]
Di et al. 2017	Heart failure	OPG levels were associated with an approximately fivefold increased risk of Heart failure.	[12]
Vik et al. 2011	General population without a prior myocardial infarction and ischemic stroke	OPG levels were associated with future risk of myocardial infarction, ischemic stroke, and mortality of ischemic heart disease.	[13]
Mogelvang et al. 2013	General population	OPG levels were associated with the risk of myocardial infarction, ischemic stroke, and mortality of ischemic heart disease.	[14]
Duan et al. 2017	Diabetes mellitus	OPG is an indicator in the pathogenesis of diabetes and is a potential biomarker of insulin resistance in subjects with diabetes and prediabetes.	[15]
Wang et al. 2015	Diabetes with nephropathy	OPG levels are associated with the development of nephropathy in diabetes	[16]
Secchiero et al. 2006	Diabetes mellitus	OPG levels are associated with endothelial dysfunction	[17]
Olesen et al., 2005	Diabetes mellitus	Increased OPG levels in the aortic tunica media are associated with vascular calcification	[18]

OPG AND CARDIOVASCULAR DISEASE (CVD)

In 2001, published the first correlation between OPG and CVD in humans, reporting that high OPG levels in plasma and increased CVD mortality was associated with a cohort of 490 women over 65 years [10]. In recent years, the relationship of vascular biology and bone-regulating proteins has shown that OPG acts as a potential mediator of calcification, and accumulation can be compensatory to calcification by vascular vessels, and thus correlates with endothelial dysfunction. It is also noted that the expression and regulation of OPG in the blood vessels is due to the fact the inflammatory response is a normal sequence of plaque rupture [19, 20]. In addition, arterial calcification is part of the atherosclerotic process that leads to clinical CVD. It should be noted that OPG is present in atherosclerotic plaques [11].

The exact function of OPG remains unknown. In contrast, there idea of OPG as a vascular calcification inhibitor and therefore a protector of the arterial wall, a series of outcome studies have recently indicated that plasma OPG is a strong predictor of cardiovascular disease CVD [21]. As OPG, works positively with calcification of the coronary artery and Hardening of the blood vessels and the presence of plaques are unstable atherosclerosis. [21, 22], and that the presence of OPG with blood platelets may be a link between OPG levels and Coagulation and thus may reflect the presence of OPG simply affliction cardiovascular disease, including heart failure [12]. Whereas, OPG levels are associated with future risks of myocardial infarction and stroke. However, the association between OPG and CVD maintains its significance even after careful control of all traditional risk factors [13, 14].

OPG AND CVD RELATED TO DIABETES

CVD remains the most common cause of death in the developed world, including cardiac disease and stroke, and in diabetes, 65% of all deaths in patients with Type 2 diabetes mellitus (T2DM) occur as a result of CVD [23]. The role of OPG in the pathogenesis of CVD in diabetes is an important topic in our research group. Clinical studies indicate that OPG serum concentrations are linked to cardiovascular, diabetic, and vascular coronary artery disease [15]. Recent studies show that OPG can be a new marker for atherosclerosis and cardiovascular diabetic complications [24]. High levels of OPG in diabetic individuals have been reported and independently associated with diabetic complications of the microvascular [25]. Moreover, recent studies indicated that RANKL and OPG play an important role in bone pathology related to DM [26]. It is well established that the NF-κB pathway and its downstream players could be triggered by the OPG/RANK/RANKL system [27], closely linked to the insulin Resistance pathogenesis [28]. Therefore, OPG may play a role in insulin resistance through the NF-κB pathway. Evidence has recently shown that the system OPG/RANK/RAKL may have a role to play in diabetes pathogenesis; blocking the pathway has been improving insulin resistance in the liver and preventing diabetes mellitus from developing [29].

Another study suggested that increased serum OPG levels in people with diabetes were considered to be inadequate compensatory auto-defensive responses against endothelial vascular dysfunction and atherosclerosis development [16]. Thus, some studies show that increasing OPG production is an early occurrence in the natural history of diabetes and may contribute to vascular endothelial cell dysfunction associated with diabetes [17]. A further study suggested that increased levels of osteoprotegerin could constitute the (incomplete) defense process against other factors that promote arterial calcification, atherosclerosis, and other forms of vascular damage [30].

The role of diabetes in the development of CVD is crucial. Indeed, in diabetic patients [31], the mortality rate from

acute myocardial infarction has been increased fivefold. Interestingly, noted no significant differences between carotid plaques in diabetics and non-diabetics. However, superficial thrombosis appears to persist longer after symptoms in ischemic plaques diabetic patients or patients with impaired glucose tolerance [32]. Moreover, hyperglycemia accelerates atherosclerosis and increases the risk of acute myocardial infarction (AMI), which worsens the prognosis in diabetic patients. Whereas, high levels of OPG cause changes in the endothelium of blood vessels in patients with diabetes that may be responsible for the association with multiple vascular complications [33, 34].

In fact, high OPG levels cause the formation of free radicals (carbonyl radicals, peroxides) that have a significant impact on atherosclerosis, and thus we find that people with heart disease have increased OPG concentration. Multiple associations between levels of OPG and cardiovascular factors of risk (including age, smoking, blood pressure, insulin resistance, obesity, and diabetes) and inflammatory diseases, such as inflammatory bowel diseases have been found to increase the risk of cardiovascular diseases [35, 36].

Interestingly, improving the treatment of risk factors or inflammation leads to lower OPG levels with age [37]. The association between OPG and cardiovascular disease maintains its significance even after careful control of all these risk factors, suggesting an additional mechanistic role of OPG. Accordingly, under certain conditions, OPG may also act as a risk factor for cardiovascular disease [38]. Moreover, OPG levels are gender-specific and mean that the levels of OPG for women are higher than for men. It has been reported that the OPG rates are increased by (30%) in women with diabetes compared to healthy individuals [10], and it was found that OPG levels accumulate in the aortic tissues of patients with first and second diabetes [18].

CONCLUSION

Given that the incidence of cardiovascular disease and cardiovascular diseases associated with diabetes is high, non-invasively monitored methods for vascular changes and biochemical markings, such as measurement of OPG, are clear and essential to know the increased risk of cardiovascular diseases. This biomarker can be used in the clinical field for early diagnosis of atherosclerosis and an increased risk for cardiovascular results in the general population is associated with a high OPG concentration. There is a need to further study the mechanism of OPG and the predictional performance of OPG in clinical routine as a biomarker.

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ETHICAL STATEMENT

The presented manuscript is the original study of the authors and each of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal. Additionally, that the Work is factually accurate and contains no matter libelous or otherwise unlawful; that I have substantially participated in the creation of the Work. All of the authors have approved the contents of this paper and have agreed to the Focus on Medical Sciences Journal's submission policies.

CONFLICT OF INTEREST

The author does not have any conflict of interest (financial and other).

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AUTHORS' CONTRIBUTION

Each of the authors participated in the study and they took all the responsibility to carry out this study. Additionally, the work described in the manuscript is our own and our individual contribution to this work is significant enough to qualify authorship. Furthermore, the authors also agree to the authorship of the article in the following sequence for names.

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