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Mini Review Open Access

Can Osteoprotegerin be a Target of Therapy in Type 2 Diabetes Mellitus?

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Abstract

Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor receptor superfamily, which exhibits the close link to Cardiovascular (CV) disease in Type 2 Diabetes Mellitus (T2DM). Recent clinical studies have been shown that elevated OPG might be a marker of vascular calcification / remodeling and CV events and CV mortality in T2DM without known CV disease. However, it remains unclear whether OPG would be a target for therapy of diabetics with antidiabetic drugs and statins. The aim of the mini review: to summarize knowledge with respect to OPG utilization as predictor of CV adverse effects and as a target of therapy in T2DM. The review is discussed the evidence regarding possibility to prevent microvascular and macrovascular complications in diabetics through control of OPG level as a target in therapy. Although there are not irresistible findings that the post-treatment OPG level in diabetics and CV events might be related, possibility to use OPG for risk stratification of vascular remodeling / ectopic calcification and CV-related mortality in T2DM appears to be attractive. The future investigations are needed to explain whether serum OPG would be informative for biomarker-guided therapy in T2DM individuals.

Keywords: Diabetes mellitus; Osteoprotegerin; Cardiovascular events; Target therapy; Prediction

Abbreviations

ApoE: Apolipoprotein E; CV: Cardiovascular; DPP-4: Dipeptidyl Peptidase 4; GLP-1: Glucagon-Like Peptide-1; GLUT1: Glucose Transporter-1; HbA1c: Glycated Hemoglobin; hs-CRP: High-Sensitive C-Reactive Protein; IL: Interleukin; LV: Left Ventricular; OPG: Osteoprotegerin; RANKL: Receptor Activator of Nuclear factor-Kappa B Ligand; SMCs: Smooth Muscle Cells; T2DM: Type 2 Diabetes Mellitus; TNF: Tumor Necrosis Factor; TRAIL: TNF-Related Apoptosis-Inducing Ligand

Introduction

Type 2 Diabetes Mellitus (T2DM) is a serious global health burden with increasing prevalence predominantly in the developing countries [1]. Development and progression of T2DM closely associate with microvascular and macrovascular complications negatively affected all cause and Cardiovascular (CV) mortality rates [2,3]. However, contemporary treatment approaches based on improved glycemic control have been exhibited an ability to contribute in decreased CV complications related to T2DM, whereas utilization of modern strategy is higher cost and appears to be economic challenge to the health care system [4-6]. In this context, several circulating biomarkers represented differential metabolic profiles, related to vascular complications and predicted CV events may be clinically helpful for risk stratification and individualized treatment for T2DM patients [7,8]. Although various biomarkers (natriuretic peptides, galectin-3, soluble ST2, growth-differentiation factor-15, signature of microRNAs, oxidative stress components, inflammatory cytokines, biomarkers of coagulation and endothelial damage) are widely used as predictors of adverse clinical outcomes in several settings [9-12], there is concern regarding their role as biological target in T2DM care [8,13].

Osteoprotegerin (OPG) is a secretory glycoprotein that belongs to the Tumor Necrosis Factor (TNF) receptor family and involves in the regulation of bone metabolism, ectopic calcification including vascular calcification processes, vascular tone enhance and endothelium regeneration [14]. Elevated level of OPG has found in CV disease patients, individuals with asymptomatic atherosclerosis, hypertension, T2DM, metabolic syndrome, chronic renal disease, and malignancy [14-18]. However, evidence regarding OPG may be causative for CV events in T2DM patients appears to be controversial [19-21] and requires more investigations. The aim of the review: to summarize knowledge with respect to OPG utilization as predictor of CV adverse effects and as a target of therapy in T2DM.

Biological Role of OPG

OPG (also known as Tumor Necrosis Factor [TNF]-SF11B) is a soluble decoy receptor for the Receptor Activator of Nuclear factor-Kappa B Ligand (RANKL) shown to be a key regulator of osteoclast differentiation and bone remodeling [22]. This effect is related to an ability of OPG to inhibit the expression of bone resorption activators Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) on surface of the target cells [23]. It has been suggested that 1α, 25-dihydroxyvitamin D3 is able to promote the secretion of OPG by osteoblasts and prevents osteopenia of bones [23], while similar assumption has not been confirmed in the clinical studies [24,25]. Overall, expression of OPG was found at the surface of wide spectrum of cells. Therefore, several cells distinguishing osteoblasts, i.e., active mononuclears, macrophages, T-cells, endothelial cells, bone-marrow progenitor cells may produce and secrete OPG due to cytokines' stimulation [26]. In this context, overproduced OPG is considered as a marker of inflammatory activation with various biological effects on target cells [27].

The Role of OPG in Vascular Remodeling and Diabetes

OPG has been hypothesized to modulate vascular remodeling and functions. As a suppressor of TNF-Related Apoptosis-Inducing Ligand (TRAIL), OPG negatively affects matrix metalloproteinase-9 activity in smooth muscle cells (SMCs) in the media of arterial wall and it prevents

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the chemo-attractive effect mediating TRAIL on SMCs [28]. As a result, TRAIL-related effects on death receptor-4 and death receptor 5 are inhibited and cell survival is increased [29]. Interestingly, among T2DM subjects OPG has associated with reduced parasympathetic function and exhibited a neuroprotective capability [30]. Additionally, OPG seems to exert proatherogenic and prodiabetogenic effects via pro-inflammatory capability mediating insulin resistance [31,32]. Furthermore, OPG may promote beta cell dysfunction directly and through the upregulation of the local renin-angiotensin system activity [33]. In dysmetabolic individuals (diabetics, obese, metabolic syndrome individuals) serum OPG correlated positively with HbA1c, adiponectin, leptin, high-sensitive C-reactive protein (hs-CRP), and RANKL levels, as well as negatively with leptin [34]. Although adipose tissue and bone tissue can influence glucose metabolism, potentiality in insulin-dependent manner, OPG seems to be a conductor of interplaying both tissues. Indeed, Glucose Transporter-1 (GLUT1) expression on osteoblasts has not altered, and insulin did not reverse most of the effects of glucose [35]. In this context, OPG might mediate capability of osteoblasts glucose uptake [36]. Finally, OPG attenuates vascular wall thickness, vascular remodeling, restores endothelial function, prevents arterial calcification and neuropathy, and stabilizes plaque formation [30,36,37].

OPG and CV Outcomes

Elevated level of circulating OPG was found in general population at higher risk of T2DM, dysmetabolic individuals including T2DM beyond CV disease and in patients with known CV and renal disease. Data of epidemiological and prospective studies have indicated that in patients with known CV disease elevated serum OPG levels are associated with several inflammatory markers (hs-CRP, TNF, interleukins), arterial stiffness, as well as atherosclerosis (based on plaque determination and calcium scores), stable angina and myocardial infarction, acute and chronic heart failure [20,21,38-40]. Modulating vascular stiffness and ectopic calcification OPG plays a pivotal role in vascular remodeling and endothelial dysfunction that are considered a clue of CV disease development and progression. In this context, OPG was found as a powerful marker of microvascular and macrovascular complications [41], while a causality role of OPG with respect to both settings are not completely defined. However, there is no confided evidence that OPG would be factor of tissue damage. Contrary, elevated OPG is rather protector from ectopic calcification and progressive remodeling that might be utilized for risk stratification among general patients' population and T2DM individuals with CV disease beyond classic CV risk factors [42]. Moreover, there are results of the clinical trials elucidated that elevated serum levels of OPG predicted CV outcomes including death in subjects with known CV disease and T2DM [42-44]. Therefore, serum OPG may be a marker for the severity of diabetic nephropathy [45]. Whether is link between elevated OPG as a marker of vascular calcification / remodeling and CV events and CV mortality in T2DM without known CV disease still remains unanswered [46,47].

The Role of OPG Gene Polymorphisms in Diabetes-Related Vascular Complications

Contributing of OPG in CV disease and events among T2DM population might mediate via OPG gene polymorphisms. Based on previous animal investigations it has found that OPG knockout associated with increased bone resorption, arterial calcification and osteoporosis [16,47]. The OPG deficient mice (OPG -/- mice) showed a higher systolic blood pressure, larger Left Ventricular (LV) chamber and reduced wall thickness than did age-matched wild type mice, as well as a greater heart weight / body weight ratio [48]. Apolipoprotein E (Apo E)-KO mice with loss of the OPG gene has exhibited reduced ability to formation of angiotensin II-induced aneurysm [49].

Clinical studies haven't reported controversial results regarding predictive relevance of OPG polymorphism. Soysal-Atile et al. [50] reported that the A163G polymorphism of the OPG gene was not associated with microvascular or macrovascular complications of T2DM. Contrary, Duan et al. [51] presented data regarding the associations of 21 single-nucleotide polymorphisms in OPG gene with elevated diastolic blood pressure. Yet, T245G, T950C, and G1181C gene polymorphisms of the OPG gene were related to the development of peripheral arterial occlusive disease and critical limb ischemia in T2DM individuals [52]. Mankoč et al. [53] have shown that polymorphisms of the OPG genes rs2073618 (located in exon I) and rs3134069 (located in the promoter region) might relate to diabetic retinopathy in Slovenian patients with T2DM. Finally, OPG gene may be implicated in the pathogenesis of target organs damage in T2DM, while the predictive value of polymorphisms in OPG gene requires more investigations.

The Effect of Antidiabetic Drugs on OPG and Vascular Remodeling

It remains unclear whether treatments for T2DM are capable of promoting or inhibiting vascular remodeling and ectopic calcification. There is evidence regarding an ability of exogenous insulin to down-regulate OPG in vitro and in vivo and attenuate vascular calcification [53]. Although insulin may reduce an expression of OPG / RANKL in vasculature in a dose- and time-dependent manner, the role of exogenous insulin in long-term control for development and progression of tissue damage appears to be controversial [54] and it requires more investigations. This controversial investigation appears to be unclear effect of insulin on calcified cells. On the one hand, insulin may induce ectopic calcification [54]. On the other hand, acute hyperinsulinemia is able to decrease plasma level of OPG in T2DM [55]. Whether increased levels of OPG in arteries' wall and plasma in T2DM subjects would be predicted CV risk related to the hyperinsulinemia is not fully clear [55].

Pre-clinical and clinical studies have been shown that novel classes of antidiabetic drugs, i.e., Glucagon-Like Peptide (GLP)-1 receptor agonist and dipeptidyl peptidase 4 (DPP-4) inhibitors GLP-1 can directly and functionally interact with osteoblastic cells, possibly through a GPI / IPG-coupled receptor [56,57]. Interestingly, that GLP-1 receptor agonist liraglutide and probably DPP-4 inhibitors might not exert osteogenic effects in diabetic states. Is this effect class specifically or not it is not unclear. By now, in animal model short administration of GLP-1 receptor agonist exenatide leaded to be increase osteocalcin gene expression and the OPG / RANKL ratio - at the expense of an augmented OPG-above corresponding control values in the tibia [58,59]. However, there is no evidence regarding novel GLP-1 receptor agonists such as taspoglutide and albiglutide on OPG-mediated vascular calcification and vascular remodeling. Overall, GLP-1 receptor agonists may probably reverse the bone alterations and attenuate ectopic calcification via OPG-depended pathways.

The effect of thiazoledinediones on circulating OPG is controversial. Nybo et al. [60] reported that rosiglitazone among patients with T2DM reduces the plasma level of OPG. Esteghamati et al. [61] have been compared the anti-inflammatory properties of pioglitazone and metformin with respect to their effect on serum concentrations of OPG newly diagnosed T2DM. Authors reported that

both drugs leaded to be comparable effect on decreased serum OPG. Park et al. [62] have revealed that pioglitazone in T2DM individuals decreased OPG and hs-CRP levels, whereas in metformin group biomarkers' levels were unchanged. Unfortunately investigators did not assay vascular calcification / remodeling in the study. Koufany et al. [63] in animal model has confirmed that pioglitazone might reduce serum level of RANKL and OPG, decreased the level of inflammatory bone destruction and protected the bone microarchitecture. However, there is evidence that Interleukin (IL)-17 / RANKL-dependent ectopic calcification could be controlled by pioglitazone via inhibition of retinoic acid receptor-related orphan nuclear receptor γt and activation of peroxisome proliferator-activated receptor γ. Whether these findings would be clinically relevant is not still clear. Further studies are needed to determine the effect of thiazoledinediones on bone formation, ectopic calcification and vascular remodeling.

Theoretically, metformin may act as an inhibitor of OPG / RANKL / RANK system, while final result of metformin on bone metabolism, ectopic calcification and vascular remodeling might be variable. Metformin attenuated the suppression on proliferation with increased expression of Col I, OCN, and OPG, meanwhile suppressing metal matrix proteinases 1 and 2 [64]. Overall, metformin has attenuated the suppression effect of high glucose to the osteoblast proliferation and gene expression, more prominently in earlier stage of T2DM [65]. On the other hand, metformin has been exhibited suppressive effect on bone resorption possibly by lowering the RANKL / OPG ratio and reducing the number of osteoclasts [66].

The role of sulphonylurea antidiabetic drugs in OPG controlling is uncertain [67] and requires explanation.

Impact of Statins on OPG Level

Statins are widely used in the patients with T2DM aimed to treat dyslipidemia, reduces vascular inflammation, and prevent CV events / CV mortality / all-cause mortality. T2DM patients with coronary artery disease / atherosclerosis showed derangements in serum levels of all vascular calcification inhibitors compared with those in healthy controls. The results of clinical studies have reported controversial effect of statins on OPG level. Usually, T2DM patients with known asymptomatic and symptomatic atherosclerosis on statin therapy had reduced serum RANKL / OPG ratio, as compared to untreated patients [68]. Short-term atorvastatin and simvastatin treatment significantly decreased serum OPG level [69,70]. Contrary, fluvastatin administration could increase the OPG levels and attenuate vascular calcification [71]. Importantly, that statins may attenuate the progenitor cell mobilization from bone marrow via RANKL-induced stimulation of cell proliferation, which is enhanced through OPG expression [72]. Rationality to use of statin aimed restore endothelium integrity and function through OPG / RANKL activation pathway in progenitor cells is widely discussed [73]. However, the role of statins in the bone-vascular axis is unknown and the clinical relevance of these findings requires further investigation.

Conclusion

Anti-diabetic drugs and statins might be uncertain effect on OPG level in T2DM patients. There is not irresistible evidence regarding possibility to use OPG as a target in therapy of diabetes. However, the future investigations are needed to explain whether serum OPG would be informative for biomarker-guided therapy in T2DM individuals with and without known CV disease.

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