Nat. Volatiles & Essent. Oils, 2022; 9(1): 729-735

NVEO
Natural Volatiles &
Essential Oils

An Overview Of Osteoprotegerin And Its Possible Relation To Diabetic Kidney Patients

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Abstract

Background: Chronic kidney disease (CKD) is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage. Osteoprotegerin (OPG) is largely expressed by osteoblast lineage cells of bone, epithelial cells of the gastrointestinal tract, lung, breast and skin, vascular endothelial cells, as well as B-cells and dendritic cells in the immune system , it is also known as osteoclastogenesis inhibitory factor (OCIF) or tumour necrosis factor receptor superfamily member 11B (TNFRSF11B), is a cytokine receptor of the tumour necrosis factor (TNF) receptor superfamily encoded by the TNFRSF11B gene located on chromosome 8 at position 8q24.

Keywords: Osteoprotegerin

Introduction

Diabetic kidney disease (DKD) is a common microvascular complication of type 1 and type 2 diabetes, diagnosed in up to 40% of patients with long-standing DM. It manifests clinically as persistent proteinuria, with a gradual irreversible decrease in glomerular filtration rate leading to end-stage renal disease (ESRD) **(1).**

Chronic kidney disease (CKD) is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage **(1).**

Its pathogenesis is complex and is characterized by increased excretion of persistent albuminuria and, or progressive decrease of glomerular filtration rate (GFR), which eventually develops into end-stage renal disease (ESRD) **(2)**.

DKD is the leading cause of CKD and end-stage renal disease. About 30–50% of the global ESRD is caused by DKD. DKD prevalence is continuously rising with disparate growth in low to middle-income countries and under-recognized as global disease burden **(3).**

Osteoprotegerin (OPG)

Osteoprotegerin (OPG), a glycoprotein traditionally implicated in bone remodeling, has been recently related to cardiovascular disease (CVD). Human studies show a positive relationship between circulating OPG, vascular damage, and CVD, and as such OPG has emerged as a potential biomarker for CVD**.**

Osteoprotegerin: Discovery and Structure

Osteoprotegerin (OPG) was first identified in 1997 simultaneously by two different research groups which were involved in a foetal rat intestine complementary deoxyribonucleic acid- (cDNA-) sequencing project when they discovered a new possible member of the tumour necrosis factor (TNF) receptor superfamily. It was named OPG because of its protective effects in bone (Latin: "os" bone and "protegere" to protect) **(4).**

At the same time, another research group, found a novel binding protein with no homology to known proteins in the conditioned medium of human embryonic lung fibroblasts which inhibited osteoclastogenesis. They termed this protein osteoclastogenesis inhibitory factor (OCIF) **(5).**

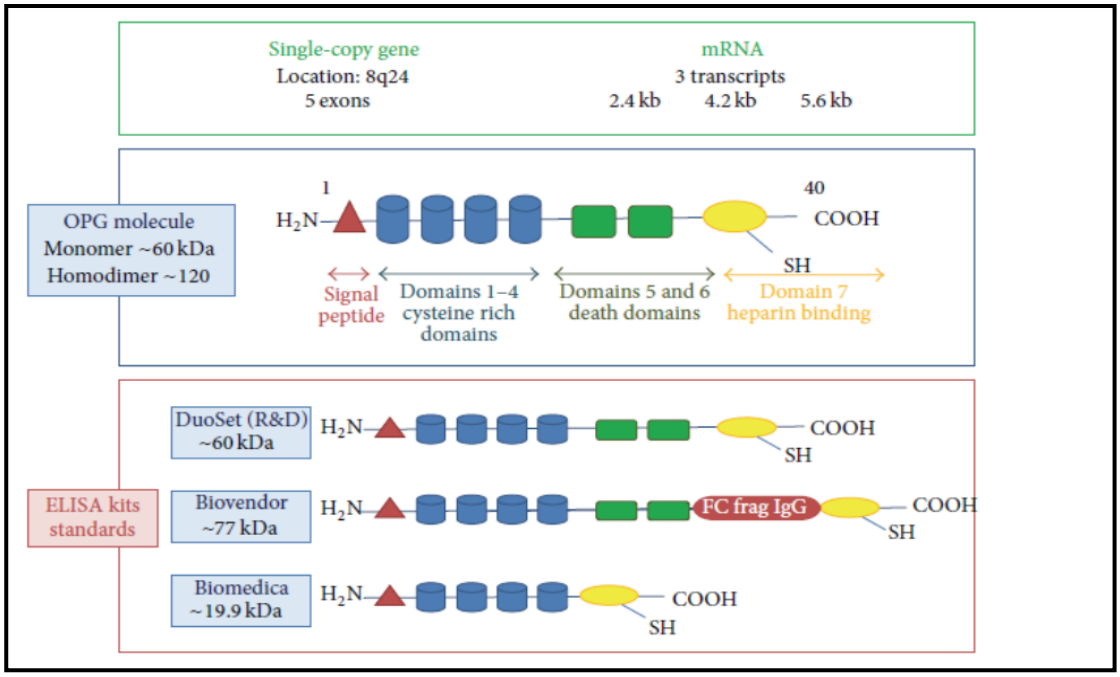

Fig. (1): Osteoprotegerin structure and different ELISA kit standards **(6).**

Biochemically, OPG is a basic secretory glycoprotein composed of 401 aminoacids (Aa) that gives a monomeric weight of 60 kilodaltons (kDa). It has seven structural domains

1) **Domains 1–4:** four cysteine rich pseudo-repeats structurally related to the TNF receptor family located in the N-terminal that is essential for the inhibition of osteoclastogenesis.
2) **Domains 5-6:** two death domains at the carboxy-terminal end of the protein contain apoptosis-mediating death domain homologous regions.
3) **Domain 7:** a heparin binding site is located in the C-terminal, capable of interacting with numerous proteoglycans as well as a free cysteine residue required for di-sulphide bond formation and dimerization .**(7).**

Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and Receptor Activator of Nuclear factor-κβ Ligand (RANKL) bind to OPG with similar affinities and they share common residues on OPG for their interaction **(7).**

OPG/RANK/RANKL Pathway:

The receptor activator of nuclear factor-κβ (RANK), another member of the TNF receptor superfamily, is a type I homotrimeric transmembrane protein consisting of 616 Aa including a signal peptide (28 Aa) with a 383-acid intracellular domain, a short transmembrane domain of 21 Aa, and a large C-terminal cytoplasmic domain. It is expressed on osteoclast precursors, mature osteoclasts, dendritic cells, B and T cells, fibroblasts, articular chondrocytes, and some cancer cells including breast and prostate cancers, tumours with very high bone metastasis potential **(8).**

After binding its ligand (RANKL), RANK assembles into functional trimeric receptor and this trimerization is required to generate multiple intracellular signals that regulate cell differentiation, function, and survival, among the other functional osteoclasts **(9)**.

Receptor activator of nuclear factor-κβ ligand (RANKL) belongs also to the TNF superfamily and it is a type II homotrimeric glycoprotein consisting of 316 Aa, which exists as a transmembrane protein (40 to 45 KDa cellular form) and in a soluble form (31 KDa). Typically, RANKL is expressed and secreted by osteoblasts. RANKL is also expressed in activated T-lymphocytes, lymph nodes, thymus, mammary glands, lungs, spleen, and bone marrow **(10).**

While OPG presents as a soluble bone protector, RANKL is considered to be a stimulator of bone resorption through the induction of osteoclasts' differentiation and activation of mature osteoclasts**. (9).**

OPG seems also to play a key role on cell survival, via its interaction with tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), another member of the TNF superfamily. TRAIL functions as a homotrimer and it is expressed as a type II transmembrane protein. The extracellular domain of this protein is proteolytically cleaved from the cell surface to act as a soluble cytokine. **(11)**.

Classically, the OPG/RANK/RANKL network is involved in bone remodelling and regulates the differentiation and activation of osteoclasts and hence the critical balance between bone formation and bone resorption.**(12)**.

RANKL binds to RANK on osteoprogenitor cells and controls osteoclastogenesis and bone resorption. Initially, this RANKL-RANK interaction leads to the activation of nuclear factor-κβ that occurs by degradation of IκB protein by IκB kinase **(13).**

This degradation of IκB protein frees the nuclear factor-κB complex, which then translocates to the nucleus initiating intracellular signalling cascades that lead to transcription of specific genes leading to osteoclast formation, differentiation, activation, and consequently bone resorption. OPG acts as a soluble decoy receptor, negatively regulating this interaction, and competes with RANK, inhibiting RANKL-RANK interactions **(8).**

Pathophysiological Role of Osteoprotegerin:

There is emerging evidence of the role of OPG in the pathogenesis of atherosclerosis, calcification, and CVD. Different studies have highlighted different potential mechanisms that may explain the association. Evidence

is accumulating that OPG may be expressed, be regulated, and function 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 **(14).**

In endothelial cells, OPG acted as a survival and antiapoptotic factor. OPG protected endothelial cells from apoptosis in vitro and promoted neovascularization in vivo. Besides, OPG increased endothelial cell proliferation in microvessels **(15).**

In addition to its effects on endothelial cells, OPG increased the expression of adhesion molecules as well as monocyte binding to endothelial cells **(16).**

It was demonstrated that leukocyte/endothelial cell adhesion and leukocyte rolling was promoted by OPG. Moreover, in plaques from different locations, OPG expression by staining was correlated with the abundance of macrophages in the lesions **(17).**

It is suggested that the association of increased OPG seen in cardiovascular disease is the result of an incomplete compensatory mechanism. It is possible that circulating OPG levels are increased in response to the initial vascular insult and ongoing process of inflammation within an atherosclerotic plaque lesion as the component of a complex compensatory mechanism **(11).**

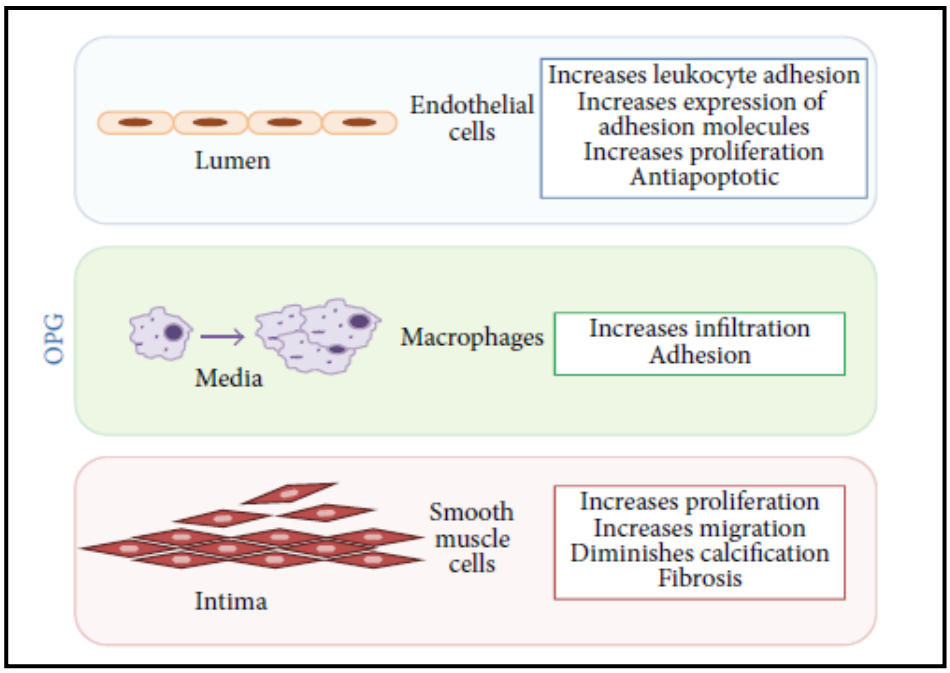

Fig. (2): Pathological role of osteoprotegerin in endothelial cells, smooth muscle cells, and macrophages. **(6).**

Osteoprotegerin in Clinical Studies:

Although OPG has traditionally been implicated in bone remodelling and it has been determined as a biomarker in osteoporosis, OPG was linked with diabetes type 1 and 2, obesity, metabolic syndrome and hypertension.

- **OPG and Diabetes Mellitus:**

Different studies have shown that OPG levels are elevated in patients with type 1 diabetes mellitus. Furthermore, prepubertal children with type 1 diabetes have significantly increased OPG levels **(18)**.

Different studies in type 1 diabetic cohorts have analysed the association between OPG and diabetic complications such as diabetic nephropathy and neuropathy **(19)**.

OPG is associated with poor glycaemic control and cardiovascular disease (CVD) in patients with type 1 diabetes, compatible with the hypothesis that OPG is associated with the development of diabetic vascular complications **(20).**

In type 1DM patients, OPG was associated with silent myocardial ischemia after correcting for other variables. The association of OPG with silent myocardial ischemia was observed in both genders, in type 1 and type 2 diabetic patients, in patients with or without nephropathy, and in patients without but not with peripheral arterial disease **(21).**

- **Osteoprotegerin in Insulin Resistance:**

Several studies have focused on the relationship between OPG and insulin resistance assessed by the homeostatic model assessment for insulin resistance (HOMA-IR) It has been showed that OPG levels significantly correlated with insulin and insulin resistance **(22).**

It was demonstrated that oral glucose suppressed OPG levels, independently of obesity and glucose tolerance status indicating that glucose may be involved in the acute regulation of these proteins. Acute hyperglycaemia increased plasma levels of OPG in nondiabetic subjects, whereas hyperinsulinaemia may suppress plasma OPG levels **(23).**

This observation showed that high glucose concentrations added to vascular endothelial cells did not modulate OPG release when used alone or in association with TNF-alpha **(23).**

Acute hyperinsulinemia decreased plasma OPG, but with diminished effect in individuals with type 2 DM and obesity. Besides, in obese adolescents, OPG levels and HOMA-IR index were significantly higher than in healthy volunteers and a significant positive correlation between OPG and insulin resistance was found **(24)**.

In premenopausal obese and normal weight women the relationship between OPG and HOMA-IR showed a negative and significant correlation with insulin and HOMA-IR **(25)**.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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