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ORIGINAL ARTICLE

Osteoprotegerin as a biomarker of Coronary Artery Disease

Shrook Muhammed El sayed Soliman[1]*,Norhan A.Sabbah[1],Mostafa Toam[2], Hanim Magdy Abdelnour[1]

[1]Medical Biochemistry and Molecular Biology Department, Faculty of medicine , Zagazig university, Zagazig, Egypt

[2] Cardiology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author*
Shrook Muhammed El sayed Soliman

Email:
shrookmohammed1@gmail.com

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ABSTRACT

Background: Coronary artery disease (CAD), including its most severe complication, myocardial infarction (MI), is the leading cause of death in the industrialized world. As the most serious clinical manifestation of CAD, MI is the condition of irreversible necrosis of the heart muscle that results from prolonged ischemia. Approximately 90 % of MI results from the formation of an acute thrombus that obstructs an atherosclerotic coronary artery. Coronary artery disease (CAD) is a major cause of mortality and morbidity in the general population worldwide. CAD has a complex etiopathogenesis and a multifactorial origin.Osteoprotegerin (OPG) that is a glycoprotein belonging to the tumor necrosis factor (TNF) receptor superfamily, functions as a dummy receptor for both the TNF-linked apoptosis-inducing ligand (TRAIL) and the nuclear factor κ-B ligand receptor (RANKL). These elevated OPG levels are linked to a wider variety of coronary artery atherosclerotic lesions and an increased mortality risk. The relationship between serum OPG (osteoprotegerin) level with the development and progression of CAD among patients is not clear. **Conclusion**: Osteoprotegerin may be potential predictor of CAD among patients and may be used in the treatment of CAD.

Keywords: Coronary artery disease, osteoprotegerin,myocardial infarction

INTRODUCTION

Gene-gene and gene-environment interactions are among the complicated events that appear as coronary artery disease (CAD), which is partially induced by inflammatory processes. The control of inflammatory mechanisms appears to involve a number of pathways as well as putative genes and loci that linkage analysis or case-control association studies have so far identified as being associated with CAD risk. Myocardial infarction has also been connected to some of these genes (MI), which is a crucial step in the pathophysiology of CAD and the event that causes many inflammatory disorders [1, 2].

TNF receptor superfamily member 11B (TNFRSF11B), Often referred to as osteoprotegerin (OPG), this protein is a TNF receptor superfamily member [3]. By attaching itself to the receptor activator of nuclear factor κ-B ligand (RANKL) and preventing it from interacting with RANK, OPG functions as a decoy receptor. OPG has been reported to be produced by a variety of tissues and cells, including smooth muscle, endothelial cells, bone, and heart. Several studies have demonstrated evidence of OPG's participation in the development of atherosclerosis, despite the fact that it was initially identified as a molecular regulator of bone metabolism [4, 5].

In human atherosclerotic plaques, the OPG protein was increased. Furthermore, there was a positive correlation found between the presence of coronary artery disease (CAD), stroke, and the progression of atherosclerosis and high circulating OPG levels. Additionally, elevated OPG levels were a highly reliable indicator of CAD patients' long-term death [6].

Osteoprotegerin

One of the many molecules being studied for their potential use as biomarkers of cardiovascular diseases (CVD) is the superfamily of tumor necrosis factor (TNF) receptors. TNF-related apoptosis-inducing ligand (TRAIL), receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin (OPG) and its ligands are members of this family [7].

TRAIL interacts with members of the TNF receptor superfamily (TNFRSF) and is a member of the TNF superfamily (TNFSF). Numerous substances, like glucocorticoids and TNF, have varying effects on the expression of OPG. One important pro-inflammatory cytokine, TNF, controls the production of several signaling pathways connected to the formation of vascular and metabolic illnesses as well as the advancement of immunological reactions [8].

Elevated oestrogen synthesis is a precursor to diabetes mellitus and may be involved in disorders related to endothelial cell (EC) dysfunction. When used as a measure of cardiovascular risk in individuals with osteoporosis, the OPG serum level has a high and independent predictive value for metabolic syndrome, and there is a substantial correlation between the plasma OPG level and endothelial function [9].

The secreted soluble receptor OPG plays a major role in regulating the ratio of bone reformation to disintegration. The interaction between ECs and osteoblasts during osteogenesis has been clarified by recent research, linking angiogenesis and osteogenesis. It is currently suggested that vascular biology and bone regulating proteins are related. It has been shown that OPG may mediate vascular calcification [6].

In individuals with illness, Vascular calcification is a risk factor for mortality from all causes as well as cardiovascular disease. Though the exact molecular mechanisms behind the connections between cardiovascular illness and vascular calcification remain largely unclear, mounting data indicates that a significant contributing element to vascular calcification may be the RANK/RANKL/OPG triad [10].

The OPG/RANKL/RANK/TRAIL system structure:

A member of the TNF receptor superfamily of cytokines is OPG. Because of its ability to protect bone, it was given the name OPG (the Latin word "os" means bone and "protegere" means to protect). Other names for OPG include osteoclastogenesis inhibitory factor (OCIF) and TNF receptor superfamily member 11b (TNFRS11B). OPG is encoded by the TNFRSF11B gene. RANKL (TNFSF11) and RANK of the TNF receptor superfamily (TNFRSF11A) receptor ligand pair has been identified as the primary molecular mechanism in bone metabolism [11].

OPG is a basic secretory glycoprotein with 401 amino acids (aa) and a monomeric weight of 60 kiloDaltons (kD) according to biochemistry. After that, it is combined to

form a 120 kD disulfide-linked dimer that is secreted at the heparin binding domain's cys-400 residue. OPG is made up of seven structural domains, each of which has a unique effect on its biological functions [12].

The 21 aa signal peptide is cleaved from the N-terminal of OPG before the monomeric and dimeric forms are secreted, resulting in a mature OPG protein with 380 aa. Following this, circulating OPG can be found either as OPG attached to its ligands, RANKL and TRAIL, or as a free monomer of 60 kD and a disulfide bond-linked homodimer form of 120 kD [13].

Although RANKL is a transmembrane protein; soluble RANKL, or sRANKL, is also present in blood. Nuclear factor κB (NF-κB) is activated on target cells when RANKL and RANK form a homotrimer. Following RANKL-to-RANK ligation, binding of TNF receptor-associated factors (TRAFs: 2,5,6) to certain locations in the cytoplasmic domain of RANK is an important first step in downstream signaling. RANK is bound by TRAFs 2, 5, and 6 [14].

The mechanism of OPG/RANKL/ RANK/ TRAIL pathway (figure 1):

Protein kinase signaling mediated by RANK/TRAF activates many signaling pathways, including NF-κB kinase (IKB)/NF-κB and activator protein-1 (AP-1). It has been more evident recently that these signaling pathways exist in a variety of cells throughout the calcification process of the arteries. **[15].**

Through its N-terminal cysteine-rich domains (CRD), OPG binds RANKL. OPG's extracellular area is divided into four CRDs, each of which has modules that are topologically unique. CRDs are enough to prevent RANKL from acting. The human RANK is made up of 616 aa. These amino acids are separated into four sections: the transmembrane domain, which has two N-glycosylation sites and four cysteines, is 21 aa long; the signal peptide is 28 aa long; and the C-terminal cytoplasmic domain is 383 aa long [16].

By attaching to RANK-TRAIL, RANKL produces a variety of intracellular signals. There is a wide tissue distribution of TRAIL and the receptors it is linked to. TRAIL protein and mRNA have been detected in ECs and vascular smooth muscle cells (VSMCs). Type II transmembrane protein TRAIL is expressed. Additionally, TRAIL is present in the body in a soluble homotrimeric form that is biologically active [6].

Under physiological settings, TRAIL, sometimes referred to as Apo2 ligand, is detectable in the serum. Concentrations of 10–100 pg/mL of soluble TRAIL are found in serum and plasma. Up to five different receptors can be bound by TRAIL, which then initiates intricate signaling cascades. Moreover, OPG has been observed to bind to TRAIL. The control and modification of apoptosis is one of the primary functions of the TRAIL/TRAIL-R system [17].

As TRAIL can both kill diseased cells and contribute to the development of numerous infections, it may play two roles in the immune system. Remarkably, it has also been proposed that TRAIL contributes to the establishment of atherosclerotic plaque. Atherosclerotic lesions exhibit elevated levels of TRAIL expression at susceptible plaque locations [8].

There has been an increased focus on comprehending the process by which RANKL and OPG interact, as changing the

OPG/RANKL ratio could provide the basis for the development of new therapies. Apart from binding RANK, OPG has the ability to interact with TRAIL and induce tumor cells to undergo apoptosis via binding to the TNFRSF family's death receptor 4 (DR4) and DR5 cell-surface receptors [10].

Molecular dynamics simulations and computational docking were used to identify the binding mode to RANKL. In vivo, osteoblasts, VSMCs, and ECs all express OPG. By using immunohistochemistry, OPG has been found in or close to VSMCs in both coronary and aortic atherosclerotic plaques [9].

When ECs are stimulated by hormones, circulating chemicals, and inflammatory cytokines, they produce OPG under baseline conditions. It was discovered that OPG levels were elevated by interleukin (IL)-1β and TNF-α. Weibel-Palade bodies are secretory granules that contain von Willebrand factor (vWF) (WPBs) is linked to OPG within ECs. The glycoprotein known as thrombospondin-1 (TSP-1) has the ability to regulate the size of vWF multimers. Through its activation of nuclear factor-E2-related factor 2 (Nrf2), TSP-1 initiates an antioxidant defense response that guards against lipotoxic stress within the endoplasmic reticulum [11].

Studies conducted in vitro demonstrate that blood cells including neutrophils and stem cells are capable of producing and releasing OPG. OPG and IL-17 are produced by neutrophils. IL-17 affects the synthesis of different proinflammatory mediators and promotes the migration of neutrophils to the site of inflammation. OPG thus seems to be a trustworthy biomarker, as multiple investigations found a marked increase in the level of circulating OPG in patients with various degrees of sepsis and in those who progressed to acute kidney injury [15].

OPG is also released by various kinds of stem cells. Vascular stem/progenitor cells are a vital source of all the many types of vascular cells needed to create and repair blood vessels cells (VSCs). VSCs come in a variety of forms, such as adipose-stromal cells (ASCs), smooth muscle progenitor cells (SMPCs), mesenchymal stem cells, and endothelial progenitor cells (EPCs). ASCs are recognized as one of the most important and promising cell sources in the field of regenerative medicine [12].

The synthesis of OPG by ASCs and its function in vascular pathology have been studied recently. It was shown that OPG caused oxidative stress, which led to EPC apoptosis. Oxidative stress and syndecan-4 acted as mediators for this impact. Plasma membrane proteoglycans are called syndecans, and their distribution in tissues is changed by oxidative stress [10].

OPG-induced damage was avoided by reactive oxygen species (ROS) scavengers such N-acetylcysteine and the NADPH oxidase (NOX) inhibitor diphenyleneiodonium apoptosis. OPG activated NOX-2 and NOX-4, which in turn phosphorylated p38 MAPK and ERK-1/2, increasing the generation of ROS [13].

It has recently been established that oxidative stress, apoptosis, and OPG are related in ASCs. In vitro, ASCs produced considerably more OPG when exposed to hydrogen peroxide (H2O2). It was also noted that ASCs transplanted into hearts damaged by ischemia-reperfusion produced OPG. ASC-secreted protective factor believed to be

involved in ASC-mediated cardioprotection is OPG. But the exact processes behind OPG-mediated cellular defense remain unclear [8].

Numerous variants in the OPG gene's promoter region have been linked to a variety of illnesses. Each polymorphism has been assessed in relation to particular illnesses. Numerous investigations planned to evaluate the connection between blood OPG levels, OPG gene variations, and the development of atherosclerosis connected—or not—to rheumatoid arthritis (RA) [16].

In RA patients, coronary atherosclerosis has been linked to one variant of the TNFRSF11B gene. Lastly, there is a correlation between high OPG levels and endothelial dysfunction, oxidative stress, inflammation, and cardiovascular disease [14].

The Heart and OPG/RANKL/RANK:

The human heart is made up of several different types of cells, the most prevalent of which consist of various connective tissue cells and fibroblasts. The remaining cell mass is composed of mast cells, EC, VSMCs, cardiomyocytes, and immune-related cells. Conversely, CM mass is around 25 times larger than EC mass [11].

Every cardiomyocyte has at least one capillary next to it. Cardiomyocytes are the heart's primary oxygen consumers, making up around 75% of the typical myocardial volume. In the microvasculature and tiny vessels of the myocardium, ECs outnumber cardiomyocytes by a ratio of around 3:1 [6].

One of the biggest and most diverse "organs" in the body is undoubtedly the endothelium. A wide variety of EC subtypes with varying phenotypes, functions, and locations can be found within the endothelium. In accordance with particular energy sources, redox balances, and metabolic patterns, the various ECs modify the flux via the metabolic pathways [17].

ECs are inactive, serve as barriers, and preserve tissue homeostasis in healthy people. In response to angiogenic factors brought on by trauma and/or pathological circumstances, such as tissue damage or hypoxia, they are able to generate new blood vessels. Capillary EC in situ in the heart can alter their shape in response to a constant flow and adjust to the contractile environment [7].

Compared to other cells, whose cellular bioenergetics are connected to oxidative mitochondrial metabolism, ECs have distinct metabolic activities. ECs have the ability to change their phenotypic and transition between quiescent, proliferative, and migratory stages. The ratio of energy metabolites obtained from the coronary circulation to their utilization by cardiomyocytes determines how well the heart functions, and ECs of the microcirculation are essential for this process [15].

It is possible for endothelium tissue derived from several organs to have distinct metabolic profiles. Compared to other cell types, ECs utilize less oxygen because they have fewer mitochondria. Similar to this, the distribution of mitochondria within the various EC changes, indicating their significant regulatory roles in maintaining cellular homeostasis [17].

Aerobic glycolysis provides up to 85% of the ATP produced by ECs. Interestingly, different EC subtypes have different rates of glycolysis. Microvascular ECs are more glycolytic, while arterial ECs are more

oxidative. Even though ECs have adapted to utilise glucose, they still require other metabolic energy sources to perform their tasks. During sprouting, fatty acids (FAs) catabolized by fatty acid-beta-oxidation (FAO) serve as a crucial source of fuel for ECs [9].

Numerous factors, notably the transcription factor family known as peroxisome proliferator-activated receptors (PPARs), influence the control of FAO. Elevated FA levels cause PPAR-α to be activated, which increases FAO. In chronic pathological situations, the heart can remodel metabolic pathways, resulting in modifications to myocardial energetics and contractile function [16].

Normal cardiac function requires a strong connection between ATP synthesis and heart contraction since the cardiomyocyte's high-energy phosphate storage is small and just long enough to sustain the beating for a few seconds. The heart, a high-energy organ, demonstrates "plasticity" in that it can employ a variety of substrates, such as FAs, carbs, and ketone bodies, to produce energy in order to maintain its function. FAs are primarily employed as an energy source in cardiomyocytes [12].

Almost 70% of ATP generated in a healthy heart comes from FA oxidation. The heart requires a lot of FA, but its ability to synthesis it is limited, therefore it must get its FA from an external source. FAs are transported into the capillary lumen via lipoprotein lipase's degradation of triglyceride-rich lipoproteins [8].

ECs provide a vital role. In the heart, ECs express the FA-binding proteins FABP4 and FABP5, which transport FAs across the endothelium. When cardiac, skeletal muscle, and brown adipose tissue release vascular endothelial growth factors-B (VEGF-B)-B, capillary endothelial cells (ECs) produce FA transport proteins via VEGF receptor 1 [11].

It is generally known that cardiac metabolism is reprogrammed during endothelial senescence, and that this state may be important in cardiac disorders like hypertrophy. Reduced FAO and enhanced glucose metabolism are the hallmarks of these alterations. Regarding the impact on glucose metabolism, it is shown that decreased total ATP production by oxidative metabolism combined with increased glucose absorption leads to increased glycolysis [13].

While Greater glucose consumption appears to be beneficial for the failing heart, while decreased FA supply to the hypertrophied and failing heart appears to be detrimental. Pathological hypertrophy was thought to be adaptive due to the shift in substrate preference to glucose, perhaps because to the higher oxygen efficiency of ATP generation from glucose. In summary, there is communication between cardiomyocytes and the endothelium, and cardiac function may be harmed by metabolic maladaptation [10].

There is an intriguing connection between the roles of the ATP/adenosine metabolism and the OPG/RANK/RANKL triad. Alternatively exocytosis or the enzymatic hydrolysis of extracellular ATP can produce adenosine, which is then released from the intracellular space. By binding to the G-protein-coupled receptor subtypes A1, A2a, A2b, and A3 on the cell surface, adenosine produces a range of physiological effects [7].

Adenosine functions as a cytoprotective modulator, preventing tissue damage in a variety of organs. Adenosine and adenosine receptor agonists have been demonstrated to decrease OPG secretion in vitro in a human osteoprogenitor cell line. Blood samples from patients with rheumatoid arthritis (RA) show an increased OPG/RANKL ratio and overexpressed A3AR in inflammatory cells. These data demonstrate the autoimmune inflammatory illness in these patients [15].

Vascular disorders are more common and atherosclerosis is accelerated by RA. The introduction of metabolomic analysis has made it possible to understand more fully how inflammation and metabolic alterations that underlie numerous diseases, including RA, interact [14].

When lipopolysaccharides or other activators stimulate ECs, they release large amounts of OPG. Nevertheless, OPG's molecular actions have an impact on the cytoskeletal structure of ECs. Endothelial colony-forming cells (ECFCs) experienced cytoskeleton remodeling when treated with OPG in vitro [17].

ECFCs, also known as late-outgrowth ECs, are a specific form of circulating EPC that has a proven function in vascular restoration. OPG activated αVβ3 integrin and controlled protein-disulfide-isomerase, its ligand. αVβ3 integrin not only facilitates cell motility but also enhances stimulated ECs' ability to survive [16].

HSPGs, or heparan sulfate proteoglycans, may control the bioavailability of OPG. The tight adherence of leukocytes to the endothelium mediated by integrin is modulated by proteoglycans belonging to the syndecan family. HSPGs, on the other hand, immobilize chemokines on luminal ECs, shielding them from changes in hemodynamics or mechanics [8].

In cases of mitral valve degeneration, anomalies of HSPGs have been observed. Endothelial to mesenchymal transition (EndMT) was evident in isolated human valve epithelial cells (ECs). It has been shown that OPG overexpression occurs during EndMT and is associated with autocrine effects that are typified by elevated ROS generation. OPG increases the levels of matrix metalloproteases (MMPs) and proteoglycan, which impedes proper valve endothelial function [15].

OPG, RANK, and RANKL are among the factors that change lipid metabolism and contribute to atherosclerosis. Subclasses of By regulating the expression of genes that make HDL, high density lipoproteins (HDL) may play an indirect role in the development of atherosclerotic plaque pro- as well as anti-calcifying proteins. Through processes involving gene control, HDLs prevent atheroma from progressing [17].

A member of the TNF receptor superfamily, such as OPG, is proposed to have a role in this. When myofibroblasts were incubated with HDL for 24 and 48 hours in vitro, OPG production increased in a time-dependent manner [6].

In terms of glucose metabolism, the transmembrane glucose gradient and the activity of glucose transporters in the plasma membrane regulate the extracellular glucose uptake. The amount of glucose that can be carried increases as insulin drives the glucose transporters to relocate to the plasma membrane [17].

Hexokinase quickly phosphorylates free glucose once it enters the cell, creating glucose-6-phosphate (G6P). G6P can either be used to synthesize glycogen or proceed via glycolysis to produce pyruvate. FAs are the myocardium's preferred substrate, as we previously reported, but during ischemia, glucose takes precedence as the myocardium's main energy source [11].

Because of its metabolism, harmful byproducts including oxygen free radicals (OFR) are avoided. Individuals suffering from diabetes mellitus have trouble absorbing glucose. Because ECs are unable to cut off the extra glucose in diabetes conditions, Glycolytic intermediates move along different routes, leading to an overall increase in oxidative stress. Peroxynitrite is produced when OFR, like superoxide, combines with nitric oxide (NO) [9].

The growth factor system influences through autocrine/paracrine and endocrine mechanisms cells of the vasculature in different ways, with a focus on glucose metabolism. One of the main regulators of EC permeability and metabolism is the growth factor system, which consists of basic VEGFs and platelet-derived growth factor (PDGF) are examples of fibroblast growth factors. Human EC metabolism is influenced by PDGF and VEGFs through Ca2+ signaling pathways [13].

There are various mechanisms that underlie the endothelial activities of these factors, and research has demonstrated their involvement in the onset and progression due to atherosclerosis. PDGF increases OPG expression in vascular cells. Statins affect endothelial function by blocking the decline of NO production caused by oxidized LDL and by increasing NO synthesis. By decreasing PDGF responsiveness and preventing Statins reduce chronic inflammation by reducing smooth muscle cell proliferation, monocyte chemotaxis, and migration [10].

OPG/RANKL/RANK and vascular signaling:

Vascular ECs are subject to wall tension, shear stress, and hydrostatic pressure, among other mechanical factors, according to their position. Shear stress controls gene expression and cellular processes, indicating the participation of putative effectors and sensors. NF-κB target gene transcriptional activation is one of the intermediate shear responses [12].

The precise impact of shear stress on the expression of OPG in vascular endothelium remains unknown to us. On the other hand, it has been documented that shear stress reduced the impact of IL-17A on TNF-α and RANKL production, increased the expression of OPG in osteocytes, and decreased the activation of osteoclastic differentiation by IL-17A [8].

The phenotypic of EC and VSMC alters with aging. Advanced atherosclerotic lesions are induced by several triggers. An essential part of the pathophysiology of vascular changes and atherosclerosis in the aged is the renin-angiotensin system (RAS). Through impacts on Angiotensin-II (Ang II), the primary mediator of RAS, endothelial function, and inflammatory processes all directly affect how the atherosclerotic process progresses [14].

By causing vascular protection, Treatments that block type 1 Ang II receptors reduce the number of cardiovascular events. It

has been shown that via activating Ang II receptor type 1, Ang II stimulation stimulates the production of VEGF. Types A and B VEGF, two members of the VEGF family, have been shown to promote proinflammatory and angiogenic processes in vascular inflammation and remodeling [7].

It was shown that OPG amplified VEGFs' proangiogenic impact. Furthermore, OPG shields EC from growth factor withdrawal-induced apoptosis [15].

OPG/RANKL/RANK and regulation of angiogenesis:

It is now acknowledged that endothelium physiology involves RANK and its ligand, RANKL. In addition to its function in cell survival, the RANKL/RANK system is also actively involved in inflammation and angiogenesis in pathology. Growth factors attach to specific cell surface receptors, which can alter gene expression and communicate growth signals to other intracellular components. VEGF is one instance of a protein growth factor that has particular characteristics on EC [9].

VEGF stimulates ECs' angiogenic reactions to RANKL and upregulates the expression of RANK. Furthermore, the survival effect that RANKL elicited in ECs was abolished by inhibiting PI3-kinase. In response to the paracrine activation of RANKL, RANK may play a critical role in maintaining EC integrity via the PI3-kinase/Akt signal transduction pathway. VEGF and hormones like insulin cause PI3-kinase/Akt activation in the endothelium [16].

Results imply that OPG controls at least two different signaling pathways: one that promotes angiogenesis via Src signaling and another that promotes cell proliferation via ERK signaling. In order to sustain skeletal integrity, blood vessels and bone cells must be closely connected both spatially and temporally, as bone is a highly vascularized tissue. There is a complex relationship between angiogenesis and osteogenesis [13].

Osteoporosis is caused by a decrease in osteoblast activity, and it has been demonstrated that angiogenesis and osteogenesis interact closely to promote bone growth. Growing data points to the function of exosomes produced by EPCs in promoting angiogenesis, which is intimately related to osteogenesis. When combined, these findings imply that RANK plays a crucial role in the preservation of endothelium integrity in relation to metabolic changes **[6].**

OPG/RANKL/RANK and inflammation (figure 2):

Several studies substantiate OPG's significance in inciting inflammation. An enhanced development of atherosclerosis was shown to be connected with a lack of OPG in the pro-atherosclerotic apolipoprotein knock-out mouse. OPG is crucial for inflammatory cell chemotaxis, according to in vitro research [17].

As mentioned earlier, OPG promotes apoptosis and matrix metalloproteinase release, which in turn causes alterations in endothelium and vascular smooth muscle cells, which are generally linked to atherosclerosis. In VSMCs, RANKL dramatically boosts MMP activity. By preventing it from binding to RANK, OPG counteracts RANKL's impact on VSMCs' induction of MMP activity [14].

Leukocyte infiltration is a crucial stage in inflammation, mostly regulated by chemokines in the case of neutrophils and

monocytes. NO produced from iNOS regulates the synthesis of these chemokines. According to certain theories, OPG is a sign of endothelial dysfunction in connection to inflammation [11].

OPG supports the pro-atherosclerotic activity of ECs by promoting by causing the expression of intercellular adhesion molecules on ECs, such as vascular adhesion molecule-1 (VCAM-1) and E-selectin, leukocyte adhesion, an early stage of EC dysfunction. These local activities impact the speed at which leukocytes are recruited from the bloodstream into the tissue, which adds to the multipurpose activity of several modulators in inflammation, including HSPGs [10].

The cultivation Treating ECs with inflammatory cytokines significantly boosts OPG release and results in the synthesis of EC adhesion molecules, which facilitates monocyte and lymphocyte transmigration into the intima of the vessel wall. The generation of cytokines and the stimulation of their receptors trigger the recruitment of neutrophils and monocytes. Consequently, it is thought that one of the main goals in the treatment of various disorders is to prevent pro-inflammatory interleukins [8].

Novel compounds offer prospective treatment approaches. Human monoclonal antibodies that target interleukin-1β, canakinumab and evolocumab, have been approved for clinical usage in a variety of illnesses due to their anti-inflammatory properties. Human monoclonal antibodies directed against IL-6 receptor-alpha (IL-6R α) include sarilumab and tocilizumab [7].

In certain cell types, IL-6R activation is protective and regenerative; nevertheless, soluble IL-6R-mediated IL-6 signaling is largely pro-inflammatory. Remarkably, it was recently discovered that IL-1β stimulated the secretion of OPG in human breast cancer cell lines, suggesting a new role for OPG as a modulator in the advancement of breast cancer driven by inflammation. The accelerated cellular invasion caused by MMP3 induction by IL-1β and OPG [12].

OPG/RANKL/RANK and the proteasome:

Atherosclerosis in connection with endothelial dysfunction processes, cancer, neurological and immunological disorders, and other diseases are all influenced by alterations to the UPS (ubiquitin-proteasome system). The connection between the oxidative stress response and the UPS has been found plays a vital function in vascular cells. Numerous evidence point to the UPS's involvement in controlling eNOS expression and activity [15].

Another significant molecular mechanism controlling vascular and EC aging is the UPS. There have been reports of decreased proteasome activity and increased ubiquitin staining in the pathophysiology of congestive heart failure. The decrease in proteasome activity is the result of several mechanisms in these sick hearts [9].

Remarkably, in comparison to subjects without heart failure, there was a marked increase in OPG mRNA expression Between ischemic and non-ischemic cardiac tissue in heart failure models used in experiments [14]. This finding raises the possibility that OPG plays a role in the myocardium's adaptation to the failure.

In the rat model of post-infarction heart failure, the OPG/RANK/RANKL axis appears to be active inside the myocardium, suggesting a possible involvement of the

RANKL/RANK interaction in this heart condition's pathogenesis. Consequently, the proteasome pathway in relation to the OPG/RANK/RANKL axis may be useful for the prevention and treatment of cardiac diseases serve as a useful therapeutic target [16].

OPG/RANKL/RANK and cellular senescence:

impaired endothelial cell renewal, increased oxidative stress, and the start of inflammatory processes are all components of endothelial dysfunction associated with aging. There are several theories explaining cellular senescence, but the most significant one seems to be the telomere shortening linked to elevated oxidative stress [13].

OPG is now known to play a role in preventing arterial calcification and atherosclerosis. There is strong evidence that suggests OPG has a role in the survival and proliferation of cells. According to recent findings, senescent tumor cells produced by radiation have an impact on the tumor microenvironment by producing more cytokines, like OPG [17].

Due to its ability to prevent tumor cells from dying, OPG is also thought to be an element that helps tumor cells survive. OPG can initiate the activation of angiogenic signaling pathways in ECs. Moreover, OPG has pro-inflammatory qualities that could be mediated by specific gene synthesis and NF-κB pathway activation [10].

OPG/RANKL/RANK and vascular calcification:

A highly regulated process that is analogous to bone development leads to arterial calcification. The exact nature of the cells that cause arterial calcification to occur is unknown. Vascular calcification is a dynamic, intricate process that is regulated by numerous signaling pathways. It has been demonstrated that SMC possess osteochondrogenic potential [17].

Recent data, however, points to a role for a variety of vascular cells, most notably pericytes, in this process. It's possible that resident vascular pericytes will prevent vascular calcification from occurring. They take involved in controlling the equilibrium of mineral production in collaboration with other cells including monocytes and macrophages [15].

Furthermore, asymptomatic lesions had larger pericyte cell densities, indicating that pericytes may play an active role in maintaining plaque stability. Pericytes may be induced by inflammatory atherosclerotic stress, according to certain theories. Pericytes may have a role in both the secretion of OPG and the beginning of the mineralized structure in plaques [6].

OPG secretion is higher in human pericytes than in SMCs or ECs. Pericytes play a major role in the control of angiogenesis in both skeletal and cardiac muscle by promoting EC migration and survival. According to recent research, pericytes may also be able to modify local tissue immune responses in response to injury through a number of different independent routes [8].

Here, vasculogenesis may be influenced by the OPG/RANK/RANKL axis in conjunction with pericyte activities. The MAPK and Akt signaling pathways are involved in OPG-mediated angiogenesis. It has been shown that pericytes can improve myocardial healing. But compared to skeletal muscle, the fundamental mechanisms here are less understood. The loss in cardiac pump function

following injury was much reduced in damaged hearts where pericytes were inserted [7].

Reduced inflammation and enhanced angiogenesis are linked to these outcomes. Since OPG−/− animals acquired OPG seemed to offer protection against vascular calcification, as evidenced by the acceleration of atherosclerotic lesion progression and calcification caused by spontaneous arterial calcification and OPG depletion in ApoE-/- mice. When it comes to the frequency of RANK/RANKL on vascular calcification, these factors both help and hinder the process [12].

A complex process driven by multiple causes, vascular calcification is linked to an early stage of chronic kidney disease (CKD). It is known that RANKL increases the calcification of vascular smooth muscle cells by binding to RANK and activating the alternative NF-κB pathway by raising BMP4 synthesis. Since it is believed that RANKL encourages the calcification of vascular muscle cells, the potential of RANKL inhibition by particular drugs, like denosumab, to stop vascular calcification has been investigated [11].

As we previously mentioned, lipid metabolism is changed by RANKL, RANK, and OPG, which contributes to the development of atherosclerosis. Through processes involving the control of pro- and anti-calcifying protein synthesis, HDLs prevent atheroma from progressing. There has been written about a relationship between the phospholipids of HDL subclasses and the calcium score [9].

In the asymptomatic stages of the disease, only lipids may be biomarkers of coronary calcification at all, and both lipid profiles and coronary artery calcification scores are separate features of atherosclerosis. Similar to osteogenesis, Vascular calcification is an active cell-mediated process that produces bone-related proteins such alkaline phosphatase (ALP) and Runt-related transcription factor-2 (Runx2), which starts the mineralization of bone and the differentiation of SMC [16].

It has been demonstrated that ALP is expressed in calcified atherosclerotic lesions. Otherwise, elevated ALP levels are linked to a higher risk of cardiovascular events as well as patient death. Numerous confounding factors, Influential factors that can impact the correlation between ALP and the coronary artery calcium score include Glomerular Filtration Rate (GFR), an inflammatory condition with mediators acting on endothelial function [13].

It is now widely acknowledged that in individuals with coronary artery disease (CAD), OPG significantly predicts early carotid atherosclerosis and is associated with endothelial function. Carotid atherosclerosis and the carotid intima-media thickness (CIMT) are correlated and CIMT is a powerful predictor of cardiovascular events. The OPG levels and the CIMT are related in CAD patients [6].

OPG has been proposed as an indicator of early endothelium pathophysiological events dysfunction. Only the OPG demonstrated a significant predictive value among the 12 inflammatory markers that were examined in predicting the development of atrial fibrillation (AF). OPG levels and incidence AF were substantially correlated [14].

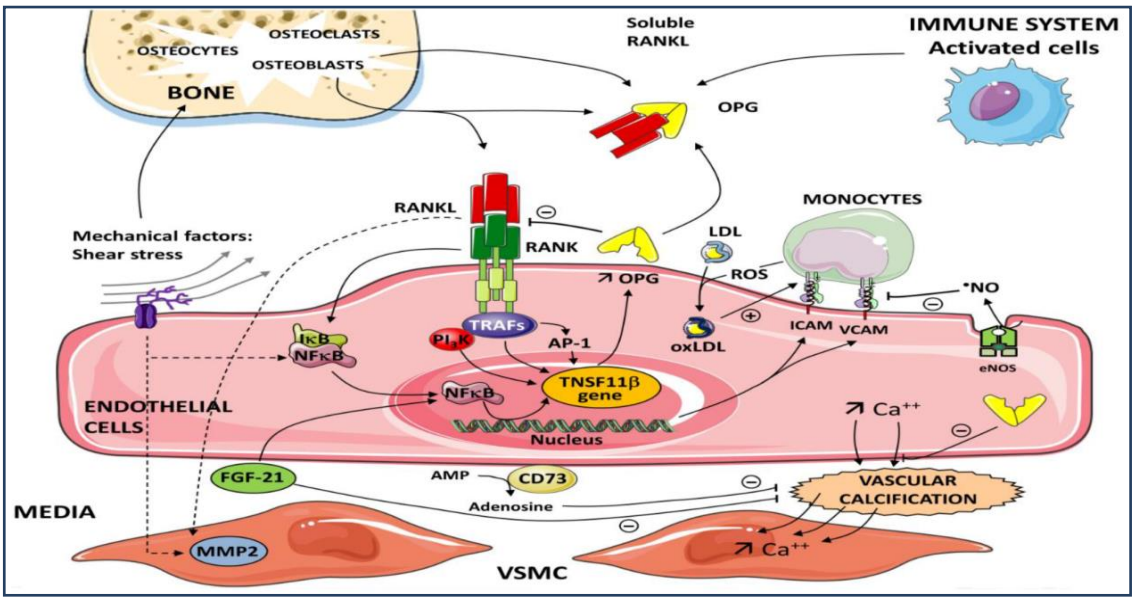

Figure (1): The OPG/RANKL/RANK/TRAIL system: structures, localization, and characterization **[6]**

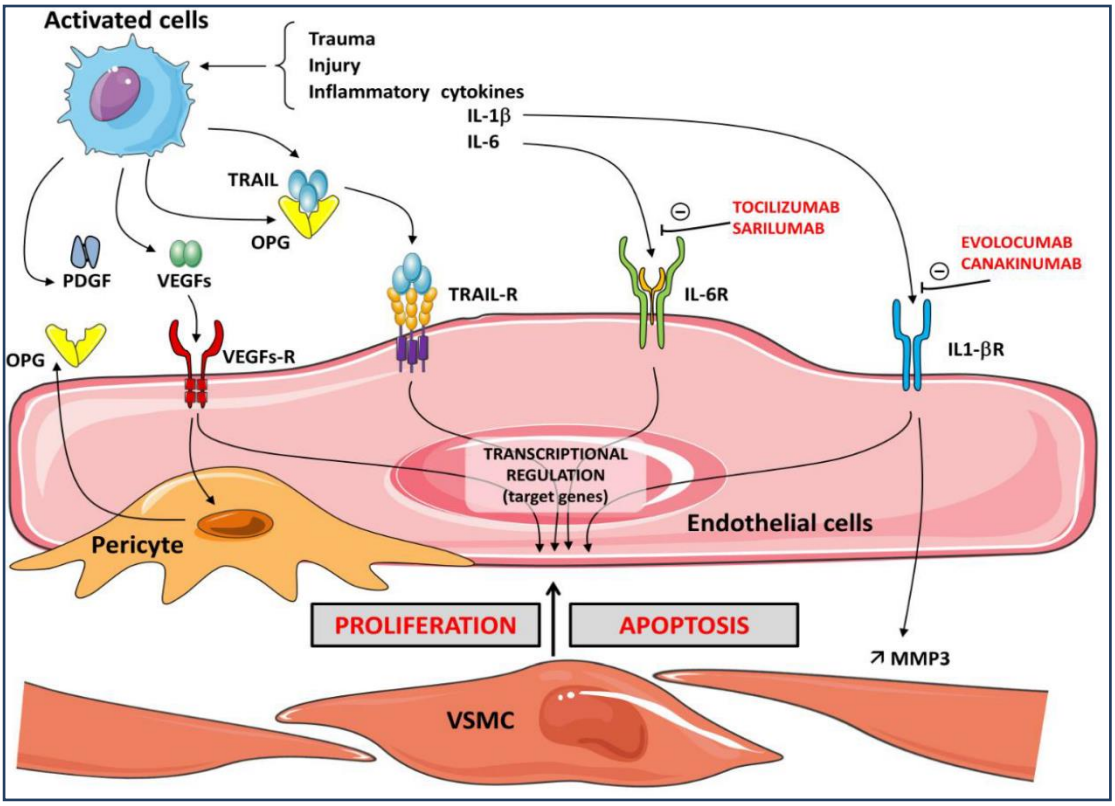

Figure (2): OPG/RANKL/RANK and inflammation **[6].**

CONCLUSION

Osteoprotegerin may be potential predictor of CAD among patients and may be used in the treatment of CAD.

Conflicts of interest: None

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