Osteoprotegerin and Soluble TRAIL Serum Levels in Patients with Coronary Artery Disease

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ABSTRACT

Osteoprotegerin (OPG) is a key factor in bone remodelling (inhibitor of osteoclastogenesis), a member of the tumour necrosis factor receptor family, and also a decoy receptor for the receptor activator of nuclear factor kappa-B ligand (RANKL) and tumour necrosis factor- related apoptosis inducing ligand (TRAIL) was recently implicated in human atherogenesis. OPG could be produced by cells of the cardiovascular system, including coronary artery smooth muscle cells and endothelial cells and may operate in vascular physiopathology regulating vascular calcification, apoptosis and immune defense raising the possibility that alterations of OPG serum levels may be associated with coronary artery disease (CAD). The present work was intended to assess the possible role of serum OPG and s-TRAIL in the pathology of CAD. Since OPG acts by neutralizing TRAIL we hypothesized that serum levels of TRAIL are also altered in vascular disease. Eighty male subjects were included in this study categorized into three groups: 28 patients with acute myocardial infarction (AMI), 32 patients with established stable CAD and 20 healthy males serving as control subjects. All groups were matched for age and body mass index. Following clinical evaluation, blood samples were withdrawn for serum OPG & s-TRAIL determination using enzyme linked immunosorbent assay (ELISA). In the present study, both AMI and stable CAD groups exhibited significantly higher serum OPG levels compared to control subjects. On the other hand, both AMI and stable CAD groups showed significantly lower serum s-TRAIL levels compared to control subjects.Furthermore, in the AMI group there was a significantly higher serum OPG and lower s-TRAIL levels compared to stable CAD group. Also, it was found that there is a progressive increase in serum OPG levels and decrease in s-TRAIL levels as the number of affected coronary vessels increase in both AMI and stable CAD groups. In conclusion, the present data showed a close association between raised serum OPG and reduced s-TRAIL in patients with CAD (both AMI and stable CAD). In view of the pro-apoptotic effects of TRAIL on vascular smooth muscle and endothelial cells, an elevation of circulating OPG levels may represent a crucial compensatory mechanism to limit further vascular damage.

INTRODUCTION

Atherosclerosis is a complex multifactorial process resulting from an excessive inflammatory response to various forms of injurious stimuli to the arterial wall[(1)]. Atherosclerotic plaques are composed of a lipid core, fibrous cap, and inflammatory infiltrates containing principally T cells and macrophages. Activated T lymphocytes

play an important role in the initiation and progression of atherosclerosis[2-4].

Acute coronary syndromes (ACS), including unstable angina and acute myocardial infarction, are caused predominantly by the rupture of the fibrous cap overlying a vulnerable coronary atherosclerotic plaque, with subsequent platelet aggregation and thrombus formation. Inflammation appears to play a key factor in these events[5, 6].

Osteoprotegerin (OPG), a secreted tumour necrosis factor receptor homologue, increases bone mineral density by acting as a decoy receptor for the receptor activator of nuclear factor kappa B ligand (RANKL), the principal regulator of osteoclast biology. Furthermore, OPG seems to play a crucial role in vascular homeostasis, since OPG-deficient mice develop both severe osteoporosis and medial calcification of the aorta and renal arteries[7]. In addition to RANKL, tumour necrosis factor–related apoptosis inducing ligand (TRAIL), an inducer of apoptosis in susceptible cells, has been characterized as a second ligand for OPG[8]. OPG protects human endothelial cells and vascular smooth muscle cells against TRAIL induced cell death[9].

TNF-related apoptosis–inducing ligand (TRAIL) is a type II transmembrane protein of TNF superfamily with an extracellular, carboxy terminal domain. Soluble TRAIL is generated through the enzymatic cleavage of this extracellular domain[10]. TRAIL transduces death signals by binding one of its two receptors, TRAIL-R1 (DR4) or TRAIL–R2 (DR5), both containing a cytoplasmic death domain which recruits procaspase-8, subsequently initiating a cascade that leads to apoptotic cell death[10,11]. TRAIL can potentially interact with decoy receptors not containing intracellular death domain motifs, including TRAIL-R3 (DcR1), TRAIL-R4 (DcR2), and the soluble receptor osteoprotegrin (OPG), all with the ability to protect cells from TRAIL-induced cell death when over expressed[8,12]. Although TRAIL has been thought to selectively induce apoptosis in cancer cells, recent studies have also demonstrated TRAIL–induced apoptosis in untransformed normal cells[13].

The aim of the present study was to assess the possible role of serum OPG and s-TRAIL in the pathophysiology of CAD.

SUBJECTS & METHODS

The present study included eighty male subjects categorized into 3 groups: **Group A:** included 28 male patients (mean age 52.8±7.5 years) hospitalized in coronary care unit for ST- elevation acute myocardial infarction (AMI). AMI diagnosis was made on the basis of typical chest pain consistent with myocardial ischemia that continued for more than 30 minutes, newly developed ischemia ST-T changes or Q waves in at least two contiguous ECG leads, and elevation of serum creatine kinase levels ≥2 times the upper limit of the normal range. Standard medication, including aspirin, unfractionated heparin, intravenous nitroglycerine, B–blockers and ACE (angiotensin–converting enzyme) inhibitors, was usually administrated following

guidelines for treatment of ST elevation AMI.

Group B: included 32 male patients (mean age 52.1±6.6 years) with an established diagnosis of coronary artery disease (CAD). Patients were eligible if they had angiographically proven CAD, defined as stenosis of 50% or more of the luminal diameter in a major epicardial coronary vessel, and if they were free of symptoms for ≥3 months. Potential participants were excluded from the study if they met the criteria for class IV congestive heart failure according to the New York Heart Association classification[14], had a pacemaker, arterial fibrillation or other arrhythmia. All patients were instructed to take all medications as usual.

Group C: included 20 healthy male subjects (mean age 51.0±5.7 years) as a control group, who were matched with the other two groups for age and BMI.

All subjects included in the present study were admitted to the intensive care units, Cairo University except for the control group which was selected from the normally proven angiography. Because CAD has a higher prevalence in men and because OPG serum levels are dependent on the gender (higher levels in women)[15], serum OPG and soluble TRAIL levels were estimated only in men in this study.

After obtaining an informed consent, all subjects were subjected to thorough clinical and laboratory assessment with special stress regarding previous MI, hypertension, diabetes, hyperlipidemia and smoking. All patients were subjected to coronary angiography.

Patients with suspected or proven long-term or intercurrent inflammatory disease likely to be associated with short term phase response (i.e. patients with infections, malignancies, autoimmune disorders, liver or renal diseases) were excluded.

Body mass index (BMI) was calculated as weight divided by the square of height in meters. Diabetes mellitus was defined as a fasting plasma glucose repeatedly ≥ 120 mg/dl or if they were receiving oral hypoglycemic drugs or insulin. Arterial hypertension was defined as systolic blood pressure repeatedly measured >140 mmHg, diastolic blood pressure >90 mmHg or current use of antihypertensive drugs.

Biochemical analysis

Whole blood was obtained by venipuncture of a peripheral vein in all studied subjects. In patients with AMI, blood samples were withdrawn within 6 hours after admission for measurement of serum OPG and s-TRAIL and a second blood sample was collected following an overnight fast for at least 12 hours for estimation of lipid profile. In patients with established CAD, venous blood samples were collected following an overnight fast before angiography. In all patients total cholesterol[16], triacylglycerol (TAG)[17] and high[18] as well as low[19] density lipoprotein cholesterol, Creatine kinase (CK)[20] and CK-MB[21] were estimated using commercially available kits immediately after drawing the venous blood. To measure OPG, s-TRAIL and hsCRP serum was separated from the blood corpuscles by centrifugation at 5000 g for 10 minutes and kept frozen at – 80° C until analysis.

OPG was measured with a commercially available ELISA kit according to manufacturer's protocol (Biovendor laboratory Medicine, Brno,

Czech Republic). In brief a monoclonal IgG antibody was used as the capture antibody, and a biotin polyclonal anti-human OPG antibody was used as the detection antibody [intra-assay CV (Coefficient Variation) 4.8%; inter-assay CV 3.4%; lower detection limit 0.4 pmol/L]. Serum level of s-TRAIL was performed using a sandwich ELISA kit with a detection limit of 20 pg/ml according to the manufacturer's protocol (Biosource international Inc., Camarillo California). High sensitivity C-reactive protein (hsCRP) was measured by commercially available ELISA kit (Diagnostic systems laboratories, Webster, TX) with intra-assay CV (1.7-3.9%) and inter-assay CV (2.8-5.1%). The sensitivity of the assay is 0.0002 mg/dl.

Statistical Methods:

Statistical Package for social science (SPSS) program version 9.0 was used for analysis of data. Data was summarized as mean ±SD. One way ANOVA (analysis of variance) was used for analysis of more than two quantitative data. Chi square test was used for analysis of two qualitative data. Pearson's correlation was also done . r was considered weak if is < 0.25, mild if >0.25- <0.5, moderate if >0.5-<0.75 and strong if > 0.75. P-value was considered significant if ≤ 0.05*.

RESULTS

The characteristics of the studied population are shown in Table 1. Age and body mass index showed no significant difference in the three groups. The percentages of patients with hypertension, diabetes mellitus, and smoking and a family history of CAD showed no significant difference in both AMI and stable CAD groups. The percentage of patients with a history of previous myocardial infarction was significantly higher in the group of patients with stable CAD compared to those with AMI. The number of vessels affected in angiography showed no significant difference in both AMI and stable CAD groups. Patients with AMI and stable CAD differed in the use of B-blockers, long acting nitrates, HMG-coA reductase inhibitors and aspirin (Table 1).

The mean serum levels of CK and CK-MB were significantly higher in the AMI group when compared to either stable CAD group or control subjects but there was no significant difference between stable CAD group and control subjects.

As regards the lipid profile, the mean serum levels of both total cholesterol and LDL-C (Low density lipoprotein cholesterol) were significantly higher in both AMI and stable CAD patients when compared to control subjects. However, there was no significant difference between AMI and stable CAD groups in these two parameters. TAG was significantly higher in patients with AMI when compared to both stable CAD and control subjects groups. There was no significant difference between stable CAD group and control subjects in TAG. HDL-C (High density lipoprotein cholesterol) level was significantly lower in both AMI and stable CAD groups when compared to control subjects. Also, HDL-C level was significantly lower in AMI group when compared to stable CAD group (Table 1).

The mean OPG serum level was significantly higher ($p<0.0001$) in

patients with AMI (8.8±3.0 pmol/l) compared to patients with stable CAD (5.2±1.6 pmol/l) and control subjects (3.3±0.9 pmol/l). Furthermore, mean OPG serum level was significantly higher ($p<0.0001$) in patients with stable CAD compared to control subjects (5.2±1.6 pmol/l vs 3.3±0.9 pmol/l)(figure 1& table 1). Analysis of the angiographic findings, showed that OPG serum levels increased significantly as the number of stenotic coronary arteries increased in both AMI and stable CAD groups. In AMI group, mean OPG serum level was 10.28 ± 1.55 pmol/l in patients with three vessels disease compared to 8.2 ± 1.2 pmol/l in those with two vessels disease and 6.43 ± 0.57 pmol/l in those with one vessel disease. In stable CAD group, mean OPG serum level was 6.3 ± 0.5 pmol/l in patients with three vessels disease compared to 5.8 ± 0.6 pmol/l in those with two vessels disease and 4 ± 0.4 pmol/l in those with one vessel disease (tables 2&3)

Mean serum s-TRAIL level was significantly lower ($p<0.0001$) in patients with AMI (259.9 ±102.3 pg/ml) compared to patients with stable CAD (515.9 ±164.2 pg/ml) and control subjects (645.7 ± 189.3 pg/ml). Furthermore, mean serum s-TRAIL levels were significantly lower ($p<0.0001$) in patients with stable CAD compared to control subjects (515.9 ±164.2 pg/ml vs 645.7 ± 189.3 pg/ml) (figure 2 & table1).Analysis of the angiographic findings, showed that serum s-TRAIL levels decreased significantly as the number of stenotic coronary vessels increased. In AMI group, mean serum s-TRAIL level was 144.48 ± 34.7 pg/ml in patients with three vessels disease compared to 231.8 ± 48.15 pg/ml in those with two vessels disease and 358.9 ± 53.1 pg/ml in those with one vessel disease. In stable CAD group, mean serum s-TRAIL level was 311.4 ± 40.5 pg/ml in patients with three vessels disease compared to 441.3 ± 65.6 pg/ml in those with two vessels disease and 615.7± 64.2 pg/ml in those with one vessel disease (tables 2&3)

Mean serum hsCRP level was significantly higher ($p<0.0001$) in patients with AMI (11.4±3.6 mg/dl) compared to both patients with stable CAD (4.41±1.9 mg/dl) and control subjects (1.6±0.6 mg/dl). Also, serum hsCRP level was significantly higher ($p<0.0001$) in patients with stable CAD compared to control subjects (4.41±1.9 mg/dl vs 1.6±0.6 mg/dl) (figure 3 & table 1).

There was a significant negative correlation between serum OPG and s-TRAIL in all studied groups (figures 4, 5, 6&Table 4). On the other hand, there was a significant positive correlation between OPG and hsCRP and significant negative correlation between s-TRAIL and hsCRP in both AMI and stable CAD groups but not in control subjects (Table 4 &5).

There was a significant positive correlation between OPG and both CK and CK-MB in AMI patients only. No correlation was found between either OPG or TRAIL and age, BMI, smoking and lipid profile in all studied groups (Table 4&5).

Table 1: Clinical Data of the three studied groups:

Variables	**Acute myocardial infarction Mean ± SD N=28**	**Coronary artery disease Mean ± SD N=32**	**Controls Mean ± SD N=20**	**P-value**
Age (yrs)	52.8 ± 7.5	52.1 ± 6.6	51.0 ± 5.7	0.7
BMI (kg/m^2)	32.6 ± 3.3	31.4 ± 4.4	33.5 ± 2.8	0.1
Family history of CAD (%)	53.6	37.5	25	0.05*
Previous MI (%)	35.71	68.75	0	0.0001*
Risk factors				
Hypertension, (%)	67.9	75	0	0.0001*
Diabetes, (%)	39.3	34.4	0	0.006*
Smoking, (%)	64.3	62.5	40	0.2
Affected coronary arteries (n)				
One	10	11	0	
Two	10	12	0	
Three	8	9	0	
Medication used (%)				
B-blockers	64.3	93.8	0	
Long acting nitrates	39.3	93.8	0	
Aspirin	75	100	0	
HMG-CO reductase inhibitors	21.4	31.3	0	
Calcium antagonist	32.1	11	0	
ACE- inhibitors	32.1	28.1	0	
Biocheistry				
CK (U/I)	725.6 ± 252.1a	48.5 ± 16.4b	34.9 ± 9.4b	0.0001*
CK-MB (U/I)	77.3 ± 17.9a	17.1 ± 4.1b	12.5 ± 2.9b	0.0001*
Total cholesterol (mg/dl)	215.2 ± 43.6a	211.4 ± 37.9a	183.1± 21.1b	0.05*
HDL-C(mg/dl)	34.3 ± 6.5a	41.5 ± 5.8b	49.4 ± 3.5c	0.05*
LDL-C(mg/dl)	145.5 ± 43.3a	145.1 ± 36.6a	117.9 ± 18.3b	0.05*
Triacylglycerol (mg/dl)	159.3±61.8a	127.9±37.9b	112.9±33.5b	0.003*
hsCRP (mg/dl)	11.4 ± 3.6a	4.4 ± 1.9b	1.6 ± 0.6c	0.0001*
OPG (pmol/l)	8.8 ± 3.0a	5.2 ± 1.6b	3.3 ± 0.9c	0.0001*
s-TRAIL (pg/ml)	259.9 ± 102.3a	515.9 ± 164.2b	645.7 ± 189.3c	0.0001*

P-value is significant if ≤ 0.05*
Different symbols indicate significant difference.

Table2: OPG and s-TRAIL levels in patients with AMI in relation to the number of affected coronary arteries

Variables	One affected coronary artery Mean ± SD N=10	Two affected coronary arteries Mean ± SD N=10	Three affected coronary arteries Mean ± SD N=8	P-value
OPG (pmol/l)	6.43 ± 0.57a	8.2 ± 1.2b	10.28 ± 1.55c	0.0001*
s-TRAIL (pg/ml)	358.9± 53.1a	231.8 ± 48.15b	144.48 ± 34.7c	0.0001*

Table 3: OPG and s-TRAIL levels in patients with stable coronary artery disease in relation to the number of affected coronary arteries

Variables	One affected coronary artery Mean ± SD N=11	Two affected coronary arteries Mean ± SD N=12	Three affected coronary arteries Mean ± SD N=9	P-value
OPG (pmol/l)	4 ± 0.4a	5.8 ± 0.6b	6.3 ± 0.5c	0.0001*
s-TRAIL (pg/ml)	615.7± 64.2a	441.3 ± 65.6b	311.4 ± 40.5c	0.0001*

P-value is significant if ≤ 0.05*
Different symbols indicate significant difference.

Table 4: Correlation between OPG and data in the three studied groups

Variables	Acute myocardial infarction		Coronary artery disease		Controls	
	r	P-value	r	P-value	r	P-value
Age (yrs)	-0.2	0.3	-0.2	0.3	0.5	0.07
BMI (kg/m^2)	-0.1	0.6	-0.3	0.09	0.2	0.4
hsCRP(mg/dl)	0.8	0.0001*	0.8	0.0001*	-0.01	0.9
CK (U/I)	0.6	0.002*	-0.02	0.9	0.4	0.1
CK-MB (U/I)	0.4	0.04*	0.05	0.8	0.3	0.3
Total cholesterol (mg/dl)	0.1	0.6	-0.03	0.9	0.4	0.09
HDL-C(mg/dl)	-0.1	0.6	-0.2	0.4	0.02	0.9
Triacylglycerol (mg/dl)	0.1	0.6	0.1	0.7	0.5	0.09
LDL-C(mg/dl)	-0.1	0.8	-0.04	0.8	0.3	0.2
s-TRAIL(pg/ml)	-0.9	0.0001*	-0.9	0.0001*	-0.9	0.0001*

Table 5: Correlation between s-TRAIL and data in the three studied groups

Variables	**Acute myocardial infarction**		**Coronary artery disease**		**Controls**	
	Variables	P-value	r	P-value	r	P-value
Age(yrs)	0.2	0.2	0.2	0.2	-0.4	0.09
BMI (kg/m^2)	0.05	0.8	0.3	0.1	-0.1	0.6
hsCRP(mg/dl)	-0.7	0.0001*	-0.8	0.0001*	0.04	0.9
CK (U/I)	-0.4	0.06	0.1	0.8	0.1	0.8
CK-MB (U/I)	-0.3	0.2	-0.01	0.9	-0.3	0.2
Total cholesterol(mg/dl)	-0.2	0.3	0.004	0.9	-0.3	0.2
HDL-C (mg/dl)	0.2	0.4	0.2	0.3	-0.1	0.7
Triacylglycerol (mg/dl)	-0.3	0.1	-0.1	0.5	-0.5	0.09
LDL-C(mg/dl)	-0.03	0.9	0.02	0.9	-0.4	0.07
OPG(pmol/l)	-0.9	0.0001*	-0.9	0.0001*	-0.9	0.0001*

P-value is significant if ≤ 0.05*

Fig 1: OPG of patients with acute myocardial infarction, coronary artery disease and controls

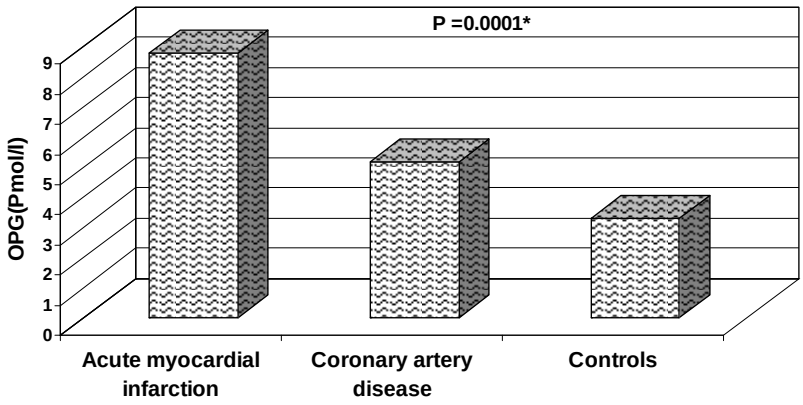


Fig 2: s-TRAIL of patients with acute myocardial infarction, coronary artery disease and controls

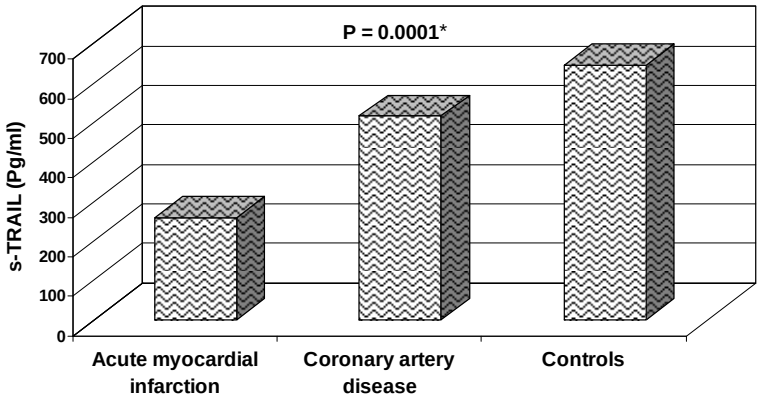


Fig 3:hsCRP of patients with acute myocardial infarction, coronary artery disease and controls

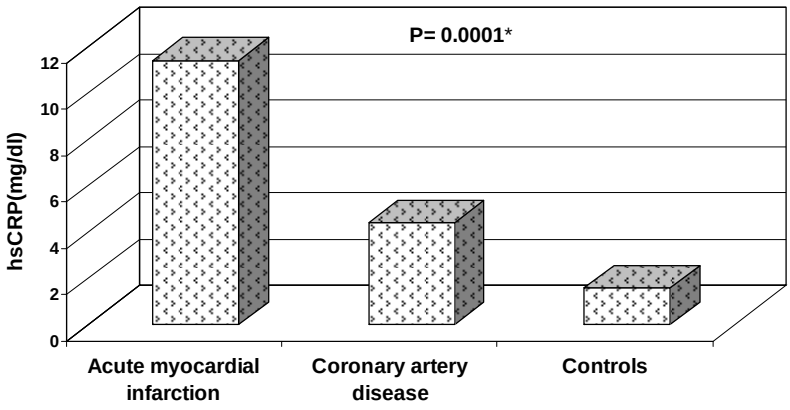


Fig 4: Correlation between OPG and sTRAIL
in patients with acute myocardial infarction
r=-0.9, P= 0.0001*

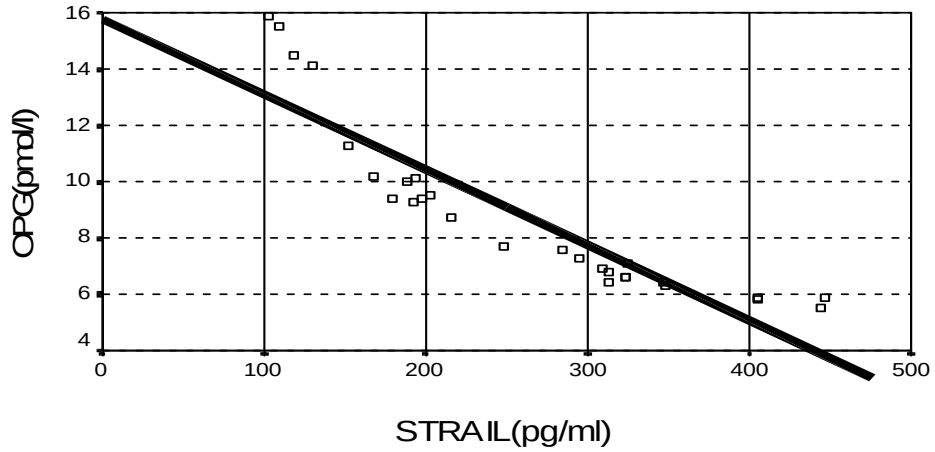


Fig 5: Correlation between OPG and sTRAIL
in patients with coronary artery disease
r=-0.9, P= 0.0001*

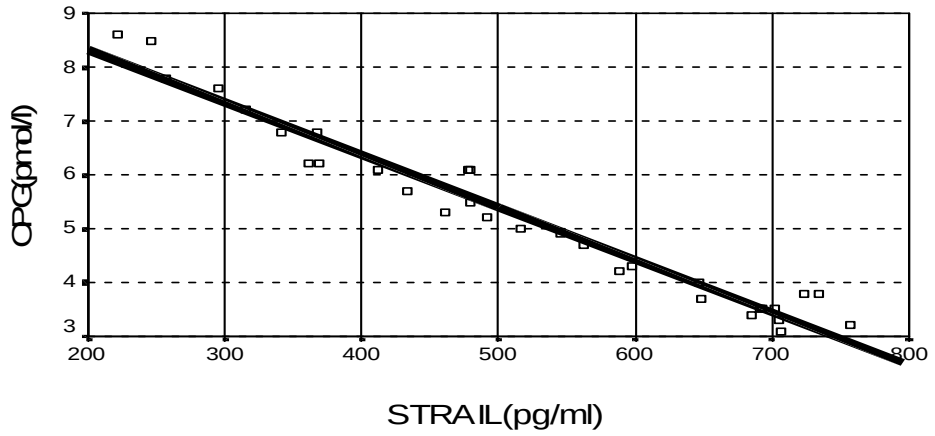
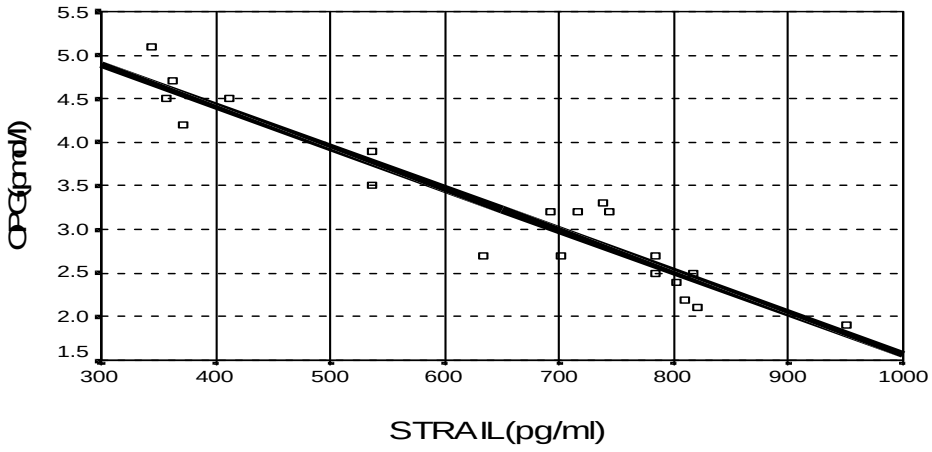


Fig 6: Correlation between OPG and sTRAIL in controls (r=-0.9, P= 0.0001*)



DISCUSSION

Acute coronary syndromes (ACS) are precipitated by rupture of the surface of the atherosclerotic plaque, giving rise to superimposed thrombosis and arterial occlusion. The atheromas vulnerability to rupture is correlated with a cellular infiltrate of macrophages and activated T-cells in the plaque tissue, leading to proteolytic degradation of connective tissue matrix, excessive proinflammtory cytokine production and apoptosis of the vascular wall cells[(5)].

OPG, a secreted basic glycoprotein and member of the TNF-receptor superfamily, is produced by cells of the cardiovascular system, including coronary artery smooth muscles and endothelial cells[(22)]. It has been suggested that alterations of serum OPG levels may be associated with CAD[(23)]. OPG and RANKL immunoreactivity was detected in early atherosclerotic lesions in human. These findings indicate a potential role for these cytokines in the process of atherosclerosis and atherosclerotic calcification[(24)].

In the present study, serum OPG levels was studied in patients with AMI and stable CAD to detect any possible correlation with the severity of CAD and the reflection of its level on different stages of ischemic cardiovascular disease. OPG serum levels were significantly higher in both AMI and stable CAD patients compared to control subjects and were significantly higher in AMI patients compared to stable CAD patients. These findings are consistent with previous reports that suggested a correlation between OPG and cardiovascular disease[(25,26)]. In addition,

a recent prospective large population based survey study has shown that the relative risk of cardiovascular mortality is increased by three folds in patients with high serum OPG levels[27].

Also, in a recent study by Crisafulli et al.[28] serum levels of OPG were significantly increased in patients with AMI within 1 hour after the onset of pain and although decreased after 1 and 4 weeks of follow up, remained higher than those observed in patients with established stable CAD and control subjects. Furthermore, they also found that the level of OPG in patients with established CAD was significantly higher compared to control subjects.

How OPG operate in the vascular pathophysiology is not known precisely. However, several clues from previous studies suggested a role of OPG in vascular calcification, inflammation and regulation of apoptosis.

Vascular calcification with its reduced compliance and altered mechanical properties is a predisposing factor for plaque rupture[29] and a predictor of vascular mortality (30). OPG counteracts calcification by its well established capacity to inhibit bone resorption and is considered to be a candidate calcification inhibitor[31]. Notably, OPG deficient mice develop severe osteoporosis and early calcium deposits in the media and subintima of the aorta and renal arteries[7].

Another possible role for OPG in vascular protection is by acting through inhibition of the inflammatory process related to atherosclerosis. Previous in vitro studies have shown that inflammatory cytokines, such as IL (interleukin)-1, TNF-alpha and PDGF (platelet derived growth factor) up regulate OPG expression in vascular smooth muscle cells (VSMCs) and endothelial cells and in turns OPG interferes with various inflammatory signaling pathways[32]. The high OPG serum levels in patients with AMI compared to those with established CAD might be related to an increase in the secretion of inflammatory cytokines in patients with acute coronary syndromes[33,34].

Previous studies have suggested a role of vascular inflammation in the pathogenesis of atherosclerosis[35, 36]. In the present study, high sensitivity CRP (hsCRP), an acute–phase reactant was measured. It has been intensively studied as a novel marker of atherosclerosis[36], and evaluated for the presence of any possible correlation between serum OPG and hsCRP levels. Interestingly, the serum hsCRP level was positively correlated with the serum OPG levels in all groups suggesting that OPG might be involved in the pathogenesis of atherosclerosis. These results are consistent with two previous studies that have reported that serum hsCRP levels had a positive correlation with serum OPG levels[27,37] but are in disagreement with other studies which did not find any association between inflammation markers and OPG[28,38]. Whether the elevated OPG levels are related to hsCRP and atherosclerosis, or whether they are both simply related to another inflammatory process such as infection are not known.

OPG serves as a decoy receptor for RANKL, but it can also bind to TRAIL, a potent activator of apoptosis[8]. Therefore, OPG may influence vascular disease by inhibiting

TRAIL- induced apoptosis in vascular cells

CD4 T-cells, the dominant type of plaque residing cells, express TRAIL upon stimulation and induce VSMCs apoptosis in a TRAIL dependent manner, a process that may lead to plaque destabilization and rupture[39]. Patients with acute coronary syndrome have increased expression of these CD4 T-cells[40].

Therefore, a third possibility by which OPG influences vascular disease is by inhibiting apoptosis in vascular cells. It can be hypothesized that OPG may be expressed by VSMCs, endothelium and macrophages in response to pro-apoptotic stimuli and thus having a protective role, as VSMCs apoptosis can weaken the cap tissue and favor plaque rupture[28].

Since OPG acts by neutralizing TRAIL, it is hypothesized that serum levels of TRAIL are also altered in vascular disease. In the current study, serum s-TRAIL levels in patients with AMI were significantly reduced compared to patients with established CAD or control subjects. Also, patients with stable CAD have significantly lower serum s-TRAIL levels compared to control subjects. These findings are in agreement with a study which showed that serum levels of s-TRAIL tended to be lower in patients with CAD compared to those without CAD[41], and also, with the results of a recent study on 40 patients with acute coronary syndromes revealing significantly lower s-TRAIL serum levels compared to patients with stable angina or normal coronary arteries. In this study there was no association between serum s-TRAIL and hsCRP[42]. However, in the present study, serum s-TRAIL levels was found to be negatively correlated with hsCRP levels.

In the present study, serum s-TRAIL levels showed a significant negative correlation with serum OPG levels. These data indicate that systemic levels of the decoy receptor OPG are elevated in vascular disease[25,27,28]. The role of s-TRAIL, the second ligand of OPG is ambiguous in vascular disease, and may play an important role in the inflammatory process during acute coronary syndrome[41].

A possible explanation for the lower s-TRAIL levels in AMI patients is that an increase of the total OPG (free plus TRAIL and RANKL-bound OPG) is associated with a decline of free TRAIL and free RANKL levels[42]. Another possibility is that TRAIL protein is consumed within the atherosclerotic plaque rather than reduced in ACS because of diminished production by CD4 T-cells[41].

The relation between serum OPG levels and the number of coronary vessels affected as a marker of severity of CAD was studied in the present work. In both AMI and stable CAD groups, the mean serum OPG level in patients with a single vessel affected was significantly lower compared to those with two or three vessels affected. Also, the mean serum OPG level was significantly lower in patients with two vessels affected compared to those with three vessels affected. These findings are in agreement with two previous studies who also found that serum OPG levels are associated with the severity of CAD and suggested that OPG may be involved in the progression of CAD and that serum

OPG levels may reflect certain stages of cardiovascular disease[23,24]. The relation between serum s-TRAIL levels and the number of coronary vessels affected was studied in the current work and it was found that in both AMI and stable CAD groups, mean serum s-TRAIL levels were significantly decreased as the number of coronary vessels affected increase. This is in disagreement with the previous study who found that serum s-TRAIL tended to be lower as the number of affected vessels increase but there is no direct association between s-TRAIL serum levels and the number of coronary vessels affected[41].

In conclusion, the present data showed a close association between raised serum OPG and reduced s-TRAIL in patients with CAD (both AMI and stable CAD). OPG may represent a novel marker of plaque instability as the OPG levels were higher in AMI compared to stable CAD patients. In view of the pro-apoptotic effects of TRAIL on vascular smooth muscle and endothelial cells, an elevation of circulating OPG levels may represent a crucial compensatory mechanism aiming to balance plaque instability and to limit further vascular damage. The precise biological role of high circulating OPG levels and OPG/TRAIL system in vascular diseases needs further evaluation.

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الاستيوبروتجرين و عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا فى مصل الدم فى مرضى الشريان التاجى

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يعتبر الاستيوبروتجرين عاملا أساسيا في أعادة تأهيل العظام وهواحدعناصرعائلة مستقبل عامل نخرالاورام و أيضا مستقبل لمنشط المستقبلات للعامل النووي وعامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا والذي تم تطبيقه مؤخرا على التصلب الشرياني البشري.

و يهدف هذا البحث إلي تقدير الدور المحتمل لكل من الاستيوبروتجرين و عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا في مرضي الشريان التاجى.

وقد اجرى هذا البحث على ثمانين شخص من الذكور البالغين تم تقسيمهم إلي ثلاث مجموعات . المجموعة الاولى شملت ثمانية و عشرين مريضا يعانون من جلطة حادة في الشريان التاجي والمجموعة الثانية شملت اثنين و ثلاثين مريضا مصابا بقصور مستقر بالشريان التاجي و المجموعة الثالثة شملت عشرين شخصا من الأصحاء الذين تم اتخاذهم كعينة ضابطة.

وقد تم اجراء الفحوصات السريرية و قياس كل من مستوى الاستيوبروتجرين و عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا فى مصل الدم باستخدام الأنزيم المتعلق لتحليل المواد الماصة المناعية.

وقد اظهرت نتائج البحث وجود ارتفاعا ذو دلالة احصائية فى مستوى الاستيوبروتجرين في مرضى الجلطة الحادة في الشريان التاجي مقارنة بمرضى قصور الشريان التاجى المستقر والمجموعة الضابطة و كذا زيادة ذو دلالة احصائية فى مرضى قصورالشريان التاجى المستقر مقارنة بالمجموعة الضابطة. كما اظهرت النتائج وجود انخفاضا ذو دلالة احصائية فى مستوى عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا فى مرضى الجلطة الحادة في الشريان التاجي مقارنة بمرضى قصور الشريان التاجى المستقر والمجموعة الضابطة و كذا انخفاضا ذو دلالة احصائية فى مرضى الشريان التاجى مقارنة بالمجموعة الضابطة، كما وجدت علاقة ذات دلالة احصائية عكسية بين مستوى الاستيوبروتجرين و مستوى عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا فى كل المجموعات.

و بذلك يمكن استنتاج ان الارتباط الوثيق بين زيادة مستوى الاستيوبروتجرين ونقص مستوى عامل نخر الاورام المرتبط بالموت المستحث المبرمج للخلايا فى المرضى الذين يعانون من مرض الشريان التاجى (سواء مرضى الجلطة الحادة في الشريان التاجي او مرضى قصور الشريان التاجى المستقر) تمثل آليةتعويض حاسمة من اجل الحد من تلف الاوعية الدموية.