ORIGINAL ARTICLE

Impact of Osteoprotegerin on Atherosclerotic Vascular Disorders in Iraqi Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease described by expanded mortality to a great extent owing to cardiovascular sickness. osteoprotegerin (OPG) is a recently distinguished glycoprotein, having a place with the tumor necrosis factor receptor superfamily, initially found as the inhibitor of bone resorption.
Aim: To explore the relationship of the level of serum osteoprotegerin (OPG) level with the finding of asymptomatic coronary artery disease in the patient with rheumatoid arthritis (RA).
Methods: The examination included 25 rheumatoid patients with CAD aided design (the positive outcomes on practice ECG stretch test) and other 26 rheumatoid patients without CAD aided design (negative outcomes on practice ECG push test and affirmed using coronary angiography). What's more, 30 age and sex coordinated typical control subjects were examined. Serum OPG was estimated utilizing Elisa test.
Results: This work showed that levels of serum OPG have been significant higher levels in rheumatoid patients without and with CAD than in controls ($P < 0.012$) also OPG was positively correlated with age, BMI, and negatively with duration of disease in patients with and without CAD.
Conclusion: Osteoprotegerin is the medically meaningful particle autonomously connected with the nearness of coronary artery disease and might be a decent pointer of damage of the atherosclerotic vascular and macro angiopathy of the rheumatoid patients. Thus, estimation of serum OPG justifies advance examination as the basic test to enhance early the CAD diagnosis of the rheumatoid patients.
Key word: Osteoprotegerin , coronary artery disease, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is one of the chronic inflammatories illness described using expanded mortality to a great extent inferable from cardio vascular disease. [1]the articular bone disintegrations is the trademark highlight of RA [2] and one of its skeletal complications and also fundamental osteopenia that outcome in the expanded danger of bone breaks.

The last research exploring the pathogenic components [3], of bones devastation in creature models of joint inflammation have given considerable confirmation that the osteoclast is the phone write fundamentally in charge of central bone disintegration, and its age and action were needy on RANKL receptors activator of kB ligand atomic factor[4,5]. OPG is a recently recognized glycoprotein, having a place with the tumor putrefaction factor receptor superfamily, initially found as the inhibitor of resorption of bones. The current inhibition is interceded during OPG's official and balance of RANKL that is the solid inducer of osteoclast differentiation[6] . Curiously it was exhibited that the OPG is created using an assortment of tissue, involving a cardio vascular framework (veins , heart and arteries), kidney , lung , and immune cells, and bone and is controlled by different hormones and cytokines[7].

Rising proof demonstrates that atherosclerotic vascular and osteoporosis sicknesses are usually discovered together. Adroitly a move of calcium from the skeleton toward the blood vessel divider can represent the two issues, yet the hidden paracrine systems that work in the bone digestion and vascular homeostasis have not characterized. Mouse hereditary qualities may have unwound the potential atomic connection amongst osteoporosis and blood vessel calcification [8].

It was demonstrated that the OPG-insufficient mouse create extreme osteoporosis and average calcification of renal veins and the aorta 9[10]**.** They have been totally prevented by restoration of the gene[11]. Therefore the, OPG was suggested as a connection between atherosclerosis and osteoporosis. Besides OPG appears to have an imperative influence in counteracting disintegrations and osteoporosis in patients with RA[12]. Where as in postmenopausal females, a solitary subcutaneous infusion of OPG quickly decreased biochemical markers of bone resorption. A solid relationship between the level of serum in OPG and seriousness of coronary vein infection was seen in previous research [13] .Besides, the level of OPG has been observed to be higher in the rheumatoid joint inflammation patients[14.]

This work aims in this manner to determine the relationship of the level of sera of OPG with the nearness of asymptomatic coronary artery disease in RA patients.

MATERIALS AND METHODS

RA patients have been selected to be recorded in this work with definite R.A, and diagnosed depending to 2010 EULAR (European League against Rheumatism)\ ACR (American College of Rheumatology) criteria of classification for the rheumatoid arthritis [15]. They have been selected from the rheumatology, in internal medicine clinic of Baghdad hospital – medical city / Iraq. The patients had no symptoms or history of the coronary event, and with the normal resting ECG (electrocardiography). the patient of

RA have been recruited depending to the absence or finding divided them to 2 groups, Group I: involved 26 rheumatoid patients (10 females and 16 males) without CAD (the negative result on the test of exercise ECG stress), and the Group II: involved 25 rheumatoid patients[13] females and 12 males) with CAD (the positive result on test of exercise ECG stress). Before starting any procedure of this study, a reported consent has been completed from each enrolled patent. Patients suffering from uncontrolled hypertension, acute infection, diseases of kidney (serum creatinine more than 2.0 mg/100ml), diabetes mellitus, or malignancies have been removed from this research.

Thirty volunteers of matched age (48.5 ±1.8) and sex (14 females and 16 males), normotensive with negative ECG stress test enrolled in this study as the control group. All states involved in this research have been introduced to the next: taking the complete history of patient and medical exam with particular stress on the symptoms of heart, finding of agents of cardio-vascular risk like hypertension, smoking, and dyslipidemia family history of premature CAD. Body mass index (BMI), through of rheumatoid, menopausal history for females. Exercise and resting ECG stress test has been done for both patients and controls.

Laboratory tests involving serum lipid profile have been documented from files on of patients their regular visits, whereas serum OPG was determined using ELISA test.

Laboratory procedures: Samples of venous blood have been collected from the patient and control under aseptic precautions, serum have been collected from samples the fasting blood, aliquot and stored at 20 C for using in the future tests. Serum OPG calculation: Serum OPG has been determined using the commercial kit (Systems of R&D, MN, and Minneapolis, USA)[16] .

Exercise test of ECG stress: The anti-hypertensive treatments with the B-adrenergic blocking agents together with beverages and food including caffeine asked to stop for at least twelve hr before testing. However, the exercise test was performed depending to the Bruce protocol by a Cardiocontrol treadmill[17]. Statistics:

Results have been expressed as mean±SD. Comparisons between groups have been made by Anova - test for continuous variables. Correlation between the 2 parameters was determined using correlation coefficient of Pearson (r). P values < 0.05 are considered statistically significant[18].

RESULTS

The results obtained from this study shows that serum OPG level was significantly lower in RA patients with CAD than in those without CAD and the control (P = 0. 012), in addition serum TG, HDL-cholesterol & LDL- cholesterol have been significantly higher levels in the patient of RA with CAD in comparison to patients of RA without CAD and control group (P= 0.05, 0.045 and 0.036 respectively) as shown in table 1.

Figure 1 shows that there is a significant positive correlation between OPG values and age of RA patients with and without CAD (P= 0.027).

Figure 2 shows that OPG values in patients of RA without and with CAD has a significant positive correlation with BMI of those patients (P=0.033).

Figure 3 demonstrated that there is a significant negative correlation between OPG levels and disease duration in rheumatoid arthritis patient without and with CAD (P=0.054).

Table 1: Laboratory and clinical findings of the rheumatoid patient with and without CAD & controls

Studied parameters	Rheumatoid patients without CAD (n=25) mean± SD	Rheumatoid patients with CAD (n= 26) mean± SD	Controls (n=30) mean± SD	P-Value
Age (years)	48.13± 2.2	50.98 ± 2.7	48.82 ± 3.3	0.63NS
BMI	28.5 ± 2.1	27.59± 4.1	29.1 ± 2.42	0.81NS
Disease duration (years)	5.2 ± 3.9	7.5± 2.1		0.72NS
Total cholesterol mg/dl	222.51 ± 1.6	258.05 ± 1.48	182.57± 1.2	0.062NS
Triglyceride mg/dl	159.48± 2.71	175.95± 3.1	149.2± 2.87	0.05*
HDL-cholesterol mg/dl	38.58 ± 2.4	34.28 ± 2.1	48.41± 2.22	0. 045*
LDL-cholesterol mg/dl	150.41 ± 1.85	168.55± 2.41	115.96± 3.5	0.036*
OPG ng/ml	2.08± 0.89	3.16±0.15	5.17± 0.08	0.012*

*Note: *= significant NS= non- significant*

Figure 1: correlation between OPG & age.

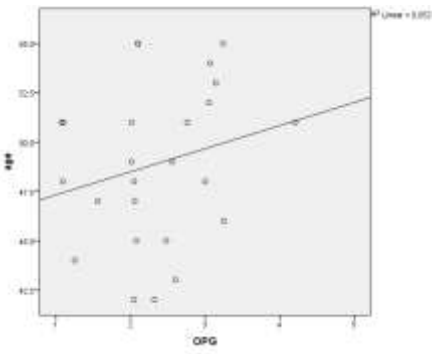


Figure 2: correlation between OPG and BMI.

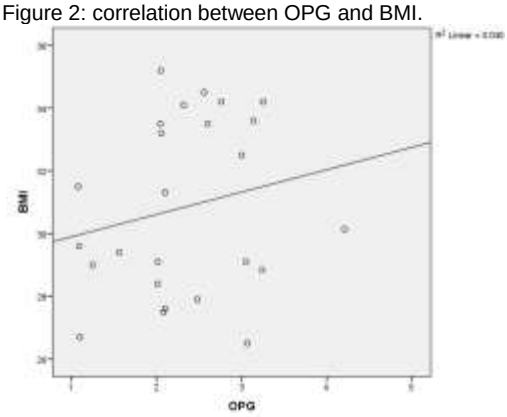
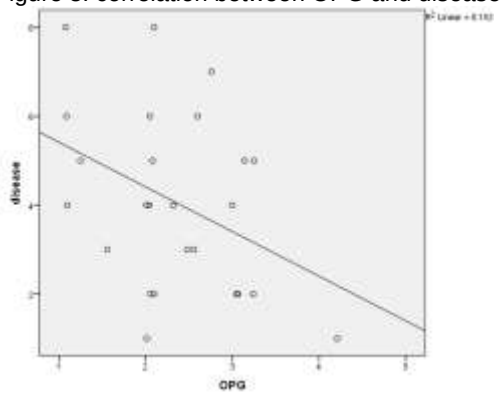


Figure 3: correlation between OPG and disease duration



DISCUSSION

The chronic inflammation assumes the essential part in pathogenesis of RA and atherosclerosis. There are expanding proofs from controlled medical examinations expressing that are high frequencies of cardio-vascular illnesses in RA [19, 20] . Levels of serum of OPG have been essentially higher in patients of RA without and with CAD contrasted with the control (P= 0.012).

It was recorded that movement of atherosclerotic calcification are contrarily related with the low mineralization of bone tissue and is related with loss of bones in elderly men, and in post-menopausal females [21, 22]. Jesper *et al* [23] archived that bone mass loss in osteoporosis prompts expanded circling calcium and phosphate and diminished parathyroid hormones , which fortify mineralization of cardiovascular tissues , additionally pointed on the significance of cytokines, for example, tumor necrosis factor and interleukin connection amongst osteoporosis and atherosclerosis.

Trial thinks about have recommended that OPG may be fill in as the inhibitor of vascular calcifications, as mouse that was treated with using fcOPG demonstrated a noteworthy diminishment in the calcified zone without fondness of the vascular cytokines [24] likewise parenteral organization of the OPG affection of vascular calcification incited using warfarin and poisonous measurements for vitamin D of the rats [25]. Subsequently, OPG is a pivotal tie amongst vascular and skeletal frameworks. Essentially, levels of OPG give prognostic data in the patients who create the heart failure after intense myocardial infarction (AMI) [26], so the OPG may speak to a newly marker of plaque flimsiness and cardiovascular mortality in the patient [27].

Levels of Serum of OPG have been altogether higher in patients RA without and with CAD in compared with controls. OPG were positively& essentially associated with age of the patients, BMI and adversely with length of the sickness. This is vital in light of the fact that it proposes that mechanisms fundamental the part of OPG in atherosclerosis might be autonomous of present focuses for cardiovascular hazard mediation. In spite of the fact that the capacity of OPG in the vasculature is begging to be proven wrong, the outcomes were good with the discoveries of Schoppet *al* [13] who depicted expanded plasma convergences of OPG in the men with CAD additionally with work consequences of Unni M *et al* [28] who could clarify the imperative part of RANKL OPG framework in pathogenesis of atherosclerosis in provocative the rheumatic illnesses. The height of OPG with regards to RA has been accounted for by past distributed investigation which clarified that the OPG is balanced by immunological system, and maybe goes about as counter-regulatory molecules which adjusts for expanded generation of RANK [29].

In spite of the fact that the exact natural part of OPG in vascular ailments stays indistinct, lifted levels serum of the present vascular defensive agent could be translated as a deficient compensatory self-protective system toward agents that advance atherosclerosis and blood vessel calcification [30], subsequently it could be accepted that increased OPG is the reaction to instead of a reason for atherosclerosis, trying to counteract advance vascular damage which connect with the discoveries of Scott DL *et al* [2] who expressed in their investigation that high levels of levels of OPG may represent to an urgent compensatory component to restrict facilitate vascular calcification. Also, Pedersen *et al* [31] showed that elevated OPG levels are related with expanded danger of intense occasion's instable angina pectoris patients however free impacts are confined to a specific subgroup with especially improved action in OPG RANKL/RANK framework, as reflected using the higher level of OPG.

There are a few impediments of this study. To start with, OPG was just estimated once and longitudinal information might be more educational. In any case, the way that OPG focus is raised in the patients with both early and long-standing illness, and that OPG are autonomously connected with coronary-artery calcification just in patients with long-standing disease proposes that height of OPG fixations may go before perceptible atherosclerosis. Second, the patients contemplated had, on average, moderate disease activity, and the outcomes may not be generalizable to different populations of patients. In this way, in spite of the fact that a relationship amongst OPG and atherosclerosis in patients with extremely dynamic RA is conceivable, prove is expected to help that.

CONCLUSION

From this investigation, it could be presumed that the osteoprotegerin are clinically imperative molecule, freely connected with nearness of the coronary artery diseases and may be the decent marker of the atherosclerotic vascular damage macroangiopathy in the rheumatoid joint inflammation. Subsequently, estimation of serum OPG justifies facilitates examination as the basic test to enhance early finding of the asymptomatic CAD for the patients of RA. Encourage bigger, planned investigations are needed to illuminate the causer connection among OPG , atherosclerotic vascular disease and rheumatoid joint pain in addition clinical tests of newly operators for rectifying causal components and to assess the conceivable remedial capability of OPG as another (vasculoprotegerin). The Future research on quality polymorphisms of OPG could assume a part in the advancement, movement and reaction for treatment in the rheumatoid vascular complications.

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