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# Serum Osteoprotegerin Association With Coronary Artery Disease And Type 2 Diabetes Mellitus In Syrian Cohort

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## Abstract:

**Background and Aim:** Osteoprotegerin (OPG) has emerged as a potential biomarker for cardiovascular diseases (CVD) and type 2 diabetes (T2D). This study aimed to evaluate the relationship between serum OPG levels, fasting blood glucose (FBG), and the presence of coronary artery disease (CAD) in patients with and without T2D.

**Materials and methods:** A total of 60 participants were enrolled in this cross-sectional study, divided into two groups based on cardiac catheterization results: Non-CAD group (16 patients) with no stenosis in epicardial arteries and CAD group (44 patients) with severe multivessel disease (>50% stenosis in one or more major epicardial arteries). Demographic data, clinical characteristics, and biochemical parameters including FBG and serum OPG levels were measured. Statistical analyses were performed to compare the two groups and assess correlations.

**Results:** Patients with CAD exhibited significantly higher FBG levels (110.39±42.05 mg/dL) compared to those without CAD (84.75±9.55 mg/dl, P=0.021). Serum OPG levels were also elevated in the CAD group (5.72±2.06 ng/mL) versus the non-CAD group (4.49±1.05 ng/ml, P<0.008). A positive correlation was observed between OPG levels and diabetes status, with higher OPG levels noted in T2D patients (5.91±2.38 ng/ml) compared to non-diabetic individuals (4.91±1.2 ng/ml). ROC curve analysis demonstrated that OPG had an area under the curve (AUC) of 0.726 for predicting CAD risk (P=0.008) and an AUC of 0.661 for predicting T2D risk (P=0.033).

**Conclusions:** Our findings suggest that elevated serum OPG levels are associated with CAD and T2D, indicating its potential role as a biomarker for cardiovascular risk assessment. Further studies are warranted to explore the mechanistic pathways linking OPG with metabolic and cardiovascular diseases.

**Keywords:** Coronary Atherosclerosis Disease, Atherosclerosis, Biomarker, Osteoprotegerin, Cardiovascular Risk Factors, Fast Plasma Glucose, Diabetes.

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# ارتباط الاوستيوبروتغرين المصلي مع مرض الشريان الاكليلي وداء السكري النمط الثاني في مجموعة سورية

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## الملخص:

**خلفية البحث وهدفه:** ظهرت الأوستيوبروتيغيرين (OPG) كواصم حيوي محتمل لأمراض القلبية الوعائية (CVD) ومرض السكري من النوع الثاني (T2D). تهدف هذه الدراسة إلى تقييم العلاقة بين مستويات OPG في المصل، ومستويات الغلوكوز في الدم الصيامي(FBG) ، ووجود مرض الشريان التاجي (CAD) لدى المرضى الذين يعانون من الداء السكري النمط الثاني وغير المصابين به.

**مواد البحث وطرائقه:** تم تسجيل 60 مشاركًا في هذه الدراسة المستعرضة، تتكون من 44 مريضًا تم تشخيصهم بمرض الشريان التاجي و16 فردًا بدون مرض الشريان التاجي. تم جمع البيانات الديموغرافية، والخصائص السريرية، والمعايير الكيميائية الحيوية بما في ذلك مستويات الغلوكوز في الدم الصيامي ومستويات OPG في المصل. تم إجراء التحليل الإحصائي لمقارنة المجموعتين وتقييم الارتباطات.

النتائج: أظهر المرضى الذين يعانون من مرض الشريان التاجي CAD مستويات الغلوكوز في الدم الصيامي أعلى بشكل ملحوظ (110.39±42.05 ملغ/دل) مقارنةً مع الذين لا يعانون من مرض الشريان التاجي (84.75±9.55 CAD ملغ/دل، P=0.021). كانت مستويات OPG في المصل مرتفعة أيضا في مجموعة مرض الشريان التاجي CAD (5.72±2.06نانوغرام/مل) مقارنةً بمجموعة غير (4.49±1.05 CAD نانوغرام/مل، P<0.008). لوحظ ارتباط إيجابي بين مستويات OPG وحالة السكري، حيث كانت مستويات OPG أعلى في مرضى الداء السكري النمط الثاني (5.91±2.38 T2Dنانوغرام/مل) مقارنةً بالأفراد غير المصابين بالسكري (4.91±1.2 نانوغرام/مل). أظهرت تحليل منحنى ROC أن OPG كان له مساحة تحت المنحنى (AUC) تبلغ 0.726 للتنبؤ بمخاطر الإصابة بمرض الشريان التاجي (P=0.008) والمساحة تحت المحنى AUC تبلغ 0.661 للتنبؤ بمخاطر الإصابة بالداء السكري النمط الثاني (P=0.033).

**الاستنتاج:** تشير نتائجنا إلى أن ارتفاع مستويات OPG في المصل مرتبط بمرض الشريان التاجي و الداء السكري النمط الثاني ، مما يدل على دوره المحتمل كعلامة بيولوجية لتقييم مخاطر القلب والأوعية الدموية. هناك حاجة لمزيد من الدراسات لاستكشاف السبل الآلية التي تربط OPG بالأمراض الإستقلابية والقلبية الوعائية.

**الكلمات المفتاحية:** مرض تصلب الشرايين التاجية، تصلب الشرايين، واصم حيوي، أوستيوبروتيغيرين، عوامل خطورة القلبية الوعائية ، غلوكوز البلازما الصيامي، داء السكري.

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# Introduction:

Osteoprotegerin (OPG) is a critical regulator of bone resorption and is increasingly recognized for its role beyond the skeletal system. It is produced by various tissues, including those in the cardiovascular system, such as the heart and blood vessels(1,2). OPG expression is regulated by numerous cytokines and hormones(3). Studies have shown that OPG-deficient mice exhibit severe osteoporosis and arterial calcification (4), indicating its significance in both bone health and vascular integrity. Additionally, OPG has been identified in early atherosclerotic lesions, suggesting its involvement in vascular disease progression(5).

Recent clinical studies have reported a significant correlation between elevated serum OPG levels and cardiovascular mortality(6), proposing that OPG may contribute to coronary artery disease (CAD) progression. This study aims to evaluate the associations between serum OPG levels and glucometabolic parameters in patients with CAD.

# 2. Materials and methods:

### 2.1. Study Design and Participants

This cross-sectional study included 60 patients (63.3% men, 36.7% women) hospitalized at the cardiac catheterization department of Al-Assad University Hospital. Patients were divided into two groups based on cardiac catheterization results: Non-CAD group (16 patients, aged 50.94 ± 9.85 years) with no stenosis in epicardial arteries and CAD group (44 patients, aged 57.66 ± 10.48 years) with severe multivessel disease (>50% stenosis in one or more major epicardial arteries). Clinical and demographic data were collected following hospital regulations and patient consent. Patients with impaired renal function, paralysis, prolonged bed rest, previous hormonal or metabolic disorders, or those taking medications affecting bone or calcium metabolism were excluded.

### 2.2.Measurements

Serum osteoprotegerin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) (BI-20403, Biomedica Immunoassays) on peripheral blood specimens collected from participants. Additional laboratory assessments included fasting plasma glucose and lipid profiles to evaluate glucometabolic status and cardiovascular risk.

### 2.3. Statistical Analysis

The data were evaluated using the Statistical Package for the Social Sciences version 26 (SPSS, Inc., Chicago, Illinois). The Kolmogorov-Smirnov test was utilized to examine the cumulative distribution of the sample. Quantitative continuous variables were expressed as mean ± standard deviation (SD). Kruskal Wallis test was used to compare the mean ranks of OPG. A p-value of less than 0.05 was considered statistically significant.

# 3. Results:

### 3.1. Patient Characteristics

The demographic, clinical, and biochemical characteristics of the participants in the study are summarized in Table 1. Fasting blood glucose (FBG) levels were significantly lower in the Non-CAD group compared to the CAD group (84.75±9.55 vs 110.39±42.05, P=0.021) as illustrated in Figure 1. A notable difference was observed in smoking rates between the two groups, with a higher prevalence in the CAD group (59.1%) compared to the Non-CAD group (12.5%, P<0.001). Additionally, obesity (defined as a BMI > 30 kg/m²) was more prevalent in the CAD group (66%) than in the Non-CAD group (25%, P<0.005). No significant differences were found in the lipid profiles of the two groups, due to 48% of participants being on statin therapy.

### 3.2. Serum Osteoprotegerin Levels (OPG) in Coronary Atherosclerosis

The levels of osteoprotegerin (OPG) were significantly elevated in the CAD group compared to the Non-CAD group (5.72±2.06 vs 4.49±1.05 ng/mL, P<0.008) as shown in Table 1 and Figure 2.

### 3.3. Correlation Between Osteoprotegerin and Fasting Plasma Glucose (FPG)

A positive correlation was observed between OPG levels and the presence of diabetes; specifically, OPG levels were higher in individuals with type 2 diabetes (T2D) compared to those without T2D (5.91±2.38 vs 4.91±1.2), as shown in Table 2 and Figure 3.

### 3.4. Correlation Between Cardiovascular Disease (CVD) and FPG

The FPG levels showed a significantly higher in the CAD group than the Non-CAD group (110.39±42.05 vs 84.75±9.65), as expected (Figure 1).

### 3.5. Receiver Operating Characteristic (ROC) Curve Analyses.

ROC curve analysis indicated that OPG has an area under the curve (AUC) of 0.726 (P=0.008) for predicting CAD risk, as shown in Figure 4. Additionally, ROC analysis for T2D risk prediction revealed an AUC of 0.661 (P=0.033), presented in Figure 5.

**Table(1): Demographic, anthropometric, and biochemical parameters data.**

| Variables | Non_CAD (n=16) | CAD (n=44) | P-value (Kruskal Wallis) |
|---|---|---|---|
| Age (yr) | 50.94±9.85 | 57.66± 10.46 | |
| BMI ($kg/m^2$) | 30.07±6.46 | 28.77±4.04 | 0.042 |
| Smoking n (%) | 2(13) | 26(59) | 0.001 |
| HDL (mg/dl) | 43±9.93 | 40±6.5 | 0.332 |
| LDL (mg/dl) | 103.94±34.58 | 107.24±46.87 | 0.907 |
| TC (mg/dl) | 145.12±37.12 | 151.81±36.67 | 0.802 |
| TG (`mg/dl) | 126.88±84.77 | 140.59±70.91 | 0.245 |
| FPG (mg/dl) | 84.75±9.55 | 110.39±42.05 | 0.021 |
| OPG (ng/ml) | 4.49±1.05 | 5.72±2.06 | 0.008 |

Result are expressed as mean ± SD; SD: Stander Deviation. TC: Total cholesterol; TG: Triglycerides; HDL: Cholesterol bound to high density lipoproteins; LDL: Cholesterol bound to low-density lipoproteins; FPG: Fasting Plasma Glucose; BMI: Body mass index NS: None statistically significant. CAD: coronary artry disease.

**Table(2): Osteoprotegerin levels according FPG levels**

| Variables | NG (n=35) | Diabetes (n=25) | P-value Kruskal Wallis |
|---|---|---|---|
| OPG (ng/ml) | 4.91±1.20 | 5.91±2.38 | 0.033 |

NG: Normal glucose < 100mg/dL. Diabetes >126mg/dL.

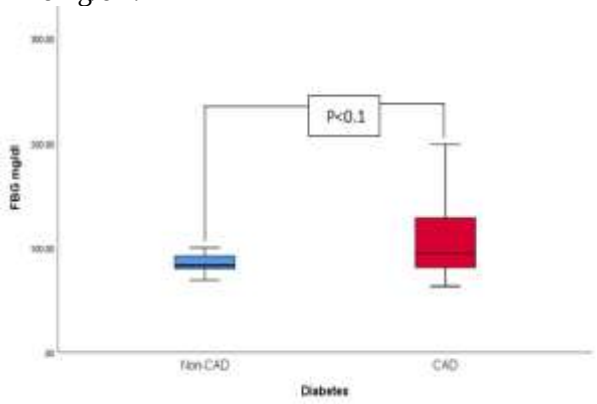



**Figure (1): Box plot defining the median and range of FPG levels across CVD groups.** FPG: Fasting Plasma Glucose

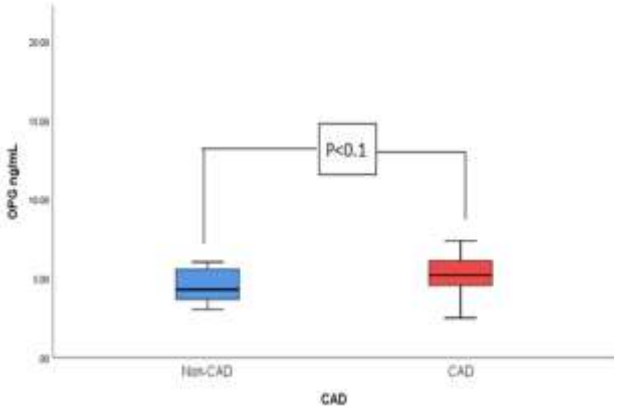



**Figure (2): Box plot defining the median and range of OPG across FPG LEVELS.** OPG: Osteoprotegerin,

FPG: Fast Plasma Glucose. NG: Normal glucose < 100mg/dL. Diabetes >126mg/dL.

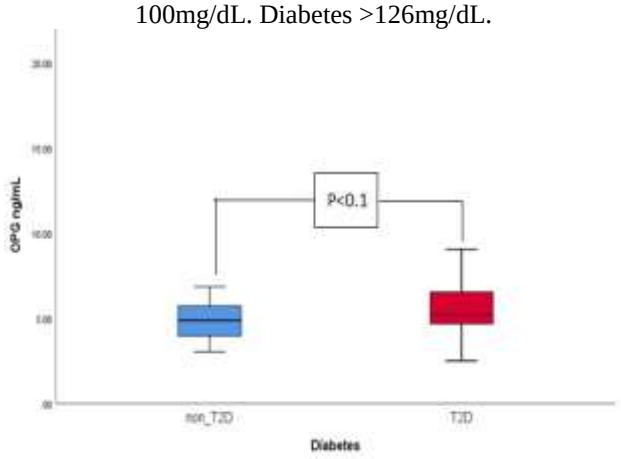



**Figure (3): Box plot defining the median and range of OPG across FPG LEVELS.** OPG: Osteoprotegerin, FPG: Fast Plasma Glucose. Non_T2D: Not type 2 diabetes: glucose < 100mg/dL. T2D: type 2 Diabetes >126mg/dL

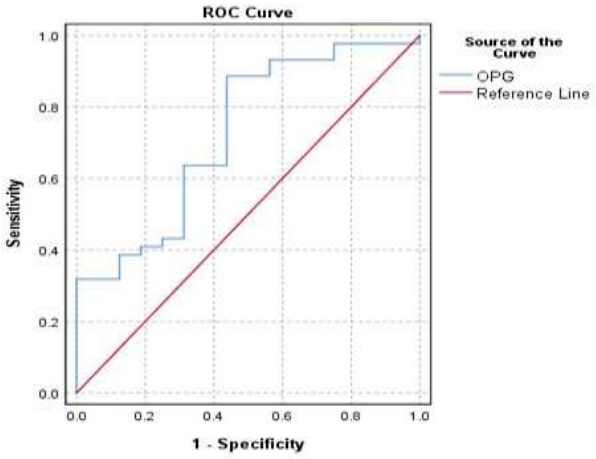
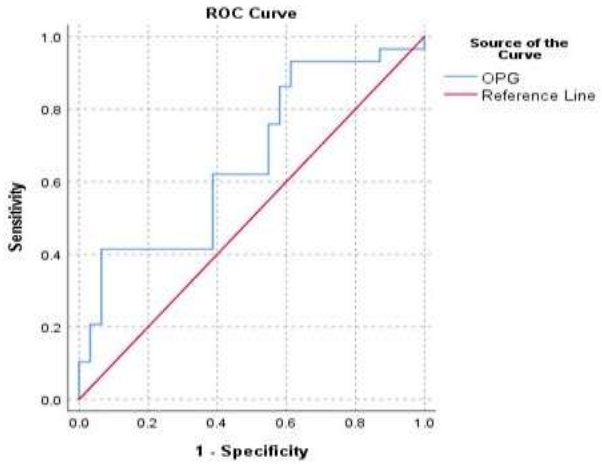



**Figure (4): Receiver operating characteristics (ROC) curve analyses (OPG: area-under-the-curve [AUC]= 0.726, P=0.008) in the risk prediction for CAD.**




**Figure(5): Receiver operating characteristics (ROC) curve analyses (OPG: area-under-the-curve [AUC]= 0.661, P=0.033) in the risk prediction for T2D.**

## 4. Discussion:

This study aimed to evaluate the relationship between serum OPG levels, fasting blood glucose (FBG), and the presence of coronary artery disease (CAD) in patients with and without T2D.

Our findings reveal significant differences in various parameters between CAD and non-CAD groups, emphasizing the multifactorial nature of CAD and its association with metabolic dysregulation.

### 4.1. Demographic and Clinical Characteristics

The observed elevation in FBG levels among CAD patients (110.39±42.05 mg/dL) compared to non-CAD individuals (84.75±9.55 mg/dL, P=0.021) corroborates existing literature that highlights hyperglycemia as a pivotal risk factor for cardiovascular diseases(7, 8). Chronic hyperglycemia contributes to endothelial dysfunction, promotes oxidative stress, and facilitates atherosclerotic changes, thereby increasing the risk of CAD (9).

Furthermore, our study found a significantly higher prevalence of smoking in the CAD group (59.1% vs. 12.5%, P<0.001). This aligns with substantial evidence indicating that smoking is a major

modifiable risk factor for CAD, contributing to arterial inflammation and plaque formation (10). The association between obesity (66% vs. 25%, P<0.005) and CAD also supports findings from previous studies that link obesity to increased cardiovascular morbidity through mechanisms such as insulin resistance and chronic inflammation (11).

**4.2. Osteoprotegerin Levels**

A particularly outstanding finding of our study is the elevated serum OPG levels in the CAD group (5.72±2.06 ng/mL vs. 4.49±1.05 ng/mL, P<0.008). OPG is a member of the tumor necrosis factor receptor superfamily and is known to play a critical role in bone metabolism, but it has also been implicated in vascular calcification and atherosclerosis (12). Elevated OPG levels may reflect an underlying inflammatory process or vascular remodeling associated with atherosclerotic changes (13). The role of OPG in CAD is further supported by studies showing that higher serum OPG levels are associated with increased cardiovascular events and mortality (14).

**4.3. Correlation with Type 2 Diabetes**

Our analysis revealed that OPG levels were significantly higher in T2D patients compared to non-T2D individuals (5.91±2.38 ng/mL vs. 4.91±1.20 ng/mL), suggesting that T2D may exacerbate the elevation of OPG levels. This finding is consistent with research indicating that diabetes mellitus is associated with increased OPG levels, potentially linking metabolic dysregulation to heightened cardiovascular risk (15). The interaction between OPG and diabetes may involve mechanisms such as increased inflammation and oxidative stress, both of which are prevalent in diabetic patients and contribute to vascular complications (16). It has been suggested that inflammation-driven hyperglycemia, rather than high glucose levels per se, is involved in the increase of OPG observed in diabetes [17].

**4.4. ROC Curve Analysis**

The ROC curve analyses indicated that OPG has moderate predictive value for CAD (AUC=0.726, P=0.008) and T2D (AUC=0.661, P=0.033). These findings suggest that OPG could serve as a valuable additional biomarker for assessing the risk of CAD and T2D in clinical practice. The identification of at-risk individuals could facilitate timely interventions aimed at reducing cardiovascular morbidity and mortality(18).

## 5. Limitations and Future Directions:

Despite these insights, our study has limitations that should be acknowledged. The exclusion of lipid profiles due to statin use may restrict our understanding of the complete lipid landscape in these patients, as dyslipidemia is a well-established risk factor for CAD (19). Additionally, the cross-sectional design limits causal inferences regarding the relationships between OPG levels, metabolic parameters, and cardiovascular outcomes. Future longitudinal studies are warranted to elucidate these temporal relationships and further explore the potential mechanisms linking OPG with CAD and T2D.

## 6. Conclusion:

In conclusion, our findings highlight significant differences in metabolic parameters between CAD and non-CAD groups, with elevated OPG levels serving as a potential biomarker for cardiovascular risk. The interplay between OPG, FBG, and T2D underscores the importance of addressing metabolic health in managing cardiovascular disease risk. Further research is needed to validate OPG's utility as a biomarker in clinical settings and to explore its role in therapeutic strategies aimed at reducing cardiovascular events.

## 7. Funding:

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