# Assessment of fibroblast growth factor 23 in relation to peripheral arterial disease in type 2 diabetes mellitus

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## Background
Peripheral arterial disease (PAD) is a major vascular complication and the leading cause of amputation in people with diabetes. Fibroblast growth factor 23 (FGF-23) is a recently discovered 30-kD secreted hormone glycoprotein that plays a role in the complex and tightly regulated mechanisms of mineral metabolism. Increase in serum FGF-23 concentration was an independent predictor of coronary artery diseases in patients with mild chronic kidney disease and of mortality in patients undergoing hemodialysis. Recently, FGF-23 has been found to be associated with total body atherosclerosis and vascular dysfunction.

## Objective
To evaluate the relation between FGF-23 and PAD in patients having type 2 diabetes with normal kidney function.

## Patients and methods
A case–control study was conducted on 120 diabetic patients, where 60 patients having type 2 diabetes with PAD were compared with 60 patients having type 2 diabetes without PAD. All patients were subjected to full history taking, thorough clinical examination, ankle-brachial index assessment, and laboratory measurement of glycated hemoglobin%, estimated glomerular filtration rate, microalbuminuria, lipid profile, serum ionized calcium and phosphorous, and serum FGF-23.

## Results
Significantly higher serum FGF-23 was found in diabetic patients with PAD compared with diabetic patients without PAD. Logistic regression analysis showed that duration of diabetes, triglycerides level, phosphorous level, glycated hemoglobin, and FGF-23 were independent predictors for PAD.

## Conclusion
FGF-23 level was higher in type 2 diabetic patients with PAD, which highlights a possible implication of FGF-23 in the pathogenesis of PAD in type 2 diabetes.

Keywords:
diabetes, FGF-23, PAD

## Introduction
Egypt has been among the top 10 countries for number of people with diabetes with 7.5 million, which is expected to project to 13.1 million in 2035. This carries a huge economic and social burden as people with diabetes are at risk of developing a number of disabling and life-threating health problems [1].

Cardiovascular disease is the most common cause of death and disability among people with diabetes. The cardiovascular diseases that accompany diabetes include angina, myocardial infarction, stroke, peripheral arterial disease (PAD), and congestive heart failure [1].

PAD is a major vascular complication and is the leading cause of amputation in people with diabetes. Diabetic foot complications are associated with a 15-fold increase for lower limb amputation [2].

Typically, diabetes-associated PAD affects the popliteal arteries [3].

Fibroblast growth factor 23 (FGF-23) is a recently discovered 30-kD secreted hormone glycoprotein that plays a role in the complex and tightly regulated mechanisms of mineral metabolism. In healthy individuals, FGF-23 is secreted from bone osteocytes in response to increase in dietary phosphate. FGF-23 acts through one of the FGF receptors, with klotho as a coreceptor, to inhibit renal phosphorus reabsorption and decrease circulating levels of 1,25 (OH)2D and possibly inhibit parathyroid hormone secretion by the

parathyroid glands. Thus, its net effect is a reduction in serum phosphorus and 1,25 (OH)2D level, which may result in hypocalcemia [4].

Increased serum FGF-23 concentration was an independent predictor of coronary artery diseases in patient with mild chronic kidney disease and mortality in patients undergoing hemodialysis. Recently, FGF-23 has been found to be associated with total body atherosclerosis and vascular dysfunction [4].

## Aim
The aim was to evaluate the relation between FGF-23 and PAD in type 2 diabetic patients with normal kidney function.

## Patients and methods
A case–control study was conducted during the period from November 2013 to May 2016 in Cairo on 120 type 2 diabetic patients. They were divided into 60 diabetic patients with PAD diagnosed clinically and confirmed by ankle-brachial index (ABI) assessment (group I) and 60 age-matched and sex-matched randomly selected diabetic patients without PAD or other macrovascular complications (group II). Patients were recruited from the outpatient diabetes clinic at Ain Shams University Hospital. This study was approved by the local ethical committee, and all patients signed an informed consent before recruitment.

### Exclusion criteria
Patients with history of kidney disease; history of recent stroke, myocardial infarction, coronary artery bypass grafting, or stent; drugs that may affect serum level of FGF-23 such as Cinacalcet, vitamin D, and intravenous saccharated ferric oxide, pregnancy; and chronic liver diseases were excluded.

All patients were subjected to full medical history taking, emphasizing on age, onset and duration of diabetes, smoking history, history of cerebrovascular, renal, and cardiovascular disease or any other comorbid conditions. Thorough clinical examination including foot examination for PAD assessment was performed for all study patients besides measurement of ABI.

### Ankle brachial index assessment
It is an easily measurable way to compare the systolic pressure of the upper extremity with that of the affected lower extremity [5]. It is done using a Doppler probe and a blood pressure cuff, measuring the systolic blood pressure in each arm and the dorsalis pedis and posterior tibial arteries of each ankle. The highest of the dorsalis

pedis or posterior tibial artery pressures is the numerator of the ABI specific to each leg, whereas the highest arm pressure on either side is the denominator. ABI between and including 0.9 and 1.3 was considered normal (free from significant PAD), whereas values less than 0.9 indicate arterial disease. ABI value of 1.3 or greater is also considered abnormal and suggests calcification of the walls of the arteries and incompressible vessels, reflecting severe peripheral vascular disease [6].

Risk categorization assessment for PAD was done for all patients in the study.

### Category risk profile

(1) Sensation intact.
(2) Diminished sensation, blood supply intact, no foot deformities.
(3) Diminished sensation, blood supply compromised or foot deformity.
(4) Previous ulceration or amputation [7].

Laboratory studies included the following: glycated hemoglobin (HbA1c%); estimated glomerular filtration rate (eGFR) using CKD-EPI creatinine 2009 equation, which incorporate in the equation patient serum creatinine level in combination with demographic data (age, race, and sex) [8]; lipid profile including total cholesterol, triglycerides, low-density lipoproteins, and high-density lipoproteins; serum calcium and phosphorous ($PO_4$) levels; and serum FGF-23 using ELISA technique [9].

### Statistical analysis
After collection of data, revision and tabulation analysis was performed using Predictive Analytics Soft Ware (PASW), version 18. Quantitative parametric data were expressed as mean±SD. Qualitative data were expressed as number and percent of total. Comparative analysis of quantitative data was done using Student $t$ test and qualitative data using $c^2$ tests. Correlations were done with Pearson correlation coefficient. Multivariate binary logistic regression was done to estimate independent predictors of peripheral vascular disease.

## Results
On comparing demographic, clinical, and laboratory data of both groups, there were statistical significant differences in both groups regarding diabetes duration, risk categorization, mean systolic blood pressure, mean diastolic blood pressure, ABI, HbA1c, serum $PO_4$, and serum triglycerides (TG), being higher in group I

**Table 1 Comparison of demographic, clinical, and laboratory data of both groups**

|  | Group I (diabetics with PAD) (N=60) | Group II (diabetics without PAD) (N=60) | P value |
|---|---|---|---|
| Age (years) | 56.58±7.32 | 55.85±8.25 | 0.607 |
| BMI (kg/m$^2$) | 30.8±8.4 | 30.12±6.3^ | 0.63 |
| Sex |  |  |  |
| Female | 25 (41.7) | 28 (46.7) | 0.581 |
| Male | 35 (58.3) | 32 (53.3) |  |
| Smoking | 28 (46.7) | 21 (35) | 0.194 |
| DM duration (years) | 14.20±7.31 | 10.17±6.14 | <0.001* |
| Systolic BP (mmHg) | 134±18.3 | 125±16.5 | 0.006* |
| Diastolic BP (mmHg) | 90±12.4 | 82.6±11.8 | 0.002* |
| DM ttt |  |  |  |
| Insulin | 48 (80) | 40 (66.7) | 0.099 |
| OHG | 12 (20) | 30 (33.3) |  |
| HTN (number of patients) | 35 (58.3) | 30 (50) | 0.36 |
| ABI | 0.81±0.11 | 1.11±0.08 | <0.001* |
| Risk category |  |  |  |
| Category 1 | 0 | 60 (100) | <0.001* |
| Category 2 | 47 (78.3) | 0 |  |
| Category 3 | 13 (21.7) | 0 |  |
| HbA1c (%) | 9.70±2.07 | 8.16±1.66 | <0.001* |
| eGFR (ml/min) | 80.97±14.62 | 79.13±15.63 | 0.508 |
| Calcium (mg/dl) | 9.33±0.73 | 9.26±0.77 | 0.612 |
| PO$_4$ (mg/dl) | 4.34±0.64 | 3.81±0.74 | <0.001* |
| Cholesterol (mg/dl) | 218.88±53.37 | 210.40±50.81 | 0.374 |
| TGs (mg/dl) | 175.13±45.90 | 144.95±61.98 | 0.003* |
| HDL (mg/dl) | 42.88±8.89 | 45.90±10.64 | 0.094 |
| LDL (mg/dl) | 121.09±43.31 | 133.78±44.67 | 0.117 |
| FGF-23 | 77.40±46.41 | 51.58±29.21 | <0.001 |

Data are presented as n (%) and mean±SD. ABI, ankle-brachial index; BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; PAD, peripheral arterial disease; PO$_4$, phosphorous; TG, triglycerides. *Indicates statistically significant.

(diabetic with PAD) than group II (diabetic without PAD) (P<0.001) (Table 1).

We also found that serum level of FGF-23 was statistically significantly higher in group I (diabetic with PAD) than group II (diabetic without PAD) (P<0.001) (Table 1).

On comparing FGF-23 level between males and females, as well as smokers and nonsmokers among studied groups, there was a statistical significant

**Figure 1**
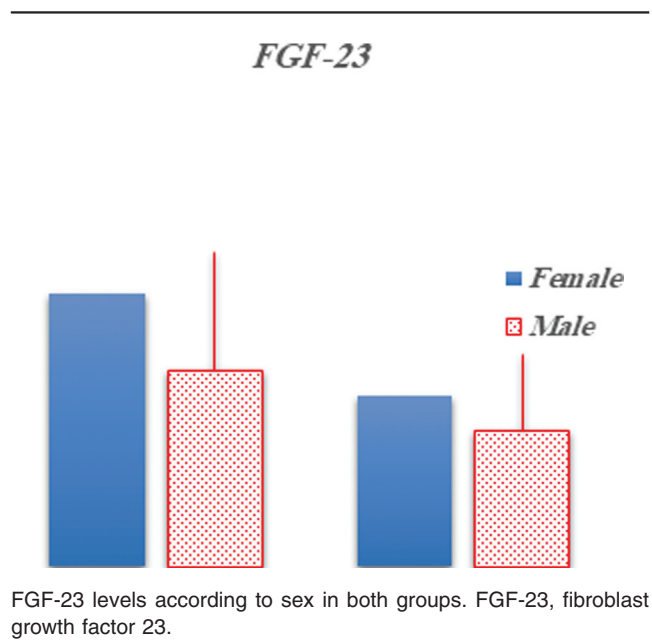


FGF-23 levels according to sex in both groups. FGF-23, fibroblast growth factor 23.

**Figure 2**
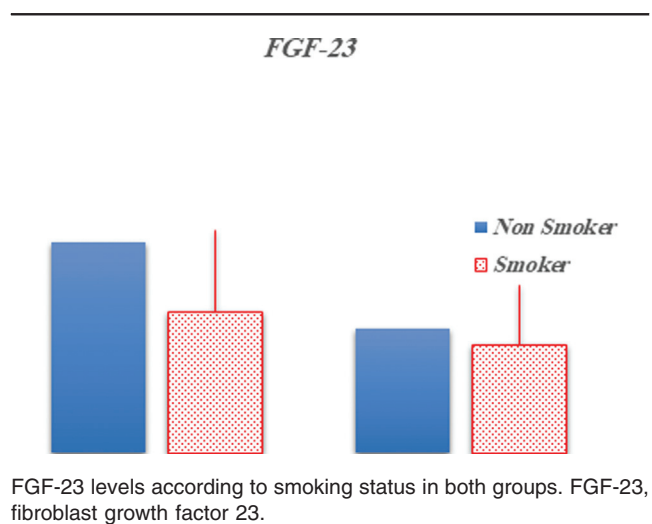


FGF-23 levels according to smoking status in both groups. FGF-23, fibroblast growth factor 23.

difference between males and females, as well as smokers and nonsmokers in group I, being higher in females and nonsmokers (P=0.031 and 0.008, respectively) (Figs 1 and 2).

A correlation study showed that eGFR positively correlated with FGF-23 in group II only (Table 2).

Logistic regression analysis was done to detect predictors for PAD. Duration of diabetes, TG level, PO$_4$ level, HbA1c, and FGF-23 were found to be independent predictors for PAD (Table 3).

## Discussion

Diabetic vasculopathy is the most important consequence of chronic hyperglycemia in patients

**Table 2 Correlation study of fibroblast growth factor 23 and other parameters**

| | All patients (N=120) | | Group I (diabetics with PAD) (N=60) | | Group II (diabetics without PAD) (N=60) | |
|---|---|---|---|---|---|---|
| | FGF-23 (pg/ml) | | FGF-23(pg/ml) | | FGF-23(pg/ml) | |
| | r | P value | r | P value | r | P value |
| Age (years) | −0.14 | 0.12 | −0.12 | 0.34 | −0.24 | 0.06 |
| DM duration (years) | 0.10 | 0.28 | 0.04 | 0.78 | −0.05 | 0.73 |
| ABI | −0.13 | 0.17 | −0.13 | 0.34 | −0.11 | 0.39 |
| HbA1c (%) | 0.10 | 0.27 | 0.03 | 0.80 | −0.13 | 0.31 |
| Cholesterol (mg/dl) | 0.03 | 0.76 | −0.08 | 0.55 | 0.14 | 0.30 |
| TGs (mg/dl) | 0.04 | 0.69 | −0.12 | 0.38 | 0.01 | 0.93 |
| HDL (mg/dl) | 0.01 | 0.95 | −0.04 | 0.74 | 0.20 | 0.12 |
| LDL (mg/dl) | 0.14 | 0.12 | 0.19 | 0.15 | 0.24 | 0.07 |
| eGFR (ml/min) | 0.11 | 0.23 | −0.04 | 0.78 | 0.30 | 0.02* |
| Calcium (mg/dl) | 0.04 | 0.70 | 0.20 | 0.13 | −0.24 | 0.07 |
| PO$_4$ (mg/dl) | 0.04 | 0.63 | −0.06 | 0.67 | −0.12 | 0.35 |

ABI, ankle-brachial index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral arterial disease; PO$_4$, phosphorous; TG, triglycerides. *Significant.

**Table 3 Multivariate binary logistic regression**

| | B | SE | P value | Odds ratio | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| DM duration (years) | 0.078 | 0.033 | 0.018 | 1.081 | 1.013 | 1.153 |
| TGs (mg/dl) | 0.008 | 0.004 | 0.046 | 1.008 | 1.000 | 1.016 |
| PO$_4$ (mg/dl) | 0.876 | 0.340 | 0.010 | 2.400 | 1.232 | 4.674 |
| HbA1c (%) | 0.330 | 0.125 | 0.008 | 1.391 | 1.088 | 1.779 |
| FGF-23 (pg/ml) | 0.020 | 0.006 | 0.002 | 1.021 | 1.008 | 1.034 |
| Constant | 10.081 | 1.958 | 0.000 | 0.000 | | |

CI, confidence interval; DM, diabetes mellitus; FGF-23, fibroblast growth factor 23; HbA1c, glycated hemoglobin; PO$_4$, phosphorous; TG, triglycerides.

with diabetes mellitus (DM), which is usually described into microvascular and macrovascular complications [10]. FGF-23 is a protein encoded in humans by the FGF-23 gene secreted by osteocytes in response to elevated calcitriol [11,12].

The aim of this work is to study the relation between FGF-23 and PAD in type 2 diabetic patients with normal kidney function.

Our study showed that group I diabetic patient with PAD had a significantly higher FGF-23 level (77.40 ±46.41 pg/ml) compared with group II diabetic patients without PAD (51.58±29.21 pg/ml) (P<0.001).

Our results are in agreement with Garimella *et al.* [13] who studied the association of FGF-23 with ABI and with incident clinical PAD events during 9.8 years of follow-up of community-dwelling adults older than 60 years. They found that higher FGF-23 was associated with incidence of PAD events in unadjusted, demographic adjusted, CVD risk factor-adjusted models and prevalent cardiovascular disease.

Moreover in concordance with our study, Mirza *et al.* [14] conducted a study in 2009 which included 967 patients aged 70 years to investigate the relation between serum FGF-23 and endothelium function and arterial stiffness. They found that higher serum FGF-23 levels were independently associated with impaired vasoreactivity and increased arterial stiffness. In a subgroup of these individuals who underwent whole-body magnetic resonance angiography, those with higher FGF-23 levels had increased odds of both overall atherosclerosis as well as stenosis.

Moreover, Jean *et al.* [15] found univariate associations between elevated FGF-23 concentrations and severe coronary artery calcification, which might reflect a potential link between FGF-23 and diffuse arterial calcification.

Another study conducted by Gutierrez *et al.* [16] included patients with CKD not on dialysis, echocardiograms and computed tomography scans were done to assess left ventricular mass index and

coronary artery calcification. It was found that increased FGF-23 concentrations, which were associated with increased left ventricular mass index and increased prevalence of left ventricular hypertrophy independent of established risk factors, such as older age, declining eGFR, diabetes, and hypertension. The associations were also independent of serum phosphate concentrations. They concluded that the univariate association between elevated FGF-23 concentrations and severe coronary artery calcification may reflect a potential link between FGF-23 and diffuse arterial calcification [16].

In contrast to our study were the results reported by Hatipoğlu et al. [17], who conducted a study in 2015 to evaluate whether FGF-23 had a common role in the pathogenesis of PAD in type 2 diabetes. They studied 21 patients with diabetic nephropathy and 20 patients with diabetes but without nephropathy. To determine the presence of atherosclerosis, bilateral colored Doppler ultrasonography (USG) of LLs were performed. Arterial wall calcifications and plaques were evaluated with gray-scale USG. They found that in all cases involving DM, FGF-23 levels did not vary with arterial wall changes recorded via Doppler USG. Moreover, in all cases with diabetes, there was no association between FGF-23 levels and arterial wall changes as determined by Doppler USG. They concluded that PAD in cases with diabetes has a more complex mechanism, and its pathogenesis includes factors other than nephropathy or nephropathy-associated increased FGF-23. Possible explanation for these different results could be that they evaluated the presence of peripheral atherosclerosis through the detection of arterial wall calcification and plaques, which may not reflect PAD [17].

In our study, FGF-23 level was higher among females than males in group I diabetics with PAD ($P=0.031$). In agreement with our study, Ix et al. [18] and Garimella et al. [13] reported in their studies that those with higher levels of FGF-23 were more frequently women. In our study, we found that FGF-23 level was not correlated with any of the studied variables except for eGFR in group II (diabetic without PAD group) ($P=0.02$), whereas there was no correlation between FGF-23 and age, diabetes duration, ABI, lipid profile, calcium and $PO_4$ levels.

These results are similar to the results reported by Hatipoğlu et al. [17] in their study in 2015 who found that FGF-23 was not associated with HbA1c

or disease duration in patients with type 2 DM. Moreover, the cardiovascular health study that was held by Garimella et al. [13] reported that FGF-23 levels were not associated with either high or low values of ABI.

In the current study, the prevalence of smoking was higher in group I (diabetics with PAD) compared with group II (diabetics without PAD) (46.7 vs. 35%), but it was not statistically significant ($P=0.194$). In agreement with previous results, many studies showed that there was a significant difference regarding prevalence of smokers among patients with PAD and those without PAD [19–22]. Another study conducted in Saudi Arabia reported that smoking was an independent risk factor for PAD [23]. Moreover, Zitton et al. [24] found in 2012 that special habits (smoking) had a positive association with PAD.In the present study, logistic regression analysis was conducted to detect predictors for PAD. Duration of diabetes, HbA1c, triglyceride level, $PO_4$, and FGF-23 were independent factors that increased the likelihood of being a case of PAD.

In agreement with our study, Jue et al. [25] reported that duration of DM was an independent risk factors for PAD. Supporting our results, other studies reported that HbA1c is an independent risk factor for developing PAD [20,22]. Moreover, similar results were reported by Al-Sheikh et al. [23] who found that dyslipidemia was an independent risk factor for PAD. Moreover, Dobnig et al. [26] identified in their study in 2008 that high serum phosphorus was an independent risk factor for CVD events.

In conclusion, our study found that serum FGF-23 was high in patients with PAD. These results suggest possible role of FGF-23 in type 2 diabetic patients with PAD. Moreover, duration of diabetes, TGs level, $PO_4$ level, HbA1c, and FGF-23 were predictors for PAD by multivariate analysis.

## Conclusion
Serum FGF-23 was higher in type 2 diabetic patients with peripheral arterial disease which highlights a possible implication of FGF-23 in the pathogenesis of PAD in type 2 diabetic patients.

**Conflicts of interest**
There are no conflicts of interest.

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