Association between Growth Differentiation Factor 15 and Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus

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Abstract:

Background: Growth Differentiation Factor 15 (GDF 15) is one of the transforming growth factor-β (TGF-β) family, which is released from different cells under conditions of stress. Increased levels of GDF-15 are associated with cardiovascular diseases and are related to the progression and prognosis of the disease. Aim: the aim of the present study was to determine the correlation between serum GDF15 level and cardiovascular risk in patients with type2 DM using Framingham risk score (FRS). Subjects and methods: this study included three groups: control group (n=20), prediabetic group (n=30) and diabetic group (n=30). The participants have been subjected to laboratory investigations including serum levels of GDF15, measured by enzyme linked immunosorbent assay (ELISA). FRS was calculated through using the 10-year CHD Risk Framingham Tables. Results: there was a statistically significant increase in serum GDF 15 in diabetic and prediabetic groups in comparison to the control group (p= 0.006, p= 0.025) sequentially and serum GDF15 was significantly positively correlated with FRS in both the diabetic and prediabetic groups (r= 0.44, p=0.015and r= 0.38, p=0.04) sequentially. Conclusion: Serum GDF15 level may be a useful clinical biomarker for predicting cardiovascular risk in patients with type2 DM.

Key words: Cardiovascular risk, Framingham Risk Score , GDF 15,type2 DM.

Introduction

Diabetes mellitus (DM) is a global public health issue. It has affected about 387 million persons in the world in 2014.This number is expected to be increased to 592 million in the year of 2035. DM leads to many morbidity complications. One of which is the cardiovascular disease (CVD) that causes nearly 70% of deaths in diabetic patients **[1]**.

Diabetes is characterized by high glucose level in due to either less insulin secretion from pancreas or developing insulin resistance in skeletal muscles. Diabetes can be categorized into many types; but the two major types of diabetes are type1 and type2 DM **[2].** Type2 DM is responsible for about 90–95% of all cases of diabetes mellitus and is characterized by defects in insulin secretion and insulin resistance of varying degrees **[3].** The risk of cardiovascular diseases is higher among type2 diabetic patients **[4].**

Different emerging biomarkers have been studied in cardiovascular conditions, growth differentiation factor-15(GDF-15) level was one of biomarkers that has taken a widespread interest as a predictor of cardiovascular disease **[5].** GDF-15, also named mac¬rophage-inhibiting cytokine 1 (MIC-1), is a member of the trans-forming growth factor-β (TGF-β) family **[6].** It is released from many cell types e.g. macrophages, cardiomyocytes and adipocytes under stress **[7].** GDF-15 increases during tissue injury and inflammatory conditions. Increased GDF-15 levels are associated with cardiovascular diseases such as hypertrophy, heart failure, atherosclerosis and endothelial dysfunction. Increased levels are also associated with the progression and prognosis of the disease **[2].**

Age, smoking, and environmental factors are other risk factors that may increase GDF15 level **[2].** The aim of this study was to determine the correlation between serum growth differentiation factor 15 level and cardiovascular risk in patients with type 2 diabetes mellitus using Framingham risk score.

Subjects and methods

This is a case control study which included 80 participants recruited from the outpatient clinic and department of internal medicine of Benha University hospital during the period from May to November 2017. The laboratory investigations were done in the clinical and chemical pathology department,

Benha University hospital. This study was approved by the ethical committee of Benha Faculty of Medicine, Benha University, Egypt. A written consent was obtained from all participants.

Subjects:

The subjects were divided into three groups: **Control group (group I):** which included 20 apparently healthy non smoker subjects. **Prediabetic group (groupII):** which included 30 patients with impaired glucose tolerance. **Diabetic group (group III):** which included 30 patients with type 2 DM.

All subjects were above 18 years old. Patients with impaired glucose tolerance had fasting glucose >110mg/dl & >126mg/dl and 2-h postprandial glucose ≥140mg/dl & >200mg/dl. Patients with type2 DM had fasting glucose ≥126mg/dl or 2–h postprandial glucose ≥200mg/dl. The subjects with malignancies, fatty liver, prior CVD and type1 DM were excluded. All participants were subjected to full history taking, physical examination including:(weight, height, BMI, systolic & diastolic blood pressure), ECHO cardiography and laboratory investigations.

Methods : Ten milliliters of venous blood were collected from subjects who fasted for 10 hours, two milliliters were put on EDTA vacutainer tube for determination of HBA1C and the rest of collected sample was kept in plain test tubes, allowed to clot for 20 minutes at room temperature and centrifuged at 2000 x g for 15 minutes. Serum was separated in two aliquots and stored at -20ºC till analysis of GDF15, creatinine, urea, uric acid, lipid profile, fasting blood glucose (FBG), fasting Insulin. Two hours post prandial sample was collected in plain test tube, allowed to clot for 20 minutes at room temperature and centrifuged at 2000 x g for 15 minutes. Serum was collected and stored at -20ºC till analysis of 2 h postprandial glucose.

All the chemical investigations were performed on Biosystem Chemistry Analyzer (BTS-310, Spain). HbA1C was measured by NycoCard HBA1C which is a boronated affinity assay **[8].** Fasting Insulin was measured by quantitative sandwich enzyme linked immunosorbent assay **[9]** using (Ylbiont (ELISA) kit, China, Catalog No.YLA1493HU) kit and performed on (BioTek™ ELx800™ Absorbance Microplate Readers). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting insulin level (μU/ml) × fasting glucose level (mmol/l) / 22.5 **[7].** HOMA β index: was calculated as follows: fasting insulin level

(µU/ml) ×20/fasting glucose level (mmol/l) – 3.5 **[7].** FRS % (which was calculated by evaluating age, systolic blood pressure, need of treatment from hypertension, smoking status, presence of diabetes, levels of high density lipoprotein cholesterol (HDL-c) and total cholesterol through using the 10-year CHD (Coronary Heart Disease) Risk Framingham **[10]** and GDF 15 was measured using a quantitative sandwich enzyme linked immunosorbent assay **[11]** using (ELISA) kit (OriGene Technologies, Rockville, MD; USA, Catalog No. EA100484) and performed on (BioTek™ ELx800™ Absorbance Microplate Readers).

Statistical analysis:

The collected data were tabulated and analyzed using SPSS version 20 software (SPSS Inc, Chicago, ILL Company USA). Descriptive statistics were calculated for the data in the form of: mean and standard deviation (± SD) for quantitative data and frequency and distribution for qualitative data. In the statistical comparison between the different groups, the significance of difference was tested using Student's t-test which is used to compare mean of two groups of quantitative data of parametric. ANOVA test (F value) and is used to compare mean of more than two groups of quantitative data of parametric. The inter-group comparison of categorical data was performed by using chi square test (X2-value). Correlation coefficient (r test) is used to find the relationship between variables. ROC curve is used to test validity of GDF15. P value <0.05 was considered statistically significant (*) while >0.05 is statistically insignificant and <0.01 was considered highly significant (**) in all analyses.

Results

In this study, regarding the age, there was a statistically significant increase in diabetic group in comparison to control group ($p \leq 0.03$).

Regarding the sex, diabetic group included 46.7 % females and 53.3% males, prediabetic group included 43.3 % females and 56.7% males. Control group included (50%) females and (50 %) males (table 1). There was a statistically significant increase in LDL-c in diabetic group in comparison to prediabetic group and control group ($p\leq 0.001$and $p\leq 0.001$ respectively) .

There was a statistically significant decrease in HDL-c in diabetic group in comparison to prediabetic group and control group ($p\leq 0.001$and $p\leq 0.001$ respectively). There was a statistically significant increase in total cholesterol, triglycerides in diabetic group

and prediabetic group in comparison to control group (p≤ 0.001, p≤ 0.001, p≤ 0.001and p≤ 0.001 respectively). There was a statistically significant increase in LDL-c in prediabetic group in comparison to control group (p≤ 0.001). There was a statistically significant decrease in HDL-c in prediabetic group in comparison to control group (p≤ 0.001) (figure 1). There was a statistically significant increase in FBS, P.P glucose, HbA1C, insulin and HOMA-IR in diabetic group in comparison to prediabetic group and control group (p≤ 0.001, p≤ 0.001, p≤ 0.001, p≤ 0.002 and p≤ 0.001) respectively and there was a statistically significant increase in FBS, P.P glucose, HbA1C and HOMA IR in prediabetic group in comparison to control group (p≤ 0.001, p≤ 0.001, p≤ 0.001 and p≤ 0.001) respectively. There was a statistically significant increase in FRS and GDF15 in diabetic group in comparison to control group (p≤ 0.001 and p= 0.006) respectively. There was a statistically significant increase in FRS and GDF15 in prediabetic group in comparison to control group (p≤ 0.005 and p=0.025) respectively. There was a statistically significant decrease in Homa β index in diabetic group and prediabetic group in comparison to control group (p≤ 0.001 and p≤ 0.001) respectively **(table 2).** There was a statistically significant increase in GDF15 in diabetic group and prediabetic group in comparison to control group (p=0.006 and p = 0.025) respectively **(table 3).** There was a statistically significant positive correlation in diabetic group between GDF15 and age (r= 0.29, p= 0.01), total cholesterol (r= 0.4,p= 0.03), triglycerides (r= 0.39,p= 0.03) LDL-c (r= 0.29, p=0.01), FBS (r= 0.45, p= 0.01), P.P glucose (r= 0.51, p= 0.003), HbA1C (r=0.37, p= 0.04), HOMA IR (r= 0.36, p= 0.04) and FRS (r= 0.44, p=0.015) **(table 4).** There was a statistically significant positive correlation in prediabetic group between GDF15 and age (r= 0.45, p= 0.01), total cholesterol (r= 0.39, p=0.02) , triglycerides (r= 0.38, p= 0.03), LDL-c (r= 0.28, p= 0.01), FBS (r=0.43, p= 0.015), P.P glucose (r= 0.45, p= 0.011), HbA1C (r= 0.36, p= 0.04), FRS (r= 0.38, p= 0.04) and SBP (r= 0.38, p= 0.03) **(table 5).** ROC curve was performed to test validity of GDF15 in prediabetes group. It has a sensitivity of 86.7% and specificity of 55% in predicting the cardiovascular risk in prediabetic subjects with area under the curve (AUC) = 0.744 and cut off value = 414.07pg/ml as shown in fig. **(2).** ROC curve was performed to test validity of GDF 15 in diabetic group. It has a sensitivity of 86.6% and specificity of 52% in predicting the cardiovascular risk in diabetic patients with (AUC) = 0.692 and cut off value = 468.3 pg/ml as shown in **table (6).**

Table (1): Comparison between the studied groups according to : Age, sex, Wt, Ht, BMI, SBP, DBP:

	Diabetic group (n=30)	Prediabetic group (n=30)	Control group (n=20)	F test	P value		
					Diabetic# prediabetic	Diabetic# control	Prediabetic# Control
Age (yr)	57.23±7.87	53.87±8.74	51.9±9.86	2.42	0.12	0.039*	0.46
Sex							
Male	16(53.3)	17(56.7)	10(50.0)	X^2=	0.80	0.82	0.64
Female	14(46.7)	13(43.3)	10(50.0)	0.22			
Wt (kg)	97.48±7.23	96.98±8.07	78.05±6.96	49.18	0.80	0.001**	0.001**
Ht (cm)	174.77±7.29	174.93±6.68	171.15±5.16	2.37	0.93	0.06	0.37
BMI (kg/m²)	32.06±3.40	31.8±3.62	26.63±2.01	20.52	0.78	0.001**	0.001**
SBP(mmHg)	132.9±12.82	134.1±12.51	126.55±6.27	2.86	0.72	0.046*	0.016*
DBP(mmHg)	81.67±8.74	85.67±7.96	79.55±5.38	4.13	0.07	0.34	0.004**

Table (2): Comparison between the studied groups according to: FBG, P.P glucose, HbA1c, Insulin, Homa IR, Homa β index, Framingham risk score (FRS).

	Diabetic Group	Pre-diabetic group	Control Group	F test	P value		
					diabetic# prediabetic	diabetic# control	Pre. # Control
FBG (mg/dl)	139.25±5.74	117.41±4.22	86.86±6.44	561.24	0.001**	0.001**	0.001**
PP gl. (mg/dl)	298.56±71.6	159.82±16.12	101.99±6.1	130.1	0.001**	0.001**	0.001**
HbA1c (%)	8.61±2.14	6.0±0.51	5.38±0.44	42.42	0.001**	0.001**	0.001**
Insulin (µU/ml)	20.06±4.47	15.31±3.37	16.07±3.7	12.43	0.002**	0.002**	0.46
Homa-IR	6.65±1.57	4.39±1.0	3.42±0.85	48.08	0.001**	0.001**	0.001**
Homa-β %	93.5±21.8	104.26±23.93	266.58±84.73	97.77	0.07	0.001**	0.001**
FRS%	13.2±2.57	11.67±3.96	8.3±3.95	11.92	0.08	0.001**	0.005**

Table (3): Comparison between studied groups aacording to GDF 15 level:

GDF15 (pg/ml)	Diabetic group (n=30)	Prediabetic group (n=30)	Control group (n=20)	F test	P value		
					Diabetic# prediabetic	Diabetic# control	Prediabetic# control
median (IQR)	652.35 (370-2002)	430.6 (180-1450.3)	222.4 (150-1150)	X2= 8.27	0.54	0.006**	0.025*

Table (4): Correlation between GDF15 and other variables among diabetic group:

Diabetes group	GDF15 (pg/ml)	
	r test	P value
Age (years)	0.29	0.01*
BMI (kg/m²)	0.21	0.26
SBP (mmHg)	0.235	0.2
DBP (mmHg)	-0.008	0.97
Urea (mg/dl)	0.33	0.08
Cr. (mg/dl)	-0.24	0.20
Uric acid (mg/dl)	0.09	0.63
TC (mg/dl)	0.403	0.03*
TG (mg/dl)	0.391	0.03*
HDL-c (mg/dl)	-0.153	0.4
LDL-c (mg/dl)	0.299	0.01*
FBG (mg/dl)	0.457	0.01*
P.P gl. (mg/dl)	0.516	0.003*
Hb A1c (%)	0.370	0.04*
Homa IR	0.366	0.04*
Homa-β %	-0.06	0.77
FRS %	0.440	0.015*
Hs CRP (mg/l)	0.217	0.25

Table (5): Correlation between GDF15 and other variables among prediabetic group:

Pre-diabetes group	GDF 15 (pg/ml)	
	r test	P value
Age (years)	0.45	0.01*
BMI(kg/m²)	0.17	0.3
SBP(mmHg)	0.38	0.03*
DBP(mmHg)	0.45	0.12
Urea(mg/dl)	-0.33	0.07
Cr.(mg/dl)	0.28	0.13
Uric acid (mg/dl)	0.25	0.18
TC (mg/dl)	0.397	0.02*
TG (mg/dl)	0.388	0.03*
HDL-c (mg/dl)	0.45	0.12
LDL-c (mg/dl)	0.289	0.01*
FBG (mg/dl)	0.437	0.015*
P.P gl. (mg/dl)	0.455	0.011*
Hb A1c (%)	0.369	0.04*
Homa IR	0.331	0.07
Homa-β %	-0.11	0.56
FRS%	0.380	0.04*
Hs Crp (mg/dl)	0.20	0.28

Table (6): Performance of GDF15 as a predictor of cardiovascular risk in diabetic patients.

GDF15	**Diabetic group (30)**	**Control group (20)**	X^2	P value
≥468.3 pg/ml	27(90%)	7(35%)	9.92	0.002**
<468.3 pg/ml	3(10%)	13(65%)		
AUC		0.692		
Cutoff point (pg/ml)		468.3		
Sensitivity %		86.6		
Specificity %		52.0		
PPV%		75.7		
NPV%		64.8		
Accuracy%		80.0		

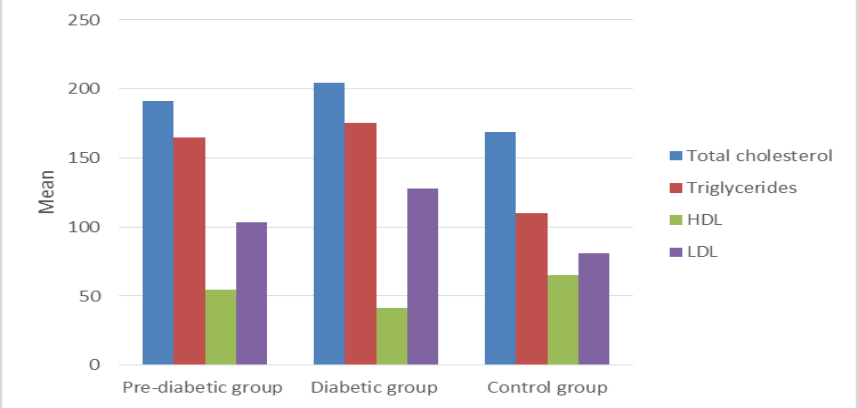

Figure (1): Comparison between the studied groups according to total cholesterol (mg/dl), triglycerides (mg/dl), HDL-c (mg/dl), LDL-c (mg/dl).

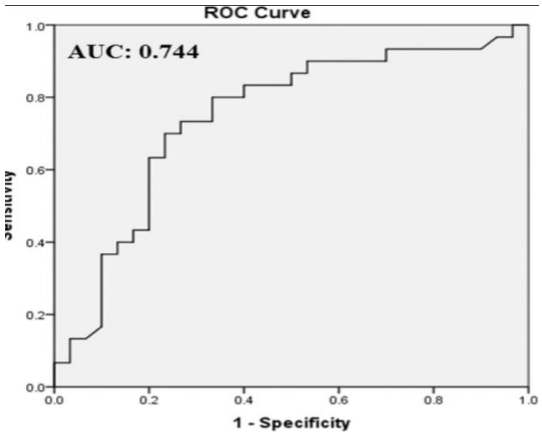

Figure (2): ROC curve of GDF 15(pg/ml) for prediction of cardiovascular risk in prediabetic patients.

Discussion

Growth differentiation factor-15 (GDF-15) is one of the transforming growth factor-β cytokine family that is produced in response to oxidative stress and inflammation by multiple cell types, including macrophages, adipocytes and cardiovascular cells **[12].** Circulating concentration of serum GDF-15 levels is associated with increased risk of cardiovascular diseases **[13].** In diabetic patients there are many factors that induce the development of cardiovascular diseases. These factors include the impairment of glucose metabolism, dyslipidemia, adipose tissue dysfunction and excessive oxidative stress **[14].**

All these factors are able to induce endothelial dysfunction, leading to cardiac remodeling and hypertrophy, worse vascular integrity and cardiac function **[15].** Among all these factors the oxidative stress is the most important which causes the release of GDF 15 from adipocytes and cardiovascular cells **[16].** The Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of individuals. It can predict the risk of developing cardiovascular diseases and also can indicate who is the most likely to benefit from prevention **[17].**

In the current study, as shown in **figure (1)** total cholesterol and triglycerides levels were higher in the diabetic group than in the control group ($p=0.046$, $p=0.001$ respectively). The total cholesterol was also significantly increased in Schindler et al**. [18],** Hong et al. **[19]** and in Shin et al. **[7]** studies ($p=0.01$, $p<0.001$ and $p= 0.035$ respectively) in diabetic group in comparison to control group.

In Hong et al. **[19]** study, there was significant increase in triglycerides among diabetic group in comparison to control group ($p=0.017$). In the present study, there were significant increase in total cholesterol, triglycerides and LDL-c in prediabetic group in comparison to control group ($p<0.001$ in each) and these results are in agreement with results of Hong et al. **[19],** Stentz et al**. [20]** and Zheng et al**. [21].**

In the current research, there was a significant decrease in HDL-c in diabetic group in comparison to prediabetic group ($p=0.001$) compared to results of Hong et al. **[22]** in which the HDL-c was significantly decreased in diabetes group in comparison to prediabetes group ($p=0.012$). The lipid profile is expected to be increased in diabetic and prediabetic patients as there is increased

incidence of metabolic syndrome which is characterized by abdominal obesity, insulin resistance, dyslipidemia and hypertension **[17].** In the present study there was significant increase in HbA1C in diabetic group in comparison to prediabetic and control groups (p=0.001) as shown in **table (2).** This is consistent with results of Navarro et al. **[23],** Schindler et al. **[18]** and Shin et al**. [7].**

HbA1C in these studies was significantly increased in diabetic patients in comparison to non diabetic persons (p<0.001 in all). Poor control of diabetes lead to increase in HbA1C level which is also affected by many factors. Factors that influence HbA1C are anemia, haemoglobinopathies, liver diseases, ingestion of alcohol, vitamin C and vitamin E., etc. **[18].** In this study, there was significant increase in insulin in diabetic group in comparison to prediabetic and control group (p=0.002) as shown in table **(2)** and this is in agreement with Hong et al. **[19]** result.

In Hong et al. **[19]** study, there was significant increase in insulin in diabetic group in comparison to control group (p<0.001). In type2 DM, there is increase in the demand of insulin by the pancreas, and balance of insulin and blood sugar are affected **[22].** Type2 DM is preceded by a long period of insulin resistance. β cells are trying to compensate for insulin resistance by adequately increasing insulin production **[24].** In the current study, the calculated HOMA-IR level was elevated in the prediabetic group (4.39±1.0), and it was the highest in the diabetic group (6.65±1.57). HOMA-IR levels in the diabetic group and prediabetic group showed the presence of IR. There is significant increase in HOMA IR in diabetic and prediabetic groups in comparison to control group (p≤0.001) and there is significant increase in HOMA IR in diabetic in comparison prediabetic group (p=0.001) as shown in **table (2)** and this result is in agreement with results of Hong et al. **[22]** and Shin et al. **[7]** (p<0.001 in both studies).

In subjects with genetic predisposition, the combination of excess caloric intake and relatively decreased physical activity, with the likely resulted obesity, can induce a condition of resistance to the insulin action. Moreover, there is accumulation of fat in skeletal muscles and liver which decreases the cell response to insulin and thus increases the insulin resistance **[24].** In the current study, there was significant decrease in Homa β index (p=0.001) in the diabetic group and prediabetic group in comparison to the control group and this result is in

agreement with results of Shin et al. **[7]** and Hong et al. **[22].** In both studies the Homa β index was significantly decreased in diabetic patients ($p < 0.001$ in both studies). Prolonged exposure to high glucose, elevated free fatty acids levels, or a combination of both lead to β-cell dysfunction **[24].**

According to the present study, there was a statistically significant increase in GDF 15 in diabetic and prediabetic groups in comparison to the control group ($p < 0.006$) as shown in table **(3)** and this result is in agreement with results of Dominguez-Rodriguez et al. **[26],** Hong et al. **[22],** Shin et al. **[7]** and Adela et al. **[27].** The impairment of glucose metabolism, dyslipidemia, adipose tissue dysfunction and excessive oxidative stress are factors that induce endothelial dysfunction in diabetic and prediabetic patients **[14].**

These factors worsen vascular integrity and cardiac function and lead to release of GDF 15 from adipocytes and cardiovascular cells **[15].** In the present study, there is statistically significant increase in FRS in diabetic and prediabetic groups in comparison to control group ($p \leq 0.001$).

In the present study, significant positive correlations were evident between GDF15 level and age ($p=0.03$), total cholesterol ($p=0.03$), FBS ($p=0.01$), Hb A1c ($p=0.04$), Homa IR ($p=0.04$) and FRS ($p=0.015$) in diabetic group as shown in table (4). In Hong et al. [22] study, GDF15 had significant positive correlation with age ($p<0.001$), FBS ($P<0.001$) and HOMA-IR ($P<0.001$) and it was negatively correlated with HDL-c ($p=0.011$).

In Shin et al. [7] study, GDF 15 was correlated with FBS ($p<0.001$), HbA1C ($p=0.001$), HOMA-IR ($p=0.02$) and FRS ($p<0.001$). In the present study, there was a significant positive correlation between the GDF 15 level and age ($p=0.02$), SBP ($p=0.03$), total cholesterol ($p=0.02$), triglycerides ($p=0.03$), LDL-c ($p=0.01$), FBS ($p=0.015$), P.P glucose ($p=0.011$), Hb A1c ($p=0.04$) and FRS ($p=0.04$) in prediabetic group as shown in table (5).

ROC curve was performed to test validity of GDF15. It has a sensitivity of 86.7% and specificity of 55% in predicting the cardiovascular risk in prediabetic subjects (figure 2) with area under the curve (AUC) = 0.744 and cut off value = 414.07 pg/ml. It has a sensitivity of 86.6 % and specificity of 52% in predicting the cardiovascular risk in diabetic patients table (6) with (AUC) = 0.69 and cut off value = 468.3 pg/ml. Studies of Anand et al. **[16],** Bonaca et al. **[28]** and Wollert et al. **[29]** have reported that there

are associations between GDF15 levels and various types of CVD. The GDF15 level was reported to be a prognostic marker of heart failure **[16].** The level of GDF15 can be a useful predictive biomarker of diabetic cardiomyopathy in patients with type2 DM **[25].** It may be used as a useful biomarker for mortality in patients with non-ST-elevation myocardial infarction **[29].** The recurrent adverse effects after the development of acute coronary syndrome were found to be associated with increased levels of GDF15 **[28].**

Conclusion

Through using of Framingham Risk Score, we noticed an association between serum GDF15 level and cardiovascular risk factors in type2 DM patients. This suggests that GDF15 serum level can be used as a useful predictive biomarker for incidence of cardiovascular diseases in patients with type2 DM.

Conflicts of interest: There are no conflicts of interest

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