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The relationship of Growth differentiation factor-15 with renal damage and dyslipidemia in non-albuminuric and albuminuric Type-2 Diabetes Mellitus

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ABSTRACT

Objective: Aim of this study is to investigate the correlation of Growth differentiation factor-15 with renal damage and dyslipidemia in Type-2 Diabetes Mellitus.

Material and Method: The study was conducted prospectively with patients diagnosed with Type-2 Diabetes Mellitus. Two groups were formed as non-albuminuric (n:47) and albuminuric (n:24). Age, gender, Growth differentiation factor-15, glycemic index, lipid panel, glomerular filtration rate, complete blood count, urine albumin/creatin and urine protein/creatin of the groups were compared, and their correlations were examined.

Results: Growth differentiation factor-15, age, and hemoglobin A1c were found to be higher in the albuminuric group, and hemoglobin and hematocrit levels were found to be lower. A positive correlation of Growth differentiation factor-15 with spot urine albumin/creatin and protein/creatin was observed in the albuminuric group. In the non-albuminuric group, positive correlation was observed with Triglyceride and a negative correlation with high-density lipoprotein cholesterol. Negative correlation of Growth differentiation factor-15 glomerular filtration rate was detected in all participants.

Conclusions: Growth differentiation factor-15 has been found positively associated with albuminuria and high triglyceride levels in Type-2 Diabetes Mellitus. It is negatively correlated with glomerular filtration rate and high-density lipoprotein cholesterol. It is strongly associated with renal damage and dyslipidemia.

Keywords: GDF-15, albuminuria, GFR, Triglyceride, HDL-C

INTRODUCTION

Growth differentiation factor-15(GDF-15) is sourced from the transforming growth factor-β(TGF-β) family (1). It is widely expressed in cardiomyocytes, endothelial cells, macrophages, adipocytes, and vascular smooth muscle cells which a critical protein associated with oxidative stress that occurs in hypoxia, organ damage and chronic inflammation (2,3,4).

GDF-15 has been found to have higher levels than healthy controls and obese persons without diabetes in Type-2 Diabetes Mellitus (DM) (5,6). Dyslipidemia is common in Type-2 DM. The most common lipoprotein disorder is increased Triglyceride (TRG) and Low density lipoprotein cholesterol (LDL-C) levels with decreased high-density lipoprotein cholesterol (HDL-C) levels. They have important roles in the formation and progression of atherosclerosis and are associated with increased cardiovascular risk (7,8,9). Also, GDF-15 is an important adipokine (10). Studies on lipid metabolism have generally been carried out with patient groups diagnosed with non-diabetic metabolic syndrome, obesity and prediabetes (11,12).

Studies examining the relationship between dyslipidemia and GDF-15 in type-2 DM are limited and uncertain. Both are important cardiometabolic risk factors, and their correlation needs to be investigated. However, increased GDF-15 levels are a potential marker of diabetic kidney disease. Recent studies suggest that it shows early renal damage independent of albuminuria (13,14).In this context, GDF-15 levels have started to become popular. The aim of our study was to investigate the correlation of GDF-15 with dyslipidemia and renal damage in albuminuric and non-albuminuric patients with a diagnosis of Type-2 DM..

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MATERIAL and METHODS

The study was conducted prospectively between April and December 2021.71 Type-2 DM patients were included. Age, gender, body mass index (BMI), hypertension(HT), hypothyroidism and smoking of all patients were recorded. Venous blood samples of the participants were taken in the morning after at least 8-10 hours of fasting. The blood samples were collected in non-anticoagulant gel tubes and centrifuged for 10 minutes at 2000xg after 30 minutes of coagulation. Approximately 0.5 mL of the obtained serum was taken into microcentrifuge tubes and stored at -80°C until the GDF-15 was studied. In biochemistry tests, serum fasting glucose, glomerular filtration rate (GFR), LDL, HDL, Total Cholesterol (T.COL), TRG, aspartate transaminase (AST), alanine transaminase (ALT), thyroid-stimulating hormone (TSH), thyroxine (T4) were studied. Protein/creatinine (PCR) and albumin/creatinine ratios(ACR) were analyzed from the first spot urine sample taken in the morning. Tests were performed in an autoanalyzer (AU 5840; BeckmanCoulter, Calif., USA) using routine laboratory methods.GFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula(15). Hemoglobin A1c (HbA1c) and complete blood count (CBC) were studied from whole blood samples taken into K2EDTA tubes.HbA1c was measured by HPLC (Premier Hb9210; TrinityBiotech, Co.Wicklow, Ireland). CBC was measured by Sysmex instrument (XN-1000-Products Detail, Japan). Serum GDF-15 concentration (Elabscience, Beijing, China) was measured using the sandwich-ELISA method. The intraassay and interassay coefficient of variation for GDF-15 wereboth<10%. The test was performed strictly according to the kit instructions. Optical density was measured at 450 nm using a microplate reader (SPECTROstarNano, BMG Labtech). Two groups were created in the study. Those with spot urine alb/cr> 30 mg/dl were included in the albuminuria group (n: 24), and those with<30 mg/dl in the non-albuminuria group (n: 47). No classification was made on urine PCR. Demographic data, additional diseases, GDF-15 levels, blood tests, and correlations of the groups were compared.

Inclusion Criteria

- >18 age
- Type-2 DM
- Presence of hypertension and hypothyroidism with type-2 DM
- No known cardiovascular disease

Exclusion Criteria

- <18 age
- Type-1 DM
- Acute or chronic infection
- Chronic obstructive pulmonary disease and asthma
- Malignancy
- Cirrhosis of the liver
- End-stage renal disease receiving replacement therapy (GFR<15 ml/min)
- Atherosclerotic vascular diseases(coronary heart disease, cerebrovascular disease, peripheral artery disease)
- Alcohol and substance addict

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS, version 20.0, Chicago, IL, USA). Data were presented as percentages and median (interquartile).

Chi-square test and Mann-Whitney U test were used to evaluate the differences between the groups. The Kolmogorov-Smirnov test was used to determine the normality of the distribution. Correlation analyzes were performed using the Spearman test. Multiple linear regression analysis was used to evaluate parameters associated with urine ACR and urine PCR levels. P-value < 0.05 was considered statistically significant.

RESULTS

The descriptive statistics and group comparisons of the variables and groups that are the subject of the study are given in **Table 1**. These results showed no difference between the groups in terms of gender distribution, BMI ratio, smoking, and comorbidities(P>0.05). However, the mean age(61) was significantly higher in the albuminuria group (P=0.038).

According to laboratory tests; GDF-15 (339 ng/mL)(P=0.007), HbA1C(8g/dL)(P=0.040), urine PCR(250 mg/dL)(P<0.001), urine ACR(81 mg/dL) levels in albuminuria group (P<0.001) was significantly higher. Hemoglobin(Hgb)(13.5 g/dL) and hematocrit (hct) (41.2g/dL) levels were found to be lower(P=0.001).

The correlation of GDF-15 with other variables is shown in **Table-2**. According to this; In the albuminuria group, positive correlations were detected with urine PCR (r=0.448*,P=0.028) and urine ACR (r=0.483* P=0.017). In the non-albuminuria group, a positive correlation was found with TRG (r=0.441** P=0.002) and a negative correlation with HDL-C (r=-0.354* P=0.015).

When the correlation was examined over all participants, urine PCR(r=0.383**,P=0.001), urine ACR (r:0.434**,P<0.001) and TRG(r=0.319**P=0.007) positive, GFR(Negative correlations were observed with r=-0.304*,p=0.010) and HDL-C (r=-0.353**,P=0.003).

These results are statistically significant. In order to evaluate the relationship between urine ACR/PCR and other factors, a linear regression model was applied using the backward elimination method.

The factors affecting the urine ACR level in all participants are shown in **Table-3**. Accordingly, it was determined that GDF-15, age, Hba1C and low hemoglobin were correlated with albuminuria.

The factors affecting the urine PCR level are shown in **Table-4**. Similarly, it was determined that low hemoglobin and increased Hba1C, GDF-15 were correlated with proteinuria. These correlations are statistically strong and significant.

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Table 1. Demographic data and laboratory characteristics of the groups

Variables/Groups	Non-albuminuric (n=47)	Albuminüric (n=24)	P value
Gender (Female%)	59,60%	70,80%	0,352
Age	56(49-62)	61(53-70)	**0,038**
BMI	30,6(28,3-34,1)	32,8(29,6-38,9)	0,056
Smoker (%)	21,3%	29,2%	0,461
Additional disease (HT, hypothyroidism)	66%	66,7%	0,952
GDF-15 (ng/mL)	210(137-297)	339(208-445)	**0,007**
Wbc (10^3/uL)	7,8(6,3-8,9)	8,4(6,4-9,9)	0,198
Hgb (g/dL)	14,4(13,7-16)	13,5(12,3-14,3)	**0,001**
Hct (g/dL)	44(41,4-46,5)	41,2(37,8-42,5)	**0,001**
Mcv (fL)	86,5(83,7-89,1)	85,4(82,2-86,8)	0,102
Mch (pg)	29,2(28-30)	28(26,1-30,15)	0,204
Mpv (fL)	10,2(9,8-10,6)	11(10-11,3)	0,070
Plt (10^3/uL)	259(228-327)	281,5(241-322,5)	0,444
HbA1C (g/dL)	7(6,2-9)	8(7,3-9)	**0,040**
Glucose (mg/dL)	151(125-190)	170(128-232)	0,256
GFR (mL/dk)	95,6(82,4-104)	88,5(69,5-100,6)	0,109
Ast (U/L)	20(17-24)	21(16,5-28,5)	0,715
Alt (U/L)	20(17-29)	20(15,5-29)	0,961
T.Chol (mg/dL)	198(176-255)	215(182-242)	0,405
LDL-C (mg/dL)	119(96-153)	130,5(105-165)	0,422
HDL-C (mg/dL)	51(42-61)	48(45-55)	0,466
TRG (mg/dL)	162(116-226)	211(115-266)	0,282
TSH (uIU/ml)	1,92(1-2,43)	1,74(1,11-2,425)	0,747
T4 (uIU/ml)	0,89(0,83-1,02)	0,98(0,88-1,095)	0,073
Urine ACR (mg/dL)	8,4(5,1-12,9)	81(42,7-179,8)	**<0,001**
Urine PCR (mg/dL)	97(67-124)	250(206-327)	**<0,001**

BMI: Body mass index;HT:Hypertension;GDF-15:Growth differentiation factor-15;WBC:White Blood Cell,Hgb:Hemoglobin;Hct: Hematocrit;Mcv:Main Corpuscüler Volüme;Mch: mean corpuscular hemoglobin;Plt:Platelet;HbA1c: Glycosylated hemoglobin; GFR: Glomerular Filtration Rate; Ast: Aspartate transaminase; Alt:Alaninetransaminase;T.Chol:Total Cholesterol; LDL-C: Low-density lipoprotein Cholesterol;HDL-C: high-density lipoprotein-cholesterol; TRG: Triglyceride;TSH: thyroid stimulating hormone;T4: Thyroxine; ACR:Albumin-creatine ratio;PCR:Protein-creatine ratio.

Table 2. Correlation of GDF-15 with other parameters

Variables/Groups	Total group		Non-albuminüric		Albuminüric	
GDF-15	Correlation coefficient (r)	P value	**Correlation coefficient (r)**	P value	**Correlation coefficient (r)**	P value
Age	0,001	0,991	-0,027	0,856	-0,281	0,184
BMI	0,115	0,340	0,104	0,486	-0,099	0,645
DM duration	-0,127	0,292	-0,084	0,575	-0,164	0,443
WBC	0,098	0,418	0,114	0,445	-0,039	0,856
Hgb	-0,080	0,509	0,154	0,303	-0,131	0,540
Hct	-0,069	0,569	0,170	0,254	-0,129	0,547
Mcv	-0,089	0,461	0,091	0,541	-0,292	0,166
Mch	-0,029	0,810	0,103	0,491	-0,178	0,406
Mpv	0,021	0,861	0,048	0,751	-0,165	0,442
Plt	0,019	0,873	-0,004	0,978	-0,002	0,994
HbA1c	0,104	0,392	0,033	0,828	-0,018	0,936
GFR	-0,304	**0,010**	-0,249	0,091	-0,278	0,188
T.Chol	0,040	0,739	0,063	0,672	-0,159	0,457
LDL-C	0,029	0,810	-0,028	0,852	-0,088	0,682
HDL-C	-0,353	**0,003**	-0,354	**0,015**	-0,252	0,235
TRG	0,319	**0,007**	0,441	**0,002**	-0,040	0,853
Urine ACR	0,434	**<0,001**	0,278	0,058	0,483	**0,017**
Urine PCR	0,383	**<0,001**	0,155	0,300	0,448	**0,028**

Table 3. Multivariate regression analysis of Urine ACR concentration as dependent value.

Variables	β	p value
Age	0,188	0,045
Hgb	-0,413	<0,001
HbA1c*	0,354	<0,001
GDF-15*	0,359	<0,001

* Logarithmic transformation was applied. Hgb:Hemoglobin; HbA1c: Glycosylated hemoglobin; GDF-15:Growth differentiation factor-15

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Table 4. Multivariate regression analysis of Urine PCR concentration as dependent value

Variables	β	p value
Hgb	-0,373	0,001
HbA1c*	0,272	0,011
GDF-15*	0,346	0,001

* Logarithmic transformation was applied. Hgb:Hemoglobin; HbA1c: Glycosylated hemoglobin; GDF-15:Growth differentiation factor-15

DISCUSSION

GDF-15; It is associated with multiple factors in patients with type-2 DM. These may include chronic inflammation, impaired glycemic index, renal damage, and dyslipidemia. These results actually lead to poor prognosis and increased cardiovascular risks. According to our results, primarily GDF-15 levels were found to be significantly higher in the albuminuric group (P=0.007) (Table-1).

Albuminuria is a characteristic feature of diabetic nephropathy (DN) and is a condition associated with chronic inflammation (16). Studies have shown that GDF-15 increases in response to tissue damage in chronic inflammation (4,17). Simons et al. also associated increased GDF-15 levels with renal damage in Type-2 DM(18).Agarwal et al. examined GDF-15 and Galectin-3 levels in healthy, prediabetes, Type-2 DM, and diabetic nephropathy groups. They found that it has the highest rate in DN (19).

This is important in terms of an important prognostic marker that affects progression. Age and Hba1c were significantly higher in the albuminuria group ($p<0.05$) (Table-1). These factors may have contributed to the increase in GDF-15 in the albuminuric group.Because GDF-15 is an important cytokine that increases with age.Oxidative stress, inflammation, and hormonal levels change with age. As a result, an increase in the expression of GDF-15 by the p53 gene is observed (20). Bilson et al. also found a positive correlation with GDF-15 and HbA1C (21). In our study, no correlation was found between GDF-15 and age and Hba1c ($p>0.05$) (Table 2).

This may be due to the low number of patients.However, a strong positive correlation was found between GDF-15 and spot urine ACR/PCR in the correlation made both in the albuminuric group and among all participants ($p<0.001$) (Table 2). Li et al. found a significant correlation of GDF-15 with Mogensen stage in a prospective study involving 80 patients. As albuminuria increased, GDF-15 increased (22). DN is the most common microvascular complication of Type-2 DM (23).

The relationship of GDF-15 with albuminuria/proteinuria can be explained by microvascular damage. Because, as a result of endothelial dysfunction in microvascular damage GDF-15 expression occurs widely (24). Our study showed that there is no correlation was observed between GDF-15 and GFR in albuminuric and non-albuminuric groups ($p>0.05$). However, a negative correlation was detected among all participants. ($p=0.010$)(Table 2). The absence of such a result in the groups may be due to the small number of participants. Chung and Li et al. found a negative correlation between GDF-15 and GFR in their studies.

They suggested that it is a marker of early renal damage independent of albuminuria (14,22). Hbg and hct levels were lower in the albuminuria group than in the non-albuminuric group (Table 1). In a study by Ito et al., the early diagnostic value of anemia in diabetic nephropathy was emphasized (25). In addition, it is known that anemia develops earlier, independent of the stage of chronic kidney disease in diabetic patients (26).

Albuminuria is a pathognomonic finding of renal damage and an important progression marker. It is also associated with increased cardiovascular risk (27). We applied a linear regression model to examine the factors affecting albuminuria and proteinuria. Accordingly, GDF-15 ($p<0.001$), age ($p=0.045$), increased Hba1c ($p<0.001$), and decreased hemoglobin ($p<0.001$) affected albuminuria (Table-3).

It was revealed that other factors, except age, had the same effect on urine PCR (Table 4). Based on these results, we can say that GDF-15 has a strong relationship with renal damage. It can be used as an important indicator. Age is a non-modifiable risk factor. However, lowering Hba1c levels by regulating the glycemic index and new treatment strategies that reduce GDF-15 levels can be used to slow down the progression. One of the important results of our study is the relationship between GDF-15 and dyslipidemia. There was a positive correlation between GDF-15 and TRG, and a negative correlation with HDL-C in the non-albuminuric group.

No relationship was observed in the albuminuric group. This is due to the small number of patients. Because the correlation results made on all participants were observed more strongly in the same direction (Table 2). GDF-15 is an important adipokine that regulates lipid and glucose metabolism. Also known as cardiokines. Ho et al. found a negative correlation of GDF-15 with HDL-C and GFR in a study that included 2991 participants, including DM, HT, smokers, elderly and healthy individuals. They showed that the genome-wide increased GDF-15-associated C allele (rs1054561) was correlated with low HDL-C (30).

Casla et al. also found a correlation between GDF-15, high TRG, and low HDL-C in patients with non-diabetic metabolic syndrome (12). High TRG and low HDL-C levels are important reasons for the development of atherosclerosis(31). The relationship between GDF-15 levels and dyslipidemia is interesting. It has been shown that TRG-rich lipoproteins significantly increase GDF-15 levels in smooth muscle cells of the coronary arteries (32).

However, although the development of GDF-15 in atherosclerosis is not fully understood, it has been shown to regulate inflammatory and angiogenesis pathways (33).

Dyslipidemia may cause the development of atheromatous plaques, resulting in endothelial dysfunction and increased local inflammation, resulting in an increase in GDF-15. Based on these hypotheses, are GDF-15 levels affected by anti-hyperlipidemic therapy? This question comes to mind. Kim et al. applied atorvastatin treatment to patients with hyperlipidemia in Type-2 DM. They observed a decrease in T.COL and LDL levels, but they did not observe any change in GDF-15 levels(34). However, studies have found that GDF-15 is more correlated with high TRG and low HDL than LDL-C (12,30). Therefore, statin therapy may not have caused a change in GDF-15 levels. We suggest conducting studies observing the interaction of anti-triglyceride therapy (fenofibrate, gemfibrozil.) on GDF-15. In our study, The low number of patients in both groups, especially in the albuminuric group, is an important reason for the limitation. We recommend that future studies be conducted with larger participants.

CONCLUSION

Increased GDF15 levels are associated with early renal damage in type-2 DM. It is an important marker in predicting progression. However, there is a significant correlation with dyslipidemia. Both renal damage and dyslipidemia cause increased cardiovascular risk. For this reason, GDF-15 may be use an indicator in the evaluation of predictable risks. Moreover, GDF-15 levels are important for new treatment strategies.

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