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

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Research Article

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Abstract

Aim: To investigate the correlation of GDF-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, comorbidities, GDF-15, glycemic index, lipid panel, GFR, urine albumin/creatin (ACR) and urine protein/creatin (PCR) ratios of the groups were compared and their correlations were examined.

Results: GDF-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 GDF-15 with urine ACR/PCR was observed in the albuminuric group. In the non-albuminuric group, was observed positive correlation with Triglyceride and negative correlation with HDL. Negative correlation of GDF-15 and GFR was detected in all participants.

Conclusions: In type-2 DM, GDF-15 is positively correlated albuminuria and TRG elevation and negatively correlated with GFR and HDL

Introduction

GDF-15(Growthdifferentiation factor-15) is from the transforming growth factor-β(TGF-β) family(1). It is widely expressed from cardiomyocytes, endothelial cell, macrophages, adipocytes and vascular smooth muscle cells (2)an important protein associated with oxidative stress that occurs in hypoxia, organ damage and chronic inflammation(3, 4).GDF-15 has been found have higher levels than healthy controls and obese 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 dansiteli lipoprotein cholesterol level with decreased high-density lipoprotein cholesterol (HDL-C) levels.They have important roles in the formation and progression of atherosclerosis and are associated within creased cardiovascular risk(7, 8, 9).GDF-15 is an important adipokine(10).Studies on lipid metabolism have generally been carried 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 levelsare 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.

Materials 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), additional diseases (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 collected in non-anticoagulant gel tubes were centrifuged for 10 minutes at 2000xg after 30 minutes of coagulation.Approximately 0.5mL of the obtained serum was taken into microcentrifuge tubes and stored at -80°C until the GDF-15 wasto be studied.In biochemistry tests, serum fasting glucose, glomerular filtration rate (GFR), LDL, HDL, T.COL, TRG, aspartate transaminase (AST), alanine transaminase (ALT), thyroid stimulating hormone (TSH), thyroxine (T4) were studied.Protein/creatinine (PCR) and albumin/creatinine (ACR) ratios were analyzed from the first urine sample taken in the morning.Tests were performed in an autoanalyzer (AU 5840; BeckmanCoulter, Calif., USA)usingroutine 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 in strument (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 nmusing a micro platereader (SPECTROstarNano, BMG Labtech).Two groups were created in the study.Those with spot urinealb/cr > 30 mg/dl were included in the albuminuria group (n: 24), and those with < 30 mg/dl in the non-albuminuriagroup (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.

Exclusioncriteria:

Acuteorchronicinfection

Chronicobstructivepulmonarydiseaseandasthma

Malignancy

Cirrhosis of theliver

End-stagerenaldiseasereceivingreplacementtherapy (GFR < 15 ml/min)

Atherosclerоticvasculardiseases(coronaryheartdisease,cerebrovasculardisease, peripheralarterydisease)

Alcoholandsubstanceaddict

Approvalwasobtainedfromtheethicscommittee of Kırşehir Ahi Evran University Faculty of Medicine (no:2021-09/90).Helsinki criteria were complied with Informed. Written consent was obtained from all participants.

Statistics

All statistical analyzes 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 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. According to these results, there was 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) 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). 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, increase in Hba1C and GDF-15 were correlated with proteinuria.

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(mg/dL)	119(96–153)	130,5(105–165)	0,422
HDL(mg/dL)	51(42–61)	48(45–55)	0,466
TRG(mg/dL)	162(116–226)	211(115–266)	0,282

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: Low-density lipoprotein;HDL: high-density lipoprotein; TRG: Triglyceride;TSH: thyroid stimulating hormone;T4: Thyroxine; ACR:Albumin-creatine ratio;PCR:Protein-creatine ratio.

Variables/Groups	Non-albuminuric (n = 47)	Albuminüric (n = 24)	P value
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: Low-density lipoprotein;HDL: high-density lipoprotein; TRG: Triglyceride;TSH: thyroid stimulating hormone;T4: Thyroxine; ACR:Albumin-creatine ratio;PCR:Protein-creatine ratio.

Discussion

In our study, 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). 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). Although age and HbA1C were not correlated with GDF-15 across groups and all participants (Table 2), they 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 of GDF-15 with HbA1C(21). However, a positive correlation was found between GDF-15 and urine ACR/PCR in the correlation made both in the albuminuric group and on 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).In addition to these, a negative correlation was found between GDF-15 and GFR overall participants in our study. Similar results were obtained in the study of Chung et al. They suggested that it is a marker of early renal damage independent of albuminuria (14). Li et al also found an independent correlation between GDF-15 and GFR(22). However, in our study, no correlation was found with GFR in the non-albumin uric group, including the albumin-uric group. This may be due to the small number of patients in the groups (Table-2). Hbg and hct levels were lower in the albuminuria group than in the non-albuminuric group (Table 1). It is an expected result. Because 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 an important prognostic marker showing increased cardiovascular risk and progression (27). In our study, we obtained important results when the factors affecting urine ACR/PCR were examined. Accordingly, we found that urinary ACR was affected by GDF-15 ($p < 0.001$), age ($p = 0.045$), increased Hba1c ($p < 0.001$) and decreased hemoglobin ($p < 0.001$) (Table-3). We found that other factors, except age, had the same effect on urine PCR (Table 4). These factors are important prognostic markers affecting progression. Age is a non-modifiable risk factor. However, lowering Hba1c levels by regulating blood sugar and new treatment strategies that reduce GDF-15 levels can be used to slow down the progression. May reduce cardiovascular risk.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.We do not think that this situation has an independent relationship from albuminuria. This is due to the small number of patients. Because the correlation results made on all participants were observed more strongly in the same directio(Table 2). GDF-15 is an important adipokine that regulates lipid and glucose metabolism. Also known as cardiokine. 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 with GDF-15, high TRG and low HDL-C in patients with nondiabetic metabolic syndrome(12). High TRG and low HDL-C levels are important reasons for the development of atherosclerosis(31). Does increased GDF-15 levels cause dyslipidemia? Does dyslipidemia cause increased GDF-15? Or both?It has been shown that TRG-rich liproteins 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. were applie 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.To summarize, GDF15 levels are associated with renal damage and dyslipidemia in Type-2 DM. It is an important marker for predicting progression and cardiac risk. Therefore, new treatment strategies that reduce GDF-15 levels are needed.

Table 2
Correlation of GDF-15 with other parameters

Participants	**Total group**		**Non-albuminüric**		**Albuminüric**	
Variables/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	0,029	0,810	-0,028	0,852	-0,088	0,682
HDL	-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**

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

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
* Logaritmik dönüşüm uygulandı.		
Hgb:Hemoglobin; HbA1c: Glycosylated hemoglobin; GDF-15:Growth differentiation factor-15		

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		

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