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Investigation the Relationship Between Myonectin Levels and Both Lipid Profiles and Liver Function Tests in Diabetic Nephropathy Patients

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Abstract Myonectin, or CTRP12, is a relatively recent adipokine—a protein released by adipose tissue that has gained interest in the context of metabolic health, including its possible implications in diabetic complications. Volunteers were divided into three groups, healthy subjects as controls (group A), they don't suffer from any disease, patients with T2D without nephropathy (group B) and T2D with nephropathy (group C), the age ranges between (35-70) years and the average duration disease of T2D (5-25) years, attending to the AL-Kindi teaching hospital, Baghdad Iraq. There was a highly significant increase $P \leq 0.01$ of FBS, Insulin level, HOMA-IR, HbA1c, TC, TG, HDL and TSB among different groups (T2D with nephropathy, T2D without nephropathy, and control), a highly significant increase $P \leq 0.01$ of myonectin levels among different groups. There was no significant difference present in AST *U/L, and* ALP *U/L.* A statistically significant increase in ALT *U/L* when compared with the control group. **Conclusion:** Levels of serum myonectin were significantly higher in patients with (T2D without nephropathy) as compared with (T2D with nephropathy) and the control group.

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Keywords: *Myonectin, T2D, HbA1c, Diabetic nephropathy, Lipid profile.*

1. INTRODUCTION

Diabetes stands as a chronic and progressive condition characterized by metabolic irregularities, and its prevalence poses a significant global health concern. Over 90% of all instances of diabetes are caused by type 2 diabetes mellitus, which is largely defined by IR and inadequate insulin production. Individuals with T2D are highly susceptible to developing microvascular and macrovascular complications, which can result in severe consequences [1].

One prevalent microvascular complication is diabetic nephropathy (DN), which ranks as the leading cause of ESRD in developed nations [2]. DN represents a frequent and severe complication of diabetes mellitus, contributing to heightened morbidity and mortality among diabetic patients [3]. Furthermore, renal disease significantly contributes to cardiovascular morbidity and mortality in diabetic individuals, potentially leading to unprecedented socioeconomic burdens. Consequently, the need for promptly establishing novel, efficient, and safe therapeutic approaches to combat DN is pressing. This endeavour hinges on comprehending the intricate molecular mechanisms underpinning the disease [4].

It has been established that lipid accumulation and abnormalities in lipid metabolism are associated with diabetic kidney disease. Despite the widespread belief that renal failure is the cause of increased lipid levels, there is strong evidence that hyperlipidemia, even in diabetes, may contribute to the onset and progression of kidney disease [5]. The results of standard liver function tests (LFTs) on people with heart disease are well-established and include abnormalities like slightly elevated levels of gamma-glutamyl transferase (ηGT), aspartic aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or bilirubin. These anomalies point to either decreased hepatic perfusion, passive congestion in the liver, or both [6].

Research on kidney function's effects on LFTs and how they vary over time is still in its infancy, although it has garnered very little attention. Patients diagnosed with T2D commonly have abnormalities in their LFTs, particularly increased ALT levels. These anomalies are frequently linked to insulin resistance and dysfunctional adipose tissue, as well as indicators of hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) [7].

Previous studies have proposed a link between diabetic nephropathy and non-alcoholic fatty liver disease. There is an

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elevated risk of cardiovascular disease (CVD) and higher mortality associated with both of these disorders. As a result, it has been proposed that coexisting NAFLD and chronic kidney disease (CKD) may increase the risk of cardiovascular events in a synergistic manner. Nevertheless, studies examining the combined effect of CKD and NAFLD on the risk of cardiovascular disease in individuals with T2D have not yet been conducted. When developing treatment plans for people with T2D, assessing the combined risk of cardiovascular disease caused by NAFLD and diabetic nephropathy may be helpful [8].

The myokine myonectin, sometimes referred to as C1q tumour necrosis factor-α-related protein isoform 15, is mostly found in skeletal muscle [9]. Its therapeutic value is still mostly unknown despite its discovery. With its N-terminal signal peptide, collagen repeat domain, and C-terminal C1q-like globular domain, myonectin and adiponectin have structural similarities. Myonectin is mostly generated and secreted by muscle tissues, in contrast to adiponectin [10]. Acute exercise and certain nutrients, such glucose and fatty acids, increase the expression of myonectin, a crucial regulator. Two adipocytes and hepatocytes are encouraged to absorb fatty acids by this increased expression. It is important to note, too, that the effects of exercise on myonectin expression in muscle tissue have shown contradictory results. Compared to its lesser expression in fast-twitch muscles, myonectin is primarily expressed in slow-twitch muscles. Myonectin has been linked to disturbances in the metabolism of glucose, fats, and energy in several studies [11]. Among these conditions contain diabetes and obesity.Moreover, hepatocytes in the liver and adipose tissue are subject to oxidative metabolism regulation, which is regulated by myokines, including myonectin. They moreover have an influence on how quickly muscle satellite cells proliferate [12].

Prior studies have extensively explored abnormalities in liver function and lipid profiles in various diseases [13], [14], [15]. As a result, the primary focus of this study was to assess Myonectin levels and their association with liver function and lipid profiles in three distinct groups: individuals with T2D nephropathy, individuals with T2D without nephropathy, and a control group. The eventual goal was to investigate the potential contribution of Myonectin in the commencement of complications related to diabetes, with a particular emphasis on nephropathy.

2. MATERIALS AND METHODS

2.1. Subjects and Study Design

The Al-Kindi Teaching Hospital served as the study's location from January 2023 to May 2023. A questionnaire was used to gather data from the 120 volunteers, including their medical history and diagnosis of T2D and diabetic nephropathy. The participants were split into three groups: T2D patients without nephropathy (n=40, 20 males and 20 females; group A), T2D patients with nephropathy (n=40, 20 males and 20 females; group C), and T2D patients with nephropathy (n=40, 20 males and 20 females). The age ranges for the groups were (35–70) years, and the average duration of the disease was 5–25 years. Specialist physicians made the diagnosis of diabetic nephropathy in the patients.

2.2. Selection Criteria of Patients

None of the patients was a smoker or alcoholic. As well, none of the patients had a family history of the disease. Patients with other diseases besides rheumatoid arthritis such as diabetes, hypertension, hyperthyroidism and psoriasis were excluded.

2.3. Sample Collection

From each individual, blood was drawn through a vein puncture using one-use syringes, as the individuals were fasting in the morning (10 ml) of blood was collected in in a gel tube. The samples in the gel tubes were centrifuged at (1000 g for 10 minutes). The resulting serum was stored at -20 ^{O}C until the time of analysis.

2.4. Sample Analysis

By using the commercially available Randox kits from Randox Laboratories Ltd. (UK), the colorimetric technique (Reitman and Frankel) was used to determine the serum levels of AST and ALT. ALP was ascertained using a colorimetric technique in accordance with the guidelines provided by Diasys Diagnostic System (GmbH, Holzheim, Germany, the company that supplies the commercial Diasys kit). By consuming spectrophotometry and the colorimetric technique in accordance with the Siemens kit given by Siemens Healthineers Erlangen, Germany, the levels of creatinine and urea were determined. By using a colorimetric approach and the available kit from Linear Chemicals, Spain, the amount of uric acid was measured. The lipid profile (cholesterol, triglycerides, and HDL) was measured enzymatically with the use of a colorimetric test, adhering to the guidelines provided by Linear Chemicals, Spain. The Friedewald equation was used to determine the levels of LDL and VLDL. Blood samples were used to measure the levels of circulating myonectin using an enzyme-linked immunosorbent test kit.

2.5 Statistical analysis

To assess the significance of differences in the mean values among the various groups, an analysis of variance (ANOVA) was performed, using SPSS program version 23, with significance level set at $P \leq 0.05$, indicating statistical significance. Furthermore, the relationships between the different factors under examination were evaluated using the Pearson correlation coefficient (r) test.

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3. RESULT

120 samples were used in this investigation, and biochemical and clinical data were collected for T2D patients without nephropathy and control people without nephropathy. There were statistically no significant age differences between the three groups under study and the control participants. Table 1 presents a summary of the mean values ± SD of the lipid profile (cholesterol, triglycerides, HDL, LDL, and VLDL) in the sera of patients with T2D with nephropathy, patients without nephropathy, and control.

Comparing T2D patients without nephropathy and T2D patients with nephropathy to control subjects, the results showed a statistically significant increase in TG (mg/dL), cholesterol (mg/dL), LDL (mg/dL), TC/HDL-C, LDL-C/HDL-C, and VLDL. However, the levels of HDL-C were significantly decreased.

Table (1): *Investigation of some biochemical Parameters among the study groups.*

Variables	Controls (G1) n=40	T2DM without nephropathy (G2) n=40	T2DM with nephropathy (G3) n=40	P Values	
TC (mg\dL)	162.15 ± 45.1	212.85 ± 37.67	214.53 ± 40.33	< 0.001	HS
TG (mg/dL)	109.62 ± 52.53	197.39 ± 44.69	251.32 ± 77.66	< 0.001	HS
HDL-C (mg/dL)	59.87 ± 9.76	44.34 ± 8.66	41.54 ± 8.12	< 0.001	HS
LDL-C	62.11 ± 27.41	139.71 ± 41.32	159.84 ± 45.23	< 0.001	HS
TC / HDL-C	2.7 ± 0.8	4.8 ± 1.00	5.16 ± 1.3	< 0.001	HS
LDL-C / HDL-C	1.03 ± 0.61	3.15 ± 1.1	3.84 ± 0.9	< 0.001	HS
VLDL	21.39 ± 9.94	40.89 ± 19.16	41.89 ± 20.58	< 0.001	HS

Data are expressed as mean ± SD * Significance: P-Value ≤ 0.05 ** High significance: P-Value ≤ 0.01

The mean values ± SD of liver enzymes (AST, ALP and ALT) for the three study groups were calculated from the obtained data and the collective results are presented in Table 2. The findings showed that T2D patients with nephropathy and T2D patients without nephropathy had significantly higher ALT concentrations than the control group ($p<0.05$), but there was no significant difference in AST and ALP levels between the patient and control groups. Furthermore, a statistical analysis reveals that there is a substantial rise in TSB levels between the control group and both patient groups ($p>0.01$).

Table (2): *Investigation of some biochemical Parameters among the study groups.*

Variables	Controls (G1) n=40	T2D without nephropathy (G2) n=40	T2D with nephropathy (G3) n=40	P Values	
AST *U/L*	23.85 ± 9.97	26.06 ± 8.93	26.41 ± 9.12	0.417	NS
ALT *U/L*	19.624 ± 5.77	23.03 ± 7.91	24.225 ± 7.88	0.015	S
ALP *U/L*	91.75 ± 26.44	93.85 ± 25.84	94.06 ± 25.58	0.909	NS
TSB (mg/dL)	0.72 ± 0.317	0.76 ± 0.249	1.075 ± 0.37	< 0.001	HS

Data are expressed as mean ± SD * Significance: P-Value ≤ 0.05 ** High significance: P-Value ≤ 0.01

The results also showed a highly significant increase in the levels of Myonectin for T2D without nephropathy patients compared to the control group ($p>0.01$), while a significant decrease in the levels of Myonectin for T2D with nephropathy patients compared to the control group ($p>0.01$), as presented in Table 3

Table (3): *Myonectin level among the study groups.*

Variables	Controls (G1) n=40	T2D without nephropathy (G2) n=40	T2D with nephropathy (G3) n=40	P Values	
Myonectin (pg\ml)	92.2 ± 33.06	162.106 ± 95.7	79.25 ± 42.61	< 0.001	HS

Data are expressed as mean ± SD * Significance: P-Value ≤ 0.05 ** High significance: P-Value ≤ 0.01

The correlation among myonectin and all parameters included in this work was studied for (T2D with nephropathy) and (T2D without nephropathy) groups, correspondingly, using Pearson correlation analysis. The collective results are displayed in Table 4. The analysis showed a negative correlation of myonectin with TG and VLDL in T2D with nephropathy. In addition, the results

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also showed a negative correlation of myonectin with Cholesterol, TG and VLDL in (T2D without nephropathy), as well as a positive correlation between myonectin duration of disease in (T2D without nephropathy).

Table 4; *Correlation coefficients of serum Decorin with all variables*

Variables	T2D with nephropathy		T2D without nephropathy	
	R	P	R	P
Ages (years)	-0.083	0.612	-0.020	0.902
BMI (kg/m2)	-0.093	0.567	-0.055	0.735
Duration (years)	-0.38	0.816	0.363*	0.021
SBP (mm Hg)	0.043	0.718	0.247	0.091
DBP (mm Hg)	0.132	0.082	0.095	0.035
Cholesterol (mg\dL)	- 0.394*	0.012	-0.341*	0.031
Triglyceride (mg\dL)	- 0.480**	0.002	-0.319*	0.045
HDL (mg\dL)	0.312	0.015	0.943	0.05
VLDL	- 0.431**	0.006	-0.346*	0.029
AST	-0.013	0.938	0.113	0.487
ALT	0.174	0.283	0.018	0.914
ALP	-0.19	0.905	0.056	0.729
TSB (mg/dL)	0.192	0.234	0.036	0.826

.Correlation is significant at the 0.01 level (2-tailed).**

.* Correlation is significant at the 0.05 level (2-tailed).

r = Spearman correlation coefficient.

P < 0.05 is significant.

4. DISCUSSION

Diabetes is a chronic metabolic disorder marked by high blood sugar levels brought on by either inadequate insulin synthesis (T1D) or poor insulin action (T2D). Elongated high blood sugar levels and the ensuing damage to several organs and tissues can lead to diabetic complications. It has been suggested that myonectin helps regulate metabolism and insulin sensitivity. An adipokine (a protein released by adipose tissue) that was just recently identified, myonectin has drawn attention in relation to metabolic health and its possible effects on troubles associated with diabetes [16].

According to some research, myonectin may enhance insulin signaling pathways in adipose tissue and skeletal muscle, hence improving glucose absorption [12], [17]. It is thought to act through mechanisms similar to adiponectin, another adipokine known for its insulin-sensitizing and anti-inflammatory effects. Diabetic nephropathy is a common complication of diabetes characterized by kidney damage due to prolonged high blood sugar levels [18]. In this study, we establish that the group of people with T2D who also had nephropathy had significantly lower serum myonectin concentrations than the T2D group without nephropathy and the control group. These results are consistent with those of Jie Zhang et al. [19], who likewise found that blood myonectin levels were lower in T2D patients with nephropathy than in those without diabetic nephropathy (DN).

Additionally, our study discovered a noteworthy contrast in serum myonectin levels among individuals with (T2D without nephropathy) in comparison to the control group. Specifically, we found that the serum myonectin levels were significantly higher in T2D patients without nephropathy when contrasted with the control group. Table (3)**.** These results stand in contrast to the findings of Jie Zhang et al., who reported lower serum myonectin concentrations in T2D patients than in healthy controls. However, another study found contrasting results, indicating that individuals with T2D and impaired glucose tolerance had higher circulating myonectin concentrations than those in the normal population [11]. This discrepancy could potentially be attributed to differences in (ethnicity, gender distribution, or variations) in sample size between the studies.

It's critical to understand that dyslipidemia, which is defined by abnormal blood lipid levels of triglycerides and cholesterol, poses a serious risk for cardiovascular illnesses. Managing the cardiovascular risk linked to lipid abnormalities may be affected by myonectin's ability to possibly control lipid metabolism. Skeletal muscle produces a protein called myonectin, which is carried by the blood. Interestingly, research has shown that a high-fat diet can lead to a reduction in myonectin expression and afterward lower its circulating levels. Furthermore, there is evidence from another study suggesting that myonectin's functions are closely associated with lipid metabolism. It seems to play a

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character in reducing the levels of free fatty acids in the blood by promoting their uptake in adipose tissue and the liver [20], [21]. Improved expression of scavenger and transporter proteins, such as fatty acid binding protein-4 (FABP-4) and fatty acid transporter protein-1 (FATP-1), appears to be the mechanism behind these assistances.

Furthermore, the introduction of recombinant myonectin causes adenosine monophosphate-activated protein kinase (AMPK) to become phosphorylated, which increases the recruitment of the GLUT4 transporter to the cell surface. This in turn promotes the oxidation of fatty acids and improves the absorption of glucose. Therefore, signaling pathways that meet the higher energy needs during muscular contraction may be activated by the augmented myonectin release produced by muscle contraction [22]. In this study, we found that blood myonectin levels were considerably lower in obese people with T2D who correspondingly had nephropathy. These results are consistent with a prior research [20], which found that those who are obese often had lower myonectin levels. Moreover, myonectin has been suggested to possess anti-inflammatory properties, potentially aiding in the attenuation of inflammation-associated processes that play a role in the development and progression of cardiovascular diseases [23]. According to several proposals, myonectin may have vasodilatory special effects, which might aid in blood vessel relaxation and advance endothelial function. This is specially significant for preserving normal blood flow and delaying the development of atherosclerosis.

5. CONCLUSION

Differences in the concentration of myonectin levels have been observed to play a key role in impaired fat and glucose metabolism in diabetic nephropathy patients, These study suggest that myonectin may be abeneficial indicator in predicting the progress of diabetic nephropathy.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Competing interests: The authors declare that they have no competing interests.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of Mustansiriyah University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Author's Contribution: Falah contributed to the study design. Zahraa carried out the experimental work, data collection and data analysis. Zahraa and Falah contributed to the results discussion, writing, drafting and editing of the paper. Falah checked and approved the overall manuscript, and all authors approved the final version of the manuscript.

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