Decreased plasma myonectin levels in female patients with type 2 diabetes mellitus and its correlation with lipid and glycemic parameters

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Abstract. – OBJECTIVE: Myonectin is a novel myokine which has significant implications on diabetes. This study aimed to investigate plasma myonectin levels in patients with type 2 diabetes mellitus (T2DM), and their correlation with body composition, lipid and glycemic parameters.

PATIENTS AND METHODS: The study participants included 40 diabetic and 33 non-diabetic healthy adult Saudi females matched for their BMI and age. Body composition was assessed by bioelectrical impedance analysis. Fasting blood samples were used to investigate plasma myonectin levels by ELISA, along with lipid and glycemic parameters.

RESULTS: We found that plasma myonectin levels were significantly decreased in diabetic patients (40.90±4.13 ng/ml, p<0.05) compared to non-diabetic participants (59.58±4.41). Diabetic patients with poor glycemic parameters had significantly decreased myonectin levels (35.18±4.03 ng/ml, p<0.05) compared to non-diabetic healthy subjects. There was no significant difference in myonectin levels between diabetic patients with good glycemic control (55.76±8.09 ng/ml p>0.05) and non-diabetic healthy participants. Pearson correlation analysis indicated a significant negative correlation with fasting blood sugar (R=-0.366, p=0.001), HbA1c (R=-0.406, p<0.0001), triglycerides (R=-0.264, p=0.024), insulin (R=-0.278, p=0.017), and HOMA-IR (R=-0.409, p<0.0001).

CONCLUSIONS: Our findings highlight an important aspect of myonectin in the pathophysiology of T2DM. They also show that myonectin has the potential to be a useful biomarker and therapeutic target in T2DM.

Key Words: Myonectin, Diabetes Mellitus, HbA1c, Insulin, Fasting blood sugar, HOMA-IR.

Introduction

Diabetes mellitus type 2 (T2DM) is a disease with a high prevalence and growing incidence rates worldwide. According to the International Diabetes Federation¹, a total of 425 million people is affected by diabetes mellitus, 50% of which are undiagnosed. A report from the World Health Organization² estimated that in Saudi Arabia, almost 7 million people are diagnosed with T2DM. Another 3 million of the total population are pre-diabetics, ranking the seventh-highest rate of diabetes in the world and the second in the Middle East. In Saudi Arabia, a systematic analytic study³ showed that in 1982, the prevalence of T2DM was only 2.5%, increasing up to 32.8% in 2015. It is estimated that the prevalence will reach 45.36% in 2030. A recent study⁴ reported a 34.6% prevalence of T2DM in the semi-urban Saudi population, particularly in the elderly population with comorbidities.

Insulin resistance is one of the pathophysiologic causes of the occurrence of T2DM⁵. Obesity increases the likelihood of insulin resistance by 80% because it increases visceral fat. As excess visceral fat accumulates in the abdominal viscera, the susceptibility of inflammation, cytokines production, and dysregulation of adipokines in the body increases, thus causing the impairment of insulin signaling⁶. Physical activity has been attributed to having a beneficial effect by increasing insulin sensitivity⁷. During exercise, skeletal muscles secrete myokines that offer and mediate a favorable effect for the body by reducing the inflammatory response. One of these myokines is myonectin, also known as CTRP15 (C1q/TNF-re-

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lated protein). It is homologous to adiponectin and is secreted from the myocytes of muscle fibers. Myonectin has been shown to promote the uptake of fatty acids by cultured hepatocytes and adipocytes and to decrease circulating levels of free fatty acids in mice. It is an important myokine that regulates metabolism via a cross-talk between skeletal muscle and metabolic components of the body, such as liver and adipose tissue. Myonectin concentrations have been correlated with insulin resistance, coronary artery disease, and metabolic syndrome. Thus, myonectin is a nutrient-sensing cytokine that may have an important role in diabetes and related disorders. In addition, myonectin could be a potential biomarker in predicting the development of pre-diabetes and diabetes. Although ample data are available, there is still a need to understand the involvement of myonectin in T2DM. Therefore, in this study, we aimed to investigate plasma myonectin in T2DM patients and its correlation with glycemic and lipid parameters.

Patients and Methods

This study was carried out in the Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, from August 22, 2021, to December 30, 2021. The Institutional Review Board approved the study. The sample size was calculated using the standard equation for two means. The values used were a confidence interval of 95%, a 5% width, a predictable power of 80%, a mean difference of 19.96, and a standard deviation of 15. The estimated sample size was 61 participants. A total of 73 Saudi adult females was recruited in the study, 40 of which were T2DM patients and 33 non-diabetic healthy females. Informed consent was obtained from all the participants.

The diabetic patients were diagnosed with T2DM according to the American Diabetes Association Guidelines and had had the syndrome for at least 12 months before the study’s start date. Patients with a pre-diabetic status and/or those who were pregnant were excluded. Additionally, diabetic patients suffering from diseases affecting the metabolic status of the body, such as thyroid disorders, acute infections, diabetic ketoacidosis, non-ketotic hyperosmolar coma, and nephrotic syndrome, were also excluded from the study.

A detailed history of each patient was recorded. It included questions about diet, exercise habits, smoking, any medications, and a history of hypertension and dyslipidemia. Anthropometric assessments, such as pulse and systolic and diastolic blood pressure, weight, height, BMI, and waist-hip ratio, were noted. Body composition analysis was performed by bioelectrical impedance analysis (BIA) using a commercially available Body Composition Analyzer (Type BC-418 MA, TANITA Corporation, Japan). Body composition analysis was performed in a fasting state in the morning with an empty bladder to secure uniformity in the analysis. The subject was requested to stand on the machine with wiped bare feet and the data were recorded. The parameters recorded were fat mass, fat percentage and distribution, and muscle mass.

Blood samples were taken after 10-12 hours overnight fast; the plasma was separated, and the aliquots were stored at −80°C. Blood samples were analyzed for clinical parameters such as total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar (FBS), insulin, and HbA1c by an automated analyzer. Plasma myonectin was analyzed by sandwich enzyme-linked immunosorbent assay kit (abx258690) following the manufacturer’s instructions (Abbexa Ltd, Cambridge Science Park, United Kingdom). Homeostasis model assessment of insulin resistance (HOMA-IR) was derived by the standard formula HOMA-IR = [FPI (mU/L) × FPG (mmol/L)]/22.517 and QUICKIE was used to calculate insulin sensitivity QUICKIE=1/log (FBS*FSI)\(^5\).

Statistical Analysis

Statistical Software for Social Sciences (SPSS v. 21, IBM Corp., Armonk, NY, USA) was used to analyze the data. Categorical and quantitative variables were analyzed by descriptive statistics (percentages, mean and standard deviation, standard error of means). Student’s \( t \)-test and Mann-Whitney test were used to analyze parametric and non-parametric variables respectively. Values of \( p < 0.05 \) were taken as statistical significance. Spearman correlations were computed to analyze the relationship of myonectin with clinical and anthropometric parameters.

Results

Characteristics of Study Participants

The mean age of the diabetic patients and non-diabetic healthy Saudi adult females was 55.58±0.979 and 49.97±1.312 (mean±SEM), respectively. The diabetic patients had a BMI of 34.07±0.853 com-
Myonectin and Type 2 Diabetes Mellitus

Myonectin and its Correlation with BMI, Lipid Profiles, Glucose and HOMA-IR

Plasma myonectin levels were analyzed by ELISA in diabetic (40) and non-diabetic (33) healthy subjects, as well as in patients with good glycemic control (GGC) and poor glycemic control (PGC). The error bars represent standards error of the mean. *Statistically significant differences and values of p<0.05 indicate statistical significance.

In diabetic patients, fasting blood sugar (9.20±0.614), HbA1c (8.46±0.308), and insulin (18.42±2.02) levels were significantly higher compared to the healthy non-diabetic control group (5.02±0.080, 5.30±0.051, 12.37±0.991, respectively) (Table II).

Table I. Demographics and anthropometric analysis.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Non-diabetic Mean ± SEM</th>
<th>Diabetic Mean ± SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.97 ± 1.312</td>
<td>55.58 ± 0.979</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.27 ± 1.093</td>
<td>155.20 ± 0.833</td>
<td>0.502</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.49 ± 2.606</td>
<td>82.00 ± 2.094</td>
<td>0.104</td>
</tr>
<tr>
<td>Waist</td>
<td>91.30 ± 11.26</td>
<td>100.73 ± 10.62</td>
<td>0.001</td>
</tr>
<tr>
<td>Hip</td>
<td>110.99 ± 12.71</td>
<td>117.73 ± 11.14</td>
<td>0.009</td>
</tr>
<tr>
<td>WHR</td>
<td>0.83 ± 0.10</td>
<td>0.85 ± 0.06</td>
<td>0.308</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.13 ± 1.005</td>
<td>34.07 ± 0.853</td>
<td>0.146</td>
</tr>
<tr>
<td>BMR (kcal)</td>
<td>1369 ± 28.796</td>
<td>1421 ± 23.478</td>
<td>0.167</td>
</tr>
<tr>
<td>Fat %</td>
<td>40.95 ± 1.314</td>
<td>43.31 ± 0.779</td>
<td>0.129</td>
</tr>
<tr>
<td>Fat mass (Kg)</td>
<td>31.50 ± 2.016</td>
<td>36.05 ± 1.524</td>
<td>0.077</td>
</tr>
<tr>
<td>FFM (Kg)</td>
<td>43.10 ± 1.258</td>
<td>45.15 ± 1.050</td>
<td>0.215</td>
</tr>
<tr>
<td>Visceral fat rating</td>
<td>10.09 ± 0.642</td>
<td>11.73 ± 0.424</td>
<td>0.038</td>
</tr>
<tr>
<td>Trunk: Fat %</td>
<td>38.11 ± 1.357</td>
<td>39.67 ± 0.895</td>
<td>0.344</td>
</tr>
<tr>
<td>Trunk: Fat mass</td>
<td>15.85 ± 0.914</td>
<td>17.39 ± 0.075</td>
<td>0.199</td>
</tr>
<tr>
<td>Trunk: FMM</td>
<td>24.75 ± 0.480</td>
<td>25.75 ± 0.376</td>
<td>0.107</td>
</tr>
<tr>
<td>Trunk: PMM</td>
<td>23.65 ± 0.457</td>
<td>24.62 ± 0.357</td>
<td>0.102</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; WHR: Waist hip ratio; BMR: Basal metabolic rate; FFM: Fat free mass; PMM: Predicted muscle mass.

pared to non-diabetic individuals (32.13±1.005), but the values were not statistically significant. There was no difference in waist-hip ratio between diabetic and non-diabetic participants (p>0.05). However, when measured individually, waist and hip measurements were significantly higher (p<0.05) in diabetics (Table I). Regarding body composition analysis, all parameters were non-significant except for the visceral fat rating, which was significantly higher in the diabetic group (11.73±0.424) compared to the non-diabetic healthy group (10.09±0.642) (Table I).

In diabetic patients, fasting blood sugar (9.20±0.614), HbA1c (8.46±0.308), and insulin (18.42±2.02) levels were significantly higher compared to the healthy non-diabetic control group (5.02±0.080, 5.30±0.051, 12.37±0.991, respectively) (Table II).

Myonectin and its Correlation with BMI, Lipid Profiles, Glucose and HOMA-IR

The circulating levels of myonectin in diabetic patients (n=40) were significantly decreased (40.90±4.13), (mean±SEM), compared to non-diabetic participants (n=33, 59.58±4.41, p<0.05, Figure 1). Myonectin levels of the control group had a median (IQR) of 60.22 (39.64), which was higher than that of the diabetic group (with a median (IQR) of 36.18 (27.62). The difference was statistically significant with a Z-value of -3.265, p<0.001 (Table III).

The diabetic patients were divided into having good glycemic parameters and poor glycemic parameters according to the American Diabetes Association criteria (7.5% and above indicate poor glycemic control). Diabetic patients with poor glycemic control had significantly decreased to non-diabetic individuals (32.13±1.005), but the values were not statistically significant. There was no difference in waist-hip ratio between diabetic and non-diabetic participants (p>0.05). However, when measured individually, waist and hip measurements were significantly higher (p<0.05) in diabetics (Table I). Regarding body composition analysis, all parameters were non-significant except for the visceral fat rating, which was significantly higher in the diabetic group (11.73±0.424) compared to the non-diabetic healthy group (10.09±0.642) (Table I).

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sed myonectin levels (n=24, 35.18±4.03 ng/ml) (±SEM), compared to non-diabetic individuals (n=33, 59.58±4.41, p<0.05, Figure 1). However, there was no significant difference in myonectin levels between patients with good glycemic control (n=16, 55.76±8.09), and non-diabetic participants (p>0.05). Myonectin correlation with triglycerides (rs=-0.264, p=0.024), HbA1c (rs=-0.406, p<0.0001), fasting blood sugar (rs=-0.366, p=0.001), and HOMA-IR (rs=-0.409, p=0.0001) were all negatively and significantly correlated. However, LDL (rs=0.198, p=0.094), HDL (rs=0.139, p=0.241), total cholesterol (rs=0.086, p=0.470), and BMI (rs=-0.102, p=0.391) were insignificant in their correlation with myonectin (Table IV).

Table II. Analysis of clinical parameters.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Non-diabetic Mean ± SEM</th>
<th>Diabetic Mean ± SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mmol/L)</td>
<td>5.02 ± 0.080</td>
<td>9.20 ± 0.614</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.30 ± 0.051</td>
<td>8.46 ± 0.308</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin (mIU/L)</td>
<td>12.37 ± 0.991</td>
<td>18.42 ± 2.02</td>
<td>0.01</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.75 ± 0.209</td>
<td>7.57 ± 1.110</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.18 ± 0.120</td>
<td>1.46 ± 0.089</td>
<td>0.065</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.08 ± 0.105</td>
<td>2.74 ± 0.136</td>
<td>0.055</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.44 ± 0.060</td>
<td>1.33 ± 0.074</td>
<td>0.219</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.01 ± 0.100</td>
<td>4.75 ± 0.147</td>
<td>0.156</td>
</tr>
</tbody>
</table>

FBS: Fasting blood sugar; HbA1c: hemoglobin A1c; HOMA-IR: Homeostasis model assessment of insulin resistance; TG: Triglycerides; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total Cholesterol.

Table III. Comparison of outcome variables between diabetic and non-diabetic groups.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Median (IQR)</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
<th>Median (IQR)</th>
<th>Non-Diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=33</td>
<td>n=33</td>
<td>n=40</td>
<td>n=40</td>
<td>p</td>
<td>Z</td>
</tr>
<tr>
<td>Myonectin ng/ml</td>
<td>60.22 (39.66)</td>
<td>36.184 (27.62)</td>
<td>5.92</td>
<td>29.64</td>
<td>-3.265</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table IV. Correlation of Myonectin with glycemic and lipid parameters.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>R</th>
<th>p</th>
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<tr>
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<td>0.001</td>
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FBS: Fasting blood sugar; HbA1c: hemoglobin A1c; HOMA-IR: Homeostasis model assessment of insulin resistance; TG: Triglycerides; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total Cholesterol.

Discussion

In this study, we demonstrated reduced plasma myonectin levels in T2DM patients compared to the non-diabetic healthy Saudi adult female subjects. Plasma myonectin levels were significantly negatively correlated with waist, fasting blood sugar, triglycerides, HbA1c, insulin, and HOMA-IR index. Similar findings had been reported by Li et al, where circulating myonectin levels were decreased in diabetic patients compared to the control subjects, and were significantly negatively correlated with BMI, lipid, and glycemic parameters (such as total cholesterol, LDL, triglyceride, HbA1c, fasting insulin, and HOMA-IR index). In another study, myonectin levels were significantly decreased in diabetic patients with peripheral artery disease (PAD) compared to non-diabetic PAD patients and were negatively correlated with HbA1c. Patients with polycystic ovary syndrome also had reduced myonectin le-
vels that were inversely correlated with HbA1c\textsuperscript{18,19}. Thus, myonectin levels are influenced by different metabolic and pathological conditions.

There are studies\textsuperscript{20} where higher myonectin levels have been reported in T2DM patients, particularly significantly higher in T2DM patients than pre-diabetic subjects, indicating its role in the progressive increase of a diabetic state. In this study\textsuperscript{20}, plasma myonectin levels were positively correlated with glycemic parameters such as fasting blood sugar, HbA1c, HOMA-IR, but negatively correlated with insulin sensitivity index. In our study, myonectin levels were negatively correlated with glycemic indices. The discrepancies observed in different studies in literature can be linked to the limitations of each study, patient diabetic status, and the use of different ELISA kits to measure myonectin levels. These findings suggest that myonectin signaling has a role in the regulation of lipid and glycemic parameters, and its levels are affected under different pathological conditions. Thus, changes in myonectin levels have the potential to be a useful marker for insulin sensitivity/resistance status in T2DM.

We also analyzed myonectin levels in our T2DM patients who had good and poor glycemic parameters. Myonectin levels were significantly decreased in patients having poor glycemic control compared to the non-diabetic healthy subjects. However, no difference was noted between T2DM patients with good glycemic parameters and healthy individuals. Thus, myonectin has a correlation with glycemic indices in diabetic patients. Diabetes is often associated with different comorbidities. T2DM patients with diabetic nephropathy exhibited lower serum myonectin concentrations when compared to healthy control subjects\textsuperscript{21}. Furthermore, the categorization of patients according to the albumin-to-creatinine ratio showed that myonectin levels were significantly decreased in patients who had macroalbuminuria than in those in the microalbuminuria and normoalbuminuria group. Thus, myonectin was associated with diabetic comorbidities such as macrovascular complications. The authors suggested a correlation between serum myonectin and a decreased risk of diabetic nephropathy.

One of the risk factors for coronary artery disease (CAD) is type 2 diabetes mellitus\textsuperscript{22,23}. It had been reported\textsuperscript{24} earlier that CAD patients exhibited reduced levels of CTRP15 or myonectin compared to the non-CAD group and that the myonectin levels were negatively correlated with age and diabetes in these patients. This correlation was significant in patients with three-vessel lesions of CAD. In our study, myonectin was not correlated with age but with the severity of disease in our diabetic patients. The authors proposed myonectin as a useful diagnostic biomarker for CAD. In the above-mentioned study, myonectin was positively correlated with triglycerides, while in our study triglycerides were negatively correlated. The difference in correlation of triglycerides and myonectin may have been due to the different study populations and comorbidities such as CAD in diabetic patients.

Changes in myonectin levels have the potential to be a useful marker for insulin sensitivity status in T2DM. Myonectin holds the potential to be a novel biomarker for diagnosis and can be a therapeutic target for T2DM and its complications.

**Limitations**

As a limitation of this study, the small sample size and inclusion of only female participants cannot be representative of the entire population. It would be interesting to investigate myonectin levels in T2DM patients of different ages and genders at different stages of the disease.

**Conclusions**

Our study demonstrates reduced myonectin levels in T2DM patients with poor glycemic control and an inverse association with glycemic indices. Thus, myonectin may be a useful biomarker and may have a role in the pathophysiology of T2DM.

**Conflicts of Interest**

The authors declare no conflict of interest.

**Ethics Approval**

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia (protocol code E-21-6151).

**Informed Consent**

Informed consent was obtained from all subjects who participated in the study.

**Funding**

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**Availability of Data and Materials**
The data used and analyzed during the current study are available from the corresponding authors upon reasonable request.

**Authors’ Contributions**
KAA, SSH and MI designed the study, supervised, reviewed and edited data, performed the statistical analysis and wrote and edited the manuscript. AOA, MSA, MAA, AAA, FSA, and BKA contributed to data collection, statistical analysis, writing, editing and formatting of the manuscript.

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