Correlation between Lower Extremity Arterial Disease and Skeletal Muscle Mass in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To evaluate skeletal muscle mass in patients with Type 2 Diabetes Mellitus (T2DM) and concomitant Lower Extremity Arterial Disease (LEAD) and its significance in macro vascular diseases.

Methods: A total of 112 patients with T2DM were divided into the T2DM group (group A) and T2DM+LEAD group (Group B). Hepatic function, renal function, uric acid, blood glucose, and glycated hemoglobin (HbA1C) were measured. Dual-energy X-ray absorptiometry was used to measure the visceral fat area and skeletal Muscle Mass Index (SMI).

Results: The waist-to-hip ratio, uric acid, and body fat percentage were significantly higher in group B than in group A, whereas SMI was significantly lower in group B than in group A. There were no significant differences in albumin, creatinine, fasting blood glucose, HbA1C, and blood lipids. Uric acid, SMI, abdominal obesity, and body fat percentage were positively correlated with T2DM and concomitant LEAD, while SMI and body fat percentage were highly correlated with LEAD. Logistic regression analyses suggested that SMI is an independent risk factor for LEAD in DM (OR= 0.693; 95% CI: 0.517–0.929).

Conclusions: Skeletal muscle mass is reduced in patients with T2DM and concomitant peripheral vascular disease and is an independent risk factor for LEAD.

Keywords: Type 2 diabetes mellitus; Lower extremity arterial disease; Skeletal muscle mass

INTRODUCTION

Increasing age is associated with a loss of skeletal muscle mass and progressive deterioration in muscle strength, power, and endurance. This reduces the skeletal muscle coordination capacity and quality, which can hinder elderly individuals from completing simple daily tasks. In severe cases, the gait and body balance can also be impacted, and affected individuals are prone to falling [1].

Lower Extremity Arterial Disease (LEAD) is also an age-related disease that can lead to decreased blood flow to the lower extremities. It can indirectly affect blood supply to the muscle, leading to mobility dysfunction in the lower extremities and reduced skeletal muscle mass [2]. LEAD is a common complication in patients with Diabetes Mellitus (DM) and is the major cause of disability and mortality in Type 2 Diabetes Mellitus (T2DM) [3].

In this study, the correlation between skeletal muscle mass and the development of LEAD was investigated in patients with T2DM by analyzing characteristic changes in skeletal muscle mass in patients with T2DM and concomitant LEAD.
PATIENTS AND METHODS

Patients

Between August 2017 and May 2018, 112 patients with T2DM admitted to the Department of Endocrinology in The Second Hospital of Shandong University were selected, including 62 males and 50 females, with a mean age of 52.47 ± 13.59 years. The duration of DM was 8.66 ± 6.03 years. All patients met the following inclusion criteria: i) Patients satisfied the diagnostic criteria for DM and LEAD in the “2010 China Guidelines for the Prevention and Treatment of Diabetes Mellitus” [4] formulated by the Chinese Diabetes Society; ii) All patients had lower extremity weakness, rest pain, chills, intermittent claudication, feeling of pain, coldness, or numbness in the tips of the toes or back of the feet, and weakened or no pulse in the dorsalis pedis artery, posterior tibial artery, or popliteal artery; iii) Presence of LEAD indicated by Doppler ultrasonography, manifested as thickening, roughness, and thrombosis in the vascular endothelium, atherosclerotic plaque formation, blood flow reduction, and a narrowing of the inner vessel diameter; and iv) Ankle-Brachial Index (ABI) of less than 0.9. Based on the inclusion criteria, the patients were divided into the T2DM-alone group (group A, N=52) and T2DM+LEAD group (group B, N=60). Exclusion criteria were as follows: i) Other types of DM; ii) Presence of acute diabetic complications and severe neuropathy; iii) Presence of severe diabetic foot ulcer; iv) Hepatic function impairment, renal function impairment, and presence of severe chronic obstructive pulmonary disease; v) Severe arrhythmia and acute cardiac insufficiency; vi) Autoimmune diseases; vii) History of cancer or recently diagnosed tumors; viii) Pregnancy; and ix) History of severe mental illness. This study was approved by the Ethics Committee of The Second Hospital of Shandong University, and written informed consent form was obtained from all patients.

Study methods

Height, weight, waist circumference, hip circumference, blood pressure, and other parameters were measured by specially assigned personnel. The Body Mass Index (BMI) was calculated according to the formula BMI=weight/height (kg/m²). Venous blood was drawn after 8–10 hours of fasting and the serum was extracted. Biochemical parameters, including Total Cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C), Low Density Lipoprotein-Cholesterol (LDL-C), Fasting Blood Glucose (FBG), post Prandial Blood Glucose (PBG), uric acid, and Creatinine (Cr), were measured using an automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA). FBG was measured using the hexokinase method, and HbA1C was measured by high performance liquid chromatography. The Hologic Discovery Wi (S/N88803) dual-energy X-ray absorptiometry system was used to measure various parameters, such as the visceral fat area and Skeletal Muscle Mass Index (SMI). A Vascular Doppler (Huntleigh Healthcare, Cardiff, UK) was used to measure the blood pressure of the bilateral forearms in patients adopting supine positions, of which the highest brachial artery pressure was used. The ankle artery pressure was taken from the highest values of the systolic blood pressures of the bilateral dorsalis pedis artery and posterior tibial artery (ABI: Ankle Artery Pressure/Brachial Artery Pressure). Color Doppler ultrasound system (GE-LOGIQ-E9) was used to perform a vascular ultrasound of the lower extremities. The inner vessel diameter, peak blood flow velocity, intima-media thickness, and blood flow spectrum were measured for the bilateral femoral artery, popliteal artery, tibial artery and dorsalis pedis artery of the patients.

Statistical analysis

All data were subjected to statistical analyses using SPSS 19.0. Quantitative data are expressed as means ± Standard Deviation (X ± SD). The K–S test was used to test the normality of all quantitative data. The t-test was used for pairwise comparisons. Quantitative data that did not follow a normal distribution were analyzed using the rank sum test. Differences with p<0.05 were considered statistically significant.

RESULTS

Comparison of baseline characteristics between groups

After applying the inclusion and exclusion criteria, 112 patients with T2DM were included in the study. There were no significant differences in age, sex, systolic blood pressure, and diastolic blood pressure, duration of DM, and BMI between the two groups (Table 1). There were statistically significant differences in the uric acid level (t=2.168, p=0.034), SMI (t=2.330, p=0.026), Waist-to-Hip Ratio (WHR) (t=0.264, p=0.09), and body fat percentage (t=-0.381, p=0.017) between the T2DM (A) and T2DM+LEAD (B) groups. Uric acid (277.94 ± 85.06), WHR [0.94 (0.89, 0.98)], and body fat percentage (29.30 (25.90, 33.80)) in group B were significantly higher than uric acid (231.78 ± 82.37), WHR [0.91 (0.88, 0.93)], and body fat percentage (34.30 (28.88, 39.50)) in group A. In contrast, the SMI of group B (6.09 ± 0.96) was significantly lower than that of group A (6.92 ± 1.22). There were no statistically significant differences in albumin, creatinine, FBG, HbA1C, TG, TC, HDL-C, and LDL-C.

Table 1: Baseline characteristics of the two groups of patients.

<table>
<thead>
<tr>
<th></th>
<th>Group A (N=52)</th>
<th>Group B (N=60)</th>
<th>t/z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.58 ± 6.55</td>
<td>58.60 ± 5.43</td>
<td>0.012</td>
<td>0.991</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.27 ± 3.92</td>
<td>27.35 ± 4.25</td>
<td>0.09</td>
<td>0.929</td>
</tr>
</tbody>
</table>
Table 2: Results of Spearman rank correlation analysis.

<table>
<thead>
<tr>
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<th>r</th>
<th>p</th>
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<tbody>
<tr>
<td>Uric acid (µmol/L)</td>
<td>0.244</td>
<td>0.056</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>0.285</td>
<td>0.016</td>
</tr>
<tr>
<td>SMI</td>
<td>0.367</td>
<td>0.002</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>0.119</td>
<td>0.325</td>
</tr>
</tbody>
</table>

Notes: *p< 0.05 denotes statistical significance

Analysis of factors correlated with T2DM and LEAD

A Spearman correlation analysis showed that uric acid (r=0.244, p=0.056), SMI (r=0.367, p=0.002), abdominal obesity (r=0.119, p=0.325), and body fat percentage (r=0.285, p=0.016) were positively correlated with T2DM and concomitant LEAD, while SMI (r=0.367, p=0.002) and body fat percentage were closely related to macro vascular disease (Table 2).

Logistic regression analysis of risk factors for T2DM and LEAD

Logistic regression analysis was performed using DM-associated LEAD as the dependent variable and the parameters with statistical significance in LEAD as independent variables. SMI was an independent risk factor for LEAD in DM (OR=0.693; p=0.016; 95% CI: 0.517–0.929) (Table 3).

DISCUSSION

LEAD is the primary cause of lower extremity amputations in patients with DM, and it has a morbidity rate that is 20 times higher in diabetics than in non-diabetics. LEAD is present in 8.0% of patients at the time of DM diagnosis and is an important factor leading to disability and mortality in patients with DM [5]. The fundamental pathological change in LEAD in DM is atherosclerosis of peripheral blood vessels; its
pathogenesis may be related to genetic factors, chronic inflammation, and lipid metabolism [6].

Table 3: Summary of logistic regression analysis.

<table>
<thead>
<tr>
<th>Group B</th>
<th>OR</th>
<th>p-value</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-adjusted SMI</td>
<td>0.417</td>
<td>0.016</td>
<td>1.082</td>
<td>2.126</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.007</td>
<td>0.049</td>
<td>1</td>
<td>1.014</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>0.88</td>
<td>0.259</td>
<td>0.937</td>
<td>1.271</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>0.426</td>
<td>0.592</td>
<td>0.323</td>
<td>7.263</td>
</tr>
<tr>
<td>Constant</td>
<td>-15.226</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: 'p< 0.05 denotes statistical significance

In this study, patients with DM and concomitant LEAD had significantly elevated LDL-C, serum uric acid levels, and body fat percentages compared with those of patients with DM alone. Uric acid has received increasing attention owing to its role as a risk factor for macro vascular diseases. A prospective cohort study found that an elevated uric acid level is independently associated with the onset of arteriosclerosis [7]. It is possible that the elevated uric acid leads to increased platelet adhesion and oxygen free radical generation. Long-term uric acid elevation can damage vascular endothelial cells, ultimately leading to the formation of atherosclerotic plaque [8]. Lipid metabolism disorders are also an important pathogenic factor for LEAD [9]. Under a hyperglycemic state, the glycosylation of LDL-C renders it prone to phagocytosis by macrophages. The glycosylation and cross-linking of collagen also lead to an increase in LDL-C deposition in the matrix [10]. In the aforementioned Italian study, the LDL-C level was significantly higher in patients with LEAD than in the T2DM-alone group, suggesting that LDL-C plays a decisive role in the pathogenesis of LEAD [11]. Therefore, the proper control of the serum uric acid and LDL-C levels in patients with LEAD will be of great significance in delaying the development of LEAD in patients with DM.

WHR and BMI are common clinical parameters that reflect the degree of obesity. From the perspective of fat distribution, BMI reflects the overall fat percentage in the whole body, while WHR reflects the local fat percentage in the abdomen [12]. Studies have shown that WHR and BMI are correlated with vascular complications in patients with T2DM [13]. There are significant differences in waist circumferences and hip circumferences among populations of different ages, races, and sexes. Nonetheless, their ratio is relatively stable and is an effective parameter for determining the degree of obesity. WHR is closely related to the level of visceral fat. A high level of visceral fat can cause adipocytes to release a variety of cytokines, such as IL-1 and TNF-α, and it is an important factor affecting the development of atherosclerosis [14]. Researchers believe that WHR is a strong predictive indicator for cardiovascular and cerebrovascular diseases in patients with DM [15]. DM is also considered a state of chronic inflammation. The amount of visceral fat in patients with abdominal obesity is significantly elevated, which will significantly increase insulin resistance and the levels of chronic inflammatory factors, ultimately leading to increased morbidity of vascular diseases [16]. In the present study, there was a more substantial increase in the WHR than in BMI in the LEAD group, demonstrating that abdominal obesity represented by WHR plays a more crucial role in DM-associated LEAD.

Furthermore, SMI was closely correlated with LEAD. Skeletal muscle mass accounts for approximately 40% of the human body weight and is known as the largest secretory organ in the human body. Skeletal muscle can express, synthesize, and secrete various biological signaling molecules [17], including interleukin-1, interleukin-6, irisin, FGF-21, leptin, and adiponectin, which can regulate skeletal muscle function and its associated microenvironment in a paracrine and/or autocrine manner. These molecules can even regulate the function of distant body organs by entering the blood circulation. Reduced skeletal muscle mass is believed to be a novel type of complication in patients with DM and is associated with increased hospitalization rates, cardiovascular events, and mortality [18]. There are relatively few studies of skeletal muscle mass in patients with DM and concomitant LEAD. A study has shown that [19] the incidence of sarcopenia in male patients with LEAD is significantly higher than that of normal men of the same age, which may be explained by multiple factors, associated with LEAD, including lower limb ischemia, reduced skeletal muscle capillary density, and hindered mobility. For patients with DM, vascular factors are involving among the mechanisms underlying the development of skeletal muscle diseases [20]. In particular, a thickening of the vascular basement membrane, non-enzymatic glycosylation, and decreased nascent blood vessels all contribute to the development of skeletal muscle diseases. Under a longterm hyperglycemic state, non-enzymatic protein glycosylation causes the thickening of the skeletal muscle capillary basement membrane, increases the distance of exchange between blood...
and tissues, hinders oxygen diffusion and the exchange of metabolites, and aggravates ischemia and hypoxia in skeletal muscles, ultimately leading to nutrition and metabolic disorders of the muscle tissues [21]. The results of the present study indicated that SMI is significantly lower in patients with T2DM and concomitant LEAD than in patients with T2DM alone, consistent with previous studies. A logistic regression analysis showed that SMI is an independent risk factor for LEAD. It is possible that the long-term hyperglycemic state causes a metabolic disorder in the skeletal muscle, leading to many reactions, such as abnormal autophagy, enhanced apoptosis, reduced secretion of growth factors and adiponectin, mitochondrial dysfunction, and oxidative stress. The exocrine function of skeletal muscle is also severely impacted [22]. Changes in the microenvironment may lead to peripheral vascular endothelial dysfunction, thereby promoting atherosclerosis [23]. These changes further demonstrate the significance of skeletal muscle function in LEAD. The study focuses on clinical parameters and does not assess inflammatory factors, oxidative stress, and other parameters. The underlying pathogenic mechanism may be further investigated in subsequent studies.

In conclusion, in patients with T2DM and concomitant LEAD, uric acid and WHR are significantly elevated and SMI is significantly reduced. SMI and WHR are independent factors contributing to the pathogenesis of LEAD. Future studies should focus on clinical analyses of skeletal muscle mass and peripheral vascular disease and relevant investigations of the underlying mechanisms.

COMPETING INTERESTS
The authors declare that they have no competing interests.

FUNDING
This work was funded by National Natural Science Foundation of China (81670753 and 81800722), Shandong Provincial Key Research and Development Program (2018GSF118108).

REFERENCES