Effects of exercise on sex hormones and glucose metabolism among male patients with type-2 diabetes mellitus

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Abstract: Objective: This study aims to reveal the influence of regular physical activity on sex hormones and glucose regulation in males with type-2 diabetes mellitus (T2DM). Methods: We enrolled 159 males with T2DM that were divided into two groups: physical activity group (n=124) and no physical activity group (n=35). The general indicators included weight, BMI, blood pressure and waist circumference. The biochemical indicators (renal function, blood glucose, insulin and glycosylated hemoglobin) and sex hormone index (total testosterone [TT], luteinizing hormone, follicle stimulating hormone, estradiol, and sex hormones binding globulin) were also determined. Furthermore, free testosterone (FT), bioactive testosterone (BT) and the homeostasis model assessment-insulin resistance index (HOMA-IR) were also calculated. The differences in general indicators and sex hormone indicators between groups were compared using different exercise times and body mass indices. Results: The levels of TT and BT were significantly higher in the activity group (P < 0.05). Furthermore, the HOMA-IR of T2DM patients differed across both groups (P < 0.05). Patients with a daily activity time of 0.5-1.0 hour had a lower HOMA-IR index, and physical activity time influenced the HOMA-IR of these patients. In addition, the FT and BT values differed between these two groups (P < 0.05), with patients with a daily activity time of less than 30 minutes showing higher levels of testosterone. TT levels were also higher in patients with normal BMI (P < 0.01). Conclusion: Hypogonadism is common amongst T2DM males. Physical activity can improve the testosterone levels of males with T2DM. The levels of testosterone are higher in individuals with normal BMI vs. obese individuals.

Keywords: Exercise, type-2 diabetes mellitus, sex hormones, metabolism

Introduction

Diabetes mellitus (DM) encompasses a range of metabolic diseases characterized by hyperglycemia and glucose intolerance [1]. In parallel to the worldwide increase in incidence and prevalence of DM, this has become an epidemic in China [2]. DM can lead to a variety of acute and chronic complications, resulting in a huge economic burden on society [3]. A study revealed that gonadal dysfunction was more common among men with type-2 diabetes mellitus (T2DM) as patients had decreased serum testosterone levels, and some patients had clinical symptoms of decreased libido and reduced sexual function, which had a further negative effect on the lives of these patients [4]. This might be due to diet-induced hypothalamic inflammatory reactions, which reduce the secretion of gonadotropin-releasing hormones [5]. Since a variety of metabolic abnormalities can induce male gonadal dysfunction [6, 7], the present study focused on finding effective interventions to treat gonadal function in diabetic patients.

Physical activity or exercise is an integral part of lifestyle interventions for the prevention or delay of DM [8]. The 2018 Standards in Medical Care of Diabetes issued by the American Diabetes Association (ADA) recommend that adult patients with DM should engage in moderate intensity of aerobic activity (50-70% of maximum heart rate) for 150 minutes per week,
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for at least three days a week, and should avoid two consecutive days of inactivity, in order to decrease insulin resistance [9]. Physical activity can control obesity, help in losing weight [10], increase bone density and muscle strength [11], improve body reactivity, and improve insulin sensitivity [12]. On the other hand, obesity [13] and insulin resistance [14] are also known risk factors for gonadal dysfunction. A study that evaluated the effects of an 8-week aerobic exercise program on obese men with T2DM revealed that physical activity can improve physical capacity and quality of life [15]. Thus, the present study aimed to determine whether physical activity can improve sex hormone levels in male patients with T2DM. Furthermore, the effects of regular physical activity on sex hormones and glucose metabolism in men with T2DM was investigated.

Methods

Subjects

A total of 1,107 male patients with T2DM, who were hospitalized between January 2015 and June 2018 in our institute, were eligible for inclusion. All patients conformed to the 1999 World Health Organization (WHO) Diabetes Diagnostic criteria [16].

Exclusion criteria: (1) patients with liver or renal insufficiency; (2) patients with decreased cardiac function; (3) patients with acute diabetes; (4) patients with diseases of sex glands, such as testicular dysfunction and primary male gonadal dysfunction; (5) patients with autoimmune and infectious diseases; (6) patients with hypertension and/or diuretics, or high blood pressure (≥ 40/90 mmHg); (7) patients with a history of rehabilitation sports; (8) patients with contraindications for physical activity; (9) patients with concomitant administration of testosterone therapy. Finally, 325 patients with liver and kidney dysfunction, 11 patients with cardiac dysfunction, 11 patients with cardiac dysfunction, 156 patients with acute complications of DM, eight patients with gonadal disease, 143 patients with infectious or immune diseases, 260 patients with poor control of hypertension or that used diuretics, 34 patients with a history of rehabilitation, and 11 patients who received testosterone replacement therapy were excluded. A total of 159 patients were included, and their age ranged within 28-78 years old. All patients provided a signed informed consent.

General Indices

Waist circumference was horizontally measured midway between the lowest rib and iliac crest. Height, body mass index (BMI), body weight and blood pressure were also assessed.

Physical activity history

Patients were inquired about regular exercise through a questionnaire, which mentioned about their daily physical activity, including physical activity time, type of physical activity, and so on. The most common physical activity among the included patients was walking, followed by light and moderate aerobic activity, such as jogging, popular calisthenics and swimming. The physical activity history of all patients was at least one year.

Blood indices

Blood was collected from 6 am to 7 am after overnight fasting for 8-10 hours. Fasting blood glucose (FBG), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), blood urea nitrogen (BUN), serum creatinine (Cr), and sex hormone (total testosterone [TT], luteinizing [LH], follicle stimulating hormone [FSH], estradiol [E2], and sex hormone binding globulin [SHBG]) levels were measured. The post prandial glucose levels were estimated after two hours of intake of anhydrous glucose (75 g in 200 mL of water). The levels of free testosterone (FT) and bioactive testosterone (BT) (http://www.issam.ch/freetesto.ht) were calculated using the software by measuring the serum SHBG, testosterone and serum albumin levels. Biochemical indicators were detected using a Swiss Roche C8000 biochemical analyzer. The HbA1c assay was performed with a US Bole D10 glycated hemoglobin analyzer, and assay used chromatography. The hormonal correlation was detected using a Swiss Roche E601 automatic electrochemiluminescence analyzer. All test kits were equipped with the corresponding instrument kit. HOMA-IR was calculated as follows: fasting blood glucose level (mmol/L) × fasting insulin level (mIU/L)/22.5.

Grouping methods

Depending on the routine physical activity, patients were sub-grouped according to physical (n=124) and non-physical activity (n=35).
The two groups were compared for age, BMI, abdominal circumference, blood glucose, HbA₁c, blood pressure and renal function. No significant differences in these parameters were observed between these groups \( (P > 0.05, \text{Table 1}) \).

### Results

#### Effect of physical activity on glucose metabolism in male patients with T2DM

Compared with the non-physical activity group, TT and BT levels significantly increased \( (P < 0.05) \). However, no significant difference was observed among FT, LH, FSH, E2 and SHBG levels \( (P > 0.05, \text{Table 2}) \).

#### Effect of different physical activity times on glucose metabolism in male patients with T2DM

No significant differences in age, BMI, blood pressure, renal function, blood glucose and HbA₁c levels \( (P > 0.05) \) were observed between these groups. However, there were statistical differences between the HOMA-IR groups \( (P < 0.05, \text{Table 3}) \). Furthermore, there was a signifi-
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Table 3. Effect of different physical activity times on glucose metabolism in male patients with T2DM

<table>
<thead>
<tr>
<th>Group</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>χ²/F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>51</td>
<td>47</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.67±9.41</td>
<td>51.73±11.25</td>
<td>51.02±12.44</td>
<td>51.64±10.14</td>
<td>0.420</td>
<td>0.739</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.89</td>
<td>25.69</td>
<td>25.36</td>
<td>24.11</td>
<td>3.465</td>
<td>0.325</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>90</td>
<td>90</td>
<td>91</td>
<td>89</td>
<td>1.560</td>
<td>0.669</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134</td>
<td>126</td>
<td>124</td>
<td>130</td>
<td>3.465</td>
<td>0.325</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84</td>
<td>80</td>
<td>80</td>
<td>79</td>
<td>0.232</td>
<td>0.972</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>5.34</td>
<td>4.94</td>
<td>5.20</td>
<td>5.22</td>
<td>0.134</td>
<td>0.988</td>
</tr>
<tr>
<td>Cr (µmol/L)</td>
<td>26.89</td>
<td>25.69</td>
<td>25.36</td>
<td>24.11</td>
<td>5.089</td>
<td>0.165</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.53±2.07</td>
<td>9.77±2.48</td>
<td>9.78±2.18</td>
<td>10.04±2.57</td>
<td>0.100</td>
<td>0.960</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>8.06</td>
<td>7.91</td>
<td>8.25</td>
<td>8.50</td>
<td>1.738</td>
<td>0.325</td>
</tr>
<tr>
<td>PBG (mmol/L)</td>
<td>16.51±2.31</td>
<td>15.79±3.94</td>
<td>16.66±4.08</td>
<td>16.22±4.10</td>
<td>0.433</td>
<td>0.730</td>
</tr>
<tr>
<td>Data: mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: urea nitrogen; Cr: creatinine; HbA1c, glycated hemoglobin; FBG: fasting blood-glucose; PBG: postprandial blood glucose; HOMA-IR: homeostasis model assessment, insulin resistance index.</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table 4. Effect of different physical activity times on sex hormone levels in male patients with T2DM

<table>
<thead>
<tr>
<th>Group</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>χ²/F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>51</td>
<td>47</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT (nmol/L)</td>
<td>15.26</td>
<td>14.16</td>
<td>12.50</td>
<td>13.18</td>
<td>6.467</td>
<td>0.091</td>
</tr>
<tr>
<td>FT</td>
<td>0.39</td>
<td>0.30</td>
<td>0.27</td>
<td>0.29</td>
<td>0.134</td>
<td>0.988</td>
</tr>
<tr>
<td>BT</td>
<td>8.86</td>
<td>7.04</td>
<td>5.87</td>
<td>6.47</td>
<td>16.198</td>
<td>0.001</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>6.53</td>
<td>6.09</td>
<td>5.48</td>
<td>5.18</td>
<td>0.614</td>
<td>0.893</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>5.95</td>
<td>4.83</td>
<td>6.16</td>
<td>7.15</td>
<td>2.037</td>
<td>0.565</td>
</tr>
<tr>
<td>E2 (pmol/L)</td>
<td>92.50</td>
<td>101.10</td>
<td>87.69</td>
<td>86.69</td>
<td>5.660</td>
<td>0.129</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>24.90</td>
<td>25.33</td>
<td>23.61</td>
<td>31.03</td>
<td>2.027</td>
<td>0.567</td>
</tr>
<tr>
<td>Data: mean ± SD or median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin.</td>
<td></td>
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</tr>
</tbody>
</table>

Discussion

Male gonadal dysfunction is common during T2DM [17]. The incidence of this dysfunction among DM patients influences the quality of life of afflicted patients [18]. Thus, the early identification of dysfunction and effective measures of intervention can improve the quality of life of these patients. At present, the treatment of male gonadal dysfunctions remains limited, and testosterone substitution is one of the intervention strategies [19]. However, testosterone replacement treatment should be preceded by a prior examination of prostate cancer, and the risks of adverse effects of testosterone should be evaluated before initiating the treatment [20]. At present, large sample size studies are still needed to clarify the benefits and risks of testosterone substitution [21]. Studies in obese mice have revealed that long-term moderate-intensity physical activity can improve the negative effects of obesity on sexual development, and increase testosterone levels in mice [22]. A meta-analysis revealed that aerobic training...
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Table 5. Sex hormone levels in T2DM patients with different BMIs in the physical activity group

<table>
<thead>
<tr>
<th>Group</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>χ²/F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>58</td>
<td>39</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT (nmol/L)</td>
<td>14.73</td>
<td>13.40</td>
<td>12.32</td>
<td>9.556</td>
<td>0.008</td>
</tr>
<tr>
<td>FT</td>
<td>0.30</td>
<td>0.31</td>
<td>0.29</td>
<td>0.586</td>
<td>0.746</td>
</tr>
<tr>
<td>BT</td>
<td>6.59</td>
<td>7.05</td>
<td>7.04</td>
<td>0.310</td>
<td>0.856</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>6.57</td>
<td>5.63</td>
<td>4.24</td>
<td>13.321</td>
<td>0.001</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>6.55</td>
<td>5.54</td>
<td>4.59</td>
<td>5.379</td>
<td>0.068</td>
</tr>
<tr>
<td>E2 (pmol/L)</td>
<td>91.44±31.73</td>
<td>88.16±38.21</td>
<td>107.79±42.64</td>
<td>3.749</td>
<td>0.026</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>31.03</td>
<td>23.31</td>
<td>20.06</td>
<td>21.740</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data: mean ± SD or median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin.

and interval training can improve basal testosterone levels [23].

Therefore, the investigators attempted to observe the effect of physical activity on testosterone levels among male patients with T2DM. A total of 159 male patients with T2DM were investigated, which included 124 patients who engaged in regular physical activity and 35 patients who did not do any physical activity. It was found that the levels of TT and BT were significantly higher in patients who engaged in physical activity for a longer period of time. Furthermore, FT and BT levels were higher in patients with less than 30 minutes of daily physical activity vs. other groups. Thus, physical activity increases testosterone levels [24]. The proposed mechanism may be as follows: physical activity stimulates the sympathetic system, and the secretion of gonads is associated with the sympathetic nerves [25]. That is, sympathetic stimulation occurs with physical activity, and leads to the increase in gonadal hormone secretion [26]. At the same time, testosterone stimulates the synthesis of protein in the body [27], which leads to muscle hypertrophy and the improvement of motor ability [28].

In the present study, it was found that according to the length of different physical activity times, male patients with T2DM had significant differences in HOMA-IR levels. These levels were lower among those who did physical activity for 30-60 minutes daily, indicating that moderate physical activity can improve insulin resistance. Researchers, such as Kim [29], also reported similar results. That is, six weeks of combined exercise was effective in improving fitness and HOMA-IR in T2DM patients. Another study also concluded that decreased testosterone levels were closely correlated with insulin resistance and hyperglycemia [30]. The skeletal muscle is an important site of insulin resistance manifestations [31], muscle cell mitochondrial dysfunction, intracellular glucose and ceramide accumulation, as well as excessive reactive oxygen generation and other damages to insulin cascade signals [32]. Physical activity can enhance the synthesis and oxidation ability of muscle cell mitochondria [33], adjust the fusion and fission of mitochondria [34], and increase the insulin-mediated glucose intake of skeletal muscles [35], thereby improving insulin resistance.

The present study also revealed that T2DM male patients with a BMI of < 25 kg/m² in the physical activity group had significantly higher levels of TT vs. overweight patients. Estradiol levels also increased in patients with a high BMI, and this is consistent with previous studies, in which testosterone levels were shown to significantly decrease in obese patients [36]. First, obesity results in the dysfunction of the hypothalamus-pituitary-gonadal axis [37]. Second, obesity causes the accumulation of white fat in the body [38]. These fat cells produce excessive aromatic enzymes, which result in the conversion of testosterone into estradiol, and the further increase in estradiol can inhibit the function of the gonadal axis, and reduce the synthesis and secretion of testosterone [39]. Third, leptin levels are altered among obese patients [40]. Leptin influences the release of gonadotropin-releasing hormones (GnRh) from the hypothalamus, which affects the synthesis of testosterone and decreases androgen secretion [41]. In addition, the present results revealed that serum SHBG levels decreased in obese patients. It has been proposed that hyperinsulinemia and insulin resis-
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tance inhibit the formation of SHBG [42]. Thus, it can be assumed that physical activity improves gonadal function by reducing weight, increasing insulin sensitivity, and promoting the synthesis and secretion of testosterone and SHBG levels.

In the present study, no positive effects in physical activity on blood glucose or glycated hemoglobin were observed in T2DM patients, which differed from the findings of Liu et al. [43]. The small sample size and use of hypoglycemic drugs may have contributed to these discrepancies. The present study was a single-center study with 159 patients, and the effects on gonadal dysfunction were only dependent on TT levels, without the consideration of clinical symptoms. The limitations of the present study include the following: the patients were mainly engaged in aerobic physical activity alone, and it was not determined whether other forms of physical activity have any distinct influence on hormone levels; the glucose metabolism was not monitored. Studies with a larger sample size can help to better analyze the association among physical activity, gonadal hormone levels and glycemic control.

Conclusion

Physical activity improves the testosterone levels in male patients with T2DM. Testosterone levels are higher in patients engaged in daily physical activity for less than 30 minutes vs. other groups. Furthermore, testosterone levels are significantly higher in patients engaged in physical activity with normal BMI vs. obese patients. These results show that regular physical activity can help in improving the testosterone levels of men with T2DM and normal BMI.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

T2DM, Type-2 diabetes mellitus; FBG, Fasting blood glucose; PBG, Postprandial blood sugar; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, Glycated hemoglobin; BUN, Urea nitrogen; Cr, Creatinine; TT, Total testosterone; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; E2, Estradiol; SHBG, Sex hormone-binding globulin; FINS, Fasting insulin; BT, Bioactive testosterone; FT, Free testosterone; HOMA-IR, Homeostasis model assessment-insulin resistance index.

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