Research Article

Association between Sex Hormone and Blood Uric Acid in Male Patients with Type 2 Diabetes

Wen Cao,1,2 Ren-Dong Zheng,2 Shu-Hang Xu,2 Yao-Fu Fan,2 Hong-Ping Sun,2 and Chao Liu2

1The First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing 210013, China
2Endocrine and Diabetes Center, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210028, China

Correspondence should be addressed to Chao Liu; proliuchao@163.com

Received 6 June 2017; Revised 4 September 2017; Accepted 14 September 2017; Published 3 October 2017

Academic Editor: Mario Maggi

Copyright © 2017 Wen Cao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The association between serum uric acid (SUA) level and sexual dysfunction in patients with diabetes is not well characterized. Type 2 diabetes mellitus (T2DM) causes metabolic disorders, including abnormal serum uric acid (SUA) levels. In this study, we enrolled 205 male patients with T2DM and investigated the relationship between sex hormone levels and SUA. Patients were divided into four groups based on SUA quartiles. On the other hand, based on the total testosterone (TT) level, patients were divided into three groups; SUA and other laboratory indices were determined. Increase in SUA level was significantly associated with decreased levels of TT, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, and increased levels of dehydroepiandrosterone, age, body mass index (BMI), waist circumference, glycated hemoglobin, serum creatinine, and HOMA-IR levels. SUA, waist circumference, BMI, and HOMA-IR showed a negative correlation with TT level, while age showed a positive correlation with TT level. SUA and body mass index were found to be risk factors for gonadal dysfunction. Therefore, we conclude that hypogonadism of male patients with T2DM is related to SUA level.

1. Introduction

Hypogonadism is characterized by decreased sexual frequency, sexual ability, and morning libido. The diagnosis of hypogonadism is based on symptom score and serum sex hormone levels. Total testosterone level <12 nmol/L is suggestive of hypogonadism; patients with total testosterone levels ≤8 nmol/L typically benefit from testosterone treatment [1, 2]. Studies have demonstrated that hypogonadism may occur in men with metabolic diseases [3, 4]. Low levels of serum testosterone (T) have been documented in male patients with metabolic syndrome (MS). The underlying mechanism may be dietary-induced hypothalamic inflammation, which reduces the release of gonadotropin-releasing hormone (GnRH) and correlates with age and body mass index (BMI) [5, 6].

In recent years, the incidence of hyperuricemia has gradually increased. In addition to the injury to the joints and kidney, hyperuricemia leads to a variety of metabolic diseases [7, 8]. Patients with type 2 diabetes often have other coexisting metabolic disorders, particularly hyperuricemia. Our previous study found that obese males with type 2 diabetes usually develop hypogonadism. Al et al. [9] also reported a close association of hypogonadism with insulin resistance [10] and lipid metabolism [11], which is consistent with our results. Hyperuricemia-related diseases, such as obesity, diabetes, and hyperlipidemia, increase the risk of gonadal dysfunction. Studies have shown that testosterone supplementation can improve body composition and glycolipid metabolism in younger subjects and in those with metabolic disturbances [12]. Testosterone supplementation was shown to improve body weight and waist circumference in patients with type 2 diabetes [13]. In this study, we sought to identify risk factors for hypogonadism by analyzing the relationship between sex hormone levels and blood uric acid levels in men with type 2 diabetes. Our findings may provide evidence for the prevention and treatment of hypogonadism.
2. Subjects and Methods

2.1. Subjects. A total of 1026 male patients with type 2 diabetes who were hospitalized at the Jiangsu Province Hospital of TCM and Western Medicine, Nanjing University of Chinese Medicine, between January 2013 and June 2016 were eligible for inclusion.

The following are the exclusion criteria: (1) acute and chronic kidney disease; (2) cardiac insufficiency; (3) acute diabetic complications; (4) history of sex gland diseases; (5) infectious and autoimmune diseases; (6) history of hypertension and use of diuretics, or patients with uncontrollable blood pressure (≥140/90 mmHg). Based on the exclusion criteria, 314 patients with liver or renal insufficiency, 143 patients with acute diabetic complications, 8 patients with heart failure, 124 patients with infectious and immune diseases, 232 patients with uncontrolled high blood pressure, or those using diuretics were excluded. Finally, 205 patients were included in the study (Figure 1). All patients were aged between 27 and 81 years and conformed to the diabetes diagnostic criteria set by the World Health Organization (WHO) in 1999. Depending on the serum uric acid levels tested on the 3 points (260, 308, and 385 μmol/L) of tangency quarter-line method; blood glucose level was determined by a glucose oxidase method; and uric acid level was determined by an enzymatic method. To measure serum SHBG, total testosterone, and serum albumin levels, a software was used to calculate the bioactive testosterone (BT) and free testosterone (FT) levels (http://www.issam.ch/). The following is the homeostasis model assessment-insulin resistance index (HOMA-IR) calculation formula: fasting blood glucose level (mmol/L) × fasting insulin level (mIU/L)/22.5.

2.2. Methods

2.2.1. General Indices. Body weight, blood pressure, and BMI were measured. All patients were made to stand with feet separated as wide as the distance between the two shoulders. The waist circumference was measured in the horizontal plane midway between the lowest rib and the iliac crest [14]. History of smoking and hypertension was noted.

2.2.2. Blood Indices. Blood samples were obtained between 6 and 7 am after overnight fasting for 8–10 hours. Indices included fasting blood glucose (FBG); glycated hemoglobin (HbA1c); blood urea nitrogen (BUN); creatinine (Cr); serum uric acid (SUA); sex hormones [total testosterone (TT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone (DHEA)]; and fasting insulin (FINS). Then, 200 mL of water containing 75 g of anhydrous glucose was administered. Two hours later, blood samples were collected to determine postprandial blood glucose. The hormone indices were analyzed by a chemiluminescence method; blood glucose level was determined by a glucose oxidase method; HbA1c level was determined by a chromatography method; and uric acid level was determined by an enzymatic method. To measure serum SHBG, total testosterone, and serum albumin levels, a software was used to calculate the bioactive testosterone (BT) and free testosterone (FT) levels (http://www.issam.ch/). The following is the homeostasis model assessment-insulin resistance index (HOMA-IR) calculation formula: fasting blood glucose level (mmol/L) × fasting insulin level (mIU/L)/22.5.

2.3. Statistical Processing. SPSS16.0 software was used for the statistical analysis. Normally distributed variables are expressed as mean ± standard deviation, and between-group differences assessed by a single-factor analysis of variance (ANOVA). Nonnormally distributed variables are expressed as median, and between-group differences assessed by the Kruskal-Wallis test. Correlations were assessed using Spearman’s method for nonnormally distributed data, and Pearson’s method was used for normally distributed data. Multiple regression analysis was performed to identify correlates of TT level. p < 0.05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics of the Participants. Significant differences were observed between the four groups with respect to age, BMI, waist circumference, HbA1c, creatinine, and HOMA-IR (p < 0.05 for all). No significant between-group differences were observed with respect to blood pressure, fasting blood glucose level, and BUN (p > 0.05) (Table 1).

3.2. Comparison of Sex Hormone Levels between Four Groups. Increased levels of SUA were significantly associated with a decrease in TT, LH, FSH, and SHBG levels (p < 0.05) and increase in DHEA levels (p < 0.05). No significant between-
Table 1: Laboratory indices of glucose metabolism and related parameters in the study population disaggregated by quartiles of serum uric acid level.

<table>
<thead>
<tr>
<th></th>
<th>Group Q1</th>
<th>Group Q2</th>
<th>Group Q3</th>
<th>Group Q4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>51 (24.9)</td>
<td>50 (24.4)</td>
<td>53 (25.8)</td>
<td>51 (24.9)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.59 ± 10.69</td>
<td>50.68 ± 11.82</td>
<td>51.94 ± 11.65</td>
<td>45.86 ± 11.07</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.25 ± 3.04</td>
<td>24.56 ± 2.48</td>
<td>25.09 ± 3.09</td>
<td>27.57 ± 4.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>27 (11.7)</td>
<td>23 (11.2)</td>
<td>16 (7.8)</td>
<td>23 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>87.11</td>
<td>88.92</td>
<td>90.40</td>
<td>93.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129.00</td>
<td>129.09</td>
<td>122.75</td>
<td>130.00</td>
<td>0.157</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.69</td>
<td>79.29</td>
<td>79.46</td>
<td>81.25</td>
<td>0.122</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>10.77</td>
<td>10.32</td>
<td>9.54</td>
<td>8.30</td>
<td>0.003</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>8.70</td>
<td>8.23</td>
<td>8.09</td>
<td>7.91</td>
<td>0.220</td>
</tr>
<tr>
<td>PBG (mmol/L)</td>
<td>14.99 ± 2.83</td>
<td>15.31 ± 2.95</td>
<td>15.07 ± 3.48</td>
<td>15.44 ± 3.95</td>
<td>0.899</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>5.41</td>
<td>4.92</td>
<td>5.39</td>
<td>4.92</td>
<td>0.100</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>63.29 ± 10.87</td>
<td>66.44 ± 10.19</td>
<td>15.28 ± 3.49</td>
<td>15.22 ± 4.23</td>
<td>0.002</td>
</tr>
<tr>
<td>SUA (μmol/L)</td>
<td>228.67</td>
<td>281.00</td>
<td>335.75</td>
<td>430.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.88</td>
<td>2.36</td>
<td>3.20</td>
<td>3.41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation or median. BMI: body mass index; BP: blood pressure; HbA₁c: glycated hemoglobin; FBG: fasting blood-glucose; PBG: postprandial blood glucose; BUN: urea nitrogen; Cr: creatinine; SUA: serum uric acid; HOMA-IR: homeostasis model assessment-insulin resistance index.

Table 2: Sex hormone levels in the study population disaggregated by quartiles of serum uric acid levels.

<table>
<thead>
<tr>
<th></th>
<th>Group Q1</th>
<th>Group Q2</th>
<th>Group Q3</th>
<th>Group Q4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>51 (24.9)</td>
<td>50 (24.4)</td>
<td>53 (25.8)</td>
<td>51 (24.9)</td>
<td></td>
</tr>
<tr>
<td>TT (nmol/L)</td>
<td>15.07</td>
<td>14.84</td>
<td>13.98</td>
<td>11.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT (nmol/L)</td>
<td>0.29</td>
<td>0.31</td>
<td>0.29</td>
<td>0.29</td>
<td>0.227</td>
</tr>
<tr>
<td>BT (nmol/L)</td>
<td>6.54</td>
<td>7.19</td>
<td>6.63</td>
<td>6.81</td>
<td>0.213</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>7.02</td>
<td>6.12</td>
<td>5.24</td>
<td>5.44</td>
<td>0.005</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>8.02</td>
<td>5.96</td>
<td>5.86</td>
<td>4.71</td>
<td>0.001</td>
</tr>
<tr>
<td>E2 (pmol/L)</td>
<td>93.46</td>
<td>93.48</td>
<td>84.29</td>
<td>93.30</td>
<td>0.917</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>31.92</td>
<td>28.61</td>
<td>23.52</td>
<td>19.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DHEA (μmol/L)</td>
<td>4.47</td>
<td>5.03</td>
<td>5.49</td>
<td>6.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as median. TT: total testosterone; BT: bioactive testosterone; FT: free testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin; DHEA: dehydroepiandrosterone.

3.3. Comparison between Different TT Groups. Owing to the observed inverse association between TT and SUA levels, we categorized patients into three groups based on TT levels (<8 nmol/L; between 8 nmol/L and 12 nmol/L; and >12 nmol/L) to further characterize the association. The results showed that SUA, BMI, waist circumference, and HOMA-IR were significantly different between the three groups (p < 0.05) (Table 3).

3.4. Multivariate Regression Analysis of Male Hypogonadism. Multivariate regression analysis was performed to assess the correlation between TT levels and related indicators. SUA, waist circumference, BMI, and HOMA-IR showed a negative correlation with TT levels, while age showed a positive correlation with TT levels (p < 0.05) (Table 4). In the multivariate regression model, total testosterone level was included as the dependent variable, while age, waist circumference, BMI, HOMA-IR, and SUA were included as independent variables. Multivariate regression analysis revealed that BMI and SUA were risk factors for gonadal dysfunction (Table 5).

4. Discussion
Uric acid is the metabolic end product of nucleic acid purines in vivo (including nucleic acids in food) that is mainly excreted through renal excretion. Increase in SUA levels is generally caused by increased uric acid production and/or reduced excretion. The level of mammalian serum uric acid
ranges between 1 and 3 mg/dL [15]. In recent years, the incidence of hyperuricemia (HUA) has increased gradually. A cross-sectional study of residents in Brazil in 2012 showed that the prevalence of HUA is 13.2% [16]. The prevalence of HUA was 25.8% according to a survey covering 9914 residents in Japan [17]. Our survey shows that the prevalence of HUA in rural residents in North and Northeast China is 10.9% [18].

The present study investigated 205 male patients with diabetes, of which 70 (34.2%) patients had TT levels < 12 nmol/L.
Among healthy male individuals, the reported percentage of individuals with sexual dysfunction varies between 20 and 80% [19–21]. In an Australian cross-sectional study of 1089 patients with type 2 diabetes, 36.5% patients had hypogonadism [21]. In an Australian cross-sectional study of 1089 individuals with sexual dysfunction varies between 20 and 80% [19–21].

We found a significant correlation between SUA and TT levels. As the SUA level increased, testosterone levels decreased and the SUA level of patients with low TT was significantly increased.

Accounting for about 95% of the total sex hormone, testosterone is a major androgen mainly synthesized by testicular interstitial cells, as well as the reticular zone of the adrenal cortex. Low testosterone level causes a series of physical changes, such as obesity, muscle hypertrophy, lipid metabolism disorders, osteoporosis, poor immunity, cardiovascular illness, and nervous dysfunction.

Epidemiological studies have shown that the incidence of hyperuricemia in men is higher than that in women [22, 23]. In the present study, an inverse association was observed between TT levels and uric acid levels among men with type 2 diabetes. A previous study has found decreased testosterone and estradiol synthesis in male patients with gout; patients with gouty kidney disease and gouty arthritis showed a significant decrease in testosterone levels [24]. The reasons may include (1) crystallization of uric acid in the testicular tissue causing oxidative damage [25] and (2) insulin resistance that can be reduced by low testosterone levels [26], resulting in reduced secretion of uric acid in renal tubular epithelial cells after absorption and the renal excretion of uric acid [27]. Therefore, the decline in body testosterone levels can lead to elevated serum uric acid levels; (3) testosterone promotes synthesis of protein and nucleic acids; decreased testosterone levels reduce protein synthesis and increase the level of endogenous purine, which causes hyperuricemia. Further research is needed to reveal the correlation between SUA and testosterone.

For patients with gonadal dysfunction, low hormone levels will stimulate hypothalamus-pituitary gonadotropin secretion. In early-stage type 2 diabetes, testosterone levels can be compensated to maintain the normal level. In elderly individuals, patients with advanced stage of type 2 diabetes and vasculopathy, compensatory function gradually declines, which results in low levels of gonadal hormones. We observed that LH and FSH decreased with elevated uric acid levels and lowered gonadal hormone levels. As TT levels decrease, patients may develop sexual dysfunction. The reason may be that hyperuricemia can lower LH levels and reduce the synthesis of testosterone and estrogen [28].

This study found that SUA was negatively correlated with SHBG and positively correlated with DHEA. SHBG specifically binds to sex hormones, participates in its transport, and regulates the concentration of biologically active sex hormones in the blood [29, 30]. Hyperuricemia can reduce the level of insulin-like growth factors binding to
with hyperuricemia [41], and the two can in
to hyperuricemia. Insulin resistance is strongly associated
excretion of uric acid in the renal tubules, which in turn leads
SUA level. Further, too much insulin action can reduce
disordered purine metabolism and consequent increase in
phoric acid (PPRP), and uric acid [40]. Insulin resistance
intermediate synthesis of ribose-5-phosphate (R-5-P), phos-
phosphorylase activity, which promotes the glycolytic metabolism of
weaken GA3PDH (glyceraldehyde-3-phosphate dehydroge-
insulinemia can interfere with carbohydrate metabolism and
improve insulin sensitivity. Testosterone level decrease is also
increased insulin resistance; (3) testosterone secretion can
the root cause of metabolic syndrome in patients with
concentration of LH and TT; (2) decrease in hormone levels
decreases GnRH secretion, which causes a decrease in
sex hormones primarily in
amus and its subsequent secretion [43]. Insulin resistance
dehydroepiandrosterone (DHEA), an adrenal steroid hormone abundant
levels in patients with type 2 diabetes may be highly suggest-
itive of gonad hypofunction.

We found that SUA levels were signifi-
cantly higher in male patients with T2DM compared to
levels in patients with benign prostate hyperplasia, "International
men are rare. DHEA, an adrenal steroid hormone abundant
in human blood [33], is a biomarker of the hypothalamic-
piotnatal adrenal (HPA) axis activity [34–36]. It seems that
sex hormones primarily influence the SUA concentration
via renal UA excretion [37–39].

We found that HOMA-IR levels in patients with higher
SUA levels were significantly higher than those in patients
with lower SUA levels, which suggests a direct association
between SUA levels and insulin resistance. Long-term hyper-
insulinemia can interfere with carbohydrate metabolism and
weaken GA3PDH (glyceraldehyde-3-phosphate dehydroge-
insulinemia can interfere with carbohydrate metabolism and weaken GA3PDH (glyceraldehyde-3-phosphate dehydrogenase) activity, which promotes the glycolytic metabolism of intermediate synthesis of ribose-5-phosphate (R-5-P), phosphoric acid (PPRP), and uric acid [40]. Insulin resistance can increase the synthesis of fat in the liver, which leads to disordered purine metabolism and consequent increase in SUA level. Further, too much insulin action can reduce excretion of uric acid in the renal tubules, which in turn leads to hyperuricemia. Insulin resistance is strongly associated with hyperuricemia [41], and the two can influence each other. Cruz-Dominguez et al. [42] found an inverse correlation between SUA levels and insulin sensitivity. We found that insulin resistance is an independent risk factor for male sexual dysfunction, which may be mediated via the following mechanisms: (1) insulin stimulates the gonadotropin-releasing hormone expression in the nerves of the hypothalamus and its subsequent secretion [43]. Insulin resistance decreases GnRH secretion, which causes a decrease in the concentration of LH and TT; (2) decrease in hormone levels in male patients leads to a rapid increase in body weight which further aggravates lipid metabolism disorders. This is the root cause of metabolic syndrome in patients with increased insulin resistance; (3) testosterone secretion can reduce the circulation of nonaromatic fatty acids and improve insulin sensitivity. Testosterone level decrease is also related to insulin sensitivity.

We found that obesity reduces sexual function as the
SUA level significantly increases. The higher the SUA level, the higher the BMI and waist circumference, which suggests that uric acid and obesity are closely related. Patients with hyperuricemia tend to have higher BMI. This is associated with the acceleration of purine synthesis and increased uric acid production.

The higher the level of uric acid, the higher the Cr, which suggests that uric acid is a predictor of kidney disease. Uric acid induces endothelial cell damage by increasing intracellular oxidative stress and by upregulating C-reactive protein expression and intracellular NO activity. In the kidney, uric acid is known to induce renal renin expression, enhance the activation of RAA5 system, and initiate renal afferent arteri-

5. Conclusion

Hypogonadism in male patients with T2DM is related to
SUA levels. In addition to blood glucose, more factors (e.g.,
uric acid and body weight) should be considered to influence
sexual function.

Abbreviations

SUA: Serum uric acid
T2DM: Type 2 diabetes mellitus
FBG: Fasting blood glucose
HbA1c: Glycated hemoglobin
BUN: Urea nitrogen
Cr: Creatinine
TT: Total testosterone
LH: Luteinizing hormone
FSH: Follicle-stimulating hormone
SHBG: Sex hormone-binding globulin
DHEA: Dehydroepiandrosterone
FINS: Fasting insulin
BT: Bioactive testosterone
FT: Free testosterone
HOMA-IR: Homeostasis model assessment-insulin resist-
tance index.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors gratefully acknowledge the grand support of the
National Natural Science Foundation of China (Grant no. 81200577) and “Six Talent Peak” Project of Jiangsu Province under Grant no. 2013-WSN-063.

References

tive, multicentre study on the impact of alfluzosin on sexual
function using the Male Sexual Health Questionnaire in
patients with benign prostate hyperplasia,” International


