The relationship between serum uric acid within the normal range and β-cell function in Chinese patients with type 2 diabetes: differences by body mass index and gender

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Background: Elevated serum uric acid (SUA) has a positive correlation with insulin secretion and insulin resistance indexes. However, whether weight- and gender-specific differences regarding the relationship between SUA within the normal range and β-cell function and insulin resistance exist is unknown in T2DM patients.

Methods: Three hundreds and eighty patients with type 2 diabetes were divided into two groups as overweight/obesity (n=268) and normal weight (n=112). Each group were again divided into low (LSUA) and high normal SUA (HSUA). The HbA1c, C-peptide, SUA, creatinine, and lipids profiles were measured. HOMA2IR and HOMA%2B were estimated using fasting glucose and C-peptide by homeostasis model assessment (HOMA). Pearson's correlations and multiple linear regression analyses were conducted to assess the associations between SUA levels and islet function indexes.

Results: In overweight/obesity subgroup, the levels of BMI, FCP, P2HCP, FCPI, PPCPI, ΔC-peptide, HOMA2%B and HOMA2IR were higher in HSUA group than in LSUA group. In contrast, the HbA1c, FBS, and P2hBS were lower in HSUA than in LSUA. In normal weight subgroup, there were on differences between the HSUA than LSUA group in terms of clinical characteristics. Pearson's correlations indicated that there were no significant correlations between SUA and insulin secretory capacity in normal weight group, but in overweight/obesity group, SUA had positive significant correlations with P2hCP, FCPI, PPCPI, ΔC-peptide, and HOMA2%B. In female group, there were no significant correlations between SUA and insulin secretory capacity. However, in male group, SUA had positive significant correlations with insulin secretory capacity include P2hCP, FCPI, PPCPI, ΔC-peptide, and HOMA2%B. Multiple linear regression showed that SUA was significantly associated with HOMA2%B, but not with HOMA2IR in overweight/obesity and male group.

Conclusions : Our study shows that SUA levels within normal range were associated with β-cell function in T2DM patients with overweight/obesity or male. This finding supports that the association between SUA within normal range and insulin secretion ability differs by weight and sex.

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Abstract

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Results： In overweight/obesity subgroup, the levels of BMI, FCP, P2HCP, FCPI, PPCPI, ΔC-peptide, HOMA2%B and HOMA2IR were higher in HSUA group than in LSUA group. In contrast, the HbA1c, FBS, and P2hBS were lower in HSUA than in LSUA. In normal weight subgroup, there were on differences between the HSUA than LSUA group in terms of clinical characteristics. Pearson's correlations indicated that there were no significant correlations between SUA and insulin secretory capacity in normal weight group, but in overweight/obesity group, SUA had positive significant correlations with P2hCP, FCPI, PPCPI, ΔC-peptide, and HOMA2%B. In female group, there were no significant correlations between SUA and insulin secretory capacity. However, in male group, SUA had positive significant correlations with insulin secretory capacity include P2hCP, FCPI, PPCPI, ΔC-peptide, and HOMA2%B. Multiple linear regression showed that SUA was significantly associated with HOMA2%B, but not with HOMA2IR in overweight/obesity and male group.

Conclusions: Our study shows that SUA levels within normal range were associated with β-cell function in T2DM patients with overweight/obesity or male. This finding supports that the association between SUA within normal range and insulin secretion ability differs by weight and sex.

Introduction

Type 2 diabetes mellitus (T2DM) has become a serious issue in China with increasing incidences over the past decades (Ogurtsova et al. 2017). Increasing evidence suggests that high serum uric acid (SUA) level is not only associated with metabolic syndrome (MS) (Babio et al. 2015), but also is regarded as a potential tool for early diagnosis of MS (Chen et al. 2016). Elevated the level of SUA is associated with increased risk of T2DM and prediabetes in individuals with normoglycaemia in a large population-based cohort study (Dehghan et al. 2008; van der Schaft et al. 2017). However, changes in SUA and blood glucose do not exhibit a linear relationship. SUA rise with increasing blood glucose concentrations in the normal and prediabetes population, while SUA levels are negatively associated with HbA1c in T2DM (Kawamoto et al. 2018).

Progressive deterioration of islet β-cell function and insulin resistance are considered as primary pathophysiological factors during the development of T2DM. SUA is the end product of an exogenous pool of pruines and endogenous purine metabolism, and the final oxidation product of purine metabolism in humans, which is responsible for the production of UA and damage of free radicals. In hyperuricemic subjects with IGT, the failure of beta-cell function to compensate variation of insulin sensitivity, compared with non-hyperuricemic (Simental-Mendia et al. 2009). Furthermore, elevated SUA harbors a positive correlation with insulin secretion and insulin resistance indexes in newly diagnosed T2DM patients (Hu et al. 2018), implying a possible role for SUA in β-cell function. However, it remains unknown of the interaction of SUA within the normal range and body mass index on β-cell function and insulin resistance in T2DM patients.

Therefore, we investigated the relationship between SUA within the normal range and β-cell function as well as their potential confounding factors such as age, gender, diabetic duration, blood pressure, blood lipid profiles, renal function, and HbA1c by body mass index (BMI) and gender.

Materials & Methods

Study Subjects. A total of 380 patients with type 2 diabetes who visited the Second Affliated Hospital of Anhui Medical University were randomly selected in this cross-sectional study. The diagnosis of T2DM was according to the criteria of the American Diabetes Association (ADA). The exclusion criteria were 1) with hyperuricemia defined as serum uric acid ≥420 umol/L in men and ≥360 umol/L in women (Fang & Alderman 2000), 2) with renal dysfunction defined as

74   serum creatinine ≥106 umol/L in male and ≥97 umol/L in female or chronic kidney disease, 3)

75   patients with severe pancreatic disease and liver disease and those who suffered recent diabetic

76   ketoacidosis and hyperosmotic nonketotic diabetic coma. Written informed consent was

77   provided by all participants. The study was approved by an Ethics Committee of the Second

78   Affliated Hospital of Anhui Medical University (approval number 2017027).

79   **Measurements**

80   Study participants were inquired about their age and family history. Body weight, height and

81   blood pressure were measured by the diabetic nurses. Body mass index (BMI) was calculated by

82   dividing weight (in kilograms) by square of the height (in meters). Normal weight and

83   overweight/obesity were defined as BMI $<$24 kg/m^2 and BMI $\geqslant$24 kg/m^2 for Chinese

84   population, respectively, according to the Working Group on Obesity in China (WGOC) BMI

85   criterias (Hou et al. 2013; Zhou 2002). Blood tests were carried out after an overnight fasting for

86   glucose, serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol

87   (HDL), low-density lipoprotein cholesterol (LDL), SUA, liver/renal functions and glycated

88   hemoglobin (HbA1c).

89   After collecting fasting blood samples, subjects received a noodle mixed-meal in patients with

90   T2DM. Blood samples were collected to measure the concentrations of glucose and C-peptide 2h

91   after the meal. HOMA2IR and HOMA%2B were assessed using homeostasis model assessment

92   based on paired of FPG and fasting C-peptide measurements (http://www.dtu.ox.ac.uk/homa)

93   (Wallace et al. 2004). Insulin secretory capacity was also evaluate by CPI and ΔC-peptide.

94   Fasting CPI (FCPI) and postprandial CPI (PPCPI) were calculated by a ratio of serum C-peptide

95   to plasma glucose concentrations at baseline and 2h after meal, which we termed CPR (nmol/L)/

96   FPG (mmol/L). The value of ΔC-peptide was defined as increment in serum C-peptide level

97   (nmol/L) at 2h after the meal.

98   Serum C-peptide was measured by chemiluminescent enzyme immunoassay. HbA1c was

99   measured by high performance liquid chromatography. Plasma glucose was evaluated with the

100   glucose oxidase method. TC, TG, HDL, LDL, SUA and liver/renal functions were analyzed by

101   the standardized enzymatic method.

102   **Statistical analyses**

103   Continuous variables were expressed as means and standard deviation (SD) or medians and

104   interquartiles. Categorical variabiles were expressed by numbers. In all the analyses, parameters

105 with non-normal distributions were used after log transformation. For categorical variables, the

106 Chi-square test was performed, while for continuous variables, Student t test was used. Pearson's

107 correlations were calculated to characterize the associations between islet function indexes and

108 SUA levels within each group. To evaluate whether SUA was an independent risk factor for β-

109 cell function in T2DM, we performed the multiple linear regression analysis. A two-tailed p

110 ≤0.05 was considered as statistically significant. All statistical analyses were conducted with

111 SPSS software (Version 21.0).

112 **Results**

113 **Clinical and laboratory data of the patients according to BMI and SUA category**

114 The characteristic of the study patients according to BMI was shown in Table 1. The levels of

115 SBP, DBP, TG, FCP, P2HCP, FCPI, PPCPI, HOMA2%B and HOMA2IR were higher in

116 overweight/obesity group than in normal weight group. Furthermore, the patients were divided

117 into two groups according the median SUA levels of patients with normal weight or

118 overweight/obesity, respectively (LSUA: low-normal SUA, ≤ 285 umol/L; HSUA: high-normal

119 SUA, >285 umol/L). In overweight/ obesity subgroup, the levels of BMI, ALT, CR, FCP,

120 P2HCP, FCPI, PPCPI, ΔC-peptide, HOMA2%B and HOMA2IR were higher in HSUA group

121 than in LSUA group. In contrast, the HbA1c, FBS, P2hBS and HDL were lower in HSUA than

122 in LSUA (Table 2). In normal weight subgroup, there were on differences between the HSUA

123 and LSUA group in terms of clinical characteristics (Table 2).

124 **Correlation between SUA and insulin secretory capacity within normal or**

125 **overweight/obesity groups**

126 The relationship between confounding factors including SUA and insulin secretory capacity

127 within normal or overweight/obesity groups was shown in Table 3. In normal weight group,

128 there were no significant correlations between SUA and insulin secretory capacity. However, in

129 overweight/obesity group, FCP, P2hCP, FCPI, PPCPI, ΔC-peptide, HOMA2%B, and HOMA2IR

130 correlated positively with SUA, while HbA1c correlated negatively with SUA. After adjusting

131 for Cr, BMI, and gender, there were no significant correlations between SUA and HOMA2IR.

132 After additional adjustment for HbA1c and Duration, SUA still had positive significant

133 correlations with insulin secretory capacity include P2hCP, FCPI, PPCPI, ΔC-peptide, and

134 HOMA2%B.

135   To further define the relation between SUA and HOMA2%B in overweight/obesity group,

136   multiple linear regression was carried out using SUA as the dependent variable (Table 4). FCP,

137   P2HCP, FCPI, PPCPI, and ΔC-peptide were excluded from the model because of high

138   correlation with HOMA2%B. FBS and P2hBS were also excluded because of high correlation

139   with HbA1c. SUA levels were significantly associated with HOMA2%B in unadjusted analyses.

140   After adjustments for sex, Cr, BMI, HbA1c and Duration, SUA remained positively associated

141   with HOMA2%B.

142   **Clinical and laboratory data of the patients according to gender and SUA category**

143   The characteristic of the study patients according to gender was shown in Table 5. There were

144   234 males and 146 females. The male group were younger and had shorter duration compared to

145   the female group. Compared with female group, the levels of SUA, ALT and CR in male group

146   were higher. Furthermore, the patients were divided into two groups according the median SUA

147   levels of patients with male (LSUA: low-normal SUA, $\leq$ 292.0 umol/L; HSUA: high-normal

148   SUA, >292.0 umol/L) or female (LSUA, $\leq$ 264.5 umol/L; HSUA, >264.5 umol/L) group,

149   respectively (Table 6). In male subgroup, the levels of BMI, ALT, HbA1c, P2HCP, FCPI,

150   PPCPI, ΔC-peptide, and HOMA2%B were higher in HSUA group than in LSUA group. In

151   contrast, the HbA1c, FBS, and P2hBS were lower in HSUA than in LSUA. In female subgroup,

152   the levels of BMI, TG, CR and HOMA2IR were higher in HSUA group than in LSUA group.

153   **Correlation between SUA and insulin secretory capacity by gender category**

154   The relationship between confounding factors including SUA and insulin secretory capacity

155   within male or female groups was shown in Table 7. In male group, FCP, P2hCP, FCPI, PPCPI,

156   ΔC-peptide and HOMA2%B correlated positively with SUA, while HbA1c correlated negatively

157   with SUA. After adjusting for Cr and BMI, there were also significant correlations between SUA

158   and HOMA2IR. After additional adjustment for HbA1c and Duration, SUA still had positive

159   significant correlations with insulin secretory capacity include P2hCP, FCPI, PPCPI, ΔC-

160   peptide, and HOMA2%B. However, in female group, SUA only correlated positively with

161   P2hCP and ΔC-peptide.

162   To further define the relation between SUA and HOMA2%B or HOMA2IR, multiple linear

163   regression was carried out using SUA as the dependent variable (Table 8). In male group, SUA

164   levels were significantly associated with HOMA2%B in unadjusted analyses. After adjustments

165   for Cr, BMI, HbA1c and Duration, SUA remained positively associated with HOMA2%B. SUA

166 levels were significantly associated with HOMA2IR in unadjusted analyses. After adjustments

167 for Cr, BMI, HbA1c and Duration, there were no significant correlations between SUA and

168 HOMA2IR. However, there were no significant correlations between SUA and HOMA2%B and

169 HOMA2IR in female group.

170 **Correlation between islet function/insulin resistance and related variables in T2DM**

171 **patients**

172 To indentify confounding factors affecting islet function and insulin resistance, multiple linear

173 regression was again performed in T2DM patients. Independent variables such as SUA, age,

174 gender, duration, SBP, DBP, BMI, TG, TCH, LDL, HDL, ALT, CR, HbA1c were enrolled

175 (Table 9). HOMA2%B had positive associations with BMI, SUA, age and duration and a

176 negative correlation with HbA1c. HOMA2IR had positive associations with BMI and TG and a

177 negative correlation with duration.

Discussion

179 In this study, we confirmed that SUA levels are significantly associated with HOMA2%B in

180 T2DM patients with overweight/obesity and male group, but not in normal weight and female

181 group. In addition, we also demonstrated that other islet function indexes, such as FCPI, PPCPI,

182 and ΔC-peptide, did correlate with SUA levels in T2DM patients with overweight/obesity and

183 male group. However, our study observed the absence of a relationship between SUA and

184 HOMA2IR after adjustment for Cr, BMI, sex, HbA1c, and diabetic duration in T2DM patients

185 with overweight/obesity or male. To the best of our knowledge, this study is the first that these

186 effects of SUA within the normal range on determinants of β-cell function and insulin resistance

187 in T2DM by BMI and gender categories.

188 Uric acid is the end product of purine metabolism and derives from the conversion of

189 hypoxanthine to xanthine and of xanthine to uric acid. We observed that SUA was higher in

190 T2DM patients with overweight/obesity group than in those with normal weight group, SUA

191 within normal range independently related to obesity in T2DM. Consistent with our results,

192 several previous studies have also shown the relationship between BMI and uric acid (Han et al.

193 2018). For example, Chen et al (Chen et al. 2017) also found that prevalence of obesity steadily

194 increased across SUA quartiles in T2DM. A 10-year follow-up study demonstrated that BMI had

195 a significant independent association with uric acid in all race-sex-groups (Rathmann et al.

196 2007). Furthermore, in subjects without diabetes or hyperuricemia, SUA levels were also

197 associated with BMI, waist circumference, and waist-to-hip ratio (Jin et al. 2013). Interestingly,

198 Zhou et al found that successful weight control, mostly >10kg weight reduction, was correlated

199 with significant uric acid reduction after 2 years observation (Zhou et al. 2017). Therefore, SUA

200 levels, even in normal range, were associated with BMI in T2DM patient.

201 In addition to strong association with BMI, SUA is also associated with β-cell function in

202 T2DM. Tang et al. (Tang et al. 2014) found that patients with higher levels of SUA had higher

203 insulin secretion, including the early phase and total insulin secretion in T2DM patients.

204 Similarly, another study (Hu et al. 2018) has also reported that SUA augments insulin secretion,

205 particularly basal insulin secretion, in the population-based study of newly diagnosed T2DM.

206 Even in nondiabetic population, higher SUA levels also significantly correlate with lower early-

207 phase insulin secretion (Shimodaira et al. 2014). However, the abovementioned studies do not

208 evaluate the relationship between SUA in the normal range and β-cell function. Most of prior

209 studies researching the association between SUA and β-cell function did not conduct subgroup

210 analyses by BMI categories. Our present results show that SUA in the normal range is

211 significantly associated with HOMA2%B in T2DM patients with overweight/obesity, but not in

212 normal weight group. Although it is not possible to explain the mechanism underlying this body

213 weight difference from our study, this observation may be due to the influence of SUA levels,

214 which our study showed that SUA levels were higher in T2DM patients with overweight/obesity

215 than in those with normal weight group. Although subjects with higher SUA secrete more

216 insulin, it does not mean that high SUA is beneficial to β-cell function. SUA becomes a strong

217 oxidant in the environment of obesity (Johnson et al. 2009), which may in turn promote lipid

218 oxidation. In addition, obesity is related to elevated SUA level via both low urinary urate

219 excretion and overproduction of SUA(Matsuura et al. 1998). A recent study found that an

220 elevated level of uric acid causes β-cell injury via the NFκB-iNOS-NO signaling axis (Jia et al.

221 2013). Furthermore, Sun et al(Sun et al. 2015) found that uric acid-associated genes have an

222 impact on insulin secrction in a Chinese patients with T2DM. Finally, another study (Seyed-

223 Sadjadi et al. 2017) showed that the associations between SUA and diabetes risk factors are

224 largely dependent on visceral fat mass in a non-diabetic population. Physicochemical properties

225 define hyperuricemia as levels above the solubility threshold (6.8mg/dl). With regard to

226 metabolic sequel, high-normal SUA levels are already associated with an increased risk in

227 patient with overweight/obesity.

228 The disposition index (DI) is thought to reflect the capacity for insulin secretion adjusted for

229 insulin sensitivity and thus to provide a useful measure of β-cell function. PP-CPI, a ratio of the

230 circulating level of C-peptide to that of glucose, is correlated with clamp DI (Okuno et al. 2013).

231 In the present study, we found that PPCPI and ΔC-peptide had positive associations with SUA

232 levels in overweight/obesity group, but not in normal weight group. Our findings agree with

233 previous report by Tang et al (Tang et al. 2014), which shows that patients with higher SUA had

234 greater disposition indices (both DI30 and DI120). Taken together, accumulated evidence

235 suggest SUA levels may be associated with insulin secretion in T2DM patients with

236 overweight/obesity.

237 Another important finding in our study was that SUA had positive significant correlations with

238 insulin secretory capacity include P2hCP, FCPI, PPCPI, ΔC-peptide, and HOMA2%B in male

239 group. Hyperuricemia affected men more commonly than women. There was a SUA difference

240 of 30-120 umol/l between men and women (Akizuki 1982). It is previously known that estrogen

241 may promote excretion of uric acid. (Hu et al. 2018) Together, these result indicate that gender

242 differences in association between SUA within normal range and insulin secretion in patients

243 with T2DM. However, a previous study (Hu et al. 2018) suggested that elevated SUA was

244 associated with insulin secretion in male and female. The mechanism underlying this sex-based

245 difference remains unclear, and requires further study.

246 The evidence of the linkage between SUA and insulin resistance in type 2 diabetes is growing,

247 but it is unclear if SUA within the normal range directly lead to declines in insulin sensitivity in

248 T2DM patients. However, our study observed the absence of a relationship between SUA within

249 normal range and insulin resistance in T2DM patients with overweight/obesity and normal

250 weight groups. Other researchers (Hu et al. 2018; Wang et al. 2011) have also demonstrated that

251 the UA levels of hyperuricemic patients have no effect on their insulin sensitivity index. Liu et

252 al. (Liu & Ho 2011) study suggested that SUA was not associated with insulin resistance after

253 adjustment for BMI, TG, and BP. There are several possible explanations for the lack of

254 independent relationship between SUA within normal range and insulin resistance in this study.

255 Firstly, this result could be driven by SUA levels that are well within the normal range.

256 Secondly, these discrepancies could be related the techniques used for measurement of insulin

257 sensitivity. Finally, UA has an important role as an antioxidant (Lippi et al. 2008), but elevated

258 SUA may cause oxidative stress (Pasalic et al. 2012) and inhibit endothelial NO bioavailability

259 (Sharaf El Din et al. 2017), all of which closely associated with the insulin resistance.
260 Collectively, the exact role of SUA within normal range in oxidation is still worth further
261 investigation in T2DM patients.

262 The relationship between SUA and HbA1c has been reported. For example, Kawamoto et al.
263 (Kawamoto et al. 2018) found a negative association between SUA and HbA1c was shown
264 particularly in men with HbA1c ≥6.5%. Cui et al. (Cui et al. 2016) showed that a negative
265 correlation between uric acid and HbA1c is conditional in newly diagnosed type 2 diabetes
266 patients. In our study, we also found that SUA within normal range negatively related to HbA1c
267 in T2DM patients with overweight/obesity. In T2DM patients with normal weight group, the
268 partial correlation analysis demonstrated the negative correlation between SUA and HbA1c, but
269 no significant difference was observed with multiple linear regression analysis. These results
270 indicated that there was negatively association between SUA, even within normal range, and
271 HbA1c in T2DM patients with overweight/obesity.

272 Unfortunately, this study has some limitations. Firstly, we do not analyses whether oral
273 hypoglycemic agents have effect on SUA. Sodium-glucose co-transporter 2 inhibitor (SGLT-2i)
274 could improve glycemic control and lower SUA levels in T2DM (Hao et al. 2018). However,
275 other hypoglycemic drugs, including metformin, rosiglitazone, glibenclamide and pharmacologic
276 insulin, do not have a large impact on SUA concentration (Hussain et al. 2018; Iliadis et al. 2007;
277 MacFarlane et al. 2015). In our study, the T2DM patients were treated with oral hypoglycemic
278 drugs (not including SGLT2i) and insulin. Secondly, the number of subjects enrolled was
279 relatively small. Thirdly, the relationship between SUA within normal range and oxidative stress
280 is still worth further investigation in T2DM.

281 In conclusion, our study shows that SUA levels within normal range are associated with β-cell
282 function in T2DM patients with overweight/obesity, and the relationship also displays sex-based
283 differences. However, SUA levels within normal range are not related to insulin resistance in
284 T2DM patients. This finding supports that the association between SUA within normal range and
285 insulin secretion ability differs by weight and gender.

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Table 1(on next page)

Clinical characteristics and islet function indexes of T2DM patients by BMI

1   Table 1 Clinical characteristics and islet function indexes of T2DM patients by BMI

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Variables	Normal weight group (N=112)	Overweight/obesity group (N=268)	$F/\varkappa$	P
SUA (umol/L)	262.5(224.3, 297.0)	290.5 (256.0, 333.0)	-5.08	<0.001
Age (years)	54.1±11.9	52.1±12.0	1.50	0.134
Male/Female	63/49	171/97	1.38	0.168
Duration (years)	5.0 (1.0, 10.0)	4.0 (0.3, 9.7)	0.51	0.613
SBP (mmHg)	120.0 (110.0, 131.5)	130.0 (120.0, 140.0)	-2.06	0.040
DBP (mmHg)	77.0 (70.0, 84.8)	80.0 (76.0, 90.0)	0.90	<0.001
BMI (kg/m^2)	22.3 (20.6, 23.4)	26.1 (25.4, 28.2)	-21.3	<0.001
TG (mmol/L)	1.38 (0.88, 2.12)	2.00 (1.22, 3.12)	-4.24	<0.001
TCH (mmol/L)	4.37 (3.87, 5.11)	4.54 (3.91, 5.20)	-1.01	0.315
LDL (mmol/L)	2.58 (2.18, 2.93)	2.58 (2.18, 3.10)	0.39	0.697
HDL (mmol/L)	1.07 (0.84, 1.38)	1.01 (0.76, 1.10)	2.86	0.004
ALT (U/L)	18.0 (14.0, 27.0)	21.0 (15.0, 33.0)	-1.87	0.063
CR (umol/L)	68.5 (58.0, 81.8)	73.0 (62.0, 85.0)	-1.73	0.084
HbA1c (%)	9.40 (7.53, 11.20)	8.90 (7.60, 10.70)	0.86	0.391
FPG (mmol/L)	9.49±3.38	9.32±3.03	0.47	0.637
P2hPG (mmol/L)	19.17±4.91	18.69±4.37	0.95	0.344
FCP (nmol/L)	1.84 (1.31, 2.82)	2.40 (1.79, 3.31)	-4.28	<0.001
P2hCP (nmol/L)	5.03 (3.52, 7.21)	5.90 (4.13, 7.74)	-2.54	0.011
FCPI	0.22 (0.16, 0.32)	0.28 (0.19, 0.37)	-3.77	<0.001
PPCPI	1.49 (0.94, 2.35)	1.78 (1.14, 2.62)	-2.24	0.026
ΔC-peptide	2.92 (1.76, 4.68)	3.23 (1.90, 4.62)	-1.16	0.245
HOMA2%B	42.2 (28.0, 69.0)	49.7 (33.9, 78.4)	-2.39	0.017
HOMA2IR	1.66 (1.17, 2.43)	2.11 (1.60, 3.11)	0.14	<0.001

4   Values are expressed as mean ±standard deviation (SD) or median (range 25th-75th percentile)

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Table 2(on next page)

Clinical characteristics and islet function indexes of overweight/obesity and normal weight group by the median of SUA

1   Table 2   Clinical characteristics and islet function indexes of overweight/obesity and normal weight group by the median of

2   SUA

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Variables	Overweight/obesity group				Normal weight group			
	LSUA	HSUA	t/κ	P	LSUA	HSUA	t/κ	P
SUA (umol/L)	<285	285~420			<285	285~420		
Age (years)	52.9±11.2	51.4±12.5	1.01	0.314	55.4±10.9	51.7±13.5	1.60	0.112
Male/Female	62/56	109/41	11.58	0.001	38/34	25/15	0.99	0.320
Duration (years)	4.0(0.3, 10.0)	4.0(0.29, 9.00)	0.14	0.886	6.0(1.0, 10.0)	4.5(0.42, 10.0)	-0.18	0.861
SBP (mmHg)	129.4±16.3	128.7±17.3	0.35	0.729	126.2±17.1	122.8±20.0	0.96	0.345
DBP (mmHg)	80.5±10.2	82.1±11.6	-1.19	0.235	76.9±9.5	77.1±9.6	-0.07	0.953
BMI (kg/m^2)	26.5±1.9	27.4±2.7	-3.14	0.002	21.8±1.9	21.6±2.0	-0.17	0.872
TG (mmol/L)	1.88(1.09, 2.58)	2.08(1.34, 3.32)	-1.42	0.156	1.21(0.84, 2.03)	1.43(1.00,2.15)	-0.51	0.614
TCH (mmol/L)	4.46(3.74, 5.35)	4.57(4.07, 5.15)	-0.83	0.407	4.37(3.95, 5.08)	4.33(3.51, 5.26)	0.53	0.595
LDL (mmol/L)	2.58(2.19, 2.95)	2.59(2.17, 3.13)	-0.59	0.550	2.58(2.31, 2.93)	2.58(2.02, 3.15)	-0.37	0.712
HDL (mmol/L)	1.07±0.38	0.97±0.40	2.35	0.020	1.24±0.49	0.99±0.29	2.94	0.004
ALT (U/L)	20.0(14.0, 30.3)	23.5(17.0, 35.0)	-2.73	0.007	18.0(14.3, 23.0)	20.0(14.0, 30.0)	-0.65	0.515
CR (umol/L)	70.9±16.1	75.4±14.9	-2.53	0.012	70.2±15.5	70.7±14.8	-0.16	0.872
HbA1c (%)	9.50±2.13	8.89±1.96	2.40	0.020	9.32±2.32	9.71±2.75	-0.78	0.434
FPG (mmol/L)	9.7±2.8	9.0±3.2	2.16	0.032	9.5±3.3	9.5±3.5	0.08	0.931
P2hPG (mmol/L)	19.4±3.9	18.1±4.7	2.44	0.015	18.9±4.9	19.5±4.9	-0.49	0.636
FCP (nmol/L)	2.24(1.71, 3.02)	2.50(1.87, 3.41)	-2.52	0.012	1.81(1.30, 2.74)	1.92(1.32, 3.09)	-0.87	0.388
P2hCP (nmol/L)	5.00(3.63, 6.73)	6.52(4.87, 8.43)	-4.45	<0.001	4.87(3.20, 6.68)	5.46(3.58, 7.69)	-0.72	0.474
FCPI	0.24(0.17,0.34)	0.31(0.22, 0.42)	-3.82	<0.001	0.22(0.16, 0.30)	0.25(0.15, 0.36)	-0.88	0.381
PPCPI	1.46(0.95, 2.36)	2.04(1.35, 2.95)	-4.52	<0.001	1.45(0.94, 2.18)	1.76(0.94, 2.60)	-0.36	0.716
ΔC-peptide	2.52(1.44, 4.07)	3.81(2.28, 5.46)	-4.26	<0.001	2.82(1.60, 4.77)	3.36(1.77, 4.66)	-0.69	0.492
HOMA2%B	45.4(30.3, 63.4)	60.3(37.6, 90.9)	-1.82	<0.001	40.3(29.2, 64.1)	43.5(26.7, 91.3)	-0.68	0.493
HOMA2IR	2.03(1.53, 2.75)	2.23(1.62, 3.16)	-4.69	0.007	1.64(1.17, 2.32)	1.86(1.12, 2.66)	-0.71	0.477

5   Values are expressed as mean ±standard deviation (SD) or median (range 25th-75th percentile)

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Table 3(on next page)

Correlation of selected variables with SUA in T2DM patients with overweight/obesity group

1   Table 3   Correlation of selected variables with SUA in T2DM patients with overweight/obesity group

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	Crude		Adjusted for Cr, BMI, sex		Adjusted for Cr, BMI, sex, HbA1c, Duration	
	r	p	r	p	r	p
HbA1c	-0.186	0.002	-0.226	<0.001		
FCP	0.194	0.001	0.130	0.034	0.115	0.085
P2hCP	0.286	<0.001	0.274	<0.001	0.220	0.001
FCPI	0.268	<0.001	0.222	<0.001	0.142	0.034
PPCPI	0.308	<0.001	0.296	<0.001	0.232	<0.001
ΔC-peptide	0.255	<0.001	0.275	<0.001	0.215	0.001
HOMA2%B	0.257	<0.001	0.235	<0.001	0.137	0.040
HOMA2IR	0.142	0.020	0.082	0.158	0.105	0.117

Table 4(on next page)

Multiple linear regression analysis for SUA and HOMA2%B in T2DM patients with overweight/obesity

1   Table 4 Multiple linear regression analysis for SUA and HOMA2%B in T2DM patients with overweight/obesity

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	Partial regression coefficient (B)	Standard error (SE)	Standard partial regression coefficient (β)	t	p-Value
HOMA2%B (unadjusted)	0.076	0.018	0.257	4.337	<0.001
HOMA2%B (adjusted for model 1: sex, Cr, BMI)	0.066	0.017	0.223	3.930	<0.001
HOMA2%B (adjusted for model 2: model 1, HbA1c and Duration)	0.049	0.022	0.182	2.135	0.013

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Table 5(on next page)

Clinical characteristics and islet function indexes of T2DM patients by gender

1   Table 5 Clinical characteristics and islet function indexes of T2DM patients by gender

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5   Values

6   are

Variables	Male (N=234)	Female (N=146)	t/Z	P
SUA (umol/L)	292.0 (256.0, 339.5)	264.5 (233.5, 297.0)	5.01	<0.001
Age (years)	49.9 ± 12.3	57.2 ± 9.9	-6.03	<0.001
Duration (years)	3.3 (0, 8.0)	5.5 (1.0, 10.0)	-3.38	0.001
SBP (mmHg)	128.0 (114.8, 136.5)	130.0 (118.0, 140.0)	-0.91	0.363
DBP (mmHg)	80.0 (75.5, 90.0)	80.0 (70.0, 84.5)	-3.24	0.001
BMI (kg/m^2)	25.5 (23.8, 27.7)	25.4 (23.4, 27.3)	-1.71	0.088
TG (mmol/L)	1.99 (1.12, 3.13)	1.54 (0.96, 2.29)	-2.89	0.004
TCH (mmol/L)	4.44 (3.87, 5.20)	4.52 (3.94, 5.15)	-0.32	0.752
LDL (mmol/L)	2.58 (2.09, 3.10)	2.58 (2.34, 3.01)	-1.23	0.220
HDL (mmol/L)	0.95 (0.74, 1.07)	1.07 (0.92, 1.34)	-4.61	<0.001
ALT (U/L)	21.5 (16.0, 35.3)	18.0 (13.0, 26.9)	-3.68	<0.001
CR (umol/L)	75.5 (64.0, 87.3)	67.0 (56.8, 76.6)	-4.89	<0.001
HbA1c (%)	9.22 (7.98, 10.70)	8.45 (7.00, 11.2)	-1.97	0.051
FBS (mmol/L)	9.50 ± 2.99	9.16 ± 3.35	1.04	0.301
P2hBS (mmol/L)	18.85 ± 4.36	18.80 ± 4.81	0.11	0.913
FCP (nmol/L)	2.25 (1.69, 3.27)	2.26 (1.58, 3.03)	-1.33	0.182
P2hCP (nmol/L)	5.53 (3.94, 7.34)	5.74 (4.21, 8.04)	-0.94	0.346
FCPI	0.27 (0.18, 0.36)	0.26 (0.17, 0.35)	-0.43	0.671
PPCPI	1.61 (1.04, 2.45)	1.71 (1.01, 2.85)	-0.91	0.365
ΔC-peptide	2.97 (1.74, 4.30)	3.29 (1.95, 5.40)	-1.97	0.053
HOMA2%B	47.3 (31.6, 75.1)	52.3 (30.5, 79.9)	-0.75	0.471
HOMA2IR	2.04 (1.47, 3.09)	2.02 (1.31, 2.63)	0.45	0.140

7   expressed as mean ±standard deviation (SD) or median (range 25th-75th percentile)

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Table 6(on next page)

Clinical characteristics and islet function indexes of male and female group by the median of SUA

1 Table 6 Clinical characteristics and islet function indexes of male and female group by the median of SUA

2

Variables	Male group (n=234)				Female group (n=146)			
	LSUA <292 umol/L	HSUA ≥292 umol/L	t/Z	P	LSUA <264.5 umol/L	HSUA ≥264.5umol/L	t/Z	P
Age (years)	50.78 ± 12.79	48.91 ± 11.76	1.16	0.247	55.90 ± 9.27	58.3 ± 10.49	-1.44	0.153
Duration (years)	4.0 (0.1, 8.0)	3.0 (0.0, 7.0)	-0.76	0.447	5.0 (1.0, 10.0)	6.0 (1.3, 10.0)	-0.70	0.481
SBP (mmHg)	128.0 (115.0, 136.0)	126.0 (114.0, 138.0)	-0.35	0.726	128.0 (118.0, 136.0)	130.0 (120.0, 140.0)	-1.26	0.209
DBP (mmHg)	80.0 (74.0, 90.0)	80.0 (76.0, 90.0)	-0.45	0.685	76.0 (70.0, 80.0)	80.0 (70.0, 88.0)	-1.20	0.229
BMI (kg/m^2)	25.4 (23.2, 26.6)	25.9 (24.5, 28.4)	-3.44	0.001	24.9 (22.5, 26.1)	25.5 (23.6, 27.9)	-2.02	0.044
TG (mmol/L)	1.93 (1.02, 2.59)	2.01 (1.27, 3.35)	-1.69	0.089	1.43 (0.91, 1.91)	1.82 (1.03, 2.72)	-2.21	0.027
TCH (mmol/L)	4.38 (3.80, 5.19)	4.57 (3.92, 5.18)	-0.99	0.319	4.55 (3.95, 5.22)	4.43 (3.91, 5.05)	-0.55	0.585
LDL (mmol/L)	2.58 (2.07, 3.10)	2.58 (2.15, 3.12)	-0.88	0.380	2.58 (2.33, 2.99)	2.58 (2.34, 3.02)	-0.36	0.720
HDL (mmol/L)	0.98 (0.74, 1.10)	0.91 (0.76, 1.07)	-0.85	0.395	1.10 (1.01, 1.63)	1.07 (0.81, 1.23)	-3.38	0.001
ALT (U/L)	18.0 (14.0, 31.0)	25.0 (18.0, 42.0)	-3.48	<0.001	19.0 (13.0, 26.5)	18.0 (13.5, 27.0)	-0.42	0.676
CR (umol/L)	76.0 (63.0, 88.0)	74.0 (65.0, 86.0)	-0.03	0.978	62.0 (52.5, 74.0)	72.0 (61.5, 78.5)	-2.95	0.003
HbA1c (%)	9.90 (8.30, 11.30)	8.80 (7.70, 10.0)	4.30	<0.001	8.10 (6.85, 10.65)	8.73 (7.02, 11.42)	-1.18	0.237
FBS (mmol/L)	10.09 ± 2.82	8.89 ± 3.05	3.10	0.002	8.75 ± 3.17	9.57 ± 3.49	-1.50	0.137
P2hBS (mmol/L)	19.78 ± 3.99	17.88 ± 4.55	3.42	0.001	18.29 ± 4.76	19.32 ± 4.82	-1.33	0.186
FCP (nmol/L)	2.20 (1.65, 2.91)	2.46 (1.73, 3.60)	-1.95	0.051	2.11 (1.29, 2.85)	2.40 (1.78, 3.23)	-1.99	0.046
P2hCP (nmol/L)	4.85 (3.54, 6.67)	6.19 (4.48, 8.06)	-3.95	<0.001	5.41 (3.79, 7.76)	6.17 (4.45, 8.65)	-1.48	0.138
FCPI	0.22 (0.17, 0.33)	0.31 (0.22, 0.47)	-3.93	<0.001	0.25 (0.16, 0.33)	0.26 (0.17, 0.41)	-0.86	0.392
PPCPI	1.35 (0.92, 1.96)	2.03 (1.41, 2.69)	-4.53	<0.001	1.69 (1.05, 2.76)	1.84 (0.99, 3.08)	-0.91	0.362
ΔC-peptide	2.32 (1.38, 3.84)	3.55 (2.26, 5.27)	-4.01	<0.001	3.08 (1.84, 5.25)	3.75 (2.19, 5.51)	-1.06	0.288
HOMA2%B	38.3 (27.9, 59.8)	59.3 (37.3, 89.0)	-4.39	<0.001	56.5 (37.2, 74.6)	48.7 (27.2, 86.7)	-0.27	0.784
HOMA2IR	1.98 (1.49, 2.65)	2.20 (1.43, 3.25)	-1.24	0.214	1.81 (1.19, 2.49)	2.18 (1.54, 2.97)	-2.38	0.017

3 Values are expressed as mean ±standard deviation (SD) or median (range 25th-75th percentile)

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Table 7(on next page)

Correlation of SUA with selected variables in T2DM patients with male and female group

1   Table 7 Correlation of SUA with selected variables in T2DM patients with male and female group

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		Crude		Adjusted for Cr, BMI		Adjusted for Cr, BMI, HbA1c, Duration	
		r	p	r	p	r	p
Male group	HbA1c	-0.291	<0.001	-0.284	<0.001		
	FCP	0.235	0.001	0.142	0.031	0.101	0.127
	P2hCP	0.331	<0.001	0.280	<0.001	0.163	0.013
	FCPI	0.356	<0.001	0.288	<0.001	0.178	0.007
	PPCPI	0.351	<0.001	0.322	<0.001	0.195	0.003
	ΔC-peptide	0.293	<0.001	0.273	<0.001	0.147	0.026
	HOMA2%B	0.350	<0.001	0.319	<0.001	0.195	0.003
	HOMA2IR	0.156	0.017	0.065	0.322	0.066	0.320
Female group	HbA1c	0.013	0.876	0.011	0.884		
	FCP	0.165	0.046	0.108	0.199	0.113	0.182
	P2hCP	0.203	0.014	0.182	0.029	0.200	0.017
	FCPI	0.171	0.039	0.137	0.101	0.155	0.066
	PPCPI	0.135	0.104	0.114	0.175	0.133	0.116
	ΔC-peptide	0.182	0.028	0.177	0.034	0.198	0.018
	HOMA2%B	0.134	0.106	0.135	0.108	0.163	0.053
	HOMA2IR	0.149	0.072	0.090	0.282	0.094	0.268

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Table 8(on next page)

Multiple linear regression analysis for SUA and HOMA2%B or HOMA2IR in T2DM patients by gender category

1   Table 8 Multiple linear regression analysis for SUA and HOMA2%B or HOMA2IRin T2DM patients by

2   gender category

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		Partial regression coefficient (B)	Standard error (SE)	Standard partial regression coefficient (β)	t	p-Value
Male group	HOMA2%B					
	unadjusted	0.514	0.090	0.350	5.69	<0.001
	adjusted for model 1: Cr, BMI	0.458	0.090	0.312	5.10	<0.001
	adjusted for model 2: model 1, HbA1c and Duration	0.319	0.107	0.217	2.99	0.003
	HOMA2IR					
	unadjusted	2.986	3.323	0.156	2.40	0.017
	adjusted for model 1: Cr, BMI	3.415	3.443	0.067	0.99	0.322
	adjusted for model 2: model 1, HbA1c and Duration	3.346	3.359	0.065	0.99	0.320
Female group	HOMA2%B					
	unadjusted	0.141	0.087	0.134	1.626	0.106
	adjusted for model 1: Cr, BMI	0.137	0.085	0.131	1.618	0.108
	adjusted for model 2: model 1, HbA1c and Duration	0.197	0.101	0.188	1.949	0.053
	HOMA2IR					
	unadjusted	4.703	2.593	0.149	1.814	0.072
	adjusted for model 1: Cr, BMI	2.783	2.578	0.088	1.079	0.282
	adjusted for model 2: model 1, HbA1c and Duration	2.940	2.646	0.093	1.111	0.268

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Table 9(on next page)

Multiple linear regression analysis on related variables for islet function indexes in T2DM patients

1

2   Table 9   Multiple linear regression analysis on related variables for islet function indexes in T2DM patients

		Partial regression coefficient (B)	Standard error (SE)	Standard partial regression coefficient (β)	p-Value
HOMA2%B	HbA1c	-9.103	0.781	-0.501	<0.001
	SUA	0.127	0.032	0.177	<0.001
	age	0.486	0.159	0.146	0.002
	BMI	1.143	0.522	0.095	0.029
	Duration	-0.697	0.327	-0.100	0.034
HOMA2IR	BMI	0.089	0.018	0.241	<0.001
	TG	0.076	0.023	0.165	0.001
	Duration	-0.029	0.010	-0.134	0.006