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# Association between triglyceride glucose index and peak growth hormone in children with short stature

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Growth hormone (GH) secretion is related to many factors, such as weight and puberty, and the reproducibility of GH provocation tests is very poor. This study aimed to evaluate whether the triglyceride (TyG) index was associated with peak GH in children with short stature. This study included 1095 children with short stature divided into two groups based on peak GH level in GH provocation tests [GH deficiency (GHD) group = 733 children; non-GHD group = 362 children]. We found that the TyG index was significantly higher in the GHD group than in the non-GHD group ( $P < 0.001$ ). A nonlinear relationship was detected between the TyG index and peak GH, whose point was 7.8. A significant negative association between the TyG index and peak GH was observed when the TyG index was greater than 7.8 ( $\beta - 2.61$ , 95% CI  $-3.98, -1.24$ ;  $P < 0.001$ ), whereas, the relationship between the TyG index and peak GH was not significant when the TyG index was lower than 7.8 ( $\beta 0.25$ , 95% CI  $-1.68, 2.17$ ;  $P = 0.799$ ). There is a nonlinear relationship between the TyG index and peak GH, and a higher TyG index is associated with decreased peak GH in children with short stature.

Short stature is defined by a height more than two standard deviation scores (SDS) below the median height for the relevant age and sex of the subject, and the most common reasons for short stature are growth hormone deficiency (GHD) and idiopathic short stature (ISS)<sup>1</sup>. Growth hormone (GH) provocation tests are indispensable in assessing the aetiology of short stature. However, GH secretion is regulated by multiple physiologic factors, including age, sex, body mass index (BMI) and onset of puberty, which sometimes may produce false-positive results<sup>2–4</sup>. Previous studies have demonstrated that obese children and adolescents have a reduced stimulated GH response to provocative testing<sup>5</sup>, and it is well known that there is a significant negative association between BMI and peak GH<sup>6,7</sup>. Furthermore, insulin resistance (IR) has been demonstrated to be involved in the relationship between BMI and reduced growth hormone secretion<sup>8</sup>. The triglyceride glucose (TyG) index, which is calculated from fasting measurements of triglycerides and glucose, has been recently suggested as a reliable surrogate marker of IR.

Considerable previous studies have demonstrated that the TyG index is significantly related to an increased risk of developing coronary artery disease (CAD), type 2 diabetes, prehypertension and hypertension<sup>9–11</sup>; among these conditions, IR plays a major role in their progression<sup>12,13</sup>. The hyperinsulinaemic-euglycaemic clamp is the “gold standard” test for measuring IR<sup>14</sup>. However, due to the complexity of the testing process, it is not commonly used in clinical settings. A previous study observed that the TyG index was more sensitive and specific for evaluating IR compared with the hyperinsulinaemic-euglycaemic clamp test<sup>15</sup>.

GH is a significant regulator of metabolic homeostasis by regulating liver uptake of triglycerides and glucose and stimulating lipolysis in adipose tissue<sup>16</sup>. Glucose and lipid abnormalities have been reported in patients with GHD<sup>17</sup>. A study has shown that GH regulates the body’s sensitivity to insulin as a direct result of its induction

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|                          | All                    | GHD                    | Non-GHD               | P       |
|--------------------------|------------------------|------------------------|-----------------------|---------|
| Number                   | 1095                   | 733                    | 362                   | –       |
| Sex (male %)             | 720 (65.75%)           | 484 (66.03%)           | 236 (65.19%)          | 0.784   |
| Age (years)              | 10.57 ± 3.30           | 10.41 ± 3.19           | 10.88 ± 3.49          | 0.027   |
| Height (cm)              | 131.44 ± 17.89         | 130.34 ± 17.12         | 133.67 ± 19.18        | 0.004   |
| Height SDS               | – 2.85 ± 0.84          | – 2.85 ± 0.85          | – 2.86 ± 0.82         | 0.971   |
| Body weight (kg)         | 31.80 ± 12.99          | 31.75 ± 13.13          | 31.91 ± 12.72         | 0.851   |
| BMI (kg/m <sup>2</sup> ) | 17.57 ± 3.44           | 17.84 ± 3.62           | 17.01 ± 2.97          | < 0.001 |
| BMI SDS                  | – 0.05 ± 1.26          | 0.01 ± 1.28            | – 0.16 ± 1.22         | 0.032   |
| SBP (mmHg)               | 107.04 ± 12.30         | 106.57 ± 12.31         | 107.99 ± 12.23        | 0.072   |
| DBP (mmHg)               | 62.67 ± 8.35           | 62.37 ± 8.30           | 63.28 ± 8.45          | 0.091   |
| IGF-1 (ng/ml)            | 198.00 (114.75–321.00) | 190.00 (120.00–283.00) | 225.50(109.00–406.00) | < 0.001 |
| IGF-1 SDS                | – 1.02 (– 1.84–0.18)   | – 1.02 (– 1.81–0.17)   | – 1.02 (– 1.90–0.24)  | 0.803   |
| IGFBP-3 (µg/ml)          | 4.87 ± 1.70            | 4.84 ± 1.82            | 4.93 ± 1.40           | 0.451   |
| Peak GH (ng/ml)          | 8.92 ± 6.07            | 5.61 ± 2.41            | 15.63 ± 5.69          | < 0.001 |
| FPG (mg/dl)              | 85.48 ± 10.71          | 84.97 ± 10.81          | 86.54 ± 10.44         | 0.026   |
| TG (mg/dl)               | 68.73 ± 33.80          | 71.89 ± 37.13          | 62.21 ± 24.39         | < 0.001 |
| TC (mg/dl)               | 147.35 ± 26.76         | 148.41 ± 26.70         | 145.15 ± 26.77        | 0.066   |
| HDL (mg/dl)              | 52.77 ± 11.91          | 52.83 ± 12.39          | 52.66 ± 10.87         | 0.832   |
| LDL (mg/dl)              | 264.03 ± 14.96         | 353.95 ± 11.14         | 77.55 ± 21.13         | 0.328   |
| TyG index                | 7.89 ± 0.43            | 7.92 ± 0.45            | 7.82 ± 0.39           | < 0.001 |
| Pubertal stage           |                        |                        |                       | < 0.001 |
| In prepuberty (%)        | 624 (56.99%)           | 454 (61.94%)           | 170 (46.96%)          |         |
| In puberty (%)           | 471 (43.01%)           | 279 (38.06%)           | 192 (53.04%)          |         |

**Table 1.** Clinical and biochemical characteristics. Abbreviations: Height SDS: height standard deviation scores; BMI SDS: body mass index standard deviation scores; IGF-1 SDS: insulin like growth factor-1 standard deviation scores; IGFBP-3: insulin-like growth factor-binding protein-3; Peak GH: peak growth hormone; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol. HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; TyG index: triglyceride glucose index. Normal distribution of data was presented as mean ± standard deviation; nonnormal distribution of data was presented as median (interquartile range) and categorical data using number (percentage).  $P < 0.05$  is considered to be statistically significant.

of lipid metabolism (release of free fatty acids) in adipose tissue<sup>18</sup>. IR may play an important role in glucose and lipid metabolism disorders associated with GHD. However, the association between IR and GH is controversial, with both positive and negative relationships reported<sup>19–21</sup>. Furthermore, the association of BMI and GH is well accepted; however, the potential mechanisms that underpin these effects are still not firmly established. It is well known that IR is closely related to obesity<sup>22</sup> and that with an increase in BMI, GH secretion is reduced, indicating that IR is associated with the level of GH. The TyG index is a useful indicator for evaluating IR, but it is not very clear whether there is an association between the TyG index and peak GH. Therefore, this study is designed to investigate whether the TyG index was independently related to peak GH in short stature.

## Results

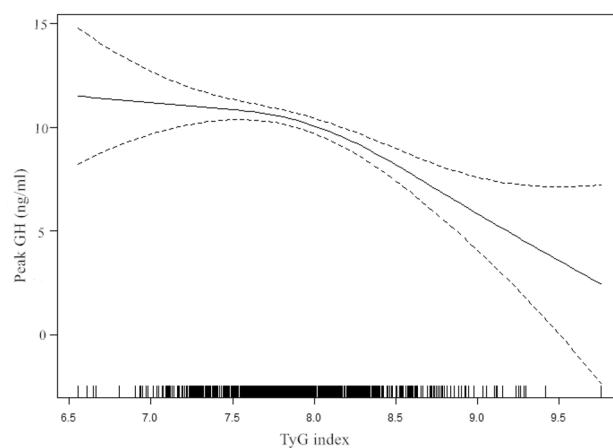
**Baseline characteristics of selected participants.** We provide the baseline characteristics of these selected participants in the GHD and non-GHD groups in Table 1. In general, the average age of the 1095 selected participants was  $10.6 \pm 3.3$  years old, and approximately 65.75% of them were male. No statistically significant differences were detected in height SDS, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), IGF-1 SDS, IGFBP-3, TC, HDL-C or LDL-C among the different GH groups (all  $p$  values  $> 0.05$ ). Participants in the GHD group had higher BMI, BMI SDS, TG and TyG values (all  $p$  values  $< 0.05$ ).

**Factors associated with peak GH in the subjects.** We list the results of univariate analyses in Table 2. By univariate linear regression, we found that sex, height SDS, weight, SBP, DBP, IGF-1 SDS, IGFBP-3, HDL-C and LDL-C were not associated with GH peak (all  $p$  values  $> 0.05$ ). We also found that BMI SDS, TG, TC, and TyG were negatively associated with peak GH (all  $p$  values  $< 0.05$ ). In contrast, univariate analysis showed that age, FPG and pubertal stage were positively correlated with peak GH (all  $p$  values  $< 0.05$ ).

**The results of nonlinearity of the TyG index and peak GH.** In the present study, we analysed the nonlinear relationship between the TyG index and peak GH (Fig. 1). Covariate screening was done to screen for possible confounders. The screening criteria included effect factors producing a  $> 10\%$  change when introducing covariates into the basic model or eliminating covariates from the regression model. The results revealed that age, sex, BMI, TC and pubertal stage met the filter criteria. The results of the smooth curve showed that the rela-

| Variables                   | $\beta$   | (95% CI)       | P value |
|-----------------------------|-----------|----------------|---------|
| Age (years)                 | 0.17      | (0.06, 0.28)   | 0.002   |
| Height SDS                  | 0.03      | (-0.40, 0.46)  | 0.225   |
| Body weight (kg)            | -0.01     | (-0.03, 0.02)  | 0.680   |
| BMI SDS                     | -0.34     | (-0.63, -0.05) | 0.020   |
| SBP (mmHg)                  | 0.02      | (-0.01, 0.05)  | 0.119   |
| DBP (mmHg)                  | 0.02      | (-0.02, 0.06)  | 0.326   |
| IGF-1 SDS                   | 0.16      | (-0.12, 0.45)  | 0.261   |
| IGFBP-3( $\mu\text{g/ml}$ ) | 0.13      | (-0.11, 0.36)  | 0.290   |
| FPG (mg/dl)                 | 0.05      | (0.02, 0.09)   | 0.002   |
| TG (mg/dl)                  | -0.03     | (-0.04, -0.02) | <0.001  |
| TC (mg/dl)                  | -0.02     | (-0.04, -0.01) | <0.001  |
| HDL (mg/dl)                 | -0.01     | (-0.04, 0.02)  | 0.395   |
| LDL (mg/dl)                 | -0.01     | (-0.01, 0.01)  | 0.459   |
| TyG index                   | -2.02     | (-2.86, -1.18) | <0.001  |
| <b>Sex</b>                  |           |                |         |
| Male                        | reference |                |         |
| Female                      | 0.47      | (-0.29, 1.23)  | 0.226   |
| <b>Pubertal stage</b>       |           |                |         |
| In prepuberty (%)           | reference |                |         |
| In puberty (%)              | 2.26      | (1.55, 2.98)   | <0.001  |

**Table 2.** Association between GH peak and different variables. Abbreviations: Height SDS: height standard deviation scores; BMI SDS: body mass index standard deviation scores; IGF-1 SDS: insulin like growth factor-1 standard deviation scores; IGFBP-3: insulin-like growth factor-binding protein-3; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol. HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; TyG index: triglyceride glucose index.  $P < 0.05$  is considered to be statistically significant.



**Figure 1.** The relationship between TyG index and peak GH by smooth curve fitting. Adjustment variables: age, sex, BMI, TC, pubertal stage. BMI: body mass index, TC: total cholesterol.

tionship between the TyG index and GH peak was nonlinear after adjusting for potential confounding factors. As shown in Table 3, we used both linear regression and two-piecewise linear regression to fit the association and select the best fit model based on P for the log likelihood ratio test.

Because the P for the log likelihood ratio test was less than 0.05, we chose two-piecewise linear regression for fitting the association between the TyG index and peak GH because it can accurately represent the relationship. Using two-piecewise linear regression and a recursive algorithm, we calculated that the inflection point was 7.8. A multivariate piecewise linear regression model revealed a significant negative association between the TyG index and peak GH when the TyG index was greater than 7.8 ( $\beta - 2.61$ , 95% CI - 3.98, - 1.24;  $P < 0.001$ ). However, we did not observe a significant relationship between the TyG index and GH peak when the TyG index was lower than 7.8 ( $\beta 0.25$ , 95% CI - 1.68, 2.17;  $P = 0.799$ ).

| Models          | Peak GH                  |         |
|-----------------|--------------------------|---------|
|                 | Adjusted $\beta$ (95%CI) | P value |
| <b>Model I</b>  |                          |         |
| One line slope  | -1.52 (-2.37, -0.66)     | 0.0005  |
| <b>Model II</b> |                          |         |
| Turning point   | 7.8                      |         |
| <7.8 slope 1    | 0.25 (-1.68, 2.17)       | 0.799   |
| >7.8 slope 2    | -2.61 (-3.98, -1.24)     | <0.001  |
| LRT test        | 0.044                    |         |

**Table 3.** The independent association between the TyG index and peak GH. Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test. ( $p$  value < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); Adjustment variables: age, sex, BMI, TC, pubertal stage. BMI: body mass index, TC: total cholesterol;  $P$  < 0.05 is considered to be statistically significant.

## Discussion

Our findings indicate that the TyG index is negatively associated with peak GH after adjusting for other covariates. Interestingly, we found a nonlinear relationship between the TyG index and peak GH in children and adolescents with short stature. The results of this study show that a stronger association was detected when the TyG index was greater than 7.8. In contrast, we did not observe an association between the TyG index and peak GH when the TyG index was less than 7.8.

We observed that the TyG index is negatively associated with peak GH. Previous studies that directly explored the TyG index and peak GH are limited, but the TyG index is an effective indicator for evaluating IR, and the TyG index has high sensitivity for recognizing IR compared with the homeostasis model assessment of insulin resistance (HOMA-IR) index<sup>23</sup>. Regarding the association between IR and GH, Husbands S et al. reported that there is increased insulin sensitivity in young GH-deficient children<sup>19</sup>, but Johansson, J. O et al. observed that there is decreased insulin sensitivity in adults with GHD<sup>20</sup>. Bredella, M. A et al. found that peak GH was inversely associated with HOMA-IR in premenopausal women with obesity<sup>24</sup>. Our results found a negative correlation between peak GH and the TyG index, which was used to assess IR in children and adolescents with short stature. In addition to its role in promoting growth, peak GH is also an anabolic hormone that affects the metabolism of lipids and glucose, which may explain the IR with GHD<sup>25</sup>.

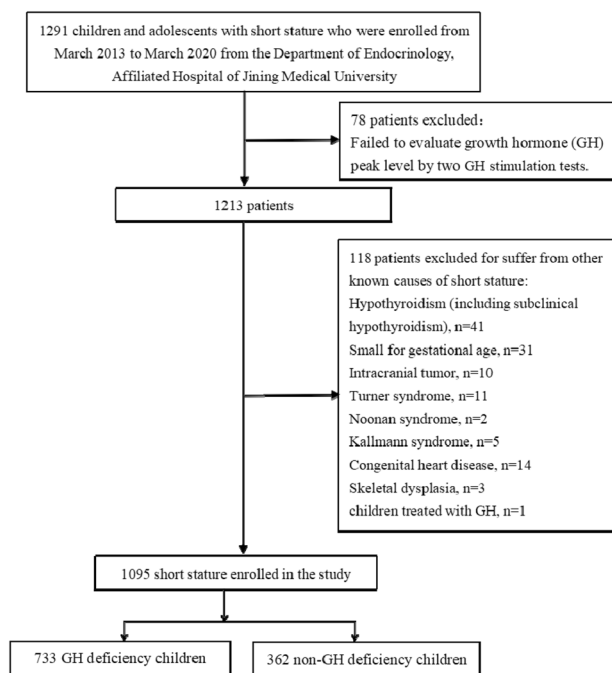
It is interesting that we revealed a nonlinear relationship between the TyG index and peak GH, suggesting that certain TyG index levels may affect the peak GH. It is well known that GHD in childhood or adulthood is associated with abnormal glucose and lipid metabolism and an increased risk of adverse cardiovascular events<sup>17,26,27</sup>, which indicates that the TyG index may be associated with peak GH. More importantly, the TyG index has been suggested as a reliable surrogate marker of IR, which is a substantial risk factor for adverse cardiovascular events<sup>28–30</sup>. The mechanisms responsible for IR in GHD are not known, but a key contributor to the markedly reduced insulin-stimulated glycogen synthase activities in GHD could be an increased availability of free fatty acids (FFAs)<sup>31,32</sup>. In addition, previous studies have shown that GH therapy can improve IR in GHD<sup>33,34</sup>.

This study demonstrates that there is an association between the TyG index and peak GH, but no causal relationship can be concluded. Our results showed that when the TyG index was greater than 7.8, a stronger association between the TyG index and peak GH was detected. This is consistent with the level of the TyG index reported in a previous study to assess the risk of IR<sup>35</sup>. Although the relationship between GH and IR has been well established, GH can also affect glycolipid metabolism<sup>36</sup>. In adipose tissue, GH facilitates lipolysis, stimulates glycerol release<sup>37</sup>, and inhibits lipoprotein lipase activity<sup>38</sup>. Increased release of FFAs from excess visceral fat may link GHD to increased glucose<sup>36</sup>. Furthermore, previous studies have shown that GH therapy can improve the blood lipid profile in GHD<sup>39</sup>.

It is well known that the secretion of GH is significantly reduced in obese individuals compared to age-matched controls<sup>40</sup>. Given the clear relationship between BMI and peak stimulated GH demonstrated in short stature, our findings are consistent with previous studies<sup>6,7</sup>. We found a negative association between BMI and peak GH in children with short stature. Our data demonstrated that the GH peak response to stimulation testing decreased with increasing BMI SDS in a large cohort of normal weight children with a range of BMIs that approximated a normal distribution (mean BMI SDS of  $-0.05 \pm 1.26$ ). In addition, peak GH likely varies according to pubertal stage<sup>41</sup>. Our study showed a positive association between puberty and GH peak. Spontaneous and stimulated peak GH levels are higher in pubertal children than in prepubertal children. As puberty progresses, the peak GH increases, which may be related to changes in sex hormones in the body<sup>41,42</sup>.

However, this study has some limitations. First, because of the cross-sectional analysis, no definitive causative relationship can be inferred in the study. Second, the present findings are only based on children with short stature, and different results might be observed in other groups, such as children with obesity. Third, there may have been interobserver variability in assessing anthropometric measurements, but the anthropometric measurements were performed by one of two trained professionals. Finally, further investigation is necessary to follow up on blood lipid and glucose changes to determine whether these changes improve after GH treatment.

In conclusion, this study demonstrated that children with GHD presented an elevated TyG index compared with non-GHD children. A nonlinear relationship between the TyG index and peak GH was observed, and an increase in the TyG index was associated with a decrease in the peak GH peak in children with short stature.



**Figure 2.** Flow chart of the study population.

## Methods

**Study population.** The subjects were enrolled from March 2013 to March 2020 at the Department of Endocrinology, Affiliated Hospital of Jining Medical University. They are part of the GDDSD study (Growth and Development Diseases in Shandong Province: a cohort follow-up study, <http://www.chictr.org.cn>, ChiCTR1900026510). A total of 1095 children and adolescents with short stature (720 males and 375 females) with an average age of  $10.6 \pm 3.3$  years were enrolled. All enrolled children were assessed for GHD and non-GHD based on the GH peak level in provocation tests. Children with GH peaks below  $10 \text{ ng/mL}$  in two different provocation tests were classified as GHD<sup>43</sup>. The subjects with a height SDS lower than or equal to  $-2$  SD after adjusting for age and sex, an appropriate birth weight for gestational age, and who completed two GH stimulation tests were included in the study. The exclusion criteria included children with skeletal dysplasia, thyroid dysfunction or other known causes of short stature, including Noonan syndrome, Turner syndrome, or having been small for gestational age. In addition, children treated with medication interfering with GH secretion or its action were also excluded. The flow chart of the study selection process is shown in Fig. 2.

**Ethics.** This proposal was reviewed and approved by the Human Ethics Committee of the Affiliated Hospital of Jining Medical University (JYFY-2015-019) and all methods were performed in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants or their parents.

**Data collection.** All of the data were collected by reviewing the medical records of the medical centre. The height was measured to the nearest  $0.1 \text{ cm}$  without shoes using a stadiometer (Nantong Best Industrial Co, Ltd., Jiangsu; China). The weight was measured by an electronic scale to the nearest  $0.1 \text{ kg}$  (Wuxi Weigher Factory Co, Ltd., Jiangsu; China) while the individual was wearing light clothes without shoes. In addition, height and weight were measured by a designated individual using the same measuring instrument in the morning. Height SDS was expressed using the growth curve of Chinese children as a reference<sup>44</sup>. The body mass index (BMI) was calculated as the ratio of the weight divided by the square of the height in metres, and the BMI SDS was calculated according to the normal children reference<sup>45</sup>. Puberty stage was evaluated by one of two pretrained physicians during a physical examination, based on the Tanner stages<sup>46</sup>. The following criteria can be considered prepubescent: boys with no pubic hair and testicular volume less than  $4 \text{ mL}$  and girls with no pubic hair and no breast development.

Fasting blood samples were obtained from all subjects for measuring laboratory parameters. Two stimulating tests were performed for GH (500 mg of levodopa for those weighing more than  $30 \text{ kg}$ ; 250 mg of levodopa for those weighing less than  $30 \text{ kg}$ , orally and  $0.1 \text{ U/kg}$  insulin, subcutaneously). Blood samples were collected at 0, 30, 60, 90, and 120 min after administration to obtain serum GH concentrations at each time point. A chemiluminescence method was used to assess GH concentration (ACCESS2, Beckman Coulter; USA). It had intra- and interassay CVs of 3.5% and 5.8%, respectively. Insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) were measured by a chemiluminescence assay (DPC IMMULITE 1000 analyser, SIEMENS, Germany) that had intra- and interassay CVs of 3.0% and 6.2% for IGF-1 and 4.4% and 6.6% for IGFBP-3, respectively. Fasting plasma glucose (FPG), lipid profiles (triglycerides (TG), total cholesterol (TC), high-density

lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C)) were determined by an auto-biochemical analyser (Cobas c702, Roche; Shanghai, China). The interassay coefficient of variation of the TG assay was 8.3%, TC was 3.3%, HDL-C was 10.0%, LDL-C was 10.0% and FPG was 3.0%. The TyG index was obtained as  $\ln [\text{fasting TG (mg/dl)} \times \text{FPG (mg/dl)} / 2]^{23}$ . The IGF-1 SDS was calculated based on IGF-1 levels matched to the age and sex of healthy children and adolescents identified in Japan<sup>47</sup>. All methods were performed in accordance with the relevant guidelines and regulations.

**Statistical analysis.** In this study, our presentation of continuous variables was based primarily on whether they were normally distributed. If it was a normal distribution, we present continuous variables as the mean  $\pm$  standard, and vice versa as the median (interquartile). Categorical variables were expressed as frequencies or percentages. We used  $\chi^2$  (categorical variables), Student's *t* test (normal distribution), or the Kruskal–Wallis *H* test (skewed distribution) to test for differences among the GHD and non-GHD groups. Univariate analysis was used to assess whether the TyG index and other variables were associated with the GH peak. Multiple linear regression adjusted for potential confounding factors was used to further analyse the independent association between the TyG index and GH peak. A smooth curve fitting was used to explore the relationship between the TyG index and GH peak. Finally, a multivariate piecewise linear regression was further used to examine the threshold correlation of the TyG index and GH peak according to the smooth curve fit. A two-tailed  $P < 0.05$  was considered statistically significant in all analyses. Statistical analysis was performed with R 3.4.3 (<https://www.R-project.org>) and EmpowerStats (<https://www.empowerstats.com>, X&Y Solutions, Inc. Boston MA).

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## Author contributions

Q.Z. carried out the studies and drafted the manuscript. Y.C. helped with the statistical analysis. H.P. revised the manuscript. B.B. and M.Z. participated in the concept and design of the study, revising it critically for important intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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