Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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ORIGINAL RESEARCH

A Novel Indicator of Children's Lipid Accumulation Product Associated with Impaired Fasting Glucose in Chinese Children and Adolescents

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Background: Diabetes is one of the most prevalent noncommunicable diseases worldwide. Children's lipid accumulation product (CLAP) is a novel indicator to show children's lipid accumulation and is effectively associated with metabolic syndrome among children and adolescents. The aim of the present study was to explore an association between CLAP and impaired fasting glucose (IFG) in Chinese children and adolescents.

Methods: A total of 683 children and adolescents aged 8–15 years were recruited using the stratified cluster sampling method in this cross-sectional study and were measured for body height, weight, waist circumference (WC), abdominal skinfold thickness (AST), triglycerides (TG), fasting plasma glucose, dietary behaviors and physical activities. A logistic regression model and receiver operating characteristic (ROC) curve were used to compare the effects of CLAP for predicting IFG.

Results: The prevalence of IFG in children and adolescents was 13.8%: 16.9% in boys and 10.1% in girls ($P<0.05$). The CLAP, height, weight, WC, AST, waist-to-height ratio (WHtR), and TG among boys with IFG were significantly higher than those among boys without IFG ($P<0.05$). The area under the ROC curve of CLAP for predicting IFG (0.637 (0.562–0.712)) was higher than those of WC, WHtR, AST, and TG. The cutoff point of P_{75} CLAP was the optimal value to predict IFG among boys, and the OR (95% CI) was 2.48 (1.40–4.42) and area under the ROC curve was 0.595 (0.513–0.676).

Conclusion: The CLAP was a novel indicator associated with IFG in Chinese boys, and it performed better than WC, WHtR, AST and TG.

Keywords: impaired fasting glucose, children's lipid accumulation product, children and adolescents

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Introduction

Diabetes is one of the most prevalent noncommunicable diseases worldwide, especially in developing countries.[1] The International Diabetes Federation reported approximately 86,000 new cases of T1DM in children per year worldwide.[2] A study showed that the prevalence of T2DM among adolescents and children increased by 30.5% in the United States from 2001 to 2009.[3] In addition, there was a high prevalence of impaired fasting glucose (IFG) in children.[4] A study from Chahkandi et al showed a prevalence of 10.6% for impaired fasting glucose in boys.[5] The individuals with impaired fasting glucose might progress to become diabetes patients.[6] The United States Preventive Services Task Force (USPSTF) recommended that screening for impaired fasting plasma glucose was important for preventing diabetes and identifying potential treatment for patients with undiagnosed diabetes.[7,8]

Previous studies reported that obesity and abdominal obesity were not only risk factors for insulin resistance syndrome but also related to abnormal glucose metabolism.[9] The BMI, waist circumference (WC), abdominal skinfold thickness (AST), and waist-to-height ratio (WHtR) are generally used to define obesity.[9–12] BMI has been considered as an effective indicator for identifying diabetes.[13] However, a recent study showed that half of obese people based on body fat percentage (BFP) were classified as normal weight by BMI. In addition, the study showed that 33% of people with normal weight according to BMI were diagnosed with prediabetes or had undiagnosed diabetes.[14] Ford et al[15] reported that WC was a better predictor of diabetes than BMI. Schulze et al[16] reported that WC and WHtR are equivalently stronger predictors of diabetes than BMI among women, and WHtR improved the predictive power of diabetes compared with WC among men. However, WC and WHtR did not show the excess body fat present in circulating blood.[17] Scholars have suggested that diabetes might be related to the accumulation of ectopic or liver fat.[18] The excess lipid fuel appeared eventually as an enlarged abdomen or as elevated circulating triglycerides (TG).[12]

Lipid accumulation product (LAP) was proposed to show the total lipid accumulation in adults: LAP for men= [WC (cm)-65]×TG (mmol/L); LAP for women= [WC (cm)-58]×TG (mmol/L).[19] In the formula above, the values 65 and 58 are the minimum WC for men and women, respectively. A growing number of studies have shown that LAP is a powerful marker for predicting fasting plasma glucose in adults. The study showed that LAP explained a greater variability in fasting plasma glucose (FPG) levels than WHtR and better predicted diabetes than BMI among young people.[18] The study from Kahn et al[19] showed that LAP was more effective in predicting diabetes than the waist-to-hip ratio (WHR) and WHtR. Zhang et al[20] developed children's lipid accumulation product (CLAP) that was calculated using the formula of WC (cm) × TG (mmol/L) × AST (mm)/100, and reported that CLAP was significantly associated with metabolic syndrome (MS), and was better than BMI and WHtR for predicting MS.

Although the LAP is an important index for predicting diabetes in adults, however, LAP cannot be directly applied to show lipid accumulation in children and adolescents. CLAP is a novel indicator to show children's lipid accumulation, however, it is not clear whether CLAP was associated with impaired fasting plasma glucose in children and adolescents. The purpose of this study was to explore a novel indicator of children's lipid accumulation product (CLAP) associated with impaired fasting plasma glucose.

Materials and Methods

Subjects

In this study, 683 students, including 366 boys (53.6%) and 317 girls (46.4%), aged 8–15 years were effectively recruited from two nine-year-system schools using a stratified cluster sampling method. The present study was approved by the Medical Ethics Committee of Bengbu Medical College (2015 No.003), and conducted in accordance with the Declaration of Helsinki. The participants' guardians signed informed consents before medical measurements.

Measurements of Anthropometric Indexes

The medical staff received standardized training to measure participants' body height, weight, WC and AST. The participants were required to have an empty stomach, be barefoot, stand straight, and wear light clothes for the measurements. Body height was measured using a mechanical height gauge with an accuracy of 0.1 cm. Weight was measured using an electronic weight scale with an accuracy of 0.1 kg. The WC that was the perimeter of the WC at 1 cm above the belly button was measured using nylon tape with an accuracy of 0.1 cm. The abdominal skinfold thickness (AST), which was the skinfold thickness at the junction of the right collarbone midline and belly button horizontal line, was measured using a skinfold thickness gauge with an accuracy of 0.1 mm.

Calculation of Derivative Indicators

BMI = weight (kg)/[height (m)]^2; WHtR = WC (cm)/height (cm); Children's lipid accumulation product (CLAP) = WC (cm) × TG (mmol/L) × AST (mm)/100.[20]

Survey of Behavioral Indexes

In this study, we surveyed the frequency of dietary behaviors, including the consumption of fresh vegetables, breakfast, fruits, eggs, milk, nuts, carbonated drinks, outside meals, Western fast food, fried foods, and high-energy snacks. Each dietary behavior score was assigned 0 points for never, 0.25 points for 1 time per month, 0.5 points for 2 times per month, 2 points for 1–3 times per week, 5 points for 4–6 times per week, and 7 points for 1 time per day. The total scores of healthy dietary behaviors (including fresh vegetables, breakfast, fruits, eggs, milk, and nuts) and risky dietary behaviors (including carbonated drinks, outside meals, Western fast food, fried foods, and high-energy snacks) were calculated.[21] According to the 75th percentile (P_{75}) of healthy and risky dietary behaviors total scores, the children were divided into two groups, ≥ P_{75} and <P_{75}, respectively. Physical activity was investigated through the Children's Leisure Activity Study Survey (CLASS) questionnaire.[22] The moderate to vigorous physical activity time was divided into ≥60 min and <60 min grades.[23] The sedentary activity time was divided into ≥120 min and <120 min grades.[24]

Measurement of Fasting Plasma Glucose and Triglyceride

Three milliliters of fasting venous blood was collected. Fasting plasma glucose and TG were detected using an automatic biochemical analyzer. A fasting plasma glucose value ≥5.6 mmol/L was defined as impaired fasting glucose (IFG).[25,26]

Statistical Analysis

Statistical analysis was performed using SPSS23.0. The mean ± standard deviation and proportion (%) were used to describe the measurement and enumeration data, respectively. The logarithmic CLAP (LnCLAP), weight, height, BMI, WC, WHtR, AST and TG were standardized for sex and age using a normal deviation method. The *t*-test and chi-square test were used to compare the differences in the factors above between children with and without IFG. In addition, the receiver operating characteristic (ROC) was determined to analyze the predictive capabilities of the standardized variables above for IFG. A logistic regression model was used to explore optimal cutoff point of CLAP for predicting IFG. P< 0.05 was considered significant. The framework was showed in Figure 1.

Results

Demographics

A total of 683 children, including 366 boys and 317 girls, aged 8–15 years were effectively recruited in this study. As shown in Table 1, the prevalence of impaired fasting glucose was 13.8%: 16.9% in boys and 10.1% in girls (P<0.05). The LnCLAP, TG and AST among girls were significantly higher than those among boys (P<0.05); however, the WHtR and fasting plasma glucose among girls were significantly lower than those among boys (P <0.05). The proportions of risky dietary behavior ≥P_{75}, moderate to vigorous physical activity time ≥60 min and sedentary activity time <120 min among girls were significantly higher than those among boys (P<0.05).

The Factors Associated with IFG

As shown in Table 2, the Sheight, Sweight, SWC, SAST, SWHtR, STG and SLnCLAP among boys with IFG were significantly higher than those among boys without IFG, respectively (P<0.05). However, there were no significant differences in the above variables between girls with and without IFG.

The Comparison of Power for Predicting IFG Among Boys

As shown in Table 3 and Figure 2, the receiver operator characteristic curve showed that the areas under the curve of SWHtR, SWC, Sweight, Sheight, SAST, STG and SLnCLAP for predicting IFG were 0.584 (95% CI 0.504–0.665), 0.606 (95% CI 0.526–0.686), 0.598 (95% CI 0.520–0.677), 0.590 (95% CI 0.513–0.667), 0.608 (95% CI 0.536–0.680), 0.635 (95% CI 0.560–0.709), and 0.637 (95% CI 0.562–0.712), respectively.

An Optimal Cutoff Point of CLAP for Predicting IFG

As shown in Table 4, the results showed that *OR* (95% CI) of P_{75}, P_{85}, P_{90}, and P_{95} of CLAP for predicting IFG were 2.48 (1.40–4.42), 2.24 (1.19–4.20), 2.34 (1.14–4.78), and 2.45 (0.96–6.29), respectively. The optimal cutoff point of CLAP for predicting IFG should be P_{75} of CLAP. In addition, the prevalence of IFG was increased with P_{75}, P_{85}, P_{90}, and P_{95} of CLAP.

Discussion

With the prevalence of obesity or overweight, unhealthy eating habits and sedentary lifestyles, impaired fasting glucose among children and adolescents is increasingly common, and it is an important public health issue.[27,28] The results of this study showed that the prevalence of IFG in children was 13.8%: 16.9% in boys and 10.1% in girls. Chahkandi et al[5] reported that the prevalence of IFG was 10.6% in boys and 4.8% in girls. A study from Wang et al[29] showed that the prevalence of impaired fasting glucose (IFG) was 2.80% in boys and 1.1% in girls. A study from Fu et al[30] showed that the prevalence of type 2 diabetes in boys aged 0–18 years was significantly higher than that in girls. A Danish study of fasting glucose in children and adolescents found that the impaired rate of fasting glucose was 11.2% in boys and 8.5% in girls. The impaired rate

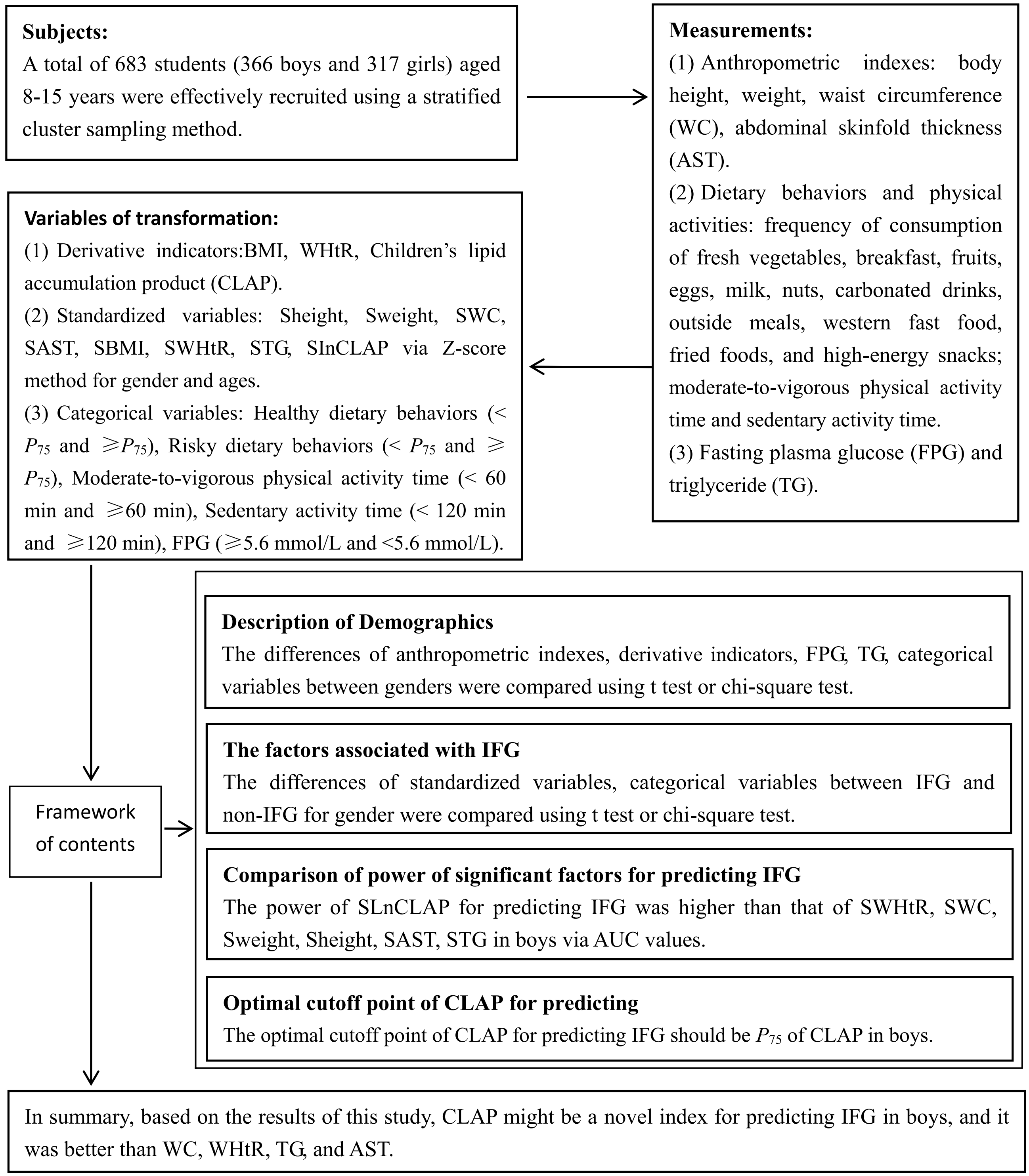

Figure 1 The framework figure of this study.

of fasting glucose increased with the increase in BMI (obesity, overweight and normal weight) in boys and girls, and fasting glucose may be associated with lipids.[31] Forbes et al[32] reported that the glycemic load (GL) in boys was higher than that in girls. One reason might be the differences in physical activity between sexes. In the present study, the rates of moderate to vigorous physical activity time ≥60 min and sedentary activity time <120 min among girls were significantly higher than those among boys, respectively. Anish et al[33] also found that women decreased their risk of diabetes by increasing their levels of physical activity. In addition, the present study showed that the AST and TG in girls were significantly higher

Table 1 The Comparisons of Demographic Characteristics, Physical Activity Time and Dietary Behaviors Between Different Sexes (Mean±(m) or n (%))

Variables	Boys (n=366)	Girls (n=317)
Age	11.28±1.79	11.47±1.82
Height	151.22±12.81	150.87±11.38
Weight	45.30±13.34	45.40±13.57
WC	67.02±11.05	65.51±9.10
AST	17.22±9.32	20.36±9.35***
BMI	19.46±3.70	19.77±5.13
WHtR	0.44±0.06	0.43±0.05*
TG	0.88±0.38	0.96±0.39**
LnCLAP	2.06±0.92	2.33±0.83***
FPG	5.19±0.42	5.10±0.45**
FPG		
<5.6 mmol/L	304 (83.1)	285 (89.9)**
≥5.6 mmol/L	62 (16.9)	32 (10.1)
Healthy Dietary Behaviors		
$<P_{75}$	266 (72.7)	248 (78.2)
$\geq P_{75}$	100 (27.3)	69 (21.8)
Risky Dietary Behaviors		
$< P_{75}$	293 (80.1)	222 (70.0)**
$\geq P_{75}$	73 (19.9)	95 (30.0)
>Moderate-to-Vigorous Physical Activity Time		
<60 min	215 (58.7)	157 (49.5)*
≥60 min	151 (41.3)	160 (50.5)
Sedentary Activity Time		
<120 min	152 (41.5)	169 (53.3)**
≥120 min	214 (58.5)	148 (46.7)

Notes: *P < 0.05 for sex difference; **P < 0.01 for sex difference; ***P < 0.001.
Abbreviations: WC, waist circumference; AST, abdominal skinfold thickness; BMI, body mass index; WHtR, waistline-to-height ratio; TG, triglyceride; FPG, fasting plasma glucose; LnCLAP, logarithmic child lipid accumulation product.

Table 2 The Comparisons of Anthropometric Indexes, Dietary Behaviors and Physical Activity Time Between Children with and Without IFG (Mean±(m) or n (%))

Variables	Boys		Girls	
	Non-IFG (n=304)	IFG (n=62)	Non-IFG (n=285)	IFG (n=32)
Age	11.20±1.79	11.63±1.80	11.48±1.82	11.36±1.85
Sheight	−0.06±0.98	0.29±1.00*	−0.02±0.99	0.14±1.01
Sweight	−0.06±0.98	0.27±1.01*	0.00±0.99	0.04±0.99
SWC	−0.06±0.97	0.31±1.06**	−0.01±0.97	0.09±1.15
SAST	−0.05±0.99	0.27±0.96*	−0.02±0.98	0.20±1.04
SBMI	−0.04±0.99	0.19±0.97	0.00±1.00	−0.02±0.92
SWHtR	−0.05±0.97	0.24±1.04*	−0.01±0.97	0.05±1.14
STG	−0.07±0.97	0.34±1.04**	−0.02±0.99	0.20±0.98
SlnCLAP	−0.08±0.98	0.39±0.97***	−0.03±1.00	0.25±0.84
Healthy Dietary Behaviors				
$<P_{75}$	221 (83.1)	45 (16.9)	222 (89.5)	26 (10.5)
$\geq P_{75}$	83 (83.0)	17 (17.0)	63 (91.3)	6 (8.7)
Risky Dietary Behaviors				
$<P_{75}$	245 (83.6)	48 (16.4)	198 (89.2)	24 (10.8)
$\geq P_{75}$	59 (80.8)	14 (19.2)	87 (91.6)	8 (8.4)
Moderate-to-Vigorous Physical Activity Time				
<60 min	181 (84.2)	34 (15.8)	142 (90.4)	15 (9.6)
≥60 min	123 (81.5)	28 (18.5)	143 (89.4)	17 (10.6)
Sedentary Activity Time				
<120 min	124 (81.6)	28 (18.4)	153 (90.5)	16 (9.5)
≥120 min	180 (84.1)	34 (15.9)	132 (89.2)	16 (10.8)

Notes: Sheight, Sweight, SWC, SAST, SBMI, SWHtR, STG and SlnCLAP are the standardized height, weight, WC, AST, BMI, WHtR, TG and lnCLAP, respectively, by sex and age using a normal deviation method. *P < 0.05 for difference between non-IFG and IFG; **P < 0.01 for difference between non-IFG and IFG; ***P < 0.001 for difference between non-IFG and IFG.
Abbreviations: SWC, standardized waist circumference; SAST, standardized abdominal skinfold thickness; SBMI, standardized body mass index; SWHtR, standardized waist-height ratio; STG, standardized triacylglycerol; SlnCLAP, standardized logarithmic children's lipid accumulation product; IFG, impaired fasting glucose.

than those in boys, and the WHtR in girls was significantly lower than that in boys. Comparing children in southern India, WHtR and TG in boys were significantly higher than those in girls, and AST in boys was significantly lower than that in girls.[34] In a study of Korean adolescents by Kim et al, TG in girls was significantly higher than that in boys.[35] Girls had a higher WHtR than boys compared with children in Amargosa.[36]

In the present study, we found that the height, weight, WC, AST, WHtR, and TG among boys with IFG were significantly higher than those among boys without IFG; however, the differences in the above variables between IFG and non-IFG were not found in girls. Liu et al[37] reported that WC and TG were significantly related to fasting plasma glucose among adolescents. A study by West et al found a significant correlation between waist circumference and type 2 diabetes in boys.[38] Misra et al shown that a high prevalence of insulin resistance in postpubertal urban Asian Indian children was associated with abdominal adiposity.[39] Studies showed that WHtR was a better obesity index for predicting diabetes than BMI.[11,40] In addition, we found that body height in boys with IFG was higher than that in boys without IFG. The study also showed that body height was related to diabetes.[40]

Table 3 The Areas Under ROC Curves of SlnCLAP, Sheight, Sweight, SWC, SWHtR, SAST, and STG for Predicting IFG Among Boys

Variables	AUC	SE	95% CI of AUC
Sheight	0.590*	0.039	0.513–0.667
Sweight	0.598*	0.040	0.520–0.677
SWC	0.606**	0.041	0.526–0.686
SAST	0.608**	0.037	0.536–0.680
SWHtR	0.584*	0.041	0.504–0.665
STG	0.635***	0.038	0.560–0.709
Slnclap	0.637***	0.038	0.562–0.712

Notes: Sheight, Sweight, SWC, SAST, SWHtR, STG, and SlnCLAP are the standardized height, weight, WC, AST, WHtR, and lnCLAP by sex-age using the normal deviation method, respectively. *$P < 0.05$ for significant AUC; **$P < 0.01$ for significant AUC; ***$P < 0.001$ for significant AUC.

Abbreviations: SWC, standardized waist circumference; SAST, standardized abdominal skinfold thickness; SWHtR, standardized waist-height ratio; STG, standardized triacylglycerol; SlnCLAP, standardized logarithmic children's lipid accumulation product; IFG, impaired fasting glucose; AUC, area under receiver operating characteristic (ROC) curve.

However, the results of this study showed that BMI did not correlate with fasting plasma glucose, which was consistent with the findings from Sayeed et al.[40]

The previous and present studies showed that WHtR, WC, TG and AST are significantly related to diabetes. The excess lipid fuel appeared eventually as an elevated circulating TG level or accumulation of fat. WHtR and WC were a better obesity index than BMI, but they were limited in indicating lipid accumulation in circulating blood.[41,42] TG was limited in showing the accumulation of adipose tissue. AST is the skinfold thickness at the junction of naval horizontal line and the right clavicle midline, and it is used to show the accumulation point of abdominal fat. Based on waist circumference and fasting triglycerides, researchers developed LAP to identify diabetes in adults. The study showed that LAP was better than BMI in predicting glucose metabolism variables and far superior in identifying adults with diabetes.[19,43] In the present study, WC, AST, and TG were used to calculate CLAP to show lipid accumulation in this study. The results showed that the AUC of CLAP (0.637) for predicting IFG in boys was higher than that of WC, AST, WHtR, and TG, indicating that CLAP had more power for

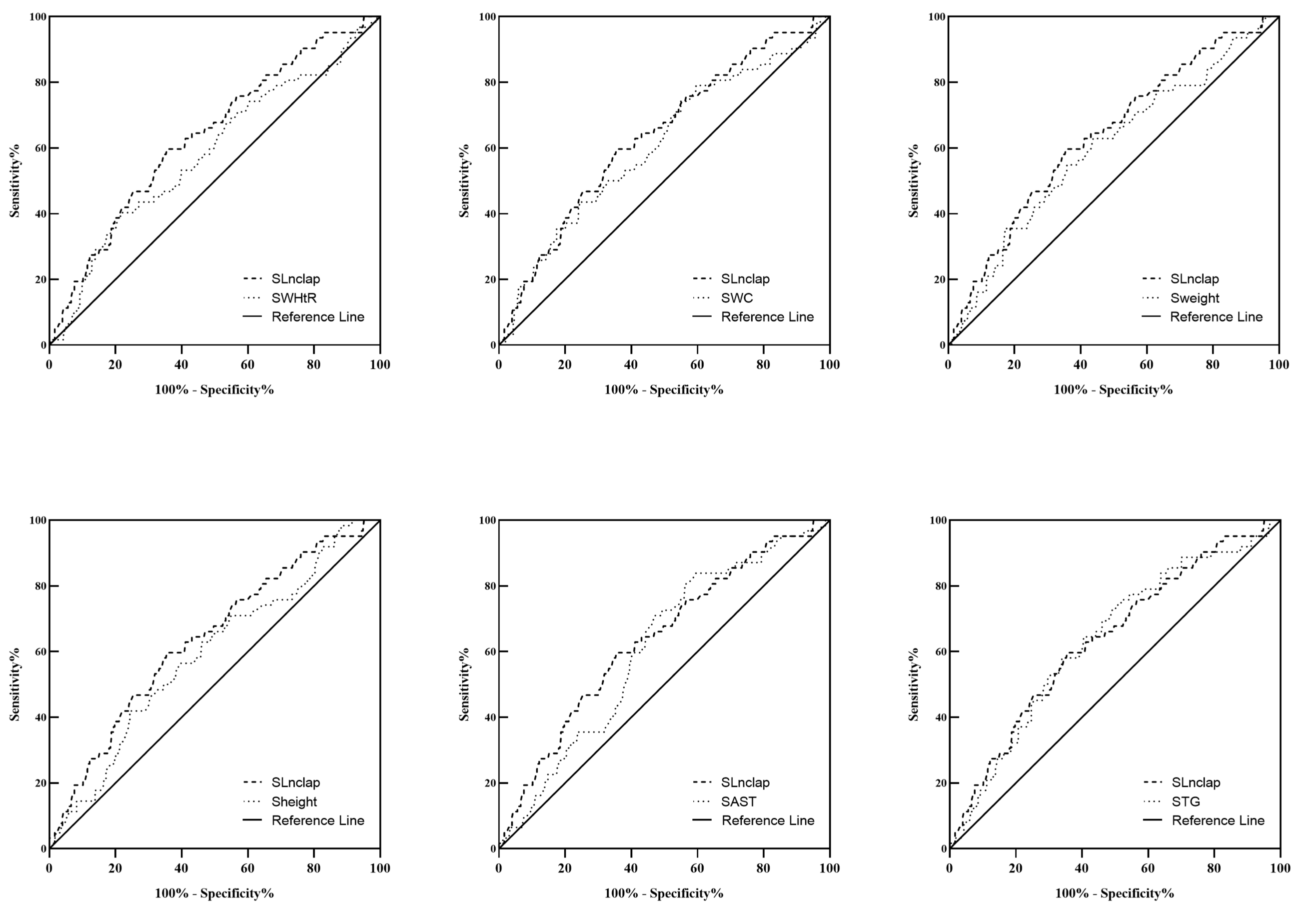

Figure 2 The respective receiver operating characteristic curves of SWHtR, SWC, Sweight, Sheight, SAST, STG and SLnCLAP for predicting IFG.

Abbreviations: Sheight, Sweight, SWC, SAST, SWHtR, STG, and SLnCLAP are the standardized height, weight, WC, AST, WHtR, TG and LnCLAP by sex-age using the normal deviation method, respectively; IFG, impaired fasting glucose.

Table 4 The Associations Between Anthropometric Indexes and IFG Using Logistic Regressions Among Boys

CLAP	Non-IFG	IFG	OR (95% CI)	AUG	95% CI of AUC
P_{75} of CLAP					
$<P_{75}$	239 (86.6)	37 (13.4)	1	0.595*	0.513–0.676
$\geq P_{75}$	65 (72.2)	25 (27.8)	2.48 (1.40–4.42)**		
P_{85} of CLAP					
$<P_{85}$	257 (85.4)	44 (14.6)	1	0.568	0.486–0.650
$\geq P_{85}$	47 (72.3)	18 (27.7)	2.24 (1.19–4.20)*		
P_{90} of CLAP					
$<P_{90}$	273 (84.8)	49 (15.2)	1	0.554	0.472–0.636
$\geq P_{90}$	31 (70.5)	13 (29.5)	2.34 (1.14–4.78)*		
P_{95} of CLAP					
$<P_{95}$	289 (84.0)	55 (16.0)	1	0.532	0.450–0.613
$\geq P_{95}$	15 (68.2)	7 (31.8)	2.45 (0.96–6.29)		

Notes: *$P < 0.05$; **$P < 0.01$
Abbreviation: CLAP, child lipid accumulation product.

predicting IFG compared with a single indicator. In addition, the optimal cutoff point of CLAP for predicting IFG was P_{75} of CLAP, with an OR (95% CI) value of 2.48 (1.40–4.42). Clearly, CLAP was a stronger risk factor for IFG compared with WC, WHtR, TG and AST. In summary, based on the results of this study, CLAP might be a novel index for predicting IFG in boys, and it was better than WC, WHtR, TG, and AST.

There were some limitations in this study. This study was a cross-sectional study, which limits inferring causality between CLAP and IFG. In addition, dietary behaviors and physical activity might be adopted before or after suffering from impaired fasting plasma glucose.

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Disclosure

Yongting Yuan and Hong Xie are co-first authors. All authors gave final approval of the submitted manuscript versions and declare no conflicts of interest in this work.

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