Association of plasma glucose, insulin, and cardiovascular risk factors in overweight and obese children

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ABSTRACT

الأهداف: دراسة العلاقة بين بين تركيز جلوكوز الدم في حالة الصوم، وتركيز جلوكوز الدم بعد 2 ساعة من الأكل، وانسولين جلوكوز الدم في حالة الصوم، وانسولين جلوكوز الدم بعد 2 ساعة من الأكل والعوامل المؤدية إلى أمراض القلب والأوعية الدموية في الأطفال المصابين بالسمنة والوزن الزائد.

الطريقة: أجريت دراسة على 452 طفل مصاب بالسمنة والوزن الزائد (312 ذكر، و140 أنثى) تتراوح أعمارهم من 6–16 عام. أجريت الدراسة في قسم الأطفال، مستشفى جامعة تينجان العام، تينجان، الصين خلال الفترة من يونيو 2008م حتى نوفمبر 2012م. أجري تحليل الدم وقياسات الجسم. استخدم تحليل العلاقة بيرسون وتحليل الانحدار الخطي المتعدد لدراسة العلاقة بين تركيز جلوكوز الدم في حالة الصوم، و تركيز جلوكوز الدم بعد 2 ساعة من الأكل، وانسولين جلوكوز الدم في حالة الصوم، وانسولين جلوكوز الدم بعد 2 ساعة من الأكل والعوامل المؤدية إلى أمراض القلب والأوعية الدموية.

النتائج: أظهرت الدراسة بأن مؤشر كتلة الجسم ومحيط الخصر ونسبة الخصر للورك وضغط الدم الانقباضي وضغط الدم الانبساطي والدهون الثلاثية ارتبطت بشكل تام مع انسولين جلوكوز الدم في حالة الصوم. كما أن انسولين جلوكوز الدم في حالة الصوم يؤثر بشكل متفاوت على العوامل المؤدية إلى أمراض القلب والأوعية الدموية أكثر من تركيز جلوكوز الدم بعد 2 ساعة و انسولين جلوكوز الدم بعد 2 ساعة من الأكل.

خاتمة: ارتبط انسولين جلوكوز الدم في حالة الصوم مع العوامل المؤدية إلى أمراض القلب والأوعية الدموية بالمقارنة مع تركيز جلوكوز الدم في حالة الصوم، وتركيز جلوكوز الدم بعد 2 ساعة من الأكل، وانسولين جلوكوز الدم بعد 2 ساعة من الأكل.

Objectives: To investigate the association between fasting plasma glucose (FPG), 2-hour post challenge plasma glucose (2hPG), fasting plasma insulin (FINS), 2-hour post challenge plasma insulin (2hINS), and cardiovascular risk factors in obese and overweight children.

Methods: This is a cross-sectional study of 452 obese and overweight children (male: 312, female: 140, aged 6-16 years). This study was conducted in the Department of Pediatrics, General Hospital of Tianjin Medical University, Tianjin, China between June 2008 and November 2012. Anthropometries and blood analysis were carried out. Pearson correlation analysis and multiple stepwise linear regression analysis were used to investigate the association among FPG, 2hPG, FINS, 2hINS and cardiovascular risk factors.

Results: Body mass index, waist circumference, waist to hip ratio, systolic blood pressure, diastolic blood pressure, and triglyceride were highly correlated with FINS. Fasting plasma insulin influenced greater variance in most cardiovascular risk factors than 2hPG and 2hINS.

Conclusions: Fasting plasma insulin was closely associated with most cardiovascular risk factors compared with FPG, 2hPG and 2hINS.

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The incidence of childhood obesity is escalating much more rapidly worldwide. Affluent lifestyle has been identified as a key issue in the development of obesity.[1,2] According to previous studies, several disorders such as abnormal glucolipid metabolism and vascular endothelial injury have been frequently noted in children with obesity. In particular, childhood obesity is correlated with increased morbidity and mortality of patients with type 2 diabetes mellitus (T2DM)

and cardiovascular diseases (CVD) in adulthood.[3,4] Atherosclerosis and coronary heart disease (CHD), commonly observed among seniors, have occurred in childhood.[5] According to our knowledge, cardiovascular risk factors mainly included age, smoking, drinking alcohol, BMI, dietary factors, lack of physical activity, waist circumference, waist to hip ratio (WHR), overweight, obesity, hypertension, hyperlipidemia, and diabetes.[6] However, insulin resistance, inflammation and activation of the endothelial system have also been confirmed to be associated with CVD.[7,8] Mellerio et al[9] established a modeling of reference values of cardiovascular risk factors in children aged 7-20 years, to monitor cardiovascular risk factors and to carry out interventions and education programs. Subsequently, numerous studies have demonstrated that diabetes is an independent risk factor for CVD. To date, extensive studies have been carried out to investigate the roles of hyperglycemia in mortality of CHD, stroke and other CVD in adults.[10-12] However, few study have investigated the influence of fasting plasma glucose (FPG), 2-hour post challenge plasma glucose (2hPG), fasting plasma insulin (FINS) and 2-hour post challenge plasma insulin (2hINS) on cardiovascular risk factors in childhood. In this study, we aim to investigate the association between FPG, 2hPG, FINS, 2hINS, and cardiovascular risk factors in obese children with normal fasting glucose levels.

Methods. This is a cross-sectional study of 452 obese and overweight children (male: 312, female: 140, aged 6-16 years). They were enrolled in the Department of Pediatrics, General Hospital of Tianjin Medical University, Tianjin, China between June 2008 and November 2012. Patients with diabetes mellitus, diagnosed heart disease, endocrine disease, and immunodeficiency were excluded from the study. Informed consents were obtained from the participants. This study was approved by the Ethics Committee of the General Hospital of Tianjin Medical University.

Parameters including height, weight, waist and hip circumferences, and blood pressure were measured in a fasting state. Body weight was measured without shoes and heavy clothes. Height was measured in a relaxed position. During the waist measurement, the subjects were required to stand erectly with the abdomen relaxed. The tape measure was placed horizontally, 1-2cm below the last rib on bare skin. Hip circumference was measured at the largest circumference around hips. Blood pressure was measured with the subject supine, using a mercury sphygmomanometer. We measured systolic blood pressure (SBP) (Korotkoff phase I) and diastolic blood pressure (DBP) (Korotkoff phase V). All the measurements were taken twice, and then the average values were calculated accordingly.

Prior to blood collection, the subjects were in a state of fasting. Then, blood samples are taken for laboratory evaluation of total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high sensitivity C-reactive protein (hsCRP). Non-HDL cholesterol was defined as total cholesterol minus HDL cholesterol. Oral glucose tolerance test (OGTT, 1.75g/kg body weight) was carried out the morning. Blood samples for measurements of FPG, 2hPG, FINS, and 2hINS were obtained at baseline (fasting) and 2 hours after an oral glucose load. The plasma glucose levels were determined using the glucose oxidase method with kits purchased from Biosino Bio-Technology & Science Inc. (Beijing, China). A kit purchased from the China Institute of Atomic Energy (Beijing, China) was used to evaluate the insulin concentration. A Hitachi 7170 automatic biochemistry analyzer (Tokyo, Japan) was used to analyze the plasma lipids. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated according to the formula: fasting insulin (uU/ml) × fasting plasma glucose (mmol/l)/22.5. The study was conducted according to the Declaration of Helsinki.

Cutoff values. Individuals with BMI of >30kg/m^2 or ≥95th percentile were considered as obese, BMI ≥85th percentile but <95th percentile or 30 kg/m^2 were considered as overweigh.[13] According to the American Diabetes Association, the cutoff value for FPG was ≥5.6mmol/l.[14] The waist circumference cut-off values for Asians are 90 cm for males and 80 cm for females according to the International Diabetes Federation (IDF) diagnostic criteria.[15] Total cholesterol of ≥5.2mmol/l, LDL ≥3.4mmol/l, HDL <0.9mmol/l, and TG ≥1.24mmol/l were considered as cutoff values.[16]

Statistical analysis. The Statistical Package for Social Sciences Version 19 for windows (SPSS Inc, Chicago, IL, USA) was used for data analysis. All values were presented as mean±standard error. Pearson's correlation coefficient was used to examine the correlation of

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CVD risk factors with FPG, 2hPG, FINS, and 2hINS. Multiple linear regression analysis was carried out to investigate the association between FPG, 2hPG, FINS, 2hINS, and cardiovascular risk factors. The significance was determined at a *p*-value of <0.05.

Results. Table 1 summarizes the subject characteristics. Results are expressed as mean ± standard error. The mean FPG was 5.12 mmol/L, and the maximum value is less than 5.6 mmol/L. The FBG of all the children was in the normal range. Correlations between plasma glucose, insulin, and cardiovascular risk factors are shown in **Table 2**. After adjustment for age and gender, BMI and WHR were positively correlated with 2hPG, and their correlation coefficients were equal (r=0.10, $p<0.05$). After adjustment for age and gender, waist circumference, TC, and non-HDL were positively correlated with 2hPG (r=0.13, r=0.13 and $p=0.16$, $p<0.01$). Although only LDL was correlated with FPG, its correlation index was higher for 2hPG compared with that of FPG (r=0.14 versus r=0.10; $p<0.01$). Compared with the correlation index of 2hINS, higher correlation was noted between FINS and BMI (r=0.28 versus r=0.21, $p<0.01$), waist circumference (r=0.33 versus r=0.24, $p<0.01$), as well as TG (r=0.18 versus r=0.15, $p<0.01$). Additionally, non-HDL (r=0.09, $p<0.05$), SBP (r=0.16, $p<0.01$), and DBP (r=0.12, $p<0.05$) were positively correlated with FINS; however, no significant correlation was noticed between these parameters and 2hINS. High-density lipoprotein was negatively correlated with 2hINS (r=-0.19, $p<0.01$).

To investigate the association between FPG, 2hPG, INS, 2hINS, and cardiovascular risk factors, stepwise multiple linear regression models were used. **Table 3** summarizes the results of multiple linear regression analysis, in which cardiovascular disease risk factors were set as dependent variables, while FPG, 2hPG, FINS, and 2hINS were set as independent variables. Regression coefficient was determined from stepwise multiple linear regression analyses to examine the extent of variance of CVD risk factors influenced by FPG, 2hPG, INS, and 2hINS. These analyses showed that FPG did not influence any variance in cardiovascular risk factors. Compared to 2hINS, FINS influenced a substantially higher proportion of the variation of BMI, waist circumference, WHR. Furthermore, the variance of SBP, DBP, and triglycerides was influenced by FINS,

Table 1 - Anthropometric, clinical, and biochemical characteristics of the included children (N=452).

Characteristics	Mean±SE
Anthropometric parameters	
Age (years)	11.4 ± 2.0
Weight (kg)	73.8 ± 17.4
Height (cm)	156.9 ± 11.9
Body mass index (kg/m^2)	29.6 ± 4.3
Waist circumference (cm)	91.5 ± 9.8
Waist-to-hip ratio	0.9 ± 0.1
Systolic blood pressure (mm Hg)	115.3 ± 13.9
Diastolic blood pressure (mm Hg)	73.2 ± 9.1
Blood analysis	
Fasting plasma glucose (mmol/l)	5.1 ± 0.7
2-hour post challenge plasma glucose (mmol/l)	6.8 ± 1.7
Insulin (mmol/L)	17.3 ± 1.8
2-hour post challenge plasma insulin (mmol/l)	177.5 ± 19.4
Total cholesterol (mmol/l)	4.2 ± 0.7
Triglycerides (mmol/l)	1.4 ± 0.6
Low density lipoprotein (mmol/l)	2.4 ± 0.5
High density lipoprotein (mmol/l)	1.1 ± 0.2
Non-high density lipoprotein (mmol/l)	3.0 ± 0.7
C-reactive protein (mg/l)	4.3 ± 0.6
Homeostasis model assessment-estimated insulin resistance	5.1 ± 0.5

Table 2 - Correlations of FPG, 2hPG, FINS, and 2hINS to cardiovascular disease risk factors.

Characteristics	FPG	2hPG	FINS	2hINS
Body mass index (kg/m^2)	0.09	0.10*	0.28**	0.21**
Waist circumference (cm)	0.08	0.13**	0.33**	0.24**
Waist-to-hip ratio	0.02	0.10*	0.07	0.10
Total cholesterol (mmol/l)	0.06	0.13**	0.06	0.02
Triglycerides (mmol/l)	0.02	0.06	0.18**	0.15**
Low density lipoprotein-cholesterol (mmol/l)	0.10*	0.14**	-0.02	0.01
High density lipoprotein-cholesterol (mmol/l)	-0.01	-0.05	-0.07	-0.19**
Non-high density lipoprotein (mmol/l)	0.06	0.16**	0.09*	0.09
Systolic blood pressure (mm Hg)	0.03	0.02	0.16**	0.05
Diastolic blood pressure (mm Hg)	0.02	0.01	0.12*	0.02
C-reactive protein (mg/l)	-0.02	0.04	-0.02	-0.01

Data presented as coefficients (R); *p-value <0.05 level; **p-value<0.01 level,
FPG - fasting plasma glucose, 2hPG - 2-hour post challenge plasma glucose, FINS - fasting plasma insulin, 2hINS - 2-hour post challenge plasma insulin

Table 3 - Multiple linear regression for cardiovascular disease risk factors as dependent variables; and FBG, 2hPG, FINS, and 2hINS as independent variables.

Dependent/ independent variables	B	SE	*P*-value	95% Confidence Interval
Body mass index (kg/m²)				
FPG	0.458	0.094	0.141	-0.153 - 1.068
2hPG	-0.189	0.404	0.233	-0.4999 - 0.122
FINS	0.033	0.007	<0.001†	0.016 - 0.045
2hINS	0.008	0.002	0.016*	0.003 - 0.013
Waist circumference (cm)				
FPG	0.54	0.202	0.461	-0.897 - 1.976
2hPG	-0.105	0.371	0.777	-0.835 - 0.625
FINS	0.078	0.015	<0.001†	0.044 - 0.133
2hINS	0.015	0.005	0.014*	0.003 - 0.028
Waist to hip ratio				
FPG	0.899	0.206	0.249	-0.632 - 2.430
2hPG	-0.531	0.296	0.180	-1.309 - 0.246
FINS	0.090	0.014	<0.001†	0.050 - 0.123
2hINS	0.020	0.001	0.002†	0.007 - 0.033
Systolic blood pressure (mm Hg)				
FPG	0.215	0.398	0.829	-1.746 - 2.177
2hPG	-0.179	0.207	0.724	-1.174 - 0.818
FINS	0.076	0.024	<0.001†	0.030 - 0.123
2hINS	0.002	0.009	0.787	-0.140 - 0.019
Diastolic blood pressure (mm Hg)				
FPG	0.278	0.683	0.684	-1.046 - 1.620
2hPG	-0.246	0.203	0.478	-0.928 - 0.436
FINS	0.041	0.014	0.012*	0.009 - 0.073
2hINS	0.003	0.006	0.635	-0.009 - 0.014
Triglycerides (mmol/l)				
FPG	-0.014	0.074	0.845	-0.16 - 0.131
2hPG	-0.008	0.021	0.840	-0.081 - 0.066
FINS	0.005	0.002	0.003†	0.002 - 0.009
2hINS	0.001	0.001	0.091	0.000 - 0.002
Total cholesterol (mmol/l)				
FPG	-0.053	0.061	0.384	-0.173 - 0.067
2hPG	0.086	0.031	0.006†	0.025 - 0.147
FINS	0.002	0.001	0.250	-0.001 - 0.005
2hINS	-0.001	0.001	0.161	-0.002 - 0.000
Low-density lipoprotein-cholesterol (mmol/l)				
FPG	0.020	0.058	0.735	-0.095 - 0.134
2hPG	0.076	0.030	0.011*	0.018 - 0.134
FINS	-0.001	0.001	0.317	-0.004 - 0.001
2hINS	0.000	0.000	0.508	-0.001 - 0.001
Non-high-density lipoprotein (mmol/l)				
FPG	-0.037	0.057	0.518	-0.14 - 0.075
2hPG	0.075	0.029	0.010*	0.018 - 0.132
FINS	0.002	0.001	0.236	-0.001 - 0.004
2hINS	0.005	0.000	0.853	-0.001 - 0.001
High-density lipoprotein -cholesterol (mmol/l)				
FPG	-0.016	0.022	0.454	-0.059 - 0.026
2hPG	0.011	0.011	0.304	-0.010 - 0.033
FINS	0.005	0.001	0.908	-0.001 - 0.001
2hINS	-0.001	0.000	0.001†	-0.001 - 0.000

Data presented as coefficients (R), **p*-value <0.05 level, †*p*-value<0.01 level. FPG - fasting plasma glucose, 2hPG - 2-hour post challenge plasma glucose, FINS - fasting plasma insulin, 2hINS - 2-hour post challenge plasma insulin

but not by FPG, 2hPG, or 2hINS. Thus, children with higher concentration of FINS were associated with higher cardiovascular risk factors. Fasting plasma insulin influence more variation of cardiovascular risk factors, such as BMI, waist circumference, WHR, SBP, DBP, and triglycerides than FPG, 2hPG, and 2hINS. On the other hand, 2hPG had the ability to influence variance in TC, LDL, non-HDL, while FINS and 2hINS cannot. The variance of HDL was only influenced by 2hINS.

Discussion. Cardiovascular disease is a leading cause of morbidity and death in many countries. Individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) are at high risk, not only for diabetes mellitus, but also an adverse cardiovascular event (myocardial infarction, stroke, CVD) later in life.[17] Obesity, especially abdominal obesity, has been recognized as the major cause of CVD and T2DM.[18] Great effects have been exposed on the intelligence, psychological behavior, growth and development of children with obesity. Additionally, endothelium balance has been disrupted through increasing endothelium-dependent vasoconstrictors such as endothelin, thromboxane-A2, angiotensin II and oxygen radical levels, as well as decreasing endothelium-dependent vasodilators such as nitric oxide and prostacyclin levels.[19] Currently, the potential roles of obesity in the patients with diabetes and CVD have been extensively investigated; however, few studies are carried out to investigate the potential roles in children. As an escalating rate has been noticed in children with obesity, it is necessary to identify the potential association between obesity and disorders such as CVD and diabetes.

Several studies have examined the association between FBG and cardiovascular risk factors. For instance, Di et al[20] reported that children with high-normal FPG (4.9-5.5 mmol/L) showed a higher risk of insulin resistance, hypertension, and high white blood cells (WBC) count compared with subjects with low-normal FPG. Shaye et al[21] reported that adults with normal fasting glucose levels (5.3-5.5mmol/L) showed an increased CVD risk compared with those with fasting glucose levels of less than 4.4 mmol/L (HR 1.53; 95% CI [1.22-1.91], p<0.001). Interestingly, a new definition has been added to IFG (FPG 100-109mg/dl [5.6-6.0mmol/l]) by the ADA Expert Committee.[22] Our study showed that a significant increase was noticed in weight, waist circumference, hip circumference, FPG, INS, 2hIN, and HOMA-IR, which suggested that several cardiovascular risk factors were available in the normoglycemic individuals. Nevertheless, correlation analysis and stepwise multiple linear regression showed

that FPG was not applicable for the prediction of any cardiovascular risk factors in our study.

It has been well known that postprandial hyperglycemia could promote the occurrence and development of endothelial dysfunction. For patients with postprandial hyperglycemia, several factors associated with oxidative stress showed up-regulation, such as fibrous protein peptide A, prothrombin fragment, coagulation factor-ß, platelet, plasma interleukin-6, tumor necrosis factor-ß, interleukin-18, CRP, intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin.[23] In addition, glucose transporter-1 (GLUT-1) excessively transported glucose into mitochondria of endothelial cells, and then caused an oxidative stress state. Moreover, an oxidative stress state decreased the expression of endothelial cell NO synthase (eNOS), and resulting in dysfunction of vasodilation.[24] Ning et al[25,26] showed that within normoglycemic range, individuals with 2hPG not return into their FPG levels during an OGTT had increased risk of CHD and ischemic stroke. Simultaneously, high 2hPG was associated with insulin resistance and increased CVD mortality.

Our study showed that compared with 2hINS, FINS can better influence variance in BMI, waist circumference, WHR, SBP, DBP, and triglyceride. Our results showed that significant HOMA-IR increase was noted in 93.4% of patients. To date, hyperinsulinemic euglycemic clamp has been considered the gold standard for the diagnosis of insulin resistance. Unfortunately, this procedure is technically demanding and labor-intensive. Qu et al[27] reported that a HOMA-IR of more than 3.80 showed higher sensitivity and specificity than the popular clinical cutoff of 2.60. Insulin resistance is commonly noted in the presence of insulin signaling impairment, which forces beta-cells to produce more insulin to meet the demands of the body and to maintain glucose homeostasis. Once the secretion of insulin is not adequate by the pancreas, the insulin resistance is decompensated, and at the same time, hyperglycemia is detected. In addition to genetic factors, obesity is the major risk factors for insulin resistance. Obesity can stimulate the chronic low-grade inflammation that leads to insulin resistance.[28] Visceral adiposity is correlated with excessive accumulation of hepatic lipid, which will lead to impairment of cells involved in insulin signaling. Visceral adipose tissue is also prone to produce inflammatory cytokines, which also contribute to the impairment of the insulin signaling pathway.[29] Phosphatidylinositol 3-kinase-dependent insulin-signaling pathways, which play important roles in the regulation of endothelial production of NO, show great similarities with metabolic insulin-signaling pathways. Further, MAPK-dependent insulin-signaling pathways play a pivotal role in the secretion of the vasoconstrictor endothelin-1 from endothelium. All these contribute to the coupling metabolic and hemodynamic homeostasis in healthy individuals. Insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol 3-kinase-dependent signaling that contributes to endothelial dysfunction.[30] Jeppesen et al[31] found that HOMA-IR was an independent predictor of incident CVD. Some researchers have shown that increasing quartiles of fasting and 2-h insulin were associated with increasing CVD risk factors, while glucose quartiles on the other hand, either fasting or at 2 hours, were not.[32,33] In our study, FINS and 2hINS were both correlated with many cardiovascular risk factors, but multiple regression analysis showed that FINS and 2hINS can influence different factors. So the combination of them is important to evaluate.

Study limitations. First, cardiovascular risk factors are affected by many factors such as age, physical activity, diet, and genetic background. Future studies are needed to derive cut-offs of FINS and 2hPG, and to describe the cardiovascular risks.

In conclusion, in obese children and adolescents, hyperinsulinemia will appear earlier than abnormal glucose metabolism such as IFG and IGT. In our study, we found that normoglycemic individuals have gathered a lot of cardiovascular risk factors. Children with higher concentration of FINS were associated with higher cardiovascular risk factors. The FINS influence more variation of cardiovascular risk factors than FPG, 2hPG, and 2hINS. Moreover, fasting plasma insulin is easier and more economic to measure than 2hPG and 2hINS.

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