Glucose metabolism disorder in obese children assessed by continuous glucose monitoring system

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Background: **Continuous glucose monitoring system (CGMS) can measure glucose levels at 5-minute intervals over a few days, and may be used to detect hypoglycemia, guide insulin therapy, and control glucose levels. This study was undertaken to assess the glucose metabolism disorder by CGMS in obese children.**

Methods: **Eighty-four obese children were studied. Interstitial fluid (ISF) glucose levels were measured by CGMS for 24 hours covering the time for oral glucose tolerance test (OGTT). Impaired glucose tolerance (IGT), impaired fasting glucose (IFG), type 2 diabetic mellitus (T2DM) and hypoglycemia were assessed by CGMS.**

Results: **Five children failed to complete CGMS test. The glucose levels in ISF measured by CGMS were highly correlated with those in capillary samples (r=0.775, P<0.001). However, the correlation between ISF and capillary glucose levels was lower during the first hour than that in the later time period (r=0.722 vs r=0.830), and the ISF glucose levels in 69.62% of children were higher than baseline levels in the initial 1-3 hours. In 79 obese children who finished the CGMS, 2 children had IFG, 2 had IGT, 3 had IFG + IGT, and 2 had T2DM. Nocturnal hypoglycemia was noted during the overnight fasting in 11 children (13.92%).**

Conclusions: **Our data suggest that glucose metabolism disorder including hyperglycemia and hypoglycemia is very common in obese children. Further studies are required to improve the precision of the CGMS in children.**

World J Pediatr 2008;4(1):26-30

Key words: **glucose metabolism disorders;**
hyperglycemia;
hypoglycemia;
impaired glucose tolerance;
obesity;
type 2 diabetic mellitus

Introduction

Childhood obesity, one of the main causes of coronary artery disease and type 2 diabetic mellitus (T2DM) in adults,[1-5] has emerged as an increasingly common pediatric disease[6,7] over the last decade. The global emergence of T2DM in youth parallels the increasing prevalence of childhood and adolescent obesity. In many parts of the world and among certain ethnic groups, the prevalence of T2DM in adolescents is equal to or greater than that of type 1 diabetes mellitus.[8] The progression from normal glucose tolerance to T2DM in adults occurs through an intermediate phase of altered glucose metabolism known as impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or pre-diabetes. Previous studies from our group and others revealed a high prevalence of IGT among obese children and adolescents.[9-11]

Common oral glucose tolerance test (OGTT) is currently used by measuring fasting, 30, 60, 90 and 120-minute blood glucose levels (capillary or vein samples),[12-14] or only by measuring fasting and 120-minute levels on large-population study.[15,16] The no more than 5 times' measurement has the potential to miss diagnosing the glucose metabolism disorder because of missing the glucose peak. More frequent measurement is often not readily accepted by parents or patients.[17] Continuous glucose measurement of interstitial fluid (ISF) is now possible. ISF glucose equilibrates with blood glucose concentration and can be measured by automatic sampling from a simply implanted subcutaneous sensor. The continuous glucose monitoring system (CGMS) has been shown to detect hypoglycemia, guide insulin therapy, and control glucose levels in children and adults.[18-22]

Herein, we assess the glucose metabolism disorder

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by the CGMS which covered the time for OGTT in 84 obese children.

Methods

Subjects

A total of 84 obese children, according to the criteria that a child is considered to be obese when the body weight exceeds 120% of the standard body weight (defined as the mean body weight corresponding to the height for that age obtained from national statistics for Chinese school children in 1995), were consecutively enrolled in the study. Obese children with hypothyroidism or Laurence Moon Beidl's syndrome were excluded. Five children failing to complete the CGMS test were excluded from the analysis of glucose metabolism. The remaining 79 children included 25 females and 54 males aged from 6.2 to 15.7 years (mean 10.53 ± 2.14 years). Their body mass index ranged from 19.73 to 44.00 kg/m^2 (mean 28.34±3.62 kg/m^2), and 53 children were pre-puberty and 26 were puberty.

The Human Study Committee of Children's Hospital of Zhejiang University approved this study. Informed consent was obtained either from each subject or from their parents.

CGMS and OGTT

The CGMS sensor (Medtronic MiniMed, Northridge, CA, USA) was inserted subcutaneously and ISF glucose levels were measured for 24 hours covering the time for OGTT. Glucose levels were measured by the glucose oxidase reaction in ISF by the CGMS. The sensor was inserted on the anterior abdominal wall, avoiding any abnormal areas of skin. The CGMS functioned for 24 hours and automatically measured ISF glucose levels every 5 minutes over the complete study period. There was an additional calibration requirement to align the device with four capillary glucose readings, which were measured by ACCU-CHEK active (GN03039190, Roche Group). The device itself is around the size of a pager. After completion of all the measurements, the data were downloaded to a personal computer for subsequent analysis. Each patient was asked to record the time when they went to bed and awoke, the time of dinner, and the time and duration of any exercise.

The sensors were inserted in the afternoon of the first day and OGTT was done in the next morning after a 12-hour overnight fasting. Flavored glucose in a dose of 1.75 g/kg body weight (up to a maximum of 75 g) was given orally. The glucose levels were obtained from the CGMS. Normal glucose tolerance (NGT), IGT, IFG and T2DM of the CGMS were defined according to the criteria of WHO in 1999 (all as capillary samples) (Table).[23] Nocturnal hypoglycemia was defined as the level of glucose lower than 2.8 mmol/L according to a previous report.[24]

Table. The definitions of NGT, IGT, IFG and T2DM in CGMS

	Definitions
NGT	an FG <5.6 mmol/L and each glucose level <7.8 mmol/L within 2 hours
IGT	an FG <5.6 mmol/L and glucose levels of 7.8-11.1 mmol/L within 2 hours
IFG	an FG of 6.1-7.8 mmol/L and glucose levels <7.8 mmol/L within 2 hours
T2DM	an FG ≥7.0 mmol/L or a glucose level >11.1 mmol/L within 2 hours or more than two glucose levels >11.1 mmol/L

NGT: normal glucose tolerance; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; T2DM: type 2 diabetic mellitus; FG: fasting glucose.

Statistical analysis

Statistical analyses were conducted by using SPSS software (version 11.5). Pearson's chi-square was used to measure the enumeration data between subgroups. Quantitative data were presented as means ± SD. The statistical significance between means was estimated by Student's *t* test and the correlation between capillary and ISF glucose was analyzed by Pearson's bivariate correlation. Differences were considered statistically significant at $P<0.05$.

Results

In 79 children, no redness, papules, or discomfort in insertion sites was complained. Slight bleeding in insertion sites was found in 6 children (7.14%), but it stopped itself and no further treatment was needed.

The capillary glucose levels of every patient were measured and compared with the data obtained by the CGMS. The mean glucose level was 5.88 ± 1.75 mmol/L in capillary and 5.75 ± 1.92 mmol/L in ISF measured by the CGMS without significant difference ($t=0.867$, $P=0.386$). The ISF glucose levels measured by the CGMS were highly correlated with capillary glucose levels ($r=0.775$, $P<0.001$). Notably the correlation between the glucose levels shown by CGMS measurement and capillary glucose levels was lower in the first hour ($r=0.722$, $P<0.001$) than that in the later time period ($r=0.830$, $P<0.001$). Moreover, the initial ISF glucose levels in 55 children (69.62%) were higher than the baseline level after excluding dietary effect, then declined to the baseline level in 1-3 hours.

As for the time-course change of ISF glucose levels in individuals during OGTT, the glucose levels

increased dramatically after oral glucose and most of them (62 children, 78.48%) peaked at 25-60 minutes, and then decreased slowly. The time-course change of the mean ISF glucose levels during OGTT peaked at 45-50 minutes as a positive normal curve. The mean glucose value of all obese children in OGTT detected by the CGMS was 5.81 mmol/L. Moreover, CGMS measurement of ISF samples from 79 obese children showed that 2 children had IFG, 2 had IGT, 3 had IFG+IGT, and 2 had T2DM.

Nocturnal hypoglycemia was noted after the overnight fasting in 11 children (13.92%). The lowest glucose levels in 5 of them were lower than the detection limit of 2.2 mmol/L. The duration of hypoglycemia ranged from 5 minutes to 6 hours and 35 minutes.

Discussion

Common OGTT which detects the blood glucose levels with vein or capillary samples is usually used to identify IGT, T2DM, insulin sensitivity and insulin secretion. However, the glucose peak in OGTT and the diagnosis of glucose metabolism disorder might be missed by just measuring 5 times. The use of the CGMS gives potential insights both into overall glucose levels, mean glucose, and variability of the full 24-hour period. The CGMS has been validated as a reliable and accurate measure of blood glucose in adults.[18-20] Studies have shown that ISF glucose levels generally follow venous blood glucose levels, and fingerstick measured capillary glucose levels.[25-28]

In this study, no redness, discomfort or papules were noted in all children during the CGMS. Only slight bleeding in insertion sites was found in a few patients and it stopped itself. This implied that the CGMS was very safe for blood glucose monitoring in obese children. Moreover, a high correlation between ISF glucose and capillary glucose levels demonstrates the accuracy and reliability of the CGMS measurement. Moreover, we observed the time-course change of glucose levels every 5 minutes in OGTT directly by using the CGMS for evaluating the glucose metabolism, which demonstrated directly that the glucose levels increased dramatically after oral glucose and peaked at 45-50 minutes, and then decreased slowly. The time-course change of glucose levels in OGTT seemed to be a positive normal curve.

The high prevalence rate of glucose metabolism abnormality (9/79, 11.39%), including IFG, IGT and T2DM, was found in these obese children measured by the CGMS as reported elsewhere,[29] but it was lower than those reported in Latin America, North America and Europe.[10,30,31] This difference might be associated with the different body mass index and the age of chidren. Whether it is associated with ethnicity is unknown.

In this study, we also noted that 2 children were diagnosed as having T2MD. They all had severe obesity and were very young. Transition from IGT to diabetes in adults is usually a gradual phenomenon that occurs over 5-10 years.[32,33] The early presentation of T2DM in youth raises the possibility of an accelerated process in these children compared with adults, thus shortening the transition time between IGT and diabetes. Several reports suggest that the tempo of β-cell function deterioration in children may be faster than in adults.[34,35] We conclude that severely obese children and obese children with risk factors for T2DM (such as a parent with T2DM, presence of acanthosis nigricans) should undergo OGTT and measurement of glucose levels by the CGMS.

Some researches have indicated that obese children with IGT can revert to have NGT on follow-up testing after cessation of weight gain.[16,36,37] Our previous study showed that metformin can reverse insulin resistance in obese children and some other circumstances.[38] So cessation of weight gain by increased physical exercise, decreased sedentary behavior and controlling diet, and using metformin may suffice to prevent or reverse the deterioration in glucose tolerance.

Interestingly nocturnal hypoglycemia was noted during the overnight fast in some obese children in this study. Why some obese children present with nocturnal hypoglycemia at night while some have hyperglycemia of unknown reason. Possibly it is associated with the day-night rhythm of some other hormone and polypeptide, and further study is required.

Problems with CGMS were noted in this study. First, the initial ISF glucose levels in most cases were higher than the baseline level with a lower correlation with capillary glucose levels and then declined to the baseline level in 1-3 hours. This finding has never been found in adults. The accurate mechanism is unknown. It might be associated with the instability in the initial short period. Whether it is associated with the stress reaction including a high glucose level when the sensor is inserted is still unclear. These results indicated that the levels of ISF glucose in the initial few hours were not accurate and should be excluded from the analysis of glucose levels by the CGMS. Second, few sensors are faulty or out-of-service, and repeated measurement is required. Third, the cost (550 RMB, about 70 dollars) is too expensive for some Chinese families. Hence some parents may refuse to use it and the widespread use in Chinese families is unfeasible.

In summary, our data suggest that glucose

metabolism disorder, including hyperglycemia and hypoglycemia, is very common in obese children. Further studies are required to improve the precision of the CGMS for glucose monitoring in children and to investigate the risk factors, preventive measures, and the mechanism of glucose metabolism disorder in obese children.

Acknowledgement

We thank all the children and their parents for participating in this research project.

Funding: This study was supported partly by grants from Zhejiang Population and Family Planning Committee (2006) and Zhejiang Science and Technology Committee (2005C24001).
Ethical approval: The Human Study Committee of Children's Hospital of Zhejiang University approved this study.
Competing interest: None declared.
Contributors: Zou CC wrote the first draft of the paper. All authors contributed to the intellectual content and approved the final version. Liang L is the guarantor.

References

1 Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. Pediatrics 2005;116:473-480.
2 Reinehr T, Andler W, Denzer C, Siegried W, Mayer H, Wabitsch M. Cardiovascular risk factors in overweight German children and adolescents: relation to gender, age and degree of overweight. Nutr Metab Cardiovasc Dis 2005; 15:181-187.
3 Reinehr T, Andler W, Kapellen T, Kiess W, Richter-Unruh A, Schonau E, et al. Clinical characteristics of type 2 diabetes mellitus in overweight European caucasian adolescents. Exp Clin Endocrinol Diabetes 2005;113:167-170.
4 Field AE, Cook NR, Gillman MW. Weight status in childhood as a predictor of becoming overweight or hypertensive in early adulthood. Obes Res 2005;13:163-169.
5 Elabbassi WN, Haddad HA. The epidemic of the metabolic syndrome. Saudi Med J 2005;26:373-375.
6 Pender JR, Pories WJ. Epidemiology of obesity in the United States. Gastroenterol Clin North Am 2005;34:1-7.
7 Neilson A, Schneider H. Obesity and its comorbidities: present and future importance on health status in Switzerland. Soz Praventivmed 2005;50:78-86.
8 Ehtisham S, Barrett TG, Shaw NJ. Type 2 diabetes mellitus in UK children: an emerging problem. Diabet Med 2000;17: 867-871.
9 Fu JF, Liang L, Dong GP, Jiang YJ, Zou CC. Obese children with benign acanthosis nigricans and insulin resistance: analysis of 19 cases. Zhonghua Erke Zazhi 2004;42:917-919. (in Chinese)
10 Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002;346:802-810.
11 Csabi G, Torok K, Jeges S, Molnar D. Presence of metabolic cardiovascular syndrome in obese children. Eur J Pediatr 2000;159:91-94.
12 Cho NH, Jang HC, Park HK, Cho YW. Waist circumference is the key risk factor for diabetes in Korean women with history of gestational diabetes. Diabetes Res Clin Pract 2006; 71:177-83.
13 Matsumoto H, Nakao T, Okada T, Nagaoka Y, Iwasawa H, Tomaru R, et al. Insulin resistance contributes to obesity-related proteinuria. Intern Med 2005;44:548-553.
14 Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, et al. Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study. J Periodontal Res 2005;40:346-353.
15 Urakami T, Kubota S, Nitadori Y, Harada K, Owada M, Kitagawa T. Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. Diabetes Care 2005;28:1876-1881.
16 Pontiroli AE, Pizzocri P, Caumo A, Perseghin G, Luzi L. Evaluation of insulin release and insulin sensitivity through oral glucose tolerance test: differences between NGT, IFG, IGT, and type 2 diabetes mellitus. A cross-sectional and follow-up study. Acta Diabetol 2004;41:70-76.
17 American Diabetes Association. Self-monitoring of blood glucose (Consensus Statement). Diabetes Care 1994;17:81-86.
18 Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WT. Limitations of conventional methods of self-monitoring of blood glucose. Diabetes Care 2001;24: 1858-1862.
19 Bode BW, Gross TM, Thornton KR, Mastrototaro JJ. Continuous glucose monitoring system used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. Diabetes Res Clin Pract 1999;46:183-190.
20 Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care 2001;24:2030-2034.
21 Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstet Gynecol 2003;101:633-638.
22 Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 2001; 107:222-226.
23 Puavilai G, Chanprasertyotin S, Sriphrapradaeng A. Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO consultation criteria, and 1985 WHO criteria. World Health Organization. Diabetes Res Clin Pract 1999;44:21-26.
24 Herbst A, Roth CL, Dost AG, Fimmers R, Holl RW. Rate of hypoglycaemia and insulin dosage in children during the initial therapy of type 1 diabetes mellitus. Eur J Pediatr 2005;164:633-638.
25 Bantle JP, Thomas W. Glucose measurement in patients with diabetes mellitus with dermal interstitial fluid. J Lab Clin Med 1997;130:436-441.
26 Fischer, U. Continuous *in vivo* monitoring in diabetes: the subcutaneous glucose concentration. Acta Anaesthesiol Scand

Suppl 1995;104:21-29.
27 Sternberg F, Meyerhoff C, Mennel FJ, Bischof F, Pfeiffer EF. Subcutaneous glucose concentration in humans. Real estimation and continuous monitoring. Diabetes Care 1995;18:1266-1269.
28 Sternberg F, Meyerhoff C, Mennel FJ, Mayer H, Bischof F, Pfeiffer EF. Does fall in tissue glucose precede fall in blood glucose? Diabetologia 1996;39:609-612.
29 Sun WX, Wang W, Wang DF, Cui YF. Oral glucose tolerance and insulin release test in 52 cases of obese and overweight children. Zhonghua Erke Zazhi 2005;43:93-95. (in Chinese)
30 Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Gruters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity: a problem that is no longer restricted to minority groups. Eur J Endocrinol 2004;151:199-206.
31 Goran MI, Bergman RN, Avila Q, Watkins M, Ball GD, Shaibi GQ, et al. Impaired glucose tolerance and reduced β-cell function in overweight Latino children with a positive family history for type 2 diabetes. J Clin Endocrinol Metab 2004;89:207-212.
32 Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997;46:701-710.
33 Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. The natural history of impaired glucose tolerance in the Pima Indians. N Engl J Med 1988;19:1500-1506.
34 Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475-1484.
35 Chou P, Li CL, Wu GS, Tsai ST. Progression to type 2 diabetes among high-risk groups in Kin-Chen, Kinmen: exploring the natural history of type 2 diabetes. Diabetes Care 1998;21:1183-1187.
36 Wong MS, Gu K, Heng D, Chew SK, Chew LS, Tai ES. The Singapore impaired glucose tolerance follow-up study: does the ticking clock go backward as well as forward? Diabetes Care 2003;26:3024-3030.
37 Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. Diabetes Care 2005;28:902-909.
38 Liang L, Fu JF, Zou CC, Hong F, Wang CL. Metformin hydrochlorides ameliorates adiponectin levels and insulin sensitivity in adolescents with metabolic syndrome. Zhonghua Erke Zazhi 2006;44:118-121. (in Chinese)

Received June 27, 2007
Accepted after revision December 26, 2007