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.

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, has emerged as an increasingly common pediatric disease 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. 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.

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), or only by measuring fasting and 120-minute levels on large-population study. 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. 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.

Herein, we assess the glucose metabolism disorder...
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/m² (mean 28.34±3.62 kg/m²), 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). Nocturnal hypoglycemia was defined as the level of glucose lower than 2.8 mmol/L according to a previous report.

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

<table>
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<th>Definitions</th>
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<tr>
<td>Definition</td>
<td>an FG&lt;5.6 mmol/L and each glucose level &lt;7.8 mmol/L within 2 hours</td>
<td>an FG&lt;5.6 mmol/L and glucose levels of 7.8-11.1 mmol/L within 2 hours</td>
<td>an FG of 6.1-7.8 mmol/L and glucose levels &lt;7.8 mmol/L within 2 hours</td>
<td>an FG ≥7.0 mmol/L or a glucose level &gt;11.1 mmol/L within 2 hours or more than two glucose levels &gt;11.1 mmol/L</td>
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<td>NGT: normal glucose tolerance; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; T2DM: type 2 diabetic mellitus; FG: fasting glucose.</td>
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Table. The definitions of NGT, IGT, IFG and T2DM in CGMS

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Glucose metabolism and CGMS in obesity children

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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. Studies have shown that ISF glucose levels generally follow venous blood glucose levels, and fingerstick measured capillary glucose levels.

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 but it was lower than those reported in Latin America, North America and Europe. This difference might be associated with the different body mass index and the age of children. 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. 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. Conclusively, 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. Our previous study showed that metformin can reverse insulin resistance in obese children and some other circumstances. Some 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.

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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.

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