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SHORT COMMUNICATION

Frequency of hypoglycaemia during the intravenous glucose tolerance test in overweight children

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Abstract
The study aimed to assess the frequency of hypoglycaemia during the insulin-modified, frequently sampled intravenous glucose tolerance test (FSIVGTT) in overweight Hispanic children. The study included 210 children, mean age = 11 ± 1.7 years, BMI percentile = 97.2 ± 2.9 who where enrolled in a longitudinal study to explore risk factors for type 2 diabetes. Two fasting blood samples were collected to determine basal glucose and insulin concentrations. At time 0, glucose (0.3 g/kg body weight) was administered intravenously. Eleven blood samples were collected until 180 min post glucose injection. Insulin (0.02 U/kg body weight) was injected intravenously at 20 min. Plasma was analyzed for glucose and insulin and used for the determination of insulin sensitivity. Hypoglycaemia, defined as a plasma glucose < 50 mg/dl, was observed in one asymptomatic subject (< 0.5% subjects). In addition, only 1.9% of subjects (n = 4) had plasma glucose < 60 mg/dl at any time during the FSIVGTT. The frequency of hypoglycaemia during the insulin modified FSIVGTT is very low in overweight Hispanic youth.

Key words: *Insulin sensitivity, hypoglycaemia, paediatrics*

The increased prevalence of overweight in childhood is associated with an increasing incidence of type 2 diabetes (1), impaired glucose tolerance (2,3) and the metabolic syndrome (4,5). The link between obesity and disease risk is thought to be due to underlying insulin resistance (6). In adults, insulin resistance or insulin sensitivity, has been measured indirectly by fasting insulin, homeostatic model insulin resistance index, and other calculated estimates of insulin sensitivity based on insulin and glucose levels obtained during an oral glucose tolerance test (7,8). These estimates of insulin sensitivity have generally been well correlated with directly measured insulin sensitivity. However, as we have recently shown, fasting insulin may give only a limited estimation of insulin sensitivity in childhood (9). In a cohort of overweight Hispanic children and adolescents, fasting insulin and other fasting insulin/glucose derived indices (including HOMA) did not significantly correlate with insulin sensitivity measured via the frequently sampled intravenous glucose tolerance test (FSIVGTT) and minimal modelling, once body composition was accounted for (9). These results imply that studies designed to measure the relationship between insulin sensitivity and disease risk in childhood may need to rely on the direct measurement of insulin sensitivity.

In the past investigators have used the hyperinsulinemic-euglycemic clamp (10,11) or the tolbutimide FSIVGTT with minimal model approach (12,13) to directly quantify insulin sensitivity in childhood. More recently, an insulin-modified protocol (as opposed to a tolbutamide protocol) was developed for determination of insulin sensitivity across the spectrum of glucose tolerance (14). The latter method has been widely used in adults with

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little risk of hypoglycaemia. Results from the Insulin Resistance and Atherosclerosis Study (IRAS), a multiethnic population based study, measured insulin sensitivity via the insulin-modified FSIVGTT protocol in 1525 adult subjects and reported only one case of hypoglycaemia (15). This corresponds to a prevalence of hypoglycaemia of less than 0.2% of the study population (15). In contrast, there are no current studies evaluating the risk of hypoglycaemia during the insulin-modified protocol in children. The principal aim of the current study was therefore to evaluate the frequency of hypoglycaemia during the insulin-modified FSIVGTT in a cohort of 210 overweight Hispanic children. In addition, this study aimed to provide a description of the insulin-modified FSIVGTT protocol to aid paediatric investigators in the use of this methodology as a valuable research tool for the investigation of insulin sensitivity in childhood.

The present study included 210 children (118 boys, 92 girls) who are part of the University of Southern California (USC) **S**tudy **O**f **L**atino **A**dolescents at **R**isk for Diabetes (**SOLAR** Diabetes Project), an ongoing longitudinal study to explore risk factors for the development of type 2 diabetes during adolescence. Subjects were of Hispanic origin, had a family history of type 2 diabetes, aged 8–13 years, were overweight (body mass index $\geq 85^{th}$ percentile) and did not have diabetes (1). Children were predominantly of Mexican-American (71%) or Central American (16%) descent and lived in the county of Los Angeles. This study was approved by the USC Institutional Review Board. Written informed consent and assent was obtained from all parents and subjects.

Insulin-modified, frequently sampled intravenous glucose tolerance test (FSIVGTT): at approximately 7:30 am, a flexible intravenous catheter was placed in each antecubital fossa. One was used for blood sampling, the other for injection of glucose and insulin. Two fasting blood samples were collected for determining basal glucose and insulin concentrations. At time 0, glucose (25% dextrose, 0.3 g/kg body weight) was administered intravenously over 1 minute. Blood samples were then collected at the following time points 2, 4, 8, 19, 22, 30, 40, 50, 70, 100 and 180 min. Insulin at a low dose (0.02 U/kg body weight; Humulin® R [REGULAR insulin for human injection; Eli Lilly, Indianapolis, IN]) was injected intravenously at 20 min (14). Plasma was analyzed for glucose and insulin, and values were entered into the MINMOD MILLENIUM 2003 computer program (Version 5.16 Richard N. Bergman) for determination of insulin sensitivity (16). Children were observed closely during the course of the procedure for symptoms or signs of hypoglycaemia. Blood glucose concentration was measured at the bedside at baseline and at the end of the 180-minute sampling period. Blood samples taken during the FSIVGTT were centrifuged immediately to obtain plasma and aliquots were frozen at -70°C until assayed. Plasma glucose was assayed in duplicate using a Yellow Springs Instrument 2700 Analyzer (YSI Inc, Yellow Springs, OH) and a glucose oxidase kit. Insulin was assayed in duplicate using a specific Human Insulin ELISA kit from Linco (St. Charles, MO). Hypoglycaemia was defined as a plasma glucose concentration ≤ 50 mg/dl at any time point during the FSIVGTT. This is the diagnostic criteria suggested for hypoglycaemia in children and adolescents and is associated with neurogenic and nueroglycopenic symptoms, and cognitive impairment (17,18).

Gender differences in physical and metabolic characteristics were examined using independent student t test. Variables that were not normally distributed were log transformed. The prevalence of hypoglycaemia (glucose <50 mg/dl) was calculated as the total number of subjects whose glucose dropped below 50 mg/dl at any time point during the FSIVGTT, expressed as a percentage of the total group. To further explore the risk of hypoglycaemia, we calculated the total number of subjects whose glucose dropped below a more conservative value of 60 mg/dl. All analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL) with a type I error set at $p < 0.05$.

Physical characteristics of subjects (Table I)

Girls were more advanced in Tanner Stage than boys ($p < 0.001$) and had higher fasting insulin ($p < 0.05$). Although there were no statistically significant differences in insulin sensitivity or the acute insulin response, girls had lower disposition index than boys ($p < 0.001$).

Figure 1 shows the mean ($\pm$standard deviation, SD) plasma glucose (A) and insulin (B) concentration during the FSIVGTT in 210 subjects. Plasma glucose increased immediately in response to intravenous glucose and declined thereafter to near fasting levels by the 180-time point (Figure 1). The nadir plasma glucose was reached at the 100-minute time point (82.9 ± 7.8 mg/dl). Hypoglycaemia, defined as a plasma glucose <50 mg/dl, was observed in 1 subject ($<0.5\%$) who was asymptomatic for hypoglycaemia. The subject was a pre-pubertal male aged 10, BMI of 20.3, BMI percentile 89.8 and who was relatively insulin sensitive ($Si = 9.07$ [$\times 10 - 4$ min^{-1}/(μU/ml)]) compared with the rest of the group (mean Si was 2.25 [$\times 10 - 4$ min^{-1}/(μU/ml)]). Hypoglycaemia

Table I. Physical and metabolic characteristics of subjects.

	Boys (n = 118)	Girls (n = 92)	Total (n = 210)
Age (years)	11.2 ± 1.6	10.9 ± 1.8	11.1 ± 1.7
Tanner Stage	1.8 ± 1.1*	2.8 ± 1.4	2.2 ± 1.3
Height (cm)	149.5 ± 11.1	147.8 ± 11.9	148.8 ± 11.4
Weight (kg)	63.6 ± 18.5	63.4 ± 20.6	63.5 ± 19.4
BMI (kg/m^2)	28.0 ± 5.4	28.3 ± 5.5	28.1 ± 5.4
Fasting glucose (mg/dl)	93.8 ± 6.4	92.2 ± 5.6	93.1 ± 6.1
Fasting insulin (μU/ml)	18.1 ± 10.5†	21.2 ± 12.4	19.4 ± 11.5
Insulin Sensitivity [$\times 10-4$ min^{-1}/(μU/ml)]	2.25 ± 1.48	2.10 ± 1.48	2.19 ± 1.48
Acute insulin response (μU/ml × 10 min)	1770 ± 1307	1605 ± 1172	1700 ± 1251
Disposition Index [$\times 10-4$ min^{-1}]	2840 ± 1237*	2276 ± 1040	2600 ± 1188

Values are means ± SD.
*Difference across gender is $p < 0.001$.
†Difference across gender is $p < 0.05$.

occurred at the 40-minute time point post glucose injection (20 minutes after insulin injection). Plasma glucose concentration increased to 60 mg/dl by the 50-minute time point and was 78 mg/dl at the 70-minute time point post glucose injection.

Four subjects (1.9%) had plasma glucose < 60 mg/dl. The mean (± SD) plasma glucose (A) and insulin (B) concentration during the FSIVGTT for these subjects is presented in Figure 2.

The main objective of this study was to establish the frequency of hypoglycaemia during the insulin modified FSIVGTT in overweight Hispanic children and to describe an insulin-modified, reduced sampling protocol for the FSIVGTT in overweight children. Results show that with this protocol, hypoglycaemia (glucose < 50 mg/dl) was uncommon and affected less than 0.5% of the population. Furthermore, only 1.9% of subjects had plasma glucose below 60 mg/dl at any time during the FSIVGTT. Our results are in agreement with those reported for adults, where the risk of hypoglycaemia using a similar protocol to ours, has been reported to be less than 0.2% (15). In the current study, episodes of hypoglycaemia may be further decreased by the use of a low insulin dose (0.02 U/kg vs. 0.05 U/kg used in adults) and to the relative insulin resistance of the study population.

The insulin-modified, reduced sample FSIVGTT protocol (19) combined with a low insulin dose (0.02 U/kg body weight (20) was chosen due to the relatively large sample of subjects (n = 210) and to initial safety concerns regarding risk for hypoglycaemia in children. We do not know if higher doses of insulin or an extended sampling protocol would

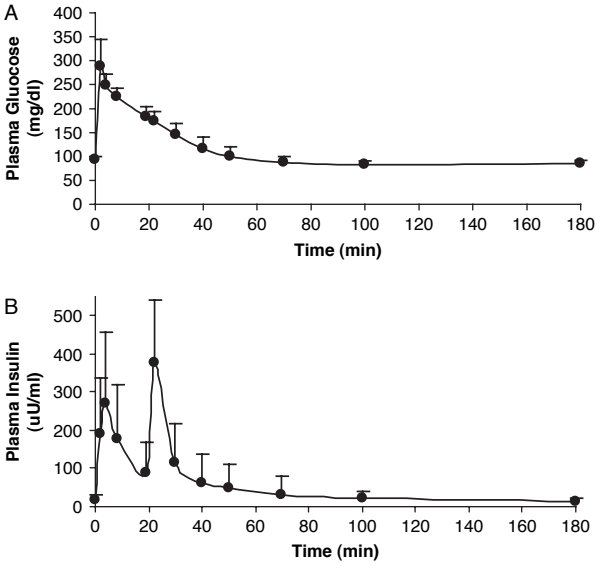

Figure 1. Mean (± SD) plasma glucose (A) and insulin (B) concentration during the insulin-modified FSIVGTT (n = 210).

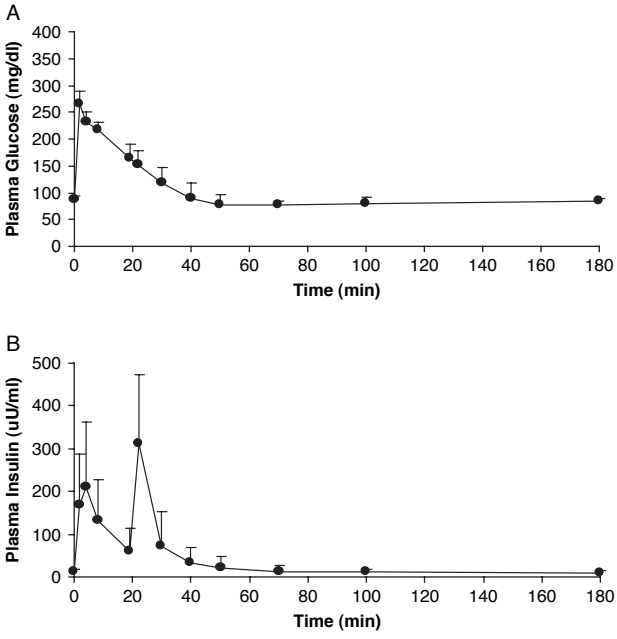

Figure 2. Mean (± SD) plasma glucose (A) and insulin (B) concentration during the insulin-modified FSIVGTT in subjects whose plasma glucose fell below 60 mg/dl at some time during the FSIVGTT (n = 4).

detect or result in higher episodes of hypoglycaemia. A recent study in 28 overweight children used an extended sampling protocol (total of 28 blood samples were taken) and an insulin dose of 0.03 U/kg (21). However, in the latter study, mean glucose and insulin concentrations during the FSIVGTT were not provided nor was information regarding episodes of hypoglycaemia in the tested subjects (21).

In conclusion, the insulin-modified FSIVGTT protocol with an insulin dose of 0.02 U/kg is safe to use in overweight Hispanic children.

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