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REGULAR ARTICLE

Blood sugar levels are higher in obese young children in Sweden than in Poland

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ABSTRACT

Aim: An elevated fasting glucose level is an early sign of metabolic dysfunction in obese children. This study compared fasting glucose levels in obese young children in Poland and Sweden.

Methods: We identified 109 obese children aged between two and 10 years from a Polish obesity register, with a mean BMI SDS (SD) of 3.72 (0.86). Each Polish child was matched by gender, age and degree of obesity, with ten children (n = 1090) from BORIS, the Swedish national childhood obesity treatment register. A group of 86 Swedish nonobese children served as controls.

Results: The mean fasting glucose values of the Polish, Swedish and nonobese cohorts were 4.73 (0.51) mmol/L, 4.92 (0.50) mmol/L and 4.56 (0.39) mmol/L, respectively. After adjusting for variables affecting fasting glucose, the mean glucose value of the Swedish obese children was 0.20 mmol/L higher than that of Polish obese children ($p < 0.0001$) and 0.41 mmol/L higher than in nonobese controls ($p < 0.0001$).

Conclusion: Swedish obese young children had higher glucose levels than Polish obese young children. This suggests that Swedish obese children face a higher risk of the prediabetic stage impaired fasting glycaemia.

INTRODUCTION/BACKGROUND

The increasing prevalence of childhood obesity has resulted in a rise in type 2 diabetes mellitus in obese adolescents, but type 2 diabetes mellitus is still rare in younger subjects (1). However, we and other research groups have shown that impaired glucose metabolism and insulin resistance can already be seen in obese young children (2–4).

Impaired fasting glycaemia (IFG) is a prediabetic stage that is defined as being where fasting glucose levels are such that the sensitivity and specificity for predicting diabetes within the next 5 years are maximised (5). As the diagnostic criteria for IFG are set for adults (6, 7), it is not possible to know whether children will suffer the same metabolic consequences. It has been suggested that the progress from prediabetes to diabetes is faster among children and adolescents than adults (8), with a 15% annual reduction in beta cell function (9) and a mean transition time from prediabetes to diabetes of 2.5 years (10).

We recently showed, in a large epidemiological study, that there was a three times higher risk of IFG among obese children and adolescents in Sweden compared with obese children and adolescents in Germany – even after adjustments for known risk factors such as age, gender and degree of obesity (11). The reasons for these differences between two similar countries within the same region of Europe are still unclear. Consequently, it is not known whether the prevalence of IFG in obese children and adolescents in Sweden is higher than in other European countries, or whether the German prevalence is lower.

This study was implemented to compare the patterns of the glucose distribution in obese children between two and 10 years of age in Poland and Sweden.

Abbreviations
BMI, Body mass index; HOMA-IR, Homoeostasis model of assessment of insulin resistance; IFG, Impaired fasting glycaemia; SDS, Standard deviation score; SD, Standard deviation.

Key notes

- An elevated fasting glycaemia is an early sign of metabolic dysfunction in obese children.
- Our study showed that the fasting glucose levels were higher in obese young children in Sweden than in Poland.
- These findings suggest that the Swedish obese children face a higher risk of the prediabetic stage impaired fasting glycaemia.

SUBJECTS AND METHODS

Fasting glucose measurements from a Polish cohort of obese children and a matched group from Sweden were obtained from registers. The children included in this study were between 2 and 10 years of age, obese (12) and with an eligible fasting glucose measurement. Exclusion criteria were syndromal obesity, secondary obesity, and patients with Down's syndrome and endocrine disorders – apart from well-controlled hypothyroidism at the time of blood sampling. In addition, children who were on drugs that could affect the glucose level, such as metformin or systemic glucocorticoids, were excluded from the data set.

Measurements

Fasting glucose values between 2.1 and 15.0 mmol/L were considered to be feasible. In the Polish group, 106 had insulin measurements and the corresponding number among the obese children from Sweden was 645. Insulin measurements below 18 pmol/L were excluded due to possible haemolysis or data entering errors.

Polish obese cohort

For this study, 109 children with obesity were available in the Polish database, including 53 boys and 56 girls. The characteristics are shown in Table 1. The data were collected from the West Pomerania province in Poland between March 2001 and April 2012, from both rural and urban areas. As the overweight and obese children came in for checks at Szczecin's only endocrinology clinic, at the Pomeranian Medical University, they were duly registered. The patients included in the local registry were under 18 years of age. The data cover approximately 95% of the overweight and obese children and adolescents in the West Pomerania province.

Venous blood samples from patients who had been fasting were drawn into Li-heparin or K3-EDTA and fluorite tubes and centrifuged within 30 min. The glucose was measured and analysed using an enzymatic method with hexokinase Glucose HK (GLUC2) by Cobas 6000 (Roche, Mannheim, Germany). Insulin was analysed using electrochemiluminescence by Cobas 6000 (Roche).

Swedish obese cohort

The Swedish data set of obese children was from a nationwide childhood obesity treatment registry (BORIS-registry, www.e-boris.se). At the time of data extraction, 20 of 24 (83.3%) paediatric clinics that treated obesity were enroled. The BORIS-registry is recommended for use by both The National Board of Health and Welfare and The Swedish Association of Local Authorities and Regions.

To each Polish patient, ten patients (in total n = 1090 patients) were matched as regards gender, age and degree of obesity – factors previously described as influencing glucose levels (11). The proportion of girls was 51.4% in both the Swedish and Polish cohorts. The group characteristics can be seen in Table 1. The age and BMI SDS did not differ between the matched obese groups (Wilcoxon two-sample test, p = 0.49 and p = 0.31, respectively).

Blood samples were obtained after an overnight fast. As the samples were collected from all over Sweden, the methods for analysis may have differed. However, the methodology for analysing fasting glucose in Sweden is regulated by 'EQUALIS', where venous plasma glucose is advocated. Fasting serum insulin was analysed using a radioimmunoassay Insulin RIA 100 (Pharmacia Diagnostics AB, Uppsala, Sweden) or electrochemiluminescence immunoassay, ECLIA (Elecsys, Roche Diagnostics, Scandinavia AB Bromma, Sweden).

Table 1 Group characteristics. Numbers are presented as mean (SD) if nothing else is stated.

	Poland n = 109	Sweden n = 1090	Non-obese controls n = 86
Age (years)	7.69 (1.64)	7.57 (1.67)	8.48 (0.33)
BMI SDS	3.72 (0.86)	3.58 (0.65)	0.21 (0.9)
Girls	51.4%	51.4%	46.5%

Swedish nonobese control group

As a control group of nonobese children, we used baseline samples that were collected from August 2011 to June 2012, within the *Stopp-8 Om3* study at the Karolinska Institutet, Stockholm, Sweden. The study aimed to observe the effects of omega-3 fatty acid supplementation on physical activity and weight development. The inclusion criteria for the *Stopp-8 Om3* study, as presented at clinicaltrials.gov id: NCT01323283, were that the children needed to be in the second grade at primary school and to have signed informed consent. The exclusion criteria were known diseases that could be negatively affected by the intervention. From 90 children, fasting venous blood samples, weight and height were obtained. Plasma glucose concentrations were determined from Vacuette tubes containing Na-fluoride and K-oxalate, using Gluco-quant Glucose/Hexo Kinas method, analysed with Modular P EVO, by Roche Diagnostics. This method is in line with the earlier mentioned 'EQUALIS' regulation.

Of the 90 participants, one declined to participate and the sample was not recorded and three were excluded due to obesity – this left a control group of 86 children. Mean (SD) age was 8.47 (0.33) years and BMI SDS was 0.21 (0.90), and 46.5% were girls.

Definitions

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared (kg/m^2). The international age- and gender-specific BMI cut-off points according to the International Obesity Taskforce (IOTF) criteria were used to define normal weight, overweight and obesity (12). The BMI standard deviation score (SDS) used is based on an equation created by Karlberg et al. (13). Impaired fasting glycaemia was defined using the ADA definition of 5.6 mmol/L (6) as the cut-off limit, and

the range for normal fasting insulin was 18–173 pmol/L, which both the Polish and the Swedish lab used for clinical purposes.

Statistics and data analyses

The specific fasting glucose level that best predicts future disease in children is unknown (14), but glucose levels in children that are within the upper normoglycaemic range have been associated with future type 2 diabetes mellitus (15). In this study, we therefore analysed the distribution of fasting glucose rather than the percentage of IFG.

Data management and statistical analyses were carried out in SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA).

Multivariate analyses (GLM) were carried out to identify differences in glucose levels among the groups. When identifying differences in glucose levels, variables adjusted for were age, gender, degree of obesity and group membership: Swedish obese, Polish obese or Swedish nonobese. Insulin levels and HOMA-IR were further investigated, and differences between the matched obese groups were identified using the *t*-test for log-transformed (LN) values.

RESULTS

The distribution curve of fasting glucose values of the children in Poland was shifted towards lower glucose levels ($p < 0.001$) with a mean (SD) value of 4.73 (0.51) mmol/L, compared with the corresponding curve from obese children in Sweden, 4.93 (0.50) mmol/L. The fasting glucose levels in healthy, nonobese Swedish children were lower than both obese groups, with a mean of 4.56 (0.39) mmol/L (Fig. 1). Multivariate analysis showed that the degree of obesity at this age did not affect the glucose levels in the groups ($p = 0.87$). However, both gender and age slightly affected fasting glucose levels, but were statistically significant ($p = 0.017$ and $p = 0.002$, respectively). After adjusting for variables affecting the glucose value, the obese children from Sweden had a 0.20 mmol/L higher mean fasting glucose value compared with the obese children from Poland ($p < 0.0001$) and 0.41 mmol/L higher than the nonobese children ($p < 0.0001$).

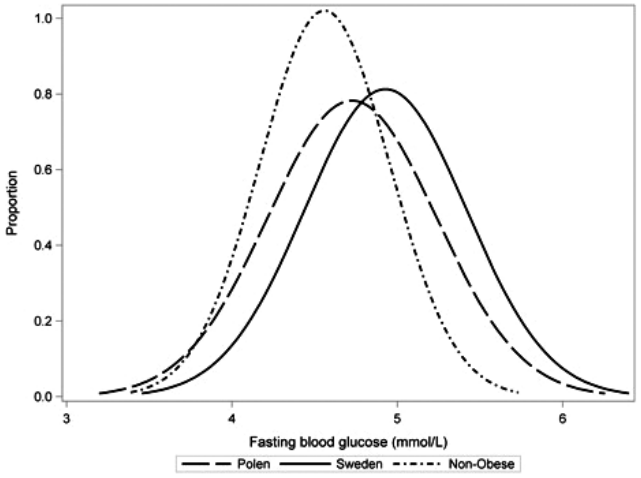

Figure 1 The Proportion of fasting glucose levels among the groups.

Insulin levels were almost 5 pmol/L higher ($p = 0.03$) in the obese Polish subjects compared with the Swedish obese ones, as seen in Table 2. Both cohorts were well within the normal range. Values are shown in Table 2. No insulin data from the nonobese group were available. No differences in HOMA-IR between the Polish and Swedish obese populations could be observed ($p = 0.15$), which is shown in Table 2.

Of the children in the obese groups, 4 (3.7%) in the Polish cohort and 99 (9.1%) in the Swedish cohort had IFG. No children in the nonobese Swedish cohort had IFG. Children with elevated fasting insulin values were 8 (7.5%) in Poland and 40 (6.2%) in the Swedish obese cohort.

DISCUSSION

The results in this study showed that fasting glucose values in obese children in Sweden are higher than in Poland. These differences are similar to those previously observed in another collaboration, which compared the prevalence of IFG and mean fasting glucose values in obese children and adolescents from Sweden and Germany (11). This current study confirms that the mean fasting glucose levels are relatively high in Sweden.

The reasons for the different metabolic profile in the obese Polish versus the obese Swedish group are not clear. No contributing factors have been identified so far. However, other studies have shown a correlation between alterations in glucose metabolism and levels of vitamin D (16), viral infections (17) and genetics (18). Dietary patterns and physical activity are also factors known to affect glucose homoeostasis (19).

There are several possible mechanistic reasons for elevated fasting glucose levels. Calí et al. (20) suggested that the primary determinant of fasting plasma glucose is the glucose sensitivity of first phase insulin secretion and that a defect in the insulin sensitivity of the basal endogenous glucose production contributes to IFG (20), which also might explain the lower insulin levels among the obese children in Sweden (21). The HOMA index, a surrogate marker for approximating insulin resistance (22), did not vary between the obese cohorts. This is understandable because the equation is based on fasting values of glucose and insulin and does not measure the physiology of the body's response to glucose or insulin. The HOMA-IR measurement is therefore not an optimal way of illustrating the actual physiological insulin resistance, and it has also been shown that HOMA-IR is not a better measure of insulin resistance than fasting insulin itself (3).

Another possible reason for the international differences seen might be due both to maternal diet during pregnancy and children's diet during the first years of life. Animal studies indicate that dietary patterns during pregnancy might affect offspring glucose homoeostasis (23, 24).

Table 2 Levels of fasting glucose, insulin and HOMA-IR in the obese cohorts.

	Glucose (mmol/L)		Insulin (pmol/L)		HOMA-IR	
	N	Mean (SD)	N	Geometric mean (IQR)	N	Geometric mean (IQR)
Sweden obese	1090	4.93 (0.49)	645	68.51 (59.72)	645	2.15 (2.03)
Poland obese	109	4.73 (0.51)	106	78.74 (62.37)	106	2.37 (1.97)
p*		<0.001		0.03		0.15

*Significance was calculated for mean using independent *t*-test. Insulin and HOMA-IR were log-transformed before analysis.

The nonobese children from Sweden had lower fasting glucose levels than the Polish obese. This indicates that high fasting glucose levels are not found in children in Sweden in general. However, we do not know whether nonobese children in Sweden have higher glucose levels than nonobese children from other European countries or whether, specifically, obese children living in Sweden are more prone to develop high fasting glucose levels.

In our previous study including both children and adolescents, the IFG prevalence increased slightly with the degree of obesity (11). However, this was not observed in the present study. One possible explanation might be that the metabolic profile seems to be more homogenous in obese children who have not gone through puberty (20, 25). Obesity-related comorbidities increase with age and duration of obesity, and this, in combination with a lower power in the present study, may also contribute to the lack of association between the degree of obesity and fasting glucose.

The clinical relevance of the high fasting glucose values in obese children in Sweden is unclear. Although the association between IFG and later type 2 diabetes mellitus is evident in adults, the predictive value of glucose and insulin levels is yet to be established in this age group. We have recently questioned whether IFG in Sweden really is a prestage of type 2 diabetes mellitus, because the high prevalence of prediabetes among obese children and adolescents in Sweden (11, 26) has not yet resulted in such an increased incidence of type 2 diabetes mellitus as would have been expected (26). However, the two to three times higher prevalence of IFG in obese children in Sweden over Germany (11) and the results in the present study coincide with a two to three times higher incidence of type 1 diabetes mellitus compared to both Poland and Germany (19). Further, environmental factors seem to be of greater importance than ethnicity in the risk of developing type 1 diabetes mellitus in Sweden (27). It has also been shown that obesity might increase the risk of developing type 1 diabetes mellitus in Sweden (28). Thus, we speculate that the higher levels of fasting glucose in obese children living in Sweden might be an indication of the risk of developing diabetes, but not specifically type 2 diabetes mellitus.

There are some important limitations with this study. The sample size of the Polish cohort is fairly small and is collected from only one region of the country, whereas the Swedish material is nationwide. In addition, we did not have a sample of normal-weight children from Poland, and furthermore, only 59% of the obese children in the Swedish cohort and none in the Swedish control group had fasting insulin measurements. This is primarily a register-based study; and therefore, the equipment, materials and analysis methods have not been cross-checked between the Polish and Swedish cohorts. This is of special importance for the insulin measurements, and the interpretations of them should therefore be made with caution. Pre-analytical and analytical differences may affect glucose levels – as we discussed thoroughly in a similar comparison between Germany and Sweden (11) – but the differences are so robust that we consider them reliable. However, before any clinical conclusions can be drawn this data needs to be confirmed in a controlled trial. Further, in this study, we have not considered ethnicity, but ethnicity did not affect IFG in children from Germany in our previous study of IFG (11).

This study does also have some strengths. To compensate for the limited sample size from Poland, we matched a ten times larger sample from Sweden. This helped to eliminate any slight differences, and therefore, we can assume that we have as true a picture as possible of the situation. All samples were collected in a clinical setting, and therefore, we can assume that all children and parents followed the request to not eat before the visit. This study also demonstrates the importance of registry-based studies, which can provide comparisons and hypothesis-generating results that would have been nearly impossible to obtain otherwise.

This is the only study, to our knowledge, that has analysed the distribution of fasting glucose in such young obese children.

CONCLUSION

Obese children between two and 10 years of age in Sweden had higher glucose levels compared with a corresponding population in Poland. This confirms that obese children in Sweden are at higher risk for the prediabetic stage impaired fasting glycaemia and thereby possibly at a higher risk for metabolic complications, compared with obese children from two other European countries – Poland and Germany.

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