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Original Article

High prevalence of prediabetes in a Swedish cohort of severely obese children

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Objective: In this cohort of severely obese children and adolescents in Sweden we investigate the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance, (IGT) and silent type 2 diabetes (T2D), in relation to insulin resistance, insulin secretion, disposition index and cardio respiratory fitness.
Methods: A total of 134 obese children and adolescents [57 females, 77 males, age 13.7 ± 2.7, body mass index (BMI) standard deviation score (SDS) 3.6 ± 0.6] consecutively referred to the National Childhood Obesity Centre performed an oral glucose tolerance test (OGTT), frequently sampled intravenous glucose tolerance test (fs-IVGTT), dual X-ray absorptiometry (DEXA), bicycle ergometer test and fasting levels of glucose, insulin and c-peptide were obtained and homeostatic model of insulin resistance (HOMA-IR) was calculated.
Results: Isolated impaired fasting glucose (i-IFG) were present in 35.8 and 6% had isolated IGT. Combined IGT and IFG were present in 14.2%. The subjects with combined IGT/IFG had significantly lower acute insulin response (AIR) compared with subjects who had normal glucose metabolism or i-IFG ($p < 0.05$). Among the prepubertal children ($n = 24$), 25% (6/24) had i-IFG and 25% (6/24) had IGT/IFG and it was predominantly males. Disposition index was the major determinant of 2-h glucose levels ($\beta = -0.49$, $p = 0.0126$). No silent diabetes was detected.
Conclusion: In this cohort of severely obese children and adolescents the prevalence of prediabetes was very high. IFG was two times higher in this cohort of severely obese children than in a recently published unselected cohort of obese children in Sweden. In spite of the high prevalence of prediabetes, no subjects with silent diabetes were found.

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Key words: child – fasting glucose – impaired glucose tolerance – insulin resistance – obese

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Type 2 diabetes (T2D) is often preceded by a long asymptomatic phase with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), and is often associated with obesity. The consequences of the prediabetic state in children are not fully understood, although it seems that children who have elevated fasting plasma glucose (FPG) in the high normal range show signs of insulin resistance and beta-cell dysfunction and have a higher risk of developing T2D in adulthood (1, 2). It is suggested that isolated impaired fasting glucose (i-IFG) and isolated impaired glucose tolerance (i-IGT) arise from different mechanisms (3–5). Earlier studies in adults and adolescents have indicated that obese subjects with i-IFG have a tendency toward decreased hepatic insulin sensitivity whereas those with i-IGT had a higher degree of peripheral insulin resistance and progressive beta-cell failure (4–7). There is great variation in reported prevalence regarding the levels of IFG and IGT in children, especially in European populations and the reason is largely unknown (8–11). We have recently studied the prevalence of IFG in Swedish obese children and adolescents and the prevalence was 17.1%, three times higher than in a comparable German cohort (12). However, the prevalence of T2D in children seems to be rather low in Sweden (13, 14) and the prevalence of silent diabetes in obese adolescents in Sweden is unknown. In a cohort of severely obese US adolescents 4% was shown to have silent diabetes (15). Cardiorespiratory fitness (CRF) appears to be of

importance for the development of insulin resistance in obese children and adolescents and could be a factor, which might contribute to the variation in prevalence of prediabetes and T2D in obese pediatric populations (16, 17).

The aims of this study were to quantify the prevalence of i-IFG, i-IGT, combined IGT/IFG, and silent T2D in a cohort of severely obese children and adolescents in Sweden, investigate the mechanisms behind the different groups of prediabetes and silent T2D, and to examine the relationship with insulin resistance, insulin secretion, disposition index (DI), and CRF.

Materials and methods

Study population

This study consists of 134 obese children and adolescents (57 females and 77 males, aged 6.2–18.3 yr) who had been referred to the National Childhood Obesity Centre at the Karolinska University Hospital, Huddinge, Sweden between April 2002 and April 2007 from all regions of Sweden, but mostly from the Stockholm county area. The cohort consisted of a population of several different ethnicities from an urban setting, representing a mixed Swedish population. Data on all participants were drawn from a nationwide childhood obesity treatment registry (BORIS-registry, www.e-boris.se) where all the participants were registered. The quality of the register is secured by frequent randomized sampling of the collected data. All study participants were consecutively investigated concerning clinical risk factors associated with obesity within a year from enrollment. The children and adolescents were included in this study if they met the following criteria: (i) classified as obese at enrollment according to the international age- and gender-specific body mass index (BMI) cutoff point defined by the International Obesity Task Force (IOTF) (18); (ii) absence of underlying chronic disease; and (iii) they had been investigated with oral glucose tolerance test (OGTT). Blood tests, clinical file data, medical examinations as well as questionnaires completed by the parents of the children were obtained at enrollment. All subjects were offered advice concerning diet and physical activity, but they were not following a specific weight-reducing diet such as very-low calorie diet (VLCD) or weight-reducing medication. None of the participants were on medication that alters glucose or lipid metabolism. Exclusion criteria were known presence of diabetes prior to investigation. The parents reported family history of diabetes. Ethical permission for data collection within the BORIS-cohort is obtained. All subjects gave a written informed consent and the Regional Committee of Ethics, Stockholm, approves studies within the BORIS-cohort. The study was conducted according to the principles of the Helsinki Declaration.

Anthropometric assessments

All anthropometric measurements were made by trained nurses in the same setting at the clinic. A calibrated wall-mounted scale (Ulmer stadiometer, Ulm, Germany) was used to measure the height to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg on a calibrated electronic scale (Vetek model T1-2001, Stockholm, Sweden) while the children were wearing light clothing and no shoes. BMI was calculated by dividing the weight in kilograms by the height in square meters (kg/m^2). BMI standard deviation score (SDS) was calculated using the equation according to Karlberg, using Swedish children as reference data (19). Body composition was measured by dual X-ray absorptiometry (DEXA) using a total body scanner (Lunar Prodigy X-R model 6830; GE Lunar Corporation, Madison, WI, USA; software version 8). Body fat content was expressed as total percent fat (fat mass %), abdominal fat was expressed as percent fat in soft tissue of the abdomen; 27 participants did not perform the DEXA for the following reasons: too heavy for the DEXA instrument, sickness on the intended examination day, and technical problems or refusal to participate. Physical maturity was assessed by a pediatric endocrinologist using the five-stage Tanner criteria of pubertal development, including breast development and testicular volume (20). Male patients with testicular volume <4 cc are considered prepubertal. Nine participants refused examination of pubertal development, two females and seven males.

Oral glucose tolerance test

The OGTT was performed at approximately 8:00 hours in the morning after an overnight fasting from 24:00 hours at the hospital. Baseline venous fasting values for insulin, glucose, and c-peptide were drawn before administration of 1.75 g glucose per kg bodyweight orally, to a maximum of 75 g. Blood samples for insulin, glucose, and c-peptide were drawn after 120 min.

Frequently sampled intravenous glucose tolerance test (fs-IVGTT)

Fs-IVGTT was used to determine Si, AIR, and DI and was performed as previously described (16, 21). Si, and AIR were calculated from the glucose and insulin values using the minimal model

computer program developed by Bergman et al. (MINMOD Millenium, 2003) (22). DI was calculated as the product of Si multiplied by AIR. The test was performed at 0800 hours in the morning after an overnight fast at the hospital from 2400 hours. At time 0 min, 0.3 g glucose per kg body weight was administered intravenously during 1 min. At time 20 min, 0.03 U insulin (Actrapid, Novo Nordisk Scandinavia AB) per kg body weight was administered as an intravenous bolus dose. Frequent blood samples for determinations of glucose and insulin were drawn during 180 min (23).

Laboratory analysis

Blood samples were obtained by venipuncture after an overnight fast for measurement of P-glucose (Glucose dehydrogenase method, Hemocue AB, Ängelholm, Sweden). Earlier B-glucose measurements (2002–2004) were adjusted by a factor of 1.11 according to international standard (24), 42% (n = 57) of the included subjects had glucose measurements converted from blood glucose to plasma glucose. All analyses were performed at a certified laboratory (Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden). Fasting serum insulin (fS-insulin) was analyzed using a radioimmunoassay insulin RIA 100 (Pharmacia Diagnostics AB, Uppsala, Sweden) or electrochemiluminescense immonoassay (ECLIA, Elecsys, Roche Diagnostics Scandinavia AB, Bromma, Sweden). Insulin RIA values were transformed to ECLIA using the formulas $1.258 \times \text{RIA} - 12.69$ (for values of insulin 1000–200 pmol/L, interassay variability r = 0.990) and $1.082 \times \text{RIA} - 2.737$ (for values of insulin <200 pmol/L, interassay variability r = 0.965). C-peptide was analyzed with ECLIA (Elecsys, Roche Diagnostics Scandinavia AB). Glycosylated hemoglobin Alc (HbAlc) was determined by high-performance liquid chromatography, HbA1c % (Mono-S – the former Swedish percentage unit for HbA1c) was converted to mmol/mol (IFCC, International Federation of Clinical Chemistry; internationally calibrated HbA1c unit) according to a linear equation $10.45 \times$ (HbA1c, Mono S, %) $- 10.62 =$ (HbA1c, IFCC, mmol/mol) (www://hba1c.nu) (25, 26).

Cardiorespiratory fitness

CRF was assessed by submaximal bicycle ergometer test according to Åstrand and Rhyming (27). Absolute VO_2 max (L/min) was estimated from the measured heart rate and work load using the nomogram provided by Åstrand and Rhyming (27). Relative VO_2 max (mL/kg/min) was calculated from absolute VO_2 max and the measured body weight (kg). Relative VO_2 max/kg fat free mass (FFM) was calculated from the DEXA results. A detailed description is presented earlier (16).

Definitions

i-IFG was defined according to American Diabetes Association (ADA, 2003) guidelines as FPG between 5.6 and 6.9 mmol/L. i-IGT was defined as 2-h post OGTT glucose between 7.8 and 11.0 mmol/L. Combined IGT was defined as 2-h post OGTT glucose between 7.8 and 11.0 mmol/L and presence of IFG, accordingly a group with IFG/IGT combined. T2D was defined as fasting glucose level of 7.0 mmol/L at two occasions or 2-h post OGTT glucose level of 11.1 mmol/L or above (28). For the specific analyses of glucose tolerance in relation to pubertal stages, three groups of glucose tolerance were used; normal glucose tolerance (NGT), IFG (i-IFG) and combined impaired glucose intolerance (IGT/IFG) as the group of i-IGT was small (n = 8). Homeostatic model of insulin resistance (HOMA-IR) was calculated using the following formula; fS-insulin (μU/mL) × P-glucose (mmol/l)/22.5 (29).

Analysis and statistics

All results are expressed as means ± SD unless stated otherwise. Analysis of variance (ANOVA) followed by a *post hoc* Bonferrroni correction was used for parametric variables and a Kruskall–Wallis test was used for multiple group comparison of non-parametric variables. Non-parametric variables such as Si, AIR, and DI were log transformed for parametric testing. Differences in gender for continuous variables were tested for significance with Mann–Whitney *U* test and the group frequencies were compared by chi-squared test. Spearman´s correlation analyses were used to evaluate univariate relationships. Multiple linear regression analyses were performed to estimate the relation between the dependent variables fasting glucose and 2 h glucose and important covariates. Statistical analyses were performed using STATISTICA® (version 8.1 Statsoft Inc., Tulsa, OK, USA). A p-value of <0.05 was considered statistically significant.

Results

Glucose tolerance status

No cases of silent diabetes were detected; 44.0% of all the children and adolescents had normal glucose metabolism (NGT). A total of 35.8% (n = 48) had isolated IFG, 6% (n = 8) of the children and adolescents had isolated IGT and 14.2% (n = 19) had a combination of IGT and IFG (IGT/IFG). Cases of prediabetes were found in all pubertal stages.

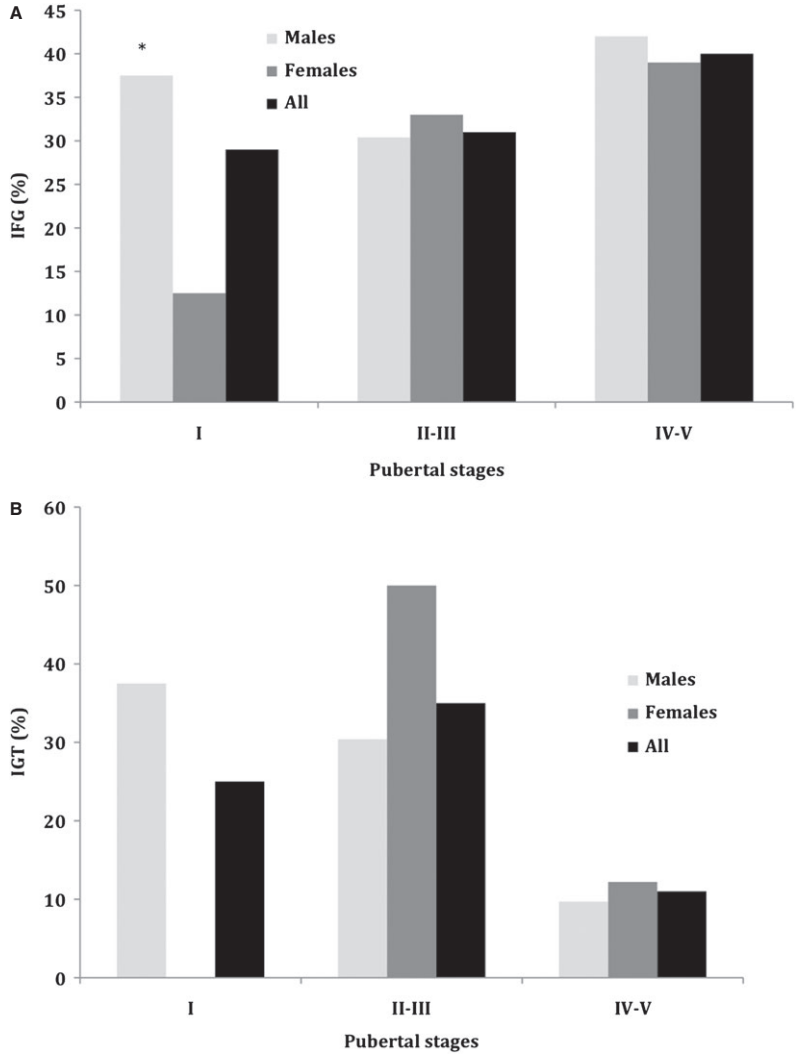

Fig. 1. (A) Prevalence of isolated impaired fasting glucose (i-IFG) across stages of pubertal development. Earlier peak incidence of i-IFG in males (Tanner stage I, $p^* = 0.0129$) than females. Peak incidence of i-IFG in the whole population at Tanner stage IV–V(group differences in prevalence were tested with chi-square test). (B) Prevalence of impaired glucose tolerance/impaired fasting glucose (IGT/IFG combined) across stages of pubertal development. No cases of IGT among the prepubertal female children. Peak incidence of IGT in the whole population at Tanner stage II–III. No cases of IGT among the prepubertal females, and three of six pubertal females had IGT. Nine of all individuals lack data regarding Tanner stage, two females and seven males.

Prevalence of i-IFG was more precocious in males compared with females, at Tanner stage I $p = 0.0128$ (Fig. 1A). A total of 37.5% (6/16) of the prepubertal males had IGT/IFG, whereas none of the prepubertal females (0/8) had IGT/IFG; 30.4% (7/23) of the pubertal males had IGT/IFG, and 50% (3/6) of the pubertal females had IGT/IFG; 9.8% (3/31) of the postpubertal males had IGT/IFG, and 12.2% (5/41) of the postpubertal females had IGT/IFG (Fig. 1B).

Clinical and metabolic characteristics in the different groups of glucose metabolism (NGT, i-IFG, i-IGT, and IGT/IFG combined) are shown in Table 1. There were no significant differences in age, BMI, BMI SDS, total fat mass, or abdominal fat mass among the four groups. Fasting glucose and 2 h OGTT glucose were different among the four groups as expected on the basis on the predefined categorization. The subjects with IGT/IFG combined, compared with NGT and i-IFG, have significantly lower AIR and higher 2 h OGTT insulin levels. The 2 h OGTT levels of C-peptide was significantly higher in the subjects with i-IGT.

In a separate analysis of AIR in relation to gender in the different groups of glucose tolerance, the males with IGT/IFG combined had a significantly lower AIR compared with the males with NGT ($p = 0.032$) (Fig. 2A). Analysing Si in relation to gender in the different groups of glucose tolerance, the males with NGT had a tendency toward lower Si compared with males with IGT/IGF ($p = 0.096$, Fig. 2B). There were no differences in DI, HOMA-IR, or relative VO2 max in the different groups of glucose tolerance in relation to gender (Fig. 2C–E).

Table 1. Clinical and metabolic characteristics of obese children and adolescents with normal, isolated impaired fasting, isolated glucose tolerance, and combined impaired glucose tolerance

	NGT	i-IFG	i-IGT	IGT (IGT/IFG)	p-Value
N (%)	59 (44.0)	48 (35.8)	8 (6.0)	19 (14.2)	
Gender (male/female)	31/28	28/20	4/4	14/5	0.419
Age (years)	13.8 ± 2.6	13.7 ± 3.0	13.9 ± 1.6	13.2 ± 2.7	0.672
Weight (kg)	101.5 ± 25.5	103.7 ± 30.2	92.9 ± 19.6	94.9 ± 24.8	0.327
Height (cm)	163.8 ± 13.2	166.5 ± 16.3	163.4 ± 10.6	162.1 ± 12.4	0.326
BMI (kg/m2)	37.3 ± 5.9	36.5 ± 6.4	34.5 ± 4.8	35.6 ± 5.4	0.590
BMI SDS	3.6 ± 0.6	3.7 ± 0.6	3.3 ± 0.6	3.7 ± 0.5	0.573
Total fat mass (%)	48.5 ± 4.8	47.6 ± 5.7	47.7 ± 5.2	48.6 ± 4.1	0.634
Abdominal fat mass (%)	48.9 ± 4.5	47.8 ± 5.6	48.8 ± 4.9	47.6 ± 3.6	0.547
fP-glucose (mmol/L)	5.1 ± 0.4	6.0 ± 0.4	5.3 ± 0.39	6.2 ± 0.4	<0.001
2 h OGTT glucose (mmol/L)	6.4 ± 0.8	6.6 ± 0.8	8.2 ± 0.36	8.4 ± 0.4	<0.001
HOMA-IR	4.2 ± 2.3	5.6 ± 5.9	3.7 ± 2.1	3.9 ± 2.1	0.489
Fasting insulin (pmol/L)	128.2 ± 67.9	144.3 ± 147.3	111.5 ± 60.9	99,8 ± 57.8	0.460
2 h OGTT insulin (pmol/L)	471.2 ± 446.7	330.1 ± 285.9	529.3 ± 255.2	575.9 ± 386.9	0.017
C-peptide (pmol/L)	1.31 ± 0.43	1.32 ± 0.48	1.08 ± 0.39	1.13 ± 0.34	0.300
2 h OGTT c-peptide (mol/L)	2.74 ± 0.88	2.29 ± 0.73	3.26 ± 0.85	2.71 ± 1.13	0.008
HbA1c (mmol/mol)	35 ± 7	36 ± 8	36 ± 7	38 ± 7	0.074
Si ($\times 10^{-5}$/min/pM)	2.11 ± 1.20	3.01 ± 2.75	1.93 ± 0.41	2.89 ± 2.12	0.471
AIR (pM)	1463 ± 946	1457 ± 915	1037 ± 617	945 ± 325	0.038
DI (10^{-5}/min)	2618.5 ± 1539.7	3012.1 ± 1996.7	1901.3 ± 899.2	2543.5 ± 1782.1	0.356
Relative VO_2max (mL/kg/min)	28.2 ± 5.8	28.3 ± 8.5	29.3 ± 4.3	27.9 ± 7.6	0.957
Relative VO_2 max (mL/kg FFM/min)	55.2 ± 10.5	57.3 ± 13.1	53.4 ± 7.0	56.7 ± 10.2	0.775
Family history of diabetes (%)	45.8	31.3	50.0	38.9	0.441
Tanner stage no. (I/II-III/IV-V/unknown%)*	11/10/35/3 (18.7/17/59.3/5.1)	7/9/29/3 (14.6/18.8/60.4/6.3)	2/2/2/2 (25/25/25/25)	4/8/6/1 (21/42.1/31.6/5.3)	0.156

AIR, acute insulin response from fs-IVGTT; BMI, body mass index; BMI SDS, BMI standard deviation score; DI, disposition index from fs-IVGTT; FFM, fat free mass; fP-glucose, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR; homeostatic model of insulin resistance; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; Si; insulin sensitivity from fs-IVGTT.
Data are expressed as mean ± SD and percentage.
*Nine individuals do not have data regarding Tanner stage.

In an ANOVA analysis of Si, insulin release (AIR) and DI in the different groups of glucose tolerance in relation to stage of pubertal development, the postpubertal subjects have a tendency toward a lower Si compared with the pubertal and prepubertal subjects irrespective of group of glucose tolerance. The prepubertal individuals with IFG and IGT had a significantly higher Si (IFG $p = 0.0003$, IGT $p = 0.0012$) compared with those with NGT (Fig. 3A), which was due to that more boys, who had higher Si, also had higher prevalence of IFG and IGT. The postpubertal individuals with NGT had a lower AIR compared with the pubertal individuals with NGT ($p = 0.002$). The pubertal individuals with IGT had a tendency toward a lower AIR compared with those with NGT (Fig. 3B). The postpubertal individuals with NGT showed lower DI compared with the pubertal individuals with NGT ($p = 0.0007$). The postpubertal individuals with IFG and/or IGT had a lower DI compared with the prepubertal individuals with IFG/IGT (IFG $p = 0.024$, IGT $p = 0.0056$, Fig. 3C).

Determinants of fasting glucose and oral glucose tolerance

Multiple regression analyses were performed with fasting glucose or 2-h OGTT glucose as the dependent variable and gender, age, AIR, Si, DI, BMI, Tanner stage, and relative VO_2 max/kg FFM as independent variables. No explanations to the variations in fasting glucose were found. DI was one of the significant determinants of the variance in 2-h glucose ($\beta = -0.49$, $p = 0.0126$). Age ($\beta = -0.48$, $p = 0.011$) and Tanner × gender ($\beta = 0.43$, $p = 0.0025$) also contributed to the variance in 2-h glucose.

Differences across gender and DI

The mean age of the study group was 13.7 ± 2.7 yr and the mean BMI SDS was 3.6 ± 0.6. Gender differences regarding anthropometric data are shown in Table 2. The females had a higher total fat mass, abdominal fat mass, and a higher relative VO_2 max/kg FFM (mL/kg FFM/min) compared with the males. The males had

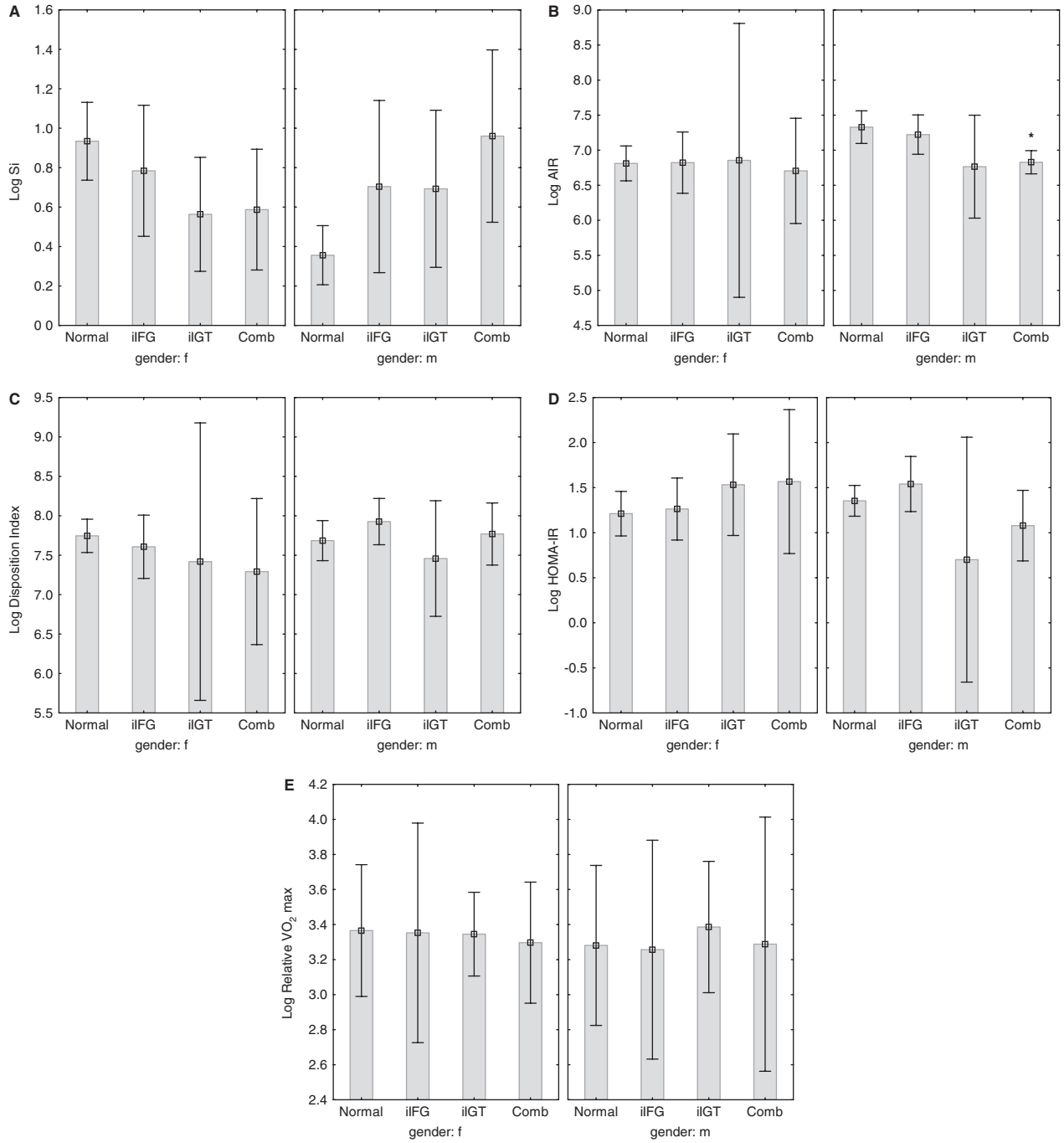

Fig. 2. Insulin sensitivity (Si), insulin release [acute insulin response (AIR)], disposition index (DI), homeostatic model of insulin resistance (HOMA-IR), and relative VO2 max in the different categories of prediabetes in relation to gender. AIR is significantly lower in males with impaired glucose tolerance/impaired fasting glucose (IGT/IFG) combined compared with males with normal glucose tolerance ($p^* = 0.032$), Fig. 2B. [Group differences in log Si, log AIR, log DI, log HOMA-IR, and log relative VO_2 max are shown with mean and 95% confidence interval (CI) and were calculated using the Kruskall–Wallis test, p-value <0.05 was defined as statistically significant].

higher AIR and a tendency toward lower Si compared with the females. The females had reached a more advanced pubertal status compared with the males, with a median Tanner stage 5 compared with 3 in males. In a comparison between children with low (the 25th percentile of DI) and high DI (the 75th percentile of DI), the children with low DI were older, had reached a more advanced pubertal status, a significantly higher 2 h glucose levels and C-peptide levels and a tendency toward a lower relative VO2 max (Table 3). There was an uneven distribution of females and males in the two groups, with more males in both the low and high DI group. There were no differences in prevalence of prediabetes in the two groups. When analysing males

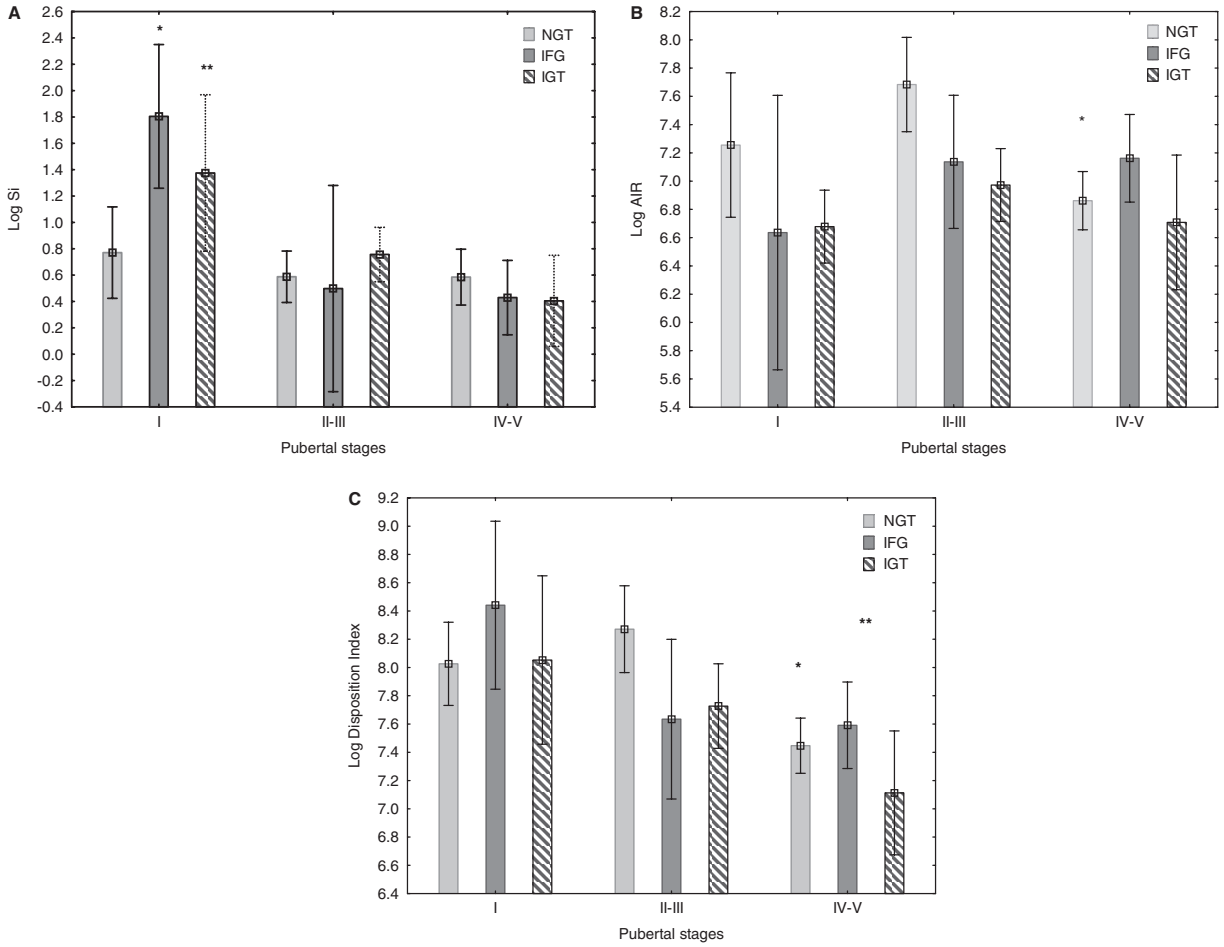

Fig. 3. Insulin sensitivity, insulin release and disposition index in different categories of prediabetes in relation to puberty stages [prepubertal (I), pubertal (II–III), and postpubertal (IV–V)] [The results are shown with mean and 95% confidence interval (CI), and the differences are calculated with Kruskall–Wallis test]. (A) In an analysis of variance (ANOVA) analysis of insulin sensitivity (Si) in the different groups of glucose tolerance in relation to stage of pubertal development, all the postpubertal individuals have a tendency toward a lower Si compared with the pubertal and prepubertal individuals irrespective of group of glucose tolerance. The prepubertal individuals with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) had a significantly higher Si (*IFG $p = 0.0003$, **IGT $p = 0.0012$) compared with those with normal glucose tolerance (NGT). (B) The postpubertal individuals with NGT had a lower insulin release [acute insulin response (AIR)] compared with the pubertal individuals with NGT ($^{*}p = 0.002$). The pubertal individuals with IGT had a tendency toward a lower AIR compared with the pubertal individuals with NGT. (C) The postpubertal individuals with NGT showed lower disposition index (DI) compared with the prepubertal and pubertal individuals with NGT ($^{*}p = 0.0007$). The postpubertal individuals with IFG and/or IGT had a lower DI compared with the prepubertal individuals with IFG/IGT (**IFG $p = 0.024$, IGT $p = 0.0056$).

and females separately in relation to DI, the females with low DI had a significantly lower AIR ($p = 0.0097$), and higher Si ($p = 0.0049$) compared with the males with low DI (Fig. 4A, B).

Discussion

In this cohort of severely obese children and adolescents a high prevalence of i-IFG (35.8%), i-IGT (6%), and IGT/IFG combined (14.2%) was found, reaching almost the same levels as in a multiethnic cohort carried out by Sinha et al. (15), and a much higher prevalence than other European studies of obese children and adolescents (8, 30). We have also recently shown that the prevalence of IFG in a large nationwide cohort of obese children in Sweden is high (17.1%) and three times higher than in a similar cohort from Germany (12). The reason remains unclear.

In this study the individuals with IGT/IFG combined have significantly lower AIR measured by fs-IVGTT, and also higher 2 h OGTT insulin and c-peptide levels as signs of beta-cell stress but similar degree of obesity and insulin resistance, which confirms earlier studies in different ethnic groups (15, 31–33). This implies that in this group of similarly obese children, who are all insulin resistant, beta-cell failure is a component of the development of IGT. The relatively high prevalence of IFG and IGT among prepubertal boys with only modestly impaired Si also supports the importance of beta-cell failure for the development of IFG and IGT

Table 2. Gender differences in anthropometric and clinical data

	Females n = 57	Males n = 77	p-Value
Age (years)	14.1 ± 2.7	13.4 ± 2.7	0.128
Weight (kg)	97.8 ± 23.2	103.1 ± 29.2	0.379
Height (cm)	161.0 ± 11.6	167.1 ± 15.3	0.009
BMI (kg/m^2)	37.2 ± 6.1	36.2 ± 5.8	0.346
BMI SDS	3.6 ± 0.5	3.7 ± 0.6	0.373
Total fat mass (%)	50.6 ± 4.2	46.2 ± 4.7	<0.001
Abdominal fat mass (%)	51.2 ± 4.2	46.2 ± 4.0	<0.001
Fasting glucose (mmol/L)	5.6 ± 0.6	5.6 ± 0.6	0.871
2 h OGTT glucose (mmol/L)	7.0 ± 0.9	6.8 ± 1.1	0.258
Fasting insulin (pmol/L)	119.9 ± 65.1	135.5 ± 122.5	0.818
2 h OGTT insulin (pmol/L)	413.1 ± 300.7	454.7 ± 433.9	0.927
Fasting c-peptide (pmol/L)	1.2 ± 0.4	1.3 ± 0.5	0.688
2 h OGTT c-peptide (pmol/L)	2.6 ± 0.8	2.6 ± 1.0	0.929
Fasting HOMA-IR	4.3 ± 2.4	4.9 ± 4.8	0.859
Si (×10^{-5}/min/pM)	2.7 ± 1.9	2.4 ± 2.1	0.059
AIR (pM)	1093.7 ± 634.5	1531.7 ± 956.6	0.009
DI (10^{-5}/min)	2382.1 ± 1040.9	2927.8 ± 2050.0	0.507
Relative VO_2 max (mL/kg/min)	29.3 ± 7.0	27.5 ± 7.0	0.238
Relative VO_2 max (mL/kg FFM/min)	59.9 ± 11.6	52.8 ± 9.8	<0.001
Glucose tolerance n (%)			
NGT	28 (49.1)	31 (40.3)	
IFG	20 (35.1)	28 (36.4)	
IGT	9 (15.8)	18 (23.4)	0.464
Tanner stage*	5 (1–5)	3 (1–5)	0.002

AIR, acute insulin response; BMI, body mass index; DI, disposition index; FFM, fat free mass; HOMA-IR, homeostatic model of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SDS, standard deviation score; Si, insulin sensitivity.
Values are means ± SD
*Values are described as median (range).

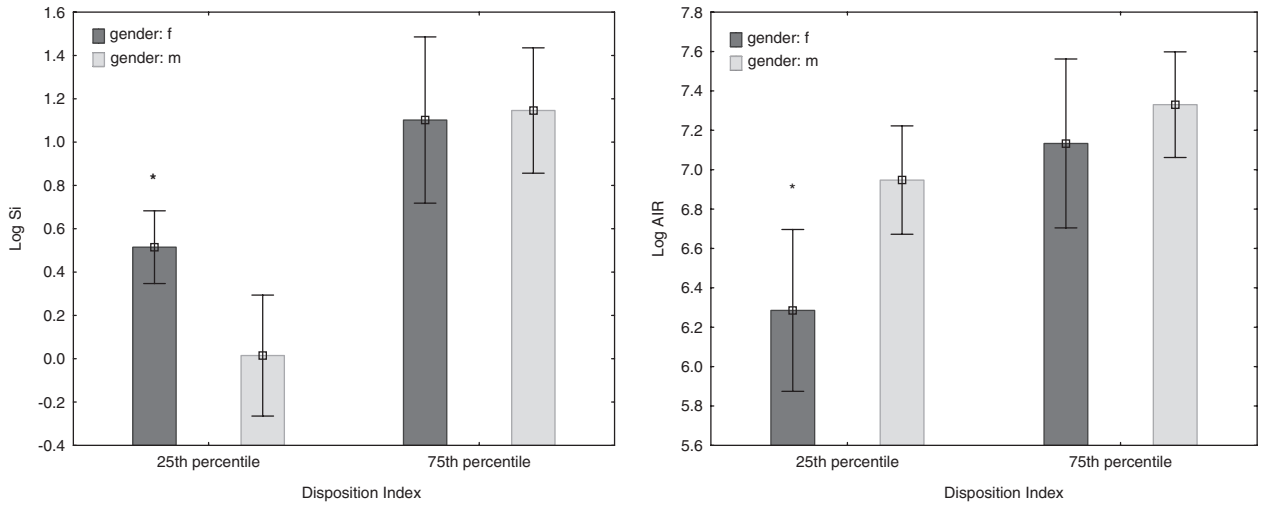

Fig. 4. Comparison between individuals with low and high disposition index (DI) in relation to gender [differences are shown with mean and 95% confidence interval (CI) and tested with Mann–Whitney *U*-test]. (A) Females with low DI had significantly higher insulin sensitivity (Si) compared with the males with low DI ($^*p = 0.0049$). (B) Females with low DI had significantly lower acute insulin response (AIR $^*p = 0.0097$).

in children, and especially in boys. We could not find any distinct features of isolated IGT, but the group was small (n = 8) which made further analyses unsuitable. We could not find explanations to the causes or risk factors of IFG. However, we did not measure hepatic Si that has been suggested to be one key cause for IFG (5, 33). The evaluation of insulin resistance was based on fs-IVGTT which has been validated through numerous studies (23, 34), but is known to reflect both peripheral and hepatic insulin resistance (35). We used 5.6 mmol/L as a cutoff level for IFG, and this level of plasma glucose might be too low to detect distinct differences in risk factors between IFG and IGT. Puberty is a developmental period that can be of

Table 3. Clinical and metabolic characteristics of obese children and adolescents with low vs. high disposition index

	25th percentile DI	75th percentile DI	p-Value
N	30	30	
Gender (male/female)	18/12	22/8	0.035
Age (years)	15.5 ± 1.5	11.9 ± 2.7	<0.001
Weight (kg)	116.9 ± 25.2	86.5 ± 21.8	<0.001
Height (cm)	172.2 ± 8.9	157.6 ± 14.1	<0.001
BMI (kg/m2)	39.2 ± 6.2	34.4 ± 5.5	0.002
BMI SDS	3.7 ± 0.5	3.8 ± 0.8	0.842
Total fat mass (%)	47.8 ± 5.0	47.4 ± 4.4	0.679
Abdominal fat mass (%)	48.0 ± 4.9	47.9 ± 4.6	0.907
fP-glucose (mmol/L)	5.6 ± 0.8	5.7 ± 0.5	0.633
2 h OGTT glucose (mmol/L)	7.2 ± 1.1	6.6 ± 1.0	0.042
HOMA-IR	6.2 ± 7.1	4.0 ± 2.7	0.153
Fasting insulin (pmol/L)	170.4 ± 174.4	112.5 ± 72.4	0.085
2 h OGTT insulin (pmol/L)	585.6 ± 581.2	394.4 ± 352.8	0.075
C-peptide (pmol/L)	1.38 ± 0.42	1.16 ± 0.44	0.045
2 h OGTT c-peptide (mol/L)	2.88 ± 0.89	2.33 ± 1.02	0.018
Si ($\times 10^{-5}$/min/pM)	1.39 ± 0.42	3.78 ± 2.39	<0.001
AIR (pM)	985.1 ± 758.1	1735.0 ± 1075.4	<0.001
DI (10^{-5}/min)	1065.9 ± 325.6	4834.3 ± 1877.5	<0.001
Relative VO_2max (mL/kg/min)	25.4 ± 6.4	29.4 ± 6.7	0.083
Relative VO_2 max (mL/kg FFM/min)	50.9 ± 10.1	55.1 ± 11.7	0.339
Glucose tolerance group no. (NGT/iIFG/iIGT/Comb %)	14/8/2/6 (47/27/6.7/20)	13/13/0/4 (43/43/0/13)	0.537
Tanner stage no (I/II-III/IV-V/unknown%)	0/2/27/1 (0/7/90/3)	11/8/8/3 (37/27/27/10)	<0.001

AIR, acute insulin response; BMI, body mass index; DI, disposition index; HOMA-IR, homeostatic model of insulin resistance; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SDS, standard deviation score; Si, insulin sensitivity.

importance in affecting the risk of diabetes (36, 37), and is a contributing factor of the variance in 2 h-glucose in this cohort of obese children. Surprisingly both IFG and IGT were present even in the prepubertal children. A lower CRF or higher insulin resistance in the prepubertal children cannot explain the high prevalence of prediabetes, in contrast they had a higher Si measured both with Si and HOMA-IR. The number of prepubertal children was small which made sub analysis unsuitable, so the reason for the unexpected high Si in the prepubertal group with IGT/IFG cannot be fully explained. The prepubertal group consisted mostly of males, and they had a high prevalence of IFG and IGT. The males in general in this study, irrespective of pubertal stage, had a higher AIR and a lower CRF compared with the females, which might contribute to the gender differences. Earlier studies have also found higher fasting glucose concentrations among boys (41) and also higher prevalence rates of IFG in adults and adolescent males compared with females (4, 38, 39). In the individuals with low DI in this study we could see gender differences with lower Si and higher AIR among the males, and there was also a tendency toward lower relative VO_2 max and higher 2 h OGTT glucose levels but a longitudinal study is required to confirm and interpret these findings.

We have previously presented a correlation between relative VO_2 max and Si (16), which implies that the CRF is a potential modifiable factor associated with insulin resistance. In this study CRF correlates with Si and pubertal development, but the level of CRF does not seem to affect the risk of developing prediabetes in this cohort of severely obese children and adolescents. Neither the degree of obesity, CRF, fasting insulin levels, gender, age, pubertal status, or family history of diabetes were sufficient to explain the different glucose metabolism patterns.

In adults both IFG and IGT are strong predictors of future T2D. The annualized risk to develop T2D seems to vary between 5 and 12% (40). The prognosis in children is unclear but a study of healthy children has shown that both fasting and 2 h glucose after OGTT were strong predictors of future T2D (41). It has been suggested that the progress is faster among children and adolescents than in adults with a 15% annual reduction of beta-cell function (42, 43) and a mean transition time from prediabetes to diabetes of 2.5 yr (44). As our study is a cross sectional study we cannot draw conclusions on the progression rate from prediabetes to diabetes in this cohort, but we do find it highly surprising that we did not find any cases of silent T2D in this high-risk group of severely obese children and adolescents. Taken together the high prediabetes prevalence in this and in our previous study (12) the prevalence of obesity in Sweden (45) and the above mentioned rate of progress from prediabetes to T2D, it can be calculated that hundreds of adolescents should develop

T2D each year which is not the case. In contrary, the prevalence of T2D among Swedish adolescents is low. The national diabetes treatment registry in Sweden where more than 95% of all children with diabetes are reported (46), have only 51 subjects with clinically diagnosed T2D registered (47). Silent diabetes, that seems to be relatively common both in the United States (17) and in Germany (30) cannot be found in the registry of obvious reasons as only symptomatic patients are registered. However, no subjects with silent diabetes were identified in this study, which might indicate that both manifest and silent T2D are relatively uncommon among obese adolescents in Sweden despite high prevalence of prediabetes.

Several limitations are to be acknowledged. The results in our study are not applicable to all overweight/obese children as this cohort consisted of a subgroup of severely obese children who were referred to a National Centre for Obese Children. Although they are only referred due to their severe obesity they might have more comorbidities associated with obesity than the general population. Earlier studies have shown differences in Si and AIR related to ethnicity (48), but we could not assess whether ethnicity explains the differences in glucose tolerance status. The children in this cohort originated from several different countries, thus being a very heterogenous group and could not be classified according to ethnicity, although the cohort is representative of a mixed Swedish population from an urban area. Another weakness of this study is that we did not measure intra patient variability; the OGTT was performed at only one occasion. Several studies have shown relatively poor correlation when performing repeated OGTTs in the same individual (27). On the other hand, Sinha et al. demonstrated a good reliability of a single OGTT in children (15), and a strength of this study is that all the investigations were performed by trained nurses in the same clinical setting and conditions and we have investigated several important clinical risk factors associated with obesity and the development of T2DM. The high prevalence rate of prediabetes among the young children could be caused by stress during the procedure, but the procedure took place in a familiar setting for the children with well-trained and experienced nurses to minimize the stress.

In summary, the prevalence of IFG and IGT among severely obese children and adolescents in Sweden is twice as high as the prevalence in the obese population in general (12) and reach the same levels as reported from the United States. Despite that, the prevalence of both silent and manifest T2D is low in Swedish adolescents. This indicates that the progress of prediabetes to diabetes is slow among adolescents in Sweden but a longitudinal study is required to confirm this.

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Conflict of interest

Authors hold no financial disclosure or conflict of interest

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