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ORIGINAL ARTICLE

# Insulin function in obese children within the low and high ranges of impaired fasting glycemia

**Emilia Hagman** | **Anna E. Ek** | **Claude Marcus**

Department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska Institutet, Stockholm, Sweden

**Correspondence**
Emilia Hagman, Division of Pediatrics, Department of Clinical Science, Intervention and Technology, Blickagången 6A Novum, Karolinska Institutet, Karolinska University Hospital, Huddinge, 141 57 Stockholm, Sweden.
Email: emilia.hagman@ki.se

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**Background/Objective:** Impaired fasting glycemia (IFG) reflects an intermediate hyperglycemia in the fasting state. Which fasting glucose level that actually is associated with impaired insulin-glucose homeostasis in children and adolescents with obesity is unknown. The aim of this study was to investigate how insulin and glucose homeostasis in children and adolescents with obesity in Sweden varies within different fasting glucose levels in the non-diabetic range.

**Subjects:** The subjects, *n* = 333, were divided into three groups based on their fasting glucose level. Normoglycemic range: up to 5.5 mmol/L (*n* = 268); the exclusive range the American Diabetes Association (ADA) has for IFG diagnosis: 5.6-6.0 mmol/L (*n* = 44); and IFG according to World Health Organization: 6.1-6.9 mmol/L (*n* = 21). The three groups were of similar age, degree of obesity, fasting insulin levels, sex, and migrant background distribution.

**Methods:** We used an insulin-modified frequent sample intravenous glucose tolerance test to study acute insulin response (AIR), insulin sensitivity (SI), and disposition index (DI) in children and adolescents with obesity. The main outcome measures were AIR, SI, and DI in three groups based on fasting glucose level.

**Results:** Fasting glucose levels ranging from 5.6 to 6.0 mmol/L were not associated with a lower AIR, SI, or DI compared with the normoglycemic range. However, glucose levels ranging from 6.1 to 6.9 mmol/L were associated with lower AIR and lower DI, but no statistical differences in SI were present.

**Conclusions:** IFG in the exclusive ADA range was not associated with disturbed glucose metabolism. This suggests that IFG contributes to adverse metabolic profile in children differently to what has been described previously in adult obese populations.

KEYWORDS

insulin resistance, intravenous glucose tolerance test, pediatric obesity, prediabetic state

## 1 | INTRODUCTION

Impaired fasting glycemia (IFG) reflects an intermediate hyperglycemia in the fasting state and is considered a prediabetic state.[1,2] IFG is highly prevalent in children and adolescents with obesity,[3] even though large international differences are evident.[4] At present, two different definitions of IFG are used in parallel. In 1997, the American Diabetes Association (ADA) announced IFG, with the choice of 6.1 mmol/L (110 mg/dL) as the lower cutoff level, based in large part on epidemiological data on the risk of microvascular and macrovascular complications.[5] In 2003, ADA reduced the lower fasting plasma glucose cut point to define IFG to 5.6 mmol/L (100 mg/dL), in part to ensure that prevalence of IFG was similar to that of IGT.[1] However, the World Health Organization (WHO) did not adopt this change in the definition of IFG.[2] In adults, IFG has been associated with increased risk for cardiovascular disease, cancer, and premature death even in the absence of the development of type 2 diabetes (T2D).[6–8]

IFG is associated with reduced hepatorenal insulin sensitivity, causing higher hepatic endogenous glucose production, combined with insufficient basal insulin secretion, resulting in elevated fasting glucose levels.[9–12] Furthermore, first-phase insulin secretion has been shown to be impaired in adolescents and adults with IFG,[12–14] corresponding to a 49% decline in β-cell function relative to insulin sensitivity.[15] Second-phase insulin secretion and peripheral insulin resistance in skeletal muscles seems to be normal in subjects with IFG.[9,11,13,14] However, some physiological differences have been observed across different populations, indicating that the pathogenesis of IFG may differ in different ethnic groups.[9,12]

The presence of IFG in adults increases the risk of T2D. The cumulative incidence over 6 to 9 years has been reported with a range of 29% to 39%.[16–18] We have previously shown, in a cohort of children and adolescents with obesity and relatively high presence of IFG in Sweden, that IFG in the exclusive interval provided by ADA, that is, a moderately elevated fasting glucose (5.6-6.0 mmol/L) did not affect the risk of developing T2D. On the other hand, children and adolescents with obesity and a fasting glucose of 6.1 mmol/L or above (WHO definition of IFG) had almost four times higher risk of developing T2D in young adulthood than normoglycemic children with obesity[19] who, in turn, had 24 times higher risk than population-based controls. After a median follow-up period of 7 years, approximately 12% with IFG WHO had developed T2D, which, although a high-risk number, is much lower than seen in adults (see above). Thus, IFG in children and adolescents in general and especially IFG according to ADA does not seem to increase the risk of T2D to the same extent as in adults.

The aim of this study was to investigate how insulin and glucose homeostasis in children and adolescents with obesity in Sweden varies within different fasting glucose levels in the non-diabetic range.

## 2 | METHODS

### 2.1 | Subjects

*Inclusion criteria*: Children and adolescents from 10 to 18 years of age, who had obesity and have undergone an intravenous glucose tolerance test at the National Center of Childhood Obesity in Stockholm, Sweden between May 1997 and May 2008, $n$ = 371. *Excluded criteria* were incomplete tests (eg, consecutive insulin samples with hemolysis), $n$ = 33; subjects on metformin or fasting glucose values in the diabetic range (≥7.0 mmol/L), $n$ = 5, Figure 1. The study was approved by the regional Ethics Committee in Stockholm, Sweden (No. 2016/922-31/1).

Anthropometric assessments were carried out by pediatric nurses trained in endocrinology. A calibrated wall-mounted stadiometer was used to measure height, and a calibrated electronic scale was used for weight measurements. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in square meters (kg/m$^2$). Age- and gender-specific BMI cutoff levels recommended by International Obesity Task Force were used to define obesity and severe obesity.[20] Pubertal status was classified according to Tanner[21] by a pediatric endocrinologist. Tanner stages 4 and 5 were pooled in the analyses.

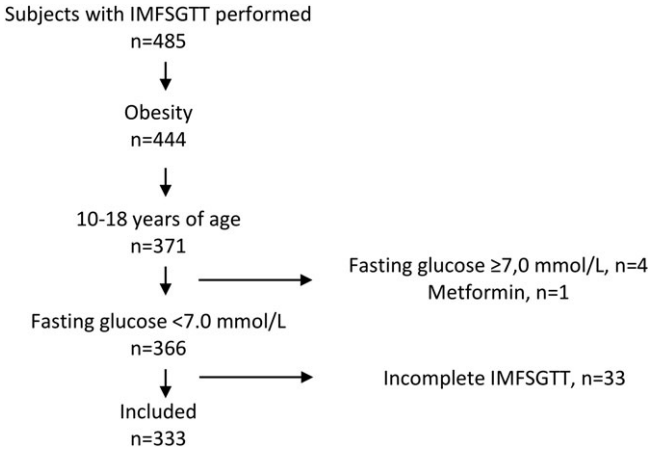


**FIGURE 1** Flowchart of included subjects with insulin-modified frequents sampling glucose tolerance test (IMFSGTT) performed

### 2.2 | Intravenous insulin-modified glucose tolerance test

Glucose/insulin metabolism was measured with an intravenous frequent sampling glucose tolerance test performed in the morning after fasting overnight. For blood sampling and infusion of glucose and insulin, one intravenous catheter was inserted in the antecubital vein of each arm. Fasting glucose and insulin were measured at the following time: −15 minutes, −10 minutes, and −5 minutes. At time 0 minutes, 0.3 g glucose per kg body weight was administered intravenously during 1 minute. At time 20 minutes, 0.02 U insulin (Actrapid; Novo Nordisk Scandinavia AB, Malmö, Sweden) per kg body weight was administered as an intravenous bolus dose. Venous blood samples for determinations of glucose and insulin were obtained at $t$ = −15, −10, −5, 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 25, 27, 30, 35, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 minutes.[22] Glucose was analyzed with a bedside instrument (HemoCue AB, Ängelholm, Sweden), and insulin was analyzed at the Karolinska University Hospital Laboratory, Sweden.

The acute insulin responsiveness (AIR) to glucose and the insulin sensitivity index (SI) were calculated from the glucose and insulin values using the minimal model computer program (MINMOD Millennium, 2003).[23] The acute insulin responsiveness to glucose assesses the capability of insulin secretion after the glucose injection. The insulin SI is a measure of the ability of insulin to enhance glucose disposal and inhibit glucose production. The disposition index (DI) was calculated as the product of the acute insulin responsiveness to glucose and the insulin SI.

### 2.3 | Definitions

The subjects were divided into three groups based on their fasting glucose level; up to 5.5 mmol/L corresponding to normal fasting glycemia (NFG), 5.6 to 6.0 mmol/L corresponding to the exclusive interval for IFG provided by ADA, and 6.1 to 6.9 mmol/L corresponding to IFG according to WHO.

Data on all participants were registered in the Swedish Childhood Obesity Treatment Register (BORIS: www.e-boris.se), and data of Scandinavian origin as defined previously[19] were retrieved from

Statistics Sweden, a governmental agency that collect and provide official statistics.

## 2.4 | Statistics

Descriptive statistics are presented with proportions or means ± SD. Differences between the glucose categories regarding descriptive measures (ie, anthropometric and demographic) were evaluated with ANOVA or $\chi^2$ test. The outcome AIR, SI, and DI were non-normally distributed and therefore transformed with the natural logarithm. These variables were analyzed with general linear model adjusted for sex, age, migrant background, and degree of obesity. Adjusted least square means were retrieved for illustrations. A *P*-value <0.05 was considered to be statistically significant. All analyses were performed in SAS statistical software (version 9.4, Cary, North Carolina).

# 3 | RESULTS

In total, 333 children and adolescents (53.5% girls) fulfilled the criteria for inclusion. The mean ± SD age was 14.8 ± 2.0 years, BMI standard deviation score (SDS) 3.09 ± 0.39, and 26.7% were of migrant background. The majority of the individuals were in Tanner stage 4/5. The fasting glucose ranged between 3.4 and 6.9 mmol/L with an average of 5.1 ± 0.6 mmol/L. NFG was present in 268 patients, the exclusive IFG interval provided by ADA (5.6-6.0 mmol/L) was found in 44 patients, and 21 patients had IFG according to WHO (6.1-6.9 mmol/L). The three groups, based on fasting glucose levels, were of similar degree of obesity and age, sex, and migrant background distribution. The groups differed by definition in the fasting glucose levels but had similar fasting insulin levels (Table 1). The excluded subjects had 0.22 higher BMI SDS, *P* = 0.0008, but were of similar age (*P* = 0.25), had similar fasting glucose (*P* = 0.26), and sex distribution (*P* = 0.91).

In models adjusted for sex, age, migrant background, and degree of obesity children and adolescents with obesity and fasting glucose levels ranging from 5.6 to 6.0 mmol/L had similar AIR, SI, and DI compared with NFG individuals. However, individuals with fasting glucose levels ranging from 6.1 to 6.9 had 48% lower AIR and 57% lower DI (both *P* < 0.0001) compared with the NFG group, and 39% lower AIR (*P* = 0.0048) and 51% lower DI (*P* < 0.0001) compared with the group of children with fasting glycemia of 5.6 to 6.0 mmol/L. There was a 17% lower SI in subjects with fasting glucose levels of 6.1 to 6.9 compared with NFG, but no statistical difference in SI was observed between any of the groups (all *P* > 0.1). This is illustrated in Figure 2.

**TABLE 1** Descriptive data population and comparative statistics between the fasting glucose category groups

| | Total *n* = 333 | NFG *n* = 268 | 5.6–6.0 mmol/L *n* = 44 | 6.1-6.9 mmol/L *n* = 21 | ANOVA/ $\chi^2$ *P* |
|---|---|---|---|---|---|
| Girls | 53.5% | 54.1% | 45.5% | 61.9% | 0.41 |
| Obesity/severe obesity | 29.4/70.6 | 28.4/71.6 | 36.4/63.4 | 28.6/71.4 | 0.56 |
| Migrant background | 26.7% | 24.3% | 36.4% | 38.1% | 0.12 |
| BMI SDS | 3.09 ± 0.39 | 3.09 ± 0.40 | 3.04 ± 0.35 | 3.14 ± 0.37 | 0.60 |
| Age (y) | 14.8 ± 2.0 | 14.8 ± 2.0 | 14.3 ± 1.7 | 14.9 ± 1.6 | 0.20 |
| Pubertal status by Tanner % (1/2/3/4-5/missing) | 3.6/8.4/7.2/63.7/17.1 | 3.7/8.2/7.8/65.3/14.9 | 2.3/9.1/6.8/50.0/31.8 | 4.8/9.5/0.0/71.4/14.3 | 0.26 |
| BMI (kg/m$^2$) | 36.4 ± 5.4 | 36.5 ± 5.6 | 35.3 ± 4.0 | 37.6 ± 5.6 | 0.26 |
| Glucose (mmol/L) | 5.1 ± 0.6 | 5.0 ± 0.4 | 5.8 ± 0.1 | 6.3 ± 0.3 | <0.0001 |
| Insulin (pmol/L) | 119.6 ± 71.4 | 116.5 ± 72.2 | 133.4 ± 71.9 | 131.2 ± 57.1 | 0.26 |

Abbreviation: BMI, body mass index.

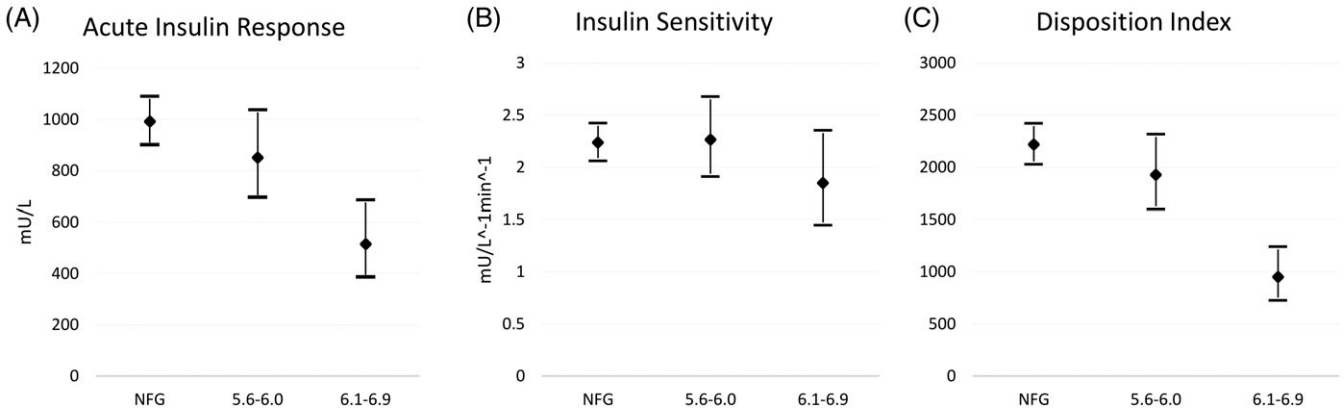


**FIGURE 2** Geometric means of A, acute insulin response (AIR); B, insulin sensitivity (SI); and C, disposition index (DI) by fasting glucose category adjusted for sex, age, migrant background, and degree of obesity. Interval represent 95% confidence limits. Normal fasting glycemia (NFG) vs 5.6-6.0 mmol/L: AIR, *P* = 0.160; SI, *P* = 0.892; DI, *P* = 0.165. NFG vs 6.1-6.9 mmol/L: AIR, *P* < 0.0001; SI, *P* = 0.135; DI, *P* < 0.0001. 5.6-6.0 vs 6.1-6.9 mmol/L: AIR, *P* = 0.005; SI, *P* = 0.174; DI, *P* < 0.0001

Hence, the lower DI in subjects with the highest fasting glucose level was primarily a result of impaired AIR and not increased peripheral insulin resistance.

Replacing age with Tanner staging in the adjusted model in the subgroup with reported pubertal status ($n$ = 276, 83% of the individuals), did not attenuate the results for AIR or DI. However, it revealed that fasting glucose levels of 6.1 to 6.9 mmol/L had lower SI than 5.6 to 6.0 mmol/L, geometric mean 1.83 vs 2.62 mU/L$^{-(1\text{min}/1)}$, $P$ = 0.03, but was not statistically significant to NFG subjects, $P$ = 0.09.

## 4 | DISCUSSION

Insulin resistance in combination with insufficient insulin secretion is cornerstones in the natural history of T2D. IFG is currently defined with different cutoff values by ADA and WHO,[1,2] but no specific recommendations for children are available. The present study was undertaken to compare AIR, SI, and DI, in children and adolescents with obesity divided into three groups depending on their fasting glucose levels. We found that fasting glucose levels ranging from 5.6 to 6.0 mmol/L, that is, the additional range ADA has for IFG diagnosis, were not associated with a lower AIR, SI, or DI compared with children in the normoglycemic range. However, glucose levels of 6.1 to 6.9 mmol/L, the WHO IFG range, were associated with lower first phase insulin secretion and lower DI. In previous studies in youths, impaired insulin sensitivity has not been found in the prediabetic range of 5.6 to 6.9 mmol/L compared with lower glucose levels.[13,15]

It is unclear why IFG in the ADA range predicts diabetes in adults but not in children. In adults, IFG is also associated with increased morbidity and mortality independently of development of T2D.[6,24] However, the causal relationship between moderately elevated glucose levels and morbidity can be questioned. Subjects with mutations in the glucokinase gene (MODY 2) display elevated fasting glucose levels in the IFG and diabetes range without any increased risk for diabetes-related comorbidities and without any treatmment.[25] Thus, given that the clinical information obtained from patients with glucokinase mutations is relevant for IFG, it is not the elevated fasting glucose levels per se, but factors causing them that are of importance as drivers of morbidity and mortality. Hence, IFG could be considered as a marker of disturbed metabolism in adults, and it is possible that this marker is less important in children. In addition, T2D can be divided in different subgroups,[26] and it is possible that IFG has different prognostic value for different subtypes.

Impaired glucose tolerance (IGT), another prediabetic stage, has also been associated with impaired first-phase insulin secretion,[27] but also within the normal glucose tolerance range, impaired insulin secretion and insulin sensitivity may be present.[28] It has also been observed that high fasting glucose precedes the development of IGT in adolescents.[29]

The major reason why it is important to define prediabetes in children and adolescents is to identify subjects with high risk to develop T2D. It is urgent to prevent T2D in adolescents as it is a devastating disease in young individuals.[30,31] We have previously shown that children and adolescents with obesity and fasting glucose levels of 5.6 to 6.0 mmol/L do not have higher risk to develop T2D as young adults than those with NFG.[19] This is in agreement with the results in the present study where we can demonstrate that the glucose homeostasis is not disturbed to a larger extent in children and adolescents with fasting blood sugar in the range 5.6 to 6.1 mmol/L than in children with NFG. Thus, our present results confirm that the risks associated with IFG in adults are becoming evident in children first when fasting glucose levels reach 6.1 mmol/L. Based on the results in the present and our previous study,[19] slightly elevated fasting glycemic levels in children and adolescents with obesity should probably not be considered as prediabetic levels but the search for more specific diabetes risk markers have continue as this group has a markedly higher risk to develop T2D early in life.[19]

The limited peripheral insulin resistance in subjects with IFG, observed in the present study, is consistent with some,[13,14] but not all, previous studies.[12,32] In a large sample of non-diabetic middle age subjects, Festa et al found a lower insulin sensitivity in subjects with IFG (6.1-7.0 mmol/L) than in NFG.[32] Hence, the importance of peripheral insulin resistance in IFG might differ between pediatric and adult populations. Recently, different non-diabetic fasting glucose levels have been shown not to differ in the risk of cardiovascular disease in adults.[33]

Even though we have used a sophisticated method to measure glucose-insulin metabolism, there are a number of limitations that should be noted. First, we defined our groups based on fasting glucose from 1 day of measurement, and because there are some variability in fasting glucose,[34] this might have resulted in some overlap between the groups. Sweden has a higher prevalence of elevated glucose levels among children than other countries[4,35,36], and despite that we have a multiethnic population in Sweden, these results need to be confirmed in other populations of children and adolescents with obesity. Second, it would have been favorable to also study how prediabetic levels of HbA1c are associated with glucose metabolism, but unfortunately, that data were only available for a small subset of the participants. However, the use of HbA1c as a prediabetic indicator in the pediatric population with obesity needs to be further studied. While some question the use of HbA1c in the pediatric population,[37] we have previously shown that prediabetic levels in this population predicts T2D.[19]

## 5 | CONCLUSION

In obese children and adolescents, IFG according to WHO (6.1-6.9 mmol/L) but not within the exclusive ADA range (5.6-6.0 mmol/L) was associated with a lower acute insulin response than in children with normal fasting glucose levels. In combination with our previous finding, that fasting glucose level of 5.6-6.0 in the pediatric obesity population does not contribute to increased T2D risk in young adults, our results suggest that the IFG contribute to future disease differently in the pediatric vs the adult population. This is of importance when risk for future T2D is estimated in obese children and adolescents.

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## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## ORCID

*Emilia Hagman* https://orcid.org/0000-0003-1433-2295

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