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Diagnosis and treatment of obese children with insulin resistance

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Chapter 4

How to screen obese children at risk for type 2 diabetes mellitus?

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Abstract

Background

Recommended screening to identify children at risk for diabetes and its precursors impaired glucose tolerance (IGT) and insulin resistance (IR) is fasted plasma glucose (FPG). This study evaluates the added value of fasted plasma insulin (FPI).

Methods

This study analyzed routinely collected data of an oral glucose tolerance test (OGTT) of 311 obese children (10.8 ± 3.2 years). Diabetes and IGT were defined according to the American Diabetes Association criteria, IR as $\text{HOMA-IR} \geq 3.4$.

Results

Cases diagnosed with an OGTT if $\text{FPG} \geq 5.6$ mmol/l, compared to an OGTT performed if $\text{FPG} \geq 5.6$ mmol/l or $\text{HOMA-IR} \geq 3.4$, were respectively four (80%) vs five (100%) with diabetes, 7 (28%) vs 16 (64%) with IGT and 0 (0%) vs 93 (100%) with IR.

Conclusions

Screening with FPG and FPI has equal burden compared to screening with FPG alone, identifies all patients with diabetes, and more patients with precursors of diabetes.

Introduction

Childhood obesity is an increasing public health problem, although some studies suggest that the prevalence may have reached a plateau [1,2]. Over the last decades, there was a worldwide increase in prevalence of overweight and obesity among children, with an obesity prevalence of 2-3% worldwide [1-5]. Childhood obesity leads to many complications such as type 2 diabetes mellitus, hypertension, dyslipidemia, and the metabolic syndrome [6].

The American Diabetes Association (ADA) advises to measure fasted plasma glucose (FPG) every 2 years in children at risk for type 2 diabetes mellitus [7, 8]. Obesity is defined as one of the risk factors for which screening is necessary. Furthermore, the guideline differentiates between FPG as a screening measure, and the oral glucose tolerance test (OGTT) as a diagnostic tool. If FPG is impaired ($\text{FPG} \geq 5.6 \text{ mmol/l}$), additional diagnostic testing with an OGTT is recommended.

In order to improve the identification of children at risk for type 2 diabetes mellitus or metabolic complications, additional screening methods have been analysed. Five studies described FPG as an insufficient predictor for impaired glucose tolerance (IGT) [9-13]. Two studies concluded that FPG alone is insufficient to detect all cases of IGT and recommended to add serum triglyceride concentrations to the screening [12, 14]. Studies on the use of HbA1c disagree with each other on the use of HbA1c for identifying children with IGT or type 2 diabetes mellitus; two studies conclude that HbA1c is a good predictor for IGT and type 2 diabetes mellitus [15, 16], while others conclude that HbA1c is an insufficient predictor [17, 18]. No studies describing the additional value of fasted plasma insulin (FPI) and type 2 diabetes mellitus precursor insulin resistance (IR) in screening for type 2 diabetes mellitus were found.

Hyperinsulinemia or insulin resistance (IR) has been identified as independent precursor for impaired glucose tolerance (IGT) or type 2 diabetes mellitus [19-22]. The prevalence of IR and IGT is higher in obese children than in normal weight children, which implicates a relation between IR and IGT and obesity [23]. Furthermore, studies in obese children have shown more children to have IGT than impaired FPG, which implicates that screening with FPG (eventually followed by an OGTT if $\text{FPG} \geq 5.6 \text{ mmol/l}$) will not identify all children with IGT [10, 11, 13, 24, 25]. Another important limitation of the recommendations of the guidelines is that although both FPG and OGTT provide information on glucose homeostasis, they fail to identify IR. For the diagnosis of IR measurement of insulin is required. Several methods are available to determine insulin resistance. The gold standard, is the hyperinsulinemic-euglycemic clamp-study, which is invasive and time-consuming. A simple method to determine insulin resistance is the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). This model uses FPG and FPI to calculate IR. Since IR is related to IGT and type 2 diabetes mellitus,

the use of FPI as an additional screening tool might distinguish more precisely which children should undergo an OGTT to diagnose IGT or diabetes.

The aim of this study was to evaluate in patients from a pediatric obesity out-patient clinic the percentages with type 2 diabetes mellitus, IGT and IR identified using FPG and an OGTT if $\text{FPG} \geq 5.6 \text{ mmol/l}$ (according to current obesity guidelines), versus the percentages diagnosed when FPI is considered in addition to FPG, followed by an OGTT if $\text{FPG} \geq 5.6 \text{ mmol/l}$ or $\text{HOMA-IR} \geq 3.4$.

Research design and methods

A retrospective chart review was performed using routinely collected information from children who visited the pediatric obesity out-patient clinic in an 850 bed hospital in the Netherlands, between the January 2006 and December 2009. During that period an OGTT was part of standard care.

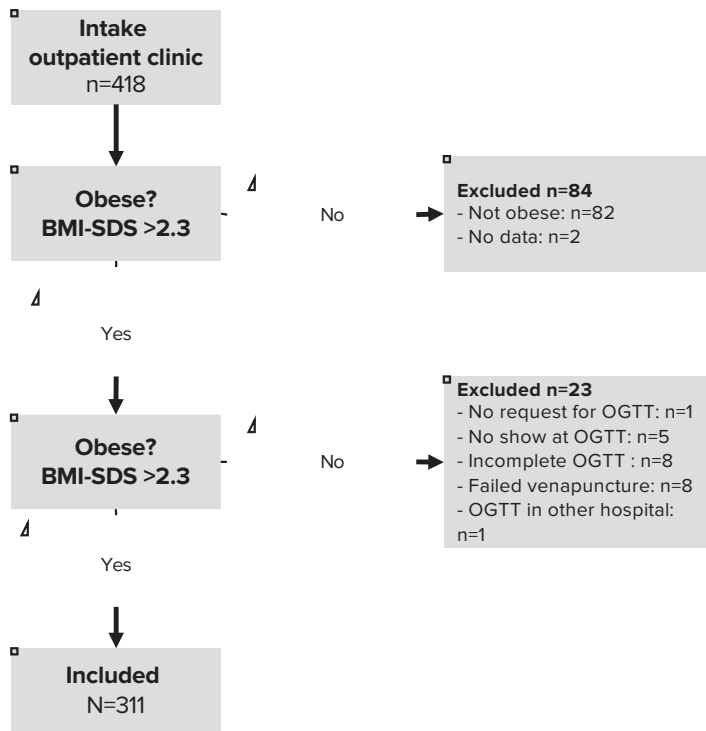
Children were selected for inclusion if there were data available on anthropometric measurements (height and weight), and an OGTT including FPG and FPI (Figure 1). Children who were not obese, did not have complete data on the OGTT or did not have an OGTT within 3 months before or after anthropometric measurements were excluded. Three hundred eleven children were included (Figure 1).

The study protocol was approved by the Medical Ethical Committee of the St Antonius hospital. As only routinely collected information was used and analysed anonymously, the need for written informed consent of the children and their parents was waived.

Data collection

All data were collected from the medical records. Age of the child at the day of anthropometric measurements was recorded. Height was measured with a precision of 0.1 cm, using a digital stadiometer (De Grood, DGI 250D) and weight to 0.05 kg accuracy using a digital scale (Seca). Body Mass Index (BMI) was calculated as $\text{kg}/(\text{height in meters})^2$. BMI-standard deviation score (BMI-SDS) was calculated using a web application of TNO (Dutch organisation for applied scientific research) prevention and healthcare: 'the TNO growth calculator for professionals' (<http://groeiweb.pgdata.nl/calculator.asp>). Obesity was defined as $\text{BMI-SDS} > 2.3$ [26].

The OGTT was performed after an overnight fast (at least eight hours prior to the test), with 1.75 gram glucose per kilogram bodyweight (maximum 75 gram glucose in 300 ml water). A baseline blood sample for FPG and FPI was drawn. A second blood sample for plasma glucose was drawn 120 minutes after glucose intake (2-hr PG).



Abbreviations: BMI-SDS, Body mass index-standard deviation score; OGTT, oral glucose tolerance test

Figure 1. Flowchart of study population

Definitions

For the interpretation of plasma glucose levels the criteria of the ADA were used: impaired FPG when FPG ≥ 5.6 mmol/l, IGT when 2-hr PG ≥ 7.8 and < 11.1 mmol/l, and diabetes when FPG ≥ 7.0 mmol/l and/or 2-hr PG ≥ 11.1 mmol/l [27]. IR was calculated using HOMA-IR. HOMA-IR is defined as fasting plasma glucose (mmol/L) $\times$ fasting plasma insulin (mU/L) / 22.5. The cut-off point for IR was defined as HOMA-IR ≥ 3.4 , based on the mean value for 95th percentile in two studies in normal weight children [28, 29].

Statistical analysis

All data were reported as mean $\pm$ SD. The percentages of patients with type 2 diabetes mellitus, IGT and IR identified with different screening strategies were calculated using IBM-SPSS statistics version 19.0. No additional statistical tests were performed.

Results

Patients

Four hundred eighteen (418) children visited the outpatient clinic between 2006 and 2009. (Figure 1) Eighty-four (84) children were excluded because they were not obese ($n=82$) or no anthropometric data were available ($n=2$) and 23 children were excluded because no OGTT was performed ($n=15$), or the OGTT results were not reliable, because of vomiting after drinking the glucose solution, or failed blood sampling at 2 hour blood sampling ($n=8$). Three hundred eleven (311) children could be included in the analysis. Patient characteristics are shown in table 1.

Table 1. Population characteristics, $n=311$

	Mean (SD)	Range
<i>Anthropometrics</i>		
Age	10.8 (3.3)	2.4 – 17.7
Female, n (%)	153 (49.2)	-
Height, cm	149.4 (44.6)	90.5 – 185.8
Weight, kg	67.0 (25.7)	20.7 – 153.9
BMI, kg/m^2	28.9 (5.2)	20.8 – 47.8
BMI-SDS	2.93 (0.49)	2.31 – 5.52
<i>Biochemical parameters</i>		
FPG, mmol/l	5.0 (0.5)	3.4 – 8.6
FPI, $\mu\text{U}/\text{l}$	12.7 (10.0)	2 – 61
2hr-PG, mmol/l	6.4 (1.5)	3.3 – 20.3
HOMA-IR	2.89 (2.48)	0.30 – 19.88

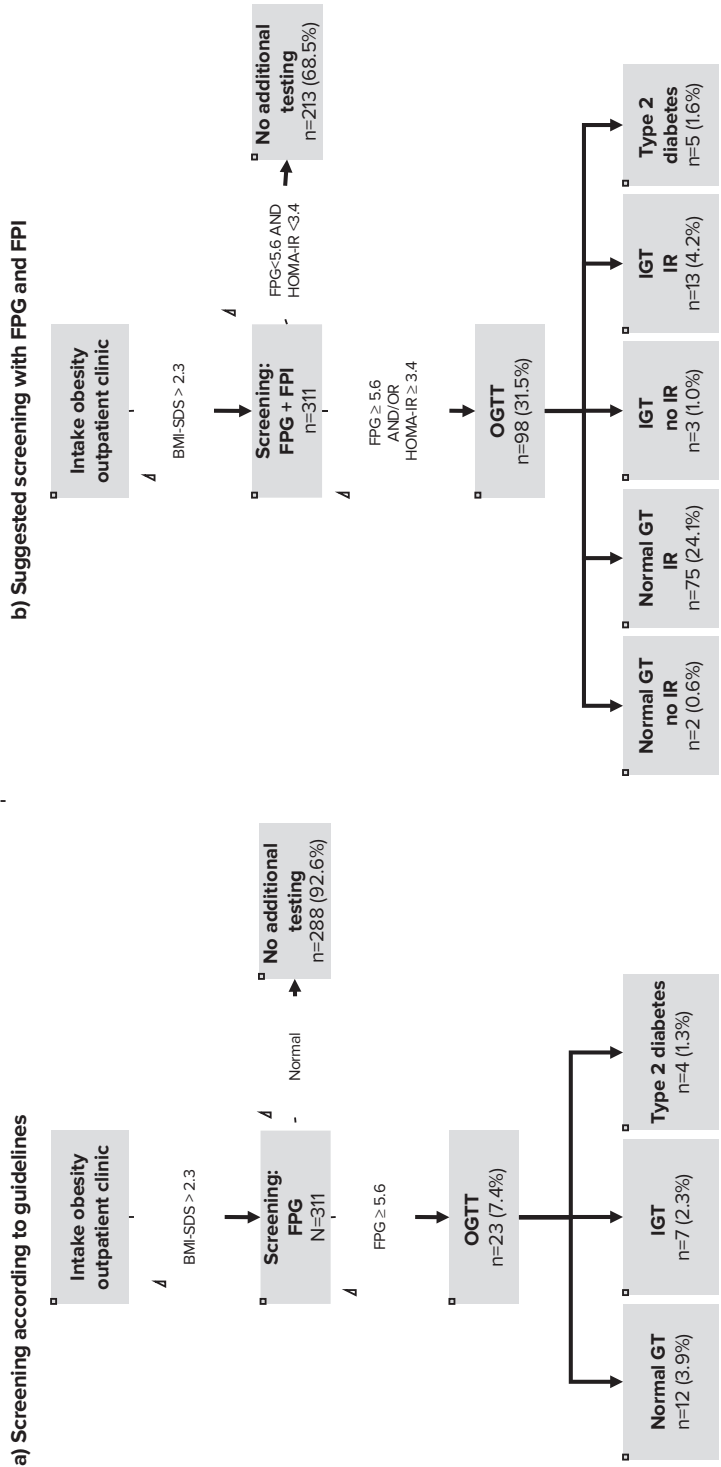
Abbreviations: BMI, body mass index; SDS, standard deviation score; FPG, fasted plasma glucose; FPI, fasted plasma insulin; PG, plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance.

Percentages of diabetes, IGT and IR

If screening would be performed with FPG alone, according to the guidelines, in 23 children (7.4%) an OGTT should be performed, because of $\text{FPG} \geq 5.6 \text{ mmol}/\text{l}$ [7, 8, 30]. The additional OGTT would result in diabetes diagnosed in four patients, and IGT in seven patients (Figure 2a), while IR could not be identified.

If FPI would be added to screening with FPG, 98 children (31.5%) would undergo an OGTT, because of $\text{FPG} \geq 5.6 \text{ mmol}/\text{l}$ ($n=22$) and/or $\text{HOMA-IR} \geq 3.4$ ($n=93$) (Figure 2b). This OGTT would result in identifying five cases of diabetes, 16 cases of IGT, and 93 cases of IR.

Overall, screening with FPG compared to screening with FPI in addition to FPG would result in 23 vs. 98 OGTTs performed, identification of four vs. five cases of diabetes, seven vs. 16 cases of IGT and zero vs. 93 cases of IR.



BMI-SDS, Body mass index-standard deviation score; FPG, fasted plasma glucose; OGTT, oral glucose tolerance test; (I)GT, (impaired) glucose tolerance; HOMA-IR, Homeostasis Model Assessment – Insulin Resistance; IR, Insulin resistance

Figure 2. Results of screening according to the guidelines (a) and screening with FPG and FPI (b)

Compared to performing an OGTT in all cases ($n=311$), screening with FPG alone (followed by an OGTT if $\text{FPG} \geq 5.6$ mmol/l) identifies 4 out of 5 patients (80%) with diabetes, 7 out of 25 patients (28%) with IGT, and 0 out of 93 patients (0%) with IR, while screening with FPG and FPI (followed by an OGTT if $\text{FPG} \geq 5.6$ mmol/l and/or $\text{HOMA-IR} \geq 3.4$) identifies 5 out of 5 patients (100%) with T2DM, 16 out of 25 patients (64%) with IGT and 93 out of 93 patients (100%) with IR.

Discussion

Identification of obese children at risk for type 2 diabetes mellitus as early as possible is of utmost importance in order to be able to prevent or delay diabetes and other metabolic and cardiovascular diseases. For early identification, it is essential to have a screening tool which is very sensitive. In this study we evaluated the use of FPI in addition to FPG for screening obese children at risk for type 2 diabetes mellitus. Our data suggest that screening with FPI in addition to FPG (to calculate HOMA-IR) identifies more children with diabetes and the precursors IGT and IR than screening with FPG alone. As FPG and FPI can be measured from the same blood sample there is no extra burden for the patient for this additional screening with FPI.

Other studies compared the use of FPI or HOMA-IR in addition to FPG in obese children to diagnose the metabolic syndrome and concluded that for screening purposes, HOMA-IR is preferred over FPG because IR has a stronger relation with the other components of the metabolic syndrome [31, 32]. Golley et al. evaluated different definitions of the metabolic syndrome and also concluded that more patients were identified with the metabolic syndrome if insulin is part of the definition [33]. Our study supports as well the use FPI in addition to FPG to identify children at risk for type 2 diabetes mellitus, because the number of patients with diabetes identified increases up to 100%, while the number of patients identified with IGT are more than doubled from 28 to 64%. For IR, the percentage of patients identified increase from 0 to 100% by adding FPI to the screening.

Although another 36% of children with IGT are not identified if screening with FPI in addition to FPG is used, results largely improve compared to screening with FPG alone (72% of children with IGT not identified). The only possibility to identify IR, IGT and diabetes in all patients is to perform an OGTT including FPI in all patients. However, performing an OGTT in all patients, as suggested by Felszeghy et al [34], leads to substantially higher burden for these patients, as two out of three OGTTs will have a normal result.

Our study shows that a cut-off value of 3.4 for HOMA-IR, is suitable in identifying children at risk of type 2 diabetes mellitus. Although there is much discussion about

the cut-off value for the HOMA-IR, the use of this cut-off value for HOMA-IR combined with FPG ≥ 5.6 mmol/l yields no false negative test results for diabetes, and up to 64% of children with IGT is identified. A lower cut-off value of HOMA-IR may decrease this number of false negatives even more, while this potentially may increase the number of false positives. An increased number of false positive leads to more additional testing with the OGTT, which leads to a higher burden for the patients with associated higher healthcare costs.

There is evidence that insulin resistance, and therefore HOMA-IR, is influenced by puberty and ethnicity [28, 29]. We did not consider these factors in our definition of insulin resistance, which is based on 95th percentile values in the study of d'Annunzio et al. [29]. The use of specific cut-off values for HOMA-IR for pubertal stage might result in even better identification of children at risk for IGT and type 2 diabetes mellitus.

In conclusion, screening with FPG and FPI identifies all patients with type 2 diabetes mellitus, and significantly more patients with precursors of type 2 diabetes mellitus (IGT (28 to 64%) and IR (0 to 100%)), while the burden for the children is equal to screening with FPG alone.

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M.A. performed data analysis and rewrote the manuscript after a first draft was made by L.K. L.K. performed data collection and wrote the first draft version of the manuscript. All authors discussed study design, data and interpreted the results. S.F, A.B, C.K. and M.V. reviewed and edited the manuscript. All authors take full responsibility for the contents of the manuscript, M.V. is the guarantor of this work. None of the authors reports a conflict of interest.

An abstract of preliminary data regarding prevalence of insulin resistance and the relation with family history has been presented at the Dutch Medicine Days 2011, and has been published in the British Journal of Clinical Pharmacology 2013; 75: 561-562.

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