



The one-hour post-load plasma glucose predicts progression to prediabetes in a multiethnic cohort of obese youths

Domenico Tricò, MD^{1,2*}; Alfonso Galderisi, MD^{3*}; Andrea Mari, PhD⁴;
Nicola Santoro, MD, PhD³; Sonia Caprio, MD³.

1. Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
2. Institute of Life Sciences, Sant'Anna School of Advanced Studies, Pisa, Italy
3. Department of Pediatrics, Yale University School of Medicine, New Haven, CT
4. Institute of Neuroscience, National Research Council, Padua, Italy

* These authors contributed equally to this work.

Correspondence

Domenico Tricò, MD

Department of Clinical and Experimental Medicine,
University of Pisa

Via Roma 67, Pisa 56126, Italy

Tel: +39 050 993640, Fax: +39 050 553235, email: domenico.trico@for.unipi.it

Short title: 1-hour hyperglycemia predicts prediabetes in youth

Word count: 3,050

Word count (abstract): 250

Figures: 2

Tables: 3

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.13640

References: 47

Disclosures: The authors have no conflicts of interest relevant to this study.

Accepted Article

Abstract

Aims. One-hour post-load hyperglycemia has been proposed as an independent predictor of type 2 diabetes in adults. We examined whether 1-hour plasma glucose (1hPG) during an oral glucose tolerance test (OGTT) can predict changes in the glucose tolerance status in a multiethnic cohort of youths with normal glucose tolerance (NGT).

Materials and methods. A total of 202 obese youths with NGT (33.7% Caucasians, 31.1% Hispanics, 32.2% African Americans) underwent a 3-hour OGTT at baseline and after a 2-year follow up. Whole-body insulin sensitivity, insulin secretion, β -cell function, and insulin clearance were estimated by modeling plasma glucose, insulin, and C-peptide levels.

Results. Obese youths with 1hPG ≥ 7.4 mmol/L (or 133 mg/dl; $n=83$) exhibited higher body mass index (BMI), plasma triglycerides, and fasting and post-load glucose concentrations, than subjects with 1hPG < 7.4 mmol/L. A 1hPG ≥ 7.4 mmol/L was associated with a lower disposition index (DI, $p < 0.0001$) and with alterations in whole-body insulin sensitivity, β -cell function, and insulin clearance. Adolescents with 1hPG ≥ 7.4 mmol/L were ~ 3 times more likely to develop prediabetes (*i.e.*, impaired glucose tolerance and/or impaired fasting glucose) over time (OR 2.92 [1.22 – 6.98], $p=0.02$), independently of age, sex, race/ethnicity, BMI, insulin sensitivity, DI, and plasma glucose concentrations. No differences emerged in the risk of prediabetes related to 1-hour hyperglycemia among different ethnic groups.

Conclusions. A plasma glucose concentration ≥ 7.4 mmol/L at 1 hour during an OGTT is associated with a worse clinical and metabolic phenotype and may be an independent predictor of progression to prediabetes in obese youths with NGT.

Introduction

Paralleling the epidemic of childhood obesity, the prevalence of type 2 diabetes in youths has rapidly grown [1, 2]. Youth-onset diabetes represents a major public health issue, in that it heralds a long duration of the disease with an increased risk of micro- and macrovascular complications occurring early in life [3]. Early detection of individuals at risk for diabetes is critical to prevent the disease and its complications [4, 5], and even more imperative in youth as they show a faster progression to diabetes than adults [6]. Current diagnostic criteria for identify conditions of high risk for diabetes, usually referred to as “prediabetes”, are based on fasting and 2-hour post-load plasma glucose as well as on glycated hemoglobin (HbA1c) levels [7]. However, only 50% of individuals with prediabetes develop diabetes within 10 years, and only 60% of subjects with diabetes had prediabetes 5 years before diagnosis [8, 9]. Thus, novel reliable glycemic markers are needed to better stratify the risk of diabetes progression in both adults and youths.

In adults, several longitudinal studies have recently identified 1-hour post-load glucose concentration (1hPG) during an oral glucose tolerance test (OGTT) as an earlier and more accurate predictor of diabetes than currently used biomarkers [10-20]. In 2007, Abdul-Ghani et al. [10] have found that the area under the ROC curve for 1hPG to predict future diabetes is significantly greater than that of fasting and 2-hour plasma glucose. Thereafter, elevated 1hPG has been consistently reported to be associated with impaired insulin sensitivity, reduced β -cell

function, and a worse cardiometabolic risk profile [11, 21-26]. Furthermore, the predictive power of 1hPG has been confirmed in large cohorts of adults from different ethnic populations [11-19].

Little is known about the ability of 1hPG to predict prediabetes and diabetes in youths. The only available longitudinal study in pediatrics showed that elevated 1hPG was associated with an increased incidence of prediabetes in 125 Hispanic adolescents with normal glucose tolerance (NGT) [27]. However, the cut point for 1hPG used in this study to identify 1-hour hyperglycemia (8.6 mmol/L, or 155 mg/dl) was established in adults [10] and has been questioned in youths [28, 29]. In fact, a lower cutoff value of 7.4 mmol/L (or 132.5 mg/dl) for 1hPG has been identified in two independent cohorts of youths by Manco et al. [28], showing a better sensitivity and a similar specificity than the 8.6 mmol/L threshold. Moreover, no longitudinal data are available in children and adolescents from different ethnic groups, in whom the risk of diabetes may be greater than in Hispanics [6].

Therefore, the primary aim of this study was to examine whether 1hPG can prospectively predict changes in the glucose tolerance status in a well-characterized cohort of Caucasian, African American, and Hispanic obese youths with NGT. Furthermore, we examined whether the cutoff value for 1hPG proposed in youths (1hPG \geq 7.4 mmol/L) is associated with early alterations in insulin sensitivity and model-derived β -cell function and insulin clearance.

Methods

Study subjects. We performed a retrospective analysis on the longitudinal cohort from the Yale Pathophysiology of Youth Onset Prediabetes/Type 2 Diabetes study (NCT01967849), a large multiethnic cohort of overweight/obese youths (body mass index [BMI] \geq 85th percentile for age and sex) between 8-21 years recruited at the Yale Pediatric Obesity Clinic [30]. Details of the study protocol have been previously published [30]. A detailed medical and family history was obtained from all participants, and a physical examination was performed, including Tanner staging and calculation of age- and sex- adjusted BMI (BMI z-score). After enrollment, youths were scheduled to be followed up every 6 months with clinical and dietary evaluations, during which they received standard nutritional guidance as well as recommendations for lifestyle changes. All participants were phenotyped with respect to their glucose tolerance status by a 3-hour oral glucose tolerance test (OGTT) at baseline and after a median follow-up of 2.3 years (interquartile range 1.8 – 4.0 years). Main exclusion criteria were systemic and endocrine disease, use of medications affecting glucose metabolism, and alcohol consumption. For the purpose of the current study, we excluded participants with impaired glucose tolerance or impaired fasting glycemia at baseline, defined according to the current criteria of the American Diabetes Association (ADA) [7]. This resulted in a study population of 202 NGT subjects with complete longitudinal data, including 68 (33.7%) Caucasians, 63 (31.1%) Hispanics, and 65 (32.2%) African Americans.

The study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Yale Human Investigation Committee. Written parental informed consent and child assent were obtained before enrollment.

Oral glucose tolerance test. Prior to the OGTT, all subjects followed a weight-maintenance diet with at least 250 g carbohydrates and were instructed to avoid strenuous physical activity for 7 days. Participants were studied at the Yale Center for Clinical Investigation (YCCI) at 8 a.m. after a 12-hour overnight fast. Two baseline venous blood samples were collected for routine biochemical analysis and measurement of plasma glucose, insulin, and C-peptide levels. Thereafter, flavored glucose was given orally (1.75 g per kilogram of body weight, up to 75 g), and venous blood samples were obtained every 30 minutes for 180 minutes. Eight participants (4%) were less than 43 kg of body weight at baseline (5 NGT-High and 3 NGT-Low, $p=0.28$) and therefore received less than 75 g glucose during the OGTT, whereas most participants at baseline (96%) and all subjects at follow up were more than 43 kg of body weight and received 75 g glucose.

Definitions. Glucose tolerance was defined according to the current ADA criteria [7]. Prediabetes was defined by the presence of isolated impaired fasting glucose (IFG; fasting plasma glucose 5.6–6.9 mmol/L, or 100–125 mg/dl) and/or impaired glucose tolerance (IGT; 2-hour plasma glucose during the OGTT 7.8–11.0 mmol/L, or 140–199 mg/dl) and/or HbA1c 5.7–6.4%.

Insulin sensitivity and β -cell function. Insulin sensitivity was assessed by the whole-body insulin sensitivity index (WBISI), which has been previously validated against the euglycemic-hyperinsulinemic clamp in obese youth [31]. Insulin secretion rate was estimated by C-peptide deconvolution [32] and β -cell function parameters were calculated by modeling insulin secretion and plasma glucose concentration throughout the OGTT, as previously described [33-36]. This mathematical model embeds a glucose dependent β -cell response (β -cell glucose sensitivity), an early response (β -cell rate sensitivity, or β -RS), and a time-dependent amplifying factor (potentiation). β -cell function was also estimated by the insulinogenic index (IGI) and the disposition index (DI) [37]. The IGI, which describes early phase insulin secretion, was calculated as the ratio of plasma insulin concentration at 30 min minus fasting insulin to the difference of plasma glucose concentration at 30 min minus fasting glucose. The DI, a measure of insulin secretion relative to insulin sensitivity, was calculated as the product of the IGI and the WBISI.

Analytical methods. Plasma glucose was measured at the bedside by a glucose oxidase method using a YSI2700-STAT-Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was measured by a radioimmunoassay (Linco, St. Charles, MO) that has <1% cross-reactivity with C-peptide and proinsulin. Plasma C-peptide levels were determined by ELISA using ALPCO-Immunoassays (Salem, NH) with a 3.87% intra-assay variability.

Statistical analysis. Continuous variables are presented as mean \pm standard deviation (SD), and nominal variables are expressed as percentage. Variables with a skewed distribution

are presented as median [interquartile range] and were log-transformed in multivariable analyses to approximate univariate normality. Differences between groups (1hPG \geq or $<$ 7.4 mmol/L) were tested by Student t test or Mann-Whitney U test for continuous variables and by χ^2 for nominal variables. Repeated measures were analyzed by repeated-measure analysis of variance (ANOVA) including group, time, and group \times time interaction as factors. *Post-hoc* pairwise comparisons were performed by Tukey's honest significant difference (HSD) tests. General linear models (GLM) were also used including age, sex, race, and BMI z -score as covariates. Logistic regression analysis was used to estimate the likelihood of developing prediabetes among subjects with 1hPG \geq 7.4 mmol/L. Sequential models were developed accounting for age, sex, time to follow up, race, as well as baseline BMI z -score, WBISI, DI_{-2} -cell glucose sensitivity, fasting and 2-hour glucose, and HbA1c. The effect modification by race was evaluated by adding a product term to regression models (group \times race). The effect of group assignment on longitudinal changes in DI was assessed by GLM controlling for baseline DI, age, sex, time to follow up, and changes in BMI z -score. Receiver operating characteristic (ROC) analysis was used to establish the optimal cut off value of 1hPG for predicting progression to prediabetes and to compare its predictive ability with other markers of incipient dysglycemia. Analyses were performed using JMP Pro 13.2.1 (SAS Institute, Cary, NC) at a two-sided \pm level of 0.05.

Results

Study participants. A total of 202 normoglycemic obese youths with complete longitudinal data were enrolled (78 boys and 124 girls, age 12.5 ± 2.9 years, BMI 33.0 ± 6.9 kg/m², BMI z-score 2.3 ± 0.6). Among them, 83 (41%) subjects had a 1hPG ≥ 7.4 mmol/L and were classified as NGT-High, while 119 (59%) subjects had a 1hPG < 7.4 mmol/L and were classified as NGT-Low. Their clinical and metabolic characteristics are shown in **Table 1**. NGT-High exhibited higher BMI z-score and plasma triglycerides than NGT-Low, while age, sex, and racial/ethnic distribution were similar between the two groups.

Glucose metabolism at baseline. At fasting, NGT-High exhibited higher concentrations of plasma glucose (5.2 ± 0.4 mmol/L vs 5.0 ± 0.4 mmol/L, $p < 0.002$) and plasma insulin (248 [179] pmol/L vs 185 [135] pmol/L, $p = 0.001$) than NGT-Low. Plasma glucose and plasma insulin levels during the OGTT were also higher in NGT-High (**Figure 1A-B**). Total insulin secretion estimated by deconvolution of plasma C-peptide levels (**Figure 1C**) was increased in NGT-High (in the context of higher glucose levels), while insulin clearance and whole-body insulin sensitivity were reduced (**Figure 1D-F**). Model-derived parameters of β -cell function, namely β -cell glucose sensitivity (β -GS) and β -cell rate sensitivity (β -RS), were significantly reduced in NGT-High as compared to NGT-Low (**Figure 2 A-B**). Consistently, OGTT-derived indexes of early insulin secretion (IGI) and of β -cell function relative to insulin sensitivity (DI) were also reduced in NGT-High than NGT-Low (**Figure 2 C-D**). Differences between groups remained statistically significant after adjustment for age, sex, race, and BMI z-score ($p < 0.05$ for all).

Most group differences persisted when participants were stratified in two subgroups with a different degree of obesity based upon a median BMI z-score of 2.4 (**Supplemental Table 1**).

Longitudinal analysis. Clinical and metabolic characteristics of study participants at follow up are shown in **Table 2**. NGT-High youths had a 19.3% incidence of prediabetes (16 of 83 subjects), while NGT-Low had a 7.6% incidence rate (9 of 119 subjects; $p=0.02$). NGT-High were ~3 times more likely to develop prediabetes over time with respect to NGT-Low (OR 2.92 [1.22 – 6.98], $p=0.02$) (**Table 3**). This finding persisted after adjustments for age, sex, race, time to follow up, as well as baseline BMI z-score, WBISI, β -cell glucose sensitivity, DI, and plasma glucose concentrations (Table 3). The area under the ROC curve of 1hPG ≥ 7.4 mmol/L for predicting progression to prediabetes in obese youth was 0.631 (95%CI [0.560-0.697], $p=0.01$), being similar to that of fasting glucose (0.545, $p=0.84$), 2-h glucose (0.563, $p=0.92$), and HbA1c (0.599, $p=0.78$). The ethnicity/race showed no significant effect on the incidence of prediabetes over time related to 1-hour hyperglycemia (1hPG \times race interaction effect, $p=0.29$). At follow up, the DI remained consistently lower in the NGT-High group as compared to the NGT-Low group (4.9 [3.9] vs 7.3 [4.9], $p<0.0001$). Changes in DI over time were similar between groups after controlling for baseline DI ($p=0.17$), and after further adjustments for age, sex, follow up duration, and BMI z-score ($p=0.26$).

The ROC analysis identified 7.4 mmol/L as the optimal cut off value of baseline 1hPG for predicting prediabetes, with 65% sensitivity and 62% specificity. A cut off value of 8.6 mmol/L showed higher specificity (86%) but considerably lower sensitivity (20%) than the 7.4

mmol/L cut point. When we stratified subjects in NGT-High and NGT-Low based on the 8.6 mmol/L threshold, group differences at baseline remained statistically significant ($p < 0.01$ for all). However, a 1hPG > 8.6 mmol/L was not associated with increased odds of developing prediabetes (16.7% vs 11.6% in NGT-High and NGT-Low, respectively; OR 1.52 [0.52-4.42], $p = 0.44$).

Discussion

In this study, a 1hPG during an OGTT equal or greater than 7.4 mmol/L was observed in a considerable proportion (~40%) of a multiethnic cohort of overweight/obese youths with NGT, defined according to the current ADA criteria [7]. Compared with the rest of the cohort, those youths showed a worse clinical and metabolic phenotype, characterized by increased age- and sex-adjusted BMI, worse lipid profile, increased fasting and post-load glucose and insulin concentrations, as well as reduced β -cell function, insulin sensitivity, and insulin clearance. One-hour hyperglycemia was able to prospectively predict progression to prediabetes over a short period of time, independently of other well-established anthropometric and biochemical risk factors. Of note, no differences emerged in the risk of future prediabetes related to 1-hour hyperglycemia among youths with different ethnic backgrounds.

Prospective epidemiological studies demonstrate the limitations of traditional glycemic markers (*i.e.*, fasting and 2-hour glucose, HbA1c) in predicting future risk of diabetes in both adults and youths [6, 8, 9], thereby highlighting the urgent need for better predictors. In this context, 1hPG has been recently proposed as an earlier, more sensitive and accurate predictor of prediabetes and diabetes than currently used biomarkers [10]. While several longitudinal studies have confirmed the ability of 1hPG to predict diabetes and its micro- and macrovascular complications in adults [10-24, 26], there is only a single longitudinal study available in pediatrics [27]. Our results extend previous findings from that study, in that we analyzed data

from a larger and more heterogeneous cohort of youths, and we used a lower cut off value to identify 1-hour hyperglycemia.

In the current study, we were able to examine the potential impact of the ethnicity/race on the ability of 1hPG to predict prediabetes in the three major ethnic groups in the US, *i.e.* Caucasians, African Americans, and Hispanics. Several studies have reported differences in the risk and prevalence of diabetes among these ethnic groups, which may relate to genetically-driven differences in insulin sensitivity, β -cell function, and hepatic insulin clearance [6, 37-39]. Nevertheless, to our knowledge this is the first longitudinal study in youth to confirm the ability of 1hPG to predict prediabetes in different ethnic groups, its predictive power being similar among Caucasian, African American and Hispanic youths.

After 1hPG was identified as an independent predictor for diabetes, a number of different cut points have been proposed for defining 1-hour hyperglycemia. In adult participants from the San Antonio Heart Study, Abdul-Ghani et al. [10] reported that a cutoff point of 8.6 mmol/L (155 mg/dl) had the best combination of sensitivity (0.75) and specificity (0.79) for predicting future diabetes. In other large adult cohorts, the optimal cut point for 1hPG to maximize the sum of sensitivity and specificity ranged from 7.2 to 8.9 mmol/L (130 – 161 mg/dl) [15, 18, 19, 22], being typically lower in studies with a longer follow up period (>10 years) [15, 18, 19]. In youth, the above-mentioned longitudinal analysis used a 8.6 mmol/L cut point to stratify subjects with low or high 1hPG [27], while previous cross-sectional analyses used a cut point of either 8.6 mmol/L [40, 41] or 7.4 mmol/L [28, 29]. The latter threshold was established and validated in

2012 by Manco et al. [28], using ROC analysis to predict impaired glucose tolerance in two cross-sectional data sets of obese children and adolescents. Remarkably, using ROC analysis in our longitudinal cohort of NGT youths, we identified the same cut point of 7.4 mmol/L, which provided a comparable predictive power to that of other well-established markers of incident diabetes, such as fasting glucose, 2-h glucose, and HbA1c. The lower cut point of 7.4 mmol/L may have some advantages in obese youth because: a) it shows a better combination of sensitivity and specificity than the 8.6 mmol/L cut point in our study and in previous cross-sectional analyses [28]; b) as a screening tool, it may help detect glucose abnormalities at an earlier stage, which would be critical to implement timely interventions to prevent the rapid progression of the disease in this high risk population [6, 42-44]. In fact, a 1hPG \geq 7.4 mmol/L was associated with early alterations in whole-body insulin sensitivity and β cell function that persisted at follow up, in agreement with previous observations [28, 29]. Furthermore, in our study the 7.4 mmol/L cut point, but not the 8.6 mmol/L threshold, was associated with increased odds of developing prediabetes over time. This finding, which is not consistent with previous observations [27], might be explained by different participants' characteristics in terms of age, sex, ethnicity/race, and BMI, which may impact on the predictive power of each threshold. Different findings might also depend on a lower conversion rate from NGT to prediabetes in our cohort, possibly due to a shorter follow up period, and/or a lower prevalence of subjects with 1hPG \geq 8.6 mmol/L (30 subjects, 15%), which would reduce statistical power.

Accepted Article

Strengths of this study include the longitudinal design, allowing us to prospectively examine the ability of 1hPG to predict prediabetes, the accurate metabolic characterization of participants by the 3-hour OGTT, and the use of a mathematical model for the estimation of insulin secretion and β cell function parameters. Compared to the aforementioned study [27], we examined the predictive power of 1hPG in a larger cohort of youths with NGT, where different ethnic groups were adequately represented. Potential limitations should be also considered. Along with insulin sensitivity, secretion, and clearance, a greater 1hPG during the OGTT may be explained by a more rapid oral glucose appearance into the systemic circulation [25, 45-47]. Since the rates of gastric emptying and intestinal glucose absorption were not measured, we could not evaluate the impact of oral glucose appearance on 1hPG levels. Furthermore, the follow up period of our study was relatively short and future longer and larger investigations are needed to confirm the utility of 1hPG as a biomarker.

In conclusion, a plasma glucose concentration ≥ 7.4 mmol/L at 1 hour during an OGTT is associated with a worse clinical and metabolic phenotype, characterized by alterations in insulin sensitivity, β -cell function, and insulin clearance, and may prospectively predict progression to prediabetes in obese youths with NGT.

Acknowledgements

The authors are grateful to the patients and their families as well as to the Yale Center for Clinical Investigation and the Hospital Research Unit personnel.

Funding

D.T. is funded by the EFSD Mentorship Programme supported by AstraZeneca. A.G. is funded by the Robert Leet Patterson and Clara Guthrie Patterson Trust Mentored Research Award (2017) and the European Medical International Framework (EMIF 115372). N.S. is funded by the American Heart Association (AHA) (13SDG14640038, 11CRP5620013, 16IRG27390002) and by the National Institutes of Health (NIH) (R01-DK114504). S.C. is funded by the NIH (R01-HD40787, R01-HD28016, R01-DK111038-01, and K24-HD01464). This work was also made possible by DK-045735 to the Yale Diabetes Endocrinology Research Center and by Clinical and Translational Science Awards Grant UL1-RR-024139 from the National Center for Advancing Translational Sciences, a component of the NIH, and NIH Roadmap for Medical Research. The contents of this scientific contribution are solely the responsibility of the authors and do not necessarily represent the official view of the NIH.

Author contributions

D.T.: study design, data collection and analysis, interpretation of results, manuscript writing; A.G. and N.S.: data collection and analysis, interpretation of results, manuscript editing; A.M.: mathematical modeling of insulin secretion and β -cell function parameters, interpretation of results, manuscript editing; S.C.: funding, data collection and analysis, interpretation of results,

manuscript editing, study supervision. All authors read and approved the final submitted version of the manuscript. D.T. and S.C. have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Figure 1

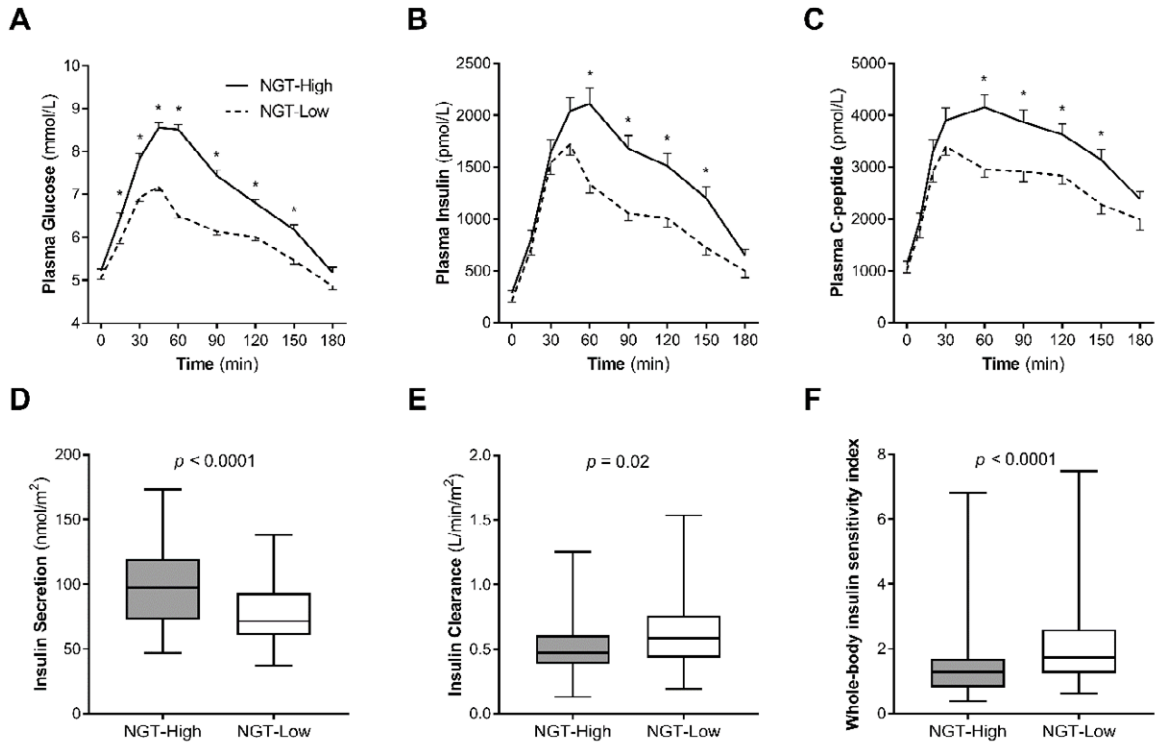


Figure 1 – Glucose and insulin metabolism in NGT-High and NGT-Low youths.

(A) Plasma glucose concentrations, (B) plasma insulin concentrations, (C) plasma C-peptide concentrations, (D) total insulin secretion estimated by C-peptide deconvolution, (E) insulin clearance, and (F) whole-body insulin sensitivity index during an oral glucose tolerance test in obese adolescents with normal glucose tolerance (NGT) and 1-hour plasma glucose ≥ 7.4 mmol/L (NGT-High, $n=83$; continuous lines/grey boxes) or < 7.4 mmol/L (NGT-Low, $n=119$; dotted lines/white boxes). Data are reported as mean \pm SEM (line charts) or median \pm interquartile range (box plots). * $p < 0.05$.

Figure 2

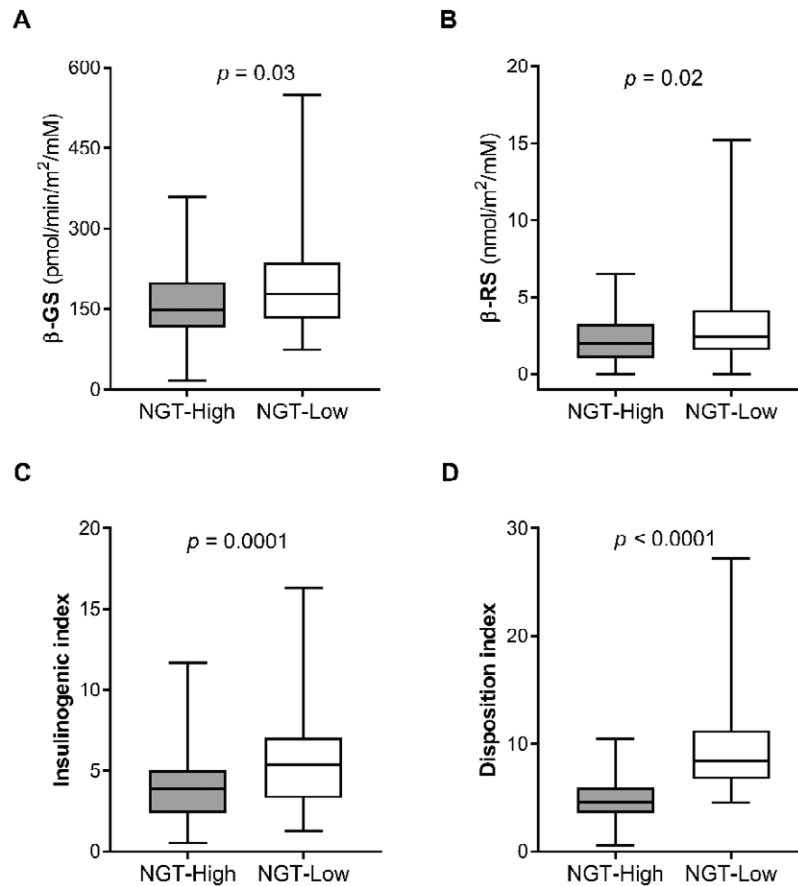


Figure 2 – β cell function parameters in NGT-High and NGT-Low youths.

(A) β -cell glucose sensitivity (β -GS), (B) β -cell rate sensitivity (β -RS), (C) insulinogenic index, and (D) disposition index measured during an oral glucose tolerance test in obese adolescents with normal glucose tolerance (NGT) and 1-hour plasma glucose ≥ 7.4 mmol/L (NGT-High, $n=83$; continuous lines/grey boxes) or < 7.4 mmol/L (NGT-Low, $n=119$; dotted lines/white boxes). Data are reported as median \pm interquartile range.

Table 1 – Clinical and metabolic characteristics of study participants at baseline.

	NGT-High (<i>n</i> = 83)	NGT-Low (<i>n</i> = 119)	<i>P</i>
Age (years)	12.3 ± 2.8	12.6 ± 2.9	0.41
Sex (M/F, %)	41/59	37/63	0.66
Race (Caucasians/African Americans/Hispanics/Others, %)	37/22/37/4	31/38/29/2	0.10
Tanner stage (I-II, III, IV-V, %)	21/44/35	9/57/34	0.10
Body Weight (kg)	83.9 ± 26.9	82.3 ± 23.6	0.88
Body Mass Index (kg/m ²)	34.0 ± 7.1	32.4 ± 6.6	0.10
Body Mass Index z-score	2.4 ± 0.5	2.2 ± 0.6	0.01
Systolic blood pressure (mmHg)	118 ± 11	119 ± 11	0.74
Diastolic blood pressure (mmHg)	67 ± 8	69 ± 9	0.09
Hemoglobin A1c (mmol/mol)	36 ± 3	36 ± 3	0.69
Total cholesterol (mmol/l)	3.9 ± 0.8	3.9 ± 0.7	0.78
LDL cholesterol (mmol/l)	2.3 ± 0.6	2.3 ± 0.6	0.53
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	0.15
Triglycerides (mmol/l)	1.0 [0.6]	0.9 [0.7]	0.05

Data are reported as mean ± SD or median [interquartile range].

Table 2 – Clinical and metabolic characteristics of study participants at follow up.

	NGT-High (<i>n</i> = 83)	NGT-Low (<i>n</i> = 119)	<i>P</i>
Age (years)	15.3 ± 3.1	15.8 ± 2.9	0.20
Tanner stage (I-II, III, IV-V, %)	9/39/52	4/37/59	0.30
Body weight (kg)	97.7 ± 26.6	100.8 ± 29.9	0.53
Body Mass Index (kg/m ²)	36.4 ± 7.9	36.2 ± 8.8	0.80
Body Mass Index z-score	2.3 ± 0.5	2.2 ± 0.7	0.27
Systolic blood pressure (mmHg)	120 ± 12	118 ± 11	0.26
Diastolic blood pressure (mmHg)	70 ± 11	69 ± 9	0.80
Hemoglobin A1c (mmol/mol)	36 ± 4	37 ± 3	0.37
Fasting plasma glucose (mmol/L)	5.0 ± 0.4	5.0 ± 0.5	0.62
1-h plasma glucose (mmol/L)	7.8 ± 1.6	6.8 ± 1.3	<0.0001
2-h plasma glucose (mmol/L)	6.7 ± 1.2	6.3 ± 1.0	0.02
Fasting plasma insulin (pmol/L)	221 [155 – 302]	205 [133 – 280]	0.17
1-h plasma insulin (pmol/L)	1243 [921 – 2272]	1047 [628 – 1855]	0.01
2-h plasma insulin (pmol/L)	1033 [693 – 1906]	865 [476 – 1563]	0.02
Whole-body insulin sensitivity index (WBISI)	1.57 [1.03 – 2.08]	1.59 [1.21 – 2.85]	0.047
Insulinogenic index (IGI)	3.44 [2.18 – 5.28]	4.43 [2.35 – 7.31]	0.03
Disposition index (DI)	4.95 [3.36 – 7.28]	7.27 [5.44 – 10.34]	<0.0001
Total cholesterol (mmol/l)	3.9 ± 0.7	3.8 ± 0.7	0.98
LDL cholesterol (mmol/l)	2.3 ± 0.6	2.3 ± 0.7	0.86
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	0.10
Triglycerides (mmol/l)	0.9 [0.7 – 1.5]	0.9 [0.6 – 1.3]	0.39

Data are reported as mean ± SD or median [interquartile range].

Table 3 – Odds ratios (OR) for incidence of prediabetes at follow up associated with 1-hour hyperglycemia in obese youths.

Covariates	OR	95% CI	<i>p</i>
Unadjusted model	2.92	1.22 – 6.98	<i>0.02</i>
Age, sex, time to FU	2.99	1.24 – 7.20	<i>0.01</i>
Age, sex, time to FU, race/ethnicity	2.89	1.18 – 7.04	<i>0.02</i>
Age, sex, time to FU, BMI <i>z</i> -score	2.77	1.13 – 6.75	<i>0.03</i>
Age, sex, time to FU, WBISI	2.88	1.09 – 7.60	<i>0.03</i>
Age, sex, time to FU, ² -GS	3.86	1.06 – 14.13	<i>0.04</i>
Age, sex, time to FU, DI	3.14	1.02 – 9.95	<i>0.046</i>
Age, sex, time to FU, fasting and 2-hour glucose	3.20	1.17 – 8.80	<i>0.02</i>
Age, sex, time to FU, HbA1c	2.92	1.13 – 7.58	<i>0.03</i>

²-GS, ²-cell glucose sensitivity; BMI, body mass index; DI, disposition index; FU, follow up; HbA1c, hemoglobin A1c; WBISI, whole-body insulin sensitivity index.

References

- [1] Mayer-Davis EJ, Lawrence JM, Dabelea D, *et al.* Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. *N Engl J Med.* 2017; **376**: 1419-1429
- [2] Imperatore G, Boyle JP, Thompson TJ, *et al.* Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care.* 2012; **35**: 2515-2520
- [3] Constantino MI, Molyneaux L, Limacher-Gisler F, *et al.* Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care.* 2013; **36**: 3863-3869
- [4] Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; **346**: 393-403
- [5] DeFronzo RA, Tripathy D, Schwenke DC, *et al.* Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med.* 2011; **364**: 1104-1115
- [6] Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care.* 2005; **28**: 902-909
- [7] American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018; **41**: S13-S27
- [8] Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med.* 2002; **19**: 708-723
- [9] Gerstein HC, Santaguida P, Raina P, *et al.* Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Res Clin Pract.* 2007; **78**: 305-312
- [10] Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M. What is the best predictor of future type 2 diabetes? *Diabetes Care.* 2007; **30**: 1544-1548
- [11] Abdul-Ghani MA, Abdul-Ghani T, Ali N, DeFronzo RA. One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. *Diabetes Care.* 2008; **31**: 1650-1655
- [12] Fiorentino TV, Marini MA, Andreozzi F, *et al.* One-Hour Postload Hyperglycemia Is a Stronger Predictor of Type 2 Diabetes Than Impaired Fasting Glucose. *J Clin Endocrinol Metab.* 2015; **100**: 3744-3751
- [13] Pareek M, Bhatt DL, Nielsen ML, *et al.* Enhanced Predictive Capability of a 1-Hour Oral Glucose Tolerance Test: A Prospective Population-Based Cohort Study. *Diabetes Care.* 2018; **41**: 171-177
- [14] Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. *Diabetes Care.* 2009; **32**: 281-286

- [15] Oh TJ, Lim S, Kim KM, *et al.* One-hour postload plasma glucose concentration in people with normal glucose homeostasis predicts future diabetes mellitus: a 12-year community-based cohort study. *Clin Endocrinol (Oxf)*. 2017; **86**: 513-519
- [16] Bergman M, Chetrit A, Roth J, Jagannathan R, Sevick M, Dankner R. One-hour post-load plasma glucose level during the OGTT predicts dysglycemia: Observations from the 24-year follow-up of the Israel Study of Glucose Intolerance, Obesity and Hypertension. *Diabetes Res Clin Pract*. 2016; **120**: 221-228
- [17] Priya M, Anjana RM, Chiwanga FS, Gokulakrishnan K, Deepa M, Mohan V. 1-hour venous plasma glucose and incident prediabetes and diabetes in Asian Indians. *Diabetes Technol Ther*. 2013; **15**: 497-502
- [18] Paddock E, Hohenadel MG, Piaggi P, *et al.* One-hour and two-hour postload plasma glucose concentrations are comparable predictors of type 2 diabetes mellitus in Southwestern Native Americans. *Diabetologia*. 2017; **60**: 1704-1711
- [19] Alyass A, Almgren P, Akerlund M, *et al.* Modelling of OGTT curve identifies 1 h plasma glucose level as a strong predictor of incident type 2 diabetes: results from two prospective cohorts. *Diabetologia*. 2015; **58**: 87-97
- [20] Bergman M, Jagannathan R, Buysschaert M, *et al.* Lessons learned from the 1-hour post-load glucose level during OGTT: Current screening recommendations for dysglycaemia should be revised. *Diabetes Metab Res Rev*. 2018; **34**: e2992
- [21] Fiorentino TV, Sesti F, Andreozzi F, *et al.* One-hour post-load hyperglycemia combined with HbA1c identifies pre-diabetic individuals with a higher cardio-metabolic risk burden. *Atherosclerosis*. 2016; **253**: 61-69
- [22] Manco M, Panunzi S, Macfarlane DP, *et al.* One-hour plasma glucose identifies insulin resistance and beta-cell dysfunction in individuals with normal glucose tolerance: cross-sectional data from the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study. *Diabetes Care*. 2010; **33**: 2090-2097
- [23] Succurro E, Marini MA, Arturi F, *et al.* Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis*. 2009; **207**: 245-249
- [24] Sciacqua A, Miceli S, Carullo G, *et al.* One-hour postload plasma glucose levels and left ventricular mass in hypertensive patients. *Diabetes Care*. 2011; **34**: 1406-1411
- [25] Trico D, Mengozzi A, Frascerra S, Scozzaro MT, Mari A, Natali A. Intestinal glucose absorption is a key determinant of 1-hour post-load plasma glucose levels in non-diabetic subjects. *J Clin Endocrinol Metab*. 2018, doi: 10.1210/jc.2018-02166. [Epub ahead of print]:
- [26] Bianchi C, Miccoli R, Trombetta M, *et al.* Elevated 1-hour postload plasma glucose levels identify subjects with normal glucose tolerance but impaired beta-cell function, insulin resistance, and worse cardiovascular risk profile: the GENFIEV study. *J Clin Endocrinol Metab*. 2013; **98**: 2100-2105

- [27] Kim JY, Goran MI, Toledo-Corral CM, Weigensberg MJ, Choi M, Shaibi GQ. One-hour glucose during an oral glucose challenge prospectively predicts beta-cell deterioration and prediabetes in obese Hispanic youth. *Diabetes Care*. 2013; **36**: 1681-1686
- [28] Manco M, Miraglia Del Giudice E, Spreghini MR, *et al.* 1-Hour plasma glucose in obese youth. *Acta Diabetol*. 2012; **49**: 435-443
- [29] Marcovecchio ML, Bagordo M, Marisi E, *et al.* One-hour post-load plasma glucose levels associated with decreased insulin sensitivity and secretion and early makers of cardiometabolic risk. *J Endocrinol Invest*. 2017; **40**: 771-778
- [30] Sinha R, Fisch G, Teague B, *et al.* Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med*. 2002; **346**: 802-810
- [31] Yeckel CW, Weiss R, Dziura J, *et al.* Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. *J Clin Endocrinol Metab*. 2004; **89**: 1096-1101
- [32] Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes*. 1992; **41**: 368-377
- [33] Mari A, Tura A, Gastaldelli A, Ferrannini E. Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. *Diabetes*. 2002; **51 Suppl 1**: S221-226
- [34] Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E. Meal and oral glucose tests for assessment of beta -cell function: modeling analysis in normal subjects. *Am J Physiol Endocrinol Metab*. 2002; **283**: E1159-1166
- [35] Mari A, Ferrannini E. Beta-cell function assessment from modelling of oral tests: an effective approach. *Diabetes Obes Metab*. 2008; **10 Suppl 4**: 77-87
- [36] Trico D, Natali A, Mari A, Ferrannini E, Santoro N, Caprio S. Triglyceride-rich very low-density lipoproteins (VLDL) are independently associated with insulin secretion in a multiethnic cohort of adolescents. *Diabetes Obes Metab*. 2018; **20**: 2905-2910
- [37] Trico D, Caprio S, Rosaria Umamo G, *et al.* Metabolic Features of Nonalcoholic Fatty Liver (NAFL) in Obese Adolescents: Findings From a Multiethnic Cohort. *Hepatology*. 2018; **68**: 1376-1390
- [38] Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in african-american children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. *Diabetes*. 2002; **51**: 3014-3019
- [39] Uwaifo GI, Fallon EM, Chin J, Elberg J, Parikh SJ, Yanovski JA. Indices of insulin action, disposal, and secretion derived from fasting samples and clamps in normal glucose-tolerant black and white children. *Diabetes Care*. 2002; **25**: 2081-2087
- [40] Tfayli H, Lee SJ, Bacha F, Arslanian S. One-hour plasma glucose concentration during the OGTT: what does it tell about beta-cell function relative to insulin sensitivity in overweight/obese children? *Pediatr Diabetes*. 2011; **12**: 572-579
- [41] Fintini D, Cappa M, Brufani C, Bernardini S, Barbetti F. Prevalence of elevated 1-h plasma glucose and its associations in obese youth. *Diabetes Res Clin Pract*. 2016; **116**: 202-204

- [42] Trico D, Prinsen H, Giannini C, *et al.* Elevated alpha-Hydroxybutyrate and Branched-Chain Amino Acid Levels Predict Deterioration of Glycemic Control in Adolescents. *J Clin Endocrinol Metab.* 2017; **102**: 2473-2481
- [43] Goffredo M, Santoro N, Trico D, *et al.* A Branched-Chain Amino Acid-Related Metabolic Signature Characterizes Obese Adolescents with Non-Alcoholic Fatty Liver Disease. *Nutrients.* 2017; **9**: E642
- [44] Umano GR, Shabanova V, Pierpont B, *et al.* A low visceral fat proportion, independent of total body fat mass, protects obese adolescent girls against fatty liver and glucose dysregulation: a longitudinal study. *Int J Obes (Lond).* 2018, doi: 10.1038/s41366-018-0227-6. [Epub ahead of print]:
- [45] Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. *Diabetes Care.* 2013; **36**: 1396-1405
- [46] Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M. Gastric emptying and glycaemia in health and diabetes mellitus. *Nat Rev Endocrinol.* 2015; **11**: 112-128
- [47] Fiorentino TV, Suraci E, Arcidiacono GP, *et al.* Duodenal Sodium/Glucose Cotransporter 1 Expression Under Fasting Conditions Is Associated With Postload Hyperglycemia. *J Clin Endocrinol Metab.* 2017; **102**: 3979-3989