Inside out the Ragbag of Glucose Intolerance in Obese Adolescents

Claudia Brufani\textsuperscript{a, b} Andrea Tura\textsuperscript{c} Giorgio Bedogni\textsuperscript{a} Rosa Luciano\textsuperscript{a}
Stefano Sbrignadello\textsuperscript{c} Danilo Fintini\textsuperscript{b} Marco Cappa\textsuperscript{b} Ram Weiss\textsuperscript{d}
Melania Manco\textsuperscript{a}

\textsuperscript{a}Research Area for Multifactorial Diseases and Complex Phenotypes, Obesity and Diabetes, Bambino Gesù Children’s Hospital, Rome, Italy; \textsuperscript{b}Unit of Endocrinology and Diabetes, Bambino Gesù Children’s Hospital, Rome, Italy; \textsuperscript{c}Institute of Neuroscience, National Research Council, Padua, Italy; \textsuperscript{d}Department of Human Metabolism and Nutrition and Section of Pediatric Endocrinology, Hadassah Hebrew University, Jerusalem, Israel

Keywords
Glucose tolerance · Insulin secretion · Insulin sensitivity · Obesity

Abstract

Background/Aims: The prevalence of impaired glucose tolerance (IGT) is rising among obese adolescents in parallel with epidemic obesity. In some cases, IGT reverts to normal glucose tolerance (NGT) by the end of puberty. The aims of the present study were to investigate metabolic factors determining changes over time of glucose at 120 min (Glu120) following an oral glucose tolerance test (OGTT), and to verify whether preserved β-cell glucose sensitivity (βCGS) protects against persistent IGT.

Methods: We performed a cohort study of 153 severely obese children and adolescents evaluated with a 5-point OGTT at baseline and at follow-up with measurements of glucose, insulin, and C-peptide to estimate several empirical parameters of insulin sensitivity (including oral glucose insulin sensitivity [OGIS] and OGTT-derived glucose effectiveness) and secretion. Results: At follow-up (range 0.9–4.8 year), 113 (73.9%) patients remained with NGT, 9 (5.9%) had IGT, and 28 (18.3%) had reverted to NGT; 3 NGT patients had developed IGT. In multivariable models, change in log$_e$(βCGS) was inversely associated with time-related change in log$_e$(Glu120), with (model 2) and without (model 1) correction for the change in log$_e$(OGIS). Model 2 was more strongly associated with change in log$_e$(Glu120).

Conclusions: Changes in βCGS and insulin sensitivity were inversely associated with changes in Glu120 at follow-up, contributing a likely explanation for the reversal of IGT to NGT.

Introduction

Since the late 1960s, the prevalence of metabolic abnormalities, including impaired glucose tolerance (IGT), has been growing exponentially in parallel with epidemic obesity [1]. Early onset of severe obesity seems to facilitate the occurrence of IGT in youth and to accelerate the progression to overt type 2 diabetes (T2D).

IGT affects 20–30% of young morbidly obese Americans [2] while the prevalence of T2D was 0.46 per 1,000 according to the latest SEARCH investigation in a 1.8-million population [3]. In a large sample of children and adolescents representative of the Italian population [4], IGT
was found in 1.6% of overweight subjects, while the prevalence rose to 11% in a population of moderately and severely obese young patients enrolled in 8 secondary health care centers across Italy [5].

With regard to the IGT status, the variability of glucose tolerance testing is such that regression from IGT to normal glucose tolerance (NGT) is an equally likely occurrence as the reverse process, making the category of IGT a “diagnostic ragbag” even in adults [6]. This diagnostic ragbag might be more spacious in obese adolescents, who are prone to present transient IGT owing to the pubertal transition that exacerbates insulin resistance (IR) [4, 7]. The defective β-cell function relative to IR would be the major determinant of the persisting IGT status and the development of overt T2D [8], along with further weight gain and no improvement of insulin sensitivity [9]. Defects in insulin secretion and action can be diagnosed even in obese adolescents with NGT, i.e. with a plasma glucose at 120 min (Glu120) between 120 and 139 mg/dL following the oral glucose tolerance test (OGTT). Such defective capacity is indistinguishable from what is seen in adolescents with a Glu120 ≥ 140 mg/dL [10, 11].

The natural history of IGT and T2D in youth has been deeply investigated in US obese adolescents [12], while very little information on the pathogenesis of IGT has been provided in obese Europeans, in whom IGT is not as prevalent as in their US peers. Furthermore, the reverse process, i.e. factors that determine normalization of IGT, has been much less studied in patients of this age class.

The RISC study [13] found that 1 in 4 young European adults (23% of the population) passes from the upper boundary of NGT to the diagnostic range of IGT and vice versa during a 3-year follow-up. Importantly, these healthy individuals showed reduced β-cell glucose sensitivity (βCGS) independent of age and body mass index (BMI).

βCGS is one of the 3 components, together with β-cell rate sensitivity (βCRS) and potentiation factor, derived from the decomposition of the dynamic response of the β cells to glucose [14]. The 3 components result in the total insulin output following the OGTT. βCGS reflects the sensitivity of the β cells to perceive the glucose stimulus, and this ability seems to be intrinsically linked to genetic inheritance rather than to BMI. In contrast, βCRS may be influenced by extrinsic factors such as hormones and metabolites [15].

The aim of the present study was to verify whether in a cohort of obese Italian adolescents, preserved βCGS (i.e., the ability of the β cells to compensate for reduced insulin sensitivity over time) predicted glucose tolerance at follow-up. In other terms, we aimed to study whether a reduced βCGS relative to IR identifies a vulnerable category of patients who are prone to develop IGT and are unable to revert to NGT.

Methods

Patients and Study Design

We reviewed all electronic charts of a cohort of patients consecutively referred for obesity and admitted to the Department of Endocrinology of the Bambino Gesù Children’s Hospital between January and June 2011. At that time, all patients were offered to participate in a standard lifestyle intervention program. Participants were given diet and exercise instruction by the Obesity Clinic’s dietitian. Sedentary activities were discouraged, and activities the child enjoyed were encouraged. Each subject was given an instructional handout and a goal sheet which was mailed to the participant’s family pediatrician. Patients and parents were supplied with educational materials.

We selected patients with a baseline diagnosis of overweight or obesity according to age and gender BMI international standards [16]: baseline age ≥4 years and ≤16 years, absence of underlying chronic diseases, Italian origin (all 4 grandparents of Italian descent), and no use of medication affecting glucose metabolism, including metformin, at enrollment.

Patients were recontacted and clinical and laboratory reevaluation was offered to all patients aged <18 years who had not been involved in any other lifestyle program, movement plan, or research project within the past 6 months, and to patients who had not undergone bariatric surgery in the meantime.

All procedures performed in the study were in accordance with the ethical standards of the Ethics Committee of Bambino Gesù Children’s Hospital, which approved the study, and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the parents before any testing procedure.

Anthropometrics and Body Composition

After a 12-h overnight fast, all subjects were admitted to the clinic for a 1-day inpatient visit. Height was measured without shoes to the nearest 0.1 cm using a wall-mounted stadiometer, and weight was measured in underwear to the nearest 0.1 kg using a medical balance beam scale. Physical maturation was assessed by expert endocrinologists (C.B., D.F., and M.C.), who staged pubertal development in boys. Subjects with Tanner stage I and stages from II to V were defined as children and adolescents, respectively.

At the baseline visit, children’s body composition was measured by dual-energy X-ray absorptiometry using Hologic QDR Delphi (Hologic Inc., Bedford, MA, USA).

Oral Glucose Tolerance Test

Two baseline fasting blood samples were taken via antecubital vein catheter, and then each individual was subjected to a 2-h OGTT (1.75 g of glucose solution per kg of body weight to a maximum of 75 g). At follow-up, in patients under metformin treat-
ment the medication was discontinued 1 week before the OGTT. A standardized 3-day diet was prescribed before the test. Impaired fasting glucose and IGT were defined in accordance with the guidelines of the American Diabetes Association [18].

Assays
Serum insulin levels were measured by a chemiluminescent immunoassay method on an ADVIA Centaur® analyzer (Kyowa Medex Co., Tokyo, Japan) with a commercial kit (ADVIA Centaur® IRI). The lower and upper detection limits were 0.5 and 300 μIU/mL (3–1,800 pmol/L), respectively. The intra- and interassay coefficient of variation (CV) range were 3.3–4.6 and 2.6–5.9%, respectively. Quantitative determinations of blood glucose were measured by an enzymatic method on a Roche® automated clinical chemistry analyzer (Hitachi 904; Roche Diagnostics, Mannheim, Germany). Glucose was assayed by a commercial kit (Glucose GOD-PAP, Roche®). The measurement range was 2–450 mg/dL (0.11–25 mmol/L); the intra- and interassay coefficient of variation were 0.9 and 1.8%, respectively.

Estimation of Insulin Sensitivity
Insulin sensitivity and IR were assessed through several indices. IR at fasting was assessed through homeostatic model assessment of insulin resistance [19]; insulin sensitivity at fasting and during the OGTT was assessed by the quantitative insulin sensitivity check index [20] and by oral glucose insulin sensitivity (OGIS) [21], metabolic clearance rate [22], and the insulin sensitivity index [23], respectively. Glucose effectiveness was computed as described elsewhere [24].

Estimation of Beta-Cell Function
Beta-cell function was assessed by several empirical parameters. We first calculated the insulinogenic index, as 30-min minus fasting insulin, normalized to the same difference in glucose; we then computed some insulinogenic-like indices: simple 30-min insulin to glucose ratio (Ins30/Glu30), insulin to glucose area under the curve (AUC) ratio (AUC Ins/AUC Glu), and suprabasal insulin to glucose AUC ratio (Δ[AUC Ins/AUC Glu]). Similar parameters were computed by using C-peptide instead of insulin. Furthermore, we calculated the C-peptide-based shape index, which has been found to be another parameter of β-cell function [25].

Beta-cell function was also assessed from the OGTT using a well-validated model that describes the relationship between insulin secretion and glucose concentration [14]. The model expresses insulin secretion (in pmol × min × m²) as the sum of 2 components. The first represents the dependence of insulin secretion on absolute glucose concentration at any time point during the OGTT through a dose-response function relating the 2 variables. The mean slope of dose response over the observed glucose range is denoted as βCGS. The dose response is modulated by a potentiation factor, which accounts for higher insulin secretion in the descending phase of the OGTT hyperglycemia than in the ascending phase at the same glucose concentration. The potentiation factor is a positive function of time and is constrained to average unity during the glucose tolerance test. The second insulin secretion component represents the dependence of insulin secretion on the rate of change in glucose concentration. This component is described by a parameter, denoted as rate sensitivity, which is related to early insulin release. Insulin secretion rates were calculated from the model every 5 min. The integral of insulin secretion during the 2-h OGTT was denoted as total insulin output. The model parameters were estimated from glucose and C-peptide concentrations by regularized least squares.

Statistical Analysis
Most variables had nongaussian distributions, and all are reported as median and standard error. Multivariable random-effect linear regression models were used to evaluate the time-related changes in Glu120 and their association with the changes in βCGS, OGIS, and total insulin output controlling for the change in BMI and for baseline age or baseline pubertal status. In such models, time was treated as continuous (years); Glu120, βCGS, OGIS, OGTT-derived glucose effectiveness, and total insulin output were log-transformed to reduce skewness, and each child was modeled as random effect. All outcome-predictors relationships were linear as detected also by using fractional polynomials. Collinearity among predictors was excluded using the Belsey-Kuh-Welsh test. The Akaike information criterion and the Bayesian information

Fig. 1. Flowchart of the study. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Reversal of Impaired Glucose Tolerance

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Results

A total of 153 obese patients out of 350 (82 males, 53.6%) were reevaluated (Fig. 1). The follow-up time ranged from 0.9 to 4.8 years, with a median of 2.0 years. At follow-up, 113 (73.9%) patients remained with NGT; 28 patients (18.3%) had reverted to NGT (IGT regressors), and 3 patients (2.0%) had progressed from NGT to IGT (NGT progressors). While the change in BMI z-score over time was not statistically different among groups of glucose tolerance, there was a difference between stable IGT and IGT progressors in ΔBMI (–1.3 ± 0.84 vs. 3.3 ± 2.7) and Δbody weight (2.0 ± 3.23 vs. 23.6 ± 10 kg), owing to the significant increase in body weight of the 3 NGT patients who progressed to IGT. The patients’ baseline measurements are given in Table 1.

By comparing groups based on glucose tolerance at follow-up, IGT patients, either stable or regressors,
Reversal of Impaired Glucose Tolerance

Table 2. Changes in glucose at 120 min between the baseline and follow-up visits

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<td>–0.13***</td>
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<td>Loge(OGIS)</td>
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Values are regression coefficients and 95% confidence intervals (in brackets) obtained from multivariable random-effect linear regression. All predictors except for baseline age are time-varying covariates. The logarithm of the disposition index [Loge(DI)] was calculated as OGIS × total insulin output. See text for details. AIC, Akaike information criterion; βCGS, β-cell glucose sensitivity; BIC, Bayesian information criterion; BMI, body mass index; IGI, insulinogenic index; ISI, insulin sensitivity index; OGE, oral glucose tolerance test-derived glucose effectiveness; OGIS, oral glucose insulin sensitivity. *p < 0.05, **p < 0.01, ***p < 0.001.

showed significant differences as compared to NGT obese patients in the indices of IR/insulin sensitivity and insulin secretion. However, we were unable to find parameters predicting stability of IGT versus reversal to NGT.

Because of the limited sample size of the IGT subgroups, we used multivariable models to evaluate the time-related change in Glu120 in the whole sample instead of models predicting risk categories; the parameters are given in Table 2. All models showed no change or a decrease in loge(Glu120) during the follow-up period.

The change in BMI was not associated with the change in loge(Glu120) in any model. Baseline age was positively...
associated with \( \log_2(\text{Glu120}) \) only in model 1, i.e. when the change in \( \log_2(\text{BCGS}) \) was used as a predictor. The change in \( \log_2(\text{BCGS}) \) was inversely associated with the change in \( \log_2(\text{OGIS}) \), with (model 2) and without (model 1) correction for the change in \( \log_2(\text{OGIS}) \). The change in \( \log_2(\text{total insulin output}) \) was positively associated with the change in \( \log_2(\text{Glu120}) \) (model 3), but this association disappeared when the change in \( \log_2(\text{OGIS}) \) was taken into account (model 4). A comparison of models 1–4 using both the Akaike information criterion and the Bayesian information criterion showed that the model more strongly associated with the change in \( \log_2(\text{Glu120}) \) was model 2, i.e. the model including \( \log_2(\text{BCGS}) \) and \( \log_2(\text{OGIS}) \). Figure 2 shows median follow-up values of OGIS, total insulin output, and \( \text{BCGS} \) in the groups. Interestingly, IGT regressors had values of \( \text{BCGS} \) not different from patients with NGT, while insulin sensitivity was reduced and total insulin output increased.

**Discussion**

Our study documents abnormalities in \( \beta \)-cell function and insulin sensitivity in obese children and adolescents at risk for impaired glucose homeostasis [2, 7, 10, 11, 27–29]. While there was a marked distinction in terms of insulin sensitivity and \( \beta \)-cell function at baseline (Table 1) between NGT patients and both classes of obese adolescents with IGT, the differences between stable IGT patients and regressors were quite subtle and probably not clinically significant.

However, stable IGT patients and regressors showed a different capacity of the \( \beta \) cells, as estimated by changes in \( \text{BCGS} \), to adapt to variations in insulin sensitivity. A relatively greater capacity of the \( \beta \) cells (change in \( \text{BCGS} \) over time) to adapt to changes in insulin sensitivity and, to a minor extent, reduced variations in insulin sensitivity were associated with reduced changes in the concentrations of Glu120 at follow-up in the whole cohort. The majority of obese adolescents with IGT (3 out of 4) in our cohort had reverted to NGT at follow-up. The baseline IGT status was not confirmed by a second test, and great intraindividual biological variability in glucose tolerance has been expected [30], so we cannot be sure that all our IGT patients were really at increased risk. Nevertheless, the risk of glucose intolerance is continuous along the spectrum of Glu120, and it is worth noting that the glucose intolerance status not necessary progresses to overt diabetes in adolescents, as already observed in healthy adults [13]. Young patients facing metabolic periods of increased IR (such as puberty or acute illness) might pass from NGT to IGT and vice versa, and their glucose tolerance may go up and down several times in their lifetime before they develop T2D.

Age, total insulin output alone or in combination with OGIS as an estimate of the oral glucose disposition index, and BMI (Table 2) did not predict Glu120.

The prevalence of IGT in our sample was much higher than that in other cohorts, even of severely obese patients [5]. The Adiposity Patients Verlaufsbeobachtung registry found 5.51% of 1,008 patients presenting with IGT. In that series, BMI correlated very modestly with Glu120 \((r = 0.04, p < 0.001)\), and 70.6% of children with initial IGT converted to NGT. The improvement in OGTT results was associated with, but not dependent on, a reduction in BMI \( z \)-score [30].

In the Yale cohort, Weiss et al. [7] observed a lower rate of IGT reversal; 45.5% of obese IGT adolescents reverted to NGT, 30.3% remained with IGT, and 32% progressed to diabetes over a period of 21 months. This occurred probably owing to significant increase in body weight and worsening of the associated IR and was observed mostly among African-American youth. The Yale cohort included cases older than the patients in our series, and this might have contributed to the different rate of IGT reversal.

**Fig. 2.** Median values of total insulin output, oral glucose insulin sensitivity (OGIS), \( \beta \text{CGS} \) (\( \beta \)-cell glucose sensitivity), and body mass index (BMI) \( z \)-score at follow-up in patients with normal glucose tolerance (NGT), patients with stable impaired glucose tolerance (IGT), IGT regressors, and IGT progressors.
In our series, there was no increase in body weight or worsening of IR. This may have influenced the rate of IGT reversal, but noteworthy allowed us to track the “spontaneous” (in the sense that the lifestyle intervention was not such intensive to produce a significant reduction in body weight) course of the glycemic status over time in obese adolescents with a relatively defective βCGS. The lack of significant changes in patients’ BMI and IR during the follow-up period is one of the major strength of this observation. Patients in our cohort were recalled after a median time of 2 years. It has been estimated that, in general, more than 50% of patients drop out of treatment after 12 months even in “virtuous” tertiary health care centers [31]. Hence, it is very unlikely that IGT reversal was the effect of any lifestyle intervention, since our patients were not intensively followed up and treated during this time frame. Furthermore, we did not observe any difference over time in BMI z-score among groups of glucose tolerance.

βCGS is intrinsic to the β cells. Indeed, it appears to be genetically determined [15] and not influenced by body weight. In keeping with this notion, the multivariable models demonstrated no significant effect of basal body weight on Glu120 at follow-up. βCGS independently predicted Glu120 at follow-up, and IGT regressors had βCGS values comparable to those of obese NGT patients, being in this way able to compensate for the reduced insulin sensitivity by increased total insulin output (Fig. 2). The concept that βCGS is the driving force and primary defect in the natural history toward IGT and T2D that results in a reduced total insulin output is not novel. It was first explored in the Yale Pathophysiology of T2D in Obese Youth Study [11, 27, 29]. βCGS was found to progressively decrease, whereas insulin secretion classically exhibited an inverted U shape in the spectrum from glucose tolerance to intolerance [11]. The evolution of β-cell performance was longitudinally followed up in a group of obese adolescents with OGTTs repeated serially over a period of about 3 years. The adolescents who progressed to IGT had lower βCGS at baseline than nonprogressors [27]. A very recent study [28] investigating β-cell performance using the Mari model [14] found that youth with IGT or T2D have a reduced incretin effect compared with their NGT peers without any reduction in GLP-1 and GIP concentrations. Interestingly, the authors speculated that the diminished incretin effect is due to the defective βCGS [28].

The limited sample size of the cohort and particularly of the IGT groups as well as the time of the follow-up evaluation are major drawbacks of the study. The use of accurate methodologies to assess β-cell function, i.e. the C-peptide deconvolution method to estimate the total insulin output independently of the hepatic insulin clearance [24, 32] and the Mari model to decompose the dynamic response of the β cells [15], is its major strength.

In conclusion, we found that changes in βCGS predict changes in glucose tolerance over time in obese adolescents. The evaluation and monitoring over time of βCGS relative to changes in IR may be useful to identify obese adolescents who are at risk of developing persistent IGT in the long run. Indeed, at follow-up stable IGT patients had the lowest βCGS (Fig. 2). With regard to the evidence that some IGT patients revert to NGT, our data do not support the idea that they are metabolically healthier than stable IGT peers, since the βCGS between the 2 groups did not differ significantly. Conversely, they may be a class at increased metabolic risk which deserves monitoring and intervention to prevent overt diabetes. Weight gain and worsening of IR may promote the worsening of glucose homeostasis leading to glucose intolerance and to diabetes.

Disclosure Statement

The authors declare that they have no conflict of interest. There was no funding.

Author Contributions

Dr. Manco conceptualized and designed the study, analyzed the data, interpreted the results, wrote the first draft, and critically revised the manuscript. Dr. Brufani conceptualized and designed the study, enrolled patients, collected growth data, and revised the manuscript for important intellectual content, Dr. Tura calculated the parameters of insulin sensitivity and secretion and critically revised the manuscript. Dr. Bedogni had full access to the data and analyzed them. Dr. Sbrignadello helped in the literature search and performed some calculations. Dr. Luciano performed the assays, analyzed the data, interpreted the results, and contributed to drafting. Dr. Fintini and Dr. Cappa enrolled patients, collected growth data, and revised the manuscript for important intellectual content. Dr. Weiss contributed significantly to the discussion and revised the manuscript for content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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