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ORIGINAL ARTICLE

The effect of impaired glucose metabolism on weight loss in multidisciplinary childhood obesity treatment

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Objective: To investigate whether children and adolescents exhibiting an impaired glucose metabolism are more obese at treatment entry and less likely to reduce their degree of obesity during treatment.

Methods: The present study is a longitudinal observational study, including children and adolescents from the Children's Obesity Clinic, Holbæk, Denmark. Anthropometrics, pubertal development, socioeconomic status (SES), and fasting concentrations of plasma glucose, serum insulin, serum C-peptide, and whole blood glycosylated hemoglobin (HbA1c) were collected at treatment entry and at follow-up. Proxies of Homeostasis Model Assessment 2-insulin sensitivity (HOMA2-IS) and Homeostasis Model Assessment 2-β-cell function (HOMA2-B) were calculated with the Homeostasis Model Assessment 2 program.

Results: In total, 569 (333 boys) patients, median 11.5 years of age (range 6-22 years), and median body mass index (BMI) z-score 2.94 (range 1.34-5.54) were included. The mean BMI z-score reduction was 0.31 (±0.46) after 13 months (range 6-18) of treatment. At treatment entry, patients with impaired estimates of glucose metabolism were more obese than normoglycemic patients. Baseline concentration of C-peptide was associated with a lower weight loss during treatment in girls (P = .02). Reduction in the insulin concentrations was associated with reduction in BMI z-score in both sexes (P < .0001, P = .0005). During treatment, values of glucose, HbA1c, HOMA2-IS, and HOMA2-B did not change or impact the treatment outcome, regardless of age, sex, SES, or degree of obesity at treatment entry.

Conclusion: The capability to reduce weight during multidisciplinary treatment in children and adolescents with overweight/obesity is not influenced by an impaired glucose metabolism at study entry or during the course of treatment.

KEYWORDS

children, impaired glucose metabolism, obesity, prediabetes, weight loss

1 | INTRODUCTION

The ongoing childhood obesity pandemic is a comprehensive health challenge in the 21st century, with major implications for mental and physical health in children and adolescents and a subsequent increased disease risk in adulthood.[1] The treatment outcomes of childhood obesity have been inconsistent, with high drop-out rates[2]

Abbreviations: ADA, American Diabetes Association; BMI z-scoreBody mass index standard deviation score; CV; Coefficients of variation; DL; Detection limits; FPG; Fasting plasma glucose; HbA1c; Glycosylated hemoglobin; HOMA2-B; Homeostasis Model Assessment 2-β-cell function; HOMA2-IS; Homeostasis Model Assessment 2-insulin sensitivity; IFGImpaired fasting glucose; IGTImpaired glucose tolerance; OGTToral glucose tolerance test; SES; Socioeconomic status; T2DMtype 2 diabetes; TCOCT; The Children's Obesity Clinic Treatment; WCWaist circumference.

and low success rates.[3] Furthermore, severe obesity has been especially difficult to treat in adolescents.[4,5] The difficulty to achieve weight loss during intervention in children and adolescents with obesity has, in previous reports, been associated to lack of motivation in the family,[6] socioeconomic status (SES) of the parents,[7] genetic background,[8,9] and/or adaptive changes in the basal metabolic rate and in the hunger and satiety hormones that take place during weight loss.[10] Whether specific metabolic variables, including insulin resistance, hyperinsulinemia, and impaired glucose tolerance (IGT)—also described as prediabetes, have an impact on weight changes is controversial due to conflicting results in both children and adults.[11,12] Some intervention studies in children and adolescents with obesity have reported insulin resistance as a predictor of a reduced ability to achieve weight loss,[13,14] whereas another report, in children and adolescents, has reported a positive association between the degree of insulin resistance and weight loss.[15] IGT and severe insulin resistance, combined with obesity and excessive weight gain during childhood, are associated with a higher risk of developing type 2 diabetes (T2DM) and cardiovascular disease in adolescents.[16,17] Furthermore, a more rapid progression from an untreated IGT to overt T2DM in children, as compared to adults, has been observed,[18] indicating the possibility of further impaired metabolic state in young people, thus shortening the transition time between IGT and T2DM.[16]

The efficacy of various treatment methods to prevent the development of T2DM has been investigated, demonstrating that extensive lifestyle changes in adults exhibiting prediabetes can prevent or delay the onset of T2DM.[19] Similar studies in children and adolescents have reported that intensive lifestyle changes, compared to standard care, can reduce the risk of developing T2DM. However, these studies are of small sample sizes, comprising 23 to 58 patients, respectively.[20,21]

The Children's Obesity Clinic Treatment (TCOCT) protocol is a long-term multidisciplinary family-centered intervention program where 64% to 74% of children and adolescents achieve a reduction in body mass index (BMI) z-score after up to 24 months of intervention.[22–24] In addition, the TCOCT protocol improves hepatic steatosis and visceral fat mass,[25] the degree of hypertension,[26] the concentrations of fasting plasma lipids[27] and, in addition, the parents reduce their degree of obesity during their child's treatment.[28] In the present study, we hypothesize that children and adolescents exhibiting an impaired glucose metabolism are more obese at baseline and less likely to reduce their BMI z-score during chronic care treatment for childhood obesity.

2 | METHODS AND DESIGN

2.1 | Population

Children and adolescents were recruited from the Children's Obesity Clinic, Department of Pediatrics, Copenhagen University Hospital Holbæk, Denmark, also comprising the Danish Childhood Obesity Biobank. The inclusion criteria were (1) an age in the range of 6 to 18 years, (2) a BMI z-score > 1.28 (BMI > 90th percentile) according to a Danish reference,[29] (3) a fasting blood sample, (4) anthropometrics and blood samples at enrollment into the chronic care childhood obesity treatment program (treatment entry) and after approximately 1 year of treatment (±6 months), and (5) no more than 60 days between treatment initiation and the first blood sampling, in order to prevent the influence of a possible weight loss on the results of the biochemical blood analyses.

2.2 | Study design

This study was a longitudinal observational study from the first year of treatment, where children and adolescents attended consultations on average once every 6 to 8 weeks. The treatment is ongoing irrespective of the evaluation of data included in the present study.

2.3 | The children's obesity clinic treatment (TCOCT)

The children and adolescents were enrolled in the multidisciplinary chronic care obesity treatment according to the TCOCT protocol at the Children's Obesity Clinic, previously described in detail.[22] The Children's Obesity Clinic offers an outpatient, multidisciplinary treatment for children and adolescents with overweight or obesity by health care professionals including pediatricians, nurses, dieticians, psychologists, and social workers. The TCOCT protocol is a best-practice, family-centered approach involving behavior-modifying techniques, where an individually tailored plan of lifestyle advices, comprising 10 to 25 advices concerning the level of physical activity, inactivity, sources and amounts of nutrition, sugar and fat-intake, psychosocial factors, eating behaviors, and sleep patterns, is given to each child and family. At the first visit, the families were explained, in a non-technical language, about the neuro-endocrinological adaptation against weight loss that promotes fat deposition and thus possible weight regain during treatment, due to the regulations of the fat mass exemplified by the leptin system.[10] This understanding focuses upon the importance of changing multiple habits from the beginning of the treatment to accomplish weight loss. At every visit, the treatment plan is evaluated and optimized and anthropometric measurements are collected. The families attend consultations on average once every 6 to 8 weeks, and a mean of 5 hours of health professional time is spent on each patient per year.[22]

2.4 | Outcome measures

Anthropometrics were collected at every visit in the Clinic. Fasting values of plasma glucose (FPG), serum insulin, serum C-peptide, and whole blood glycosylated hemoglobin (HbA1c) were collected at treatment entry and at follow-up.

2.5 | Anthropometrics

The patients wore light indoor clothing during measurements. Weight was measured to the nearest 0.1 kg using a Tanita® Digital Medical Scale, WB-110 MA (Tanita Corp., Tokyo, Japan). Height was measured by stadiometer to the nearest 1 mm. BMI was calculated as weight in kilograms divided by height in meters squared. BMI z-score was calculated using height and weight and the LMS method[30] which

uses a measure of skewness (L), the median (M) and the coefficient of variation (S) in a Box-Cox transformation to normalize the data based on a Danish reference[29] and used to determine the degree of obesity.

2.6 | Blood samples

After an overnight 10-hour fast, a peripheral intravenous catheter was inserted into a cubital vein. Concentrations of plasma glucose (intra- and interassay coefficients for variation for the concentration (CV): 2.3% and detection limits (DL): 0.06 mmol/L) were determined on a Dimension Vista® 1500 Analyzer (Siemens, Erlangen, Germany). Serum insulin (CV: 2.0%; DL:1.4 pmol/L) and C-peptide (CV: 3.4%; DL: 0.003 nmol/L) concentrations were analyzed on a Cobas® 6000 Analyser (Roche Diagnostic, Mannheim, Germany). Whole blood HbA1c (CV: 1.9%; DL: 24.6 mmol/mol) was analyzed on a Tosoh high-performance liquid chromatography G8 analyser (Tosoh Corporation, Tokyo, Japan). Blood samples were collected at baseline and annually.

Serum C-peptide has only been analyzed at treatment entry and not at follow-up, because this variable has not been a part of the routine blood samples analyzed during the TCOCT protocol.

2.7 | Definition of prediabetes

In this study, prediabetes was defined as impaired fasting glucose (IFG) with plasma glucose concentration between 5.6 and 6.9 mmol/L or an HbA1c concentration between 39 and 48 mmol/mol/ (5.7%-6.6%) according to the classification by the American Diabetes Association (ADA).[31]

2.8 | Indices of insulin sensitivity and secretion

The updated computer model of Homeostasis Model Assessment 2 -(HOMA2) was downloaded from the internet (https://www.dtu.ox.ac.uk/homacalculator) and used to calculate the proxies of the β-cell function (HOMA2-B) and the insulin sensitivity (HOMA2-IS) from fasting plasma glucose and serum insulin. The HOMA2-model defined normal insulin sensitivity and normal β-cell function at 100%.[32] HOMA2-IS correlates well with the hyperinsulinemic-euglycemic clamp in adolescents across the continuum of glucose tolerance including children exhibiting diabetes and obesity.[33] The computer software calculating HOMA2 has been recalibrated using modern insulin assays, in contrast to HOMA1 that was originally calibrated to insulin assays from the 1970s, and thus will overestimate insulin sensitivity using current insulin assays.[32]

2.9 | Socioeconomic status

Information of the parents' occupation was obtained at the first visit. The SES of the parents was classified into the classes 1 to 5 in accordance with the Danish version of the International Classification of Occupation (DISCO-88).[34]

2.10 | Statistical analyses

To investigate weight loss, the mean values of BMI z-score were modeled separately for each gender as a function of time using linear mixed models with a covariance structure includes a random intercept and slope allowing each patient to have its own level and development of BMI z-score and an exponential residual structure, allowing the covariance between 2 measurements on the same participant to decrease as the time between measurements increases. The analyses were adjusted for age and SES. Time was included as a cubic spline with 3 a priori cut-points at the 10th, 50th, and 90th percentiles, corresponding to 1, 14, and 33 months of treatment, respectively. For further description of the model, please refer to Reference [22]. Associations between changes in BMI z-score and FPG, HbA1c, insulin, C-peptide, HOMA2-IS, and HOMA2-B were analyzed by testing for an interaction between dichotomized baseline characteristics of the aforementioned estimates of the glucose metabolism and treatment duration. Glucose was dichotomized into FPG ≥ 5.6 mmol/L vs <5.6 mmol/L, HbA1c ≥ 38 mmol/L/ (5.7%) vs <38 mmol/L/(5.7%) according to the definition of prediabetes.[31] Dichotomization of insulin and C-peptide was done according to the median values of insulin and C-peptide; insulin >107 pmol/L vs low insulin ≤107 pmol/L, C-peptide >0.82 nmol/L (median value) vs ≤0.82 nmol/L. HOMA2-IS and HOMA2-B were separated into high and low (> 100% vs <100%) according to the definition of normal HOMA2-IS and HOMA2-B.[32]

The associations between changes in concentrations of FPG, HbA1c, insulin, HOMA2-IS, HOMA2-B, and changes in BMI z-score were analyzed using linear regressions adjusted for the treatment duration, age, and baseline concentrations of FPG, HbA1c, insulin, C-peptide, HOMA2-IS, and HOMA2-B. A period of no more than 18 months of treatment between the blood samples collected at baseline and at follow-up were used when describing the changes in variables of the glucose metabolism during the first year of treatment. Statistical analyses were performed using SAS software version 9.4 (SAS institute Inc, Cary, NC 27513-2414, USA).

2.11 | Ethics and permissions

Informed written consent was obtained from patients older than 18 years and from parents if the patient was below the age of 18 years. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki 2013, approved by the Danish Data Protection Agency (REG-06-2014) and the Ethics Committee of Region Zealand, Denmark (SJ-104), and is registered at ClinicalTrials.gov (NCT00928473).

3 | RESULTS

In total, 752 (333 boys) children and adolescents were included at baseline. At treatment entry, the median age was 11 years (range 6-22) and the median BMI z-score was 2.91 (interquartile range, IQR: 2.48-3.33). Baseline characteristics and estimates of the glucose metabolism in boys and girls are shown in Table 1.

At follow-up, 182 patients were excluded due to more than 18 months of treatment between the blood samples at treatment

entry and at follow-up even though they continued following the treatment, leaving 569 children and adolescents eligible for the follow-up study.

3.1 | Weight loss during treatment

In the 569 children and adolescents included in the follow-up study, a mean reduction of 0.31 ± 0.46 SD BMI z-score was observed after a median of 13 months (range 6-18) of intervention (Table 2).

136 (24%) children and adolescents increased their BMI z-score with a median of 0.14 (IQR; 0.06; 0.26) during the first year of treatment.

3.2 | Associations of estimates of glucose metabolism with the degree of obesity at baseline and later weight loss during intervention.

3.2.1 | Prediabetes-IFG

At treatment entry, IFG was present in 68 (12%) patients. No significant differences in degree of obesity at treatment entry were observed between the patients with and without IFG (boys, $P = .38$; girls, $P = .74$; Table 3). In both sexes, IFG at treatment entry did not significantly influence the ability to reduce the BMI z-score during treatment ($P = .58$, $P = .80$; Table 3) (Figure 1).

3.2.2 | Prediabetes-HbA1c

At enrollment, 74 (9.8%) patients had an HbA1c concentration above 38 mmol/mol/(5.7%). Girls with an HbA1c concentration above 38 mmol/mol/(5.7%) exhibited a higher BMI z-score than girls with HbA1c below this threshold ($P = .02$). At enrollment, a high concentration of HbA1c did not influence the ability to reduce BMI z-score in boys ($P = .72$). Girls with high concentrations of HbA1c at treatment entry tended to exhibit a higher degree of weight loss during treatment compared to girls with low concentrations of HbA1c ($P = .06$).

3.2.3 | Serum insulin

Boys and girls with high concentrations of insulin exhibited a higher degree of obesity at treatment entry compared to girls and boys with a low fasting insulin concentration ($P < .0001$ and $P < .0001$; Table 3). A high insulin concentration at treatment entry was not associated with the degree of weight loss during treatment in boys or in girls ($P = .18$, $P = .50$).

3.2.4 | Serum C-peptide

High concentrations of C-peptide in boys and girls were associated with lower degrees of obesity at treatment entry than patients with low concentrations of C-peptide ($P < .0001$ and $P < .0001$). At treatment entry, a high concentration of C-peptide was associated with a higher degree of weight loss during treatment in girls ($P = .02$), but not in boys ($P = .15$).

3.2.5 | HOMA2-IS

At treatment entry, 660 (87.7%) children and adolescents exhibited a low insulin sensitivity (HOMA2-IS < 100%). At treatment entry, low insulin sensitivity was associated with a higher degree of obesity in boys ($P = .0002$), but not in girls ($P = .13$). However, low insulin sensitivity at treatment entry was not associated with the degree of weight loss during intervention in boys or girls ($P = .19$; $P = .61$).

3.2.6 | HOMA2-B

An augmented β-cell function (HOMA2-B > 100%) was present in 629 (83.6%) patients at baseline. At treatment entry, the girls and boys with high HOMA2-B exhibited a higher degree of obesity than those with low HOMA2-B ($P < .001$; $P < .001$). No significant

TABLE 1 Baseline characteristics of the 752 study patients

	Boys	Girls	P-value
Number	333	419	
Age at baseline, years	11.58(9.71-13.18)	11.18(8.68-13.74)	0.12
BMI z-score	3.16(2.71-3.60)	2.75(2.34-3.09)	<0.0001
Plasma glucose, mmol/L	5.10(4.90-5.50)	5.10 (4.53-5.67)	0.03
HbA1c, mmol/mol/%	34(32-37)/ 5.3(5.1-5.5)	34(32-37)/5.3(5.1-5.5)	0.57
Insulin, pmol/L	104.40(68.81-144.00)	109.50(73.10-160.90)	0.88
C-peptid, nmol/L	0.79(0.59-1.03)	0.84(0.64-1.11)	0.39
HOMA2-B, %	138.90(108.00-180.60)	151(155.50-188.20)	0.39
HOMA2-IS, %	53.10(37.20-78.00)	49.30(34.40-74.70)	0.51
Prevalence rates of SES			0.77
SES 1	7.19%	9.09%	
SES 2	25.16%	25.71%	
SES 3	30.07%	30.39%	
SES 4	26.80%	23.12%	
SES 5	10.78%	11.69%	

Abbreviations: BMI, body Mass Index; HbA1c, glycosylated hemoglobin; HOMA2-B, Homeostasis Model Assessment 2-β-cell function; HOMA2-IS, Homeostasis Model Assessment 2-insulin sensitivity; SES, socioeconomic status.
Values are medians with interquartile range.

TABLE 2 Characteristics at baseline and after the first year of treatment in 569 patients

	Baseline	Follow-up	Changes ± SD	95%CI
BMI z-score	2.94 ± 0.68	2.63 ± 0.82	−0.31 ± 0.46	−0.34;-0.27
Plasma glucose, mmol/L	5.15 ± 0.53	5.15 ± 0.39	−0.0001 ± 0.56	−0.05;0.04
HbA1c, mmol/mol	34.53 ± 3.31	34.20 ± 3.14	−0.32 ± 2.22	−0.50;-0.14
Insulin, pmol/L	127.22 ± 101.24	113.73 ± 76.34	−11.34 ± 71.95	−18.78;-3.89
HOMA2-B, %	155.93 ± 71.60	155.95 ± 74.34	−0.05 ± 46.99	−3.91; 3.81
HOMA2-IS, %	61.00 ± 37.48	59.62 ± 36.72	−1.39 ± 19.75	−3.02;0.24

Abbreviations: BMI, body Mass Index; CI, confidence intervals; HbA1c, glycosylated hemoglobin; HOMA2-B, Homeostasis Model Assessment 2-β-cell function; HOMA2-IS, Homeostasis Model Assessment 2-insulin sensitivity; IQR, interquartile range.
Values are means and standard deviations at baseline and after 1 year, and mean and standard deviation of change between baseline and 1 year, and the confidence interval from corresponding paired *t* test. The measurement of variables of glucose metabolism closest 1 year after the baseline measurement was used, only measurements between 6 and 18 months have been used (median 13 IQR (11.8-14.6)).

associations between β-cell function at baseline and weight loss during treatment were observed (boys, $P = .10$; girls, $P = .36$).

3.3 | Changes in the glucose metabolism variables during treatment

3.3.1 | Fasting plasma glucose

No significant association was observed between the changes in fasting glucose concentration and the changes in BMI z-score (boys, $P = .17$; girls, $P = .27$; Table 4). During treatment, 76% (51% boys) of the patients with IFG at treatment entry reduced their concentration of fasting plasma glucose below 5.6 mmol/L during the first year of treatment. However, 10% (52% boys) developed fasting plasma glucose above 5.6 mmol/L during the first year of treatment.

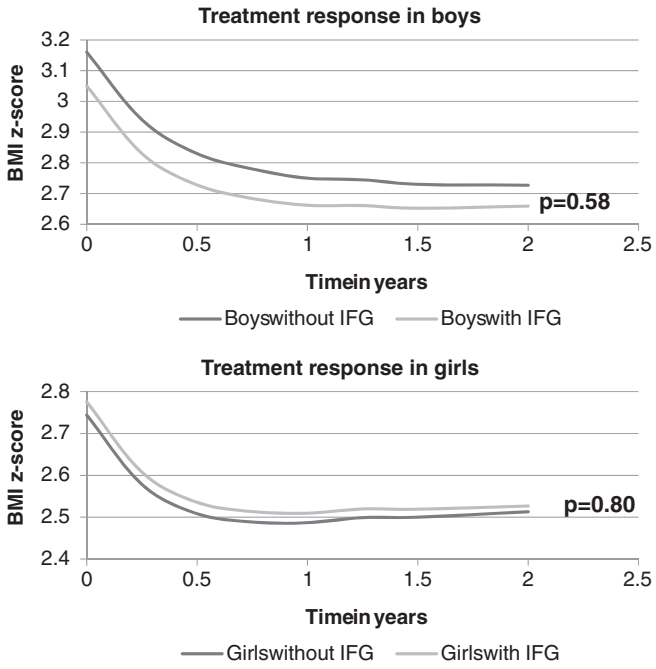

FIGURE 1 Changes in degree of obesity in boys and girls during treatment. Changes in body mass index (BMI) z-score during treatment. P-value describes no difference in weight reduction during treatment in girls or boys with impaired fasting glucose (IFG) compared to boys and girls without IFG

3.3.2 | HbA1c

During treatment, reductions in BMI z-score were associated with reductions in Hba1c, with a reduction of 0.85 mmol/mol in HbA1c for each unit of BMI z-score declines in girls ($P = .002$).

3.3.3 | Fasting serum insulin

During treatment, the insulin concentration was reduced by 55.8 pmol/L (95% confidence intervals (CIs): 37.00; 72.69, $P < .0001$) and 34.04 pmol/L (95%CI: 15.02; 53.06, $P = .0005$) for each unit of BMI z-score reduction in boys and in girls, respectively (Table 4).

3.3.4 | HOMA2-IS and HOMA2-B

No associations were found between reductions in HOMA-IS or HOMA2-B and reduction in BMI z-score (HOMA-IS: boys, $P = 17$; girls, $P = .20$; Table 4) (HOMA2-B: boys, $P = .21$; girls, $P = .42$) during treatment.

4 | DISCUSSION

In the present study, estimates of the glucose metabolism at treatment entry did not influence the capability to reduce weight in children and adolescents during multidisciplinary chronic care treatment.

Although IFG is a surrogate measure of abnormal glucose metabolism, IFG or elevated HbA1c at treatment entry did not influence the ability to reduce weight in the present study. Girls with higher concentrations of HbA1c at treatment entry were more obese at treatment entry. A previous report from our group has demonstrated that children with a familial predisposition to T2DM have a higher degree of obesity at treatment initiation.[35] In addition, Altinli et al. observed that children with parents with T2DM exhibits a higher degree of obesity compared to children with parents without diabetes.[36] We did not investigate whether or not the girls with high HbA1c were predisposed to T2DM in the present study.

No changes were observed in the concentrations of fasting glucose during weight loss in either boys or girls. The efficacy of fasting plasma glucose as a surrogate measure of abnormal glucose metabolism has previously been demonstrated in 1020 normoglycemic children with obesity, showing a decline in insulin sensitivity and secretion when moving from low to high concentration in the range of normal fasting plasma glucose (3.42-5.54 mmol/L).[37] Moreover, a

TABLE 3 Baseline associations of the estimates of glucose metabolism and the degree of obesity at treatment entry and the effects of the glucose metabolism on weight loss in 333 boys and 419 girls

Boys n = 333	Estimate ± SE[a]	P-value	95%CI	Sex Girls n = 419	Estimate ± SE	P-value	95%CI
At treatment entry							
Glucose	−0.11 ± 0.13	0.38	−0.36;0.14		0.33 ± 0.10	0.74	−0.16; 0.22
HbA1c	0.14 ± 0.14	0.32	−0.13;0.41		0.28 ± 0.12	**0.02**	0.06; 0.52
Insulin	0.46 ± 0.09	**<.0001**	0.29;0.63		0.28 ± 0.07	**<0.0001**	0.15; 0.41
C-peptide	−0.52 ± 0.09	**<0.0001**	−0.69;-0.34		−0.29 ± 0.07	**<0.0001**	−0.43; −0.14
HOMA2-IS	−0.46 ± 0.12	**0.0002**	−0.70;-0.22		−0.17 ± 0.11	0.13	−0.39; 0.05
HOMA2-B	−0.49 ± 0.10	**<0.001**	−0.69;-0.28		−0.33 ± 0.10	**0.0008**	−0.52; −14
Effects on weight loss							
Glucose	−0.02 ± 0.03	0.58	−0.10;0.05		0.008 ± 0.04	0.81	−0.06; 0.08
HbA1c	−0.015 ± 0.04	0.72	−0.10; 0.07		0.08 ± 0.04	0.06	−0.004; 0.16
Insulin	−0.04 ± 0.03	0.18	−0.09;0.01		−0.02 ± 0.03	0.50	−0.06; 0.03
C-peptide	0.04 ± 0.03	0.15	−0.02;0.10		0.05 ± 0.02	**0.02**	0.01; 0.10
HOMA2-IS	−0.05 ± 0.04	0.19	−0.13;0.03		0.02 ± 0.04	0.61	−0.06; 0.10
HOMA2-B	−0.06 ± 0.03	0.10	−0.12;0.01		0.03 ± 0.04	0.36	−0.04; 0.10

Abbreviations: CI, confidence intervals; HbA1c, glycosylated hemoglobin; HOMA2-B, Homeostasis Model Assessment 2-β-cell function; HOMA2-IS, Homeostasis Model Assessment 2-insulin sensitivity.

[a] Estimated group difference in baseline degree of obesity (BMI z-score ± SE) and estimated group difference in rate of weight loss (BMI z-score/year) ± SE. The estimates of the glucose metabolism and the association to the degree of obesity at baseline are dichotomized into children exhibiting glucose; > 5.6 mmol/L vs < 5.6 mmol/L, HbA1c; > 38 mmol/mol /(5.7%) vs < 38 mmol/mol/(5.7%), insulin; >107 pmol/L vs < 107 pmol/L, C-peptide; > 0.82 nmol/L vs < 0.82 nmol/L, HOMA2-IS; > 100% vs < 100%, HOMA2-B; < 100% vs > 100%. Standard Error (SE), 95% Confidence Interval (95%CI). Significant p-values are in bold.

high normal fasting plasma glucose (4.8-5.5 mmol/L) has also been associated with a 7-fold higher risk of presenting with IGT and insulin resistance in 323 children with obesity.[38]

The majority of the patients presenting with hyperinsulinemia exhibited a higher degree of obesity at treatment entry than those without hyperinsulinemia. Nevertheless, high concentrations of insulin or reduced insulin sensitivity did not influence the capacity to lose weight during chronic care treatment. This is in line with a study in 249 children with obesity followed for up to 15 years, where later weight regain during adolescence, was associated with degree of obesity and fat mass at baseline and not with insulin concentrations or insulin resistance.[39] In contrast, several reports have described insulin resistance as a predictor of difficulties to achieve weight loss during lifestyle intervention in children and adolescents with obesity.[13,14,40] Moreover, fasting hyperinsulinemia has been described as a predictor of later weight gain in Pima Indian children (n = 328) and Hispanic adolescents (n = 96) with obesity exhibiting a strong genetic predisposition of obesity,[41,42] leading to an increased focus on whether improvement of the insulin sensitivity can prevent further weight gain.

TABLE 4 Reduction in variables of the glucose metabolism for each unit of BMI z-score reduction during the first year of treatment

Changes during 13 ± 2 month of treatment	Estimate	95% CI	P-value
Boys (n = 263)			
Glucose, mmol/L	0.07	−0.03;0.16	0.17
HbA1c, mmol/mol	0.07	−0.30;-0.13	0.18
Insulin, pmol/L	54.85	37.01;72.69	**<0.001**
HOMA2-IS, %	(−3.48)	−8.44;1.48	0.17
HOMA2-B, %	7.34	−4.28;18.96	0.21
Girls (n = 306)			
Glucose, mmol/L	0.06	−0.04;0.16	0.27
HbA1c, mmol/mol	0.85	0.32;1.37	**0.002**
Insulin, pmol/L	34.04	15.02;53.06	**0.0005**
HOMA2-IS, %	−3.13	−7.89;1.64	0.20
HOMA2-B, %	4.81	−6.98;16.60	0.42

Abbreviations: BMI, body Mass Index; HbA1c, glycosylated hemoglobin; HOMA2-B, Homeostasis Model Assessment 2-β-cell function; HOMA2-IS, Homeostasis Model Assessment 2-insulin sensitivity; IQR, interquartile range.
The association between change in variables of glucose metabolism and change in degree of obesity during treatment is analyzed using linear regression of change in variables of glucose metabolism on change in BMI z-score adjusted for exact treatment duration, age, and baseline glucose metabolism. Values are in mean and 95% confidence intervals. The measurement of variables of the glucose metabolism closest 1 year after the baseline measurement was used, only anthropometric measurements between 6 and 18 months have been used (median 13 IQR (11.8-14.6)). Significant p-values are in bold.

At treatment entry, a high concentration of C-peptide, which is another proxy for the insulin secretion by the β-cell, was associated with a higher degree of weight loss during treatment in girls, but not in boys. From these results, it could be hypothesized that girls with a low concentration of C-peptide, due to an impaired β-cell function, responded poorer to multidisciplinary childhood obesity treatment. The same trend was observed when using the HOMA2-B to estimate the β-cell function, however, this association was non-significant. Variations in the 2 estimates of β-cell function might be explained by the use of insulin in the equation of HOMA2-B calculation instead of C-peptide.

During treatment according to the TCOCT protocol, the concentrations of insulin in both sexes declined independent of age, SES, and degree of obesity at enrollment. However, no significant improvements in insulin sensitivity were observed in either sex during intervention. The lack of improvement in insulin sensitivity, despite a reduction in insulin concentration during weight loss, may be explained by the transient development of insulin resistance and ectopic fat deposition during puberty.[43] However, reports on the association between fasting glucose, insulin sensitivity, and changes in ectopic fat are inconsistent.[25,44]

Despite reductions in the degree of obesity and insulin concentrations, we did not observe any significant improvements in the concentrations of fasting plasma glucose or insulin sensitivity during treatment. These observations indicate that other factors influence glucose homeostasis in children with obesity. Since IFG is associated with insulin resistance in the liver,[45] during weight loss, liver insulin resistance may be reduced due to the reduction of ectopic fat in the liver.[25] This in combination with the higher peripheral insulin resistance that occurs during puberty,[46] may explain why we do not observe a reduction in the fasting plasma concentrations of glucose despite a reduction in the degree of obesity and insulin concentrations in boys and girls. However, this hypothesis requires further investigation.

In contrast to the present study, other reports have demonstrated an improvement in insulin sensitivity measured by whole-body insulin sensitivity index derived from glucose and insulin concentrations from an oral glucose tolerance test (OGTT) during intensive lifestyle changes compared to standard care treatment in 23 and 58 patients, respectively, aged 10 to 16 years.[20,21] However, in these studies, indices from an OGTT were used to describe the insulin sensitivity making these studies less comparable with the present study, where we included a larger number of patients and used HOMA2-IS as an estimate of insulin sensitivity.

Difficulties in achieving weight loss during chronic care treatment have been reported to be associated with higher age, higher degree of obesity at treatment initiation,[4,5] insulin resistance, and parental obesity.[40] In contrast to these reports, the TCOCT protocol has attained a significant and biologically relevant[47] weight loss in elder children (age above 11.7 years),[22] and further documented that girls with familial predisposition to obesity lost more weight than girls without familial predisposition to obesity[35] and that parents reduced their degree of obesity during their child's treatment with the TCOCT protocol.[28] In addition, the present study shows that weight loss is attainable in children and adolescents with obesity and impaired glucose metabolism irrespective of age, degree of obesity, and SES.

There are several limitations to our study. The concentrations of insulin were measured routinely on 1 sample per patient in the in-house clinical laboratory, whereas the gold standard is a mean of 3 samples due to the pulsatile secretion of insulin.[48] In addition, we were not able to adjust for the natural day-to-day variation of FPG,[49] since we only included 1 measurement of FPG. However, the large number of patients and the blood samples being collected at the same time every morning in the fasting condition minimize this day-to-day variation. Proxies of insulin sensitivity and β-cell function as estimated by the HOMA2 program have been demonstrated to correlate well with similar values derived from the hyperinsulinemic-euglycemic clamp in adolescents across the continuum of glucose tolerance including children exhibiting diabetes and obesity.[33] When using the HOMA2-B to estimate the β-cell function, it is recommended to use C-peptide rather than insulin when available, since it is a more direct marker of the secretion of insulin. However, C-peptide was not part of the routine blood samples during the TCOCT protocol until year 2013, why insulin was used in the computer-based equation of HOMA2-B in the present study.

In conclusion, children and adolescents with obesity successfully achieve weight loss during treatment according to the TCOCT protocol, irrespective of impaired glucose metabolism, age, degree of obesity, and SES.

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Conflict of interest

The authors declare no potential conflict of interests.

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