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Reversibility of Hyperglycemic States in Children with Obesity - Diagnostic Pitfalls in the Assessment of Glucose Metabolism in Children and Adolescents with Obesity

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What is already known on this topic?

The current rate of weight gain in the child and adolescent population is worrying. As the prevalence of obesity increases, so does the occurrence of associated comorbidities, one of which is disordered glucose metabolism. Unfortunately, the data regarding glucose metabolic alterations in children and adolescents with obesity is both limited and varies greatly from study to study.

What this study adds?

Therefore, in this study we established high prevalence of prediabetes in pediatric patients with obesity as well as high reversibility of this condition. Moreover, our study showed that every change in body mass index Z-score had a significant impact on changes in carbohydrate metabolism parameters and low density lipoprotein cholesterol.

Abstract

Objective: Disorders of glucose metabolism in children with obesity are less common than in adults. There is also evidence that they may be transient. The aims of this study were to determine the prevalences of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM2) and its reversibility in pediatric patients with obesity and to define the factors determining the reversibility of prediabetes or progression to diabetes.

Methods: Retrospective analysis included of young patients with obesity. Patients presented and were treated between 2000-2022 at a single center.

Results: The study included 573 (316 girls; 55.15%) Caucasian patients with median body mass index (BMI) Z-score of 3.95 (range 2.0-9.9) and median age 13.9 (2.9-17.1) years old. OGTT results were normal in 90.8% (n=520) and signs of prediabetes occurred in 9.2% (n=53); IFG 17%, IGT 88.7%, DM 0%. Among those who underwent OGTT twice (n=53), impaired glucose regulation was present in 9.3% (n=5) (IFG 40%, IGT 80%, DM 0%) at baseline and in 14.8% subject (n=8) (IFG 25%, IGT 50%, DM 25%) at follow-up after lifestyle modification only. After 12-36 months of follow up, in those with a history of IGT, 60% reverted to normal glucose tolerance, while IFG and IGT persisted in 20% and 20%, respectively, and none progressed to DM. The risk factors for progression of glucose metabolism disorders were increase of BMI Z-score, higher insulin levels and elevated homeostatic model assessment-insulin resistance.

Conclusion: IFG and IGT are common in pediatric patients with obesity, while the progression to DM2 is rare. Disorders of glucose metabolism have reversible character.

Keywords: Childhood obesity, glucose metabolism, type 2 diabetes

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Introduction

According to World Health Organization data, up to 35.5% of boys and 23.1% of girls at school-age in Poland are affected by overweight or obesity (1). Moreover, the current rate of weight gain in Polish children and adolescents is the greatest in Europe (2). As the prevalence of obesity increases, so does the occurrence of associated comorbidities. The most important impact on the risk for morbidity and premature death during adulthood is associated with a number of metabolic changes, including hypertension, dyslipidemia, atherosclerosis, steatohepatitis and glucose metabolism disorders (3). These glucose metabolism disorders are defined as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The progression from normal glucose tolerance (NGT) to type 2 diabetes mellitus (DM2) through IFG and IGT, also termed prediabetes, is well described in obese adult population (4). Although the underlying pathophysiology of this development is multifactorial, one of the most important factor is the balance between insulin sensitivity and insulin secretion (5). The data regarding the natural history of glucose metabolic alterations in children and adolescents with obesity is limited (6). It seems that, and in contrast to adults, both impaired fasting plasma glucose and 120 minute and later postload glucose measurements, as well as increased insulin resistance (IR), may be reversible in the pediatric population.

Aim

The aim of this study was to determine the prevalence of hyperglycemic states, including IFG, IGT and DM2 and its reversibility in Polish pediatric patients with obesity. In addition, the factors determining the reversibility of prediabetes or progression to diabetes would be investigated.

Methods

This was a retrospective study performed in the Department of Pediatric and Adolescent Endocrinology, Children's University Hospital in Kraków. Bioethics Committee of Jagiellonian University in Kraków was provided (protocol no: KBET/169/B/2014, date: 12.06.2014). The study population consisted of young Caucasians diagnosed and treated from 2000 to 2022. The inclusion criteria for the study were: body mass index (BMI) greater than or equal 95th percentile for age and sex; age below 18 years at the first visit; and undergoing a two hour oral glucose tolerance test (OGTT) (7). Of the patients, a proportion underwent a second OGTT within 12-36 months. A week prior to the OGTTs, patients received a normo-caloric, mixed diet. The OGTTs were performed after an overnight fast, at 08:00 a.m. after admission to the hospital. Two baseline samples were obtained for measurements of plasma glucose, insulin, total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) fractions of cholesterol, triglycerides, uric acid and liver enzymes, alanine aminotransferase and aspartate aminotransferase. Thereafter, flavored glucose at a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) was given orally and blood samples were obtained after 120 minutes for the measurement of plasma glucose and insulin. Glucose concentration was measured by the dry chemistry method with a Vitros 5.1.FF machine (Ortho-Clinical Diagnostics). Insulin levels were measured by an immunoluminometric assay (ADVIA Centaur, Siemens). Homeostatic model assessment-IR (HOMA-IR) was calculated using the standard formula: fasting insulin level (mU/L) × fasting glucose level (mmol/L)/22.5. Each time weight, height, BMI, pubertal stage, systolic and diastolic blood pressure (mean of three measurements) were recorded and standardized in all patients. Weight and height were measured using a standardized calibrated scale and blood pressure was measured using an automatic sphygmomanometer. The presence of hypertension was assessed by 'Paediatric office blood pressure calculator' by HyperChildNET COST Action (8). The diagnostic criteria for IFG was a fasting blood glucose of 100-125 mg/dL (5.6-6.9 mmol/L), IGT was defined as a 2-hour plasma glucose level between 140 and 199 mg/dL (7.8-11.0 mmol/L) and DM as a fasting glucose level of 126 mg/dL (7.0 mmol/L) or higher (two abnormal readings required) or a two-hour plasma glucose level of more than 200 mg/dL (11.1 mmol/L) (one abnormal reading required) (9). In the duration of follow up, the interventions consisted of dietary and psychological guidance in order to achieve sustainable, long-term lifestyle changes. The patients were not put on medications affecting glucose metabolism.

Statistical Analysis

To assess the differences between groups, an ANOVA or Kruskal-Wallis tests were used. Calculations were performed using the Statistica 13.0 software (10). A p value of < 0.05 was assumed to indicate statistical significance.

Results

The study population consisted of 573 patients, of whom 316 (55.15%) were girls. All patients were Caucasian and the median age was 13.9 (2.9-17.11) years. The median BMI Z-score of the study group was 3.95 (range 2.0-9.9). Most patients (n = 520, 90.8%) had normal results on OGTT. Prediabetes, including IFG and IGT was present in 9.2% subjects (n = 53). In this group, including 34 (64.15%)

girls, with a median age 14.5 years old (range 3.5-17.11) the median BMI Z-score was 5.1 (range 2.1-9.6) The mean fasting glucose level was 4.5 mmol/L (standard deviation: 0.7). IFG was detected in 1.6% cases (n = 9). The mean post-load glucose level was 5.9 mmol/L (standard deviation: 1.0). IGT was detected in 8.2% of participants (n = 47). Three exhibited both IFG and IGT. No case of DM was detected at baseline.

Of the participants, 54 (29 girls; 53.7%) with a median age of 12.5 years old (range 3.7-16.1), including 13 children with a positive family history for DM2, underwent OGTT twice within 12-36 month of baseline measurements (Table 1). Of these 54, 49 (91%) had normal OGTT results at the baseline and 46 (85%) had normal results at follow up. At the baseline, prediabetes was diagnosed in 9.3% subjects (n = 5). The mean value of fasting glucose level was 4.7 mmol/L (standard deviation: 0.4). IFG was detected in two cases (40%). The mean post-load glucose level was 5.8 mmol/L (standard deviation: 1.4). Prediabetes was detected in four participants (2 girls) (80%) - one patient presented with both IFG and IGT. In the repeated test, prediabetes was diagnosed in 14.8% subject (n = 8). The mean value of fasting glucose level was 4.8 mmol/L (standard deviation: 0.4). IFG was detected in two cases (25%). The mean post-load glucose level was 6.1 mmol/L (standard deviation: 1.8). IGT was detected in four participants (2 girls) (50%). Two cases (25%) of DM were diagnosed. These were a 17.6 year-old boy with BMI Z-score 4.4 (BMI 33.4) who had baseline plasma insulin level of 28 mIU/L (168.0 pmol/L) and a two-hour insulin of 207 mIU/L (1242.0 pmol/L) together with positive autoantibodies to islet cell and protein tyrosine phosphatase (IA2). The second patient was a 13.7 year-old boy with BMI Z- score 3.4 (BMI 29.6) who had undergone treatment for acute lymphocytic leukemia. After 12-36 months of follow up, in patients with baseline IGT (3 girls and 2 boys at median age 12.9 years old (range 11.2-14.7) and median BMI Z-score 3.4 (range 2.3-6.0), one child with a positive family history for DM2), 60% (n = 3) reverted to NGT (1 girl and 2 boys, median age 12.9 years old (range 11.5-14.7), median BMI Z-score 3.1 (range 2.3-6.0), 20% persisted as IFG (one girl with a positive family history of DM2, aged 11.2 years old, BMI Z-score 3.4, BMI 27.3) and 20% had IGT (one girl, age 14.3 years old, BMI Z-score 3.9, BMI 29.6); none progressed to DM. In 11.1% of all subjects (n = 6) a new disorder, not present at baseline, developed (Figure 1). One who developed IGT had a positive family

Table 1. Clinical and metabolic characteristics of those who underwent oral glucose tolerance test twice

	Clinical and metabolic characteristics of the study group	
Parameter (units) **Median and range or mean and (standard deviation) or % and number of patients**	**At the first assessment (n = 54)**	**At the second assessment (n = 54)**
Age (years)	12.5 (3.7-16.1)	14.1 (6.6-17.11)
Sex - Female	54% (n = 29)	54% (n = 29)
Tanner stage - Prepubertal	35% (n = 19)	14% (n = 8)
BMI Z-score	3.7 (2.1-10.0)	4.2 (0.5-8.1)
Hypertension - Isolated systolic hypertension - Hypertension 1 grade - Hypertension 2 grade	 14% (n = 8) 16% (n = 9) 0%	 5% (n = 3) 12.5% (n = 7) 2.5% (n = 1)
Glucose at time zero (mmol/L)	4.7 (0.4)	4.8 (0.4)
Glucose at 2-hours (mmol/L)	5.8 (1.4)	6.1 (1.8)
Insulin at time zero (mIU/L) **Insulin at time zero (pmol/L)**	24.0 (12.0) 134.5 (71.8)	20.1 (12.0) 127.2 (72.0)
Insulin at 2-hours (mIU/L) **Insulin at 2-hours (pmol/L)**	111.2 (73.4) 645.7 (440.6)	107.2 (78.4) 609.2 (473.7)
Total cholesterol (mmol/L)	4.2 (0.8)	4.3 (0.9)
LDL cholesterol (mmol/L)	2.6 (0.7)	2.7 (0.7)
HDL cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.2)
Triglycerides (mmol/L)	1.6 (1.0)	1.6 (0.8)
Uric acid (µmol/L)	329.4 (69.4)	357.6 (72.6)
ALT (U/L)	34.9 (16.1)	32.6 (19.2)
AST (U/L)	29.0 (9.8)	28.6 (10.9)

HDL: high density lipoprotein, LDL: low density lipoprotein, BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase

history for DM2. All the metabolic changes within these groups are presented in Table 2.

There was no significant correlation between the incidence of disorders of glucose metabolism at the first or second OGTT and age, BMI Z-Score, blood pressure, total cholesterol, LDL, HDL, triglycerides, uric acid, and liver transaminase levels. However, in children progressing from NGT to IGT, the increase of BMI Z-score (mean 3.1 vs. 4.0, median 3.1 vs. 4.1), increase of the insulin levels both at time zero [mean 17.3 mIU/L (103.8 pmol/L) vs. 29.7 mIU/L (178.2 pmol/L)

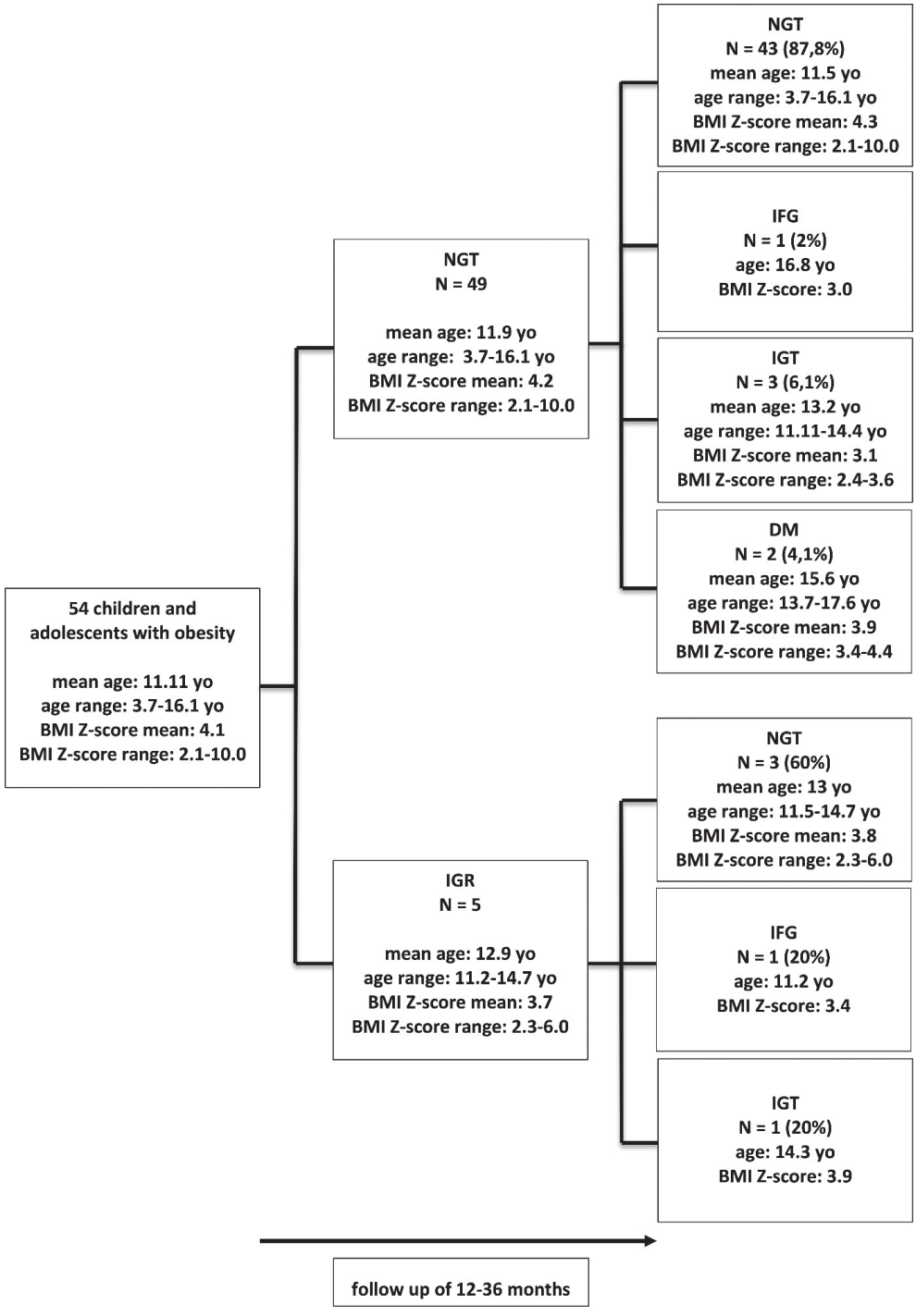

Figure 1. Trajectories of changes in carbohydrate metabolism disorders in the study group

NGT: normal glucose tolerance, IGR: impaired glucose regulation, IFG: impaired fasting glucose, BMI: body mass index, IGT: impaired glucose tolerance, DM: diabetes mellitus, yo: years old

Table 2. Detailed analysis of changes in a range of parameters between the groups with different glucose metabolic alterations

Parameter (units)	NGT -> IGR	IGR -> IGR	IGR -> NGT
Δ BMI Z-score	1.0	0.4	-0.3
Δ Glucose at time zero (mmol/L)	0.2	-0.5	-0.1
Δ Glucose at 2-hours (mmol/L)	3.5	0	-2.8
Δ Insulin at time zero (mIU/L)	12.4	-20.4	-3.9
Δ Insulin at time zero (pmol/L)	74.4	-81.6	-23.4
Δ Insulin at 2-hours (mIU/L)	114.6	9.9	-135.6
Δ Insulin at 2-hours (pmol/L)	687.6	59.4	-813.6
Δ HOMA-IR	3.0	-6.6	-0.9
Δ Total cholesterol (mmol/L)	0.2	-0.9	-0.1
Δ LDL cholesterol (mmol/L)	0.4	-0.4	0.1
Δ HDL cholesterol (mmol/L)	-0.1	-0.1	-0.1
Δ Triglycerides (mmol/L)	-0.3	-0.4	0.6
Δ Uric acid (μmol/L)	31.7	10.0	118.0
Δ ALT (U/L)	5.9	-34.7	2.0
Δ AST (U/L)	13.0	-20.0	-8.6

NGT: normal glucose tolerance, IGR: impaired glucose regulation, HDL: high density lipoprotein, LDL: low density lipoprotein, BMI: body mass index, HOMA-IR: homeostatic model assessment-insulin resistance, ALT: alanine aminotransferase, AST: aspartate aminotransferase

and at 2-hours (mean 92.5 mIU/L), (555.0 pmol/L) vs. 207.1 mIU/L (1242.6 pmol/L)] and decrease of insulin sensitivity measured by HOMA IR (3.8 vs. 6.8) were observed. In patients who had persistent prediabetes, the increase of BMI Z-score between the two OGTTs were evident but smaller than in previous group (mean 3.6 vs. 4.0), the insulin levels at time zero [mean 51 mIU/L (306.0 pmol/L) vs. 37 mIU/L (222.0 pmol/L)] and at 2-hours [mean 131.1 mIU/L (786.6 pmol/L) vs. 141 mIU/L (846.0 pmol/L)] were comparable. In those who reverted from IGT to NGT, the patients maintained comparable BMI Z-score (mean 2.7 vs. 2.8, median 3.1 vs. 2.8), there was a decrease in insulin levels both at time zero [mean 21.2 mIU/L (127.2 pmol/L) vs. 17.3 mIU/L (103.8 pmol/L)] and at 2-hours [mean 213.4 mIU/L (1280.4 pmol/L) vs. 77.7 mIU/L (466.2 pmol/L)] and an increase in insulin sensitivity between the assessments (mean HOMA IR 4.5 vs. 3.5). The 2-hour insulin level at presentation was particularly high in this group. Changes in values did not seem to be dependent on age or sexual development. In addition, there were significant correlations between the BMI Z-score changes between the first and the second assessment and changes in glucose level at time zero ($R = 0.3$, $p < 0.05$), insulin levels at time zero and 2-hours ($R = 0.3$ and $R = 0.4$, both $p < 0.05$), HOMA-IR ($R = 0.3$, $p < 0.05$) and LDL levels ($R = 0.3$, $p < 0.05$).

Discussion

As reported in the literature, the prevalence of IFG in children and adolescents with obesity ranges from 3.7% to 6.5%, whereas the prevalence of IGT ranges from 2.1% to 31% (11,12,13). In these studies, depending on ethnicity, BMI Z-score at baseline, the increase in the oral disposition index or the amount of gained weight during the follow up, the reversibility of prediabetes in pediatric patients with obesity varies from 45% to 65% (lifestyle modification alone) or even up to 84.2% (lifestyle modification and metformin) (13,14,15). In adults, these types of intervention achieve a reversal rate of 24% (16). Better results may also be attained but through second-line treatments, including glucagonlike peptide-1 analogues or bariatric surgery. These differences are explained by age-related changes leading to diminished insulin secretion (16,17). Obese youth usually exhibit higher insulin levels during OGTT but rates of progression from IGT to DM2 are lower in pediatric population than in adults. On the other hand, mean transition time from prediabetes to DM2 in children with obesity is more rapid due to faster deterioration of the beta cells. In addition, and in contrast to adults, because of reduction in insulin sensitivity particularly expressed at mid-puberty, some obese youth may improve their results on OGTT upon repeated testing at later pubertal stage (6). Glucose levels depend on many hormonal, neural and metabolic factors. This interplay is governed by insulin and glucagon secreted from beta and alpha cells respectively. The reduced insulin sensitivity in children with obesity is mostly associated with increased visceral, intra-hepatic and intramyocellular lipid deposition. To compensate for IR, both enhanced insulin secretion and reduced insulin clearance by the liver are activated. This continuous stress on the beta cells leads to firstly, their deterioration, and secondly, increasing glucose levels needed to stimulate them to secrete adequate amounts of insulin. It explains why children with obesity, and with IGT are comparable insulin resistant while those with NGT

may range from highly sensitive to markedly resistant. It has been shown that the ability of the child with obesity to compensate is limited by genetic and epigenetic factors in which ethnic background is the main clinical modifier. Genetic factors may affect both individual insulin sensitivity and beta cell response (6,13). The results of the present study showed the prevalence of prediabetes amounting to 9.2% (including 1.6% of IFG and 8.2% of IGT) in obese Polish youth and a low prevalence of DM2 (none at the first and two cases at the second assessment). Those two patients had additional risk factors for DM development, one with two autoantibodies and the other having treatment for acute lymphocytic leukemia. Furthermore, high reversibility of prediabetes has been shown, with 60% of the patients reverting from IGT to NGT. No one progressed from IGT to DM2. Although the study did not identify significant factors determining the reversibility of prediabetes or progression to diabetes, the results suggested that not only weight loss but also maintenance of BMI Z-score increases a chance of regression from IGT to NGT in our pediatric population. We found a significant correlation between BMI Z-score changes between the two assessments and changes in LDL levels. In Galderisi et al.'s (12) prospective study (39% Non-Hispanic White, 31% Non-Hispanic Black and 30% Hispanic) after median follow-up of 2.9 years, 65% of youth with IGT at baseline reverted to NGT, 27% adolescents had persistent IGT and 8% progressed to DM2. Participants who reverted from IGT to NGT showed a four-fold increase in the oral disposition index. Among youth with persistent IGT and those who progressed to DM2, insulin secretion declined. Non-Hispanic White ethnic background conferred an odds ratio of reverting from IGT to NGT five times greater than Non-Hispanic Black (13). In Weiss et al.'s (13) initial cohort (47% Caucasians, 32% African Americans and 21% Hispanics), all with IGT at baseline, 45% reverted to NGT, 30% remained IGT and 24.2% developed DM2. Those who exhibited improvements in glucose tolerance had lower BMI Z-scores at baseline and gained much less weight on follow-up than those who developed DM2. In youth who progressed to DM2, seven of eight subjects were African-American with a significantly higher BMI and BMI *Z*-score and they continued to gain excessive weight during the follow-up period. In Numbenjapon et al.'s (14) prospective study (100% Thai, all with IGT at baseline), apart from lifestyle modification, some patients received at least six months of treatment with metformin. In this group, 84.2% reverted to NGT. The patients who reverted also had lower LDL levels than patients who had persistent IGT, in both pre- and post-intervention periods (15). Conversely, in the adult population (55% Caucasian, 20% African-American, 16% Hispanic, 5% American Indian and 4% Asian-American, all with IFG and IGT at baseline) in the Diabetes Prevention Program, only 24% reverted to NGT over three years of follow up. Predictors for revertion to NGT were lower baseline fasting and 2-hour glucose, younger age and greater insulin secretion response to the oral glucose load. Intensive lifestyle modification and greater weight loss had significant and independent effects on revertion (16,18).

Study Limitations

A limitation of our study is that the classification of glucose tolerance relied on a single OGTT. Previous studies showed poor reproducibility of the OGTT in obese youth, in particular for the 2-hour plasma glucose (18). Another potential limitation is limited number of patients resulting in lack of some statistically significant correlations. The final limitation is the retrospective nature of the study.

Conclusion

IFG and IGT are common consequences of obesity in a Polish pediatric population, while the progression to DM2 is rare. Glucose metabolism disorders appear to be largely reversible in this pediatric population. Every change in BMI Z-score had a significant impact on changes in carbohydrate metabolism parameters and LDL cholesterol. However, these results should be validated by further, larger, prospective studies.

Ethics

Ethics Committee Approval: Bioethics Committee of Jagiellonian University in Kraków was provided (protocol no: KBET/169/B/2014, date: 12.06.2014).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Anna Iwańska, Małgorzata Wójcik, Ewa Szczudlik, Anna Stępniewska, Concept: Anna Iwańska, Małgorzata Wójcik, Design: Anna Iwańska, Małgorzata Wójcik, Jerzy B. Starzyk, Data Collection or Processing: Anna Iwańska, Małgorzata Wójcik, Ewa Szczudlik, Anna Stępniewska, Analysis or Interpretation: Anna Iwańska, Małgorzata Wójcik, Literature Search: Anna Iwańska, Małgorzata Wójcik, Writing: Anna Iwańska, Małgorzata Wójcik, Jerzy B. Starzyk.

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References

1. WHO European Regional Obesity Report 2022. Copenhagen: WHO Regional Office for Europe; 2022. Licence: CC BY-NC-SA 3.0

IGO. Available from: https://www.who.int/europe/publications/i/item/9789289057738

2. Pawel B, Chomiuk T, Gałązka-Sobotka M. Zalecenia kliniczne dotyczące postępowania u chorych na otyłość 2022 - stanowisko Polskiego Towarzystwa Leczenia Otyłości. Med Prakt. 2022:1-87.
3. Skelton JA, Klish WJ. Overview of the health consequences of obesity in children and adolescents. UpToDate. 2023.
4. Wu J, Ward E, Threatt T, Lu ZK. Progression to Type 2 Diabetes and Its Effect on Health Care Costs in Low-Income and Insured Patients with Prediabetes: A Retrospective Study Using Medicaid Claims Data. J Manag Care Spec Pharm. 2017;23:309-316.
5. D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. Diabetes Care. 2011;34(Suppl 2):161-165.
6. Weiss R, Santora N, Giannini C, Galderisi A, Umano GR. Prediabetes in youths: mechanisms and biomarkers. Lancet Child Adolesc. 2017;1:240-248.
7. Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. StatPearls Publishing, 2022.
8. Álvarez J, Aguilar F, Lurbe E. Blood pressure measurement in children and adolescents: key element in the evaluation of arterial hypertension. An Pediatr (Engl Ed). 2022;96:536. Epub 2022 Jun 1
9. Czupryniak L. Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2022 Stanowisko Polskiego Towarzystwa Diabetologicznego. Current Topics in Diabetes. 2022;2:1-134.
10. Wabitsch M, Hauner H, Hertrampf M, Muche R, Hay B, Mayer H, Kratzer W, Debatin KM, Heinze E. Type II diabetes mellitus and impaired glucose regulation in Caucasian children and adolescents with obesity living in Germany. Int J Obes Relat Metab Disord. 2004;28:307-313.
11. Martos-Moreno GÁ, Martínez-Villanueva J, González-Leal R, Chowen JA, Argente J. Sex, puberty, and ethnicity have a strong influence on growth and metabolic comorbidities in children and adolescents with obesity: Report on 1300 patients (the Madrid Cohort). Pediatr Obes. 2019;14:e12565. Epub 2019 Aug 2
12. Galderisi A, Giannini C, Weiss R, Kim G, Shabanova V, Santoro N, Pierpont B, Savoye M, Caprio S. Trajectories of changes in glucose tolerance in a multiethnic cohort of obese youths: an observational prospective analysis. Lancet Child Adolesc Health. 2018;2:726-735. Epub 2018 Aug 24
13. 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.
14. Numbenjapon N, Nakavachara P, Santiprabhob J, Kiattisakthavee P, Wongarn R, Likitmaskul S. Successful strategy to improve glucose tolerance in Thai obese youth. J Med Assoc Thai. 2010;93(Suppl 6):131-138.
15. Perreault L, Kahn SE, Christophi CA, Knowler WC, Hamman RF; Diabetes Prevention Program Research Group. Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. Diabetes Care. 2009;32:1583-1858. Epub 2009 Jul 8
16. Shibib L, Al-Qaisi M, Ahmed A, Miras AD, Nott D, Pelling M, Greenwald SE, Guess N. Reversal and Remission of T2DM - An Update for Practitioners. Vasc Health Risk Manag. 2022;18:417-443.
17. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. Diabetes Care. 2000;23:1619-1629.
18. Libman IM, Barinas-Mitchell E, Bartucci A, Robertson R, Arslanian S. Reproducibility of the oral glucose tolerance test in overweight children. J Clin Endocrinol Metab. 2008;93:4231-4237. Epub 2008 Aug 19