Demographic, Clinical and Biochemical Characteristics of Pediatric Obesity: Interim Analysis of a Larger Prospective Study

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Abstract

Introduction: Pediatric obesity is a common nutritional disorder that affects more than a third of the young population and predisposes individuals to greater future morbidity and mortality.

Materials and methods: Sixty-two children were recruited in the study. Demographic and clinical information regarding the patients and their parents was collected. Data about the weight, height, systolic (SP) and diastolic (DP) blood pressure, lipid metabolic profile, thyroid hormone levels, glucose and insulin levels before and after oral glucose tolerance test (OGTT) of participants were also collected. Body mass index (BMI) was calculated and patients were classified into groups according to the International Obesity Task Force criteria. Descriptive, comparative parametric, non-parametric tests and Spearman's ranked correlations were used in the statistical analysis.

Results: The study sample consisted of 34 males and 28 females aged 11.6 and 11.8 years, respectively (p=0.781). The mean BMI was 30.5 (SD 5.5): 8 of participant had normal weight (≤25 BMI), 22 were overweight (25-30 BMI), and 32 were obese (≥30 BMI). The children’s BMIs were significantly associated with parental BMIs (r=0.395, p=0.004). Both SP and DP were significantly different between BMI subgroups (p=0.005 and p=0.001, respectively) with the obese group having the highest values (post-hoc Benjamini, p=0.004).

Obese children had lower average T4 levels when compared to the comparators (7.5 µg/dL vs. 9.9 µg/dL, p=0.021). Obese children had significantly lower baseline glucose levels and higher insulin levels when compared to the overweight/normal BMI children (73.8 mg/dL vs. 86.4 mg/dL, p<0.001 and 21.8 µIU/mL vs. 132 µIU/mL, p=0.003). Obese children had the greatest numerical increase in glucose levels during the OGTT (Δ63.0 mg/dL vs. Δ43.2 mg/dL, p=0.063) and numerically smaller absolute insulin response (Δ86.1 µIU/mL vs. Δ125.7 µIU/mL, p=0.307).

Conclusions: Pediatric patients demonstrate familial type of obesity and premorbid asymptomatic endocrine impairments. In order to maintain normal glucose levels, obese pediatric patients demonstrate high levels of resting insulin levels and diminished response after OGTT load.

Keywords
diabetes, glucose, insulin, obesity, OGTT, pediatric, pre-diabetes
INTRODUCTION

The number of overweight or obese infants and young children (aged 0 to 5 years) increased globally from 32 million in 1990 to 41 million in 2016. Developing countries are places where the vast majority of overweight or obese children live, with rate of obesity 30 percent higher than that of developed countries. If current trends persist, the number of overweight or obese infants and young children globally will increase up to 70 million by 2025. Obesity-associated comorbidities represent the most significant economic and social public health burden. They can be debilitating, with an increased risk of premature death and morbidity primarily related to the onset of cardiometabolic diseases. Abnormally excessive adiposity has a direct effect of accelerating atherosclerotic disease, while the sum of cardiometabolic risk (CMR) factors such as hypertension, insulin resistance, dyslipidemia, and type 2 diabetes constitutes the cardiac disease risk. What is further crippling for the community health is that with a younger age of onset for obesity, cardiovascular disease and diabetes will emerge during the peak productivity years. The Republic of North Macedonia, a developing country, unfortunately follows the world trend of childhood obesity; however due to a lack of official epidemiological data, only rough estimations of the percentage of childhood and adolescence obesity were performed. Based on this background, our study aimed at determining the demographic, clinical, and biochemical characteristics of pediatric patients referred from primary physicians due to concerns of obesity or prediabetes. Determining early signs of premorbid abnormalities would substantially help in creating preventive strategies regarding reduction of pediatric obesity and future obesity-related complications.

MATERIALS AND METHODS

Study population

Between 2017 and 2018, 62 pediatric patients were referred to the Endocrinology and Genetics Department at the University Pediatric Clinic of Skopje, N. Macedonia. All referrals included weight as a primary concern. The inclusion criteria for this specific study included: 1) age from 6 months to 18 years and 2) presence of both parents during study visit. The patients were examined by experienced pediatric endocrinologist and cardiologist. Basic demographic and clinical information regarding patient and parental age, sex, height, weight, waist circumference were acquired during structured in-person interview. Body mass index (BMI) was calculated using the standard formula. Based on the results for BMI and the International Obesity Task Force (IOTF) criteria, the children were classified into normal (<25 BMI), overweight (25-30 BMI), and obese (>30 BMI). Patients’ parents gave written consent for study participation and the study was approved by the Ethics Committee of Sts Cyril and Methodius University in conformity with the declaration of Helsinki.

Cardiovascular, biochemical, and oral glucose tolerance analyses

Quantitative echocardiographic studies were performed on Philips Affinity 70 diagnostic ultrasound system. Left ventricular ejection fraction (LVEF) was acquired from the apical four-chamber view. The ejection fraction (EF) was measured in M mode and was derived based on the fractional shortening (FS) measurement. As recommended by the American Society of Echocardiography, the summation of discs method was used to assess end-diastolic and end-systolic volumes. LVEF was calculated by the formula:

\[ LVEF = \left(\frac{end-diastolic area - end-systolic area}{end-diastolic area}\right) \times 100. \]

LV function is objectively classified as normal (EF ≥ 55%), slightly reduced (EF 41%–55%), moderately reduced (EF 31%–40%), and markedly reduced (EF ≤ 30%). The thickness of the interventricular septum (IVS) and the posterior wall of the left ventricle was significant for the heart hypertrophy (normal values 0.8-1.2 cm), and is associated with higher systolic blood pressure.

Biochemical analysis for free T4 and thyroid stimulating hormone (TSH)

Serum concentrations of thyroid stimulating hormone (TSH) and fT4 were determined with a chemiluminescent immunometric assay (Siemens, Immulite 2000 fT4, Immulite 2000 Third-Generation TSH, USA). The reference levels for TSH and fT4 were 0.58–4.1 µIU/mL (children), 0.39–4.0 µIU/mL (adolescents), and 0.74–1.28 ng/dL (children), 0.80–1.27 ng/dL (adolescents), respectively. All binding assays were performed according to manufacturer’s instructions. All samples in this study were measured using the same primary standard. Both internal quality control and external quality assessment programs indicated no detectable deterioration over the period of the study for the assay system.

OGTT test

After overnight fast, an oral glucose tolerance test (OGTT; 2 g/kg for children aged < 3 yrs, 1.75 g/kg for children aged 3-10 yrs [max 50 g], or 75 g for children aged >10 yrs) was administered orally. Blood glucose concentrations were measured before administration of oral glucose and 2 hours after. Fasting whole-blood glucose levels higher than 120 mg/dL (6.7 mmol/L) or a 2-hour value higher than 200 mg/dL (11 mmol/L) indicated diabetes.
Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY, USA). Both data and residual distribution was determined by Kolmogorov-Smirnov test for normality and by visual assessment of data histograms and Q-Q plots. Only insulin levels before and during the OGTT procedure were not normally distributed. Comparative analyses were performed using $\chi^2$ and Student’s t-test for parametric data, and Mann-Whitney U test for non-parametric data. Associations between the pediatric patients’ and their parental BMI were performed by Spearman’s ranked correlations. P-value lower than 0.05 was considered statistically significant. Graphical representation of the data was produced by GraphPad Prism, version 8.0 (GraphPad Software, Inc. La Jolla, CA, USA).

RESULTS

Demographic and clinical characteristics

Demographic, clinical, and cardiovascular characteristics of the study population are shown in Table 1. The total study group consisted of 28 (45.2%) females and 34 (54.8%) males, mean age 11.6 years, average waist circumference of 98.3 cm, and average weight and height of 73.4 kg and 153.7 cm, respectively. The mean BMI was 30.5: 32 children were classified as obese, 22 as overweight, and only 8 had normal weight (normal BMI). The study population had mean systolic BP of 117.4 mmHg, diastolic BP of 76.3 mmHg and LVEF of 68.4%. There were no significant differences between the female and male children in age ($p=0.538$), weight ($p=0.678$), height ($p=0.897$), BMI nor prevalence of obesity ($p=0.834$ and 0.446, respectively), waist circumference ($p=0.684$), or cardiovascular indices (systolic BP, $p=0.961$, diastolic BP, $p=0.913$, and LVEF, $p=0.835$). The obese children had significantly greater systolic BP (122.5 mmHg vs. 112.1 mmHg vs. 110.7 mmHg, one-way ANOVA, $p=0.005$) and diastolic BP (80.6 mmHg vs. 72.6 mmHg vs. 67.9 mmHg, one-way ANOVA, $p=0.001$) when compared to the overweight and normal BMI counterparts. There were no differences in LVEF (68.9% vs. 67.8% vs. 67.8%, one-way ANOVA $p=0.844$).

The weight, height, and BMI of both maternal and paternal parents were also recorded (Table 1). The maternal parent had an average BMI of 28.7, whereas the paternal parent had an average BMI of 30.9. There was a significant correlation between BMI of the children and of their parents ($r=0.385$, $p=0.004$) (Fig. 1).

Table 1. Demographic characteristics of the total study population and for male and female pediatric patients separately

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Total cohort (n=62)</th>
<th>Female (n=28)</th>
<th>Male (n=34)</th>
<th>Female vs. Male p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>28 (45.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>11.6 (2.5)</td>
<td>11.8 (2.7)</td>
<td>11.4 (2.3)</td>
<td>0.538</td>
</tr>
<tr>
<td>Weight, mean (SD)</td>
<td>73.4 (20.7)</td>
<td>72.2 (13.1)</td>
<td>74.4 (23.9)</td>
<td>0.678</td>
</tr>
<tr>
<td>Height, mean (SD)</td>
<td>153.7 (13.5)</td>
<td>153.4 (13.1)</td>
<td>153.9 (14.0)</td>
<td>0.897</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30.5 (5.5)</td>
<td>30.4 (4.6)</td>
<td>30.7 (6.2)</td>
<td>0.834</td>
</tr>
<tr>
<td>Obese/overweight/normal, n</td>
<td>32/22/8</td>
<td>16/10/2</td>
<td>16/12/6</td>
<td>0.446</td>
</tr>
<tr>
<td>Waist circumference, mean (SD)</td>
<td>98.3 (14.7)</td>
<td>97.4 (10.3)</td>
<td>99.0 (17.7)</td>
<td>0.684</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mmHg</td>
<td>117.4 (12.9)</td>
<td>117.3 (14.1)</td>
<td>117.5 (12.1)</td>
<td>0.961</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mmHg</td>
<td>76.3 (10.2)</td>
<td>76.1 (10.4)</td>
<td>76.4 (10.4)</td>
<td>0.913</td>
</tr>
<tr>
<td>Ejection fraction, mean (SD)</td>
<td>68.4 (7.2)</td>
<td>68.1 (6.9)</td>
<td>68.5 (7.4)</td>
<td>0.835</td>
</tr>
<tr>
<td>Maternal BMI, mean (SD)</td>
<td>28.7 (6.2)</td>
<td>28.1 (4.7)</td>
<td>29.5 (7.4)</td>
<td>0.662</td>
</tr>
<tr>
<td>Paternal BMI, mean (SD)</td>
<td>30.9 (5.6)</td>
<td>31.3 (6.3)</td>
<td>30.7 (4.9)</td>
<td>0.385</td>
</tr>
</tbody>
</table>

BMI: body mass index; BP: blood pressure; SD: standard deviation. Statistical differences were obtained using $\chi^2$ and Student’s t-test as appropriate.
Biochemical and Oral Glucose Tolerance Test findings

The biochemical and OGTT findings for total study population and for each BMI subgroup classification (normal/overweight vs. obese) are shown in Table 2. Out of 62 participants, 46 (74.2%) had available data regarding lipid levels (cholesterol and total triglycerides), thyroid hormone levels (T4 and TSH), and OGTT-derived insulin and glucose levels both before and after 75 g of glucose dose. Due to the small sample size of normal BMI children (n=8), they were combined with the overweight ones into one group.

There were no significant differences in cholesterol and total triglyceride levels between the groups ($p=0.54$ and $p=0.467$). On the other hand, obese children had lower average T4 levels when compared to the comparators (7.5 µg/dL vs. 9.9 µg/dL, t-test, $p=0.021$). Although not statistically significant, obese children had also numerically lower TSH levels (2.6 mU/L vs. 3.3 mU/L, t-test $p=0.155$). The obese group of children had significantly lower baseline glucose levels and higher insulin levels when compared to the overweight/normal BMI groups (73.8 mg/dL vs. 86.4 mg/dL, t-test, $p<0.001$ and 21.8 µgU/mL vs. 13.2 µgU/mL, Mann-Whitney U test, $p=0.003$). Although not significantly different at follow-up, the obese children had the greatest numerical increase in glucose levels during the OGTT ($Δ63.0$ mg/dL vs. $Δ43.2$ mg/dL, $p=0.063$). Similarly, the obese children had numerically smaller absolute insulin response when compared to the remaining subjects ($Δ86.1$ µU/mL vs. $Δ125.7$ µU/mL, $p=0.307$). The glucose and insulin responses from both normal/overweight and obese children are shown in Fig. 2.

Table 2. Biochemical and OGTT analysis of the study population

<table>
<thead>
<tr>
<th>Biochemical analyses and OGTT</th>
<th>Total cohort (n=46)</th>
<th>Normal or overweight (n=22)</th>
<th>Obese (n=24)</th>
<th>Obese vs. other p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mean (SD)</td>
<td>4.1 (0.7)</td>
<td>4.1 (0.6)</td>
<td>4.2 (0.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Total triglycerides, mean (SD)</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.6)</td>
<td>1.4 (0.8)</td>
<td>0.467</td>
</tr>
<tr>
<td>T4, mean (SD), µg/dL</td>
<td>8.5 (3.2)</td>
<td>9.9 (3.1)</td>
<td>7.5 (2.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>TSH, mean (SD), mU/L</td>
<td>2.9 (1.3)</td>
<td>3.3 (1.1)</td>
<td>2.6 (1.3)</td>
<td>0.155</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose at baseline, mean (SD), mg/dL</td>
<td>79.2 (0.7)</td>
<td>86.4 (0.6)</td>
<td>73.8 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose during OGTT, mean (SD), mg/dL</td>
<td>135.1 (1.8)</td>
<td>131.5 (1.9)</td>
<td>136.9 (1.6)</td>
<td>0.586</td>
</tr>
<tr>
<td>Insulin at baseline, mean (SD), µIU/mL</td>
<td>17.7 (9.2)</td>
<td>13.2 (5.5)</td>
<td>21.8 (9.8)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Insulin during OGTT, mean (SD, µIU/mL)</td>
<td>120.0 (119.7)</td>
<td>134.2 (153.5)</td>
<td>107.9 (82.9)</td>
<td>0.885*</td>
</tr>
</tbody>
</table>

OGTT: oral glucose tolerance test; TSH: thyroid stimulating hormone; SD: standard deviation; IQR: interquartile range; Student's t-test was used to assess differences between the obese and the remaining BMI groups (overweight and normal BMI); *: the Mann-Whitney U test was used as the variables were non-parametric; P-value < 0.05 was considered statistically significant.

Figure 2. Bar plot representation of the oral glucose tolerance test results from the study populations. Data are presented as means ± SEM.
DISCUSSION

This interim analysis of an ongoing nation-wide study shows emerging endocrinological abnormalities in obese but otherwise healthy pediatric population. Despite the small study power, obese children demonstrated lower baseline glucose levels with concurrent high levels of insulin. Furthermore, obese children show a trend towards greater glucose increase and smaller insulin response during OGTT test. The findings of lower thyroid functioning warrants further investigation. Lastly, we demonstrated significant association between parental and child BMI values, which points towards familial type of obesity.

Overweight and obesity in the youth population correlates with diverse risk factors for cardiovascular disease and they are also associated with an early atherosclerotic lesions development. Many studies have reported that obesity is associated with accelerated coronary atherosclerosis in adolescents, which could lead to an increased cardiovascular disease incidence later in adulthood. In spite of the abundant research, the etiology of impaired glucose tolerance, type 2 DM and risk of CVD in overweight and obese children is still not clearly delineated. According to Arslanin et al., the insulin hyper-production followed by rapid deterioration of insulin secretion in obese children and adolescents precedes the onset of type 2 diabetes. This hyperproduction is in line with our findings demonstrating significantly higher resting insulin levels and lower insulin response after OGTT in our obese children.

Our findings of lower T4 hormone levels in obese children are also consistent with the research in the literature. For example, a recent and larger US-based study showed that higher BMI in obese children was associated with both lower free T4 and corresponding high levels of TSH. The presence of these associations in different geographical and cultural settings further corroborates the validity of the results. Instead of thyroid-targeted treatment, studies have also shown that exercise and weight loss programs can improve the structural and functional thyroid changes which can result from an early obese states. Furthermore, bidirectional relationship between thyroid functioning and leptin-based or feeding mechanisms has been hypothesized. Lastly, an association between obesity-induced thyroid dysfunction and potentially greater risk for future thyroid autoimmunity should be further investigated.

The results presented in a study by Stunkard et al. indicate that the environmental variables are less significant determinants of children’s BMI when compared to genetic factors. Furthermore, a German study with children aged 5 to 7 years found that parental BMI explains 7.6% of the variation in children’s BMI. Children with one obese parent are more likely to have excess body weight when compared to children with one overweight parent. Similarly, we corroborated this finding and showed significant association between pediatric and parental BMI. Recent studies show that regular physical activity actually plays a major role against the risk of cardiovascular disease, metabolic syndrome and altered blood pressure in children. More importantly, these results underline the significance of a common family environment as a multi-factorial contributor to the epidemic of childhood obesity and the need for introducing preventive programs with focus on the family.

A limitation of this study is the small sample size. However, these findings are only an interim cross-sectional analysis from a currently ongoing, 5-year, nation-wide study that aims at evaluating the demographic, clinical, and biochemical characteristics of pediatric obesity. Future in-depth analysis regarding metabolic panel abnormalities which would include in-depth lipid analysis, associations between thyroid and pancreatic functioning and demographic/ethnic attributes of pediatric obesity will be performed. Lastly, detailed assessment of the obesity effects on the changes in pediatric cardiovascular functioning are also planned.

CONCLUSIONS

Obese children present with familial type of obesity and are characterized with premorbid asymptomatic endocrinological abnormalities. In order to maintain normal glucose levels, obese pediatric patients demonstrate high levels of resting insulin levels and diminished response after OGTT load. Failure of these compensatory mechanisms may lead to early development of diabetes type 2.

What is already known on this topic?

Overweight and obesity in youth population correlate with diverse risk factors for future cardiovascular disease and are associated with an early atherosclerotic lesions development. Obesity is related to accelerated coronary atherosclerosis in adolescents, which could lead to an increased cardiovascular disease incidence later in adulthood. The insulin hyper-production followed by rapid deterioration of insulin secretion in obese children and adolescents precedes the onset of type 2 diabetes. This hyperproduction is in line with our findings which demonstrated significantly higher resting insulin levels and lower insulin response after OGTT in our obese children.

What this study adds?

This study is important to our country and such obesity growth trend has never been observed before in North Macedonia. Namely, we demonstrated significant association between parental and child BMI values, which points toward familial type of obesity. Due to the rapid westernization, the children from Macedonia are joining the global trend of obesity and prediabetes. Based on these findings, development of social programs addressing familial health habits may provide decrease in obesity and future development of type 2 diabetes.
Clinical and Biochemical Characteristics of Pediatric Obesity

Ethics Statement

Ethics Committee Approval: The research protocol was approved by the local Institutional Review Board. All participants signed informed and written consent forms.

Authors Contributions

Surgical and Medical Practices: All authors contributed equally. All authors contributed equally to the concept of the study. MT, DJ, BGA, SK, KKM, and MKK participated in the design of the study. All authors compiled and analyzed the data. MT, DJ, KKM, and MKK helped in the analysis and interpretation of data. MT, DJ, AS, KKM, and MKK did the literature search. MT, DJ, AS, KKM, and MKK wrote the manuscript.

Conflicts of Interest

The authors declare no conflict of interest and no financial disclosure.

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Демографические, клинические и биохимические характеристики ожирения у детей: промежуточный анализ крупного проспективного исследования

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Резюме

Введение: Детское ожирение – это распространённая форма расстройства пищевого поведения, которым страдает более одной трети молодого населения и которое предрасполагает людей к более высокой заболеваемости и смертности в будущем.

Материалы и методы: Для исследования было отобрано 62 ребёнка. Была собрана демографическая и клиническая информация о пациентах и их родителях. Также были собраны данные о весе, росте, систолическом (CД) и диастолическом (ДД) артериальном давлении, липидном метаболическом профиле, уровнях гормонов щитовидной железы, уровне глюкозы и инсулина до и после перорального глюкозотолерантного теста (ПГТТ) участников. Был рассчитан индекс массы тела (ИМТ), и пациенты были разделены на группы в соответствии с критериями Международного общества борьбы с ожирением (International Obesity Task Force). Для статистического анализа использовались описательные, сравнительно-параметрические, непараметрические тесты и ранговые корреляции Спирмена (Spearman’s ranked correlations).

Результаты: В выборку вошли 34 мальчика и 28 девочек в возрасте 11,6 и 11,8 лет соответственно (p=0.781). Средний ИМТ был 30,5 (SD 5,5); 8 участников имели нормальный вес (≥25 ИМТ), 22 имели избыточный вес (25-30 ИМТ), а 32 страдали ожирением (≥30 ИМТ). ИМТ детей был в значительной степени связан с ИМТ родителей (r=0.395, p=0.004). И CД, и ДД значительно различались между подгруппами по ИМТ (p=0.005 и p=0.001, соответственно), а в группе с ожирением были самые высокие значения (post-hoc Benjamini, p=0.004). Дети с ожирением имели значительно более низкий исходный уровень глюкозы и более высокий уровень инсулина в состоянии покоя по сравнению с детьми с избыточным весом и нормальным ИМТ (73.8 mg/dL против 86.4 mg/dL, p<0.001 и 21.8 µgU/mL против 132 µgU/mL, p=0.003). У детей с ожирением было наибольшее численное увеличение уровня глюкозы во время ПГТТ (Δ63.0 mg/dL против Δ43.2 mg/dL, p=0.063) и численно более низкий абсолютный ответ на инсулин (Δ86.1 µIU/mL против Δ125.7 µIU/mL, p=0.307).

Заключение: Пациенты детского возраста демонстрируют семейный тип ожирения и преморбидные бессимптомные эндокринные нарушения. Для поддержания нормального уровня глюкозы у детей с ожирением наблюдаются высокие уровни инсулина в состоянии покоя и снижение ответа после нагрузки глюкозой при ОГТТ.

Ключевые слова
diabetes, glucose, insulin, obesity, OGTT, pediatrics, prediabetes