Predictive Biological Markers in Post-therapeutic Evolution in Obese Patients

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Childhood obesity is a leading public health concern because it represents a risk factor for many comorbid conditions in youth, such as cardiovascular disease, metabolic syndrome and sleep apnea [1, 2]. Taking into account that obesity is a chronic condition, we consider that early diagnosis, treatment and multidisciplinary counseling absolutely necessary to prevent long-term disabling complications.

We conducted a complex dietary-exercise-psychological intervention program. The purposes of the study were to evaluate the effect of the intervention program at 6 months after the first visit and determine the predictive factors. We realised a retrospective study that included 69 obese children and adolescent, boys and girls, followed-up at Saint Mary Children’s Hospital and Regional Center of Diagnosis, Counselling and Monitoring of Overweight and Obese Children from “Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania, aged 12 to 18 years. The patients were included in two groups: group 1 included 38 patients received a hypocaloric diet only and group 2 included 31 patients received a hypocaloric diet associated with kinetotherapy and psychoterapy [3]. We assessed obese children and adolescent before and after 6 months of program. Initial screening included physical examination (weight, height, BMI and waist circumference (WC)), fasting blood profile (total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, tryglicerides (TG)). Visceral adiposity was assessed by measuring WC, expressed in absolute value and percentile by age and sex [4]. TG and cholesterol values were interpreted according to percentile for sex and age. Hypertriglyceridemia refers to a fasting plasma TG measurement that is increased, typically above the 95th percentile for age and sex: between 10 - 14 years old boys ≥125 mg/dL, between 15 - 19 years old boys ≥ 148 mg/dL, between 10 - 14 years old girls ≥ 131 mg/dL, between 15 - 19 years old girls ≥ 124 mg/dL [5]. The diet prescribed was a balanced hypocaloric diet according to the child’s age and eating habits. Each child’s exercise scheme was prescribed by trained physiotherapists.

Participants with medical illness (diabetes, cardiovascular, renal or neurological diseases), eating disorders, chronic medications were excluded.

Keywords: obesity, body mass index, waist circumference, cholesterol, triglycerides.

Experimental part

Material and methods

We realised a retrospective study that included 69 obese children and adolescent, boys and girls, followed-up at Saint Mary Children’s Hospital and Regional Center of Diagnosis, Counselling and Monitoring of Overweight and Obese Children from Grigore T. Popa University of Medicine and Pharmacy Iasi, Romania, aged 12 to 18 years. The obese patients (body mass index - BMI percentiles between 95 - 97th in obesity and BMI percentiles > 97th in severe obesity) were included in two groups: group 1 included 38 patients received a hypocaloric diet only and group 2 included 31 patients received a hypocaloric diet associated with kinetotherapy and psychoterapy [3].

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Participants with medical illness (diabetes, cardiovascular, renal or neurological diseases), eating disorders, chronic medications were excluded.
Statistical analysis was performed in SPSS 24. In interpreting the statistical results the reference value of the significance level p=0.05 was considered, which corresponds to a confidence interval of 95%. Continuous type variables were presented as mean ± standard deviation. For the comparison of the parameters corresponding to the study groups, specific statistical parameters (F-tests, t-test, ANOVA) and non-parametric (Yates Chi-square) were applied depending on the type and characteristics of the analyzed data.

Results and discussions

Group 1: The BMI of our subjects was 30.4 ± 7.8. 39.5% of children were obese (BMI between 95 - 97th percentiles) and 60.5% of children were severe obese (BMI > 97th percentiles). Mean age was 12.8 ± 1.9 years, 13 ± 1.9 for boys and 12.6 ± 1.9 for girls. After 6 months of hypocaloric diet in 73.7% of cases WC it was maintained at higher values (WC > 90th percentiles) even though weight and BMI had decreased. It was noted that 26.3% of the cases had a BMI percentile < 90%.

Group 2: The BMI of our subjects was 29.1 ± 3.4, 45.2% children were obese (BMI between 95 - 97th percentiles) and 54.8% were severe obese (BMI > 97th percentiles). Mean age was 13.7 ± 2.4 years, 13 ± 1.9 for boys and 13.5 ± 2.9 year for girls. After 6 months of hypocaloric diet and kinetotherapy, 51.6% of cases WC it was maintained at higher values (WC > 90th percentiles) even though weight and BMI had decreased. It was noted that 26.3% of the cases had a BMI percentile < 90%. It was noted that 48.4% of the cases had a BMI percentile < 90%.

BMI and WC values significantly decreased in study group 2, compared to the study group 1. If in the first group at 6 months, 13.2% had BMI over the 97% percentile, in the case of the group 2 patients only 6.5% of them had BMI values over the 97% percentile (table 1). Similar results have been highlighted for WC (WC > 90 percentiles: group 1 - 73.7% vs group 2 - 51.6%), TG and TC (table 1). TG values decreased significantly less for group 1 patients compared to TG decreases in patient group 2. The values of HDL-cholesterol levels were normal in both groups.

The study demonstrated that cardiovascular risk was slightly improved in group 1 patient; the percentage of cases initially presenting an medium risk decreased insignificantly from 7.9 to 5.3% (p = 0.068), while in group 2, the percentage of cases with medium risk decreased significantly (p = 0.0092) from 19.4 to 23.3% at 6 months after initiation of therapy (table 2).

In both groups a positive association was observed between WC and increased risk for cardiovascular disease. The results showed a significant correlation between cardiovascular risk, BMI (r = 0.65, p = 0.002) and WC (r =

| Group 1 (N=38) | Female (n=15) | Male (n=23) |
|----------------|---------------|-------------|
| BMI (>97)      | All           | 23(60.5%)   | 5(13.9%) |
|                | Male          | 7(46.7%)    |           |
|                | Female        | 16(69.6%)   |           |
| WC (>90)       | All           | 28(73.8%)   |           |
|                | Male          | 19(82.6%)   |           |
|                | Female        | 9(60%)      |           |
| TG (triglycerides) (>95) | All | 6(15.8%)    |           |
|                | Male          | 3(13.1%)    |           |
|                | Female        | 3(20%)      |           |
| Total cholesterol (>97) | All | 2(5.3%)     |           |
|                | Male          | 0(0%)       |           |
|                | Female        | 2(13.3%)    |           |

| Group 2 (N=31) | Female (n=11) | Male (n=20) |
|----------------|---------------|-------------|
| BMI (>97)      | All           | 17(54.8%)   | 2(6.5%)   |
|                | Male          | 13(68.5%)   |           |
|                | Female        | 4(36.4%)    |           |
| WC (>90)       | All           | 10(31.6%)   |           |
|                | Male          | 11(53%)     |           |
|                | Female        | 5(45.5%)    |           |
| TG (triglycerides) (<95) | All | 2(6.5%)     |           |
|                | Male          | 2(10%)      |           |
|                | Female        | (0%)        |           |
| Total cholesterol (<95) | All | 2(6.5%)     |           |
|                | Male          | 2(10%)      |           |
|                | Female        | 0(0%)       |           |

| Table 1 |
|---------|
| CLINICAL-BIOLOGICAL PARAMETERS INITIALLY AND AFTER 6 MONTHS |

| Table 2 |
|---------|
| CARDIOVASCULAR RISK ASSESSMENT |

**Values were expressed as number (percent)%; (*) Marked effects are significant at p<0.05; † Yates Chi-square test or Fisher's exact test.**
Dyslipidemia in obese children. Furthermore, assessing the significant predictors in the evolution of obesity.

For developing CVD, obesity and abdominal adiposity are associated with high TG, TC, and low HDL cholesterol [6], which represents a significant prognostic factor (OR = 5.9, p < 0.001) in the favorable evolution of the child with obesity. Important prognostic factors were the TG and TC values, weight and BMI values were associated with high TG, TC, and low HDL cholesterol [6], which was moderate (r = 0.358, p = 0.037), similar results being recorded for TC values. In group 2, the correlation between decrease of TG and WC values was moderate (r = 0.358, p = 0.037), similar results being recorded for TC values. In group 2, the correlation between decrease of TG and WC was significant (r = 0.669, p = 0.0132).

Based on the statistical analysis, the predictive factors regarding the evolution of obese patients could be evaluated (table 3).

Multivariate analysis has shown that the type of therapy represents a significant prognostic factor (OR = 5.9, p < 0.01) in the favorable evolution of the child with obesity. Important prognostic factors were the TG and TC values, weight decreases were significantly associated with decreases in these parameters. A lower impact on the patient's post-treatment evolution was seen by BMI value, demonstrating that therapy is more important for favorable evolution, and the initial nutrition status represents just an additional factor. The diet associated with phisical exercise is extremely important for decreases cardiovascular risk in obesity.

Limitations of the present study includes the brief follow-up period, the exact assessment of physical activity performed by each child as well as sedentarism outside of specialized kinetotherapy.

In this study were included obese children and adolescents who received only a prescriptive diet alone group 1) compared with the prescriptive diet and physical activity (group 2). Our results confirm that the hypocaloric diet combined with physical activity is more effective in reducing the weight, BMI, WC and biological parameters (TC, TG), compared to hypocaloric diet without physical activity.

Literature studies had shown that children at high-risk for developing CVD, obesity and abdominal adiposity are associated with high TG, TC, and low HDL cholesterol [6], significant predictors factors in the evolution of obesity.

WC, particular visceral fat, is an independent risk factor for diabetogenic–atherogenic abnormalities in adolescents [7, 8, 10, 11]. In our study, we found a high percentage of dyslipidemia in obese children. Furthermore, assessing the cardiovascular risk by TC levels, we found that 13.16% of patients from group 1 and 22.16% of patients from group 2 had important risk that needs an early approach. Children with body weight above the 95 percentiles have usually an increased level of TG, being an important cardiovascular risk factor [14].

Dietary constituents of a weight loss diet have a small but significant impact on the lipid level changes. Even in the absence of significant weight loss, dietary therapy can be beneficial and should be encouraged [15].

Duration of exercise had a significant impact on the total cholesterol levels and improves the cardiovascular risk factors [12, 13, 16]. Exercise alone is usually not enough to induce significant weight loss. It is recommended that patients exercise for 150 min or more per week (30 min - 5 times per week). The more intensive exercise program is, the greater the effect on weight and lipid levels will be [18].

Conclusions

The implementation of a multidisciplinary nutrition and kinetotherapy program, doubled by psychological counseling to ensure optimal nutritional control of childhood obesity and superior quality of life is extremely important. Our results confirm that diet and physical activity affects significantly the serum lipid profile. Obesity and overweight remain risk factors for the development of hypercholesterolaemia and hypertriglyceridaemia. In summary, we have found that diet combined with sustained exercise improve WC and cholesterol and triglycerides levels in obese children, the main risk factors of cardiovascular diseases. In this context, decreasing obesity in children through diet and exercise should be an important strategy for preventing cardio-metabolic disease in adult.

References

1. EKLOGLU BS, ATABEK ME, AKYÜREK N, ALP H. Assessment of Cardiovascular Parameters in Obese Children and Adolescents with Non-Alcoholic Fatty Liver Disease. J Clin Res Pediatr Endocrinol., 7, no. 3, 2015, p. 222-7.
2. DE JONG E, VISSCHER TL, HIRASING RA, HEYMANS MW, SEIDELL JC, RENDERS CM. Association between TV viewing, computer use and overweight, determinants and competing activities of screen time in 4- to 13-year-old children. Int J Obes (Lond), 37, no.1, 2013, p. 47-53.
3. KUCZMARSKI RJ, OGDEN CL, GUO SS, GRUMMER-SWANN LM, FLEGAL KM, MEI Z, WEI R, CURTIN LR, ROCHE AF, JOHNSON CL. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat, 11, no. 246, 2002, p 1-190.
4. MATSUISHITA R, ISO, JIMA T, TAKAYA R, SATAKE E, YAMAGUCHI R, KITSUDA K, NAGATA E, SANO S, NAKANISHI T, NAKAGAWA Y, OHZeki T, OGATA G, FUJ ISAWA Y. Development of waist circumference percentiles for Japanese children and an examination of their screening utility for childhood metabolic syndrome: a population-based cross-sectional study. BMC Public Health., 13, no.15:1121, 2015, p 1-10.
5. NESLIHAN KOYUNCUOGLU GUNGOR. Overweight and Obesity in Children and Adolescents. J Clin Res Pediatr Endocrinol. 6, no. 3, 2014, p. 129-143.

| Table 3 THE PREDICTIVE FACTORS REGARDING THE EVOLUTION OF OBESE PATIENTS |
|-----------------------------|-----------------|-----------------|-----------------|
| Type of therapy            | p-value         | Exp(B) OR       | 95% CI for Exp(B) |
|------------------------------|-----------------|-----------------|-----------------|
| TG (triglycerides)          | <0.001          | 5.981           | 2.187           | 9.453           |
| Total Cholesterol           | 0.001           | 3.129           | 1.907           | 7.882           |
| WC (≥90)                    | 0.027           | 2.574           | 1.882           | 3.158           |
| BMI (≥79)                   | 0.003           | 2.172           | 1.855           | 5.619           |
| O2 - Odd ratio; CI - interval de confidență |

0.71, p = 0.003). Decrease of TG was significantly correlated with the decrease of WC in group 2 (r = 0.084, p < 0.001), while in group 1 the correlation was lower (r = 0.31, p = 0.035). After 6 months, it was observed a significantly difference in the TC levels from the subjects who exercised compared to those who were not involved (p=0.0053). A significant decrease of WC (p < 0.013) (WC < 90th percentiles), weight and BMI values were observed in group 2, significantly higher compared to that recorded in group 1 (p = 0.042). Also, the decrease of TG values showed a significantly greater association (r = 0.824, p = 0.003) with the decrease of WC values in group 2 compared to group 1. There is a significant correlation (r = 0.703, p = 0.002) between the decrease of TG values and the reduction of WC in group 2. In group 1, it was observed that the correlation between the decrease of TG and WC values was moderate (r = 0.358, p = 0.037), similar results being recorded for TC values. In group 2, the correlation between decrease of TG and WC was significant (r = 0.669, p = 0.0132).

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6. Lee L, Sanders RA. Metabolic syndrome. Pediatr Rev. 33, no. 10, 2012, p 459-66.
7. Suliga E. Visceral adipose tissue in children and adolescents: a review. Nutrition Research Reviews 22, no. 2, 2009, p 137-147.
8. Huang RC, Prescott SL, Godfrey KM, Davis EA. Assessment of cardiometabolic risk in children in population studies: underpinning developmental origins of health and disease mother-offspring cohort studies. J Nutr Sci. 4, 2015, p e12.
9. De Koning L, Denhoff E, Kellogg MD, De Ferranti SD. Associations of total and abdominal adiposity with risk marker patterns in children at high-risk for cardiovascular disease. BMC Obes. 2, 2015, p 15.
10. Ramirez-Velez R, Correa-Bautista JE, Carrillo HA, Gonzalez Jimenez E, Schmidt-Riovalle J, Correa-Rodriguez M, Garcia-Hermoso A, Gonzalez-Ruiz K. Tri-Ponderal Mass Index vs. Fat Mass/Height4 as a Screening Tool for Metabolic Syndrome Prediction in Colombian Children and Young People. Nutrients. 10, no. 4, 2018, p E412.
11. Do K, Brown RE, Wharton S, Ardern CI, Kuk JL. Association between cardiorespiratory fitness and metabolic risk factors in a population with mild to severe obesity. BMC Obes. 5, 2018, p 5.
12. Mitu O, Roça M, Leon MM, Gherasim A, Graur M, Mitu F. Association of health-related quality of life with cardiovascular risk factors and subclinical atherosclerosis in non-diabetic asymptomatic adults. Biomedical Research. 27, no. 3, 2016, p 687-694.
13. Pescatello LS, Schifano ED, Ash GI, Panza GA, Corsi LML, Chen MH, Deshpande V, Zaleski A, Cilhoroz B, Farinatti P, Taylor BA, O'Neill RJ, Thompson PD. Deep-targeted sequencing of endothelial nitric oxide synthase gene exons uncovers exercise intensity and ethnicity-dependent associations with post-exercise hypotension. Physiol Rep. 5, no. 2, 2017, p e13510.
14. MacDonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. Eur J Nutr. 55, Suppl 2, 2016, p 17-23.
15. Lakshman R, Elks CE, Ong KK. Childhood obesity. Circulation. 126, no. 14, 2012, p 1770-9.
16. Lean Mej, Astrup A, Roberts SB. Making progress on the global crisis of obesity and weight management. BMJ. 361, 2018, p k2538.
17. Colberg SR, Sigal Rj, Yardley J, Ridell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 39, no. 11, 2016, p 2065-2079.

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