UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

DOCTORAL SCHOOL

OBESITY TREATMENT IN CHILDREN AND ADOLESCENTS

DOCTORAL THESIS

(Abstract)

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1. INTRODUCTION

Obesity is a chronic multi-etiological disease, but which can also be avoided [1]. Given the current worldwide spread of this disorder, the early therapeutic intervention in the treatment of this pathology is particularly important [2].

The key factor of the psycho-socio-medical intervention is the Family Physician who has an extremely important task, in the child and teenager growth, this way the obesity on a later stage can be avoided.

In this study we followed the evolution of children and adolescents identified with overweight and obesity at the family practitioner for a period of three years after the application of methods of prevention and a specific and individualized therapeutic management.

This Doctoral Thesis has two parts: the general part dealing with the current state of knowledge in the field of childhood obesity and our personal study which includes both research on the presence of predictive factors in the occurrence of obesity in children and adolescents registered in the primary clinical record, and evaluation of the evolution of excess weight in the group of children studied depending on the treatment applied.

This study could not have been completed without the special support that we have received during all these years from Mrs Florica Popescu, PhD Professor, the scientific supervisor of our Doctoral Thesis. We thank her for the guidance received, and also for her patience.

2. THE GENERAL PART particularly deals with the most important scientific knowledge on obesity in children and adolescents.

The first two chapters present the definition of obesity [3], the different methods to estimate body fat, the method of calculation of BMI, of percentile in the case of children, and also the standardization of nutritional status in children depending on the value of these parameters [4,5]; we dealt in this chapter with topical notions, such as adiposity rebound [6,7], body adiposity index and the newly proposed classification of obesity – EOSS (Edmonton Obesity Staging System) [8].

Chapter 3 contains epidemiological data on overweight and obesity in the world [9,10], in Europe [11,12] and in Romania [13].

Chapter 4 details the aetiology of obesity showing the main factors involved in the occurrence of excess weight [14]: genetic factors, congenital factors, sex – female/male, endocrine factors, infectious factors, psychological and behavioural factors, medication, social and environmental factors, physical inactivity; there are also presented topical data – obesogenic substances, sleep duration [15], gut microbiota [16,17].

Chapter 5 presents the morphological and physiological properties of the childhood obesity structure [18]. We presented the two types of adipose tissue: white adipose tissue and brown adipose tissue, adipose tissue development, the factors involved in adipocyte determination and differentiation, stages of obesity and the different types of obesity.

Chapter 6 discusses the mechanisms of the occurrence of obesity, by a description of the obesogenic environment, the eating behaviour and its mechanisms of control; we showed the role of food in the occurrence of obesity by its quantity and quality, and we detailed the importance of physical activity [19] and the mechanisms by which it influences body weight.

Chapter 7 describes the clinical and biological picture of obesity in children [20] and *Chapter 8* presents the short-term and long-term complications of this disorder in children and adolescents [21].

Chapter 9 presents the treatment of childhood obesity, *Chapter 10* deals with the pharmacokinetics of drugs in obese children [22,23,24], and *Chapter 11* looks over the main drugs used in obesity, classified by the mechanism of action and their general characteristics [25].

3. PERSONAL RESEARCH

Obesity is a disorder that occurs at any age, with multiple factors involved. There are factors that cannot be influenced (genetic predisposition, sex), but there are also factors over which we can intervene (food, physical activity level). There are predictive factors of obesity in adulthood and their identification and change during childhood and adolescence prevents disease in adulthood.

The study assumes that non-pharmacological treatment consisting of lifestyle change is the main therapeutic means for overweight and obesity in children and adolescents. The purpose of our Doctoral Thesis was to systematically identify

overweight and obesity in children and young people on a representative group and to apply, as earliest as possible, several effective methods of treatment.

We made an observational analytical study in order to examine the effectiveness of various therapeutic interventions in the case of children and adolescents with excess weight.

The main objectives of the study were to estimate the effectiveness of diet therapy compared with movement therapy. Evaluation of patients' evolution was conducted over a period of 3 years, at regular intervals: 6 months, 12 months, 18 months, 2 years, and 3 years.

3.1. Material and Methods Applied

The *material* studied was represented by the children and adolescents selected from the 1036 patients registered in the records of the family practitioner, Family Physician Dr. Bărbulescu Cristiana-Paula from Craiova [26]. It was established a sample of 48 children and adolescents with overweight and obesity who were followed for a period of 3 years, from January 2011 to December 2013. Patients were followed according to certain variables: age, sex, anthropometric indices, personal history and family history, eating behaviour, physical activity level, socioeconomic status, associated diseases. There were also used the results of laboratory tests. All these data were collected in worksheets, which then were centralized, statistically processed, thereby obtaining conclusions about the correlations between the different variables studied. There repeatedly took place educational meetings on food and physical activity according to the international standards and results were quantified after each medical examination. We had the patients or parents' approval for the study and also the approval of the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

3.2. Statistical Processing

Medical data obtained were statistically processed using Microsoft Office Excel programs in order to create the database and SPSS program (Statistical Package for Social Sciences) for the applied statistical analysis. It was performed the descriptive statistics and analytical statistics (comparison, correlation and

regression). Continuous variables are presented as means ± standard deviation, and discrete variables as number and / or percentage.

3.3. Research Results

The group studied was represented by the 202 children and adolescents aged between 0 – 19 years old, who are registered in the records of the family practitioner, divided into three age groups:

- Pre-school and primary (under the age of 11): 78 patients out of the 202 patients (38.61%);
- Secondary (under the age of 15): 53 patients out of the 202 patients (26.24%);
- Adolescent (from puberty until the completion of growth at 19 years old): 71 patients out of the 202 patients (35.15%).

Depending on the BMI value and the classification on growth curves we classified patients in:

- Underweight – BMI values below the 5th percentile;
- Normal weight – BMI values between the 5th and the 85th percentiles;
- Overweight – BMI values between the 86th respectively the 95th percentile;
- Obesity – BMI values exceeding the 95th percentile.

The next stage of the study was to select a sample of children and adolescents identified with excess weight – overweight or obesity.

We established a group of 48 children and adolescents, boys and girls, who met the inclusion criteria in the study – aged between 0 – 19 years old and with BMI > 85th.

After the explanations regarding the conduct of research, all the 48 patients identified as eligible agreed, with their parents, to participate in the study and signed the informed consent. In these patients there were identified the predictive factors of obesity through personal investigation, food investigation and physical activity investigation.

3.3.1. Analysis of the personal investigation results in the group of subjects with obesity and overweight

In the personal investigation we analyzed the family history of children identified with excess weight, their nutrition during their breastfeeding period – duration of breastfeeding, the age at which their food was diversified, the age at

which there were introduced into infant nutrition farinaceous products and animal protein from meat, by analyzing the relationship between BMI and these factors. We noticed that the short breastfeeding period, less than 4 months, and also the food diversification before the age of 4 months with the early introduction of farinaceous products (before 4 months) and the introduction of animal protein from meat before six months are factors that increase the BMI in children, so they are risk factors for obesity. Logistic regression was used in order to evaluate the association between obesity and birth weight, early diversification, short period of breastfeeding, the age of introduction of farinaceous products and meat into infant nutrition; we noticed that a short period of breastfeeding, less than 4 months, triples the risk of obesity, the early introduction of meat to feed the infant, before the age of 6 months, doubles the risk of obesity and the early introduction of farinaceous products, before the age of 4 months, increases the risk of obesity by 67%.

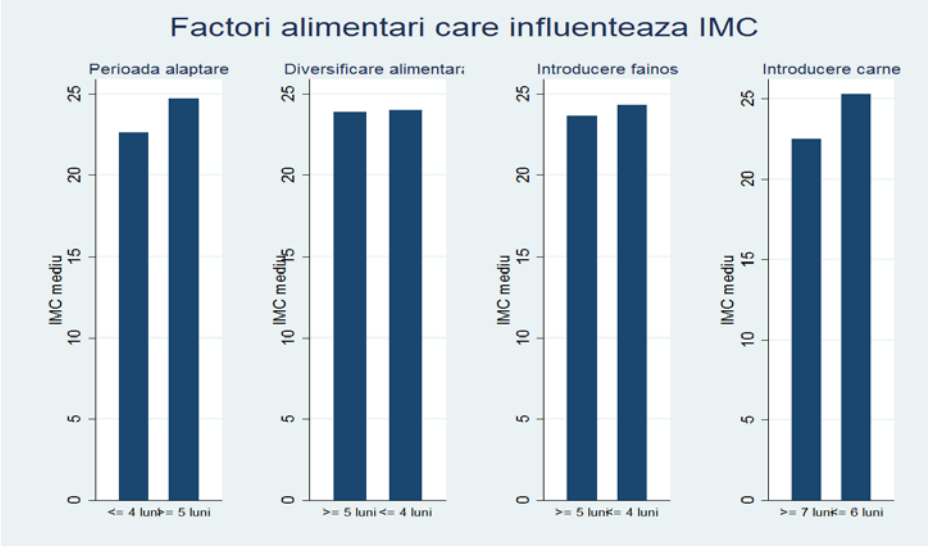


Fig.1. The influence of various food factors on BMI depending on the age of their introduction in infant nutrition

3.3.2. Analysis of the food investigation results in the group of subjects with obesity and overweight

The analysis of answers to questions in the food investigation questionnaire allowed us to have a view of the eating habits of the patients included in research. The study of the eating habits consisted of the analysis of the number of meals, the meals schedule – eating between meals, the portion size, the consumption of foods rich in fats and with a high glycemic index, the consumption of concentrated sweets and sweet drinks. We tried thereby to identify any errors in the nutrition of

participants in the study, but also to find out whether the families involved have notions about healthy eating. We noticed that males inversely influence BMI, the consumption of cold meats has a positive and statistically significant influence on the BMI value (p = 0.014), the consumption of sweet drinks has a positive and a highly statistically significant influence on BMI (p = 0.000), the low consumption of fruit has a direct and statistically significant influence on BMI (p = 0.006), the consumption of cereals has a positive and statistically significant influence on BMI (p = 0.002) and fats positively influence BMI, a statistically significant influence being in the case of solid fats (p = 0.012); also, the consumption of convenience food has a direct influence on BMI, but which is not statistically significant.

In the case of the consumption of juices we noticed that the BMI value sharply increases at a rate of 250 ml / day and continues to increase along with the increasing intake of sweet drinks, reaching a value of 27.6 BMI for a consumption of 500 ml of juice / day and a BMI value of 29.77 at a rate of 750 ml of juice / day (p = 0.000).

We found that any family did not have any notions about the *glycemic index* of food and its importance (0%), only 4 families (8.33%) had notions about *saturated and unsaturated fats* and about *dietary fibres* and only 11 families (22.92 %) read the *food labels* to find out information about their composition. Nutrition education elements were absent in most families interviewed reinforcing the idea that a lot of patients do not know the factors that may influence BMI, or if they know them, they do not pay any attention to them.

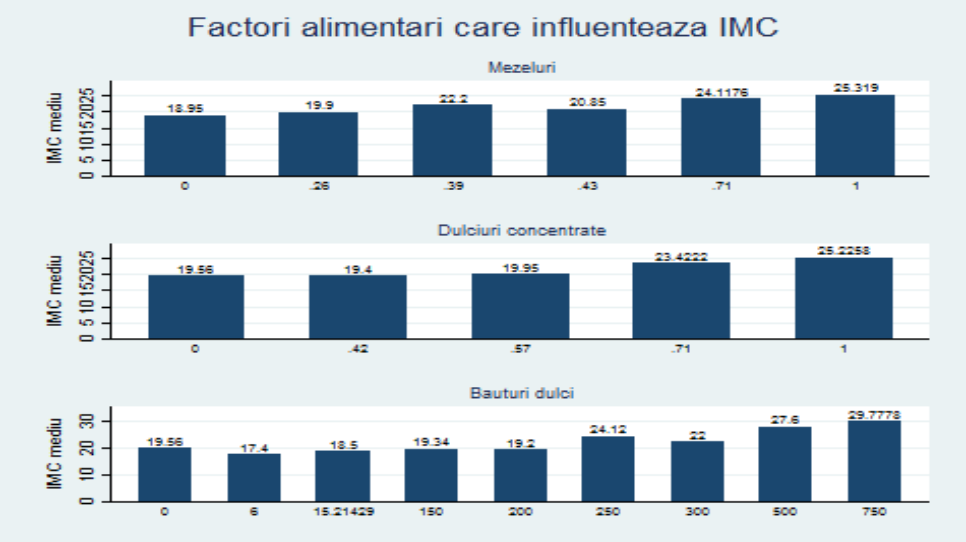
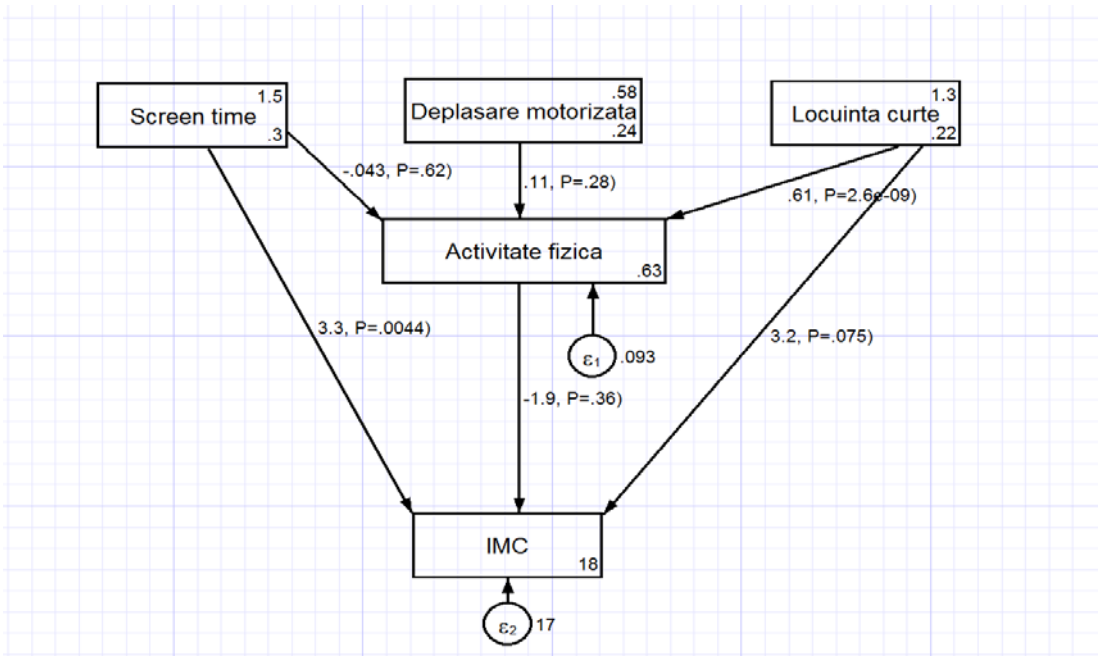


Fig.2. The influence of certain food factors on BMI

3.3.3. Analysis of the physical activity investigation results in the group of subjects with obesity and overweight

In order to quantify the physical activity of children and young people included in the study we created questionnaires on physical activity – these questionnaires set the rate of physical exercise did by patients every day, taking into account the housework, walking, physical activity at school, physical activity during leisure time, preferences for certain recreational activities.

By doing a multivariate analysis we obtained a SEM model showing that physical activity is inversely correlated with BMI, living in a house with yard positively influencing physical activity, $p < 0.00001$ so having a highly statistically significant influence; at the same time we noted that the screen-time has a positive and statistically significant influence on BMI ($p = 0.0044$) and it has a negative influence, but not statistically significant, on physical activity.



SEM Model 1. BMI Multivariate Analysis

3.3.4. Analysis of the psychosocial investigation results in the group of subjects with obesity and overweight

In the psychosocial investigation we analyzed sleep duration in the case of children with excess weight, their school results and circle of friends. We found that there is an inverse correlation between the BMI value and income per family member, and the higher is the BMI value, the lower is the income; We found an average BMI value of 24.86 in the case of children in whose families the income per

family member is below 600 RON / month and an average BMI value of 21.53 in the case of children in whose families the average income is higher than 600 RON / month; the difference of 3.33 BMI points is highly statistically significant (p = 0.027).

Another factor analyzed in the psychosocial investigation was the education attainment level of the parents of children with overweight and obesity; we found that there is an inverse correlation between BMI and education attainment level, BMI having a higher value if parents have primary education: average BMI of 26.66 +/- 6.56 in the case of children whose parents have primary education, average BMI of 24.50 +/- 4.16 in the case of children whose parents have secondary education and average BMI of 21.47 +/- 4.12 in the case of children whose parents have higher education; p = 0.0460 indicates a statistically significant difference between the 3 groups.

3.3.5. Analysis of the clinical and paraclinical evaluation of the group of subjects with obesity and overweight

When registering children with overweight and obesity, we determined fasting blood sugar, lipid profile, liver transaminases; CRP, ESR and fibrinogen in order to identify an inflammatory process witnessing early atherosclerosis lesions. We determined *apolipoprotein B as a marker of atherogenic lipoproteins concentration and realized leptin dosing in patients diagnosed with obesity*. By comparatively analyzing the values of CT, LDL-cholesterol, HDL-cholesterol and BMI value we noticed that total cholesterol values are positively correlated with BMI in all age groups, both girls and boys; LDL-cholesterol average values are positively correlated with BMI, the correlation being statistically significant in the case of patients who are both girls and boys from the age group of 15-19 years old (p = 0.0092 in girls and p = 0.0005 in boys); HDL-cholesterol average value is negatively correlated with BMI in all age groups in both sexes; in the case of TG we noticed that the values recorded in all obese patients were higher than those recorded in overweight patients, the difference being statistically significant (p = 0.0163) in the case of boys from the age group of 15-19 years old; TG average value was positively correlated with BMI value, a statistically significant value being obtained in the case of the boys group of 15-19 years old; inflammation markers represented by ESR and CRP had values positively correlated with BMI in all age groups. Apolipoprotein B value increases with age and is positively correlated with BMI in all age groups, both in the case of girls and boys; values are higher in obese patients compared to overweight patients, the difference

being statistically significant in the case of girls groups of 0-10 years old ($p = 0.0030$), girls of 15-19 years old ($p = 0.0001$) and boys of 0-10 years old ($p = 0.001$). Leptin determined in children and adolescents with obesity significantly increased with age, in the age group of 11-14 years old with double value compared to the age group of 0-10 years old and being three times higher than the average value in the age group of 15-19 years old compared to the age group of 0-10 years old.

3.4. Individualized Therapeutic Management

Therapeutic management of obesity initially involved a patient evaluation (degree of obesity, general health situation) and then the management of obesity with weight loss and then maintenance of the weight gained. The treatment was individualized, being adapted to the child's age, his / her growth and development needs, and also to the family's socio-economic and cultural level.

Dietary treatment was aimed at achieving some changes in the eating habits of the child / adolescent and his / her family; the objectives were to choose healthy food, to control food intake, to understand notions of nutrition – hunger, satiety, pleasure; we insisted on the fact that diets are not recommended and we did not forbid any type of food / food group.

Treatment by physical activity was aimed at changing habits related to the physical activity of the child / adolescent and his / her family [27]; the objectives were to increase physical activity – travel, games, relaxing methods, sports and reducing sedentary lifestyle – Decreasing the time spent in front of the screen [28,29]. A total of 16 patients (33.33%) agreed to attend a sporting activity into an organized environment, under specialized guidance – sports clubs.

3.5. Analysis of patients' evolution

Patients' follow-up was performed every 3 months, 6 months, 12 months, 18 months, 2 years and 3 years; at each medical examination there were determined height and weight, BMI was calculated and it was made the classification on growth curves – the same curves as at the beginning of the study; this allowed us to study the patients' evolution in time according to the therapeutic methods used – food change and / or movement therapy.

We noticed that during the study the patients' BMI in the sample studied recorded a decrease in its average value – calculating BMI at 3 years resulted in an

average value of 22.8646, with 1.09167 points lower than the initial average value of 23.9563; BMI decreased after the first 3 months, even if it had a low value of 0.0855 BMI points; its value continued to decrease reaching a minimum value of 22.7979 after 2 years of follow-up; the highest decrease occurred after 1 year of individualized treatment – a decrease of 0.3084 BMI points between 1 year and 1 year and a half since the beginning of the therapeutic intervention; BMI had an average quarterly decrease of 0.1365 points.

If initially there were 25 patients with obesity, in the end there were only 6 obese patients; in the case of overweight there were 23 patients initially registered, and in the end there were only 18 overweight patients. In conclusion, half of the patients who took part in the study gained normal weight according to their age and sex, and of the 24 patients remaining with excess weight only 6 are obese, the rest being overweight. In all cases we noticed that weight began to fluctuate after 6 months (6 months after the beginning of the study most patients had almost the same BMI and percentile values) and it was stabilized after two years.

All patients who did sport gained normal weight.

3.6. Conclusions

1. Childhood obesity is not considered to be a disease – none of the patients in the study sample went to medical examination due to excess weight.
2. In the study there were analyzed cases of common obesity, there were not any cases of secondary / syndromic obesity.
3. Excess weight had a higher prevalence in women compared to men, statistically significant difference ($p = 0.020$).
4. Obesity had a higher prevalence in girls (64.52%), while overweight had a higher prevalence in boys (70.59%).
5. The prevalence of overweight and obesity was higher in the age group of 0-10 years old.
6. The presence of parent obesity was identified in 66.66% of cases.
7. Among the personal factors, the period of breastfeeding and the early diversification had an increased risk of obesity (the period of breastfeeding less than 4 months and the food diversification before 5 months). The early introduction of farinaceous products (before 4 months) and the introduction of

animal protein from meat before 6 months were factors that led to an increased BMI in children, so they are risk factors of obesity.

8. An eating behaviour including eating errors was identified in all cases (100%).
9. Among the food factors, the consumption of solid fats such as processed pork fat such as lard and margarine had a high risk – the highest BMI value = 26.22 was found in children who used to eat pork fat, followed by BMI = 26.04 in those who use to eat margarine and BMI = 21.13 in those who use to eat butter.
10. Low consumption of fruit was associated with a higher BMI, the optimal consumption being of 3 portions / day.
11. In the case of consumption of sweet drinks it was noticed that BMI value sharply increases at a rate of 250 ml / day and continues to increase along with an increased consumption of sweet drinks, reaching a value of 27.6 for a consumption of 500 ml of juice / day and a value of 29.77 at a rate of 750 ml of juice / day.
12. Analyzing BMI value based on the consumption of cold meats, it was found that in the case of children who eat cold meats every day BMI has an average value of 25.32, not very different from that of children who eat cold meats 5 days / week – 24.11, but much higher than that found in children who eat cold meats only 2 times / week – 19.9 (a difference of 5.42 BMI points, statistically significant: $p = 0.014$).
13. Sedentary behaviour prevailed in the group (71% of subjects).
14. Any patient, child or adolescent, with overweight or obesity did not do a sporting activity.
15. BMI value was statistically significant higher in children who had medical exemption – which demonstrates the importance of sport in school.
16. There is a direct correlation between BMI and the number of hours spent in front of the screen (TV, tablet, etc.): the highest BMI value had children who spent more than 4 hours / day in front of the screen; the difference in BMI between children with a screen-time shorter than 2 hours / day and those with more than 4 hours / day is statistically significant ($p = 0.0051$).
17. Walking to school influences BMI by decreasing its value.

18. Living in a house with yard influences BMI – living in a house with yard resulted in an increase of physical activity by about 28 min / day which led to a decrease in BMI.
19. Living in a block of flats / house with yard is correlated with the duration of screen-time, patients who live in a block of flats spending more time in front of a screen compared to those living in a house with yard, a highly statistically significant difference ($p = 0.00001$).
20. The parents' education attainment level influences children's BMI – there was an inverse correlation between BMI and education attainment level, BMI having a higher value if parents have primary education (average BMI of 26.66 + / - 6.56 in the case of children whose parents have primary education, average BMI of 24.50 +/- 4.16 in the case of children whose parents have secondary education and average BMI of 21.47 +/- 4.12 in the case of children whose parents have higher education; $p = 0.0460$ indicates a statistically significant difference between the 3 groups).
21. Family income and income per family member influences BMI – there was an inverse correlation between the BMI value and income per family member, and the higher is the BMI value, the lower is the income. We found an average BMI value of 24.86 in the case of children in whose families the income per family member is below 600 RON / month and an average BMI value of 21.53 in the case of children in whose families the average income is higher than 600 RON / month; the difference of 3.33 BMI points is statistically significant ($p = 0.027$).
22. Sleep duration influences BMI – in the case of obese children sleep duration was on average of 8.68 hours / night, shorter with 50 minutes than the average sleep duration of overweight children; there is a positive correlation between BMI and decreased sleep duration.
23. Cholesterol and complications such as hepatic steatosis / hepatic cytolysis were found in adolescents, so after a period of time since the occurrence of obesity.
24. There were not found any cases of obesity with metabolic syndrome (high blood pressure, dyslipidemia, hyperleptinemia, carbohydrate metabolism disorders with high blood sugar).
25. Biological inflammatory syndrome was found in 30 cases (66.56%).

26. After a 3-years management of the obesogenic syndrome in children and adolescents in the group, the evolution was favourable in all cases, all patients in the study finally coming under in a lower percentile.
27. A significant decrease occurred in the case of children who did an intense physical activity of at least 120 min / week.
28. All children or adolescents who did a sporting activity gained normal weight at the end of the study (100% of the children in the subgroup who did physical activity, so movement therapy).
29. A study on individual cases of children and adolescents with conduct disorder, followed for 1 year, who were treated with neuroleptics showed that sedative neuroleptics such as levomepromazine result in a more marked increase in weight and especially in waist circumference compared to other types of neuroleptics from the second generation (olanzapine, quetiapine, risperidone, amisulpride).
30. However, the low number of cases does not allow us to say that the sedative neuroleptics group is more likely to generate a significantly higher weight gain because comparison is made with a group of neuroleptics from the second generation with different capacities to determine weight gain (olanzapine > quetiapine > amisulpride > risperidone).
31. Following the results obtained we can mention that considering the obesogenic syndrome as a disease, the role of the family physician has a great influence on the subsequent evolution to obese adult and non-pharmacological therapeutic management in primary care has an important role in the case of children and adolescents.
32. At the same time, in the management of this syndrome together with the physician there should be also actively involved parents, educational factors (school) and children or adolescents.
33. Our study is among the few studies that analyze obesogenic syndrome in a group of children and adolescents both as regards the anthropometric development and BMI and also the biological changes, being the first study of this kind in the country.

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