

METABOLIC SYNDROME IN CHILDREN

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ABSTRACT

Introduction. The worldwide alarming rise in the incidence of metabolic syndrome (MS) in children has made the prevention and early treatment of obesity an important medical goal.

The objective of the study was to assess the role of proinflammatory markers, such as tumour necrosis factor-alpha (TNF- α) and high-sensitivity C-reactive protein (hs-CRP), and adipokines (leptin, adiponectin) in the development of MS in children and the impact of treatment with gastrointestinal lipase inhibitors on the degree of obesity and blood pressure values.

Material and methods. The study included 24 children with metabolic syndrome. The serum values of leptine, adiponectin, TNF- α and hs-CRP were determined in children with MS compared to a control group of 50 children of similar age.

Results. The serum level of leptin, hs-CRP, and TNF- α was higher in children with MS as compared with the control group. The adiponectin level was lower in children with MS, compared to the control group. After eight weeks of drug treatment with gastrointestinal lipase inhibitors in all children, a decrease in body mass index, abdominal circumference and blood pressure values was found, but the most important decreases were found in children who received non-pharmacological treatment in combination with

RÉSUMÉ

Syndrome métabolique chez l'enfant

Introduction. L'augmentation alarmante du syndrome métabolique (SM) chez les enfants dans le monde entier a fait de la prévention et du traitement précoce de l'obésité un objectif médical important.

L'objectif de l'étude a été d'évaluer le rôle des marqueurs pro-inflammatoires (IL-6, TNF α , hs-PCR) et adipokines (leptine, adiponectine) dans le développement du syndrome métabolique chez les enfants et impacts du traitement par inhibiteurs gastro-intestinaux de la lipase sur le degré d'obésité et les valeurs de la pression artérielle.

Matériel et méthodes. L'étude a inclus 24 enfants atteints du syndrome métabolique. Les niveaux sériques de lépine, adiponectine, TNF- α et hs-CRP ont été mesurés chez les enfants atteints du SM par rapport à un groupe témoin de 50 enfants d'âge similaire, normotendus et de poids normal. On a également examiné l'impact du traitement par des inhibiteurs de la lipase gastro-intestinale sur l'obésité et sur les valeurs de la pression artérielle.

Résultats. Le taux sérique de leptine, de hs-CRP, de TNF- α s'est avéré plus élevé, et celui de l'adiponectine plus faible chez les enfants atteints de SEP, par rapport au groupe témoin. Après huit semaines de traitement

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gastrointestinal lipase inhibitors and angiotensin-converting enzyme inhibitors.

Conclusions. Hypoadiponectinemia, hyperleptinemia, increased serum hs-CRP and TNF- α suggest that these adipokines/cytokines contribute to subclinical inflammation in children with MS and may also serve as biomarkers of MS. In combination with a low-calorie diet, regular exercise and lifestyle changes, treatment with gastrointestinal lipase inhibitors may help to reduce the prevalence of obesity and hypertension in children.

Keywords: metabolic syndrome, children, gastrointestinal lipase inhibitors, obesity, hypertension.

List of abbreviations:

MS – metabolic syndrome
TNF- α – tumour necrosis factor-alpha
hs-CRP – high-sensitivity C-reactive protein
IDF – International Diabetes Federation
LDL-C – low-density lipoprotein cholesterol
HDL-C – high-density lipoprotein cholesterol
BMI – body mass index
HOMA-IR – Homeostatic Model Assessment of Insulin Resistance
ELISA – enzyme-linked immunosorbent assay
AC – abdominal circumference
ACE – angiotensin-converting enzyme
SBP – systolic blood pressure
DBP – diastolic blood pressure

INTRODUCTION

The worldwide alarming rise in the incidence of metabolic syndrome (MS) in children has made the prevention and early treatment of obesity an important medical goal. The International Diabetes Federation (IDF) definition of MS in children is inspired, in part, by the definition of MS in adults. However, the definition of MS in children takes into consideration the age groups, due to age-related differences. IDF suggests that the MS should not be diagnosed in children younger than 10 years, but a strong indication for weight reduction should be done for those with abdominal obesity. For children aged more than 10 years, the diagnosis of MS can be established in the presence of abdominal obesity plus at least two or the following criteria: elevated triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), high blood pressure, increased plasma glucose. In the absence of contemporary definitive data, the criteria adhere to the absolute values in the IDF adult definition of MS, except that the use of waist circumference percentiles is recommended

avec inhibiteurs de la lipase gastro-intestinale chez tous les enfants, une diminution de l'indice de masse corporelle, de la circonférence abdominale et des niveaux de pression artérielle a été trouvée, mais les diminutions les plus importantes ont été trouvées chez les enfants qui ont reçu un traitement non pharmacologique en combinaison avec des inhibiteurs de la lipase gastro-intestinale et des inhibiteurs de l'enzyme de conversion de l'angiotensine.

Conclusions. L'hypoadiponectinémie, l'hyperleptinémie et l'augmentation des hs-CRP et TNF- α sériques suggèrent que ces adipokines/cytokines contribuent à l'inflammation sous-clinique chez les enfants atteints de SM et peuvent également servir de biomarqueurs de la SM. En combinaison avec un régime hypocalorique, les exercices réguliers et des changements de comportement, le traitement par les inhibiteurs de la lipase gastro-intestinale peut aider à réduire la prévalence de l'obésité et hypertension.

Mots-clés: syndrome métabolique, enfants, inhibiteurs de la lipase gastro-intestinale, obésité, hypertension.

and one (rather than a sex-specific) cut-off is used for HDL-C levels. For children older than 16 years, the IDF adult criteria can be used¹.

MS can be associated with other comorbidities, including non-alcoholic fatty liver disease (NAFLD), diseases of the reproductive system, etc^{2,3}. Most studies have found that MS is associated with a high risk of cardiovascular disease and a 5-fold increased risk of type 2 diabetes⁴. In a study involving 1,930 children, 545 (28.2%) were overweight or obese, and the overall prevalence of MS was 21.8% (11% in children aged 6-10 years and 30.6% in children aged 11-16 years). A family history of cardiovascular disease, diabetes, obesity and hypertension was present in 42.7% of patients³.

Lifestyle changes and weight loss is the first step in preventing or treating MS. The fight against childhood obesity is also the best way to reduce the number of premature deaths caused by atherosclerotic cardiovascular diseases. Lowering the body mass index (BMI) in obese patients is also needed to improve physical and mental health, as well as quality of life⁵.

The main therapeutic means for childhood obesity are lifestyle changes. However, with traditional treatment methods, only 10% of obese patients can achieve a decrease in body weight. A higher efficacy in fighting obesity can be achieved by combining lifestyle changes with pharmacological treatment. However, pharmacological interventions in children are limited by certain side effects. The combined treatment would facilitate the decrease of body weight, which will subsequently result in the reduction of blood pressure values and lower need for antihypertensive medication. The only drug indicated by the Food and Drug Administration (FDA) for the treatment of childhood obesity is orlistat, a gastrointestinal lipase inhibitor⁶⁻⁸.

THE OBJECTIVE OF STUDY was to assess the role of proinflammatory markers (TNF- α , hs-CRP) and adipokines (leptin, adiponectin) in the development of metabolic syndrome in children and the impact of treatment with gastrointestinal lipase inhibitors on the degree of obesity and blood pressure values.

MATERIAL AND METHODS

The study is part of the research project entitled „*Evolutionary aspects of metabolic syndrome in children treated with gastrointestinal lipase inhibitors*“, number 20.80009.8007.33, of the State Program 2020-2023, and was conducted in the Pediatric Cardiology Department of the Institute of Cardiology, Chisinau, Republic of Moldova, between January 2020-December 2020. The study protocol was approved by the Medical Ethics Committee of the Institute of Cardiology (protocol no. 2, 20th of February, 2020) and written informed consent was obtained from the parents of children included in the study.

The criteria for inclusion in the study: children with MS, aged between 10-18 years, diagnosed according to the IDF criteria (2007)¹. The exclusion criteria from the study were age <10 years, treatment with

medication that may affect blood pressure, children who have experienced an acute infectious disease or exacerbation of a chronic illness in the previous 6-8 weeks.

The study included 24 children with MS. The female/male ratio was 1/1. The lipid profile (total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides), carbohydrate profile (fasting blood glucose, serum insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index), TNF- α , hs-CRP, leptin and adiponectin were determined. Their values were analyzed in comparison with the control group, consisting of 50 children of similar age, normotensive, with normal weight.

Student's test was used to estimate the differences between the two groups. The differences were considered statistically significant for $p < 0.05$.

TNF- α , leptin and adiponectin were assessed by the enzyme-linked immunosorbent assay (ELISA), hs-CRP by latex-immunoturbidimetry method, and serum insulin by immunochemical method with detection by electrochemiluminescence (ECLIA).

The children from the study were divided in three groups: group 1 - two children who received non-pharmacological treatment and ACE inhibitors (lisinopril - starting dose 0.08-0.6 mg/kg, daily), group 2 - 11 children who received non-pharmacological treatment and gastrointestinal lipase inhibitors (one capsule of orlistat 120 mg three times a day, during or up to one hour after meal) and group 3 - 11 children who received non-pharmacological treatment, gastrointestinal lipase inhibitors (one capsule orlistat 120 mg three times a day, during or up to one hour after the meal) and ACE inhibitors (lisinopril - starting dose 0.08-0.6 mg/kg, daily).

RESULTS

From the MS components, hypertriglyceridemia was encountered in 66.7% of cases, low levels of HDL-C in 62.5% of cases, and increased fasting

Table 1. The distribution of components of MS in the group of study.

Components of the metabolic syndrome		Value	N	%
Triglycerides (mmol/L)		<1.7	8	33.3
		≥ 1.7	16	66.7
HDL - C (mmol/L)	10-16 years	<1.03	9	37.5
	≥ 16 years	<1.03 boys, <1.29 girls	15	62,5
Systolic blood pressure (SBP) (mmHg)		<130	11	45.8
		≥ 130	13	54.2
Fasting glucose (mmol/L)		<5.6	9	37.5
		≥ 5.6	15	62.5

Table 2. Lipid profile in children with MS versus the control group.

	Group of study		Control group		p
	Mean	Std. error mean	Mean	Std. error mean	
Total cholesterol (mmol/L)	4.48	0.048	4.22	0.172	>0.05
LDL-C (mmol/L)	2.80	0.13	1.73	0.043	<0.001
HDL-C (mmol/L)	0.93	0.059	1.82	0.021	<0.001
Triglycerides (mmol/L)	1.83	0.179	0.97	0.039	<0.001

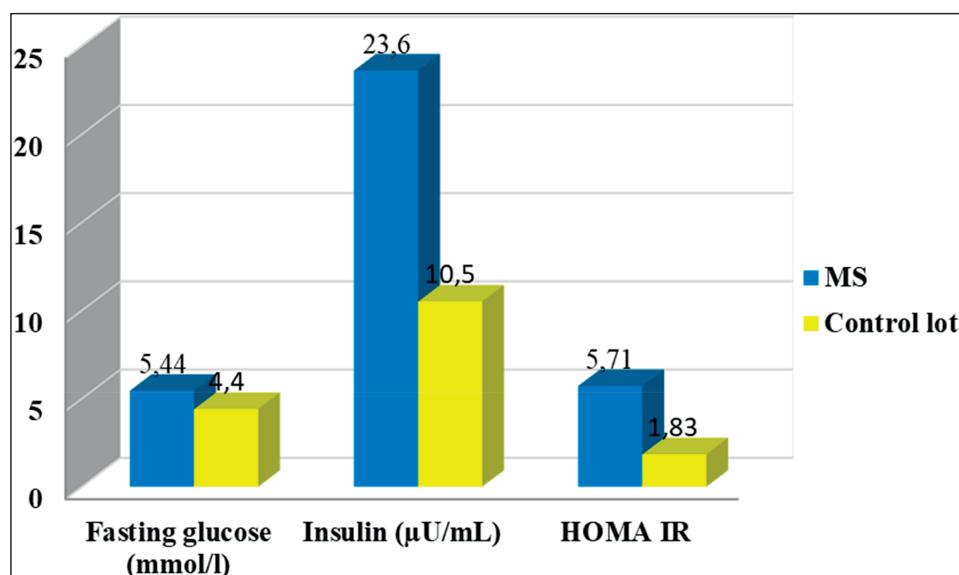


Figure 1. Carbohydrate profile in children with MS versus the control group.

blood glucose and hypertension were registered in 54% of cases (Table 1).

Regarding the lipid profile, LDL-C values were significantly higher in children with MS, compared to the control group (2.80 ± 0.13 vs 1.73 ± 0.04 mmol/L, $p < 0.001$), HDL-C were lower in children with MS compared to the control group (0.93 ± 0.059 vs 1.82 ± 0.21 mmol/L, $p < 0.001$), and triglycerides were higher in children with MS versus the control group (1.83 ± 0.179 vs 0.97 ± 0.039 mmol/L, $p < 0.001$). Hypertriglyceridemia was encountered in 16 patients (66.7%) and low HDL-C in 15 patients (62.5%) (Table 2).

Although the mean fasting serum glucose (5.44 ± 0.114 vs 4.40 ± 0.096 mmol/L) in children with MS did not exceed the reference value (5.6 mmol/L)¹, it was higher in children with MS compared to the children of the control group. Fifteen children (62.5%) had a fasting blood glucose ≥ 5.6 mmol/L. Both mean values of serum insulin (23.57 ± 1.96 vs 14.77 ± 1.031 µU/mL) and HOMA-IR (5.71 ± 2.49 vs 1.83 ± 0.76) were higher in children with MS, compared to the control group (Figure 1).

Serum insulin was positively correlated, statistically significant, with HOMA-IR index ($r = +0.97$; $p < 0.01$), BMI ($r = +0.56$; $p < 0.01$), abdominal

circumference (AC) ($r = +0.48$; $p < 0.05$), leptin ($r = +0.68$; $p < 0.01$) and systolic blood pressure (SBP) ($r = +0.42$; $p < 0.05$).

Mean serum leptine values (35.79 ± 3.81 vs 7.93 ± 0.23 ng/mL) were higher, and those of adiponec-tin (5.65 ± 0.56 vs 10.95 ± 0.41 ng/mL) lower in children with MS, compared to the control group (Figure 2). Also, hs-CRP (2.91 ± 0.561 vs 0.23 ± 0.013 pg/mL) and TNF- α (8.80 ± 0.47 vs 3.12 ± 0.10 mg/pL) mean values were higher in children with MS, compared to the control group, meaning that these children have a high risk for cardiovascular diseases (Figure 3).

Leptin correlated positively, statistically significant, with BMI ($r = +0.46$; $p < 0.05$), AC ($r = +0.54$; $p < 0.01$), HOMA-IR index ($r = +0.66$; $p < 0.01$), serum insulin ($r = +0.68$; $p < 0.01$), hs-CRP ($r = +0.49$; $p < 0.05$), and SBP ($r = +0.45$; $p < 0.05$), and adiponec-tin was negatively correlated with CA ($r = -0.45$; $p < 0.05$). hs-CRP correlated positively, statistically significant, with LDL-C ($r = +0.53$; $p < 0.01$) and IL-6 ($r = +0.64$; $p < 0.01$) (Figure 4).

The BMI correlated positively, statistically significant, with the HOMA-IR index ($r = +0.54$; $p < 0.01$), AC ($r = +0.65$; $p < 0.01$), serum insulin ($r = +0.56$; $p < 0.01$) and serum leptin ($r = +0.46$; $p < 0.05$).

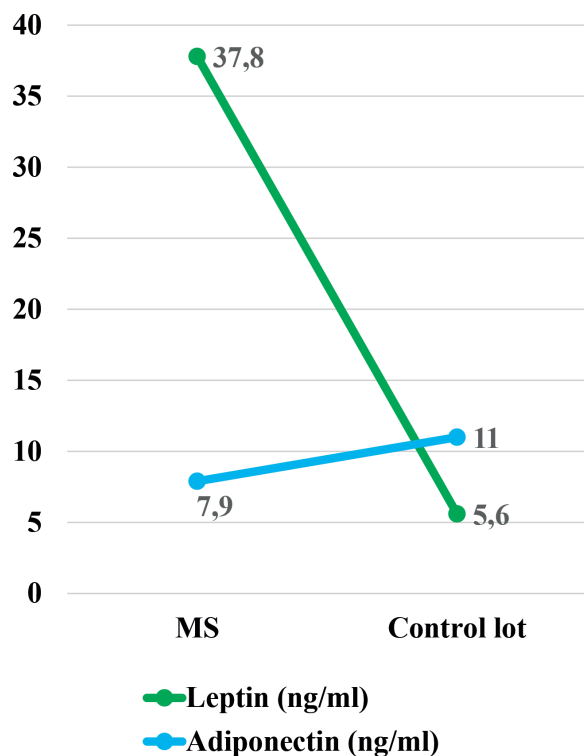


Figure 2. Comparative values of adipokines/cytokines.

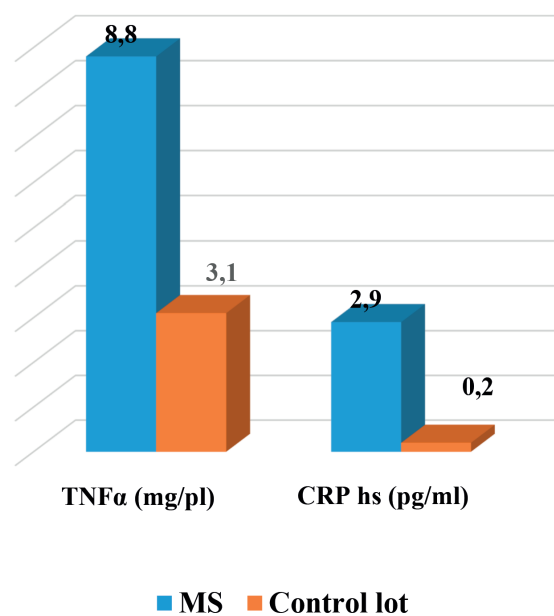


Figure 3. Comparative values of TNF- α and hs-CRP.

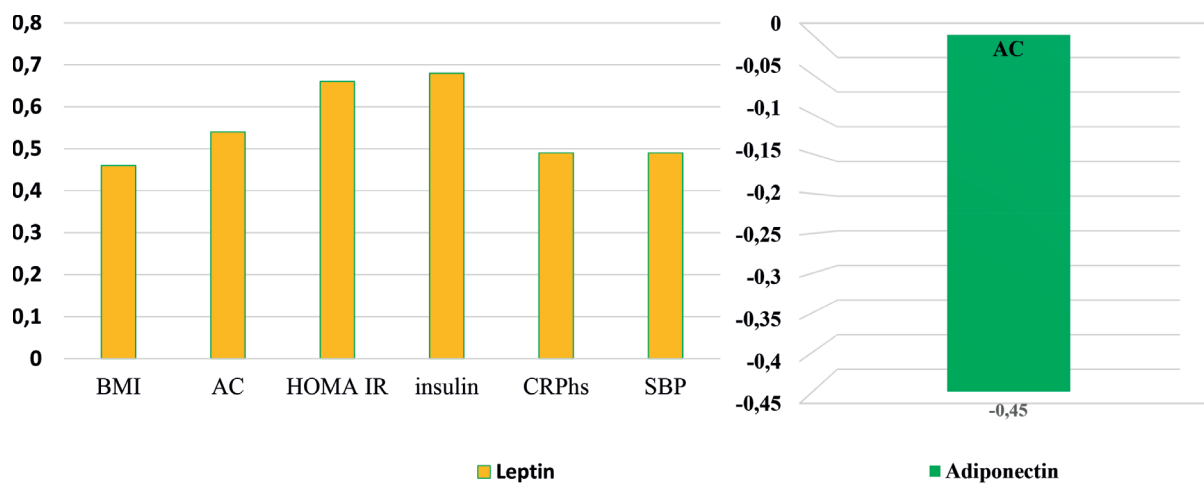


Figure 4. Statistically significant correlations of leptin and adiponectin.

Abdominal obesity correlated positively, statistically significant, with HOMA-IR ($r=+0.45$; $p<0.05$), BMI ($r=+0.59$; $p<0.01$), serum insulin ($r=+0.48$; $p<0.05$), serum leptin ($r=+0.54$; $p<0.01$) and SBP values ($r=+0.59$; $p<0.01$). AC also correlated negatively, statistically significant, with serum adiponectin ($r=-0.45$; $p<0.05$).

Although the study does not allow to draw definite conclusions, because of the small number of children included in the research so far, as well as because of the inhomogeneity of the research groups, we found that, regardless of the medication

administered, all drug combination formulas have contributed to the decrease of body weight (Mean = -6.61 , Std. error mean ± 1.70 ; $p<0.01$), AC (Mean = -4.88 , Std. error mean ± 0.82 ; $p<0.001$), SBP (Mean = -11.46 , Std. error mean ± 2.24 ; $p<0.001$) and BMI (Mean = -2.38 , Std. error mean ± 0.64 ; $p<0.01$) after 8 weeks of treatment. The most important decreases were found in group 3 - children who received non-pharmacological treatment, gastrointestinal lipase inhibitors and ACE inhibitors, although statistical significance was obtained only for SBP values (Tables 3 and 4).

Table 3. Dynamic evaluation of anthropometric parameters and blood pressure values under treatment in children with MS.

	Mean	Std. error mean	p
Body weight	-6.61	1.70	<0.01
AC	-4.88	0.82	<0.001
SBP	-11.46	2.24	<0.001
DBP	-3.42	1.34	<0.05
BMI	-2.38	0.64	<0.01

Table 4. Comparative dynamic evaluation of anthropometric parameters and blood pressure values according to the treatment administered.

	Group 1			Group 2			Group 3			F	p
	N	Mean	Std. error mean	N	Mean	Std. error mean	N	Mean	Std. error mean		
Body weight	2	-3	2	11	-3.97	1.04	11	-9.91	3.38	1.693	>0.05
AC	2	-4	1	11	-4.27	1.55	11	-5.64	0.90	0.352	>0.05
SBP	2	-5.5	5.5	11	-3.82	2.48	11	-20.18	2,09	13.366	<0.001
DBP	2	+2	2	11	-5.73	1.51	11	-2.09	2.31	1.695	>0.05
BMI	2	-1.20	0.88	11	-1.41	0.36	11	-3.57	1.29	1.515	>0.05

DISCUSSION

Different definitions of MS have prevented the development of a consensus for diagnostic criteria in the pediatric population. Children with MS have an increased risk of MS in adulthood and possibly an increased risk of type 2 diabetes and cardiovascular disease. Thus, it has become crucial to identify MS in children as early as possible by using non-invasive biomarkers. Due to the fact that the pathogenesis of abdominal obesity is mediated by the adipocytes production of biologically active molecules (adipokines), they could serve as diagnostic biomarkers of MS. In children with abdominal obesity, the synthesis of these adipokines is affected: the secretion of proinflammatory adipokines is increased, while that of anti-inflammatory ones is reduced. Leptin is the first adipocytokine identified. It is a product of the obesity gene and is known as the “satiety hormone” because it decreases food intake and increases energy expenditure. The leptin concentration has been shown to reflect body fat mass and can therefore be considered a reliable marker of adipose tissue mass and energy homeostasis in people who are not insulin resistant⁹. Obese people not only tend to have elevated plasma levels of leptin, but are also resistant to leptin, denying the beneficial effects of leptin. Some studies have found a positive association between fat mass and leptin concentration in children¹⁰. Moreover, leptin is positively associated with insulin resistance in pre-pubertal children after adjusting for sex, age and BMI, and for each 1 ng/

dL increase in leptin level, the chances of developing MS increase by 3%, which suggests an important role for leptin as a marker of cardiovascular risk and metabolic diseases¹⁰. In our research, the serum values of leptin were higher in children with MS, compared to the control group.

Adiponectin is another adipocytokine secreted mainly by the adipocyte and is actually decreased in plasma after an increase in adipose tissue mass. Adiponectin has several functions, including anti-inflammatory and anti-atherogenic effects, as well as insulin sensitization and lipid regulation⁹. Studies have found that plasma adiponectin level is inversely correlated with BMI, AC, fasting insulin level and insulin resistance, and is 25% higher in healthy overweight girls compared to those with MS¹¹. Another study involving 5,088 adolescents found that a decrease in adiponectin concentration was associated with an increased risk of MS, regardless of age, BMI, AC and total cholesterol¹². In our research, the serum values of adiponectin were lower in children with MS, compared to the control group. At the same time, serum adiponectin correlated negatively with AC ($r=-0.45$, $p<0.05$).

The proinflammatory status of children with MS can be clinically recognized by variable increases in hs-CRP, frequently encountered in patients with MS. The excess of adipose tissue in obese children releases inflammatory cytokines that lead to the proinflammatory state⁹. Elevated hs-CRP levels in obese subjects could be explained by the expression of cytokine interleukin-6 (IL-6) in adipose tissue and its

release into the circulation. IL-6 is a proinflammatory cytokine that stimulates the production of CRP in the liver. Furthermore, TNF- α and IL-6, secreted by fat cells, and hs-CRP have been associated with obesity and other cardiovascular risk factors^{6,13}. In our research, children with MS had hs-CRP and TNF- α values higher than the control group. At the same time, hs-CRP in our research correlated positively, statistically significant, with LDL-C and IL-6.

The detection of cardiometabolic risk factors (hypertension, dyslipidemia, diabetes) should be performed in all obese children, in order to intervene as early as possible. The National Heart, Lung, and Blood Institute group of experts recommends lipid profile screening for all children aged ≥ 2 years with BMI $\geq 85^{\text{th}}$ ¹⁴. The American Diabetes Association recommends screening for type 2 diabetes in young people who are overweight/obese and who have at least two additional risk factors¹⁵.

Changing diet and lifestyle is the cornerstone of obesity management. The positive effect of weight loss on improving cardiometabolic risk factors has been demonstrated in several randomized controlled trials. In one study, a weight loss of $\sim 1\text{kg/m}^2$ of BMI with an intense lifestyle change reduced serum glucose over two hours in 42% of young people, compared to 7% by the standard of care¹⁶. Another meta-analysis of 133 randomized controlled trials in young people found that a modest weight loss (5-7% of initial body weight) was sufficient to improve lipid profile and SBP and may help prevent or delay the appearance of future adult cardiovascular diseases¹⁷. Regarding the drug treatment of obesity, the Endocrine Society Clinical Practice Guidelines (2017) recommend pharmacotherapy for children after a formal program of intense lifestyle changes has failed to limit weight gain or improve comorbidities. In addition, lifestyle changes should be continued in parallel with pharmacotherapy⁶. Orlistat, a lipase inhibitor, is the only FDA-approved drug for weight loss in children over 12 years of age who are overweight/obese⁷. In some studies, orlistat has been associated with a modest improvement in blood pressure, but its cumulative effect on reducing cardiometabolic disease remains to be elucidated. At the same time, despite the benefits of medication, lifestyle changes must be sustained during treatment⁸.

Further research is needed to optimize the clinical approaches of prevention, screening and pharmacological treatment of pediatric obesity.

Limitations of the study: the small number of patients included in the study at this stage, as well as the numerical inhomogeneity of the children in the research groups.

CONCLUSIONS

Hypoadiponectinemia, hyperleptinemia, and increased serum hs-CRP and TNF- α suggest that these adipokines/cytokines contribute to subclinical inflammation in children with MS and may also serve as biomarkers of MS. In combination with a low-calorie diet, regular exercise and behavioral changes, treatment with gastrointestinal lipase inhibitors may help to reduce obesity and hypertension, respectively.

Author Contributions:

N.M., S.C., L.B.T., were responsible for clinical diagnosis, paraclinical investigations, treatment decisions and follow up of the patients. N.M., S.C., L. B.T., N.R., L.M.N. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patients included in the study"

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