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The positive impact of lifestyle intervention on selected mio- and chemokines levels in prepubertal children with obesity

Pozytywny wpływ modyfikacji stylu życia na poziom wybranych mio- i chemokin u dzieci z otyłością w okresie przedpokwitaniowym

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Abstract

Introduction: It is proven that life style modification (diet and physical exercises) have positive effect on the metabolic functions in patients with obesity, even without significant weight reduction.

Aim of the study: The objective of the present study was to check whether the intensive controlled lifestyle intervention (personalized diet modification and monitored, regular physical activity) may have positive impact on the concentration of irisin and chemerin in children with obesity.

Material and methods: Twenty children (mean age 8.9) were included in the prospective, cross-over study. They were randomly assigned to group A (with three months intensive intervention), and B (standard intervention). After three months, the groups were switched.

Results: Mean irisin level increased significantly after the phase of intensive intervention (4.8 to 5.1 μg/ml; $p = 0.03$), regardless of whether the intervention was applied from the beginning (Group A) or after 3 months from the advice of healthy-lifestyle (Group B). A period without intensive monitoring was associated with a significant reduction of irisin level. For chemerin in the group A (starting from intensive intervention) mean level decreased after the phase of intensive intervention (65.8 to 57.0 ng/ml), and then increased to 67 ng/ml during the standard intervention. In the group B after the standard intervention period chemerin level increased 67.5 to 68.8 ng/ml ($p = 0.03$), and then after introduction the intensive intervention decreased to 63.7 ng/ml.

Conclusion: Personalized diet modification and regular, daily exercises may positively influence on the levels of irisin and chemerin.

Key words:
childhood obesity, physical exercises, diet, irisin, chemerin.

Streszczenie

Wstęp: Udowodniono, że modyfikacja stylu życia (dieta i aktywność fizyczna) korzystnie wpływa na parametry metaboliczne u pacjentów z otyłością, nawet bez istotnej redukcji masy ciała.

Cel pracy: Sprawdzenie, czy intensywna kontrolowana modyfikacja stylu życia może pozytywnie wpłynąć na stężenie iryzyny i chemeryny u dzieci z otyłością.

Materiał i metody: Prospektywnym, krzyżowym badaniem objęto 20 dzieci (14 dziewcząt, średnia wieku 8,9 roku). Zostali oni losowo przydzieleni do grupy A (z trzymiesięczną intensywną interwencją) i B (z interwencją standardową). Po 3 miesiącach nastąpiła zamiana grup.

Wyniki: Po zakończeniu sześciomiesięcznego badania nie stwierdzono różnicy w redukcji BMI *Z-score* i tłuszczowej masy ciała (fat%) pomiędzy grupą A i B (ΔBMI *Z-score* (–) 0,5 vs. (–) 0,2; A % tłuszczu (–) 2,9 vs. (–) 1,4; $p = 0,1$). Średnie stężenie iryzyny istotnie wzrosło po fazie kontrolowanej, intensywnej interwencji (4,8 do 5,1 μg/ml; p = 0,03), niezależnie od tego, czy intensywna interwencja była stosowana od początku (grupa A), czy po 3 miesiącach (grupa B). Okres bez intensywnego monitoringu wiązał się z istotnym zmniejszeniem stężenia iryzyny (5,3 do 4,7 μg/ml; $p = 0,02$). Dla chemeryny w grupie A średni poziom obniżył się po fazie kontrolowanej intensywnej interwencji (65,8 do 57 ng/ml), a następnie wzrósł do 67 ng/ml podczas standardowej interwencji. W grupie B po standardowym okresie interwencji poziom chemeryny wzrósł z 67,5 do 68,8 ng/ml ($p = 0,03$), a następnie po wprowadzeniu intensywnej interwencji obniżył się do 63,7 ng/ml).

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Wniosek: Spersonalizowane zalecenia żywieniowe oraz regularna, codzienna, monitorowana aktywność fizyczna mogą pozytywnie wpływać na poziom iryzyny i chemeryny.
Słowa kluczowe:
otyłość dziecięca, ćwiczenia fizyczne, dieta, irizyna, chemeryna.

Introduction

Childhood obesity, that is an abnormal or excessive fat accumulation that presents a risk to health, is currently called the epidemic of the 21st century.Over the last 40 years, according to the World Health Organization (WHO), the prevalence of obesity among adolescents and children has increased from 4% to 18% [1]. In 2019, the World Obesity Federation estimated there would be 206 million children and adolescents aged 5–19 years living with obesity in 2025, and 254 million in 2030 [2, 3] . Obesity, which is in fact a complex, multifaceted metabolic disorder results from a pathological collection of fat mass, rise the risk of subsequent metabolic abnormalities, and therefore is associated with an major risk of serious medical conditions. Therefore, the treatment of childhood obesity and the prevention of its complications are among the most important challenges of 21st century medicine around the world. The aim of the obesity treatment in children and adolescents are reducing body fat, improving related physical and psycho-social complications, and preventing the development of chronic diseases [1]. So far, the basic and most effective methods are dietary intervention and physical exercises. As showed metaanalysis of 70 randomized control trials, multi-component life-style interventions focused on healthy diet, physical activity and life style change may be beneficial for children aged 6–11 causes reductions in weight, BMI and BMI Z-score [4]. However, the degree of BMI reduction needed to improve obesity related complications is currently unknown. In recent years, more and more attention is paid to the benefits resulting not so much from a significant reduction in body weight, but rather from improving the proportions of its composition by reducing adipose tissue and increasing the content of muscle mass. Such a change seems to have very beneficial metabolic effects, reducing the risk of complications. Increasing muscle mass is possible with regular physical exercise. Therefore, exercises seem to be particularly important. There are clear evidences that regular physical activity is associated with significant health benefits in young people, independent of other lifestyle factors [5]. The 2020 physical ativity guidelines call for children and adolescents aged from 5 to 17 to accumulate at least an average of 60 minutes of moderateto vigorous physical activity (MVPA) per day, mostly aerobic. They also recommend that vigorous physical activities and exercise to strengthen muscles and bones be undertaken at least 3 days a week [6]. Compliance with these recommendations, along with adherence to dietary recommendations, allows to reduce body weight. Weight loss has been associated with improvements in prevalence and severity of several obesity associated comorbidities such as insulin resistance, inflammation, dyslipidemia, hypertension, metabolic syndrome, diabetes, pulmonary disease and cardiovascular disease [7]. Despite the documented effectiveness of such methods of obesity treatment, adherence to these guidelines is low and decreases even more with the age of the child [8–10]. Nevertheless, it seems that children with obesity who exercise less or less often may also benefit. Aside from fat tissue reduction and increasing lean tissue mass, physical activity has positive impact on metabolism [11]. Many of these effects depend on changes in the secretion of cytokines and myokines. It is suspected that beneficial changes in the activity of these substances can occur even with short intense exercises and do not depend on changes in body weight [12]. In the presented study, we hypothesized that in children and adolescents who exercise regularly, but not so intensively as to gain a significant muscle mass and reduce body weight, there may be beneficial changes in metabolism. We focused on the relationship between physical exercises and two cytokines: irisin and chemerin, possibly related to the development of metabolic complications of obesity. Irisin was first described in 2012 by-Boström et al., as myokine induced in exercise [13]. It is an out-membrane part of fibronectin type III domain–containing 5 protein (FNDC5), activated by Peroxisome proliferator-activated receptor γ (PPARγ), coactivator-1α during physical exercise in skeletal muscle tissues [14, 15]. In the first reports of this substance, attention is drawn to the fact that increased levels of circulating irisin were associated with improved glucose homeostasis by reducing insulin resistance [13]. Further studies have shown that irisin may be also produced by white adipose tissue [16]. The beneficial effect of irisin is associated with the activation of profound changes in the subcutaneous adipose tissue, stimulation of its browning and induction of thermogenesis. This causes a significant increase in the total energy expenditure of the body, which prevents the development of insulin resistance. Although the exact role of irisin in many of the major mechanisms of glucose metabolism has not yet been elucidated, its potential contribution to improving energy balance may be a significant factor in improving some metabolic disorders, such as obesity, insulin resistance and inflammation. Thus, the action of irisin explains some of the most important benefits of physical activity [13, 16]. Chemerin initially has been identified as an immunomodulating factor secreted by the skin [17]. Further investigations showed that it is one of those proteins whose systemic levels increase in obesity. Chemerin is predominantly secreted in liver and in adipose tissue, and plays important roles in many metabolic processes such as lipolysis adipogenesis, glycolipid metabolism, insulin resistance inflammation, energy expenditure, immunity, and cell proliferation and differentiation [18–20]. Positive correlations of chemerin with obesity-related conditions such as insulin resistance and serum triglycerides, suggest a role of this adipokine in metabolic diseases [21]. Data on the role of chemerin in metabolic disease are not fully understood. Chemerin most likely weaken skeletal

muscle insulin sensitivity, although it seems to have a modulatory role in the liver and adipose tissues. Excessive chemerin secretion has been shown to increase glucose-induced insulin secretion [22, 23]. The raised level of serum chemerin was found in adolescents with obesity and metabolic syndrome, and endothelial dysfunction [24, 25]. The elevated chemerin level may by also associated with increased systolic blood pressure in obese children [26]. Recently it was shown, that physical activity may reduce chemerin level, and reduce the metabolic risk associated with obesity [27, 28]. It was also shown, that exercise-induced decrements of chemerin in is were mediated by PPARγ [29]. The aim of the study was to compare the effect of a standard intervention in obesity treatment with an intensive intervention involving personalized dietary recommendations and daily physical activity on selected physical and biochemical parameters in prepubertal obese children. Primary endpoints were the effects of the two models of intervention on the levels irisin and chemerin.. The objective of the present study was to check whether the lifestyle intervention may have positive impact on the concentration of irisin and chemerin in children with obesity Research hypothesis No. 1: intense controlled physical exercises increases the concentration of irisin. Research hypothesis No. 2: intensive controlled physical activity decreases the concentration of chemerin. This is the first study simultaneously investigating the relationship between irisin and chemerin levels and metabolic complications of obesity in children. The effect of controlled intervention on the concentration of both cytokines at the same time has not been described so far.

Material and Methods

Study design and study group

Study group consisted of twenty prepubertal children with obesity (6 boys, 14 girls, mean age 8.9 ±SD 1.4, Tanner stage 1). Obesity was defined as BMI above 95th percentile for age and sex – references for Polish school-aged children and adolescents [30].

All participants were selected among children with obesity referred for the first time to an endocrine outpatient clinic. Exclusion criteria were: overt arterial hypertension, type 2 diabetes mellitus, diagnosed irregularities of the endocrine system or lack of consent. No children have previously participated in obesity treatment programs. Baseline level of physical activity was low to moderate (physical activity was assessed on the basis of a questionnaire). None attend to additional physical activities after school. Children were randomly assigned to group A (with three-months intensive intervention), and B (standard intervention – general advice on a healthy lifestyle). The order of reporting to the clinic during the recruitment period decided about the assignment to the group. Sample size was calculated based on measured SD and anticipated differences in mean results (95% confidence level).

After three months, the groups were replaced, i.e. intervention and adherence were no longer closely monitored in group A, but introduced in group B. The groups were randomly selected with allocation ratio 1.22.

The intense intervention consisted of personalized dietary counselling and regular, monitoring daily physical exercises. At the first visit current diet was assessed by the dietician based on the 24-hour nutritional interview. On this basis, individual dietary recommendations were established. The energy value of the diet was estimated according to the child's age and was in the range of 1200–1500 kcal. The distribution of nutrients was as follows: protein (5–15%), carbohydrates (5–-65%), fats (30%; < 10% saturated), polyunsaturated fatty acids up to 10%, monounsaturated fatty acids up to 15% and fiber range: age (year) plus 5–10g. Each participant was instructed to perform daily exercises at home (based on EUROFIT program). Everyone received the recommendation to do every day exercises at home. In the first week: 10 crunches, 10 sit-ups and 5 minutes of aerobic exercise – running or cycling. Each week during the intervention, there was added: 1 additional crunch, 1 sit-up and 1 minute of aerobic exercise. Participants and their families were asked to keep a diary and a written confirmation of their exercises [31]. Participants and their families were asked to keep a food diary and a written confirmation of their exercises. In control visits, every 2–3 weeks, diets and progress in physical activity were discussed on the basis of nutritional records, and diet modifications were introduced. Although the study did not involve a psychologist, dietitian and doctor, tried to give the children positive motivation to change their lifestyle.

In the standard intervention patients received a general nutrition recommendations and advise to increase daily physical activity according to WHO Global Recommendations on Physical Activity for Health [32]. They were not followed and controlled until the next visit after three months. Each phase of intervention lasted for three months followed by the cross-over of the groups for next 3 months.

Antropometric parameters

Height were measured using a stadiometer (SECA, Germany). Body mass and body composition was measured using bioelectrical impedance analyser (Tanita BC 418 S MA, Tokyo, Japan). The measurements were performed according to the manufacturer's guidelines, at least 2 h after ingestion of a light breakfast and urination. BMI was calculated and assessed in reference to the national standard (OLAF study) Obesity was defined as BMI above 95th percentile for age and sex [30].

Anthropometric and bioimpedance tests were performed at the beginning of the study and after each stage of the study. From the bioelectric impedance such as data were collected – fat mass (kg), fat percent (fat%), fat-free mass (FFM) (kg), and total body water (TBW) (kg).

Blood parameters

The concentrations of irisin and chemerin in serum were measured in singlets using commercially available ELISA kits (BioVendor, Czech Republic, intra-assay precision CV 4.9–8.2%, inter-assay CV 8.0–9.7%). The concentrations of chemerin in serum were measured in singlets using commercially available ELISA kits (R&D, USA), intra-assay precision CV 2.8–4.5%, inter-assay CV 6.4–7.9%. Insulin levels were measured in serum

with machine Advia Centaur (Siemens, USA). All biochemical analysis were performed in the fasting blood sample by the dry chemistry method with a Vitros 5.1.FF machine (Ortho-Clinical Diagnostics, Rochester, NY, USA). Biochemical tests were performed in fresh material, irisin and chemerin concentrations in frozen samples.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Jagiellonian University Medical College Committee of Bioethics - Decision number 1072.6120.231.2017.

Data analysis

Categorical variables or categorized continuous variables were expressed as counts and percentages. In order to compare the two groups, the two-sided Mann–Whitney U-test and ANOVA tests were applied. To compare matched samples, the Wilcoxon signed-rank test was used. A *p*-value less than 0.05 was considered an indication of a statistically significant result. All statistical analyses were performed using the Statistica 12 PL software. (StatSoft Cracow, Poland).

Results

The reduction of BMI Z-score and fat body mass (fat%) was observed independently from the type of intervention. (intense and standard intervention respectively: ΔBMI Z-score –0.5 vs. –0.2; Δ fat% –2.9 vs. –1.4, without statistically significant differences). In the group A (starting from intensive intervention) the reduction of BMI Z-score was 0.6 after intensive intervention and subsequent 0.2 after following standard intervention. In the group B (starting with standard intervention) the reduction of BMI z-score was 0.7 after standard intervention and subsequent 0.3 after intensive intervention (Table I).

During the period of intensive intervention (daily, monitored physical exercise and individual nutritional recommendations) the concentration of irisin increased and chemerin decreased. It did not depend on whether the study participants started with an intensive lifestyle modification phase or whether it was preceded by more standard recommendations.

In the group A (starting from intensive intervention) the mean irisin level during intensive phase increased from 4.8 to 5.3 μg/ml ($p = 0.02$), and then decreased back during the standard intervention (4.7 μg/ml, $p = 0.04$). In the group B during the standard intervention period, the concentration of irisin decreased from 5.1 to 4.8 μg/ml ($p = 0.03$), and then remained stable (4,7 ug/ml, $p = 0.8$). Generally, in the whole group the average irisin level increased significantly after the phase of intensive intervention (4.8 to 5.1 μg/ml; $p = 0.03$), regardless of whether the intervention was applied from the beginning or not.

In the group A (starting from intensive intervention) mean chemerin level decreased after the phase of intensive intervention (65,8 to 57.0 ng/ml, $p = 0.03$), and then increased to 67.0 ng/ml ($p = 0.04$) during the standard intervention. In the group B after the standard intervention period chemerin level increased 67.5 to 68.8 ng/ml ($p = 0.03$), and then after introduction the intensive intervention decreased to 63.7 ng/ml ($p = 0.04$) (Table IThe intense intervention compared to standard intervention was more favourable for the values of the following parameters: fasting glucose, AST, ALT, GGT, creatinine, uric acid, total cholesterol, HDL cholesterol and triglycerides (Table I).

Discussion

Paediatric obesity continues to be one of the most important health issues facing children, families and health care professionals today. The primary cause of excess body fat accumulation is an energy imbalance between calories consumed and calories expended. It might therefore seem that restoring the proper caloric intake and/or increasing energy expenditure is sufficient to achieve a cure. However, as clinical practice and research results show, the effects of intervention in the form of an attempt to change lifestyle are not always as expected and are often short-term. In part, this may be due to the fact that the assumptions of most of the therapeutic programs subject to evaluation are very demanding, and the recommended physical activity is much higher than what patients can accept and consolidate in everyday life. Therefore, there is still a need for novel management options, because treating childhood obesity is difficult, frustrating and often ineffective. In recent years the approach to the treatment of obesity is evolving from focusing on weight reduction to the improvement of "metabolic health". It seems, that such improvement can be achieved by life style modification, diet and especially increase of daily physical activity [33]. As it was shown low levels of total physical activity and especially vigorous physical activity could play an important role in the development of overweight and excess central adiposity in children and adolescents, independently of a number of factors such as television viewing and birth weight [34]. On the other hand, recently published metanalysis of 70 randomized controlled trials with a total number of participants 8,461revealed, that life style interventions including diet change and increase of physical activity demonstrate positive effects on BMI reduction at the end of the intervention, and even up to six months post-intervention [4]. Moreover, such action has positive effects on metabolism, effectively reducing the known risk factors of obesity complications. A beneficial effect of a short term (5 months) intervention on low-level systemic inflammation, and the adipokine profile in children with obesity was recently described by Mayerhofer et al. [33]. Similarly to previously published studies, the first visible effects of the present study were body weight reduction and improvement of body composition. The decrease of BMI Z-score after standard intervention was (–) 0.2, comparable with previously published short-term interventional trials [33, 35]. As expected much better result was achieved after intense intervention phase [ΔBMI Z-score (–) 0.5 vs. (–) 0.2; Δ fat% (–) 2.9 vs. (–) 1.4]. This observation confirms that frequent contact and motivation is more efficient than just passing on recommendations. It is worth repeating after Reinher, that the intensity of the program, defined as more contact time with professional support during the intervention rather than the total duration of the intervention, ap-

Table I. Mean changes of selected anthropometric, metabolic parameters and irisin, chemerin values after intense and standard intervention in studied groups

	Group A				Group B			
	Baseline	After intensive intervention	After standard intervention	*p*-value	Baseline	After intensive intervention	After standard intervention	*p*-value
Mean BMI SDS	3.1 (1.3)	2.6 (1.6) (Δ = –0.6)	2.4 (1.4) (Δ = –0.2)	$p = 0.006$ * $p = 0.4$**	4.5 (1.8)	3.8 (1.6) (Δ = –0.7)	3.5 (1.6) (Δ = –0.3)	$p = 0.02$* $p = 0.007$**
Mean FAT%	35 (6.4)	31.4 (5.9) (Δ = –3.6)	30 (5.7) (Δ = –1.4)	$p = 0.005$ * $p = 0.5$**	38.6 (3.9)	36.2 (4.7) (Δ = –2,4)	34 (5.2) (Δ = –2,2)	$p = 0.02$* $p = 0.007$*
Chemerin (ng/ml)	65.8 (14.0)	57.0 (Δ = –8.8)	67.0 (Δ = 10)	$p = 0.03$* $p = 0.04$**	67.5	68.8 (Δ = 1.3)	63.7 (Δ = –5.1)	$p = 0.3$* $p = 0.04$**
Irisin (μg/ml)	4.8 (0.96)	5.3 (Δ = 0.42)	4.7 (Δ = –0.6)	$p = 0.02$* $p = 0.04$**	5.1	4.8 (Δ = –0.3)	4.7 (Δ = –0.1)	$p = 0.03$* $p = 0.8$**
Fasting blood glucose (mmol/l)	4.5 (0.4)	4.4 (0.2) (Δ = –0.1)	4.7 (0.3) (Δ = +0.3)	$p = 0.8$* $p = 0.1$**	4.6 (0.7)	4.6 (0.3) (Δ = 0)	4.6 (0.3) (Δ = 0)	$p = 0.4$* $p = 0.8$**
Fasting blood insulin (μIU/ml)	13.5 (5.6)	12.7 (7.1) (Δ = –0.8)	16.9 (12.5) (Δ = –0.8)	$p = 0.4$* $p = 0.1$**	21.5 (14.6)	13.6 (7.1) (Δ = –7.9)	18.7 (15.7) (Δ = +5.1)	$p = 0.3$* $p = 0.6$**
HOMA IR	2.6 (0.9)	3.6 (3.2) (Δ = +1)	1.6 (2.9) (Δ = –2)	$p = 0.6$* $p = 0.2$**	4.6 (3.9)	2.8 (1.6) (Δ = –1.8)	3.9 (3.4) (Δ = +1.1)	$p = 0.03$* $p = 0.1$**
Fasting ALT activity (IU/l)	32.3 (6.2)	25.7 (5.9) (Δ = –6.6)	25 (7.8) (Δ = –0.7)	$p = 0.01$* $p = 0.8$**	45.4 (10.9)	38.6 (25.7) (Δ = –6.8)	30.7 (7.7) (Δ = –7.9)	$p = 0.1$* $p = 0.4$**
Fasting AST activity (IU/l)	29.1 (4.5)	27.8 (2.8) (Δ = –1.3)	27.7 (4.0) (Δ = –0.1)	$p = 0.6$* $p = 0.3$**	33.3 (8.2)	33.3 (16.6) (Δ = 0)	28.5 (4.3) (Δ = –4.8)	$p = 0.2$* $p = 0.4$**
Fasting GGT activity (IU/l)	18 (6.4)	16 (5.1) (Δ = –2)	17.4 (10.6) (Δ = +1.4)	$p = 0.2$* $p = 0.32$**	18.8 (3.8)	17.2 (3.8) (Δ = –1.6)	16.9 (4.5) (Δ = –0.3)	$p = 0.08$* $p = 0.1$**
Fasting creatinine level (μmol/l)	43.6 (4.8)	42.9 (5.0) (Δ = –0.7)	45.2 (6.4) (Δ = +2.3)	$p = 0.4$* $p = 0.8$**	41.7 (3.9)	41.5 (3.4) (Δ = –0.2)	42.4 (4.0) (Δ = +0.9)	$p = 0.5$* $p = 0.9$**
eGFR	118.5 (16.8)	122.3 (19.7) (Δ = +3.8)	117.8 (16.5) (Δ = –4.5)	p=0.08* $p = 0.6$**	121.6 (12.5)	123 (8.2) (Δ = +1.4)	124 (9.9) (Δ = +1)	$p = 0.6$* $p = 0.9$**
Fasting uric acid (μmol/l)	286.2 (76.2)	266.3 (76) (Δ = –19.9)	270.9 (89) (Δ = +4.6)	$p = 0.5$* $p = 0.8$**	322.5 (37.1)	319.9 (51.6) (Δ = –2.6)	325.2 (31.4) (Δ = +5.3)	$p = 0.9$* $p = 0.4$*
Fasting total cholesterol (mmol/l)	4.5 (0.9)	4.3 (0.6) (Δ = –0.2)	4.5 (0.6) (Δ = +0.2)	$p = 0.1$* $p = 0.3$**	4.4 (0.6)	4.3 (0.6) (Δ = –0.1)	4.4 (0.6) (Δ = +0.1)	$p = 0.6$* $p = 0.5$**
Fasting LDL (mmol/l)	2.8 (0.7)	2.6 (0.6) (Δ = –0.2)	2.5 (0.5) (Δ = –0.1)	$p = 0.1$* $p = 0.7$**	2.8 (0.5)	2.5 (0.6) (Δ = –0.3)	2.5 (0.5) (Δ = 0)	$p = 0.7$* $p = 0.2$**
Fasting HDL (mmol/l)	1.1 (0.2)	1.2 (0.2) (Δ = +0.1)	1.3 (0.3) (Δ = +0.1)	$p = 0.04$* $p = 0.2$**	1.1 (0.3)	1.1 (0.4) (Δ = 0)	1.2 (0.3) (Δ = +0.1)	$p = 0.8$* $p = 0.04$**
Fasting TG (mmol/l)	1.4 (1.3)	1.1 (0.9) (Δ = –0.3)	1.4 (1.3) (Δ = +0.1)	$p = 0.06$* $p = 0.07$**	1.5 (0.5)	1.4 (0.6) (Δ= –1)	1.3 (0.5) (Δ= –1)	$p = 0.5$* $p = 0.7$**

* *p*-value after intensive intervention,
** *p*-value after standard intervention (Δ = change value)

pears important for its efficacy [36]. The most frequently used measures of the effectiveness of interventions in the treatment of obesity, both in clinical practice and in scientific research, are anthropometric measurements and their results expressed as BMI. These measurements are simple to use and repetitive. They can be performed in almost every facility with very limited equipment. However, they do not really track changes in body composition, and what is even more important in health status. The results of the present study indicate that despite the lack of a spectacular BMI reduction, daily, controlled physical activity had a beneficial effect on metabolic parameters. Even more spectacular effects of intense intervention were observed in relation to changes in the concentrations of analysed irisin and chemerin. After intense intervention phase significant increase of irisin level (4.8 to 5.1 μg/ml) and decrease of chemerin level (66.4 to 60.1 ng/ml) were noticed. Interestingly, the analysis of subgroups revealed the importance of the order of the type of intervention on irisin concentration. Much better results were obtained by the group that started the program with intense intervention. To some extent, this can be explained by the fact that the group starting from standard intervention had a higher initial concentration of irisin at the time the intense intervention began. This, in turn, could be the result of the introduction of any physical activity, compared to its almost complete absence prior to the study. These results confirm that beneficial changes in the secretion of irisin and chemerin also occur in obese children who exercise regularly, but not always as much as recommended by the recommendations. This new observation seems to be of great practical importance, as studies have shown that full adherence to physical activity guidelines in children is low [8, 10]. As it was shown in some studies, in humans, the duration of exercise seems to be important for changes in circulating levels of irisin. Its peak occurs after 3–60 min of exercise [37]. Other investigators have reported that resting irisin levels remained unchained after the 6 weeks of training, indicating that acute, but not chronic, exercise triggers irisin release from muscle [38]. The effect of intense intervention on chemerin concentration level appears to be more predictable. In both subgroups, a clear reduction in concentration occurred after the intense phase, regardless of the sequence of the intervention. In several studies on adults it has been shown that change of the diet, increase of physical activity and subsequent reduction of body weight are associated with the significant reduction of the chemerin concentration level [39, 40]. What more, reduced chemerin expression and serum concentration may contribute to improved insulin sensitivity and subclinical inflammation beyond significant weight loss [40]. These observations seem to be further arguments in favour of changing the classic approach to the treatment of childhood obesity focused mainly on weight reduction. Currently, many studies confirm that myokines, cytokines and adipokines in obesity are perpetuated through maintenance of positive feedback and suppression of protective negative feedback mechanisms. These ultimately result in insulin resistance and endothelial dysfunction, which give rise to the metabolic syndrome and its complications [33, 41–43]. As it was recently noticed by Akgul Balaban et al. both irisin and chemerin have a role in the pathophysiology of type 2 diabetes mellitus [44]. In the study for the first time exploring the relationship of these two cytokines with metabolic disorders, they revealed, that irisin levels in the group of patients newly diagnosed with type 2 diabetes mellitus were significantly lower, and chemerin levels significantly higher than in the control group [44]. According to the literature, there was no study that evaluated both irisin and chemerin levels in paediatric patients with obesity. Also, interventions in the form of controlled physical activity on their concentration were not assessed. The results of the present study indicate the existence of such a relationship, even despite the lack of a significant reduction in body weight, BMI or improvement in the value of classic biochemical markers of obesity complications. That is in line with current views on the pathogenesis of obesity complications in children, adolescents and young adults [45]. The unique value of this study is that the observations were carried out under controlled conditions on a homogenous group of participants. The limited number of patients, enrolled from a single referral centre is a main limitation of our study. The obvious weak point of the study is the size of the group. However, given these preliminary results, it seems that they can be a good starting point for further projects. The second major limitation is that the intervention was conducted at home and the results reported by participants. There was no objective tool for controlling physical activity or adherence to dietary recommendations. Undoubtedly, more research is needed to understand the complex structure of the irisin and chemerin signalling pathways, and the importance of these molecules as regulators of metabolism in obese people. The results of the study can be applied to modify the recommendations for physical activity in obese children and to introduce control tools, even as simple as activity diaries.

Limitations of the study: Our sample size was small, and, thus, the statistical power of the study was limited. This requires further research on larger groups.

Conclusions

It seems that abnormal values of biochemical parameters such as lipid profile, glucose, insulin, activity of liver enzymes may be visible only at a later stage of obesity complications and therefore do not reflect well the effects of the intervention in children. However, personalised diet modifications and regular and monitored daily exercises may positively influence on the levels of irisin and chemerin.

References

1. Obesity and overweight. https ://www.who.int/news-room/fact-sheet s/detai l/obesi ty-and-overweight (accessed May-12-2020).
2. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. Lancet Diabetes Endocrinol 2022; 10: 351–365.
3. Lobstein T, Brinsden H. Atlas of childhood obesity. World Obesity Federation, London 2019.
4. Mead E, Brown T, Rees K, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. Cochrane Database Syst Rev 2017; 6: CD012651. doi: 10.1002/14651858.CD012651.
5. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Behav Nutr Phys Act 2010; 7: 40.
6. Bull FC, Al-Ansari S S, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British Journal of Sports Medicine 2020; 54: 1451–1462. https://doi.org/10.1136/bjsports-2020-102955
7. Celik O, Yildiz BO. Obesity and physical exercise. Minerva Endocrinology 2021; 46: 131–144. doi: 10.23736/S2724-6507.20.03361-1.
8. Jakubec L, Gába A, Dygrýn J, et al. Is adherence to the 24-hour movement guidelines associated with a reduced risk of adiposity among children and adolescents? BMC Public Health 2020; 20: 1119. https://doi.org/10.1186/s12889-020-09213-3
9. Lien A, Sampasa-Kanyinga H, Colman I, et al. Adherence to 24-hour movement guidelines and academic performance in adolescents. Public Health 2020; 183: 8–14. https://doi.org/10.1016/j.puhe.2020.03.011
10. Okely AD, Trost SG, Steele JR, et al. Adherence to physical activity and electronic media guidelines in Australian pre-school children. Journal of Paediatrics and Child Health 2009; 45: 5–8. https://doi.org/10.1111/j.1440-1754.2008.01445.x
11. Stoner L, Rowlands D, Morrison A, et al. A. Efficacy of Exercise Intervention for Weight Loss in Overweight and Obese Adolescents: Meta-Analysis and Implications. Sports Medicine 2016; 46: 1737–1751. https://doi.org/10.1007/s40279-016-0537-6
12. Eaton M, Granata C, Barry J, et al. Impact of a single bout of high-intensity interval exercise and short-term interval training on interleukin-6, FNDC5, and METRNL mRNA expression in human skeletal muscle. Journal of Sport and Health Science 2018; 7: 191–196. https://doi.org/10.1016/j.jshs.2017.01.003
13. Boström P, Wu J, Jedrychowski MP, et. al. A PGC1-a-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012, 481*:* 463–468. doi: 10.1038/nature10777.
14. Liu S, Cui, F, Ning, K, et al. Role of irisin in physiology and pathology. Frontiers in Endocrinology 2022; 13. https://doi.org/10.3389/fendo.2022.962968
15. Nie Y, Dai B, Guo X, Liu D. Cleavage of FNDC5 and insights into its maturation process. Molecular and Cellular Endocrinology 2020; 510: 110840. https://doi.org/10.1016/j.mce.2020.110840
16. Roca-Rivada A, Castelao C, Senin LL, et al. FNDC5/irisin is not only a myokine but also an adipokine. PLoS ONE 2013; 8: e60563.
17. Meder W, Wendland M, Busmann A, et al. Forssmann, W.G. Characterization of human circulating TIG2 as a ligand for the orphan receptor ChemR23. FEBS Lett 2003; 555: 495-499.
18. Goralski KB, McCarthy TC, Hanniman EA, et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007; 282: 28175–28188.
19. Zylla S, Pietzner M, Kühn JP, et al. Serum chemerin is associated with inflammatory and metabolic parameters-results of a population-based study. Obesity (Silver Spring) 2017; *25*: 468–475.
20. Eichelmann F, Weikert C, di Giuseppe R, et al. Methodological utility of chemerin as a novel biomarker of immunity and metabolism. Endocr Connect 2017; 6: 340–347.
21. Takahashi M, Okimura Y, Iguchi G, et al. Chemerin regulates beta-cell function in mice. Sci Rep 2011; 1: 123. doi: 10.1038/srep00123.
22. Ernst MC, Issa M, Goralski K.B, Sinal CJ. Chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes. Endocrinology 2010; 151: 1998–2007. doi: 10.1210/en.2009-1098
23. Rourke JL, Dranse HJ, Sinal CJ, et al. Towards an integrative approach to understanding the role of chemerin in human health and disease. Obes Rev 2013; 14: 245–262. doi: 10.1111/obr.12009.
24. Liu M, Lin X, Wang X. Decrease in serum chemerin through aerobic exercise plus dieting and its association with mitigation of cardiometabolic risk in obese female adolescents. J Pediatr Endocrinol Metab 2018; 31*:* 127–135.
25. Gu P, Cheng M, Hui X, Lu B, et al. Elevating circulation chemerin level is associated with endothelial dysfunction and early atherosclerotic changes in essential hypertensive patients. J Hypertens 2015; 33: 1624–1632.
26. Wójcik M, Kozioł-Kozakowska A, Januś D, et al. Circulating chemerin level may be associated with early vascular pathology in obese children without overt arterial hypertension – preliminary results. Journal of Pediatric Endocrinology and Metabolism 2020; 33: 729–734.
27. Lakhdar N, Landolsi M, Bouhlel E, Tabka Z. Effect of diet and diet combined with chronic aerobic exercise on chemerin plasma concentrations and adipose tissue in obese women. Neuro Endocrinol Lett 2019; 40: 262–270.
28. Liu M, Lin X, Wang, X. Decrease in serum chemerin through aerobic exercise plus dieting and its association with mitigation of cardiometabolic risk in obese female adolescents. J Pediatr Endocrinol Metab 2018; 31: 127–135.
29. Lin X, Yang Y, Qu J, Wang X. Aerobic exercise decreases chemerin/CMKLR1 in the serum and peripheral metabolic organs of obesity and diabetes rats by increasing PPARγ. Nutrition & Metabolism 2019; 16: 17. https://doi.org/10.1186/s12986-019-0344-9
30. Kułaga Z, Litwin M, Tkaczyk. M. Polish 2010 growth references for school-aged children and adolescents. Eur J Pediatr *2011*; 170: 599–609.
31. Committee of Experts on Sports Research (1988) European test of physical fitness (EUROFIT). Fitness levels of Greek primary schoolchildren in relationship to overweight and obesity. Eur J Pediatr 2006; 165: 867–874.
32. https://www.who.int/dietphysicalactivity/factsheet_recommendations/en/ (accessed May-12-2022).
33. Mayerhofer E, Ratzinger F, Kienreich NE, Stiel A, et all. A Multidisciplinary Intervention in Childhood Obesity Acutely Improves Insu-

lin Resistance and Inflammatory Markers Independent From Body Composition. Front Pediatr 2020; 8: 52.
34. Ortega FB, Ruiz JR, Sjostrom M. Physical activity, overweight and central adiposity in Swedish children and adolescents: the European Youth Heart Study. Int J Behav Nutr Phys Act 2007; 4: 61.
35. Vos RC, Wit JM, Pijl H, Houdijk EC. Long-term effect of lifestyle intervention on adiposity, metabolic parameters, inflammation and physical fitness in obese children: a randomized controlled trial. Nutr Diabetes 2011; 3:1(10): e9. doi: 10.1038/nutd.2011.5.
36. Reinehr T, Widhalm K, l'Allemand D, et al. Two-year follow-up in 21 784 overweight children and adolescents with lifestyle intervention. Obesity (Silver Spring) 2009; 17: 1196–1199
37. Nygaard H, Slettaløkken G, Vegge G, et al. Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training. PLoS ONE. 2015; 17: 10(3):e0121367. doi: 10.1371/journal.pone.0121367. PMID: 25781950; PMCID: PMC4363689.
38. Huh JY, Mougios V, Skraparlis A, et al. Irisin in response to acute and chronic whole-body vibration exercise in humans. Metabolism 2014; 63: 918–921.
39. Lakhdar N, Landolsi M, Bouhlel E, Tabka Z. Effect of diet and diet combined with chronic aerobic exercise on chemerin plasma concentrations and adipose tissue in obese women. Neuro Endocrinol Lett 2019, 40: 262–270. PMID: 32200585.
40. Chakaroun R, Raschpichler M, Klöting N, et al. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. Metabolism 2012; 61: 706–714. doi: 10.1016/j.metabol.2011.10.008.
41. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol 2017; 13: 633.
42. Gonzalez-Gil AM, Peschard-Franco M, Castillo EC, et al. Myokine–adipokine cross-talk: potential mechanisms for the association between plasma irisin and adipokines and cardiometabolic risk factors in Mexican children with obesity and the metabolic syndrome. Diabetol Metab Syndr 2019; 11: 63.
43. Eriksson JG, Venojärvi M, Osmond C. Prenatal and Childhood Growth, Chemerin Concentrations, and Metabolic Health in Adult Life. Int J Endocrinol 2016; 2016: 3838646. doi: 10.1155/2016/3838646.
44. Akgul Balaban Y, Yilmaz N, Kalayci M, et al. Irisin and chemerin levels in patients with type 2 diabetes mellitus. Acta Endocrinol (Buchar) 2019; 15: 442–446. doi: 10.4183/aeb.2019.442.
45. Drozdz D, Alvarez-Pitt J, Wójcik M, et al. Obesity and Cardiometabolic Risk Factors: From Childhood to Adulthood. Nutrients 2021; 13: 4176. doi: 10.3390/nu13114176.

