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Changes in inflammatory biomarkers after successful lifestyle intervention in obese children

Zmiany w zakresie wskaźników stanu zapalnego po skutecznym wdrożeniu zmiany stylu życia u otyłych dzieci

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Abstract

Background: Obesity has been associated with low-grade systemic inflammation, potentially leading to insulin resistance, type 2 diabetes, dyslipidemia, and cardiovascular diseases. Even moderate weight loss through dietary changes and physical exercise is effective in preventing and managing obesity-associated disorders. The aim of this study was to determine the effect of weight loss in response to a lifestyle modification on the serum levels of inflammatory markers in obese children and adolescents.

Material and methods: Fifty obese subjects completed a six-month programme consisting of combined hypocaloric diet and moderate physical activity. High-sensitive C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen (FB), white blood count (WBC), glucose, insulin, insulin resistance index (HOMA IR), glycosylated haemoglobin (HbA_{1c}), lipids as well as systolic (SBP) and diastolic blood pressure (DBP) were measured before and after intervention.

Results: Patients had a 5.3 ± 3.4 kg average weight loss, with significant decreases of SDS-BMI, percentage of body fat, SDS-waist, SBP and DBP, HOMA-IR, HbA_{1c} and reductions in serum IL-6, CRP, WBC, FB. In the multivariable linear models, changes in percentage of body fat and HOMA-IR were positively associated with favourable changes in inflammatory parameters.

Conclusion: This study demonstrates that weight reduction after successful lifestyle intervention results in improvements of blood inflammatory markers in obese children and adolescents. **(Pol J Endocrinol 2011; 62 (6): 499–505)**

Key words: *inflammatory markers, weight loss, obesity, children*

Streszczenie

Wstęp: Otyłość wiąże się z obecnością niewielkiego stopnia stanu zapalnego, potencjalnie prowadzącego do insulinooporności, cukrzycy typu 2, dyslipidemii i chorób sercowo-naczyniowych. Nawet umiarkowane obniżenie masy ciała dzięki zmianie diety i zwiększonej aktywności fizycznej zapobiega występowaniu zaburzeń związanych z otyłością. Celem pracy była ocena wpływu obniżenia masy ciała (w wyniku modyfikacji stylu życia) na stężenie wskaźników stanu zapalnego w surowicy otyłych dzieci i młodzieży.

Materiał i metody: W 6-miesięcznym programie polegającym na stosowaniu ubogokalorycznej diety i umiarkowanej aktywności fizycznej uczestniczyło 50 otyłych pacjentów. W warunkach podstawowych i po 6 miesiącach oznaczano: białko C-reaktywne (CRP), interleukinę 6 (IL-6), fibrynogen (FB), leukocyty (WBC), glukozę, insulinę, wskaźnik insulinooporności (HOMA-IR), hemoglobinę glikozylową (HbA_{1c}), lipidy, ciśnienie tętnicze krwi skurczowe (SBD) i rozkurczowe (DBD).

Wyniki: Średni spadek masy ciała u pacjentów wynosił 5,3 ± 3,4 kg, ze znaczącą redukcją wartości SDS-BMI, procentowej zawartości tłuszczu, SDS-obwodu pasa, SBP i DBP, HOMA-IR, HbA_{1c} oraz obniżeniem stężeń IL-6, CRP, WBC, FB w surowicy. W wieloczynnikowej analizie regresji zmiany w procentowej zawartości tłuszczu i HOMA-IR były pozytywnie skorelowane z podobnymi zmianami wskaźników stanu zapalnego.

Wnioski: Redukcja masy ciała w efekcie zmiany stylu życia wpływa na poprawę wskaźników stanu zapalnego u otyłych dzieci i młodzieży. **(Endokrynol Pol 2011; 62 (6): 499–505)**

Słowa kluczowe: *wskaźniki stanu zapalnego, redukcja masy ciała, otyłość, dzieci*

Introduction

Obesity is known to be an important risk factor for the development of insulin resistance potentially leading to several life-threatening disorders such as type 2 diabetes mellitus, atherosclerosis and hypertension [1]. A common cause of these co-morbidities of obesity may be the chronic, low-grade systemic inflammation, characterised by increased serum levels of inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β,

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tumour necrosis factor-α, and many other blood markers suggesting systemic inflammation such as C-reactive protein (CRP), white blood count (WBC) and fibrinogen (FB) [2, 3].

Main sources of inflammatory cytokines are adipocytes *per se* as well as the immune cells localised within expanded adipose tissue [4, 5]. It is now recognised that the expansion of fat tissue associated with obesity results in more blood vessels, more connective tissue fibroblasts, and especially more macrophages. Apart from adipocytes, other cells located in adipose tissue such as endothelial cells, fibroblasts, and immune cells, may secrete inflammatory cytokines and chemokines. In particular, visceral adipose tissue is known to release a larger amount of interleukins and inflammatory cytokines than abdominal subcutaneous adipose tissue [4].

The principal inflammatory molecule is C-reactive protein, which is primarily synthesised and secreted by the liver in response to adipocyte-derived interleukin-6, and both molecules are strongly associated with obesity and cardiovascular disease [6].

Numerous studies in obese adults and children have shown that even moderate weight loss through dietary changes and physical exercise is effective in preventing and managing obesity-associated disorders [7]. The achieved weight loss is associated with diminished cardiovascular risk and an improved quality of life [8]. Since a hypocaloric diet and physical training have been shown to improve body composition through reduction of body fat stores, it is hypothesised that an intervention utilising dietary changes and increased physical activity may also improve markers of inflammation.

There have been only a few studies concerning the effect of weight loss on circulating levels of inflammatory biomarkers, with contradictory results. Some of these studies have shown a reduction of proinflammatory cytokine IL-6 [9] and retinol binding protein-4 [10] in response to weight reduction. With regard to CRP, Heilbronn et al. [11] found that its elevated concentration in obese individuals decreased in parallel with decreasing body weight, whereas Bastard et al. [9] showed no change in response to weight loss.

As a result of these controversial findings, and the small amount of longitudinal data, we studied the changes in selected blood inflammatory markers after weight reduction in obese children and adolescents.

Material and methods

We examined anthropometric parameters, fasting glucose, insulin and blood inflammatory markers in 50 obese children and adolescents (boys and girls), aged 8 to 18 years, attending the Outpatients Clinic for Children with Metabolic Disorders. Obesity was recognised on the basis of body mass index (BMI) above the 97th percentile for age and sex on BMI percentile charts. Reference data for Polish children were used [12]. Children with acute or chronic infections, as well as children with significant medical conditions such as genetic syndromes, cancers, autoimmunologic diseases, hepatic or renal dysfunction, and endocrine disorders were excluded. All patients were non-smokers without any regular medication.

The protocol of the study was approved by the Ethical Committee of the Pomeranian Medical University.

All patients participated in the six-month obesity intervention programme. Our outpatient intervention programme for obese children was based on increased physical activity, nutrition education, and behaviour therapy including individual psychological care of the child, and, if necessary, the child's family. The exercise therapy included instructions in physical exercise as part of everyday life and in reducing the amount of time spent watching television or playing computer games. The nutritional intervention consisted of a targeted reduction in fat and sugar intake.

Anthropometric measurements (body height and weight, waist circumference) were performed by trained personnel. Height was measured to the nearest centimetre using a rigid stadiometer. Weight was measured in underwear to the nearest 0.1 kg using an electronic scale. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square metres (kg/m^2). Since BMI changes with age, standard deviation score (SDS)-BMI was also calculated [12]. A substantial weight loss over the course of six months was defined as a reduction of SDS-BMI greater than 0.5.

Percentage body fat (% FAT) and fat mass (in kg) were measured using the bioimpedance method (Bioelectrical Impedance Analyzer Tanita 131, Japan) with an applied current of 0.8 mA at a fixed frequency of 50 kHz. Waist circumference was measured as the minimal abdominal circumference between the xiphoid process and iliac crest. Because waist circumference changes with age, waist-SDS was also calculated, separately for boys and girls [13]. Pubertal development stage was assessed using the standards of Marshall and Tanner. In girls, breast stage was used if there was a discrepancy between breast and pubic hair development. In boys, pubic hair was used if there was a discrepancy between genitalia and pubic hair staging.

Systolic and diastolic blood pressure (SBP and DBP) were measured according to guidelines at the right arm after a 10-minute rest by using a calibrated sphygmomanometer.

Blood samples were obtained in the fasting state at 8a.m. and centrifuged immediately. Serum specimens for IL-6 were frozen at –80°C and thawed only once for analysis, whereas all blood glucose, insulin, CRP, fibrinogen, HbA_1c, lipids and WBC determinations were performed immediately. Circulating IL-6 levels were determined by the ELISA method using the Quantikine kit (R&D System, Minneapolis, MN, USA). The minimum detectable concentration was 0.10 pg/mL, and the interassay coefficient of variation was 7.0% for this kit. CRP was measured by the high-sensitivity immunoturbidimetric method (CRP-Latex, Olympus) and FB — in citrated plasma with a modified clot-rate assay using the Diagnostica STAGO ST4 instrument. Serum glucose levels were measured with the glucose oxidase technique (Glucose HK Analyzer, Olympus). Free insulin concentration was determined by RIA (Pharmacia RIA kit). HbA_{1c} was measured by the immunoturbidimetric method. Total cholesterol (T-chol), HDL cholesterol (HDL-chol) and triacylglycerol (TG) levels were measured in serum by automated enzymatic procedures (Olympus). LDL cholesterol (LDL-chol) was determined after separating LDL fraction from fresh sera by sequential ultracentrifugation, using an Olympus commercial kit.

Fasting glucose and insulin concentrations were used to calculate the homeostasis model assessment for insulin resistance (HOMA-IR). The formula for HOMA-IR is as follows:

$$HOMA\text{-}IR = fasting\ blood\ glucose\ [mmol/L] \times fasting\ insulin\ [mIU/mL]/22.5$$ [14]

Statistical analyses were performed using the STATA 11 software package. Data was presented as mean and standard deviation (± SD), and changes were shown as mean difference change from baseline (Δ) ± SD. Changes were expressed as Δ variable and calculated as variable measured at baseline minus variable measured six months later. Non-normally distributed variables were log-transformed before statistical analysis.

For analysis (the baseline study vs. the follow-up assessment at six months), a paired Student *t* test was used for parametric data and Wilcoxon sign rank test for nonparametric data. Inflammatory markers' levels were correlated to other variables by Pearson's correlation, whereas Spearman's correlation was used to assess the relationships between changes in inflammatory markers and changes in other continuous measurement improvements. Multiple linear regression analyses with inflammatory markers as dependent variables were performed with the independent variables such as age, sex, pubertal stage, SDS-BMI and others that had shown a significant correlation to the dependent variable in univariate analysis. Sex and pubertal stage were used as categorical markers in all these models. P value < 0.05 was considered as significant.

Results

There were significant differences between all studied parameters, both clinical and biochemical, at baseline and following the intervention (Table I). After six months, a significant reduction of glucose and insulin concentration, HOMA-IR, HbA_{1c} as well as SBP and DBP were observed. Furthermore, concentrations of IL-6, CRP, WBC and FB decreased significantly.

Pearson's correlation coefficients of patients' characteristics and inflammatory biomarkers at baseline are presented in Figure 1.

At baseline, univariate Pearson's correlation analysis showed a significant positive correlation between degree of overweight (as SDS-BMI) and IL-6 ($p < 0.000$), CRP ($p = 0.001$), WBC ($p < .000$) and FB ($p = 0.004$), percentage of body fat and IL-6 ($p = 0.003$), CRP ($p = 0.02$), WBC ($p < 0.000$) and FB ($p = 0.01$), SDS-waist and IL-6 ($p < 0.000$), CRP ($p = 0.002$), WBC ($p < 0.000$) and FB ($p < 0.000$). Strong positive associations were also found between IL-6 and other blood inflammatory markers and HOMA-IR, insulin, (but not glucose), systolic and diastolic blood pressure (Figure 1).

Correlation of the magnitude of changes (Δ) between different parameters are presented in Table II. Regarding all 50 patients who participated in the lifestyle intervention programme, changes of SDS-BMI and percentage body fat correlated positively with changes in IL-6 and CRP. Changes of IL-6 correlated significantly with HOMA-IR, CRP, and FB. There were strong correlations between changes of different inflammatory markers.

Clinical and biochemical parameters of subjects were used in multivariable models with changes of blood inflammatory markers' concentrations (Δ) as a dependent variable. Results are presented in Table III.

Changes in blood inflammatory markers after six months of lifestyle intervention, with the exception of fibrinogen, were independently correlated with changes in HOMA-IR and changes in adiposity.

Discussion

In this study, we examined blood inflammatory markers and their correlation to weight status and insulin resistance in obese children and adolescents before and after successful lifestyle intervention. Significant correlations were found between the degree of adiposity (as SDS-BMI and percentage of body fat) and blood inflammatory markers. Moreover, in our study, serum

Table I. *Physical and biochemical characteristics at baseline and following six months of obesity intervention programme*
Tabela I. *Charakterystyka badanej grupy w warunkach podstawowych i po 6 miesiącach modyfikacji stylu życia*

Parameter	Baseline	6 months later	D	p value
Age (years)	14.2 ± 2.6	14.8 ± 2.6	(+) 0.6 ± 0.2	0.000
Male/female, n (%)	21 (42)/29 (58)	21/29	–	–
Pubertal stage				
1 n (%)	4 (8)	3 (6)	–	–
2 n (%)	8 (16)	5 (10)		
3 n (%)	5 (10)	4 (8)		
4 n (%)	4 (8)	6 (12)		
5 n (%)	29 (58)	32 (64)		
Body mass [kg]	83.6 ± 17.5	78.25 ± 16.9	(–) 5.3 ± 3.4	0.000
BMI	30.8 ± 3.9	28.1 ± 4.2	(–) 2.7 ± 1.5	0.000
SDS-BMI	3.9 ± 1.4	2.9 ± 1.6	(–) 1.0 ± 0.6	0.000
% FAT	35.6 ± 6.9	30.9 ± 9.1	(–) 4.7 ± 4.5	0.000
Fat mass [kg]	29.9 ± 10.2	24.6 ± 10.5	(–) 5.3 ± 4.3	0.000
Waist [cm]	102.1 ± 11.5	96.7 ± 11.6	(–) 5.4 ± 4.1	0.000
SDS-waist	4.4 ± 1.4	3.5 ± 1.5	(–) 0.8 ± 0.5	0.000
SBP [mm Hg]	126.9 ± 10.7	115.2 ± 8.2	(–) 11.7 ± 7.6	0.000
DBP [mm Hg]	79.7 ± 9.3	69.2 ± 8.8	(–) 10.5 ± 6.5	0.000
IL-6 [pg/mL]	2.1 ± 0.8	1.0 ± 0.6	(–) 1.1 ± 0.6	0.000
CRP [ng/mL]	1.5 ± 0.8	0.7 ± 0.5	(–) 0.8 ± 0.5	0.000
WBC [G/L]	7.3 ± 1.4	5.9 ± 1.1	(–) 1.4 ± 0.8	0.000
FB [mg/dL]	329.2 ± 55.7	278.1 ± 40.0	(–) 51.1 ± 41.5	0.000
Glucose [mmol/L]	5.1 ± 0.5	4.9 ± 0.4	(–) 0.3 ± 0.01	0.001
Insulin [μU/mL]	21.5 ± 9.3	14.0 ± 5.6	(–) 7.5 ± 5.7	0.000
HOMA-IR	4.9 ± 2.4	3.0 ± 1.4	(–) 1.9 ± 1.5	0.000
HbA_{1c} [%]	5.7 ± 0.3	5.3 ± 0.3	(–) 0.4 ± 0.25	0.000
T-chol [mg/dL]	166.2 ± 27.0	155.4 ± 21.9	(–) 10.9 ± 8.4	0.002
HDL-chol [mg/dL]	43.5 ± 11.7	50.5 ± 11.8	[+) 7.0 ± 5.4	0.000
LDL-chol [mg/dL]	100.4 ± 24.6	85.3 ± 20.6	(–) 15.0 ± 12.7	0.000
TG [mg/dL]	128.5 ± 49.9	93.2 ± 41.0	(–) 35.3 ± 28.9	0.000

levels of inflammatory parameters positively correlated with insulin resistance, expressed as fasting insulin and insulin resistance index (HOMA-IR). Therefore, our data suggests that proinflammatory cytokine IL-6 and other blood markers of systemic inflammation are associated with insulin resistance and that these correlations can mainly be attributed to obesity [3]. A previous study also clearly demonstrated that obesity in children is associated with higher C-reactive protein concentrations and higher white blood cell counts compared to normal weight children [2]. In our study, a control group (subjects with normal body mass) was not included, because the main goal of this study was to determine the changes in inflammatory parameters associated with weight loss in obese children.

Six months of lifestyle modification through combined diet and physical exercise significantly reduced body weight and adiposity, waist circumference, blood pressure, fasting glucose, insulin, and HbA_{1c}, and improved insulin resistance and lipids' profile. Successful intervention was also associated with a significant reduction in serum IL-6, CRP, WBC, and fibrinogen levels.

It has been shown that IL-6 concentrations increase with adiposity, and that ~ 30% of circulating IL-6 may

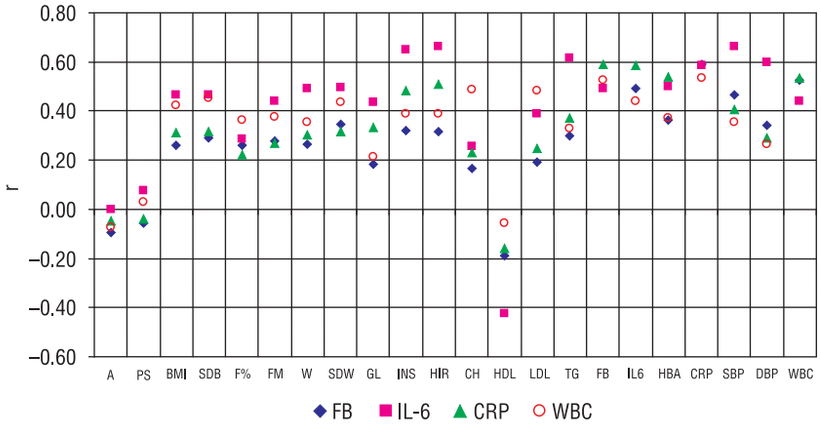

Figure 1. *Pearson's correlation coefficients of patients' characteristics and inflammatory parameters at baseline. r — correlation coefficients; A — age; PS — pubertal stage; BMI — body mass index; SDB-SDS BMI; F% — percentage body fat; FM — fat mass; W — waist; SDW — SDS waist; GL — glucose; INS — insulin; HIR — HOMA-IR; CH — total cholesterol; HDL — HDL cholesterol; LDL — LDL cholesterol; TG — triacylglycerol; FB — fibrinogen; IL6 — cytokine IL-6; HBA — HbA1c; CRP — C-reactive proteins; SBP — systolic blood pressure; DBP — diastolic blood pressure; WBC — white blood count*

Rycina 1. *Ocena zależności między badanymi parametrami a wskaźnikami stanu zapalnego w warunkach podstawowych w korelacji Pearsona*

Table II. ***Pearson's correlation coefficient of weight status, HOMA-IR, and inflammatory parameters before and after six-month lifestyle intervention***

Tabela II. ***Ocena zależności między wielkością zmian parametrów antropometrycznych, HOMA-IR i wskaźników stanu zapalnego w efekcie modyfikacji stylu życia w korelacji Pearsona***

FB		Δ SDS-BMI	Δ % fat	Δ SDS-waist	Δ HOMA-IR	Δ IL-6	Δ CRP	Δ WBC	Δ FB
Δ SDS-BMI	r	–				0.33	0.22	0.15	0.03
	P					**.020**	.128	.290	.862
Δ % fat	r		–			0.48	0.33	0.13	0.03
	P					**.000**	**.019**	.369	.835
Δ SDS-waist	r			–		0.39	0.18	0.08	0.11
	P					**.007**	.230	.605	.465
Δ HOMA-IR	r				–	0.64	0.29	0.37	0.14
	P					**.000**	**.049**	**.007**	.336
Δ IL-6	r	0.33	0.48	0.39	0.64	–	0.32	0.09	0.30
	P	**.020**	**.000**	**.007**	**.000**		**.022**	.521	**.043**
Δ CRP	r	0.22	0.33	0.18	0.28	0.32	–	0.18	0.09
	P	.128	**.019**	.230	**.052**	**.022**		.209	.568
Δ WBC	r	0.15	0.13	0.08	0.37	0.09	0.18	–	0.09
	P	.290	.369	.605	**.007**	.521	.209		.532
Δ FB	r	0.03	0.03	0.11	0.14	0.30	0.09	0.09	–
	P	.862	.835	.465	.336	**.043**	.568	.532	

be released by subcutaneous fat tissue [15]. Our results showed that serum IL-6 concentrations decreased significantly after weight loss in obese children. IL-6 seems to play an important role in weight-regulating processes: it inhibits lipoprotein lipase, down-regulates fat tissue triacylglycerol deposition, stimulates thermogenesis and satiety through the synthesis of prostaglandins and corticotrophin-releasing factor, therefore contributing to body weight homeostasis [16]. The decrease in IL-6 concentration indicates that, in the absence of acute infection, changes in body fat mass may influence serum IL-6 levels. However, previous

Table III. *Results of multivariable linear regression for associations of patients' characteristics with inflammatory parameters*

Tabela III. *Korelacje między wielkościami zmian wybranych parametrów i wskaźników stanu zapalnego w wieloczynnikowej analizie regresji*

Variable	Partial β-coefficient	p value	R^2 for multivariable model
			0.77 for Δ IL-6
Δ HOMA-IR	0.63	**.000**	
Δ Age	–0.42	**.004**	
Δ % fat	0.33	**.027**	
			0.44 for Δ CRP
Δ % fat	0.35	**.019**	
Δ Age	–0.26	.082	
Δ HOMA-IR	0.22	.160	
			0.54 for Δ WBC
Δ HOMA-IR	0.52	**.000**	
Δ % fat	0.31	**.040**	
Δ Age	–0.17	.261	
			0.29 for Δ FB
Δ HOMA-IR	0.21	.185	
Δ Age	–0.19	.226	
Δ % fat	0.19	.231	

investigations examining the ability of weight loss to alter serum IL-6 concentrations have provided mixed results. Monzillo et al. [17] found that weight reduction in obese subjects with insulin resistance was associated with a significant decrease in circulating IL-6. On the other hand, Roth et al. [18] did not find a reduction of IL-6 in the successful weight reduction group of obese children, confirming results from Olson et al. [19], who did not find changes of IL-6 and CRP after weight loss in overweight women participating in a one-year dietary and fitness programme. These disparities may be related to acute and chronic phases of the inflammatory response to exercise training. The decrease in IL-6 and CRP levels due to reduction of overweight was counterbalanced by increased muscular injury and inflammation caused by increased physical activity [20], which is an integral part of all weight reduction programmes.

C-reactive protein, a marker of inflammation and a powerful predictor of cardiovascular risk, has been previously shown to be elevated in obese patients, suggesting a state of chronic, low-grade systemic inflammation [21]. The current study showed that serum CRP concentrations decreased significantly after the intervention, although this finding was less evident than the reduction in IL-6. Heilbronn at al. [11] found that elevated CRP levels in obese women were reduced by 26%, but not normalised, after a very low-fat, energy restricted diet for 12 weeks. Previous studies have shown that serum CRP concentration is regulated by IL-6 derived from adipose tissue. We found positive correlations between serum CRP and IL-6 at baseline and after intervention, confirming that CRP is, at least in part, regulated by IL-6 from fat tissue store.

This study was the first to analyse prospectively WBC after a weight loss programme. WBC significantly decreased in response to the lifestyle intervention. Whether WBC is altered in response to weight reduction and/or plays a role in insulin resistance remains to be seen.

Conclusion

Our data showed that weight reduction in obese children, in addition to improving insulin sensitivity and lipids' profile, also leads to a significant reduction in blood inflammatory markers.

Further studies are necessary to investigate whether the association between weight loss and changes of several proinflammatory adipocytokines is causally associated with improvement of insulin resistance, and may be useful in the prevention of obesity-related disorders.

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