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Statin therapy and lipids-lowering supplements – safe and effective treatment of lipids disturbances in children

Leczenie statynami i suplementami – bezpieczna i skuteczna terapia zaburzeń lipidowych u dzieci

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Abstract

Introduction: There is a significant correlation between elevated LDL cholesterol (LDL-C) levels sustained from childhood and future vascular disease. The study aimed to evaluate the effectiveness and safety of the therapy chosen for children with lipid disorders.

Material and methods: The study group consisted of 37 children with increased LDL-C (13 boys) aged 8.99 ±4.03 years. After 6 months of behavioral treatment, study group was divided into G1 (n = 24) which continued non-pharmacological treatment supported by dietary supplements and G2 (n = 13) in which statin (5–10 mg/day) was added to non-pharmacological treatment. Analysis included: BMI Z-score, total cholesterol (TCh), LDL-C, HDL cholesterol (HDL-C) and triglycerides (TG) measured at several time points.

Results: The concentrations of TCh and LDL-C before treatment were significantly higher in G2 than in G1 ($p < 0.001$). Due to the treatment, these differences were no longer noticeable at the last visit. In G1 and G2 concentrations of TCh and LDL-C were reduced significantly, greater reduction after the treatment in TCh and LDL-C was observed in G2 than in G1. Moreover, in G1 we noticed reduction of TG after treatment ($p < 0.05$). The BMI Z-score did not change significantly through the treatment in both groups. G1 also showed a significant negative correlation between BMI Z-score and HDL-C before and after treatment ($r = –0.57$, $p = 0.009$; $r = –0.52$, $p = 0.02$). Same relationship was noticed also in G2 after treatment ($r = 0.67$, $p = 0.05$).

Conclusions: In children with dyslipidemia, regardless of its background, statin therapy is the most effective in lowering LDL-C. However, therapy with lipids-lowering supplements seems to be safe and effective.

Key words:
children, dyslipidemia, hypercholesterolemia, statins.

Streszczenie

Wprowadzenie: Istnieje istotna korelacja pomiędzy zwiększonym stężeniem cholesterolu LDL (LDL-C) w dzieciństwie a chorobami naczyniowymi w przyszłości. Celem pracy jest ocena skuteczności i bezpieczeństwa wybranych terapii u dzieci z zaburzeniami gospodarki lipidowej.

Materiał i metody: Do grupy badanej włączono 37 dzieci z podwyższonym stężeniem LDL-C (13 chłopców, 24 dziewcząt) w wieku 8.99 ±4.03 roku. Po 6 miesiącach leczenia behawioralnego, grupa została podzielona na G1 (n = 24), która była leczona niefarmakologicznie i suplementami diety i G2 (n =13), leczona niefarmakologicznie i statynami (5–10 mg/dziennie). Analizie poddano: BMI Z-score, cholesterol całkowity (TCh), LDL-C, cholesterol HDL (HDL-C) i trójglicerydy (TG), których stężenia były oceniane kilkukrotnie w trakcie obserwacji.

Wyniki: Stężenia TCh i LDL-C przed leczeniem było istotnie wyższe w G2 niż w G1 ($p < 0,001$). Dzięki leczeniu różnice te nie były dłużej istotne na ostatniej wizycie. W G1 i G2 stężenia TCh i LDL-C spadły istotnie, istotnie większa redukcja stężenia TCh i LDL-C po leczeniu była obserwowana w G2 niż w G1. Co więcej, w G1 obserwowaliśmy również istotną redukcję stężenia TG po leczeniu ($p < 0,05$). BMI Z-score nie zmienił się istotnie w badanych grupach w trakcie leczenia. Ponadto w G1 stwierdzono istotną korelację

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pomiędzy BMI Z-score i HDL-C przed terapią i po leczeniu ($r = –0,57$, $p = 0,009$; $r = –0,52$, $p = 0,02$, odpowiednio). Taka korelacja była również obecna w G2 po leczeniu ($r = –0,67$, $p = 0,05$).
Wnioski: U dzieci z dyslipidemią, niezależnie od jej przyczyny, leczenie statynami jest najbardziej efektywne w redukcji LDL-C. Aczkolwiek, leczenie suplementami diety wpływającymi na profil lipidowy wydaje się również skuteczne i bezpieczne.
Słowa kluczowe:
dzieci, dyslipidemia, hipercholesterolemia, statyny.

Introduction

Lipid disorders, known also as dyslipidemias, are the most common and poorly controlled risk factors leading to cardiovascular complications such as myocardial infarction, stroke and other cardiovascular diseases which stand for 40% of death causes among men and 49% among women in Europe [1]. Among dyslipidemia relevant to the pediatric population we can distinguish atherogenic dyslipidemia (AD) and familial hypercholesterolemia (FH). Atherogenic dyslipidemia (AD) is associated with abnormal nutritional status and includes an elevated triglycerides (TG) concentration as well as high levels of small-dense low-density lipoprotein (sdLDL) and low levels of high-density lipoprotein cholesterol (HDL-C) [2]. Around 1 in 5 children meets the criteria for childhood overweight or obesity, which are often associated with AD. Familial hypercholesterolemia is a genetic disorder inherited in an autosomal dominant pattern [3]. What is more, current data suggest a high prevalence of occurring heterozygous familial hypercholesterolemia (FH). The incidence of heterozygous FH is 1:500 in the general population [4–7]. For an individual who is left untreated, the risk of premature cardiovascular disease is increased by 100-fold [8].

According to published data, there is a significant correlation between elevated LDL cholesterol (LDL-C) levels sustained from childhood and future vascular disease. Children with high LDL-C are likely to become adults with high LDL-C [9–11]. What is more, most of guidelines are based on extrapolated data from the studies on lipid disorders in adults or FH, not from specific investigations [12]. There is a lack of reliable information about LDL-C concentration in children, which can contribute to early atherosclerosis and following cardiovascular diseases. It means, that we still do not know what LDL-C level in children is low enough to avoid future cardiovascular complications [13]. On the other hand, childhood is the optimal period for implementing treatment of dyslipidemia to prevent future cardiovascular complication. However, pharmacological intervention in children with dyslipidemia is still controversial. Especially for statin therapy.

Our study aimed to evaluate the effectiveness and safety of the therapy chosen for children with lipid disorders. Modes of therapy include a non-pharmacological intervention by a low-fat diet, physical activity and dietary supplements, such as red yeast rice, ω-3 fatty acids, plant sterols, plant stanols, as well as statin therapy.

Material and methods

The study group consisted of 37 children with increased LDL-C concentration (13 boys, 24 girls) aged 8.99 ±4.03 years (range: 2.0–17.4 years), managed in the Metabolic Outpatient Clinic. All children underwent 6 months of dietary treatment supported by increased physical activity. Every 3 months patients went to the clinic for check-ups to control fasting lipid profile (total cholesterol [TCh], LDL-C, HDL-C, TG) and periodic height, weight and BMI Z-score control.

After 6 months patients lipid results were reevaluated and due to unsatisfactory treatment results (Table I), our study group was divided into two subgroups: subgroup 1 (G1; $n = 24$) which continued non-pharmacological treatment (low-fat diet, increased physical activity) supported by dietary supplements (plant stanols, plant sterols, red yeast rice and ω-3 fatty acids); subgroup 2 (G2; $n = 13$) in which a statin preparation has been added to non-pharmacological treatment. Qualification to a particular mode of treatment and assessment of the effectiveness and safety of therapy chosen for a specified group of children with lipid disorder were based on the guidelines of the Polish Lipid Association (PoLA) from 2016 [12]. In accordance with these guidelines, after 6 months of low-lipid diet children with LDL-C concetration persistent ≥ 190 mg/dl or ≥ 160 mg/dl with other risk factors were classified to G2 treated with non-pharmacological treatment together with statins. Children under the age of 6 years and whose LDL-C concentrations on non-pharmacological treatment were still increased but below 190 mg/dl continued lifestle modification treatment with the inclusion of dietary supplements.

Further treatment was continued for the next ±3 years (range: 0.5–10.7 years). 4 children from G1 were treated with

Table I. Lipid profile of studied subjects befor and after 6 months of behavioral treatment

Parameter	Study group ($n = 37$)		
	Before behavioral treatment	After behavioral treatment	*p*
Total cholesterol [mg/dl]	257.10 ±54.51	267.89 ±53.46	NS
HDL-cholesterol [mg/dl]	62.53 ±23.91	60.14 ±17.60	NS
LDL-cholesterol [mg/dl]	177.79 ±70.00	188.79 ±57.32	NS
Triglycerides [mg/dl]	133.62 ±76.54	127.72 ±56.45	NS

NS – non-significant

monacolin K (10 mg daily). Statins, which were used in therapy in G2 were: atorvastatin (4 children) and rosuvastatin (9 children). Doses of statins were individualized and varied from 5 to 10 mg daily, depending on age, weight and impact on lipid profile of the child. Analysis included: age, sex, nutritional status (measured via BMI Z-score), fasting lipid profile including TCh, LDL-C, HDL-C and TG measured at several time points (at least 3 times – before treatment, after 6 month of initial treatment and at the last recorded visit). To monitor possible side effects of treatment alanine aminotransferase (AlAT), aspartate transaminase (AspAT) and creatine kinase (CK) were measured every 6 months during the treatment.

Anthropometrical measurements were performed by trained health care professionals (nurses/physicians) using validated equipment. Body weight was measured to the nearest 0.1 kg on a calibrated balance beam scale and body height was measured to the nearest 0.1 cm. All the lipid measurements we performed in fasting state in the same laboratory using enzymatic calorimetric method.

The study was conducted according to the Helsinki declaration and approved by the Ethics Committee of The Medical University of Silesia (KNW/0022/KB1/80/18).

Auxological data and biochemical results were compared using the Statistica 13.3 PL software. All values were expressed as mean±standard deviation. We use Wilcox test to compare the effects of treatment in each group. Differences between the groups were assessed by using U Mann-Whitney test. *P*-value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the study groups is presented in Table II. The studied groups did not differ in terms of age, BMI Z-score and time of observation. The concentrations of TCh and LDL-C before treatment were significantly higher ($p < 0.001$) in G2 than in G1 (Table III). Due to the treatment, these statistically significant differences were no longer noticeable at the last visit. In both G1 and G2 concentrations of TCh, LDL-C were re-

Table II. Characteristics of the study groups: G1 ($n = 24$, non-pharmacological treatment supported by dietary supplements) and G2 ($n = 13$, non-pharmacological treatment supported by statins)

Group	Age [years]	Sex [F/M]	BMI [kg/m^2]	BMI Z-score	Observation period [years]
G1 ($n = 24$)	8.74 ±3.57	15/9	17.25 ±3.13	0.10 ±1.31	2.82 ±2.37
G2 ($n = 13$)	9.47 ±4.88	9/4	19.32 ±4.76	0.68 ±1.06	3.59 ±3.03
p	NS	NS	NS	NS	NS

NS – non-significant

Table III. Lipid profile before and after the following treatment in the subgroups: G1 ($n = 24$, non-pharmacological treatment supported by dietary supplements) and G2 ($n = 13$, non-pharmacological treatment supported by statins)

Parameter	G1			G2		
	Before treatment (range)	After treatment (range)	*p*	Before treatment (range)	After treatment (range)	*p*
Total cholesterol [mg/dl]	274.02 ±36.79 (200.7–323.0)	206.48 ±36.11 (118.0–268.0)	< 0.0001	306.42 ±59.16* (243.0–459.0)	190.84 ±43.59 (128.0–266.0)	< 0.0001
HDL cholesterol [mg/dl]	63.47 ±18.36 (37.0–104.3.0)	58.49 ±17.08 (30.0–95.6)	NS	54.12 ±15.05 (34.3–75.1)	52.77 ±12.62 (36.2–75.1)	NS
LDL cholesterol [mg/dl]	164.92 ±35.17 (120.0–249.0)	130.87 ±36.87 (54.8–203.0)	< 0.01	232.21 ±65.11* (163.5–398.4)	115.61 ±42.57 (60.0–181.6)	< 0.0001
Triglycerides [mg/dl]	125.87 ±53.39 (43.0–221.4)	95.14 ±49.53 (46.1–257.0)	< 0.05	130.79 ±63.58 (60.0–259.0)	110.56 ±39.67 (59.0–213.0)	NS

NS – non-significant
* G1 vs. G2, $p < 0.0001$

Table IV. Delta [Δ] changes in lipid concentrations due to the treatment in both subgroups: G1 (n = 24, non-pharmacological treatment supported by dietary supplements) and G2 (n = 13, non-pharmacological treatment supported by statins)

Lipids	G1	G2	p
Δ Total cholesterol [mg/dl]	–40.54 ±42.26	–115.59 ±37.72	< 0.0001
Δ HDL-cholesterol [mg/dl]	–3.73 ±13.51	–1.07 ±10.17	NS
Δ LDL-cholesterol [mg/dl]	–32.39 ±43.12	–113.47 ±45.49	< 0.0001
Δ Triglycerides [mg/dl]	–33.70 ±61.24	–9.66 ±44.53	NS

NS – non-significant

duced significantly, however significantly bigger reduction after the treatment in TCh and LDL-was observed in G2 than in G1 (Table IV). Moreover, in G1 we noticed also significant reduction in TG concentration after treatment ($p < 0.05$). The BMI Z-score did not change significantly through the treatment in both groups (Fig. 1).

What is more, G1 also showed a significant negative correlation between nutritional status of the child (measured via BMI Z-score) and HDL-C concentration before and after treatment ($r = –0.57$, $p = 0.009$; $r = –0.52$, $p = 0.02$, respectively). Same relationship was noticed also in G2 after treatment ($r = –0.67$, $p = 0.05$). Moreover, in G2, TG concentration before statins implementation correlated with BMI Z-score ($r = 0.62$, $p = 0.04$). Neither TCh, nor LDL-C correlated significantly with BMI Z-score.

Based on clinical and biochemical evaluation (AlAT, AspAT, CK), no adverse effects of supplements and statin therapy were observed (Table V). AlAT, AspAT and CK (average CK during treatment 130.0±72.2 IU/l) stayed within the normal range in 100% of patients. Patients did not report any side effects of the statin and monacolin K treatment, including muscle aches.

Discussion

The study aimed to evaluate the effectiveness and safety of the therapy chosen for 37 children with lipid disturbances enrolled into two subgroups with different treatment modes – G1 treated with non-pharmacological treatment supported by dietary supplements and G2, where non-pharmacological treatment was supported by statins. We found that, in both groups,

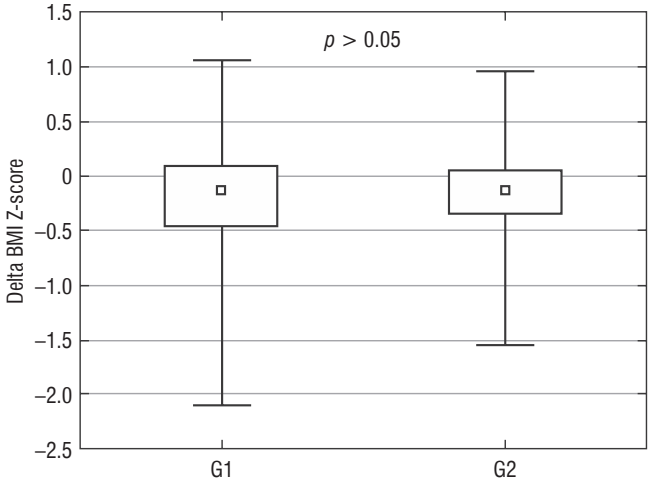

Figure 1. Delta BMI Z-score in G1 (n = 24, non-pharmacological treatment supported by dietary supplements) and in G2 (n = 13, non-pharmacological treatment supported by statins)

Table V. Alanine aminotransferase and aspartate aminotransferase evaluation in both subgroups: G1 (n = 24, non-pharmacological treatment supported by dietary supplements) and G2 (n = 13, non-pharmacological treatment supported by statins)

Parameter	G1			G2		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Alanine aminotransferase [μU/ml]	17.67 ±2.58	15.92 ±2.96	NS	24.40 ±14.94	24.58 ±19.68	NS
Aspartate aminotransferase [μU/ml]	31.80 ±8.23	31.60 ±8.08	NS	28.50 ±10.11	29.07 ±7.28	NS

NS – non-significant

G1 and G2 concentrations of TCh, LDL-C were reduced significantly, however significantly bigger reduction after the treatment in TCh and LDL-C was observed in G2 than in G1. Moreover based on clinical and biochemical evaluation no adverse effects of supplements and statin therapy were observed.

Dyslipidemia can affect up to 70% of children and tends to maintain from childhood to adulthood, leading to increase cardiovascular disease risk (CVD). However, lipids disturbances are modifiable CVD risk factor and it is extremely important to manage them from the earliest years of life to prevent or to slow down atherogenic process. First line of treatment in childhood dyslipidemia is behavioral treatment which should be implemented regardless of the disorders background [13, 14]. The pharmacological therapy is recommended in children with severe lipid disturbances in whom diet intervention, physical activity and weight management are insufficient in lowering lipids concentration [15]. In most children with secondary dyslipidemia (obesity-related, lifestyle-related) lifestyle changes tend to improve the disorders significantly. In many of these cases the problem is long-term adherence to lifestyle modification. So, as in children with FH, additional treatment is needed also in this group. We decided to include into our study children with lipids disorders regardless of disorder's cause, and after the 6 months of lifestyle modification in whose with unsatisfactory treatment results, add the pharmacological therapy or supplements lowering lipids concentration. Nowadays statins are recommended as the first choice drugs to treat dyslipidemias. Current studies suggest that for the most beneficial effect statin treatment it should be started in childhood [16]. Delay of the treatment can be a cause of a future cardiovascular diseases developed in young age [12]. Effectiveness and safety of statin usage is well studied in adults, but its ability to reduce intima media thickness was also shown in children with FH. Statins can lower not only LDL-C but also TG levels, as well as raise HDL-C [17]. In our cohort we observed significantly bigger reduction of TCh and LDL-C in children treated with statins than with supplements. But the concentration of TG and HDL-C did not change due to statin treatment. The reduction of TCh and LDL-C in children treated with lifestyle modification and supplements was also significant. In these group of children we decided to use plant stanols, plant sterols, red yeast rice and ω-3 fatty acids [18]. CHILD 2 diet recommends plant stanols and sterol esters in the lipids disorders therapy in children. They were shown to inhibit intestinal cholesterol absorbtion, leading to reduction in LDL-C up to 12%. Additionally mild reduction of TG during their usage is reported [19]. Also ω-3 fatty acids are widely accepted as a supplement used in children. Their exact mechanism of action is not clear but they reduce maily TG level [20]. We can assume that significant reduction in TG concentration after treatment in G1 can be related with both – plant stanols and sterol esters and ω-3 fatty acids supplementation. Red yeast rice supplement, monacolin K, also known as lovastatin, is an inhibitor of liver cholesterol synthesis. It is able to reduce LDL-C on average of 1.02 mmol/l (39.4 mg/dl) compared to placebo [21]. Usually it reduces LDL-C between 15–25% within 6–8 weeks of therapy [22]. Moreover monacolin K, although it has a mechanism of action similar to statins, administration was not associated with increase risk of muscle-related side effects [23]. Unfortunately most of the data about red yeast rice suplements come from observations of adult patients [24]. Data about safety and effeciency in children are very scarse [25]. So we decided to apply monacolin K in only 4 teenagers above the age of 15 years and put those children in G1, as monacolin K is still considered as a dietary supplement and not registered as a medication.

Statin-associated muscle symptoms (SAMS), such as myalgia and muscle weakness, usually mild and completely reversible after treatment discontinuation, can occur in 7–29% of patients and it is associated with CK increase [26]. Patients from our cohort did not report any side effects of the statin and monacolin K treatment, including muscle aches. AlAT, AspAT and CK stayed within the normal range in 100% of patients. Most probably the lack of side effects was related with relatively low dosage of statins and supplement. Also in the short time research of Guardamagna *et al.* [25] no adverse effects were detected when liver and muscular enzymes (AST, ALT, and CK) were determined in children treated with monacolin K. Our study showed that monacolin K can be a part of successful treatment of dyslipidemia in some cases. Despite no adverse effects reported in our study, further long-term studies are required to predict potential long-term adverse effects of statin and monacolin K as an alternative to statins usage in children [24].

Conclusions

The effectiveness of therapy in children with lipid disorders is highly related to the proper qualification of the patient for the appropriate treatment strategy and must be individualized. Regardless of the decision on pharmacotherapy, the implementation and conduct of appropriate non-pharmacological treatment is of key importance, especially in the case of atherogenic dyslipidemia associated with an abnormal nutritional status. Statin therapy is the most effective in lowering LDL-C. However, therapy with lipids-lowering supplements seems to be safe and effective.

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