Hepato-Splenic and Lipid Profile Abnormalities – Do They Exist in Children Affected with Vitiligo?

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SUMMARY Autoimmune disturbances and metabolic abnormalities observed in vitiligo, a disease of still unclear etiology, may provide evidence on the systemic nature of the disease. The aim of the study was to assess functional and morphological parameters of the liver and spleen, as well as the lipid profile in vitiligo-affected children, in order to ascertain whether any metabolic abnormalities or structural changes in these organs accompanied the course of vitiligo. The study included 34 patients with vitiligo hospitalized at the Department of Dermatology at the Medical University of Lublin and a control group of 35 healthy individuals, aged 7-15 years. Children with the active phase of vitiligo and at least 6 month history of vitiligo lesions were studied. Ultrasound examination of the liver and spleen enabled assessment of the size and parenchyma of the organs. Liver and spleen functions were assessed by means of the following additional examinations: blood test, transaminases, protein electrophoresis, lipid profile, autoantibodies, and HCV antibodies. The size of the liver was not significantly different in the vitiligo and control groups. The ultrasonographic pictures of the spleen revealed no abnormalities in organ size and structure. The concentration of HDL-cholesterol was significantly lower, whereas the concentration of LDL-cholesterol was significantly higher in patients with vitiligo than in healthy controls. The value of the LDL/HDL ratio was significantly higher in vitiligo patients. The results of our study indicate lipid disturbances in vitiligo-affected children. Since no structural and functional abnormalities in the liver and spleen were found, it seems likely that lipid disturbances in vitiligo may result from disturbed metabolic processes in the adipose tissue as well as from oxidative stress.

KEY WORDS: vitiligo, lipids, liver, spleen, melanocytes

INTRODUCTION

Vitiligo is an acquired depigmenting skin disease of still unclear, multifactorial etiopathogenesis. Even though the disease does not lead to physical ailments, its disfiguring effect may be responsible for stigmatization and decreased quality of life of the patients. A recent study has revealed that psychological disturbances, such as obsession and phobia, are more prevalent in vitiligo patients in whom autoimmune markers are present, confirming the hypothetical psychoneuro-endocrine-immunological pathogenesis of vitiligo (1). This finding seems to be suggestive of a systemic nature of vitiligo in which the clinical and psychological manifestations are interwoven and interdependent. In vitiligo, various autoantibodies are

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present and trigger autoimmune co-morbidities such as alopecia areata, autoimmune thyroid disease, Addison's disease, pernicious anaemia, diabetes mellitus, and myasthenia gravis (2,3). When diabetes mellitus is diagnosed in addition to vitiligo, and if other components of a metabolic syndrome are detected, may eventually lead to the development of cardiovascular diseases as well as cardiovascular death. A recent study has found that insulin resistance as well as some lipid profile disturbances may be observed in patients with vitiligo (4). Since research into immunological and metabolic abnormalities indicates that these may occur in patients with vitiligo, it seems essential to check these patients for such disturbances or abnormalities. Metabolic processes take place in bodily organs such as the liver, spleen, and pancreas, so these organs should therefore be subjected to close scrutiny in patients with vitiligo. However, it still remains unclear when these abnormalities start occurring in the course of vitiligo, and if they can appear in children with vitiligo. So far, few published reports have provided information on metabolic disturbances detected in adults suffering from vitiligo, let alone children.

The aim of this study was to assess the size and structure of the liver and spleen using ultrasound, along with the functional parameters of the organs and a lipid profile in children with vitiligo.

MATERIAL AND METHODS

The study included 34 children with vitiligo hospitalized in the Department of Dermatology, Venereology and Paediatric Dermatology at the Medical University of Lublin, Poland, as well as 35 healthy subjects. All the studied children had negative history of lipid disturbances and familial dislipidaemia. None of the patients was on special diet nor had any special dietary habits. The age of the children in the vitiligo and control group was 7-15 years, the mean age being 10.9 and 10.5 years respectively. Only those children with vitiligo who had the active phase of the disease and at least six months of skin lesions exacerbation were included in the study. Information on the children's gender, duration of vitiligo, type of disease, total skin involvement (Figure1), family history, and presence of concomitant autoimmune disease was obtained from patients' records and physical examination (Table 1). The children who had a history of heart disease, arterial hypertension, diabetes mellitus, obesity, or systemic diseases were excluded from the study.

Vitiligo activity was assessed with the use of Vitiligo Disease Activity (VIDA) Score which is a six-point scale with the following grading: VIDA Score +4 – activity of 6 weeks or less duration; +3 – activity of 6 weeks to 3 months; +2 – activity of 3 – 6 months; +1 – activity of 6 – 12 months; 0 – stable for 1 year or more; and -1 – stable with spontaneous repigmentation since 1 year or more (5).

In both the vitiligo and control group the liver and spleen ultrasound examinations were performed using Siemens Sonoline Elegra ultrasonoghraph (Siemens, Erlangen, Germany) with 3.5 HHz and 5 MHz transducers of a convex type. The size and parenchyma of the organs was assessed. In order to determine liver size, measurements in three vertical lines were

Table 1. Demograpical and clinical characteristics of children with vitiligo and healthy children*

Characteristics	Category	Parameter	Vitiligo	Healthy children	p
Number of patients		n	34	35	
Gender	Male	%	61.8	45.7	>0.05
	Female	%	38.2	54.3	
Age (years)		Min-Max	7-15	7-15	>0.05
		M±SD	10.9±2.0	10.5±2.3	
Height (cm)		Min-Max	115-170	110-173	>0.05
		M±SD	141.6±13.4	143.0±17.0	
Weight (kg)		Min-Max	19-50	19-63	>0.05
		M±SD	34.6±8.2	37.2±12.5	
BMI (kg/m^2)		Min-Max	13.2-23.6	13.4-25.0	>0.05
		M±SD	17.0±2.1	17.6±2.8	
Duration of vitiligo (years)		Min-Max	0.5-9.0		
		M±SD	2.1±0.8		
Total skin involvement	<5%	%	35.3		
	5%-10%	%	47.1		
	10%-15%	%	14.7		
	>15%	%	2.9		

* Abbreviations: Min – minimum, Max – maximum, M – mean, SD – standard deviation.

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performed: in the right front axillary line, in the central line of the right clavicle, and in the central line of the body in the section going through the long axis of the aorta. The spleen was measured in two dimensions, longitudinal and transverse.

Blood samples were collected from both group after a 12-hour fast. The following examinations were performed: blood test, transaminases, glucose, electrophoresis of proteins, lipid profile, autoantibodies, and HCV (hepatitis C virus) antibodies. Concentrations of lipid profile were assayed using bio-Merieoux (Craponne, France) kits: LDL (Low-density lipoprotein) Cholesterol/Phospholipides; HDL (High-density lipoprotein) Cholesterol/Phospholipides; Cholesterol enzymatique PAP; Phospholipides enzymatique PAP; and Triglycerides enzymatique PAP UV 250, in accordance with the manufacturer's instructions.

Statistical analyses were performed using STATISTICA Software (StatSoft, Tulsa, OK, USA). Categorical variables were given as percentages and compared with a χ^2 test. For numerical variables, minimums, maximums, means, and standard deviations were estimated. Numerical variables were compared between group using independent-samples Student's test, Cochran-Cox test, or Mann-Whitney U test. In order to examine the correlation between

Table 2. Comparison of ultrasonographic and laboratory examinations between children with vitiligo and healthy children*

Characteristics	Vitiligo		Healthy children		p
	Min-Max	M±SD	Min-Max	M±SD	
Liver size					
Liver anterior axillary line (cm)	9.0-14.8	12.4±1.5	10.1-16.0	12.4±1.5	>0.05
Liver medioclavicular line (cm)	7.0-13.1	10.7±1.4	8.7-14.0	11.1±1.4	>0.05
Liver sternal line (cm)	6.4-12.8	9.1±1.3	6.8-12.0	9.5±1.3	>0.05
Spleen size					
Spleen longitudinal section (cm)	7.0-13.0	9.3±1.4	7.2-12.0	9.4±1.4	>0.05
Spleen transverse section (cm)	2.8-5.1	3.6±0.5	2.8-4.5	3.5±0.5	>0.05
Blood tests					
HBG (g/dL)	10.7-15.5	13.0±1.1	11.4-14.8	13.3±0.9	>0.05
RBC (M/mm^3)	3.6-5.4	4.4±0.4	3.9-4.9	4.4±0.3	>0.05
WBC (K/mm^3)	3.8-12.4	6.8±2.4	4.2-11.4	7.0±1.6	>0.05
Plt (K/mm^3)	140.8-330.0	248.2±80.8	176.0-343.2	245.0±68.1	>0.05
Transaminases					
ALT (IU/L)	9.0-33.6	19.7±7.9	6.0-38.4	17.7±8.4	>0.05
AST (IU/L)	5.0-38.0	19.0±8.0	9.3-36.0	22.6±8.0	>0.05
Electrophoresis of proteins					
Total proteins (g/L)	6.0-7.8	7.0±0.5	6.5-7.9	7.2±0.4	>0.05
A/G	0.9-1.8	1.4±0.2	0.9-1.7	1.3±0.2	>0.05
Albumin (%)	48.0-64.3	58.2±4.4	47.8-62.4	56.9±3.7	>0.05
Alpha1-globulins (%)	3.4-6.6	4.4±1.1	3.3-7.3	4.7±1.3	>0.05
Alpha2-globulins (%)	7.4-13.7	10.3±2.2	7.8-15.7	11.2±2.0	>0.05
Beta-globulins (%)	10.4-16.0	12.7±1.8	9.9-16.5	13.0±1.8	>0.05
Gamma-globulins (%)	7.8-22.1	14.3±4.3	11.8-17.1	14.3±1.7	>0.05
Lipid profile					
Total cholesterol (mg/dL)	125.8-199.5	170.8±15.2	112.8-190.6	161.6±21.3	0.055
HDL-cholesterol (mg/dL)	32.8-65.0	49.4±8.0	37.5-75.5	53.8±7.7	0.001
LDL-cholesterol (mg/dL)	70.8-134.8	107.2±15.8	52.0-123.4	92.4±18.9	0.030
LDL/HDL	1.3-3.1	2.2±0.5	0.9-2.5	1.7±0.4	0.000
Triglyceride (mg/dL)	44.7-146.0	104.3±29.9	44.6-150.0	101.3±27.1	>0.05
Phospholipids (mg/dL)	137.6-216.0	174.9±17.5	112.6-222.0	171.9±25.8	>0.05
HDLF (mg/dL)	59.5-108.0	81.1±13.0	63.2-102.3	81.7±10.9	>0.05
LDLF (mg/dL)	51.4-108.0	74.8±14.4	38.1-111.0	74.0±16.7	>0.05

*Abbreviations: Min – minimum, Max – maximum, M – mean, SD – standard deviation. HDL – high-density lipoprotein, LDL – low-density lipoprotein, LDLF – LDL cholesterol/phospholipides; HDLF – HDL cholesterol/phospholipids, HGB – hemoglobin , RBC – red blood cells, WBC – white blood cells, Plt – platelets)

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ultrasonographic liver size and lipid profile parameters, Pearson's correlation coefficient was used. A p-value<0.05 was considered statistically significant.

RESULTS

Table 1 presents demographic information and medical data concerning both groups of children. No significant differences were observed with reference to the height, weight, and body mass index (BMI) of children with vitiligo and the healthy children. Three children with vitiligo (8.82%) had a positive family history of vitiligo. In one child, concomitant autoimmune thyroid disease was present. Nineteen children (55.88%) had a common type of vitiligo, whereas 15 (44.12%) had a focal type of vitiligo. None of the children presented mucosal vitiligo changes.

The 3 mean values of liver size were not significantly different in the experimental and control group (Figure 2). Ultrasonographic assessment did not reveal any abnormalities in the size and structure of the organ (Figure 3). There were no significant differences between patients with vitiligo and healthy individuals in the following parameters: blood test, transaminases, glucose, and electrophoresis of proteins.

Lipid profile analysis revealed a significantly lower HDL-cholesterol concentration (p=0.001) and a significantly higher LDL-cholesterol concentration (p=0.030) in patients with vitiligo in comparison with the healthy children. Moreover, the value of the LDL/HDL ratio was significantly higher in patients with vitiligo than in healthy individuals (p=0.000096). The difference in the total cholesterol concentration between the vitiligo and control group was close to statistical significance (p=0.055). The concentrations of other lipids including triglyceride, HDL-phospholipids, and LDL-phospholipids, were not statistically different between the experimental and control group (Figure 4, Table 2). The statistical analysis of possible correlation between ultrasonographic liver size and lipid profile parameters revealed a positive correlation between the size of the liver measured in the anterior axillary line and the LDL/HDL ratio, a phenomenon which was not observed in healthy children (Figure 5).

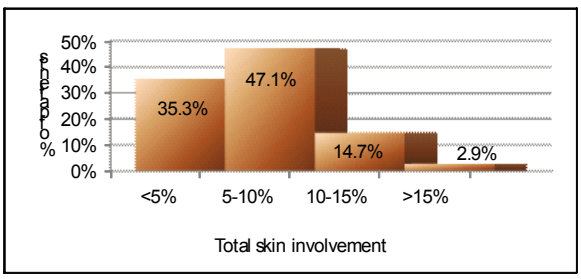

Figure 1. Histogram showing total skin involvement in the 34 cildren with vitiligo

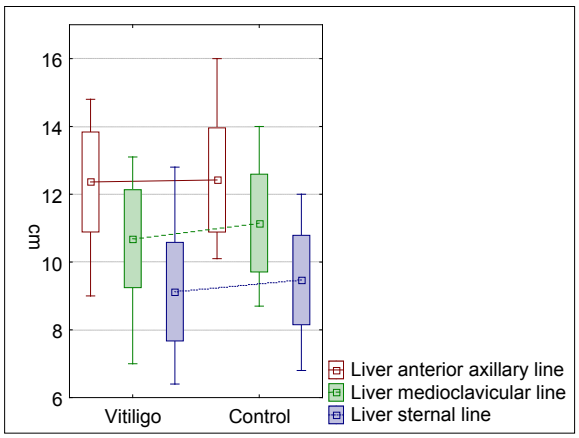

Figure 2. Box and whisker plots comparing liver size in children with vitiligo and healthy controls

DISCUSSION

The process of lipid digestion would be incomplete without the contribution of the bile salts as well as pancreatic lipase, therefore, the role of the liver and pancreas must be perceived as indispensible in the normal lipid metabolism.

Having reacted with water-soluble proteins (usually apoproteins), lipids, which are insoluble in blood, are transported as chylomicrons or lipoproteins. Next, they are absorbed by the liver cells to produce various lipoprotein forms, such as VLDL, LDL, which carry the lipids to the body cells, whereas their excess will be invariably converted into the adipose tissue. Another form of lipoprotein, such as HDL, which transports the lipids back to the liver, has an important role in reverse cholesterol transport (6).

According to some recent reports, the adipose tissue not only accumulates the excess energy but it is also an important organ fulfilling the endocrine (secretory) function. The white fat tissue, for example, secretes a number of bioactive substances (hormones, cytokines, other proteins) known as adipokines, e.g. leptin, adiponectin, resistin, vaspin, visfatin as well as

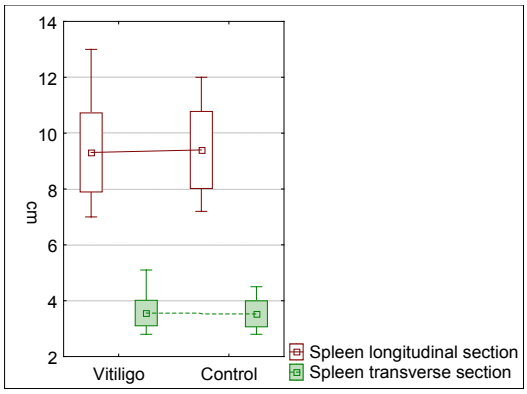

Figure 3. Box and whisker plots comparing spleen size in children with vitiligo and healthy controls

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TNFα, IL-6, MCP-1, which are involved in various processes such as glucose and lipid metabolism as well as immunity. Nevertheless, it appears that should any disturbances in their secretion occur, they may contribute to the development of the metabolic syndrome and cardiovascular disease. Thus, it is quite plausible that obesity is associated with insulin resistance, hyperglycemia, dyslipidaemia, hypertension and prothrombotic and proinflammatory states (7, 8).

The number of recent studies on various concomitant disturbances in patients with vitiligo indicates a growing interest among specialists who have started seeing vitiligo not merely as a separate entity but rather as a much more complex condition with a potential to trigger the development of generalized abnormalities of a systemic nature. Thus, it seems essential that once vitiligo has been diagnosed, the doctor should be on the lookout for possible comorbidities. Vitiligo pathogenesis, in which genetic, immunological, autoimmunological, cytotoxic, neuronal, and inflammatory factors are involved, is complex and still unclear, which may explain a wide spectrum of its systemic manifestations. Karadag *et al.* (4) have found that even in patients with vitiligo that are free of diabetes a higher insulin resistance as well as higher insulin and C-peptide levels were observed in comparison with the control group. The same study also reported a statistically significant decrease in HDL-cholesterol concentration in patients with vitiligo, and an increase in LDL/HDL ratio. Our study, performed on a group of children, generated similar results; however, we detected a statistically significant higher LDL-cholesterol concentration.

In 2000, we published a report on lipid serum parameters in vitiligo-affected girls, in which we demonstrated a statistically relevant decrease in HDL cho-

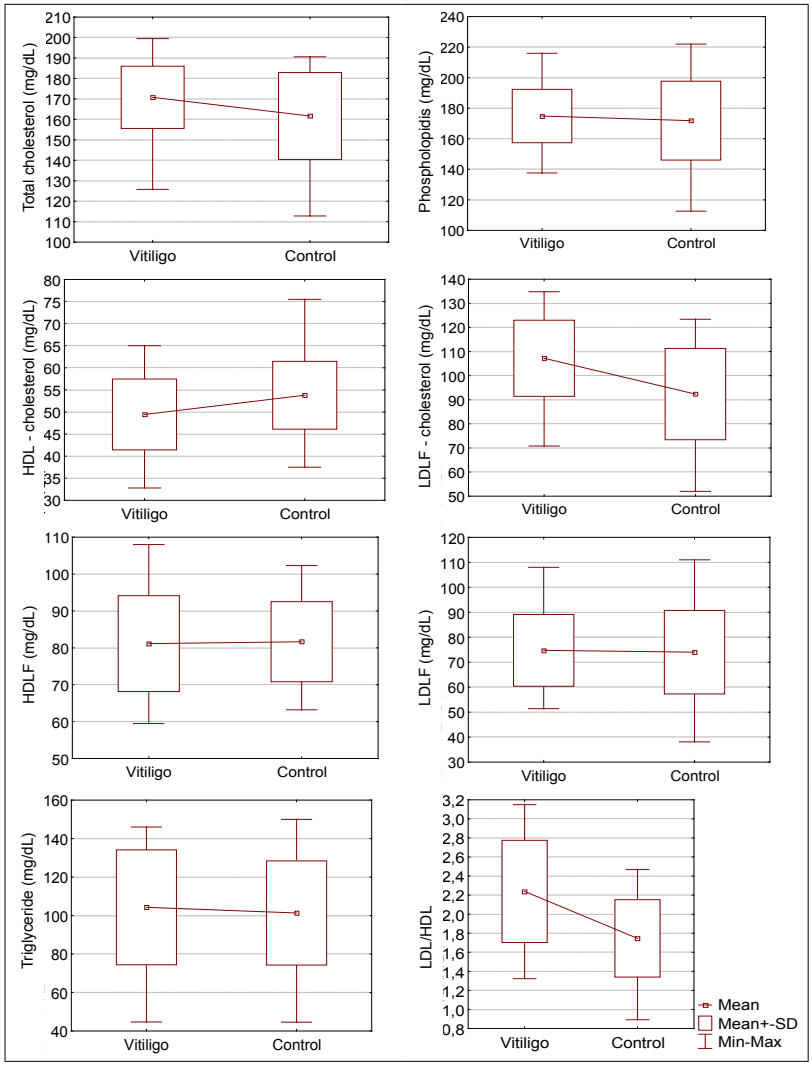

Figure 4. Box and whisker plots comparing lipids in the experimental and control group. Min – minimum, Max – maximum, SD – standard deviation. HDL – high-density lipoprotein, LDL – low-density lipoprotein, LDLF – LDL cholesterol/phospholipides; HDLF – HDL cholesterol/phospholipids

lesterol as well as increased triglyceride concentrations in the group of girls with vitiligo. Additionally, a tendency increased LDL cholesterol and decreaseed HDL phospholipid concentrations in patients with vitiligo was noted (9).

These findings may reflect some ongoing abnormal metabolic processes in patients with vitiligo which should be regarded as significant contributing factors worth considering in the management of patients with vitiligo.

Interestingly, Noel *et al.* (10) describe a 55- year-old male in whom treatment with high doses of simvastatin resulted in the regression of vitiligo. This unexpected effect of HMG-Co reductase inhibitor may indicate that lipid profile abnormalities are in some way connected with the presence and severity of vitiligo. The authors concluded that the use of statins as immuno-modulators could be beneficial in the treatment of vitiligo.

The above mentioned lipid and glucose abnormalities are components of a metabolic syndrome, a condition which may lead to the development of cardiovascular complications. Numerous researchers have made an attempt to evaluate the prevalence of metabolic disturbances and cardiovascular disease in inflammatory conditions, including skin and rheumatological diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, lupus erythematosus, or lichen planus. Studies have shown that, among others, proinflammatory cytokines (tumor) necrosis factor (TNF), interleukin 1, interleukin 6 (IL-1, IL-6) and other inflammatory factors (e.g. C-reactive protein) are involved in evoking insulin resistance as well as other metabolic complications and atherosclerosis (11). In a very recent report, Karadag *et al.* (12) demonstrated that patients with vitiligo had higher levels of homocysteine, which not only inhibits tyrosinase, but also increases cardiovascular risk.

In 2010, Nunes and Martins (13) published a case report presenting a male patient with long-lasting vitiligo in whom a myocardial infarction was diagnosed. The patient had also been instructed to avoid sun exposure. Laboratory investigations performed on the patient revealed, among others, a low plasma 25-hydroxy vitamin D level, which is known to be associated with cardiovascular disease. The authors concluded that vitiligo could be associated with hypovitaminosis D.

According to recent reports, the role of melanocytes in the development of metabolic complications should be considered in greater detail. Melanocytes are found not only in the skin and hair follicles but also in the retinal pigment epithelium cells as well as in some cells of the inner ear and other parts of the central nervous system. This provides explanation for the occurrence of such clinical syndromes as Alezzandrini's syndrome or Vogt-Koyanagi-Harada's syndrome (10). Melanocytes have also been detected in adipose tissue where they take part in anti-inflammatory reactions and in the reduction or binding of reactive oxygen species (ROS), acting as scavengers of free radicals and other oxidative species. While it has been shown that melanogenesis is higher in obese humans in comparison with individuals with healthier BMI values (7), this is beyond the scope of the present study since we have excluded obese children from our study. The lack of metabolic disturbances such as obesity, hypertension, diabetes mellitus, insulin resistance in the studied children as well as a relatively short vitiligo history (M 2.1±0.8 years) may explain the not statistically different values of the total cholesterol, triglyceride, HDL-phospholipids and LDL-phospholipids between the studied and control groups as well as the absence of a more advanced lipid disturbances' development.

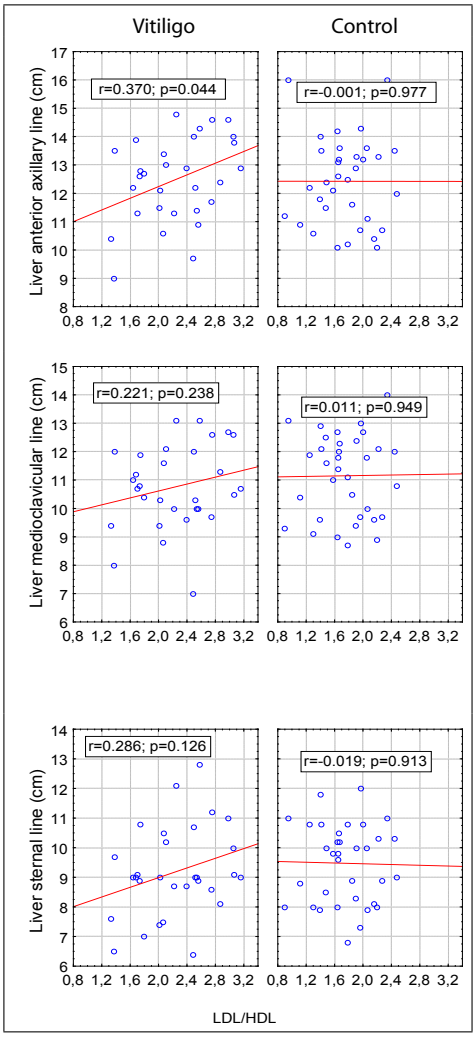

Figure 5. Scatter diagrams investigating the relationships between LDL/HDL ratio and liver size, separately for the children with vitiligo and healthy controls (HDL - High-density lipoprotein, LDL - Low-density lipoprotein)

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As previously mentioned, there is a strong correlation between melanocytes and oxidative stress, i.e. the higher the activity of melanogenesis the lower the oxidiative stress. However, there have been no studies on the contents or activity of melanocytes in the adipose tissue or on the metabolic processes taking place in vitiligo-affected patients. It is possible that lipid abnormalities detected in patients with vitiligo are the result of disturbed metabolic processes in the adipose tissue.

Interestingly, Page *et al.* (14) have suggested a hypothesis that agonists of melanin production such as melanocyte-stimulating hormone (α-MSH) or its synthetic analogues should be tested as potential therapeutic agents for prevention of development of metabolic syndromes.

Since the synthesis of carbohydrates, proteins, and lipids takes place in the liver, one might expect its involvement in vitiligo. However, it is worth noting that in our ultrasonographic assessment both the liver and spleen remained unchanged.

As oxidative stress is known to be present in the course of vitiligo, it is held responsible for the cytotoxic effects that it exerts on melanocytes, e.g. high H_2O_2 levels that are found throughout the epidermis (15). The processes promoting lipid peroxidation that occur in the epidermis, and perhaps in the adipose tissue as well, may be a plausible explanation for the lipid abnormalities detected in our study.

CONCLUSIONS

The results of our study are indicative of lipid disturbances in vitiligo-affected children .

Ultrasound examination revealed no abnormalities with reference to the size and structure of both the liver and spleen, nor did biochemical investigation reveal any dysfunctions of the liver and spleen.

Since no structural and functional abnormalities in the liver and spleen were found, it seems plausible that lipid disturbances in vitiligo may result from disturbed metabolic processes in the adipose tissue.

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