

SEA BUCKTHORN PULP OIL TREATMENT CAN PREVENT METABOLIC SYNDROME IN HYPERTRIGLYCERIDEMIC WAIST FENOTYPE OBESE CHILDREN

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Abstract

The aim of this study was to determine the effects of Sea Buckthorn pulp oil intake (800 mg/day, 60 days) in hypertriglyceridemic waist phenotype obese children.

Forty one obese children (10-18 years old) and thirty controls were involved. Modified ATP III (Adult Treatment Panel III) cut points for serum triglycerides (≥ 110 mg/dL) and waist circumference (≥ 90 th percentile for age and sex) were used to divide obese children. Hypertriglyceridemic waist phenotype (n=17) and obese nonhypertriglyceridemic (n=24) obese groups were formed. Metabolic and inflammatory parameters were measured before and after sea buckthorn therapy.

Metabolic syndrome was present in 14.25% obese children and all these subjects were from hypertriglyceridemic waist phenotype group. Comparing the obese groups, in hypertriglyceridemic waist phenotype obese children, the values for triglycerides (p<0.001), uric acid (p<0.004), C peptide (p<0.04), leptin (p<0.04), alanine aminotransferase (ALT) (p<0.05) and waist circumference (p<0.02), were increased, while high density lipoprotein-cholesterol (HDL-C) (p<0.01) was decreased. After treatment, triglycerides, blood pressure, leptin, C peptide and ceruloplasmin were decreased, while albumin was increased.

In conclusion, in hypertriglyceridemic waist phenotype obese children, sea buckthorn pulp oil therapy (800mg/day, 60 days) prevents metabolic syndrome, by reducing triglyceridemia and blood pressure. Also, the treatment has a weak antiinflammatory effect.

Rezumat

Scopul acestui studiu este de a determina efectul uleiului din fructul de cătină (800 mg/zi, 60 zile) la copiii obezi cu hipertrigliceridemie și cu circumferința taliei mare.

Patruzeci și unu de copii obezi (10-18 ani) și treizeci de subiecți control au fost implicați în studiu. Criteriile ATP (*Adult Treatment Panel III*) modificate pentru trigliceridemie (≥ 110 mg/dL) și pentru circumferința taliei (≥ 90 percentile conform vârstei și sexului) au fost utilizate pentru a forma subgrupe. Astfel, s-au format subgrupa copiilor obezi cu hipertrigliceridemie și cu circumferința taliei mare (n=17) și subgrupa copiilor

obezi cu normotrigliceridemie (n=24). Parametrii metabolici si de inflamatie au fost masurati inainte si dupa tratament.

Sindromul metabolic a fost prezent la 14.25% dintre copiii obezi si toti acesti subiecti erau din subgrupa celor cu hipertrigliceridemie. Comparand subgrupele copiilor obezi, cei cu hipertrigliceridemie aveau valori crescute pentru: trigliceride ($p<0.001$), acid uric ($p<0.004$), peptidul C ($p<0.03$), leptina ($p<0.04$), alanin aminotransferaza (ALT) ($p<0.05$) si circumferinta taliei ($p<0.02$), iar HDL-C ($p<0.01$) era semnificativ scazut. Dupa tratament, trigliceridele, tensiunea arteriala, leptina, peptidul C si ceruloplasmina au fost reduse, iar albumina a crescut.

In concluzie, la copiii obezi cu fenotip hipertrigliceridemic si cu circumferinta mare a taliei, tratamentul cu ulei din fructul de catina (800 mg/zi, 60 zile) previne sindromul metabolic, prin reducerea trigliceridemie si a tensiunii arteriale. De asemenea, tratamentul are un efect slab antiinflamator.

Keywords: childhood obesity, metabolic syndrome, sea buckthorn

Introduction

It is estimated that four percent of all youth and 30 percent to 50 percent of overweight children suffer from metabolic syndrome. It was demonstrated that every 0.5 kg/m^2 increase in body mass index (BMI) in overweight children and adolescents was associated with approximately a 50 percent increase in the risk of metabolic syndrome. The identification of children with metabolic syndrome is very important, because appropriate management may decrease the progression to type II diabetes mellitus (T2DM) [1].

Puberty is a crucial time for the development of the metabolic syndrome because of hormonal and lifestyle modifications (decrease in physical activity and unhealthy eating habits). Body fat, blood pressure and lipids are all affected by puberty [2,3,4,5]. Transient insulin resistance peaks at mid puberty. Central obesity or ectopic fat storage, coupled with increased susceptibility to insulin resistance, may contribute to the development of the metabolic syndrome in childhood [2].

Puberty alerts some of the inflammatory markers associated with endothelial dysfunction in obese children. Leptin concentration rises and soluble leptin receptor decreases in pubertal time period in lean adolescents, indicating leptin resistance. What happens with leptin in obese children remains unknown [5]. Leptin did not appear to have a major role in metabolic syndrome, even though it was strongly associated with obesity parameters [6, 7].

It was demonstrated that daily consumption of food rich in natural antioxidants may improve endothelial function in adolescents with metabolic syndrome [8]. The sea buckthorn pulp oil is rich in vitamin E, K,

carotenoids, fatty acids (67% unsaturated) and phytosterols and has antioxidant, anti-inflammatory and hypolipidaemic effects [9]. We designed this study to determine the effect of Sea buckthorn (*Hippophae rhamnoides*) pulp oil treatment in obese children.

Materials and Methods

A total of 41 overweight and obese children (obese group, 22 boys and 19 girls) and 30 healthy lean children (control group, 16 boys and 14 girls) were enrolled. Children under medication or those with chronic disease (endocrine disease, hereditary disease, or systemic inflammation) were excluded. All subjects were nonsmokers. The study protocol was approved by the Ethical Commission of "Carol Davila" University of Medicine, Bucharest, Romania and a written informed consent was obtained from each parent.

In the first two months patients were given a placebo. In the next two months the dietary supplement (400mg/tablet, Hofigal product) was administered, 2x1 tablets/day, during meals. A washout period was not considered necessary. The children took the supplement without changing their life style (diet habit or physical activity) during the two months of treatment. The general practitioner was involved in monitoring the treatment. The analytic evaluations were performed after two months of treatment with the dietary supplement *versus* after placebo treatment.

Modified ATP III (Adult Treatment Panel III) cut points for serum triglycerides (≥ 110 mg/dL) and waist circumference (≥ 90 th percentile for age and sex) were used to divide obese children. Hypertriglyceridemic waist phenotype (HTW, n=17) and obese nonhypertriglyceridemic (nonHTW, n=24) groups were formed. IDF (International Diabetes Federation) criteria for metabolic syndrome were used to identify children with this disease.

Clinical characteristics. Anthropometric measurements: body mass index (BMI), waist/hip ratio (WHR), waist circumference (WC), hip circumference (HC), were assessed. BMI was calculated as body weight (kg) divided by square height (m^2) (Table I) [10].

Biochemical measurements. Blood samples were taken after an overnight fast. Metabolic markers: serum creatinine, urea, uric acid were measured by colorimetric methods in the clinical laboratory. Standard enzymatic methods were used for measuring levels of fasting serum glucose, serum lipids (total cholesterol, high-density lipoprotein-cholesterol - HDL-C, triglycerides) [7, 11]. Low-density lipoprotein-cholesterol (LDL-C) was calculated according to the Friedewald equation [11]. Enzymes activities for alanine aminotransferase (ALT) and for γ -Glutamyl transferase

(γ -GT) were performed by standard methods using an automatic analyzer HITACHI and kits from Diasys (Germany). Enzyme-linked immunosorbent assays (ELISA) methods were used for: leptin (EIA-2395 kit, DRG Instruments GmbH, Germany) and C peptide (DNOV112-kit, NovaTec Immunodiagnostica GmbH, Germany). The source of variation between the control group and the obese subjects was assessed by the unpaired Student t-test. Correlations were calculated using Pearson coefficient.

Results and Discussion

Clinical data are presented in tables I-III.

Table I

Comparison of clinical data between groups

Parameters	Control group (n=30)	HTW group (n=17)	nonHTWgroup (n=24)	<i>p</i>	<i>p''</i>
Age (years)	13.2± 4.9	12.75 ± 4.84	12.9±4.7	Ns	Ns
Sex (F/M)	14/16	7/10	12/12	Ns	Ns
Weight (kg)	44.82 ± 10	84.66 ±16.02	68.16 ±15.1	<0.00 1	Ns
Height (m)	1.60± 0.11	1.62 ± 0.05	1.57 ± 0.06	Ns	Ns
BMI (kg/m ²)	18.81 ± 1.7	30.2 ± 2.4	29.7±3.1	<0.00 1	Ns
WC (cm)	67.4 ± 6.6	102.83 ± 16.75	86.75 ± 9.2	<0.00 1	p<0.0 2
HC (cm)	83.46 ± 7.1	109.97 ± 15.5	99.97 ± 10.5	<0.00 1	Ns
WHR	0.8 ± 0.07	0.93 ± 0.05	0.86 ± 0.03	<0.00 1	Ns
SBP mmHg	97.3 ± 5.2	116.62 ± 8.78	110.02 ± 5.08	<0.00 1	Ns
DBP mmHg	59.25 ± 2.6	76 ± 4.9	72.36 ± 5.3	<0.00 1	Ns
Cholesterol mg/dL	134.46± 16	162.16± 28.27	185.16± 34.5	<0.01	Ns
Triglycerides mg/dL	68.4±28.7	159.5±49.4	79.15±33.5	<0.00 1	<0.00 1
HDL-C mg/dL	53.37±12.98	44.8±13.5	58.31±12.44	<0.04	<0.01
LDL-C mg/dL	81.7 ± 7.7	91.4±30.4	111.63±13.5	Ns	Ns

HTW group-hypertriglyceridemic waist phenotype obese children, **nonHTWgroup**-nonhypertriglyceride-mic waist phenotype obese children, BMI-body mass index, WC-waist circumference, HC-hip circumference, SBP-systolic blood pressure, DBP-diastolic blood pressure; *p* value represents the *t* test result of comparison the obese *versus* the control groups and *p''* value represents the t-test result of comparison hypertriglyceridemic waist phenotype obese children (HTW) *versus non* hypertriglyceridemic waist phenotype obese children (nonHTW).

Table II
Metabolic parameters

Parameters	Control	HTW group	nonHTWgroup	<i>p</i>	<i>p</i> "
Uric Acid mg/dL	4.48 ± 0.5	6.43± 1.45	5.17±0.7	<0.002	<0.004
γ -GT (UI/L)	13.85 ± 1	18.9 ±5.8	14.33 ±4.9	<0.001	<0.01
Glycemia mg/dL	85.2 ± 3.4	84.33±6.8	87.4±7.1	Ns	Ns
ALT(UI/L)	13.07 ± 2	23.0± 9.1	16.78±8.3	<0.04	<0.05
Creatinine mg/dL	0.80±0.15	0.77±0.07	0.75±0.1	Ns	Ns
Bilirubin mg/dL	0.55±0.29	0.48 ±0.29	0.56 ±0.33	Ns	Ns
Leptin (ng/mL)	2.16±1.3	23.14± 12.3	13.7±7.8	<0.001	<0.04
C peptide(ng/mL)	1.08±0.4	2.38±1.48	1.4±0.9	<0.01	<0.03
Fibrinogen (g/L)	3.23±0.12	3.26± 0.27	3.27±0.22	Ns	Ns
CRP (mg/dL)	0.95±0.5	2.18±2.10	2.21±1.7	<0.04	Ns
Ceruloplasmin(mg/dL)	27.55 ± 3	35.89 ±4.45	33.79 ±4.33	<0.01	Ns

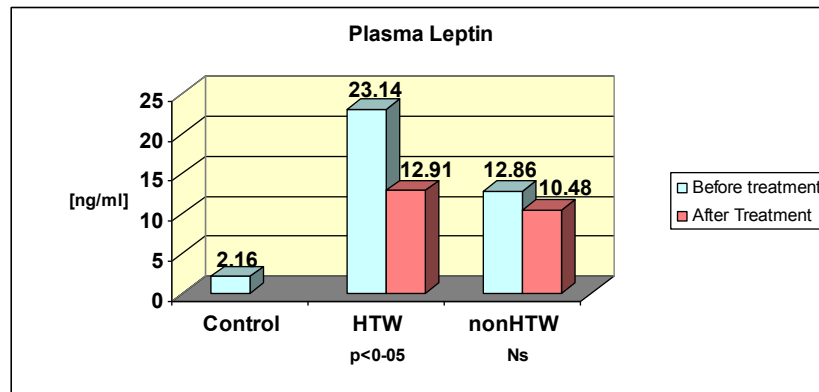
HTW group-hypertriglyceridemic waist phenotype obese children, **nonHTWgroup**-nonhypertriglyceride- mic waist phenotype obese children, (γ-GT), gama glutamyl transferase; (ALT), alanine aminotransferase; (CRP), C-reactive protein ; *p* value represents the ttest result of comparison obese versus control groups and *p*" value represents the t-test result of comparison the hypertriglyceridemic waist phenotype obese children (HTW) versus the **non** hypertriglyceridemic waist phenotype obese children (nonHTW).

Table III
Modified parameters after treatment

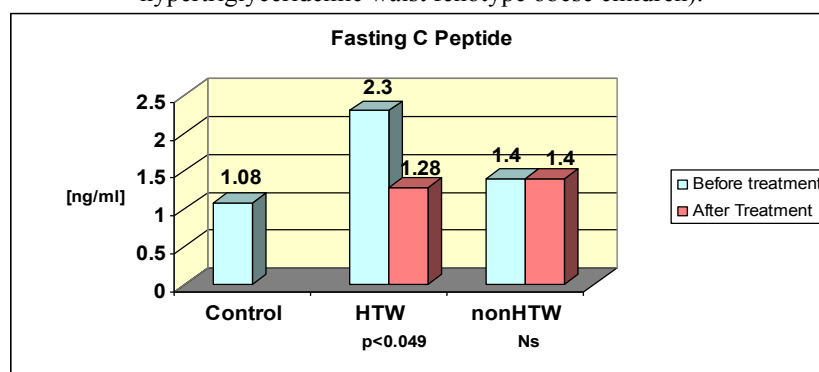
Parameters	HTW, hypertriglyceridemic waist phenotype obese children (n=17)		nonHTW, non hypertriglyceridemic waist phenotype obese children (n=24)	
	Before treatment	After treatment	Before treatment	After treatment
Triglycerides (mg/dL)	159.5±49.4	99.72±36.8*	79.15±33.5	80.21±30.8
SBP mmHg	116.62 ± 8.78	105.8 ± 6.68**	110.02 ± 5.08	103.15 ± 4.2*
DBP mmHg	76 ± 4.9	66.36 ± 5.04*	72.36 ± 5.3	66.31 ± 4.95*
Leptin ng/mL	23.14± 12.3	12.91± 8.9**	12.86±7.8	10.48± 6.8
Ceruloplasmin (mg/dl)	35.89 ±4.45	27.55 ± 5.07**	33.79 ±4.33	30.49 ± 5.5
Albumin (g/dl)	3.87 ± 0.29	4.17 ± 0.35**	3.9 ± 0.29	4.18 ± 0.24*
C peptide (ng/mL)	2.3±1.48	1.28±0.28**	1.4±0.41	1.4±0.46

The *t* test results. **p*<0.01, ***p*<0.05

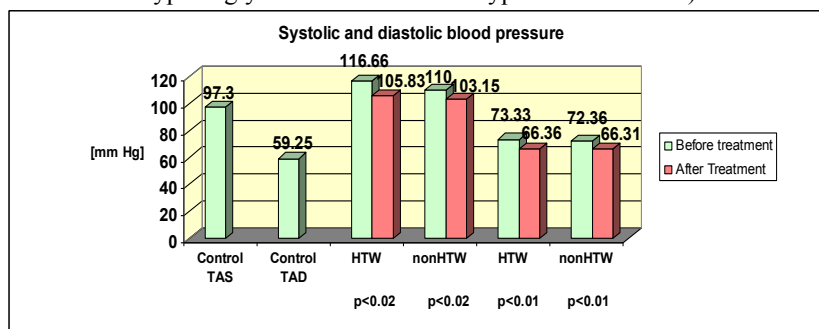
In order to better observe the effects of treatment, in figures 1,2,3,4,5,6 the modified plasma parameters are presented.

**Figure 1**

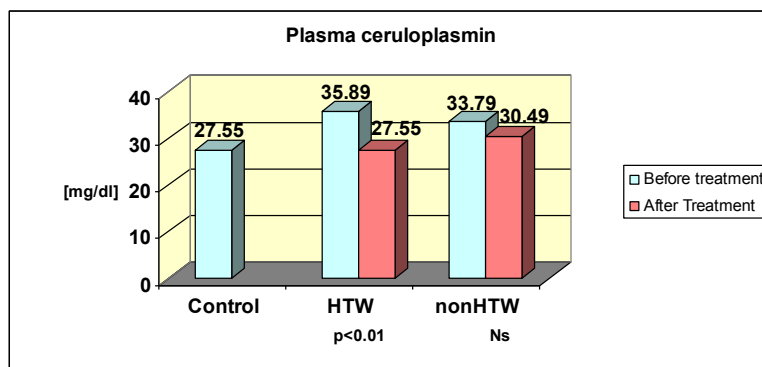
Fasting plasma leptin before and after treatment in the two obese groups (HTW- hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

**Figure 2**

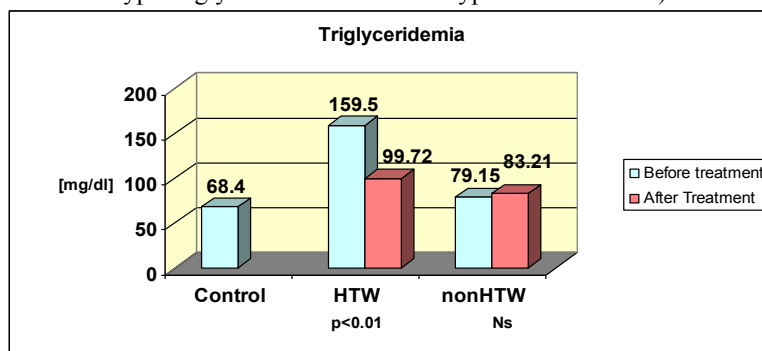
Fasting C peptide before and after treatment in the two obese groups (HTW- hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

**Figure 3**

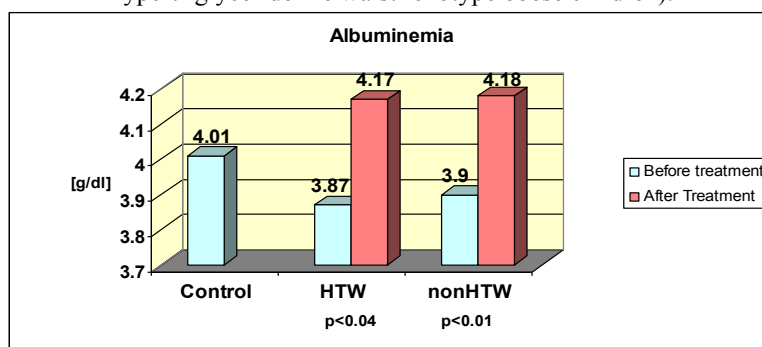
Systolic and diastolic blood pressure before and after treatment in the two obese groups (HTW- hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

**Figure 4**

Ceruloplasmin before and after treatment in the two obese groups (HTW-hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

**Figure 5**

Triglyceridemia before and after treatment in the two obese groups (HTW-hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

**Figure 6**

Albuminemia before and after treatment in the two obese groups (HTW-hypertriglyceridemic waist phenotype obese children and in nonHTW- non hypertriglyceridemic waist phenotype obese children).

Table IV
Correlations between parameters

Parameter	Fasting C peptide ng/mL	Fasting leptin ng/mL	Fasting glycemia mg/dL
SBP mmHg	0.48	0.50	0.37
DBP mmHg	0.52	0.47	0.36
Waist circumference cm	0.36	0.40	0.37

Calculated Pearson correlations (r value, for $p < 0.05$).

Obese children, who more commonly show features of metabolic syndrome, exhibit a clustering of phenotypes associated with increased cardiovascular risk. Dyslipidemia, insulin resistance, inflammation and a prothrombotic state are present in metabolic syndrome [12]. Many researchers argue that insulin resistance precedes the development of the metabolic syndrome [5,10,12,13,14,15].

Increased sympathetic tone has been associated with obesity in adolescents, and both insulin and leptin appear to have a direct effect on sympathetic nervous system activity. Fasting insulin, used as an estimate of insulin resistance has been significantly correlated with blood pressure in children and adolescents. Insulin infusions stimulate sodium retention by the kidney and insulin stimulates vascular smooth muscle growth [4].

In our study we measured fasting plasma C peptide (known as a surrogate marker of insulin resistance), fasting plasma leptin, fasting glycemia and blood pressure and we assessed the Pearson correlations between these parameters. We showed that in obese children, fasting C peptide, fasting glycemia and leptin were correlated with blood pressure (with r between 0.36-0.52, for $p < 0.05$) and with waist circumference (with r between 0.36-0.40, for $p < 0.05$) (Table IV). These correlations suggest that a cluster of pathogenic mechanisms influence two important parameters (waist circumference and blood pressure) included in the metabolic syndrome definition. In hypertriglyceridemic waist phenotype obese children, with high risk for developing metabolic syndrome, the levels of C peptide and leptin were higher compared to nonhypertriglyceridemic waist phenotype obese children.

Sea buckthorn pulp oil treatment (60 days of 800 mg/day) decreased both leptin and C peptide concentrations but the levels were significantly reduced only in hypertriglyceridemic waist phenotype obese children (Table III). Interestingly, this reduction was not associated with a significant decrease in weight or waist circumference, after treatment (Figures 1 and 2).

It must be mentioned that blood pressure values (both systolic and diastolic) were reduced significantly after treatment, in all the groups (Figure 3).

Leptin, as a proinflammatory biomolecule, stimulates the proliferation of monocytes and macrophages and the production of inflammatory cytokines such as IL-6 and TNF- α [16].

A few studies in obese children have shown increased plasma levels of inflammatory markers, such as leptin, IL-6, CRP, fibrinogen. These markers are known to affect endothelial function *via* either direct or indirect mechanisms such as reducing NO production and stimulating inflammation-oxidative stress pathways [5]. Other studies performed on obese children, haven't found any differences in plasma concentrations of TNF- α , IL-6, adiponectin, resistin or intraabdominal fat volume, suggesting that these factors do not play a primary role in causing insulin resistance in the early stages of the metabolic syndrome [12]. Moran *et al.* suggest that insulin resistance may precede the development of CRP elevation in the evolution of the metabolic syndrome [17].

In our study, there wasn't any difference in the fibrinogen level between obese and control subjects, but CRP and ceruloplasmin were higher in obese *versus* lean children (table II). Comparing the obese groups, there weren't any differences for inflammatory markers and the oil treatment had a weak effect on the inflammatory parameters because it lowered the ceruloplasmin and leptin levels (table III).

Ceruloplasmin, known as a plasma antioxidant and an acute phase protein, can act also as a prooxidant because copper bound at specific sites on protein surfaces can cause oxidative damage to macromolecules in their environment. It can oxidize LDL lipoproteins [18], so the high level of ceruloplasmin in the hypertriglyceridemic waist phenotype obese children reveals their increased risk for atherosclerosis. In this group, sea buckthorn pulp oil treatment reduced significantly the ceruloplasmin plasma level (Figure 4).

MRS/MRI/stable isotope studies (MRS - magnetic resonance spectroscopy, MRI - magnetic resonance imaging) demonstrated that insulin resistance in skeletal muscle, due to decreased muscle glycogen synthesis, can promote atherogenic dyslipidemia by changing the pattern of ingested carbohydrate away from skeletal muscle glycogen synthesis into hepatic *de novo* lipogenesis, resulting in an increase in plasma triglyceride concentrations and a reduction in plasma high-density lipoprotein concentrations. This type of dyslipidemia is present in the metabolic syndrome and increases the risk for cardiovascular diseases [12]. In

hypertriglyceridemic waist phenotype obese children, high values for triglycerides are associated with low values for HDL-C and the treatment reduced significantly the levels of triglycerides and improved the HDL-C concentration (Figure 5). Hepatic *de novo* lipogenesis is augmented in hypertriglyceridemic waist phenotype obese children and can be demonstrated by the high values of ALT in this group.

Even hyperuricemia is not a metabolic syndrome criteria, many of the manifestation of the metabolic syndrome are mediated by the rise of uric acid level [19]. Impaired nitric oxide-dependent dilatation was demonstrated in hyperuricemia. Higher serum γ -GT activity is also associated with cardiovascular disease risk factors, because the enzyme can increase the production of reactive oxygen species and can catalyze oxidation of circulating low-density lipoprotein cholesterol (LDL-C) [20]. In our study, uric acid and γ -GT were significantly higher in the obese groups than in the control subjects and the highest values were recorded in the hypertriglyceridemic waist phenotype obese children (Table II). The treatment didn't modify the values of these two cardiovascular risk factors.

Conclusions

It is very important to prevent and treat metabolic syndrome in order to reduce the incidence of type 2 diabetes mellitus and cardiovascular diseases. The benefic effects demonstrated in our study by the sea buckthorn products, make them desirable for medicinal purposes. In our study, the treatment with sea buckthorn pulp oil reduced triglyceridemia and improved blood pressure levels. By lowering the values of these parameters sea buckthorn pulp oil may prevent metabolic syndrome in obese children. The treatment is recommended in hypertriglyceridemic waist phenotype obese children.

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References

1. LaFontaine T., Overweight Among Youth: An Evolving American Tragedy? *American College of sports medicine*. 2005;15 (4):2-5.
2. Jessup A., Harrell J.S., The metabolic syndrome: look for it in children and adolescents, too! *Clinical diabetes*. 2005;1(23):26-32.
3. Vos M., Barlow S.E., Update in childhood and adolescent obesity. *Pediatric clinics of North America*. 2011; 58(6): xv-xvii.

4. Steinberger J., Daniels S.R., Eckel R.H., Hayman L., Lustig R.H., McCrindle B., Mietus-Snyder M.L., Progress and Challenges in Metabolic Syndrome in Children and Adolescents. *Circulation*. 2009;119:628-647.
5. Montero D., Walther G., Perez-Martin A., Roche E., Vinet A., Endothelial dysfunction, inflammation and oxidative stress in obese children and adolescents: markers and effect of lifestyle intervention. *Obesity Review*. 2012;13:441-455.
6. Dubey S., Kabra M., Bajpai A., Pandey R.M., Hasan M., Gautam R.K., Menon P.S.N., Serum Leptin Levels in Obese Indian Children: Relation to Clinical and Biochemical Parameters. *Indian Pediatrics*. 2007;44:257-262.
7. Hamidi A., Fakhrzadeh H., Moayyeri A., Heshmat R., Ebrahimpour P., Larijani B., Leptin is related to the levels of triglycerides. *Indian J. Pediatr*. 2006; 73 (7):593-596.
8. Kelishadi R., Gidding S.S., Hashemi M., Hashemipour M., Zakerameli A., Poursafa P., Acute and long term effects of grape and pomegranate juice consumption on endothelial dysfunction in pediatric metabolic syndrome. *J. Res. Med. Sci*. 2011;16(3):245-253.
9. Băcanu EV, Lixandru D, Stoian I, Virgolici B, Mohora M, Arsene AL, Ionescu-Tîrgoviște C, Correlations between obesity antropometric markers, adipocytokines and monocytes oxidative stress status in type 2 diabetic patients, *Farmacia*, 2012, 60(2), 194-205
10. Mancini M.C., Metabolic syndrome in children and adolescents-criteria for diagnosis. *Diabetol Metab Syndr*. 2009;1: 20.
11. Friedewald W.T., Levy M., Frederickson D.S., Estimation of the concentration of low density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.
12. Petersen K.F., Dufour S., Savage D.B., Bilz S., Solomon G., Yonemitsu S., Cline G.W., Befroy D., Zeman L., Kahn B.B., Papademetris X., Rothman D.L., Shulman G.I., The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc Natl Acad Sci U S A*. 2007;104(31):12587-12594.
13. Cruz M.L., Goran M.I., The Metabolic Syndrome in Children and Adolescents, *Current Diabetes Reports*. 2004; 4:53-62.
14. Gligor R, Pușchiță M, Zdremțan D, Crîșnic I, Ionescu-Tîrgoviște C, Relationship between adiponectin and some metabolic parameters in obese and diabetic patients, *Farmacia*, 2012, 60(2), 293-306
15. Stapleton P.A., Milinda E.J., Goodwill A.G., Frisbee J.C., Obesity and vascular dysfunction. *Pathophysiology*. 2008;15 (2):79-89.
16. Valean C., Ichim G., Tatar S., Samasca G., Leucuta A., Nanulescu M., Prevalence of metabolic syndrome and serum profile of adipokines (leptin and adiponectin) in children with overweight or obesity. *Acta Endocrinologica*. 2010;VI (3):343-354.
17. Moran A., Steffen L.M., Jacobs D.R.Jr, Steinberger J., Pankow J.S., Hong C.P., Tracy R.P., Sinaiko A.R., Relation of C-reactive protein to insulin resistance and cardiovascular risk factors in youth, *Diabetes Care*. 2005;28(7):1763-1768.
18. Ștefănescu E, Cristea AN, Chiriță C, Putina G, Experimental pharmacological research regarding the anti-obesity effect and the motor behavior induced by some newly synthesized β_3 adrenergic receptors agonists in normal mice, *Farmacia*, 2012, 60(3), 342-349
19. Ishizaka N., Ishizaka Y., Toda E.I., Nagai R., Yamakado M., Association Between Serum Uric Acid, Metabolic Syndrome, and Carotid Atherosclerosis in Japanese Individuals. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;25:1038-1044.
20. Paolicchi A., Emdin M., Passino C., Lorenzini E., Titta F., Marchi S., Malvaldi G., Pompella A., Beta-Lipoprotein- and LDL-associated serum gamma-glutamyltransferase in patients with coronary atherosclerosis, *Atherosclerosis*, 2006;186: 80-85.

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