



Serum visfatin concentration in eutrophic and overweight/obese male children in early childhood

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Abstract

Background and Purpose: Childhood overweight/obesity is considered a global epidemic, which began earlier in pediatric patients and presents a major health risk in adulthood. It is well known that adipose tissue is an active endocrine inflammatory organ in obese adults, but its neurohormone activity in the childhood is not yet clarified. Visfatin is one of adipokines with insulin-mimetic and proinflammatory-atherosclerotic effect, whose role in the child's age is still unknown as well as its physiological concentrations in serum of prepubertal children. The aim of this study was to determine visfatin serum concentration at the early age in eutrophic and overweight/obese male children and its association with arterial blood pressure.

Materials and Methods: Healthy boys, 2-14 years old, hospitalized for elective inguinal hernia surgery has been included in the study (N=31) and were divided into two groups according to percentile curve: a) overweight/obese (O/O:above the 85th percentile) and b) eutrophic (E:5th-85th percentile). Anthropometric and biochemical measurements and specific serum levels of visfatin by enzyme immunoassay were determined.

Results and Conclusion: Both groups of examinees, eutrophic and overweight/obese, had a normal metabolic profile band on percentile ranks (fasting glucose values and all fractions of lipid profile) and values of blood pressure. However overweight/obese boys had significant higher systolic blood pressure than eutrophic boys, $p=0,028$. Serum visfatin were 6.90 ± 3.97 ng/ml in eutrophic boys, while in overweight/obese were 7.82 ± 3.75 ng/ml, $p=0,57$. There is a tendency of visfatin serum concentration to increase with increase of body weight and growing. This suggests possible role of visfatin in future metabolic and cardiovascular processes related to increase in body mass.

INTRODUCTION

Obesity is a complex clinical syndrome that represents a major, world public health problem (1). The childhood obesity with overweight is dramatically increased in industrial countries over the last 20 years (1-4). Overweight is causing increased morbidity and mortality due to its association with insulin resistance, dyslipidemia, diabetes, hypertension and cardiovascular disease in adulthood (5-7). Overweight in adolescence is significantly correlated with obesity in adulthood (8, 9). In the childhood, obesity is defined as a body mass index (BMI) which is correlated with percentile curves by age and gender (above 95. percentile - obese, between the 85th-95th percentile - over-

weight, below the 85th-5th percentiles - eutrophic children) (10, 11).

Multiple factors lead to a high incidence of childhood obesity, genetic and external factors contribute to the development of a high degree of obesity at an early age (12, 13). Endocrine function of adipose tissue is achieved by synthesis of numerous adipocytokines such as leptin, adiponectin, resistin, visfatin, adipon, angiotensinogen, tumor necrosis factor α , interleukin-6, retinol-binding protein, plasminogen activator inhibitor-1, fibrinogen. The effect of listed adipocytes chemokine are realized by autocrine/paracrine and systemic effects, which means that they have their major effects locally as in distant tissues and organs. Adipokines produced in adipose tissue have immunological, cardiovascular and metabolic functions (14-16). Altered glucose metabolism, manifested as impaired glucose tolerance appears early in obese children and adolescents which is characterized by marked peripheral insulin resistance and a relative β -cell failure. Other elements of the metabolic syndrome, such as dyslipidemia, hypertension and markers of systemic 'low-grade inflammation' are already present in obese youngsters and worsen with the degree of obesity (17).

The visfatin is an adipokine which was detected in peripheral lymphocytes (18). According to literature, visfatin has a physiological role in the maturation of lymphocytes, inhibition of neutrophils apoptosis and biosynthesis NAD (19). It has insulin mimetic activity, by binding to insulin receptors and mimic the effects of insulin, causing hypoglycaemia (20). High expression of visfatin was observed in visceral adipose tissue (21). In tissues visfatin is found in the bones, liver, muscle, brain, kidneys, spleen, testes, lungs, predominantly in visceral and subcutaneous adipose tissue (22, 23). Apart from fat cells, a significant source of visfatin are macrophages which were found in fat cells and in the submucosa of bowel wall (24, 25). Visfatin was considered a proinflammatory adipokine, and visfatin expression in neutrophils of peripheral blood is responsible for the stimulation of inflammatory factors such as TNF- α (26). Research suggest that elevated levels of visfatin in obese children presents good "surrogate marker" for visceral obesity in children and as for later atherosclerosis as adults (27), but it is still a question what are the „normally“ visfatin serum values in early childhood and what relation it has to physiological process in healthy eutrophic and obese children. The aim of the present study was to determine visfatin serum concentration at the early age in eutrophic and overweight/obese male children and its relation to arterial blood pressure.

MATERIALS AND METHODS

The study was a prospective cohort study conducted at the University Hospital Center of Osijek, at the Department of Surgery, Clinical Department of Pediatric Sur-

gery. Study protocol was in a timely manner reported to the Ethical Committee of the Clinical Hospital Centre Osijek and Ethical Committee of Faculty of Medicine University of Osijek, approved by the same committees. Parents of involved subjects were informed about the research and its protocol and they gave us written consent for participation.

Patients

31 boys aged from 2 to 14 year were included in this study. All patients were hospitalized for elective inguinal hernia surgery at the Department of Paediatric Surgery. Including criteria for the study were: children who were matured and from regular pregnancy and delivered by natural birth, until now according to previously taken anamnestic data without serious illnesses and without previous surgical procedures. This study hasn't involved the children who had inguinal hernia incarceration. The parents in anamnesis did not suffer from chronic diseases (diabetes, hypertension, metabolic syndrome). Exclusion criteria for the study were: preterm birth and prematurity, previous surgery, children who have diabetes or they constantly are taking medications for chronic diseases (epilepsy, bronchial asthma etc.). Subjects were divided into two groups according to body weight expressed in percentiles: regular body weight (percentile 5.th to 85.th) and overweight/obese (above 85.percentile) (28).

Anthropometric and biochemical data

In all participants anthropometric and biochemical measurements were performed. Anthropometric measurements included measurement of body height (measured by measuring tape in centimetres), body weight (measured in kilograms), the waist circumference (measured by measuring tape in the projection of the umbilicus) and circumference of hips (measured by the measuring tape in the field below the big trochanter). BMI was calculated by formula: weight/squared projected through the percentile curve. Venous blood samples were taken for biochemical analysis: complete blood cell count, C-reactive protein, fasting serum glucose, total cholesterol, LDL, HDL, triglycerides, urea, creatinine levels. Laboratory values were all done on the appliance AU 480 (Beckman Coulter, Brea, CA, USA). Blood pressure included measuring blood pressure with kid sleeves manometer (with 5 cm), at admission and during hospitalization three times at day.

Serum visfatin concentrations

During elective surgery, just before the anaesthetic procedure, venous blood samples were taken to determine the concentration of visfatin by standard laboratory technique. The total concentration of visfatin in serum was determined by enzymatic ELISA immunoassay test (Fenix Pharmaceuticals, Inc., Belmont, CA, USA). The in-

traassay coefficient is <10% and interassay coefficient is <15%.

Statistical analysis

For statistical analysis was used descriptive statistics. Data are presented as mean \pm SD. All statistical tests were two-sided and carried out at a significance level (*P*) of 0.05. Shapiro-Wilks test of normality was used to test distribution of variables in both group of patients. According to results of Shapiro-Wilks test we used nonparametric Mann-Whitney test. Spearman method was used to assess univariate relations. The value *P*<0.05 was considered statistically significant. Statistical analysis was performed by using Statistica program packages and statistical program R.

RESULTS

Characteristics for both groups of examiners are given in Table 1. All the patients were children without significant differences in their body build except their body fat status. They all had normal fasting blood glucose level and serum creatinine in the morning, without glucose intolerance and impaired renal function.

TABLE 1

Demographic, anthropometric and biochemical data.

	EUTROPHIC	OVERWEIGHT/ OBESE
n	17	14
Age (years)	3,02 \pm 1,32	5,67 \pm 2,63
Weight (kg)*	16,94 \pm 4,55	30,75 \pm 14,62
Height (cm)*	103,90 \pm 13,50	117,18 \pm 24,05
Waist circumference (cm)*	50,36 \pm 5,29	62,12 \pm 16,45
Hip circumference (cm)*	30,77 \pm 4,11	42,00 \pm 10,39
Body mass index (kg/m ²)*	15,26 \pm 1,53	20,94 \pm 3,80
Percentile value	29,09 \pm 23,71	94,56 \pm 2,30
Morning glucose level (mmol/L)	4,61 \pm 0,75	4,81 \pm 0,50
Cratinine level (μ mol/L)	30,68 \pm 8,26	36,98 \pm 13,89
C reactive proteine (mg/L)	0,50 \pm 0,49	0,96 \pm 0,85
Cholesterol (mmol/L)	4,10 \pm 0,87	4,46 \pm 0,89
LDL (mmol/L)	2,47 \pm 0,72	2,83 \pm 1,01
HDL (mmol/L)	1,29 \pm 0,22	1,38 \pm 0,25
Triglycerides (mmol/L)	0,81 \pm 0,38	0,77 \pm 0,19
Systolic BP (mmHg)*	97,27 \pm 9,47	105,00 \pm 13,66
Diastolic (mmHg)	67,50 \pm 9,22	72,18 \pm 8,75

**p* < 0,05

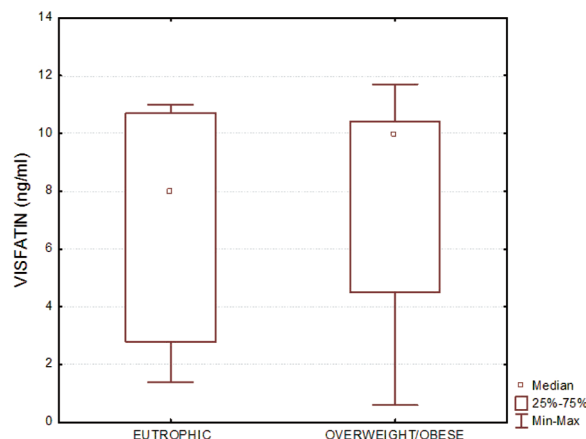


Figure 1. Serum visfatin level in eutrophic and overweight/obese male children.

By analysis of obtained values in both groups of respondents (eutrophic-E and overweight/obese-O/O) wasn't found to be statistically significant differences in the individual components of the lipid profile: cholesterol level (*p*=0.285); triglycerides (*p*=0.671); LDL (*p*=0,334); HDL (*p*= 0,236). It was also not found differences in fasting glucose in both groups of respondents, *p* = 0.356. CRP were higher in the group of overweight/obese children, however, not statistically significant compared to eutrophic, *p*=0.095.

Results of visfatin concentration amounts in the serum were 6.90 \pm 3.97 ng/ml in eutrophic boys and 7.82 \pm 3.75 ng/ml in overweight/obese boys with *p* = 0.57. Visfatin values in the group of overweight/obese were elevated but not statistically significant (Figure 1).

Overweight/obese children had significantly higher systolic blood pressure compared to eutrophic children (105 mmHg compared to 97 mmHg, *p*=0.028). Diastolic pressure showed no difference in both groups, (E:67mmHg, O/O:72mmHg, *p*=0.129). Relation between visfatin concentration with systolic and diastolic blood pressure (BP) in eutrophic group of patients showed positive relation without statistical significance (systolic BP/visfatin, *p*=0.167, diastolic BP/visfatin, *p*=0.454), while systolic and diastolic BP in overweight/obese showed negative correlation without statistical significance (systolic BP/visfatin, *p*=0.368, diastolic BP/visfatin, *p*= 0.435) (Figure 2).

According to Spearman coefficient, there were no statistically significant correlation in overweight/obese group between serum visfatin level and weight (*p*=0.258), BMI (*p*=0.160), waist circumference (*p*=0.623), cholesterol (*p*=0.626), triglycerides (*p*=0.369), LDL (*p*= 0.583), HDL (*p*=0.115). All reported relation between serum visfatin level with anthropometric parameters and lipidogram profile, except for HDL, showed negative relation. In the eutrophic group of patients, there was statistically sig-

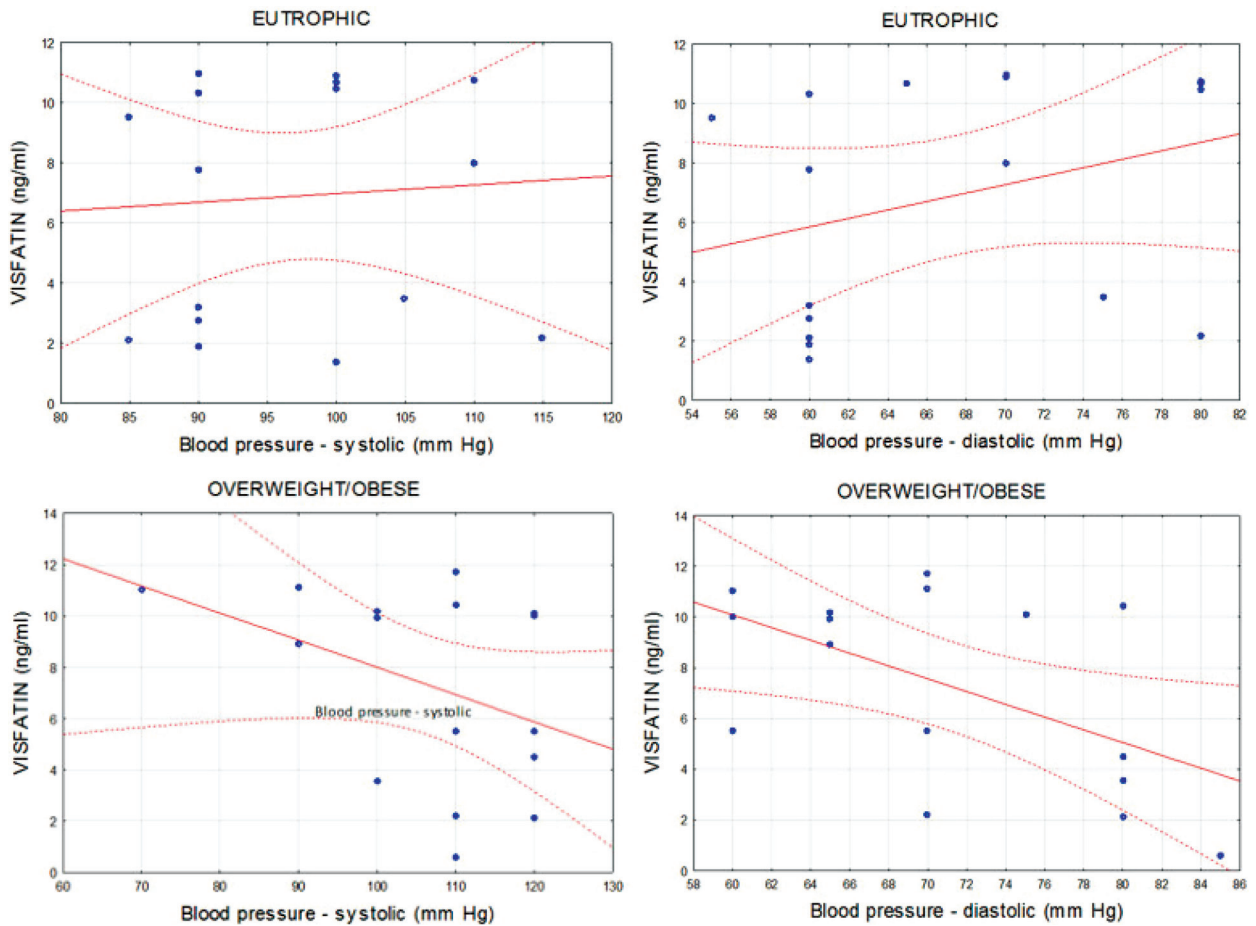


Figure 2. Correlation between systolic and diastolic blood pressure with serum visfatin concentration in eutrophic and overweight/obese examinees.

nificant correlation between waist circumference and serum visfatin level ($p=0.012$). Also, there were no significant correlation in eutrophic group between visfatin level and weight ($p=0.069$), BMI ($p=0.263$), cholesterol ($p=0.134$), triglycerides ($p=0.362$), LDL ($p=0.196$), HDL ($p=0.125$), except for triglycerides, all parameters had positive relation.

DISCUSSION

The main results of this study are values of visfatin serum concentrations in male eutrophic and overweight/obese middle-european children in early childhood, and it's relation to anthropometric parameters, systolic and diastolic blood pressure and metabolic profile.

According to the few previous research, most studies in children age have tried to explain the relationship between obesity with atherosclerotic-metabolic disease in later adult age, but it is still unknown the value of visfatin in an early age, what are the referent values and what effect obesity has on visfatin serum concentration in relation to anthropometric parameters and metabolic profile,

which was the main purpose of this study (27-34). Some studies have shown association with elevated visfatin concentrations in children serum and its correlation with diseases such as diabetes mellitus, metabolic syndromes and obesity (29-30).

In the literature, studies from 2006-2013 showed different values of visfatin blood values levels in eutrophic and obese children (Table 2). The differences in values of serum visfatin can be explained with unstandardized laboratory procedures, due to use of different kits for determination of visfatin, but probably greater impact had a racial differences of treated subjects. In our study, we compared the values of visfatin in healthy male children with no previous illness history with the difference in body mass. The obtained values results of visfatin are different compared to other studies, which can be explained with racial and gender differences, with level of obesity and age of included patients.

Studies that have investigated the relationship between visfatin levels in serum and obesity in childhood gave the opposite conclusions. Davutoglu *et al.* referring positive

TABLE 2

Visfatin serum level of eutrophic and obese children according to literature.

Recent studies	Visfatin serum level (mg/nL)	
	Eutrophic	Obese
Heider <i>et al.</i> (2006) ³⁰	0,6± (0,6-6,0)	1,1±(0,2-6,6)
Jin <i>et al.</i> (2008) ³³	27,82± (20,04-34,73)	36,38± (28,88-47,03)
Araki <i>et al.</i> (2008) ²⁷	8,6±0,6	14,7±0,9
Dovutoglu <i>et al.</i> (2009) ³²	2,2±1,5	4,0±3,0
Kolsgaard <i>et al.</i> (2009) ²⁹	15,2±(11,6-21,1)	19,0±(11,9-37,1)
Taskesen <i>et al.</i> (2012) ³⁴	7,5±(3,3-10,5)	11,6±(3,3-26)
Ko <i>et al.</i> (2013) ³¹	10,56±6,55	12,63±6,55

correlation between visfatin levels and obesity and abdominal volume ratio of waist/hip (WHR) (32). Haider published a study that found twice a bigger value of visfatin in obese children than in the control group, but found no correlation with anthropometric measures, CRP and lipid profile²⁹. With a study carried out on Chinese adolescents it was noted a significant positive correlation between visfatin and HDL cholesterol (33). Taskesen proved the elevated levels of visfatin in obese children between the ages of 9-17 years but not the correlation with body weight, BMI and WHR (34). Korean studies at pre-puberty children demonstrated that visfatin was higher in male children with overweight in comparison to girls, and that the level of visfatin in serum is positively correlated with BMI and triglycerides in children with overweight (26). In our study, in overweight/obese group there was negative relation between visfatin level and anthropometric and lipide profile parameters, which can be explained by functional healthy fat tissue in this early life time even in group of patients with increased body fat. Also, systolic and diastolic BP in overweight/obese patients showed negative relation to visfatin level, so the question is what the visfatin role is in future obesity -related hypertension development? Visfatin is produced predominantly by visceral fat tissue, which grows by time (adults), stimulating proinflammatory cytokines production. Cytokines affect vascular function and cause endothelial dysfunction, presenting important part of complex pathophysiologic mechanism of hypertension in adults (35, 36).

Children's obesity is still not sufficient explored area and the presence of visfatin in serum in early childhood. These results contribute to world knowledge about visfatin level in early childhood with need for further investigation because of various influences and possible gender differences on serum visfatin concentrations, although the

limit of this study is small sample size. We can conclude that visfatin levels in serum increases with increasing of body weight, but also that obesity alone is not a unique causative factor that affects the increase of its concentration. Our results can be explained by the fact that the physiological and pathophysiological processes of obesity are highly complex, metabolic-inflammatory character with subsequently proatherosclerotic risk that is not manifested in an early development age, probably as a result of still present healthy functioning of adipose tissue without inflammation. One of the first cardiometabolic effects of obesity influence at early childhood could be the effect on the increasing blood pressure (systolic), since it is well known pathophysiological impact of obesity on hypertension development. Further studies of childhood obesity, the adipose tissue dysfunction and neurohormonal activities are necessary at early childhood together with recognizing the risks for later developing of disease in adulthood. We can conclude that in the early age, fat tissue has not yet developed a pathological activity in full scale, as has been shown for adults (23). The visfatin levels in our study showed different correlation in eutrophic and overweight/obese patients and need for further investigation in this area suggesting possible role of visfatin in future metabolic and cardiovascular processes related with body mass.

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