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Leptin, adiponectin, and leptin/adiponectin ratio in adolescents with metabolic syndrome.

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Abstract: ***The aim of the current study was to analyze the correlation of leptin, adiponectin and their ratio with obesity-related clinical, anthropometric, hormonal and biochemical variables in adolescents from Bulgarian origin.***
Patients and methods: The study population included 51 overweight and 21 normal weight schoolchildren – 40 boys and 32 girls, aged 16-19 years. Waist circumference (WC), Body Fat Mass (BFM) and the Body Fat Percentage (BFP) were measured, and Body Mass Index (BMI) and waist-to-hip ratio (WHR) were calculated. The blood pressure (BP) - systolic (SBP) and diastolic (DBP), was also measured. Circulating levels of fasting glucose, total cholesterol (TC), high-density lipoproteins (HDL-C), triglycerides (TG), uric acid, fasting insulin, leptin and adiponectin were determined and leptin/adiponectin (L/A) ratio was calculated.
Results: In order to find the relationship between leptin and BMI we divided the patients into 3 subgroups according to the BMI. In the overweight (BMI=25-29.9 kg/m^2) and obese adolescents (BMI≥30 kg/m^2) leptin concentration was significantly higher, compared to the normal weight ones. In 64% of the overweight ones (n=28) leptin levels were below 25 ng/ml, in 21% leptin was in the range between 25-50 ng/ml, and in 14% leptin was over 50 ng/ml. In the obese adolescents (n=23), 13% of the subjects had leptin <25 ng/ml, in 57% of them leptin levels were in the range between 25-50 ng/ml, and in 30% the value of leptin was over 50 ng/ml. We did not find gender specific differences in the distribution of patients in the different subgroups according to the levels of leptin (p=0.114), adiponectin (p=0.922). The mean L/A ratio was also similar between the boys and the girls. Leptin correlated significantly with insulin (p<0.001), BMI (p<0.001), WC (p<0.001), WHR (p=0.001), BFM (p<0.001), BFP (p<0.001), SBP (p<0.001), and DBP (p<0.001). Interestingly, adiponectin did not show any significant correlations with all of the investigated clinical, anthropometric and biochemical variables.
Conclusions: Our results demonstrate a positive relationship between leptin levels, L/A ratio and parameters of metabolic syndrome, including BP values in normotensive adolescents with overweight/obesity. Leptin and L/A ratio could be used as markers of metabolic syndrome development in adolescents. Obesity and related disturbances put these children at a higher cardiovascular risk.

Keywords: Adolescent obesity, leptin, adiponectin, leptin/adiponectin ratio

1. Introduction

Overweight and obesity are one of the largest socio-medical problems worldwide and the second most common cause of premature death. Overweight and obesity among children and adolescents also rapidly increase, especially in developed countries. Childhood obesity predisposes to insulin resistance and type 2 diabetes, hypertension, hyperlipidaemia, liver and renal diseases, and reproductive disorders. Overweight in children and adolescents also increases the risk of adult-onset obesity and cardiovascular diseases [1].

Adipose tissue is an active endocrine organ that synthesizes and releases a number of adipokines, such as adiponectin and leptin, that are involved in maintaining the homeostasis, lipid and carbohydrate metabolism, reproductive function, blood pressure.

Leptin is a peptide hormone that is secreted in small amounts from a number of tissues, but it is considered that the main secretion is by the adipose tissue [2]. Plasma levels of leptin are directly proportional to the amount of adipose tissue of the body. They are higher in obese patients than in normal weight individuals, fall rapidly during fasting and rise after a meal. This regulation of leptin secretion is controlled partly by insulin. The data from recent studies showd that leptin interacts with almost all known neuropeptides, which are included in the regulation of energy balance and food intake.

Adiponectin (Adipo) is known as an adipocytokine which is paradoxically decreased in obesity. The hormone favorably affects glucose and lipid metabolism. Conversely, the reduction leads to decrease of HDL-cholesterol and triglycerides, and increase of the atherogenic small dense LDL-particles. The lower adiponectin level is associated with increased production of proinflammatory proteins like interleukin-6, TNF-α, C-

reactive protein. The adiponectin inhibits inflammation and perhaps atherogenesis, so it is possible to play a role in prevention of atherosclerosis. Lately, it was confirmed that low hormone levels correlated positively with the development of coronary heart disease.

Aim: To analyze the correlation of leptin, adiponectin and their ratio with obesity-related clinical, anthropometric, hormonal and biochenical variables in adolescents from Bulgarian origin.

2. Patients and Methods

The study was conducted at the Clinic of Endocrinology and Metabolic Diseases, University Hospital "St. George", Faculty of Medicine, Medical University Plovdiv, Bulgaria. The Ethics Committee of Medical University - Plovdiv approved this study, and a signed informed consent was obtained from each of the subjects before recruitment.

The study population included 51 overweight and 21 normal weight schoolchildren – 40 boys and 32 girls, aged 16-19 years. Over the three months preceding the study no subject had been on hormonal contraceptives or other medications which could affect lipid and carbohydrate metabolism.

At their initial visits, all subjects underwent medical evaluation and demographic data were recorded. A detailed clinical history was taken for all participants. The diagnosis of overweight or obesity was made according to the World Health Organization (WHO) criteria since 2000 [3]. The BMI was calculated as the ratio of weight divided by height squared (kg/m^2). Waist circumference (WC) was measured and waist-to-hip ratio (WHR) was calculated. The Body Fat Mass (BFM) and the Body Fat Percentage (BFP) were measured by Bioelectrical Impedance Analysis (BIA) using Tanita BC-420 Body Composition Analyzer. The blood pressure (BP) - systolic (SBP) and diastolic (DBP), was measured using a standard mercury sphygmomanometer with the participant in a seated position, after 10 min of rest [4]. Three BP measurements were taken, at least 3 minutes apart. The mean of the second and the third measurements was calculated to represent participants' BP.

Blood samples were drawn in the morning, between 7:30 and 8:00 AM, after at least a 10-hour overnight fast. The collected blood samples were allowed to clot and were centrifuged within 60 minutes after venipuncture. Glucose and hormone levels were determined immediately after centrifugation. For the determination of adiponectin and leptin levels, serum samples were apportioned into 0.5 ml aliquots and stored at ≤20°C until processing.

Fasting serum glucose, total cholesterol (TC), high-density lipoproteins (HDL-C), triglycerides, and uric acid were measured by a commercially available Konelab 60i, Thermo Electron Corporation (Finland) chemistry auto analyzer. Insulin was measured by chemiluminescence methods using Access 2 Immunoassay System, Beckman Coulter, Inc., USA. The homeostatic model assessment–insulin resistance (HOMA-IR) was calculated according to the well-known formula [5]. Other biochemical variables were determined using standard procedures.

Serum leptin (Biovendor, Brno, Czech Republic) and adiponectin (Biovendor, Brno, Czech Republic) levels were measured by using commercially available enzyme-linked immunosorbent assays (ELISA) according to the manufacturers' instructions. For leptin assays, the intra- and inter-assay coefficients of variation were <6.7% and <7.6%, respectively. The minimum detectable concentration was 0.2 ng/mL. For adiponectin assays, the intra- and inter-assay coefficients of variation were 3.0% and 8.3%, respectively. The minimum detectable concentration was 0.3 ng/mL. Then, leptin/adiponectin (L/A) ratio was calculated.

Statistical analysis

Data analysis was performed by using IBM SPSS Statistics for Windows, version 17.0. Values are presented as mean±standard deviation. The degree of association between nominal variables was tested by Fisher's exact test. The correlation between continuous or ordinal variables were calculated by Kendall's Tau-b correlation coefficient. The level of statistical significance was set at 5%.

3. Results

The following mean values of the investigated variables in the whole group were found: BMI - 27.6±6.3 kg/m^2, WC - 91±15 cm, WHR - 0.82±0.07, BFM - 22.5±13.6 kg, BFP - 25.0±10.4%, SBP - 126±9 mmHg, DBP - 81±9 mmHg, glucose – 5.0±0.6 mmol/l, insulin – 10.0±6.0 IU/l; HOMA-IR – 2.3±1.4; TC – 4.4±0.7 mmol/l; HDL-C – 1.4±0.4 mmol/l; TG – 0.9±0.4 mmol/l; uric acid - 373±84 mcmol/l. Since leptin and adiponectin levels in some patients (n=17) were below or above the range of the commercial kits, we divided the patients into subgroups according to the concentrations of the hormones. Thus, the concentration of leptin was divided in 11 subgroups and the distribution of the patients in each subgroup was indicated (Table 1).

Table 1. Distribution of leptin levels in subgroups.

Leptin - binned		
	N	%
5 <= x	6	8,3
5 < x <= 10.0	13	18,1
10 < x <= 15	6	8,3
15 < x <= 20	9	12,5
20 < x <= 25	4	5,6
25 < x <= 30	5	6,9
30 < x <= 35	3	4,2
35 < x <= 40	4	5,6
40 < x <= 45	1	1,4
45 < x <= 50	10	13,9
x > 50	11	15,3
Total	72	100,0

Similarly, the concentration of adiponectin was divided into 7 subgroups (Table 2).

Table 2. Distribution of adiponectin levels in subgroups.

Adiponectin - binned		
	N	%
3 < x <= 4	7	9,7
4 < x <= 5	10	13,9
5 < x <= 6	15	20,8
6 < x <= 7	16	22,2
7 < x <= 8	7	9,7
8 < x <= 9	8	11,1
x > 10	9	12,5
Total	72	100,0

In order to find the relationship between leptin and BMI we divided the patients into 3 subgroups according to the BMI -

BMI<25 kg/m^2; 25≤BMI≥29.9 kg/m^2; BMI≥30 kg/m^2. 21 of the participants were with normal body weight (BMI<25 kg/m^2). In 81% of them a relatively low concentration of leptin (<25 ng/ml) prevailed. The remaining 19% concentration was between 25-50 ng/ml. In the overweight (BMI=25-29.9 kg/m^2) and obese adolescents (BMI≥30 kg/m^2) leptin concentration was significantly higher. In 64% of the overweight ones (n=28) leptin levels were below 25 ng/ml, in 21% leptin was in the range between 25-50 ng/ml, and in 14% leptin was over 50 ng/ml. In the obese adolescents (n=23), 13% of the subjects had leptin <25 ng/ml, in 57% of them leptin levels were in the range between 25-50 ng/ml, and in 30% the value of leptin was over 50 ng/ml (Fig. 1).

We did not find gender specific differences in the distribution of patients in the different subgroups according to the levels of leptin, adiponectin (p=0.114 and p=0.922, respectively), The mean L/A ratio was also similar between the boys and the girls (p>0.05). Having in mind the above data me made the correlations of leptin, adiponectin and their ratio for the whole group.

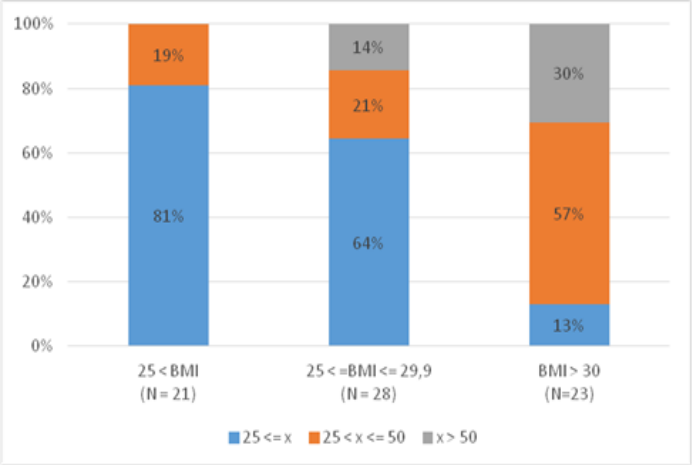

Fig. 1. Relationship between leptin (ng/ml) and BMI (kg/m²).

Leptin correlated significantly with insulin (p<0.001), BMI (p<0.001), WC (p<0.001), WHR (p=0.001), BFM (p<0.001), BFP (p<0.001), SBP (p<0.001), and DBP (p<0.001). Interestingly, adiponectin did not show significant correlations with all of the investigated clinical, anthropometric and biochemical variables. But there were significant correlations of L/A ratio with insulin (p<0.001), BMI (p=0.001), WC (p<0.001), WHR (p=0.026), BFM (p=0.001), BFP (p<0.001), SBP (p=0.021) and DBP (p=0.014) (Table 3).

4. Discussion.

Overweight and obesity are leading risk factor for death, and have become a severe worldwide socio-economical problem increasingly affecting the younger age groups. According to the WHO, 35% of adults aged 20 years and over were overweight in 2008, and around 12% were obese [6][i]. Obesity is a serious public health threat, as it significantly increases the risk of chronic diseases such as coronary heart disease and cardiovascular disease [7] and is associated with insulin resistance, dyslipidemia, and hypertension[8,9] also in adolescents. The relationship between overweight/obesity and hypertension has been already investigated, with the risk of hypertension being up to five times higher among obese people than among those of normal weight [7]. A number of mechanisms have been suggested explaining that relationship, but lately researchers focus more on the neurohormonal aspect.

In our study in adolescent Bulgarian population we found positive correlations between blood pressure parameters and all anthropometric and biochemical parameters of metabolic syndrome - BMI, WC, BFM, BFP, glucose, insulin, HOMA-IR, TC, HDL-C, TG, uric acid. Leptin and L/A ratio but not adiponectin correlated with SBP and DBP in our study. Similar data about leptin were reported in patients with essential hypertension [10,11].

Associations between elevated blood pressure and WC have been documented before [12]. In their cross-sectional study Choy et al. found elevated blood pressure had a higher association with WC than BMI [13]. This can be explained by the fact that BMI represented whole-body obese status, while WC was considered an indicator of central obesity or abdominal obesity and was associated with metabolic syndrome and cardiovascular diseases. Hirschler et al. showed that WC was a predictor of insulin resistance in children and could be included in clinical practice as a simple tool to help identify children at risk [14].

Recently, it has been shown that adipose tissue is an important endocrine organ, secreting several bioactive molecules, which regulate whole-body metabolism. One of these so called adipokines is leptin. Leptin is elevated in obese individuals, and its increased levels have been associated with future cardiovascular events [15]. We also found significantly higher leptin concentration in the overweight and obese adolescents compared to the normal weight ones. Leptin's primary role is to control appetite by inducing the feeling of satiety and by increasing sympathetic outflow [16]. Although obese individuals seem resistant to the first effect of leptin, the increased sympathetic activity remains, resulting in raised BP [17].

In contrast, adiponectin levels are reduced in obese individuals, and that reduction correlates significantly and independently with coronary artery disease [18]. However, we did not find significant difference in the adiponectin levels between the normal weight and the overweight/obese adolescents. In the adult population, a gender-depending differences in adiponectin concentrations were observed, with higher values in women [19]. In children and adolescents, these changes were not clearly marked. In our study, no significant differences between girls and boys in terms of adiponectin concentrations were found, as reported by other authors [20][ii].

Recent data also suggest that hyperleptinemia and hypoadiponectinemia are associated with insulin resistance [21]. Insulin has an essential impact on cardiovascular as well as muscle tissue. It leads to increase in NO production and therefore to vasodilation. Hence, any reduction in insulin sensitivity will apparently have unfavorable effects on BP [22]. Furthermore, insulin resistance leads to increased blood stream to skeletal muscles to recoup the reduced glucose transfer, which in turn also raises BP [23]. At the end, it results in increased sympathetic nervous system activity especially in the kidney, causing sodium retention, an important component in the control of BP [24].

Later evidence showed that L/A ratio correlated with insulin resistance better than either leptin or adiponectin levels alone [25]. The L/A ratio in our study was significantly higher in the overweight/obese adolescents compared to the normal weight ones. But the correlations between leptin itself and most of the

parameters of metabolic syndrome were stronger than those of L/A ratio.

5. Conclusions.

In conclusion, our results demonstrate a positive relationship between leptin levels, L/A ratio and parameters of metabolic syndrome, including BP values in normotensive adolescents with overweight/obesity. Leptin and L/A ratio could be used as markers of metabolic syndrome development in adolescents. Our data support the hypothesis that hyperleptinemia preceeds hypertension in normotensive obese individuals and that the increased leptin itself could become a crucial parameter imposing the rise of BP. As it is demonstrated earlier, there is a linear relationship between blood pressure and the relative risk of ischemic heart disease and stroke. The latter are affecting predo diseases of adolescence. Nevertheless, obesity and related desturbances put these children at a higher cardiovascuar risk.

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Disclosure Statement

No potential conflicts of interest were disclosed.

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Table 3. Correlations of leptin, adiponectin and L/A ratio with some clinical, anthropometric, and biochemical variables.

		Leptin ng/ml	Adipo mg/ml	L/A ratio	Fasting Glucose mmol/l	Fasting Insulin μIU/mL	HOMA	TC mmol/l	HDL-C mmol/l	TG mmol/l	Uric Acid μmol/l	BMI kg/m²	WC sm	WHR	FBM kg	FBP %	SBP mmHg	DBP mmHg
Leptin ng/ml	r																	
	p-value																	
Adipo mg/ml	r	-0.041																
	p-value	0.737																
L/A ratio	r	**0.843**	-0.183															
	p-value	0,000	0.168															
Fasting Glucose mmol/l	r	**0.201**	-0.070	0.130														
	p-value	0.020	0.425	0.171														
Fasting Insulin μIU/mL	r	**0.475**	0.018	**0.399**	**0.303**													
	p-value	0.000	0.832	0.000	0.000													
HOMA	r	**0.447**	0.011	**0.369**	**0.405**	**0.902**												
	p-value	0.000	0.894	0.000	0.000	0.000												
TC mmol/l	r	0.119	-0.043	0.072	0.057	0.068	0.075											
	p-value	0.166	0.624	0.445	0.500	0.407	0.362											
HDL-C mmol/l	r	-0.270	-0.017	**-0.354**	**-0.163**	**-0.294**	**-0.289**	**0.182**										
	p-value	0.001	0.847	0.000	0.049	0.000	0.000	0.028										
TG mmol/l	r	0.151	-0.016	**0.216**	0.009	**0.273**	**0.254**	**0.244**	**-0.219**									
	p-value	0.076	0.851	0.021	0.911	0.001	0.002	0.003	0.007									
Uric Acid μmol/l	r	0.096	-0.024	0.071	**0.242**	**0.246**	**0.257**	**0.209**	-0.071	**0.175**								
	p-value	0.255	0.782	0.446	0.003	0.002	0.002	0.011	0.381	0.031								
BMI kg/m²	r	**0.535**	-0.084	**0.399**	**0.212**	**0.527**	**0.501**	*0.161*	**-0.194**	**0.330**	**0.397**							
	p-value	0.000	0.476	0.001	0.010	0.000	0.000	0.051	0.017	0.000	0.000							
WC sm	r	**0.555**	0.030	**0.468**	**0.187**	**0.497**	**0.468**	0.093	**-0.182**	**0.304**	**0.379**	**0.776**						
	p-value	0.000	0.802	0.000	0.025	0.000	0.000	0.262	0.026	0.000	0.000	0.000						
WHR	r	**0.398**	0.145	**0.276**	0.132	**0.289**	**0.270**	0.027	-0.045	**0.191**	**0.318**	**0.463**	**0.654**					
	p-value	0.001	0.216	0.026	0.111	0.000	0.000	0.740	0.576	0.018	0.000	0.000	0.000					
FBM kg	r	**0.535**	0.014	**0.420**	**0.206**	**0.527**	**0.509**	*0.164*	**-0.262**	**0.319**	**0.336**	**0.795**	**0.810**	**0.476**				
	p-value	0.000	0.905	0.001	0.016	0.000	0.000	0.055	0.002	0.000	0.000	0.000	0.000	0.000				
FBP %	r	**0.570**	0.029	**0.449**	**0.198**	**0.454**	**0.430**	0.141	**-0.279**	**0.226**	**0.208**	**0.733**	**0.765**	**0.479**	**0.888**			
	p-value	0.000	0.803	0.000	0.021	0.000	0.000	0.099	0.001	0.007	0.013	0.000	0.000	0.000	0.000			
SBP mmHg	r	**0.301**	0.036	**0.230**	**0.267**	**0.519**	**0.523**	0.157	**-0.205**	**0.356**	**0.423**	**0.673**	**0.639**	**0.482**	**0.530**	**0.368**		
	p-value	0.001	0.698	0.021	0.003	0.000	0.000	0.076	0.019	0.000	0.000	0.000	0.000	0.000	0.000	0.000		
DBP mmHg	r	**0.328**	0.079	**0.244**	**0.252**	**0.541**	**0.545**	0.025	**-0.220**	**0.265**	**0.342**	**0.609**	**0.652**	**0.515**	**0.540**	**0.388**	**0.732**	
	p-value	0.000	0.392	0.014	0.005	0.000	0.000	0.776	0.012	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

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2016 – An assistant at Department of Internal Medicine, Clinic of Endocrinology and Metabolic Diseases, University Hospital "St. George", Medical University, Plovdiv, Bulgaria
Since 2014 till now - A resident, Clinic of Endocrinology and Metabolic Diseases, University Hospital "Sveti Georgy", Plovdiv, Bulgaria
Work experience and professional activities:
Medical training in Department of Palliative Medicine, Plovdiv
2010 - 2012 – Medical practice in Department of Internal Medicine, Division of Endocrinology and Nephrology, "Dr Atanas Dafovsky" Hospital, Kardzhali, Bulgaria
2012 - 2016 – a participant in 2 projects of Medical University of Plovdiv in the field of PCOS
Membership in scientific societies: Bulgarian Society of Endocrinology, Bulgarian Medical Union, Endocrinology European Association of Gynecological Endocrinology
Management Board Scientific interests and publications in the field of: neuroendocrinology, adipocytokines and insulin resistance, metabolic syndrome, PCOS.

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Relevant Education:
1986 - Higher education, Specialty in Medicine, Higher Medical Institute, Medical Academy, Medical University - Sofia;
1991 - Specialty Internal Medicine, Higher Medical Institute, Medical University - Sofia;
1993 - Specialty Endocrinology and Metabolic diseases, Higher Medical Institute, Medical University - Sofia;
2005 - Academic degree Associate Professor, Medical University – Sofia;
2011 - Master degree in Public Health and Health Management, Medical University – Sofia; WOAR Journals Page 18 2013 - Academic degree Professor, Medical University – Plovdiv;
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1987 -2005 - Senior Research Fellow, Assistant Professor, Clinical Centre of Endocrinology and Gerontology, ″Acad. Iv. Penchev″ University Hospital, Medical University – Sofia
1986 -1987 – Intern, Department of Internal Medicine with intensive sector, Primary Regional Hospital – Byala Slatina; "Pioner" and "9th Septemvri" Factories, Byala Slatina, Municipality of Montana, Bulgaria.
Relevant Job Related Training:
1993 - Specialization (IDF scholarship), Clinic of Endocrinology and Diabetes, Medical School, Department Medicine, University New Castle, England;
1997 - Course "Practical Diabetology", Steno Diabetes Centre, Gentofte and Copenhagen, Denmark; 1999 - Specialization, Clinic of Arterial Hypertension, "Brousse" Hospital, Paris, France;
2009 - Training course for treatment of diabetic foot, Diabetic Foot Clinic, King's College Hospital, London;
2012 - Qualification course in the field of diabetes, University "St. Andrew", United Kingdom.
Other Activities:
Pertinent to Professional Qualifications Project Manager in 4 and collaborator in 6 Projects of Ministry of Education and Science;
Project Manager in 12 Projects of Medical University -Sofia and Medical University -Plovdiv, Bulgaria Collaborator in MEDUCATOR - an International Project of Medical University - Plovdiv – E -learning in medicine Supervisor of 8 PhD students, consultant of 4 PhD students, Supervisor of 15 specializations in Endocrinology;
Editor -in -Chief of "ENDOCRINOLOGIA" Journal - printed edition of the Bulgarian Society of Endocrinology
Membership in scientific societies: Bulgarian Society of Endocrinology; Management Board Bulgarian Institute of Metabolic Syndrome; Management Board Bulgarian Association of Endocrine Hypertension /Alliance/; Management Board European Society of Endocrinology; European Association of Gynecological Endocrinology; European Association for the Study of Diabetes and Diabetes Education Study Group; European Thyroid Association
Scientific interests and publications in the field of: PCOS, reproductive disorders and hyperandrogenic states in women; insulin resistance, metabolic syndrome, obesity, adipocytokines and appetite regulator hormones, diabetes mellitus; Cushing's syndrome; endocrine hypertension; pituitary tumours; osteoporosis.

[i] World Health Organization. Fact Sheet No 311. Obesity and overweight. Geneva 2013. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/
[ii] K.A. Majewska, D. Majewski, B. Skowrońska, W. Stankiewicz, P. Fichna. "Serum leptin and adiponectin levels in children with type 1 diabetes mellitus - Relation to body fat mass and disease course". Adv Med Sci., 61(1), pp. 117-122, 2016.