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Correlation of Leptinemia with Components of Metabolic Syndrome in Moroccan Youths: Influence of Obesity, Blood Pressure, Gender and Stage of Puberty

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Abstract

Objective: To evaluate correlation of leptinemia with components of Metabolic Syndrome (MetS) in Moroccan youths, and effect of obesity, Blood Pressure (BP), gender and puberty stage on MetS-components.

Study design: Anthropomorphic, metabolic and clinical parameters [Body Mass Index (BMI), Waist Circumference (WC), energy intake, Blood Pressure (BP), Plasma levels of lipids, leptin, Alanine-Amino Transferase (ALT), Apo-B, Uric Acid (UA), glucose, insulin and Insulin Resistance (IR) (Homeostasis-Model-Assessment (HOMA-IR) and Fcβ (intra hepatic-IR)] were determined in 82 obese and 51 non-obese, male and female youths at different stages of puberty.

Results: Obesity was a major but not the only determinant of levels of leptin, BP, triglycerides, insulin, UA and ALT, and HOMA-IR, Fcβ; BMI was correlated with WC, BP and UA. Girls had higher leptin levels than boys, irrespective of obesity. Higher puberty stage was associated with higher values of BP, leptin, and ALT, irrespective of gender. Leptinemia was correlated with MetS-components: BMI, WC, BP, cholesterol, triglycerides, Apo-B, insulin, UA and HOMA-IR in all subjects; 10.8 - 16.2% of obese youths had MetS.

Conclusions: Leptinemia was correlated with several MetS-components. Hyperleptinemia in youths, indicating leptin resistance and IR, could predict development of MetS and cardiovascular disease in adulthood. Early detection of MetS may be helpful in identifying those at risk for T_2DM and CV disease, and preventive measures may be protect them from development of metabolic and cardiac disorders in the future.

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Abbreviations: ALT: Alanine-Aminotransferase; Apo-B: Apolipoprotein-B; BMI = Body Mass Index; BP: Blood Pressure; BW: Body Weight; CV: Cardiovascular; HDL-Cholesterol: High Density Lipoprotein Cholesterol; HTN: Hypertension; IR: Insulin Resistance; HOMA-IR: Homeostasis-Model-Assessment of IR; Fcβ: intrahepatic-IR; LDL-cholesterol: Low Density Lipoprotein Cholesterol; MetS: Metabolic Syndrome; NHANES-ATPIII: National Health and Nutrition Examination Survey-Adult Treatment Panel III; T_2DM: Type 2 Diabetes Mellitus; TG: Triglycerides; UA: Uric Acid; WC: Waist Circumference; WHR: Waist/Hip Ratio; WHO-EGIR: World Health Organization-European Group for the Study of Insulin Resistance

Introduction

The rising worldwide epidemic of obesity in adults (more than 1.9 billion overweight, over 600 million obese) and pediatric population (42 million children under the age of 5 overweight or obese)[1-4] is quite alarming, since obesity, is associated with metabolic disorders, such as glucose intolerance and Insulin Resistance (IR), which are risk factors for Cardiovascular (CV) disease and mortality[5-7]. The increased prevalence of obesity has also increased the incidence of Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T_2DM) not only in adults but also in the young[8,9]. MetS, also called insulin resistance syndrome and syndrome X, is one of the fastest growing health problem worldwide, and is a risk factor for not only CV disease, but also for stroke, T_2DM, chronic kidney disease, and all-cause mortality, it may also hasten the development of Hypertension (HTN)- and T_2DM-related complications[10]. In addition to the clustering of the traditional metabolic abnormalities [visceral obesity, glucose intolerance, IR, atherogenic dyslipidemia (low levels of High-Density-Lipoprotein (HDL) – cholesterol, high levels of Low-Density-Lipoprotein (LDL)-cholesterol and Triglycerides (TG)] and elevated Blood Pressure (BP),many other CV-risk factors co-occur with MetS including leptinemia[11,12], elevated levels of Uric Acid (UA)[8,12], Alanine-Aminotransferase (ALT, a marker of liver function)[13], and Apolipoprotein B (Apo-B, reflecting the entire spectrum of pro-atherogenic lipid particles)[14].

Leptin a 16-kDa (cytokine-like) hormone expressed by the ob gene (on chromosome 7q31.3) and synthesized and secreted primarily by the white adipose tissue plays a key role in the regulation of Body Weight (BW) and metabolism by affecting food intake and energy expenditure[15]. Hyperleptinemia an indicator of (selective) leptin resistance may cause IR and β-cell dysfunction increasing the risk of T_2DM and it may also play a role in the development of HTN and HTN-related end-organ damage, as well as obesity-associated CV disease[16-18].

Leptin levels are higher in female adults and children as compared to male counter parts[19] and in obese versus non-obese individuals[11,19]. Previous studies have shown that leptin levels increase with puberty stage much more in girls than in boys[20] and that leptin might play an important role during the initial stage of puberty and it effect on sexual development is more predominant in girls than in boys[20]. Relationships between circulating leptinemia, gonadal steroids, BMI and different stages of pubertyin healthy boys and girls have also been described[21-23].

We have previously shown that leptin levels are correlated with some components of MetS in adults[11]. The present study aimed at determining the influence of obesity, gender and stage of puberty on some components of MetS and their relationship with leptinemia in male and female, obese and non-obese Moroccan children and adolescents. The data obtained will help in establishing if leptinemia can be a biomarker to predict development of MetS, T_2DM, and CV disease in later life of obese youths. Also, if youths are identified with MetS preventive measures may be taken which may be able to protect them from development of metabolic and cardiac disorders in the future.

Methods and Procedures

Study subjects

The study population consisted of 82 obese children and adolescents (27 females, 55 males), aged 10.1 ± 4.0 yr (range 10 months to 18.6 years), average weight 55.0 ± 21.0 kg and average Body Mass Index (BMI) 27.5 ± 5.2 kg/m^2 (range 19.8 to 47.0 kg/m^2), with average BMI-z score of 4.25 ± 1.79. The obese individuals were selected after screening the patients visiting the paediatric endocrinology clinic. Obesity was defined as BMI > 97th percentile for chronological age [French reference population curves and doorstep as established by the International Obesity Task Force][24]. The control (non-obese) group consisted of 51 subjects (30 females, 21 males) matched for age and gender with the obese individuals [average age 9.9 ± 4.8 years (range 10 months to 20 years), average weight 30.6 ±15.0 kg, average BMI 16.1 ± 2.4 kg/m^2 with average BMI-z score of 0.42 ± 0.86].

The eligibility criteria included absence of physical disability, pregnancy or diabetes. The study, approved by the institutional review board, adheres to the ethical principles of "Declaration of Helsinki"[25]. Informed written consent was obtained from participants and/or parents/legal guardians of minors.

Methods and procedures

Subjects (with permission of parents of children and adolescents) were invited to the clinic to obtain anthropomorphic parameters (BW, height, waist and hip circumference), and dietary history. Waist Circumference (WC) was measured around the shortest circumference of the trunk while hip circumference across the maximum width of the hips, Waist/Hip Ratio (WHR, marker of weight distribution) was calculated. BMI was calculated as: BW (kg)/height-squared (m^2). Puberty stage, ascertained by Tanner criteria for breast development in females[26], and genital development in males[27], was assigned by physical examination (Tanner staging). It was also assessed by measurement of plasma estradiol, testosterone, and pituitary-gonadal axis hormones.

The food-intake data (24-hr recall) were evaluated by a dietitian for energy intake at baseline. A method was designed to determine food and nutrient consumed and translate the data to energy intake by measuring the portion size and composition (carbohydrates, fat, protein) of each food and nutrient and calculating the total energy intake by the formula: each gram of carbohydrate and protein contributing to 4 kcal, and each gram of fat to 9 kcal.

Systolic and diastolic BP was measured in a sitting position after 5 min of rest using a mercury sphygmomanometer and appropriate sized cuff.

Fasting (12 hr) blood samples were drawn and serum was obtained for determination of metabolic/clinical parameters [glucose, lipids (total-cholesterol, HDL-cholesterol, LDL-cholesterol), and triglycerides, ALT, Apo-B, and UA]. Glucose, lipids, ALT and UA were measured by standard enzymatic methods. Apo-B was determined by immune turbidimetry (Hitachi Analyzer-Kits: Boehringer-Mannheim). LDL-cholesterol was calculated by Friedewald's formula[28]: LDL = TC - HDL - TG/5.0 (mg/dL). Serum leptin and insulin levels were determined by ELISA (Biochemistry Service, Hospital-Southern, Lyon, France), IR was ascertained by homeostasis-model-assessment

ratio (HOMA-IR) and Fcβ index (marker of intra-hepatic-IR) using fasting serum insulin (μU/mL) and glucose (mmol/L): HOMA-IR = (insulin x glucose)/22.5, Fcβ = 20 x (insulin/glucose) - 3.5. BMI z-scores, reflecting the standard deviation score for the age- and sex-appropriate BMI distribution, were calculated as $z = (X-\mu)/\sigma$, where X = raw score to be standardized, μ = mean of the values, and σ = standard deviation.

Modified criteria from the NHANES-ATPIII and the World Health Organization-European Group for the Study of Insulin Resistance (WHO-EGIR) were applied to classify the obese youths as having MetS, if they met any three of the following criteria adjusted for age, gender and ethnicity: BMI > 97th percentile (BMI z-score > 2), WC > 75th percentile, fasting glucose >100 mg/dL, TG > 90th percentile, HDL-cholesterol < 10th percentile, LDL-cholesterol > 130 mg/dL, systolic or diastolic BP > 90th percentile[29].

Statistical analysis

The data were analyzed with SPSS.12 statistical software. Qualitative variables were expressed as mean ± standard deviation. Group means were compared using the Student's t test. Relationships between different variables were determined by multiple linear regression analysis, a P value < 0.05 was taken as the level of statistical significance.

Results

Anthropometric, clinical and metabolic parameters

Effect of obesity: The measured anthropometric, clinical and biological parameters of 82 obese and 51 control (non-obese) subjects are summarized in Table 1. The mean age of subjects in the two groups was similar, however, the mean BW (55 ± 21 kg *vs.* 31 ± 15 kg, p < 0.001), BMI (27.5 ± 5.2 kg/m^2 *vs.* 16.1± 2.4 kg/m^2, p < 0.001), WC (83 ± 15 cm *vs.* 60 ± 10 cm, p < 0.001), WHR (p < 0.001), and energy intake (3423 ± 680 kcal/day vs 1833 ± 549 kcal/day , p < 0.001), as well as BP (113 ± 19 mmHg *vs.* 103 ± 16 mmHg, p < 0.01) and IR-HOMA (1.90 ± 1.3 mU/mmol.L*vs.* 1.10 ± 0.70 mU/mmol.L, p < 0.01) were significantly higher in obese versus non-obese youths (Table 1). The concentration of total-cholesterol (1.73 ± 0.37 g/L *vs.* 1.62 ± 0.28 g/L, P < 0.001), TG (0.97 ± 0.61 g/L *vs.* 0.68 ± 0.25 g/L, p < 0.001), insulin (9.3 ± 5.9 mU/mL *vs.* 4.5 ± 3.3 mU/mL, p < 0.001), leptin (29.2 ± 21.2 ng/mL *vs.* 3.7 ± 0.7 ng/mL, p < 0.001), ALT (23.7 ± 15.6 U/L *vs.* 10.8 ± 4.6 U/L, p < 0.001) and UA (41.0 ± 16.7 mg/L *vs.* 28.9 ± 8.3 mg/L) were also higher, but HDL-cholesterol levels were lower (0.48 ± 0.14 g/L *vs.* 0.55 ± 0.10 g/L, p < 0.05) in obese than in non-obese individuals (Table 1). Plasma-levels of glucose, LDL-cholesterol and Apo-B were not different in the two groups (Table 1). There was a high incidence of IR (as determined by HOMA-IR) in the obese individuals.

Table 1: Anthropometric, metabolic and clinical parameters in non-obese and obese subjects.

Parameter	Non-obese subjects	Obese subjects	Non-obese males	Obese males	Non-obese females	Obese females
N	51	82	21	55	30	27
Age (yr)	9.9 ± 4.8	10.1 ± 4.0	7.6 ± 4.6	10.2 ± 3.5 §	11.2 ± 4.2 $^{¥¥}$	9.7 ± 4.8
BW (kg)	31 ± 15	55 ± 21	24.0 ± 12.9	54.9 ± 19.8$^{\%}$	35.0 ± 14.8 $^{¥¥}$	55.2 ± 24.7$^{\$}$
BMI (kg/m^2)	16.1 ± 2.4	27.5 ± 5.2	15.3± 1.8	26.8 ± 4.1$^{\&}$	16.6 ± 2.6	29.0 ± 6.8
BMI-z score			-1.18 ± 1.53	4.07 ± 1.53$^{\&}$	0.61 ± 1.06	4.80 ± 2.50$^{\&\&}$
WC (cm)	60 ± 10	83 ± 15$^{¥}$	56 ± 10	82 ± 15$^{\%}$	63 ± 8	85 ± 15$
WHR	0.84 ± 0.09	0.91 ± 0.08$^{\epsilon}$	0.88 ± 0.11	0.91 ± 0.09	0.82 ± 0.08$^{\$}$	1.00 ± 0.41
Systolic BP (mmHg)	103 ± 16	113 ± 19$^{\epsilon}$	89 ± 36	114 ± 18$^{\%}$	103 ± 12	112 ± 20‡‡
Diastolic BP (mmHg)	63 ± 12	70 ± 14*	62 ± 16	69 ± 13	64 ± 9	70 ± 12‡‡
Total-cholesterol (g/L)	1.62 ± 0.28	1.73 ± 0.37$^{\epsilon}$	1.61 ± 0.30	1.72 ± 0.46	1.62 ± 0.26	1.72 ± 0.40
HDL-cholesterol (g/L)	0.55 ± 0.10	0.48 ± 0.14*	0.52 ± 0.07	0.47 ± 0.19	0.55 ± 0.11	0.50 ± 0.13
LDL-cholesterol (g/L)	1.09 ± 0.26	1.02 ± 0.31	1.14 ± 0.29	1.02 ± 0.30	1.05 ± 0.23	0.99 ± 0.34
Triglycerides (g/L)	0.68 ± 0.25	0.97 ± 0.61$^{¥}$	0.64 ± 0.22	0.93 ± 0.53§	0.71 ± 0.26	1.02 ± 0.75‡‡
Leptin (ng/mL)	3.7 ± 0.7	29.2 ± 21.2†	1.0 ± 0.7	24.4 ± 17.4$^{\&}$	6.0 ± 5.8††	39.9 ± 29.0$^{**,\&\&}$
Insulin (mU/mL)	4.5 ± 3.3	9.3 ± 5.9†	2.7 ± 1.6	8.4 ± 5.1$^{\&}$	5.8 ± 3.5$^{¥¥}$	11.2 ± 7.2$^{\&\&}$
Glycemia (mg/dL)	86 ± 11	85 ± 17	85 ± 9	83 ± 19	88 ± 13	87 ± 12
HOMA-IR (mU/mmol.L)	1.10 ± 0.70	1.90 ± 1.3$^{\epsilon}$	0.58 ± 0.37	1.74 ± 1.09$^{\&}$	1.31 ± 0.75††	2.42 ± 1.59$^{\$,\%\%}$
Fcβ (mU/mmol.L)	21.6 ± 15.8	32.0 ± 25.3$^{¥}$	23.2 ± 6.2	28.4 ± 20.4$^{\epsilon}$	21.6 ± 15.8††	40.3 ± 30.6$^{**,\epsilon\epsilon}$
ALT (U/L)	10.8 ± 4.6	23.7 ± 15.6†	13.1 ± 5.3	24.4 ± 17.4%	9.2 ± 3.3††	21.7 ± 11.5**
Apo-B (g/L)	0.82 ± 0.27	0.92 ± 0.16	0.82 ± 0.27	0.93 ± 0.15	0.83 ± 0.29	0.90 ± 0.17
UA (mg/L)	28.9 ± 8.3	41.0 ± 16.7†	30.4 ± 8.8	42.8 ± 18.0%	27.7 ± 7.8	37.3 ± 13.2$^{\$}$
Energy intake (kcal/day)	1833 ± 549	3423 ± 680†	1691 ± 485	3459 ± 723$^{\&}$	2074 ± 503††	3347 ± 586$^{\pounds}$

The values are Mean ± standard deviation.
For abbreviations, see text.
Statistical significance:
All subjects--non-obese versus obese: *P < 0.05; $^{\epsilon}$P < 0.01; $^{¥}$P < 0.005; †P < 0.001
Males--non-obese versus obese: §P < 0.05; $^{\epsilon}$P < 0.01; $^{\%}$P < 0.005; $^{\&}$P < 0.001

Females--non-obese versus obese: ‡‡P < 0.05; $P < 0.01;††P < 0.005; §§p < 0.001
Non-obese males versus non-obese females: ¢¢P < 0.05; ¥¥P < 0.01; £P < 0.005; **p < 0.001
Obese males versus obese females: €€P < 0.05; %%P < 0.01; &&P < 0.005; ‡‡‡‡P < 0.001

When grouped according to gender, obese males and females still had higher BW, BMI, WC, energy intake, systolic BP, and levels of TG, leptin, insulin, ALT and UA, and IR than their non-obese cohorts (Table 1).

Gender differences

Among the non-obese subjects, BW, BMI, WHR, energy intake and levels of leptin, insulin, UA, and IR were higher, and ALT lower in girls than in boys, there was no gender difference in BP, and levels of glucose, lipids, TG and Apo-B. In obese subjects, girls had higher levels of leptin (39.9 ± 29.0 ng/mL vs 24.4 ± 17.4 ng/mL, p < 0.001), ALT and IR (HOMA-IR: 2.42 ± 1.59 mU/mmol.L *vs.* 1.74 ± 1.09 mU/mmol.L, p < 0.01, Fcβ : 40.3 ± 30.6 mU/mmol.L *vs.* 28.4 ± 20.4 mU/mmol.L, p < 0.05) than boys. But, gender had no effect on all other parameters (Table 1).

Effect of obesity and pubertal stage: Non-obese subjects in the higher puberty stage (IV-V) were older and had significantly higher BW, BMI, systolic BP, energy intake, as well as levels of insulin and leptin, and IR, and lower Apo-B as compared to non-obese lower puberty stage (I-III) individuals, puberty status had no effect on diastolic BP and plasma levels of glucose, lipids, triglycerides, ALT and UA (Table 2). Obese subjects in the higher puberty stage had significantly higher BW, BMI and WHR, and levels of insulin (12.2 ± 6.7 mU/mL *vs.* 8.2 ± 5.3 mU/mL p < 0.01, p < 0.001), leptin (35.1 ± 19.2 ng/mL *vs.* 25.2 ± 16.4 ng/mL, p < 0.001) and IR (HOMA-IR: 2.51 ± 1.42 mU/mmol.L *vs.* 1.7 ± 1.2 mU/mmol.L, p < 0.05, Fcβ: 37.4 ± 19.2 mU/mmol.L *vs.* 28.7 ± 27.6 mU/mmol.L, p < 0.05) but lower Apo-B than those at the lower puberty stage. However, puberty stage had no effect on energy intake, diastolic BP, and levels of glucose, lipids, TG, UA and ALT (Table 2).

At the same low puberty stage, the obese individuals were older and had significantly higher BW, BMI, WC and systolic BP, energy intake, as well as levels of leptin, insulin, IR, ALT and UA compared to the non-obese subjects, but, obesity had no effect on the lipid profile, Apo-B and glycemia. At the same high puberty stage, the obese individuals were younger, and their BW, BMI, WC, WHR, BP, caloric intake, and levels of TG, leptin, insulin, IR, ALT, Apo-B and UA were higher, and HDL-cholesterol lower compared to the non-obese individuals (Table 2).

Table 2: Anthropometric, metabolic and clinical parameters: effect of obesity, puberty stage and hypertension.

Parameter	Puberty Stage I-III		Puberty Stage IV-V		Obese subjects	
	Non-obese subjects	Obese subjects	Non-obese subjects	Obese subjects	Without HTN	With HTN
N	34	54	17	20	74	4
Age (yr)	6.9 ± 3.3	10.2 ± 3.9†	14.8 ± 2.3£	11.8 ± 3.7§	9.8 ± 3.8	12.8 ± 4.2
BW (kg)	22 ± 8	52 ± 18¥	47 ± 10£	70 ± 23††,€	52 ± 19	79 ± 24€€
BMI (kg/m²)	14.9 ± 1.5	26.4 ± 3.7¥	18.2 ± 12.3§	31.3 ± 6.7¥¥,%	27.0 ± 4.7	33.0 ± 7.1€€
WC (cm)	56 ± 7	79 ± 14¢	67 ± 8§	92 ± 17¢¢,%	81 ± 13	90 ± 28
WHR	0.87 ± 0.09	0.91 ± 0.08	0.78 ± 0.05	1.10 ± 0.40§	0.94 ± 0.25	0.92 ± 0.02
Systolic BP (mmHg)	99 ± 15	110 ± 18¢	110 ± 13‡‡	12.6 ± 23††,§	109 ± 14	151 ± 13&&
Diastolic BP (mmHg)	61 ± 12	68 ± 14	67 ± 10	77 ± 17¢¢,§	66 ± 10	97 ± 13&&
Total-cholesterol (g/L)	1.61 ± 0.28	1.74 ± 0.37	1.61 ± 0.28	1.77 ± 0.51	1.75 ± 0.35	1.42 ± 0.47§§
HDL-cholesterol (g/L)	0.53 ± 0.07	0.49 ± 0.15	0.56 ± 0.12	0.46 ± 0.09§	0.49 ± 0.14	0.41 ± 0.07
LDL-cholesterol (g/L)	1.17 ± 0.22	1.02 ± 0.29	0.99 ± 0.26	0.98 ± 0.37	1.03 ± 0.28	0.69 ± 0.50€€
Triglycerides (g/L)	0.69 ± 0.25	0.94 ± 0.69*	0.66 ± 0.22	1.11 ± 0.63§	0.94 ± 0.58	1.18 ± 0.94
Leptin (ng/mL)	1.6 ± 1.5	25.2 ± 16.4†	7.9 ± 6.4**	35.1 ± 19.2¢¢,&	26.0 ± 20.0	38.0 ± 23.0§§
Insulin (mU/mL)	3.2 ± 2.2	8.2 ± 5.3¥	7.0 ± 3.6£	12.2 ± 6.7¥¥,%	9.1 ± 5.8	11.4 ± 6.8
Glycemia (mg/dL)	86 ± 12	81 ± 11¢	86 ± 7	79 ± 32	84 ± 18	90 ± 13
HOMA-IR (mU/mmol.L)	0.72 ± 0.53	1.7 ± 1.2¥	1.60 ± 0.69£	2.51 ± 1.42¢¢,§	1.91 ± 1.29	2.51 ± 1.42%%
Fcβ (mU/mmol.L)	21.6 ± 15.8	28.7 ± 27.6¢	28.8 ± 15.7‡‡	37.4 ± 19.2¢¢	31.0 ± 24.0	43.0 ± 30.0
ALT (U/L)	11.6 ± 5.1	22.0 ± 13.0¥	9.2 ± 2.6	25.0 ± 21.0%	23.0 ± 15.0	22.0 ± 13.0
Apo-B (g/L)	0.91 ± 0.24	0.91 ± 0.15	0.58 ± 0.20§	0.97 ± 0.15€	0.92 ± 0.16	1.00 ± 0.12
UA (mg/L)	29.4 ± 9.6	38.0 ± 14.0¢	27.6 ± 4.2	47.0 ± 23.0¢¢,€	47.0 ± 23.0	55.0 ± 21.0§§
Energy intake (kcal/day)	1630 ± 373	3442 ± 651†	2488 ± 237**	3693 ± 631%	3397 ± 661	3731 ± 895

The values are Mean ± Standard Deviation.
For abbreviations, see text.

Statistical significance:
Puberty stage I-III--non-obese versus obese individuals: *P < 0.05; ᵉP < 0.01; ¥P < 0.005; ᵀP < 0.001
Puberty stage IV-V--non-obese versus obese individuals: §P < 0.05; €P < 0.01; %P < 0.005; &P < 0.001
Non-obese subjects--puberty stage I-III versus stage IV-V: ‡‡P < 0.05; $P < 0.01; £P < 0.005; **P < 0.001
Obese subjects--puberty stage I-III versus stage IV-V: ₹₹P < 0.05; ¥¥P < 0.01; ᵀᵀP < 0.005
Obese non-hypertensive's versus hypertensive's: §§P < 0.05; €€P < 0.01; %%P < 0.005; &&P < 0.001

Table 3: Anthropometric, metabolic and clinical parameters effect of puberty stage, obesity and gender.

Parameter	Puberty Stage I-III				Puberty Stage IV-V			
	Non-Obese Males	Obese Males	Non-obese Females	Obese Females	Non-obese Males	Obese Males	Non-obese Females	Obese Females
N	18	38	16	15	3	8	14	9
Age (yr)	6.3±3.5	10.7± 3.3ᵉ	7.5±3.0	8.5±4.9§,£	14.5±1.8$$$	10.8±3.2	14.9±2.5₹₹₹	11.9±4.3
BW (kg)	19±6	56±17¥	24±10	44±18€,₹₹	47±10$$$	77±23§§§,€€	47±11₹₹₹₹	71±25%%%,$$
BMI (kg/m²)	14.8±1.7	26.6±3.9¥	15.0±1.4	25.8±3.5%,ᵀᵀ	17.3±0.5&&&	29.0±4.2§§§,&&	18.4±2.5***	33.3±8.8€€€,$$
BMI z-score	-1.1±1.6	3.7±1.3ᵉ	-0.8±0.9	4.4±1.7%	-1.2±1.0	1.6±1.7	-0.4±1.2	4.8±3.2£££
WC (cm)	53±6	80±14ᵉ	60±8	78±13§,₹₹	71±14	91±19	66±8	92±17‡‡‡‡
WHR	0.89±0.11	0.92±0.08	0.86±0.08	0.87±0.04	0.83±0.11	0.91±0.06	0.77±0.04££	1.32± 0.55‡‡‡‡
Systolic BP (mmHg)	98±19	111±18*	100±12	103±20₹₹	120±16&&&	127±27§§§	107±11****	124±18€€€,‡‡‡‡
Diastolic BP (mmHg)	59±16	69±13*	62±7	65±16£	73±32&&&	76±17	66±10	78±18
Total-chol (g/L)	1.64±0.31	1.74±0.38	1.59±0.24	1.73±0.39	1.43±0.14	1.91±0.55	1.66±0.29	1.61± 0.43
HDL-chol (g/L)	0.54±0.06	0.48±0.16	0.51±0.07	0.51±0.15	0.49 ±0.09	0.45±0.08	0.59±0.12	0.47± 0.12
LDL-chol (g/L)	1.24±0.27	1.03±0.31	1.11±0.14	1.00±0.25	0.91±0.19	1.05±0.27	1.01±0.29	0.89± 0.47
Triglycerides (g/L)	0.66±0.21	0.90±0.55	0.72±0.29	1.05±0.98£	0.54±0.26	1.25±0.78§§	0.69±0.22	0.95± 0.36
Leptin (ng/mL)	1.05±0.77	23.9±13.5ᵀ	2.1±1.8‡‡	28.8±22.5&,ᵀᵀ	0.80±0.20&&&	25.0±10.4%%	9.5±6.0₹₹₹	47.4±20.8%%%££,₹₹₹,
Insulin (mU/mL)	2.3±1.4	7.7±4.3¥	4.1±2.6	9.1±7.2€,£	4.3±1.9&&&	11.1±5.8§§§,§§	7.6±3.7****,***	13.5±7.7€€€,‡‡‡‡
Glycemia (mg/dL)	83±9	86±9	88±13	85±13	87±5	72±18§§§	85±5	90±11
HOMA-IR (mU/mol.L)	0.81±0.32	1.68±1.01¥	0.92±0.62	1.93±1.61€,£	0.93±0.43	2.04±1.02€€	1.77±0.65****,***	2.97± 1.66€€€,‡‡‡‡
Fcβ (mU/mmol.L)	21.6±5.8	25.7±19.5*	12.9±10.2$	33.8±30.9€,£	14.3±7.9&&&	33.6±20.7€€	32.4±15.1₹₹₹₹,***	41.5±17.6‡‡‡‡,₹₹₹
ALT (U/L)	18.0±5.1	23.0±13.0ᵉ	9.2±3.9‡‡	22.1±13.0%,₹₹	9.3±3.2&&&	30.0±28.0€€	9.1±2.6	17.0±8.9$$,¥¥¥
Apo-B (g/L)	0.83±0.29	0.93±0.15	1.00±0.16	0.87±0.16	0.77±0.16	0.97±0.11	0.53±0.20****	0.96± 0.20‡‡‡‡
UA (mg/L)	30.0±9.0	39.1±15.3*	28.8±10.1	35.4±9.0	33.5±5.5	55.6±24.9§§§,§§	26.2±2.6***	38.4±19.6‡‡‡‡,₹₹₹
Energy intake (kcal/day)	1563±390	3478±685ᵀ	1705±350	3347±561&,ᵀᵀ	2457±183$$$	3940±469%%	2496±253¥¥¥¥	3419± 698‡‡‡‡

The values are Mean ± Standard Deviation.
For abbreviations see text.
Statistical significance:
Puberty stage I-III--non-obese versus obese males:*P < 0.05; ᵉP < 0.01; ¥P < 0.005; ᵀP < 0.001
Puberty stage I-III--non-obese versus obese females: §P < 0.05; €P < 0.01; %P < 0.005; &P < 0.001
Puberty stage I-III--non-obese males versus non-obese females: ‡‡P < 0.05; $P < 0.01
Puberty stage I-III--obese males versus obese females: £P < 0.05; **P < 0.01; ₹₹P < 0.005; ᵀᵀP < 0.001
Puberty stage IV-V--non-obese versus obese males: §§P < 0.05; €€P < 0.01; %%P < 0.005; &&P < 0.001
Puberty stage IV-V--non-obese versus obese females: ‡‡‡‡P < 0.05; $$P < 0.01; ££P < 0.005
Puberty stage IV-V--non-obese males versus non-obese females:***P < 0.05
Puberty stage IV-V--obese males versus obese females: ₹₹₹P < 0.05; ¥¥¥P < 0.01; ᵀᵀᵀP < 0.005
Obese males--puberty stage I-III versus stage IV-V: §§§P < 0.05

Obese females--puberty stage I-III versus stage IV-V: €€€P < 0.05; %%%P < 0.01
Non-obese males--puberty stage I-III versus stage IV-V: &&&P < 0.05; ‡‡‡‡‡‡P < 0.01; $$$P < 0.005
Non-obese females--puberty stage I-III versus stage IV-V: £££P < 0.05; ****P < 0.01; ¢¢¢¢P < 0.005; ¥¥¥¥P < 0.001

Effect of obesity, gender and stage of puberty: In the lower puberty stage group, both the obese boys and girls were older and had significantly higher BW, BMI, WC, BP, energy intake, levels of leptin (28.8 ± 22.5 ng/mL *vs.* 23.9 ± 13.5 ng/mL, p < 0.001), insulin (9.1 ± 7.2 mU/mL *vs.* 7.7 ± 4.3 mU/mL, p < 0.05), IR (HOMA-IR:1.93 ± 1.61 mU/mmol.L *vs.* 1.68 ± 1.01 mU/mmol.L, p < 0.05, Fcβ: 3.8 ± 30.9 mU/mmol.L *vs.* 25.7 ± 19.5 mU/mmol.L, p < 0.05) compared to the respective non-obese cohorts, but, there was no effect of obesity on WHR, lipids, glycemia and Apo-B levels (Table 3).

In the higher puberty stage group, the obese males had higher values for BW, BMI, energy intake, levels of leptin (47.4 ± 20.8 ng/mL *vs.* 25.0 ± 10.4 ng/mL, p < 0.001), insulin (11.1 ± 5.8 ng/mL vs 4.3 ± 1.9 ng/mL, p < 0.05), IR (HOMA-IR : 2.04 ± 1.02 mU/mmol.L *vs.* 0.93 ± 0.43 mU/mmol.L, p < 0.01, Fcβ : 33.6 ± 20.7 mU/mmol.L *vs.* 14.3 ± 7.9 mU/mmol.L, p < 0.01), ALT (30.0 ± 28.0 U/L *vs.* 9.3 ± 3.2 U/L, p < 0.01) and UA (55.6 ± 24.9 mg/L *vs.* 33.5 ± 5.5 mg/L, p < 0.05) than the non-obese males, there was no effect of obesity on other parameters. The obese girls in the higher puberty stage had higher values of BW, BMI, WC, WHR, systolic BP, energy intake, levels of leptin (47.4 ± 20.8 ng/mL *vs.* 9.5 ± 6.0 ng/mL, p < 0.001), insulin (13.5 ± 7.7 ng/mL vs 7.6 ± 3.7, p < 0.05), IR (HOMA-IR: 2.97 ± 1.66 mU/mmol.L *vs.* 1.77 ± 0.65 mU/mmol.L, p < 0.05, Fcβ : 41.5 ± 17.6 mU/mmol.L *vs.* 32.4 ± 15.1 mU/mmol.L, p < 0.05), ALT (17.0 ± 8.9 U/L *vs.* 9.1 ± 2.6 U/L, p < 0.01), UA (38.4 ± 19.6 mg/L *vs.* 26.2 ± 2.6 mg/L, p < 0.05), and Apo-B (0.96 ± 0.20 g/L *vs.* 0.53 ± 0.20 g/L, p < 0.05) compared to their non-obese cohorts (Table 3).

Non-obese males at a higher puberty stage were older, heavier, and had higher BMI, WC, BP, energy intake and insulin, and lower levels of leptin, Fcβ and ALT than those at lower puberty stage. The non-obese females in the higher puberty stage were older, heavier and had higher BMI, energy intake, leptin, insulin, IR and lower Apo-B levels than those in the lower puberty stage (Table 3).

In obese youths, the effect of puberty stage was less marked: only BW, BMI, systolic BP and UA were higher in both boys and girls at the higher puberty stage compared to those at the lower puberty stage: all other parameters were not affected (Table 3).

Effect of hypertension: In addition to the elevated BP, individuals with HTN had higher BW, BMI, IR and UA levels compared to normotensive subjects, other parameters were not different (Table 2).

Correlation of leptin levels and body mass index with some components of the metabolic syndrome

In the total population, leptin levels were highly correlated with BMI (p < 0.001), WC (p < 0.01), total-cholesterol (p < 0.01), TG (p < 0.001), Apo-B (p < 0.01), insulin (p < 0.001), BP (p < 0.01), HOMA-IR (p < 0.001), and UA (p < 0.001). In obese subjects, all correlations were significant except for BP. The BMI was correlated with BP, WC, and UA in obese male and female subjects (Table 4).

Table 4: Correlation of leptin levels and Body Mass Index (BMI) with components of the metabolic syndrome.

Correlation of leptin levels with:	BMI		WC		Systolic BP		Diastolic BP		Cholesterol	
	All*	Obese¢	All	Obese	All	Obese	All	Obese	All	Obese
R^2	0.49	0.25	0.24	0.07	0.08	0.03	0.07	0.04	0.08	0.06
R	0.700	0.495	0.493	0.270	0.284	0.182	0.268	0.201	0.289	0.249
P	0.000	0.000	0.002	0.017	0.002	0.114	0.003	0.082	0.001	0.026
Correlation of leptin levels with:	**Triglycerides**		**Apo-B**		**Insulin**		**HOMA-IR**		**UA**	
	All	Obese	All	Obese	All	Obese	All	Obese	All	Obese
R^2	0.17	0.11	0.09	0.08	0.36	0.23	0.34	0.23	0.10	0.01
R	0.408	0.330	0.295	0.286	0.603	0.480	0.586	0.481	0.317	0.112
P	0.000	0.003	0.006	0.024	0.000	0.000	0.000	0.000	0.000	0.330
Correlation of BMI with:	**Systolic BP**		**Diastolic BP**		**WC**			**UA**		
	All	Obese	All	Obese	Obese boys¥	Obese girls†		Obese boys	Obese girls	
R^2	0.32	0.40	0.19	0.23	0.15	0.36		0.19	0.26	
R	0.568	0.696	0.439	0.484	0.390	0.597		0.437	0.514	
P	0.000	0.000	0.000	0.000	0.004	0.002		0.001	0.012	

*All = all subjects (n = 133); ¢Obese = obese subjects (n = 82); ¥obese boys (n = 55); †obese girls (n = 27)
R = Pearson correlation coefficient; for other abbreviations, see text

Prevalence of metabolic syndrome in obese youths

The prevalence of MetS in obese children and adolescents was 10.75% (NHANES ATP III criteria) and 16.21% (WHO-EGIR criteria).

Discussion

Obesity and its associated MetS and CV- risk factors, such as dyslipidemia, high BP, and IR, have been increasing in children and adolescents[8,9,29-32]. Childhood-onset overweight/obesity can be a precursor to T_2DM, CV disease, HTN, stroke, osteoarthritis, etc., contributing to an earlier onset of overall morbidity and mortality[14,30].

In the present study, obesity in children and adolescents was associated with higher levels of several MetS components, including BP, insulin, IR, total-cholesterol, TG, leptin, ALT and UA, and lower levels of HDL-cholesterol. Previous studies have also reported a higher frequency of MetS components: elevated BP, total cholesterol, LDL-cholesterol, TG, insulin, IR, ALT, and UA, and low concentration of HDL-cholesterol[12,13,31,32] in obese versus non-obese youths. In the present study, BMI was correlated only with WC, BP and UA, but obesity had no effect on levels of Apo-B, LDL-cholesterol, and glucose. Thus, obesity, *per se*, did not contribute to the elevated levels of all the measured components of MetS. Leptin, a crucial hormone in energy homeostasis playing an important role in the pathogenesis of obesity, is related to several components of MetS[11,33].

In this study, leptin levels in obese youths were several-fold higher than in non-obese cohorts, as has been reported previously in adults and children by us and others[11,32,34,35]. Leptin levels were strongly correlated with indices of obesity (BMI and WC) in the whole group as well as in obese youths. However, a previous study[36] reported no correlation between leptin levels and BMI in obese youths, suggesting ethnic differences[37].

There was a significant effect of gender on the components of MetS in non-obese individuals, in that, the girls had higher levels of leptin, insulin, and IR, and lower levels of ALT and UA than in boys, however, gender had no effect on the values of BP, glucose, lipids, TG and Apo-B. In obese subjects, only the levels of leptin and IR were higher in girls compared to boys, otherwise, gender had no effect on all other parameters. Higher levels of leptin[34,35], TG[36] and IR[37] and lower levels of ALT[38] have previously been reported in females compared to males.

The stage of puberty had a marked influence on certain components of MetS, as both the non-obese and obese individuals in the higher puberty stage had significantly higher values for BMI, systolic BP, insulin, leptin, and IR compared to those at lower puberty stage, however, puberty status had no effect on diastolic BP, glucose, lipids, TG, UA and ALT.

UA is an important (non-traditional) component of MetS and is associated with several CV risk factors, such as high BP, high WC[39,40], and the risk of diabetes[41]. In our cohort, UA levels were higher in obese boys at the higher puberty stage, and were associated with higher leptin, insulin and IR levels compared to younger obese boys at a lower puberty stage. At puberty, the higher UA in obese individuals was associated with higher WC, BP, TC, TG, leptin, IR, and with lower HDL-C compared to non-obese cohorts.

In the present study, leptin levels were lower in older non-obese boys at a higher puberty stage as compared to the younger ones at a lower puberty stage. In contrast, leptin levels were much higher in older girls at a higher puberty stage as compared to the younger ones at the lower puberty stage. In obese boys, the puberty stage did not influence leptin levels, but, in obese girls, higher puberty stage was associated with higher leptin levels compared to obese females at a lower puberty stage. In adolescents, leptin levels gradually rose with age prior to puberty, suggesting a role of leptin in triggering puberty. However, there is a sexual dimorphism in leptin levels as youths progress towards puberty, in that, leptin levels in boys increased and then decreased with increasing age, while in girls the levels kept on increasing with age[42], the lower leptin levels in pubertal stage boys may be due to the suppressive effect of androgens[42]. Our results are in agreement with previous findings of higher leptin levels in pubertal obese girls than in prepubertal obese girls[35] and decrease in leptin levels after the onset of puberty in boys, but an increase in girls[35].

In this study, plasma leptin concentrations in the total population were correlated with BMI, WC, BP, total-cholesterol, TG, Apo-B, Insulin, IR and UA. Previous studies have also reported correlation of leptin levels with BMI, BP, WC, TG, IR and UA[17,34,43]. Hyperleptnemia may indicate leptin resistance[33] as well as IR[44], and it could be a predictor for the development of MetS and CV disease in adulthood. Thus, measurement of leptin levels may be helpful in identifying youths at risk of developing these disorders.

The findings that up to 16.2% of the obese youths have MetS is disturbing, because these individuals are at high risk of developing T_2DM and CV disease. Previous studies also report high prevalence of MetS in obese youths (19% -31%)[31,32], the variation in the prevalence may be due to differences in the criterion used for diagnosing MetS and the ethnicity of the population[45]. Early identification of youths with MetS may be useful in predicting future development of CV disease and T_2DM, as well as, implementing strategies, such as lifestyle modification and/or clinical intervention to manage overweight during childhood with the ultimate goal of preventing the development of T_2DM and CV disease in adulthood.

Conclusions

There was an association of obesity with several (conventional and non-conventional) components of MetS, including high levels of BP, insulin, IR, total-cholesterol, TG, leptin, ALT and UA, and lower levels of HDL-cholesterol. Like in the adults[11], leptin levels were correlated with several components of MetS, including BMI, WC, BP, total-cholesterol, TG, Apo-B, insulin, IR and UA, both in children and adolescents. There was significant effect of obesity, gender and pubertal age on leptin levels. Measurement of leptin levels in youths may be useful in predicting the development of MetS and CV disease in later life. Detecting youths with the MetS may be helpful in identifying those who are at risk for T_2DM and CV disease and in preventive measures may be able protect them from development of metabolic and cardiac disorders in the future.

Conflict of Interest Disclosures: None

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