Front. Biol. 2018, 13(6): 452–457
https://doi.org/10.1007/s11515-018-1515-1

RESEARCH ARTICLE

The comparison of insulin and uric acid levels in adolescents with and without metabolic syndrome

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BACKGROUND and AIM: The prevalence of metabolic syndrome (MS) increased in recent years in both adolescents and children groups. The aim of the study is evaluating the relationship between insulin and uric acid (UA) level in MS in adolescents

MATERIALS and METHODS: we studied 120 adolescence aged 10 to 19 in two groups: control group without metabolic syndrome and case group with metabolic syndrome. The Criteria of ATP III was considered as a diagnosis factor for metabolic syndrome.

DISCUSSION: Various studies have been conducted in various populations to evaluate the relationship between UA level and MS in adolescents. Abdominal obesity, low HDL, hypertriglyceridemia and hypertension are associated with high UA level. In their analysis, the MS OR in UA level $\leqslant$4.9, 4.9-5.8 and $\geqslant$5.8 mg/dl was 1, 2.53 and 9.03, respectively, which were higher than our findings in current study. Hyperinsulinemia caused by insulin resistance is one of the complications associated with MS, which puts individuals at risk of diabetes and cardiovascular events.

RESULTS: Uric acid level in the Case group was significantly higher than the control group ($p = 0.0001$, 43.8 ± 1.4 vs. 4.1 ± 1 mg/dl, respectively). Insulin level was significantly higher in the case group in compare to the control group ($p = 0.008$, 9.8 ± 5.3 vs. 12.2 ± 6 μU/ml, respectively).

CONCLUSION: The findings of this case-control study showed that adolescents with metabolic syndrome have a higher uric acid and insulin level in compare to normal subjects. We hypothesis that increase in serum insulin and uric acid level can be a risk factor in the development of metabolic syndrome.

Keywords metabolic syndrome, uric acid, insulin, adolescents

Introduction

Metabolic syndrome (MS) is a group of disorders that relates to hypertension, anthropometric indices, and the metabolism of lipid and glocuse. The prevalence of MS in adolescents is lower in compare to the adult population, but its rate is noticeable, especially regarding to the increase of the obesity trend in the societies. The prevalent of MS is 2 to 10% among 10 to19 years old age adolescence group (de Ferranti et al., 2004; MacPherson et al., 2016). MS increase the risk of cardiovascular diseases development. Criterion such as hypertension is considered to be a risk factor for cardiovascular events (Ritchie and Connell, 2007; Kassi et al., 2011; Han and Lean, 2016), recent studies suggest there are various biochemical factors such as C- reactive protein (CRP), low vitamin D levels and proteinuria associate with cardiovascular events and MS (Anderson et al., 2010; Currie and Delles, 2014). Adding high-sensitivity C-reactive protein (hs-CRP) to the definition of the MS can be predictive biomarker in predicting both CVD and MS (Haffner, 2006). Several risk factors such as cholesterol, uric acid and have been presented as stimulus for cardiovascular events and heart ischemia (Haybar and Zayeri, 2017). Recent studies showed increase in uric acid (UA) and insulin levels associate with the development of MS (Sung et al., 2011; Li et al., 2015). MS is a high-risk situation for diabetes and CVD and the information about its prevalence in diabetic population is low (Orchard et al., 2005). Previous studies revealed gouty patients who have higher level of uric acid increase the risk of

Received May 29, 2018; accepted July 30, 2018
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developing MS, cardiovascular diseases and mortality. Hyperuricemia, add to MS, can lead to the development of hypertension and type 2 diabetes (Li et al., 2013; Perez-Ruiz and Becker, 2015), and Diabetic patients are in higher risk of CVD development (Haybar et al., 2018). The prevalence of hyperuricemia is 10%, 39% in adolescents, healthy men and 11.5% in women, respectively (Chen et al., 2009; Li et al., 2015). Insulin resistance and obesity are the main factors in MS development (Kaur, 2014). Increase in insulin level which is caused by insulin resistance not only plays a role in the development of MS and impairment of its indices, but also its footprint has also been observed in cardiovascular diseases, arthrosclerosis, renal failure, and some cancers (Kelly et al., 2014). Several tracer elements such as zinc (Zn), selenium (Se), magnesium (Mg) and copper (Cu)) are population-dependent and it might be different among the different populations (Shahbazian et al., 2018).

So far, limited reports have been published on the relationship between serum UA and insulin level with MS and its indices, especially in adolescents. Measuring these two indices can be a cheap, safe and available tool for predicting and diagnosing MS thereby preventing cardiovascular diseases. The aim of this study was to compare the level of serum UA and insulin in healthy adolescents and adolescents with MS.

Materials and methods

This case-control study was carried out at Jundishapur University of Medical Sciences in Ahvaz, Iran after being approved by the University's Ethics Committee and the committee code is ajums.REC.1392.182. A total of 240 subjects were selected from the adolescents who had participated in Ahvaz's large MS study, which consist of 25 health care centers. They were divided into two groups of 120 patients with MS as our case group and 120 healthy individuals. Systolic, diastolic blood pressure was measured two times every 30 min intervals using a standard mercury sphygmomanometer for 15 min in the sitting position, and its mean value was expressed in mmHg. Body mass index (BMI) was also calculated through dividing the weight to the square of the height (kg/m^2). The weight of the subjects was measured by using the same scale in kilogram (kg).

After 12 h of fasting, blood samples were collected to evaluate glucose, lipid, and UA and serum insulin levels. FBS was measured by glucose oxidase/peroxidase method using Biosystems SACosta Brava30, Spain. Triglyceride, total cholesterol and HDL-cholesterol were measured by point enzymatic-calorimetric (PAP- CHOD) method, (Pars Azmun Co. Iran) kit. The UA was measured by Pars Azmun Co. Iran. Uric Acid | 400ML in mg/dl kit. The serum insulin levels were calculated in μU/ml by immunoenzymatic assay using (Biosource INS-IRMA kit). According to the American Society of Heart Association UA levels were classified into two categories: $\leqslant 4.9$, 4.9–5.8 and $\geqslant 5.8$ mg/dl (21), and compared together.

Data analysis was carried out using t and Chi- square tests in SPSS ver. 15. Also, Spearman or Pearson test, and odds ratio (OR) were used to determine data correlation and the probability of developing a MS and its indices based on UA level. Findings were considered significant at $p < 0.05$.

Inclusion

Ten to 19 years old. Individuals with at least 3 criteria for ATPIII were defined as those who suffer from MS. The MS ATP-III criteria are defined as the fallowing section (Chen et al., 2009): 1) waist circumference over 40 inches in men or 35 inches in women, 2) blood pressure over 130/85 mmHg, 3) fasting triglyceride (TG) level over 150 mg/dl, 4) fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl in men or 50 mg/dl in women and 5) fasting blood sugar over 100 mg/dl.

The Waist circumference (WC) index measured at midpoint, between the 12th rib and the iliac crest from the skin per cm.

Exclusion criteria

Patients with underlying chronic disease, pregnancy, taking anticonvulsants, corticosteroids and other drugs that interfere with the metabolism of UA. The MS diagnosis was according to the Adult Treatment Panel III criteria (ATPIII) in 2005 criteria.

Results

The mean age of the individuals in case and control groups were 14.5 ± 2.5 and 15.3 ± 2.6 years, respectively ($p = 0.6$). There were 63 boys (52.5%) and 57 girls (47.5%) in the control and case groups, respectively ($p = 1$).

Table 1 compares the variables of the two studied groups. As the table show, systolic blood pressure, diastolic blood pressure, WC, BMI, serum UA ($p < 0.0001$) and insulin levels ($p = 0.008$) were significantly higher in the patient group. In addition, there was no significant difference between the two groups in terms of FBS and triglyceride levels ($p > 0.05$).

Considering the levels of triglyceride < 110 mg/dl and $\geqslant 110$ mg/dl, the insulin level of triglycerides in $\geqslant 110$ mg/dl was higher (12.2 ± 6 vs. 10 ± 5.4 μU/ml, $p = 0.02$). Considering the WC percentile $> 90\%$ or less, insulin levels were higher in subjects with abdominal obesity with $> 90\%$ percentile (13.9 ± 5.5 9 vs. 10.2 ± 5.6 μU/ml, $p = 0.001$). There was no significant difference between the two groups in terms of serum insulin level in the < 40 mg / dl and $\geqslant 40$ mg/dl HDL (10.6 ± 5.5 vs. 11.5 ± 6.1 μU/ml, $p = 0.4$). Considering systolic blood pressure (12.8 ± 2.1 vs. 10.6 ± 5.3

Table 1 Comparison of variables in two groups

Variables	(n = 2 × 120) group		p
	Healthy	Patient	
Age (year)	15.3±2.6	14.5±2.5	0.1
Systolic blood pressure (mm/Hg)	104.6±9.8	112.4±9.7	0.04
Diastolic blood pressure (mm/Hg)	64.2±9.9	67.8±9.7	0.04
Triglyceride (mg/dl)	74.4±17.9	179.6±73.3	0.3
Fasting blood glucose (mg/dl)	86.1±7.6	95.1±12.1	0.1
Waist circumference (cm)	65.1±6.9	80.1±13.6	0.01
Uric acid (mg/dl)	4.1±1	4.8±1.4	0.000
Body mass index (kg/m^2)	19.2±3.3	22.9±8.7	0.00
Insulin level (μU/ml)	9.8±5.3	12.2±6	0.008

μU/ml, p = 0.02) and diastolic blood pressure (10.8±6.8 vs. 11.8±5.8 μU/ml, p = 0.4), IN < 90% and ⩾ 90% percentile, insulin levels increased in the percentile group ⩾ 90% significantly only for the systolic blood pressure. Considering the FBS level of < 100 and ⩾ 100 mg/dl, no significant difference was seen in the insulin level (10.9±5.7 vs. 10.9± 6.19 μU / ml, p > 0.9). According to one-way ANOVA, considering percentiles of > 95%, 85%-95% and < 85% for BMI (4.1±5.5, 5.7±16 and 10±12.6 kg/m^2 respectively, p = 0.003), the insulin level was higher in the cases who had BMI > 95% in compare to cases who had BMI95%. Analysis of variance was used to compare the mean insulin level in head groups, which had a significant difference (p < 0.002). The Tukey test was used to determine the groups that differed significantly between the mean levels of insulin in groups 1 and 3 and p = 0.003.

The UA level ranged was 1.9 to 12.1 mg/dl in the whole population. Table 2 shows the distribution of MS indices in the healthy and patients groups in three categories of UA. As the table shows, in the case group, all variables except the FBS level, BMI and HDL level, showed an increase which was associated to UA levels increase.

Considering all individuals in three UA categorizes, Table 3 shows odds ratio (OR) for the MS and its indices in terms of ATPIII criteria. According to Table 3, UA level (⩽4.9 mg/dl) did not lead to an increase in the OR of MS and its related indices (OR = 1). The OR for MS and its indices increased significantly at UA levels of 4.9-5.8 mg/dl and ⩾ 5.8 mg/dl. The highest mean OR was related to abdominal obesity (OR = 5.8), hypertriglyceridemia (OR = 4.4) and MS (OR = 3.7) in 4.9-5.8 mg/dl of UA serum level. Like the previous group, the highest OR for abdominal obesity (OR = 11), hypertriglyceridemia (OR = 5.8) and MS (OR = 5.9), respectively was observed at of ⩾ 5.8 mg/dl of UA serum level.

The impaired FBS led to no significant increase in ORs of all UA levels (p > 0.05). The OR for the low HDL level was significant only at the (4.9-5.8 mg/dl) of UA serum level (OR = 36.2, p = 0.02). The hypertension OR showed a significant increase in ⩾ 5.8 mg / dl of the serum UA (OR = 3.3, p = 0.004). The increased UA level generally led to an increase in OR for MS, abdominal obesity, hypertriglyceridemia, hypertension and high FBS and low HDL levels.

The Pearson test also showed that there was no correlation between UA serum level and insulin level in the control (p = 0.2, r = –0.13) and patient groups (p = 0.07, r = 0.2). The UA level was not significantly correlated with insulin level in all subjects (p = 0.2, r = 0.1).

Discussion

Various studies have been conducted in various populations to evaluate the relationship between UA level and MS in adolescents, which reported relatively similar findings. In a study on adolescents aged 12 to 17 years, the American Heart Association (Ford et al., 2007) reported that the abdominal obesity, low HDL, hypertriglyceridemia and hypertension are associated with high UA level. In their analysis, the MS OR in UA level ⩽4.9, 4.9-5.8 and ⩾ 5.8 mg/dl was 1, 2.53 and 9.03,

Table 2 The distribution of metabolic indices in patients and healthy in three serum UA categories.

Uric acid level (mg/dl)	4.9⩾		5.8-4.9		⩾5.8	
Group	(n = 98) Healthy	(n = 61) Patient	(n = 13) Healthy	(n = 27) Patient	(n = 9) Healthy	(n = 32) Patient
Age ^{year}	15.3±2.7	14.1±2.6	15.5±2.5	14.3±2.4	44±1.4	2.3±14.8
Systolic blood pressure $^{mm/.Hg}$	104.68±10.41	111±10.5	105.4±8.3	114±10.4	102.5±4.6	112±9.04
Diastolic blood pressure $^{mm/.Hg}$	64.5±10.1	67.04±9	63.3±10.7	67.6±10.	62.8±7.5	96.6±10.6
Triglyceride $^{mg/dl}$	73.6±16.9	156.8±74.1	75.08±21.9	174.2±61.6	82.5±21.7	182.6±79.3
Fasting blood glucose $^{mg/dl}$	86.45±7.6	96.47±12.8	82.6±4.8	93.2±10.5	86.5±10.1	11.8±94.1
Waist ^{cm}	64.6±6.8	74.49±12.7	65.8±6.5	84.9±13.3	68.2±7.4	86.7±10.8
Uric acid $^{mg/dl}$	3.8±0.7	3.7±0.8	5.3±0.2	5.3±0.2	6.4±0.4	6.4±0.7
HDL $^{mg/dl}$	63.4±13.1	44.9±8.2	56±6.7	47.4±10.6	18.7±1.7	21.9±5.7
Body mass index $^{kg / m2}$	19.1±12.2	21.6±4.7	19.5±2.4	26.8±15.5	18.7±1.7	21.9±5.7

Table 3 The odds ratio of MS and its indices in three categories of UA serum levels.

Uric acid level mg / dl		4.9⩾	5.8-4.9	p_1	⩾5.8	p_2	p-Trend
OR	Metabolic syndrome	1	3.7(1.7-8.04)	0.001	5.9(2.4-14.35)	0.001	0.0001
	Abdominal obesity	1	5.8(2.4-13.45)	0.001	11.01(4.1-29.3)	0.001	0.0001
	High triglycerides	1	4.36 (2.01-9.47)	0.001	5.75(2.43-13.6)	0.001	0.0001
	High blood pressure	1	1.8(0.8-4)	0.1	3.3(1.46-7.48)	0.004	0.001
	Higher blood sugar	1	1.27(0.55-2.92)	0.5	1.68(0.74-3.84)	0.2	0.03
	Low HDL	1	2.36(1.12-4.90)	0.02	2.15(0.98-4.7)	0.05	0.001

p_1, Comparison between⩽4.9 and 4.9-5.8 mg/dl of UA categories.
p_2, Comparison between⩾5.8 with⩾4.9 and 4.9-5.8mg/dl UA groups.

respectively, which were higher than our findings in current study. In a study on adolescents aged 11 to 16, Wang et al. showed that increase in the level of UA was associated with obesity, increase in WC, hypertension and MS. This relationship was not significant in case of hypertension among girls. Additionally, in < 4.7 mg/dl level of UA, the MS OR was 7.67 (22.75±2.58), which was higher than our findings in this study (Li et al., 2015). also stated that UA cut-off point in boys and girls was higher than 7.3 and 6.2 mg/dl, respectively, was a good predictor of hypertension in both genders and MS in boys; however, there was no relationship between UA level with type 2 diabetes, triglyceride, HDL, and WC. Their findings showed that the UA level in subjects with MS was significantly higher than healthy subjects (7.8± 1.7 mg/dl VS. 6.7±1.6 mg/dl in boys and 6.0±1.3 mg/dl VS. 5.4±1.2 mg/dl in girls) (Sun et al., 2015). Nejatinamini et al. showed UA level in adolescents with MS was higher than healthy subjects. Based on the National Cholesterol Education Program (NCEP) criteria, the increased UA levels, independent of age, gender, and BMI, was associated with an increase in triglyceride and a decrease in HDL level. Their multi-regression analysis showed a 2.1 time increase in the risk of MS with 1 mg/dl increase in the UA level (Nejatinamini et al., 2015). Cardoso et al. assessed children and adolescents, and determined the UA serum levels as < 3, 3-3.9, 4-4.8, and 4.9⩽mg/dl. They observed that increase in UA level is associated with increase in WC, hypertension and hypertriglyceridemia. Their findings showed that UA level of > 5.5 mg/dl was associated with MS. The incidence rate of hyperuricemia in adolescents aged 10-18 years old was higher than the children (OR = 9.24) and the risk of MS in adolescents was reported to be 3.5 times more than the children (Cardoso et al., 2013). The hyperinsulinemia in patients with MS was one of the other findings of this study. Hyperinsulinemia caused by insulin resistance is one of the complications associated with MS, which puts individuals at risk of diabetes and cardiovascular events (Rutter et al., 2005; Sung et al., 2011).

Sung et al. measured the baseline insulin level of over 2300 Korean adults during their 5-year follow up study. They observed that increasing serum insulin levels lead to higher likelihood of developing MS and its related indices. At the insulin level of 8.98 μU/ml, which is close to the insulin level in our study, the incidence and OR of the MS were recorded to be 16.4% and 5.1(3.1-8.2). They also showed that insulin levels > 8.23 μU/ml led to the incidence and likelihood ratio of MS was 5.4% and 10.7 (2.4%, 47.9) (Sung et al., 2011). DeBoer et al. showed the insulin levels in adolescents was directly related to MS (WC, systolic blood pressure, triglyceride and FBS), inversely related with HDL, and did not related to diastolic blood pressure(DeBoer et al., 2011), which is consistent with the findings of the present study except of the FBS and HDL level. The findings of the present study showed that increasing BMI and abdominal obesity levels led a significant increase in the insulin levels. Obesity seem to play a key role in insulin resistance and hyperinsulinemia (Lteif et al., 2005). In a study done by Anthony J.G. Hanley et al. examined 822 subjects in the Insulin Resistance Atherosclerosis Study aged 40 to 69 years who were nondiabetic at baseline. After 5.2 years, 148 individuals had developed DM. impaired glucose tolerance (IGT), MS definitions, and insulin resistance (IR) markers all significantly predicted DM, with odds ratios ranging from 3.4 to 5.4 (all $p < 0.001$), although there were no significant differences in the areas under the receiver operator characteristic (AROC) curves between the definitions. This study conclusion let The International Diabetes Federation and NCEP metabolic syndrome definitions predicted DM as well as World Health Organization (WHO) definition. In this study they did not used the oral glucose tolerance testing or IR (Hanley et al., 2005). In another study by Balkau et al. (Balkau et al., 2002) run a study to describe the frequency, in some European populations.WHO defined MS and to compare the frequency of this syndrome with an alternative definition for non-diabetic subjects, called the insulin resistance syndrome in this study they studied eight European countries by a protocol to study the abnormalities of these two syndromes, by sex and age, as well as the overall frequencies of the syndromes and the average number of abnormalities. They studied 8200 men and 9363 women and the conclusion says there is great variability in the frequency of the syndrome between different populations, due to the differing frequencies of the abnormalities and methodologies of measurement in other hand they the frequency of both syndromes increased with age and was almost always higher in men. In non-diabetic subjects the frequency of the WHO syndrome varied between 7% and

36% for men 40 to 55 years; for women of the same age, between 5% and 22% (Balkau et al., 2002).

Conclusion

The findings of this study indicate that patients with MS have an increased UA and insulin levels; The UA level of > 4.9 mg/dl led to an increase in the OR for MS, abdominal obesity, hypertriglyceridemia, hypertension, increased FBS and Low HDL. Hyperinsulinemia was associated with triglyceride level of 110 mg/dl, abdominal obesity with > 90% percentile, and systolic blood pressure with > 95% percentile. In a clear word we can say insulin and UA level are can be predictive biomarkers in estimating MS risk. Finally, the findings of this case- control study showed that adolescents with MS develope higher levels of serum UA and insulin in compare with normal people. Additionally increase in UA level increase the risk of MS and its indices. It seems that if hyperuricemia and hyperinsulinemia be noticed in routine adolescent tests, they might predict other MS-related disorders and prevent the complications of this syndrome.

Acknowledgment

This study was supported by Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Compliance with ethics guidelines

The authors declare no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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