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Plasma Aldosterone Level in Metabolic Syndrome Patients Compared with Individuals without Metabolic Syndrome. A Survey on Iranian Population

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Abstract

Background: previous studies showed the role of aldosterone in pathogenesis of metabolic syndrome. The aim of this study was analysis the relation between plasma aldosterone (PA) and metabolic syndrome (MetS) and its components by comparison of PA in subjects with and without MetS.

Methods: This cross-sectional study was designed on an Iranian sample in two groups with and without MetS (240 people in all). Aldosterone level in both groups was measured and then compared with presence of MetS and its components (waistline circumference, HDL, FBS and TG). Finally al of gathered data was analyzed using SPSS-17 software.

Results: No significant differences between mean PA level in subjects with and without MetS were seen. In subjects without MetS, HDL was positively correlated with plasma aldosterone (r=0.294, p<0.001) and TG was inversely correlated with PA (r=-0.220, p=0.012). In subjects with MetS plasma aldosterone correlated positively with FBS (r=0.228, p=0.021). With increasing age and metabolic risk factors, PA level was decreased.

Conclusion: This result suggests that aldosterone may contribute some roles in early stages of metabolic syndrome, not in late stage of the syndrome. These findings need to be evaluated in future studies and the positive association of aldosterone with HDL needs to be more explained.

Keywords: Aldosterone; Diabetes; Hypertension; Myocardial infarction

Introduction

The increasing prevalence of obesity, diabetes, hypertension, cardiovascular diseases and chronic kidney diseases are the major health problems of both developing and developed countries [1,2] Obesity as a worldwide problem is considered as the sixth risk factor of chronic diseases and also its prevalence has an accelerative pattern especially in children [1]. Metabolic syndrome (MetS) is characterized by hypertension, lipid metabolism dysfunction, insulin resistance and abdominal obesity. There are several studies related to this syndrome [3-6] previous studies suggested a prevalence of 20 to 25% of MetS between people living in the middle east [7,8]. According to the pathogenesis of MetS, the specific role of aldosterone as a steroid hormone was more clarified [2] and studies on its plasma level among patients with MetS had various results in relation with sex and race [9]. In this cross-sectional study we aimed to compare the plasma aldosterone (PA) level in Iranian patients with and without MetS.

Method and Materials

This research study was done at Isfahan University of Medical Sciences with project number of 390089. At the first step of case and control sampling, individuals participating in Isfahan healthy heart program were analyzed. Primarily, 435 patients with MetS and 352 individuals without MetS were obtained. At the next step of sampling, individuals of both groups were asked about hypertension, consumption of anti-hypertensive drugs, and cerebrovascular accident or myocardial infarction during 6 months ago and people with any of above condition were not included into the study. Included individuals were invited and informed about the study, and then they fulfilled the testimonial form. Presence of diseases, drugs, sport, nutritional habits, history of diabetes mellitus, hypertension, cerebrovascular accident and myocardial infarction of both case and control groups were recorded. The exclusion criteria were as the following: A) history of taking anti-hypertensive drugs, especially aldosterone antagonists and ACEIs, ARBs, beta blockers and diuretics (although alpha blockers, hydralazine and some of the calcium channel blockers [CCBs] could be used as substitute of above drugs because of its lesser effects on plasma aldosterone level [10], but because of moral consideration in this study, all of the individuals using anti-hypertensive drugs were excluded of the study) B) presence of chronic heart disease, end stage renal disease, cerebrovascular accident or myocardial infarction during past 6 months, unstable angina, surgery during past 3 months, history of taking Licorice, taking non-steroidal anti-inflammatory drugs (NSAIDS), taking drugs containing estrogen or using contraceptive pills and pregnant women (the aldosterone level increase to tenfold at the 3rd trimester of pregnancy) [11]. Finally there were 105 individuals in case group (patients with MetS) and also 135 individuals in control group without MetS.

Body weight was measured by the least dresses and using a digital balance with the accuracy of 100 grams. Body height was measured by standard meter and in a position of person which he was stand-up and

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his talon, buttock, behind of shoulders and behinds of occipital bone of the skull were in a line. The waistline circumference was measured using a standard meter which moved on a line crossing umbilicus and superior border of iliac crest of individuals in stand up position, the meter was on skin or slim underwear of individuals [12]. Evaluating of blood pressure was done twice. The first evaluating was after 10 minutes of sitting, at the beginning of visit and the last one at 10 minutes later. Finally the average of both numbers of blood pressures was considered as the person's blood pressure. After all of above assessment, 270 individuals were chosen to take apart into the study and they were referred to the laboratory for further assessment of blood biochemical parameters (fasting blood sugar [FBS], triglyceride [TG] and high density lipoprotein [HDL]). Two hundred fifty four individuals of all, recourse to the laboratory. Because of the effect of body position on PA level [13], all of them had to sit down for at least half an hour before blood sampling and for decreasing undulation of PA level all of blood samples obtained at 8 am to 10 am. On the sampling time, the people were requested not to wisp their hand and after needle penetration, sampling was done after 5 second of opening the tourniquet so that no hemolysis and stasis occurred in the vein. The blood samples were gathered into an EDTA saturated tube and then centrifuged in a time less than 30 minutes of sampling, and then the plasmas were sent for aldosterone level assessment [14] FBS was assessed by biosystem kit using oxydase method, TG and HDL were assessed by Pars azmoon kit using photometric method. IBL International kit, made in Germany, was used for measuring the plasma aldosterone level and the numbers of aldosterone were changed from nanogram per milliliter to picomole per liter by multiplying into 2.77. In further assessments of people in both groups, four people were excluded of the study because of very high or very low PA level and three people were excluded due to use of antihypertensive drugs. According to NCE ATP-III, presence of three or more of these conditions in people participating in the study lead to MetS diagnosis: 1- waistline circumference more than 102 centimeters in men and more than 88 centimeters in women. 2-blood triglyceride equal or more than 150 milligram per deciliter or patients on treatment 3- HDL lesser than 40 in men and 50 milligram per deciliter in women or patients on treatments 4-blood pressure equal or more than 130/85 mmHg or patients on antihypertensive therapies 5-FBS equal or more than 100 milligram per deciliter or patients on diabetes treatment [10].

Finally people of both groups were assessed about all of factors and their data were analyzed using SPSS-17 software. Chi-square test, Pierson correlation coefficient test, multiple regression test, independent T-test and covariance analysis test were used for data analyzing. Data with P value<0.05 were considered as significant.

Results

Two-hundred forty people had taken part into full assessments of our study, out of them, 102 people were female (42.5%) and 138 people were male (57.5%). The prevalence of MetS was higher in female group compared with males (50% *vs.* 39%). According to (Table 1), body mass index (BMI) and HDL were higher in female group compared with males but average of height, weight and TG were lower in females. In other factors such as PA level there was not any significant difference between male and female groups. Eight people (3%) fulfilled all of 5 criteria for MetS, 38 people (16%) had 4 criteria, 59 people (25%) had 3 criteria, 46 people (19%) had 2 criteria, 48 people (20% had 1 criteria and 41 people (17%) did not have any diagnostic criteria for MetS. considering above data, 105 people (44%) of all of individuals had MetS. the mean number of PA level was 327.47 ± 170.30 picomole per liter in MetS patients and 390.71 ± 162.22 picomole per liter in people without MetS. Primarily the P value of 0.004 between groups with and without MetS, showed a difference on PA level between groups, but after adjustment the effects of age, sex, waistline circumference, diastolic blood pressure (dBP) , systolic blood pressure (sBP), HDL, TG and FBS between groups, there were not any statistical difference of PA level between groups with and without MetS.

Though we had deleted people who consumed antihypertensive drugs from our study, there were 47 people (44%) in MetS group who had sBP disorder (sBP ≥ 130 mmHg) and 54 people (51%) in the same group with dBP disorder (dBP ≥ 85 mmHg), however in the group without MetS 6.7% had sBP disorder and 12.7% had dBP disorder according to ATPIII criteria. In MetS group, 78% (81 individuals) had abnormal HDL level and in group without MetS there were 28% (37 individuals) with same disorder according to ATPIII criteria. 80 people (76%) in MetS group had TG ≥ 150 milligram per deciliter but just 27 people (20%) in group without MetS had the same disorder. 81 people (77%) had abnormal waistline circumference in MetS group although there were 34 people (25%) with same disorder in non-MetS group. considering (Table 2), all of variables except height are significantly different between groups.

Because of decreasing the PA level in relation with age, we controlled the age effect in all of computations and Kolmogrov-Smirnov test demonstrated that PA level followed a normal distribution (Figure 1).

In men, PA had a reverse relation with TG (p=0.001, r=-0.271) and also a straight relation with HDL (P<0.001, r=0.0396). In women, the significant relation between PA and waistline circumference, sBP and dBP diminished after controlling the age effect. (Table 3) shows the

	Female	Male	P value
N	102(42.5%)	138(57.5%)	-
Age, y	44.3 ± 8.2	43.6 ± 8.0	0.498
Height, cm	157.2 ± 6.2	172.7 ± 7.4	<0.001
Weight, kg	71.3 ± 12.1	81.8 ± 13.2	<0.001
BMI, kg/m^2	28.9 ± 4.9	27.4 ± 3.7	<0.001
Waist, cm	95.9 ± 14.5	97.9 ± 15.4	0.307
Fasting blood glucose, mg/dl	106.2 ± 45.4	107.8 ± 37.2	0.771
HDL cholesterol, mg/dl	48.6 ± 11.7	41.6 ± 10.7	<0.001
Triglycerides, mg/dl	144.7 ± 101.7	174.9 ± 106.1	0.028
systolic BP, mmHg	115.3 ± 18.2	116.4 ± 11.9	0.556
diastolic BP, mmHg	77.1 ± 10.3	79.3 ± 7.7	0.064
Plasma aldosterone, pm/L	348.1 ± 175.9	374.1 ± 162.4	0.239

Table 1: Baseline sex characteristics of subjects.

Characteristic	Metabolic syndrome (n=105)	No Metabolic syndrome (n=135)	P value
Age, y	46.1 ± 7.5	42.1 ± 8.2	<0.001**
Women, n(%)	51(48.5%)	51(38%)	<0.001**
Height ,cm	165.4 ± 11.5	166.6 ± 9.3	0.359
Weight ,kg	83.3 ± 14.7	72.7 ± 10.9	<0.001**
BMI, kg/m^2	30.4 ± 4.1	26.2 ± 3.5	<0.001**
Waist circumference, cm	104.6 ± 14.4	91.1 ± 12.7	<0.001**
Woman, cm	103.7 ± 13.6	88.0 ± 10.7	<0.001**
Man, cm	105.6 ± 15.2	92.9 ± 13.5	<0.001**
Fasting blood glucose, mg/dl	123.5 ± 48.9	94.2 ± 27.2	<0.001**
HDL cholesterol, mg/dl	38.9 ± 9.4	49.0 ± 11.3	<0.001**
Woman, mg/dl	43.0 ± 9.7	54.4 ± 10.8	<0.001**
Man, mg/dl	35.1 ± 7.4	45.9 ± 10.4	<0.001**
Triglycerides, mg/dl	220.4 ± 122.8	116.0 ± 55.8	<0.001**
systolic BP, mmHg	123.2 ± 14.9	110.2 ± 12.3	<0.001**
diastolic BP, mmHg	82.0 ± 8.7	75.6 ± 8.1	<0.001**
Pulse pressure, mmHg	13.8 ± 3.4	12 ± 4.4	0.001*
Plasma aldosterone, pm/L	327.5 ± 170.3	390.7 ± 162.2	0.004*
History of DM, n(%)	32(30.5%)	7(5.2%)	<0.001**
Family history DM, n(%)	41(39.0%)	26(19.2%)	0.001*
Family history HTN, MI, stroke	37(35.2%)	43(31.8%)	0.583

Results are means ±SD, unless specified otherwise. Metabolic syndrome was defined using NCE ATP-III criteria, HTN: hypertension, MI: myocardial infarction, DM :diabetes mellitus,*P value<0.05 ,**P value<0.001

Table 2: Basic characteristics of subjects with and without metabolic syndrome.

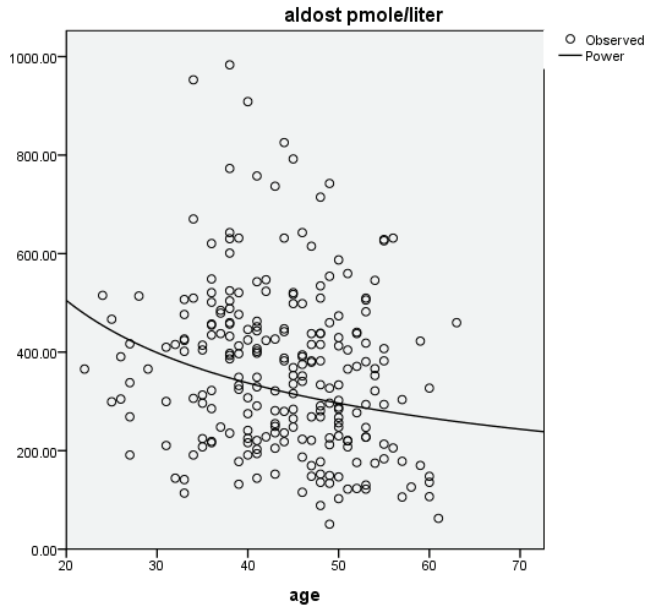

Figure 1: Relation between aldosterone and age.

coefficients of relations between PA and MetS variables in both MetS group and non-MetS group computed by Pierson correlation test.

PA had a straight relation with FBS in patients suffering MetS (r=0.228, P=0.021). PA had a reverse relation with TG (P=0.012, r=-0.220) and a straight relation with HDL (P<0.001, r=0.294) in people without MetS, after controlling the effect of age and sex.

Of 240 volunteers for this study, 16% (39 people) had Diabetes mellitus (DM). 32 individuals (82%) of those with DM, had MetS in non-diabetic people, PA showed a straight relation with HDL. In people without a family history of DM, PA had a reverse relation with TG, BMI, waistline circumference and also a straight relation with HDL. In 152 people without positive family history of myocardial infarction, hypertension and cerebrovascular accident (both ischemic and hemorrhagic), PA had straight relation with HDL and a reverse relation with TG (Table 3).

Discussion

In past decades, large studies were investigated to gain diagnostic criteria to characterize the metabolic syndrome and sometimes paradoxical parameters considered as its diagnostic criteria [15]. Finally, convergence of all of those studies led to access some descriptions for this syndrome such as IDF and ATP-III and also theirs modifications for different locations. But these descriptions are under modifications yet [16].

In African race, a recent study on 2011 in a sample group of 1266 volunteers, showed that a higher percentage of total cholesterol consist of HDL and although HDL<1.03 millimole per liter had a higher risk for cardiovascular diseases, its level equal or higher than 1.29 millimole per liter had also an increased same risk [17].

Considering the increasing prevalence of diagnostic criteria for metabolic syndrome in our country, Iran, evaluations for the prevalence of hypertension and impaired blood pressure [14] the prevalence of metabolic syndrome in people with normal blood pressure was <13% in Isfahan (center of Iran) evaluated by Isfahan healthy heart program [18].

As researchers though before, insulin resistance played a major role in the pathogenesis of metabolic syndrome but recent studies suggested other diagnostic variables for this syndrome. A study on 1276 volunteers which was done for finding a threshold of insulin resistance in metabolic syndrome (HOMA-IR) showed that in patients with metabolic syndrome, especially those with disorder in waistline

Groups		BMI Kg/m²	Waist cm	sBP mmHg	dBP mmHg	FBS mg/dl	TG mg/dl	HDL mg/dl
Metabolic syndrome n=105	r	0.112	-0.060	0.036	0.010	0.228	-0.052	0.117
	p	0.262	0.551	0.720	*0.923*	0.021*	0.601	0.240
No metabolic syndrome n=135	r	-0.159	0.002	-0.091	-0.031	-0.043	-0.220	0.294
	p	0.073	0.978	0.305	0.731	0.632	0.012*	** <0.001
Normal dBP n=163	r	-0.103	-0.072	-0.013	0.021	-0.058	-0.178	0.281
	p	0.186	0.359	0.865	0.793	0.460	0.022*	<0.001**
Normal sBP n=177	r	-0.154	-0.148	-0.054	-0.045	-0.028	-0.180	0.327
	p	0.039*	0.047*	0.474	0.554	0.708	0.016*	<0.001**
Abnormal waist n=108	r	0.081	-0.009	0.050	-0.051	0.202	-0.045	0.242
	p	0.400	0.928	0.606	0.598	0.034*	0.641	0.011*
Normal FBS n=143	r	-0.179	-0.099	-0.168	-0.183	-0.061	-0.325	0.366
	p	0.031*	0.238	0.043*	0.028*	0.464	<0.001**	<0.001**
No DM n=192	r	-0.112	-0.073	-0.152	-0.120	-0.027	-0.155	0.320
	p	0.121	0.313	0.034*	0.096	0.714	0.031*	<0.001**
No family history DM n=164	r	-0.185	-0.163	-0.069	-0.100	-0.018	-0.182	0.302
	p	0.017*	0.036*	0.376	0.199	0.823	0.019*	<0.001**
No HTN MI STROKE n=152	r	-0.126	-0.005	-0.073	0.017	0.040	-0.213	0.334
	p	0.120	0.951	0.368	0.839	0.620	0.008*	<0.001**
Women n=102	r	-0.035	-0.072	-0.095	-0.126	0.195	0.019	0.082
	p	0.734	0.482	0.350	0.215	0.054	0.850	0.423
Men n=138	r	-0.085	-0.067	0.015	0.050	-0.087	-0.271	0.396
	p	0.326	0.439	0.867	0.565	0.313	0.001*	<0.001**
All subjects n=240	r	-0.081	-0.081	-0.068	-0.051	0.052	-0.156	0.256
	p	0.216	0.218	0.305	0.440	0.430	0.018*	<0.001**

BMI :body mass index , sBP and dBP :systolic and diastolic blood pressure, HTN: hypertension, MI: myocardial infarction ,DM :diabetes mellitus ,r:pierson regression, P: P value,*P value<0.05 ,**p-value<0.001

Table 3: Plasma aldosterone relation with each metabolic risk factors in selected groups (age adjusted).

circumference, the prevalence of insulin resistance is higher. But one third of patients with insulin resistance had none of else criteria for the syndrome [19]. Another study on people with high normal blood pressure showed that metabolic syndrome and insulin resistance are not equal to each other due to entropometric, metabolic, hemodynamic and hormonal findings [20]. According to this issue that obesity and visceral fat are some of the most prevalence features of metabolic syndrome, it seems to be probable that insulin resistance is caused by overweight, not a reason for it, and obesity is a strong catalyst for starting metabolic disorders [15].

Some researchers suggested that a multi reasonable pattern instead of thinking about just insulin resistance as a reason, could better explain the complexity of this syndrome [21]. further studies suggested the probable role of leptin, uric acid, fibrinogen, albuminuria and decreased adiponectin [21,22] because of presence of a chronic inflammation in patients suffering metabolic syndrome, some previous studies posed a causational role for IL-6, TNF-α, CRF and fibrinogen in this syndrome [17,23]. But there is not a response to this question that whether inflammation is caused by this syndrome or it, itself plays a reasonable role [15]. Recent studies have worked on the role of Renin-Angiotensin aldosteron system (RAAS) in oxidative stress, chronic kidney diseases and insulin resistance in cardiovascular diseases [2]. The classic effect of aldosterone (which secreted by adrenal gland) is controlling extracellular volume, sodium and potassium. This effect caused by hormone attachment to cytoplasmic receptor, transporting to nucleus, genomic translation and finally, production of proteins in ribosome. So there is a delay between hormone production and cellular response caused by hormone. In 1990, researchers explained rapid and non-genomic effects of aldosterone. The following effects suggested causing by aldosterone activity: effects on intracellular cations, cellular

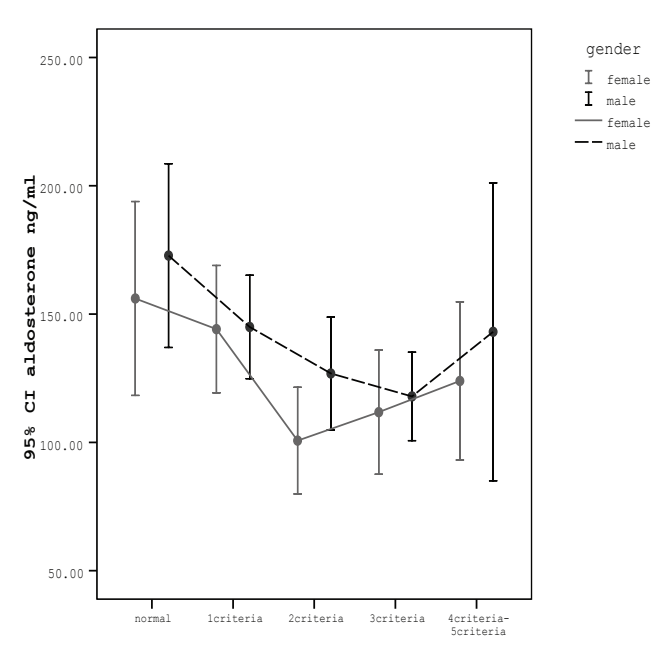

Figure 2: Aldosterone changes due to number of risk factors for metabolic syndrome.

volume, oxidation/reduction state (redox state), dysfunction in intracellular signaling due to insulin hormone, inflammation, fibrosis and elevating the level of PAI-1 (plasminogen activator inhibitor 1) which is effective on heart repairing after myocardial infarction. An

increased level of aldosterone, lead to maladaptive remodeling in vascular system, Kidneys and the heart due to endothelial dysfunction and insulin resistance. So the leading cause is resistant hypertension (needing 3 or more antihypertensive drugs for treatment) in obese people. Moreover, in obese people, there is more sensitivity to angiotensin II for producing aldosterone in their adrenal gland and also oxidation of linoleic acid in the fat tissue, lead to produce a substance which stimulates production of aldosterone [1,2]. The aldosteron level decrease during atrophic regimen [12,24]. Above concepts, helped us to find a better relationship between aldosterone and metabolic syndrome [25,26] in a study on African raced American people, an association between aldosterone and hypertension was suggested [9]. Some studies posed a hypothesis which said that mineralocorticoid's receptors are activated by glucocorticoids and oxygen radicals with evidences of increased cortisole [2,27] another study on 201 patients with metabolic syndrome, showed a relationship between increased aldosterone level and left ventricle hypertrophy [28] pharmacologic studies showed hopeful effects of aldosterone receptor blocking by spirino lactone and Eplerenone in patients with MetS which led to improving the rate of cardiovascular complications, diabetes, chronic kidney disease and decreasing proteinuria [29-32].

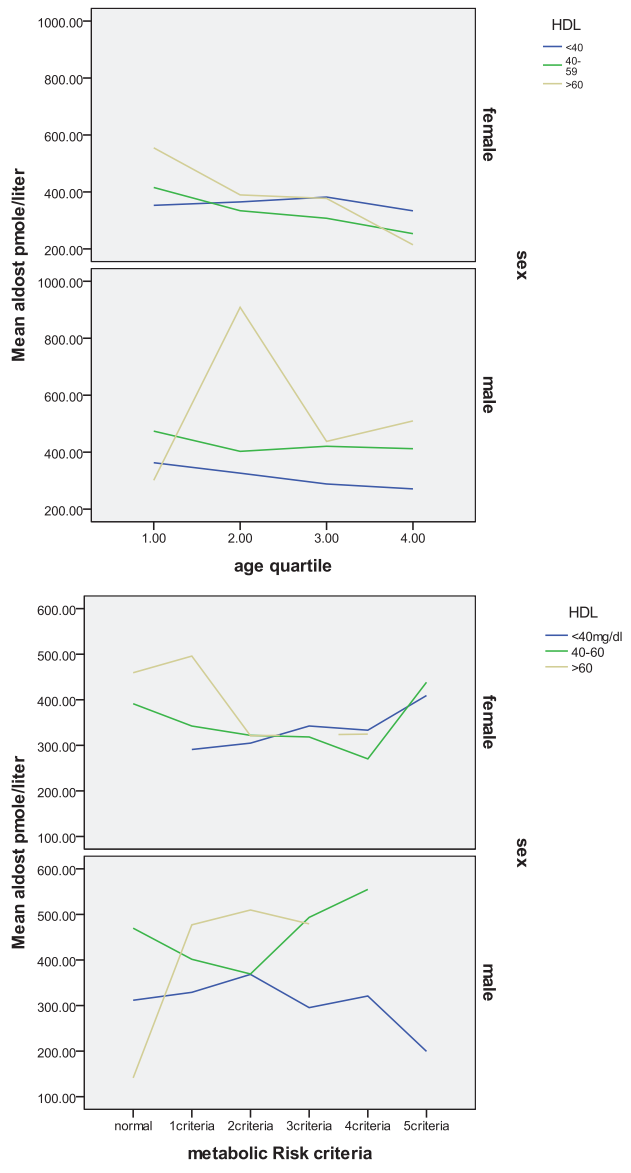

Figure 3: Relation between HDL level with aldosterone in men and women due to age (quartiles) and number of metabolic risk criteria.

We designed this study to evaluate whether or not there is a probable relationship between PA level andcomponents of MetS. Our data didn't show differences in PA level between people with MetS and those without the syndrome. (Figure 2) shows that by increasing the number of MetS risk criteria, the mean of PA level decrease. Egan BM et al. had also showed the same relationship as ours [20] in patients with MetS, FBS had a straight relation with aldosterone. Evaluation of individuals without MetS showed that plasma aldosterone level has a reverse relation with TG and a straight relation with HDL. In other words, people with higher HDL, had higher aldosterone level and the highest plasma levels of aldosterone were seen in younger people without MetS. This hypothesis is suggested that aldosterone is more responsible for primary processes of metabolic syndrome and the role of aldosterone -not mineralocorticoid's receptors and other aldosterone agonists- decrease during development of the syndrome. The significant straight relation between aldosterone and HDL is another hesitating issue. Different components of HDL do not work same as each other and various therapeutic methods don't raise same HDL components. HDL-ApoA-I with lower percentage of fat, cause to gathering peripheral cholesterol and its transport to the liver but destination of that round, full of fat HDL is not well-defined. The quality of HDL-not just its quantity- is effective on cardiovascular system [33,34].

Evaluating of (Figure 3) may suggest this hypothesis that those levels of HDL higher than normal level have various effects on aldosterone level. Non-reachable data of potassium, urine excretion of sodium and plasma rennin activity are limitations of our study. Various explanations of metabolic syndrome and statistical models make it hard to compare the results of different studies. The complexity of syndrome due to explanation of criteria and true pathophysiologic processes tell us that this syndrome needs further studies and probable accurate reevaluations [7].

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