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Understanding the Association between Coronary Artery Disease and Hyperandrogenism in Women

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Abstract: Hyperandrogenism which is characterized by excessive production of androgen by ovaries or adrenal glands, is regarded as one of the probable risk factors for cardiovascular diseases. This study was conducted to determine the association between coronary artery disease and hyperandrogenism in women. In this cross-sectional study, the research population was women under 60 who were admitted to Imam Ali Hospital of Kermanshah for angiography. The sample size included 116 people who were selected through available sampling. Coronary artery disease risk factors were evaluated using interview technique and taking patients' medical history. Blood sample was taken and tested to measure testosterone and blood glucose and lipids variables. Then, all patients were undergone coronary angiography. Data were analyzed using SPSS-16 software and Chi-square, t-test and regression statistical tests.Out of 116 patients under study, 58 people had abnormal angiography and 58 patients normal one. Among the studied heart risk factors, history of diabetes, family history of CAD and the history of previous MI in abnormal angiography group were significantly greater than normal group ($p<0.05$). Considering the hyperandrogenism symptoms, hirsutism and androgenetic alopecia in abnormal angiography group were significantly greater than normal group ($p<0.05$). In addition, the regression test results also indicated the presence of a significant relationship between BMI, history of previous MI and the presence of hirsutism symptom with the incidence of positive findings in angiography ($p<0.05$). The results of this study showed that hyperandrogenism symptoms could be considered as one of the risk factors associated with cardiovascular diseases.

Key words: Hyperandrogenism, coronary artery disease, women, angiography, hirsutism

INTRODUCTION

At the present time, cardiovascular diseases are the most common cause of death all over the world that includes 30% of deaths in the world and despite the remarkable developments in prevention and treatment of atherosclerosis, complications and mortality from it are still high. It is expected that with the increased age of population, obesity, prevalence of diabetes type 2 and the rise of the other cardiovascular diseases risk factors, the rate of coronary artery diseases will increase still further in the future decades.

Risk factors for cardiovascular diseases are similar in both sexes, but men start to represent coronary artery disease 10-15 year earlier than women. According to the obtained information from Framingham's studies, probability of the manifestation of symptomatic coronary heart disease after age 40 is estimated to be 49% for men and 32% for women. Estrogen is regarded as the leading factor responsible for protecting women against coronary heart disease before menopause which has direct protective effects on the wall of arteries and also leads to the improved blood lipids (Fiebig *et al*., 2002). On the contrary, researches have revealed that the excessive level of androgen in the body might result in the increased cardiovascular diseases risk in women through affecting lipid profile, blood pressure and glucose metabolism (Liu *et al*., 2001). Furthermore, some retrospective studies have showed the relationship between high androgen level in the body and cardiovascular disease in postmenopausal women (Barrett-Connor and Goodman-Gruen, 1995; Gruen and Connor, 1996; Haffner *et al*.,

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1996); however, this subject has not been confirmed in prospective studies as yet (Rexrode *et al*., 2003).

Hyperandrogenism, characterized by the increased production of androgen by ovaries or adrenal glands, includes clinical manifestations such as hirsutism, acne androgenic alopecia and menstrual disorders. Among the other effects of hyperandrogenism are insulin resistance and elevated insulin level, increased prevalence of hypertension during menopause to about 40%, the increased incidence of atherosclerosis and cardiovascular diseases and the increased risk of myocardial infarction (Safari and Ziapour, 2016). In addition, in the surveys conducted in different areas of the world, the prevalence of metabolic syndrome among women suffering hyperandrogenism was reported in between 7-43% (Apridonidze *et al*., 2005; Carmina *et al*., 2006; Ehrmann *et al*., 2006; Soares *et al*., 2008; Weerakiet *et al*., 2007; Barber *et al*., 2007; Pekhlivanov *et al*., 2007; Goverde *et al*., 2009; Cheung *et al*., 2008). Metabolic syndrome, characterized by high triglycerides and low HDL, has a direct relationship with cardiovascular diseases. The role of testosterone in development of heart diseases in women is still unknown and yet there is uncertainty regarding high or low testosterone level and its association with coronary artery diseases. However, most studies conducted on this subject have examined males' group and less studied the role of hyprandrogenism in females (Pekhlivanov *et al*., 2007; Mohmmadi *et al*., 2014). Accordingly, regarding the new understanding of the role of hyperandrogenism as cardiovascular diseases risk factor, we decided to study the relationship between the coronary artery disease and hyperandrogenism in women in a research.

MATERIALS AND METHODS

In this cross-sectional study, the research population was women under 60 who had been undergone angiography at Imam Ali Hospital of Kermanshah in 2013. The sample size was calculated using resources and HDL variable and 58 people was obtained for each of the two case and control groups; the total number of sample was 116 people, overall. Individuals' selection was done using available sampling. Inclusion criteria included being female, age under 60 and indications for coronary angiography. Exclusion criteria also included patient's reluctance to participate in the research and age over 60. After obtaining consent from patients, all were examined. The examinations included studying hirsutism condition using Ferriman-Galwey table and its rating and the examining of androgenetic alopecia.

Moreover, risk factors of coronary heart disease including "history of hypertension, history of diabetes, history of coronary artery disease, high blood lipids, history of cigarette smoking, BMI, age and family history of heart disease" were evaluated through taking interview and patients' medical history. Blood sample was taken from all patients candidate for angiography and forwarded to the reference laboratory for assessing Total Testosterone, TSH, FBS, Triglycerides, LDL, HDL and Total Cholesterol. In this research based on laboratory report, normal testosterone level and normal TSH level were considered to be 0.1-0.95 and 0.4-6.21, respectively. BMI over 30 is also regarded as obesity and blood pressure over 140.90 or antihypertensive drugs use as hypertension.

Afterwards, all patients were undergone angiography and divided into two groups based on the results: positive CAD (abnormal group) (that is, at least one of coronary arteries had involvement and stenosis over 50%) negative CAD (normal group) (coronary artery involvement under 50%).

Data obtained from interview and medical history, clinical examination and laboratory results were entered into SPSS-16 Software after encoding and were analyzed. Statistical tests used included chi-square, t-test and regression and descriptive statistics was arranged in the form of tables and diagrams. In this study, the accepted significance level was considered to be 0.05.

RESULTS

In this study, 116 people, who were undergone coronary artery angiography were studied in two groups of 58 individuals with normal and abnormal angiography. The average age of patients was 49.13±8.86 in the first group and 51±6.69 in the second group that there was no significant difference between two groups ($p = 0.199$).

Furthermore, with regard to patients BMI conditions, 13.8% of individuals in abnormal group and 34.5% of individuals in normal group had normal BMI range. Data analysis demonstrated that high BMI in individuals of normal group was significantly greater ($p = 0.024$) (Table 1).

In addition, among heart risk factors under study, history of diabetes, family history of CAD and prior history of MI in abnormal group were significantly greater than the normal group ($p<0.05$), however, in terms of hypertension history, lipid profile, history of cigarette smoking and alopecia, a significant difference was not found between two groups ($p>0.05$) (Table 1).

Table1: Frequency values and comparison of hyperandrogenism symptoms, hormonal properties and various background variables in two normal and abnormal groups of patients undergone coronary angiography

Patients undergone coronary angiography			
Property	Abnormal group Number (%)	Normal group Number (%)	p value
BMI			
≤19.5	3(5.17)	4(6.90)	0.024
19.6-25	8(13.8)	20(34.48)	
25.1-30	16(27.59)	19(32.76)	
30.1-40	28(48.27)	14(24.14)	
40<	3(5.17)	1(1.72)	
History of diabetes			
Positive	23(39.65)	12(20.69)	0.026
Negative	35(60.35)	46(79.31)	
History of hypertension			
Positive	36(62.06)	32(55.17)	0.699
Negative	22(37.94)	26(44.83)	
Lipid profile			
Disturbed	28(48.27)	20(34.48)	0.132
Normal	30(51.73)	38(65.52)	
Family history of CAD			
Positive	21(36.20)	9(15.51)	0.011
Negative	37(63.80)	49(84.49)	
History of smoking			
Positive	3(5.17)	4(6.89)	0.679
Negative	55(94.83)	54(94.11)	
Family history of Alopecia			
Positive	2(3.44)	4(6.89)	0.402
Negative	56(96.56)	54(94.11)	
History of previous MI			
Positive	16(27.58)	6(10.34)	0.018
Negative	42(72.42)	52(89.66)	
Hirsutism			
Positive	25(43.10)	13(22.41)	0.035
Negative	33(56.90)	45(77.59)	
Androgenic alopecia			
Positive	12(20.68)	4(6.89)	0.031
Negative	46(79.32)	54(93.11)	
Testosterone level			
Increased	12(20.68)	7(12.06)	0.210
Normal	46(79.32)	51(87.94)	
Level TSH Serum			
<0.4	2(3.45)	1(1.72)	0.214
0.5<TSH<6.2	55(94.83)	52(89.65)	
>6.2	1(1.72)	5(8.63)	

The study results of hyperandrogenism symptoms in patients under study showed that 43.1% of abnormal group patients and 22.4% of those in normal group had positive clinical symptoms for hirsutism and there was a statistically significant difference between them (p = 0.018) (Table 1). Additionally, hirsutism average scores of people in abnormal and normal groups were 12.07±2.15 and 9.30±3.59, respectively, in which a significant difference was observed (p = 0.035).

Patients' examination for androgenic alopecia also indicated that hyperandrogenism clinical symptom presented in 20.7% of abnormal group patients and 6.9% of patients in normal group while majority of them were low in grade. The analytical results showed that there was a significant difference between study groups in terms of androgenic alopecia (p = 0.031). Also, people were divided into two groups based on testosterone level (considering the laboratory kit, the normal range of testosterone was 0.1-0.95) and in this respect, the difference between two abnormal and normal groups of angiography was not statistically significant (p = 0.210) (Table 1).

Table 2: Frequency values and comparison of hyperandrogenism symptoms and hormonal properties in group of patients with abnormal angiography result

	Hirsutism(%)			Testosterone (%)		
Type of artery	Positive	Negative	p-value	Increased	Normal	p-value
LAD						
Involved	24(96)	27(81.8)	0.101	40(87.0)	11(91.7)	0.656
Not involved	1(4)	6(18.2)		6(13.0)	1(8.3)	
RCA						
Involved	13(52)	12(36.4)	0.234	18(39.1)	7(58.3)	0.232
Not involved	12(48)	21(63.6)		28(60.9)	5(41.7)	
LCX						
Involved	14(54)	14(42.4)	0.306	20(43.5)	8(66.7)	0.152
Not involved	11(44)	19.0	(57.600)	26(56.5)	4(33.3)	

The laboratory results demonstrated that testosterone level difference in patients of abnormal (0.62±0.47) and normal (0.58±0.33) groups was not statistically significant (p = 0.602). Examining serum TSH level also revealed that the mean of this variable was 2.68±1.71 in abnormal group patients and 3.40±2.66 in patients of normal group which was not statistically significant (p = 0.088).

In Table 2, the type of involved artery in abnormal group patients has been shown separated according to the presence or absence of hirsutism and testosterone level. Results revealed that there was no significant association between involved arteries and variables studied in patients (p>0.05). Results also indicated that LAD artery involvement was seen in 51 patients (85%) that was the most common involved artery (Table 2).

Additionally, for all risk factors of the study, the relative risk for heart disease was calculated. Results showed that the history of previous ischemic disease included the highest relative risk (OR = 3.302) for the incidence of abnormal findings on patients' angiography (p = 0.018). Moreover, the values of relative risk were 2.519 (p = 0.026) for the history of diabetes, 0.018 (p = 0.018) for the family history of CAD, 2.622 (p0.018) for hirsutism symptoms and 1.063 (p = 0.031) for alopecia. The value of relative risk for other variables under study such as hypertension, hyperlipidemia, family history of alopecia, cigarette smoking, increased testosterone level and TSH changes was not significant (p>0.05).

The results of Regression analysis to specify the function of cardiovascular diseases risk factors, hyperandrogenism clinical symptoms, serum testosterone levels (increased and normal) and TSH (hyperthyroidism, euthyroid and hypothyroidism) showed that there was a significant relationship between BMI, prior history of MI and the presence of hirsutism symptom with the incidence of positive findings on angiography (p<0.05) (Table 3).

Table 3: Results of regression test about effective factors on abnormal results of angiography

Regression test	B	S.E	df	Sig.
BMIgroup	-0.711	0.242	1	0.003
Hirsutism	0.886	0.610	1	0.036
Alopesi	1.040	0.778	1	0.181
DM	0.459	0.552	1	0.405
HTN	0.131	0.484	1	0.786
HLP	0.157	0.502	1	0.754
FH	0.978	0.597	1	0.102
FH of Alopesi	-1.873	1.077	1	0.082
Smok	-0.258	0.924	1	0.780
FH of MI	1.518	0.676	1	0.025
Testosteronegroup	0.381	0.730	1	0.602
TSHgroup	1.737	0.914	1	0.057
Constant	-6.803	3.823	1	0.075

DISCUSSION

The present study, conducted to determine the relationship between coronary artery disease and hyperandrogenism in women, demonstrated that hyperandrogenism symptoms could be considered as one of cardiovascular diseases risk factors. After examining hyperandrogenism in people under study, hirsutism and its score and androgenic alopecia in patients with abnormal angiography was found to be significantly graeter than patients with normal angiography but the results of regression analysis showed that hirsutism was significantly higher just in group of patients with abnormal angiography. Similarly, in the study conducted by Orio *et al.* (2004), PCO and hyperandrogenism symptoms was observed to act as a risk factor on women's cardiovascular system even in young women with no heart disease symptoms. In Sablik *et al.* (2006)'s study, it was also observed that in contrast to 84% of patients with positive CAD, only 30% of patients with negative CAD had hirsutism symptoms and a significant relationship between hirsutism and cardiovascular diseases was observed (Sablik *et al.*, 2006). The research of Wild *et al.* (1990) was also revealed that hirsutism and baldness would increase cardiovascular diseases risk. In addition, in the research of Mansouri *et al.* (2005), a direct association was observed between androgenic alopecia and the incidence of cardiovascular events. However in their study, no significant relationship was found between cardiovascular diseases and hirutism, acne and amenorrhea which didn't correspond with the results of the present study (Mansouri *et al.*, 2005).

In our study, the association between androgenic alopecia and the abnormal results of angiography was significant; however, this relationship was not confirmed in regression analysis. Researches included different results in this field. In the last decade, various studies have examined the relationship between male pattern androgenic alopecia and incidence of cardiovascular diseases of which some expressed male androgenic alopecia as a risk factor for such diseases (Cotton *et al.*, 1972; Hirsso *et al.*, 2007) and some could demonstrate such relationship as well (Ellis *et al.*, 2001). The study of Lesko *et al.* (1993) showed that baldness on the vertex scalp of men had a direct relationship with the incidence of myocardial infarction. Additionally, some studies that were conducted on the relationship between androgenic alopecia in women and the incidence of cardiovascular diseases have confirmed the presence of such relationship (Mansouri *et al.*, 2005; Santiago *et al.*, 2010).

In this research, the family history of alopecia had no association with the abnormal results of angiography but Mansouri *et al.* (2005) observed that there was a direct association between family history of alopecia and incidence of cardiovascular events which did not correspond with the results of our studies.

Furthermore, in the present study, testosterone level in patients with abnormal angiography was observed to be higher than those with normal angiography but it was not statistically significant. Concerning TSH, no significant relationship was observed between thyroid disorders and findings of patients' angiography as well. Similarly, Nasr observed in their study that testosterone average in patients with involved coronary artery was 0.63 and in patients with normal coronary artery was 0.58 while their difference was not statistically significant (Wehr *et al.*, 2011), they did not found any association between total and free testosterone levels and SHBG with mortality in postmenopausal diabetic women. Schartz and Frishman (2010) did not observe any relationship between testosterone level and the incidence of cardiovascular diseases, too (Kaczmarek *et al.*, 2003). While inconsistent with the present study, it was observed in the study of Kaczmarek and Reczuch that higher testosterone levels would result in cardiovascular diseases risks in women under study (Nettleship *et al.*, 2009). In the study of Nettleship, high testosterone level was negatively associated with the severity of coronary artery diseases in men and it was stated that testosterone could play a role in preventing the incidence of coronary artery disease (Webb and Collins, 2010). In the study of Webb and Collins, testosterone was observed to be one of cardiovascular diseases risk factors and had an increasing effect on the incidence of atherosclerosis (Phillips *et al.*, 1994). In the study of Philips *et al.* (1994), free high testosterone level and cholesterol were associated with

increasing cardiovascular diseases. In the research of Sablik *et al*. (2006), testosterone level in patients with positive CAD was observed to be significantly greater than those with negative CAD as well (Sablik *et al*., 2006). In addition, other studies obtaining different results from those mentioned above indicated that low testosterone levels (total and free) had direct association with incidence of cardiovascular diseases due to the fact that low testosterone levels could have negative effects on cardiovascular risk factors which could lead to increasing risk of cardiovascular diseases (Rosano *et al*., 2007; Li *et al*., 2012).

Furthermore in the present study, a significant difference was observed between two groups of abnormal and normal angiography in terms of BMI and prior history of MI. However, a significant difference was observed between two groups concerning diabetes and positive family history of CAD disease as well, but this association was not confirmed with regression statistical test. Similarly, in the study of Mansouri *et al*. (2005), a direct association was observed between prior history of MI and high blood pressure with the incidence of cardiovascular diseases while no significant relationship was observed between cardiovascular diseases with smoking, high level of serum cholesterol. In the study of Reinecke, the results demonstrated that LDL level, triglyceride, basal insulin and index of insulin resistance in patients with positive angiography was higher than those with normal angiography but this difference was not significant. It was also observed that cigarette smoking, advanced age and apolipoprotein B were considered as risk factors in patients with abnormal angiography. It was found in the study of Orio *et al*. (2004) that in women with PCOS symptoms and normal weight there was no significant increase in left ventricular mass index, reduced diastolic filling and no alteration in TC, LDL, HDL and TG compared with the control group. In the study of Sablic *et al*. (2006), between the incidence of hypertension, smoking and dyslipidemia with the incidence of cardiovascular diseases was observed to be a direct association. In the study of Nasr *et al*. (2004), no association was observed between cardiovascular risk factors and heart disease in women.

CONCLUSION

The results of the present study indicated that hyperandrogenism symptoms could be considered as one of the risk factors of cardiovascular diseases while testosterone level difference in patients with abnormal angiography was not significant compared to patients with normal angiography. Given that menopausal and premenopausal women in this study were not separated from each other and considering that in some studies testosterone effects on these two groups were different, we suggest conducting a research in this regard in which menopausal and non-menopausal women with positive CAD be compared with each other in order to compare testosterone effects on them separately as well.

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