RELATIONSHIPS OF OVERWEIGHT AND OBESITY WITH HORMONAL AND METABOLIC PARAMETERS IN HIRSUTE WOMEN

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Abstract- Obesity is the common clinical sign in hirsutism which can cause metabolic disturbances like dyslipidemia, insulin resistance and hypertension. To investigate relationships of overweight and obesity with hormonal and metabolic parameters in suspected hirsute women, in a cross-sectional study, 184 suspected hirsute women were selected in a reproductive endocrinology outpatient clinic in north of Tehran from February 1997 to May 1999. Weight, height, waist and hip circumferences were measured and serum levels of lipids, hormones and glucose were determined. Overweight and overall obesity (OO-body mass index: BMI ≥ 25 kg/m^2) and android obesity (AO-waist to hip ratio: WHR>0.85) were calculated. Hirsutism score of OO and AO women was higher than that of nonobese women (NO, P<0.001). OO women had significantly lower levels of serum LH, estradiol, HDL and higher levels of triglyceride (TG), LDL and LDL/HDL ratio than nonobese women (P<0.05). In addition, the mean BMI, LH/FSH ratio and serum levels of testosterone (T), dehydroepiandrostenedione sulfate (DHEAS), insulin, and TG of AO women were higher (P<0.05) and their glucose/insulin ratio were lower than nonandroid obese women (NAO: WHR≤ 0.85; P<0.03). Multiple regression analysis of the data showed that WHR correlated most significantly with serum cholesterol, LDL and HDL levels; serum androstenedione with LDL/HDL ratio and serum glucose; and less significantly serum LH with serum insulin levels (P<0.02). Metabolic disturbances in these women are mostly due to obesity (especially android obesity), and high serum androstenedione levels.
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Key Words: Hirsutism, BMI, WHR, hormone, lipid

INTRODUCTION

Hirsutism is a common disorder resulting from androgen activity specified in women as excessive growth of terminal hairs in androgen-dependent regions of the body. The causes of hirsutism in most women are idiopathic or polycystic ovary (PCO) (1). Abnormalities associated with androgen augmentation are: acne, dyslipidemia [high serum TG, Chol, LDL and low HDL levels], diabetes, hypertension, insulin resistance (IR), android obesity, coronary heart disease (CHD), alopecia and endometrial cancer (2). Obesity, a common clinical sign in hirsute women, is a health problem observed as an etiological factor of increasing chronic disease morbidity and mortality. Android obesity is a more important factor in predicting the risk of related diseases than the overall obesity. Obesity is associated with menstrual disorder, chronic anovulation and PCO syndrome. Women with android obesity are particularly susceptible to menstrual disorder progression (3). Obesity reported in 50-80% of women with PCO is mostly in upper body segment (4,5). Obesity is associated more with CHD and its risk factors (6,7). A likely role of augmentated androgenic activity in the pathogenesis of upper body fat deposition and its accompanying metabolic disturbances has been shown

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(8). Association between increasing andro-genicity and increasing waist to hip ratio (WHR) with an increasing size of abdominal fat cells, raised plasma glucose and insulin levels and diminished insulin sensitivity in healthy, nonhirsute premenopausal women has been observed. On the other hand, in women with android obesity having high serum testosterone (T) level and diminishing conversion of androstenedione to estrone have been reported (9). Therefore, metabolic disturbances due to obesity, particularly android obesity in women, are very important. Association between overall and android obesity with blood parameters has not been shown in hirsute women. The purpose of this study was to determine the relationship between overweight and overall obesity and android obesity with hormonal and metabolic parameters in suspected hirsute women.

MATERIALS AND METHODS

Patients

This study began in February 1997 and finished in May 1999. Three-hundred women complaining of hirsutism or suspected to have hirsutism, because of excessive hair growth in face in a reproductive endocrinology outpatient clinic in the north of Tehran were enrolled in this study. The subjects who received hormonal drugs, antiandrogen therapy or other drugs known to affect endocrine function or glucose and lipid metabolism up to 3 months prior to participating in the study or the ones with thyroid disorders, hyperprolactinemia and diabetes were excluded. At the end, the data of 184 women were analysed. None of them were smoking more than 6 cigarettes per day.

Hirsutism was evaluated according to Ferriman and Gallwey scores in 9 sites of body (10). Each site was scored 0-4 points based on the severity of hirsutism. On this basis, total scores of 8 and over were considered as hirsute and below this range as nonhirsute (1,11).

Hormonal, lipids and glucose analyses

Fasting serum LH, FSH, T, androstenedione, dehydroepiandrostenedione sulfate (DHEAS), estradiol, progesterone and insulin levels were determined on the 20th (±2) day of menstrual cycle by radioimmunoassay (RIA). In addition, serum TG, Chol and glucose were determined by enzymatic methods (CHOD-PAP, TGO-PAP, and GOD-PAP methods respectively) using commercial kits. The HDL fraction was separated by the Mg^{2+}/phosphotungestic acid precipitation technique. Serum LDL levels were estimated according to Friedewald et al procedure (12).

Anthropometric measurments

Height was measured without shoes against a wall-fixed tape and weight with light clothing and without shoes on a platform scale with a 1.5 kg subtraction to correct for clothing weight (13). Waist circumference was measured at the level of the umbilicus without clothing and in standing position. Hip circumference was measured at the utmost circumference with undergarment (14). The body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and the WHR as the ratio between the waist and the hip circumferences. Overweight and overall obesity (OO: BMI ≥25 kg/m^2) and android obesity (AO: WHR> 0.85) were calculated for the patients (3,15).

Statistical analysis

Data were analysed using SPSS for Windows (SPSS INC, 1993). X^2 test was used for relationships between the variables and Student-t test for differences between the means. Analysis of covariance was used to compare the means of weight, height, serum hormones, lipids and glucose levels adjusted for age between the 2 typical obese groups. Pearson correlation coefficient was used to examine the relationships between the variables and stepwise multiple linear regression analysis was used to determine the variables most significantly related to serum lipids, insulin, glucose and glucose/insulin ratio.

RESULTS

Table 1 shows that the mean age and hirsutism score of OO and AO women were significantly higher and their literacy levels were lower than non-obese women (NO: BMI<25 kg/m^2) and non-android obese women (NAO: WHR< 0.85; P< 0.003 and lower). Table 2 shows significant relationships between obesity status with marital and hirsutism status (P<0.02 and lower).

The mean serum LH and estradiol levels of OO women were significantly lower than NO women (P<0.05 and lower, Table 3). The mean weight, BMI, serum LH/FSH ratio, T, DHEAS and insulin levels of AO women were significantly higher and their glucose/insulin ratio were lower than NAO women (P<0.05 and lower, Table 4). The mean serum TG, LDL levels and LDL/HDL ratio of OO women were significantly higher and their HDL levels significantly lower than NO women (P<0.05 and lower, Table 5). In addition, the mean serum TG levels of AO women were

significantly higher than NAO women (P<0.02, Table 6). Table 7 shows correlations between obesity indices and other variables adjusted for age. There were significant correlations between BMI and WHR with literacy level, hirsutism score, serum insulin, glucose/insulin ratio, serum TG and LDL levels (P<0.05 and lower). For the other hormones, there were only significant correlations between BMI and progesterone levels, and WHR and T levels (P<0.02). In addition, there were significant correlations between BMI with serum Chol levels and LDL/HDL ratio (P<0.02) and WHR with serum HDL levels (P<0.05). Stepwise multiple regression analyses of the levels of serum lipids, glucose and insulin and glucose/insulin ratio with other variables are shown in table 8. WHR correlated, most significantly with serum Chol, LDL and HDL levels; age with serum TG levels; serum androstenedione with LDL/HDL ratio and serum glucose levels; literacy with glucose/insulin ratio (P<0.0001) and serum LH levels less significantly with insulin levels (P<0.02).

Table 1. The mean and SD age, literacy and hirsutism score of women

	BMI		WHR	
	< 25 (n=68)	≥ 25 (n=116)	≤ 0.85 (n=47)	> 0.85 (n=135)
	Mean (SD)		Mean (SD)	
Age (year)	23.2 (5.6)[b]	27.2 (6.1)	23.4 (5.6)[a]	26.6 (6.2)
Literacy (year)	12.3 (3)[b]	10.5 (3)	12.6 (2.6)[b]	10.7 (3.2)
Hirsutism score	6.7 (3.8)[b]	9.6 (5.1)	6.8 (4.6)[b]	9.1 (4.8)

Significant statistical difference (student-t) between two groups: a) p< 0.003, b) p< 0.001

Table 2. Distribution of marital status, occupation and hirsutism morbidity by anthropometric indices in women

	BMI		WHR	
	< 25	≥ 25	≤ 0.85	≥ 0.85
	n (%)		n (%)	
Marital status				
Single	36 (66.7)[d]	18 (33.3)	26 (49.1)[d]	27 (50.9)
Married	32 (24.6)	98 (75.4)	21 (16.3)	108 (83.7)
Occupation				
Housewife	29 (25)[d]	87 (75)	18 (15.7)[c]	97 (84.3)
Teacher	4 (33.3)	8 (66.7)	3 (25)	9 (75)
Student	23 (76.7)	7 (23.3)	15 (51.7)	14 (48.3)
Other	12 (50)	12 (50)	11 (45.8)	13 (54.2)
Hirsutism				
Yes	28 (27.4)[b]	74 (72.6)	19 (18.8)[a]	82 (81.2)
No	40 (48.8)	42 (51.2)	28 (34.6)	53 (65.4)

Significant statistical relationship (x^2) between anthropometric indices with independent variables: a) p< 0.02, b) p< 0.003, c) p< 0.0001, d) p< 0.00001

Table 3. The mean and SD serum hormones and glucose levels by BMI adjusted for age in women

	n	BMI< 25	n	BMI≥ 25
		Mean (SD)		Mean (SD)
LH (mIU/ml)	30	15.3 (11.5)[a]	50	10.3 (9.2)
FSH (mIU/ml)	30	4.1 (1.4)	50	4.2 (1.8)
LH/ FSH ratio	30	3.8 (3)	50	3 (3)
T (nmol/l)	24	2.2 (0.5)	46	2.4 (0.8)
Androstenedione (ng/ml)	8	1.9 (0.7)	17	2 (0.7)
DHEAS (ng/ml)	26	2302.1 (855.5)	54	2326 (969.1)
Estradiol (pg/ml)	29	134.1 (53.2)[b]	52	110.5 (53)
Progesterone (ng/ml)	28	4.5 (4)	21	3.1 (3.7)
Insulin (uIU/ml)	26	14.5 (25.7)	46	17.4 (18.8)
Glusose (mg/dl)	30	87.1 (10.6)	64	90.9 (11.3)
Glucose/ Insulin ratio	26	13.6 (10.7)	46	9.7 (8.4)

Significant statistical difference (analysis of covariance) between two groups: a) p< 0.05, b) p< 0.03

T= testosterone; DHEAS= dehydroepiandrostenedione sulphate

Table 4. The mean and SD serum hormones and glucose levels by WHR adjusted for age in women

	n	WHR≤ 0.85	n	WHR> 0.85
		Mean (SD)		Mean (SD)
Weight (kg)	47	60 (9.9)[d]	135	72.7 (11.5)
Height (cm)	47	159 (5.4)	135	159.2 (5.8)
BMI (kg/m^2)	47	23.2 (4.1)[d]	135	28.4 (4.3)
LH (mIU/ml)	23	9.7 (7.2)	56	13.1 (11)
FSH (mIU/ml)	23	4.1 (1.4)	56	4.2 (1.7)
LH/ FSH ratio	23	2.4 (1.7)[b]	56	3.6 (3.3)
T (nmol/l)	23	2 (0.5)[c]	46	2.5 (0.8)
Androstenedione (ng/ml)	8	2 (0.8)	17	1.9 (0.6)
DHEAS (ng/ml)	21	2147.3 (929.5)[b]	57	2406.7 (930.5)
Estradiol (pg/ml)	22	122.8 (39.5)	58	119 (58.5)
Progesterone (ng/ml)	22	4.5 (3.9)	56	3.3 (3.8)
Insulin (uIU/ml)	20	9.1 (9.9)[a]	50	20 (24.5)
Glusose (mg/dl)	24	90.9 (12.8)	69	88.9 (10.8)
Glucose/ Insulin ratio	19	15.7 (11.4)[b]	35	8.9 (7.6)

Significant statistical difference (analysis of covariance) between two groups: a) p<0.05, b) p< 0.03, c) p< 0.02, d) p< 0.001

Table 5. The mean and SD serum lipids levels by BMI adjusted for age in women

	n	BMI< 25	n	BMI≥ 25
		Mean (SD)		Mean (SD)
TG (mg/dl)	31	88.7 (35.4)[c]	64	113.9 (40.9)
Chol (mg/dl)	31	179.3 (38.3)	64	188.5 (39)
LDL (mg/dl)	29	97.4 (32.3)[a]	61	113.5 (36.5)
HDL (mg/dl)	30	65.8 (22.4)[a]	61	55 (22.1)
LDL/HDL	29	1.7 (0.8)[b]	61	2.4 (1.2)

Significant statistical difference (analysis of covariance) between two groups: a) p< 0.05, b) p< 0.03, c) p< 0.02

Table 6. The mean and SD serum lipids levels by WHR adjusted for age in women

	n	WHR≤ 0.85	n	WHR> 0.85
		Mean (SD)		Mean (SD)
TG (mg/dl)	25	89.4 (36.2)[a]	69	110.6 (41)
Chol (mg/dl)	25	183 (36.5)	69	186.4 (40.8)
LDL (mg/dl)	24	101.3 (28)	65	110.9 (35.8)
HDL (mg/dl)	25	66.3 (23.3)	65	55.8 (21.8)
LDL/HDL	24	1.8 (1)	65	2.3 (1.2)

Significant statistical difference (analysis of covariance) between two groups: a) p< 0.02

Table 7. Correlation coefficient (r) between anthropometric indices and other variables adjusted for age in women

	n	BMI	WHR		n	BMI	WHR
Literacy	181	-0.29[h]	-0.36[h]	Insulin	68	0.34[e]	0.24[a]
Hirsutism score	181	0.33[h]	0.24[g]	Glucose	91	0.32[g]	NS
Weight	181	-	0.57[h]	Glucose/insulin	52	-0.32[b]	-0.38[c]
BMI	181	-	0.59[h]	TG	92	0.29[d]	0.31[g]
Waist circumference	181	0.88[h]	-	Chol	92	0.26[b]	NS
Hip circumference	181	0.9[h]	-	LDL	87	0.31[e]	0.22[a]
T	67	NS	0.29[b]	HDL	88	NS	-0.22[a]
Progesterone	76	-0.29[b]	NS	LDL/HDL	87	0.26[b]	NS

a) p< 0.05, b) p< 0.02, c) p< 0.009, d) p< 0.006, e) p< 0.004, f) p< 0.003, g) p< 0.002, h) p< 0.001

T= testosterone

Table 8. Multiple linear regression analyses of serum lipids, glucose, insulin, glucose/insulin and independent variables in women

Independent	Chol		TG		LDL		HDL		LDL/HDL		Glucose		Insulin		Glucose/Insulin	
Variables	b	p<	b	p<	b	p<	b	p<	b	p<	b	p<	b	p<	b	p<
WHR	208.4	0.0001	-		127.9	0.0001	65.7	0.0001								
Age			3.9	0.0001												
Androstenedione									1.2	0.0001	40.1	0.0001				
LH													0.5	0.02		
Literacy															0.5	0.0001
R^2	0.96		0.84		0.97		0.86		0.83		0.85		0.8		0.59	

DISCUSSION

The results achieved in this study showed that disturbances in hormonal and metabolic parameters in women were probably due to overweight and overall obesity and android obesity. Our results agree with the other studies which demonstrated increasing means of WHR and BMI with increasing age and decreasing literacy levels (16-19). The higher means of BMI and WHR for married women as compared to nonmarried women were also reported in other study (17) Those increases may depend on higher age of such women. Higher WHR in women is associated with hirsutism (4). In addition, obesity with lowering hepatic synthesis of sex hormone binding globulin (SHBG) which results in a higher level of serum free T, may cause hirsutism (2). This is shown in this study by higher hirsutism score of OO and AO women than nonobese women. In this study the prevalence of overweight and obesity was higher among hirsute women than nonhirsute women. The higher prevalence of obesity in housewives was probably due to higher availability of food in comparison to employed women, which increased their chance for obesity (20).

In this study, unexpected lower mean serum LH levels in OO women was found, contrary to high serum LH levels which has been reported in obesity (21). The lower mean serum estradiol levels in OO women is probably due to obesity which causes an increased peripheral conversion of estrogens to androstenedione in adipose tissue(2).

Similar to the findings of this study, some authors have reported higher serum insulin levels in AO women (3,22,23). Subjects with android obesity are more sensitive to the effect of excess body fat than those with lower body obesity (8). Diabetes, hypertension and CHD are more common in subjects with android obesity (8). In this study, android obesity may be due to high androgens levels in the women, since AO women had higher serum T and DHEAS levels. It has been shown that higher serum T and DHEAS levels lead to higher distribution of fat in the upper body segments (24). A close relationship between hyperandrogenism and hyperinsulinemia and IR was reported from studies in females with elevated androgen levels due to PCO (8).

Hyperinsulinemia and IR in android obesity are due to the lower hepatic removal of hormone which leads to a decrease in peripheral insulin sensitivity (8). Moreover, hyperinsulinemia results in increased production of androgen by ovaries (25). On the other hand, high serum LH/FSH ratio in AO women, observed in PCO, leads to higher release of androgens (26). Furthermore, serum LH levels of AO women are higher than that of the other women (27). In this study the majority of mean serum lipids levels of obese women were significantly higher than nonobese ones. Lipids disturbances are directly related to BMI. In women higher BMI is related to higher serum TG and lower HDL levels (28). The relationships between BMI with most lipids were shown in other studies (18,29).

In this study we could not find any relationship between WHR and Chol levels. Some studies have reported no relationship between WHR and Chol levels (30,31), whereas, others have shown this relationship (32). It has been proposed that increased intra-abdominal fat (high WHR) is associated with high concentration of free fatty acids in the portal vein which leads to high production of VLDL by liver, which in turn leads to high serum total Chol and TG and low HDL levels (32). On the other hand, androgens affect lipid metabolism and cause high serum TG, Chol, LDL and low HDL levels (2).

In the present study both types of obesity indices had significant correlation with insulin and glucose/insulin ratio (Table 7). High insulin levels may increase the availability of T through the suppression of SHBG synthesis and enhance ovarian androgen production. On the other hand, high T levels lead to disturbances in insulin metabolism and cause hyperinsulinemia (33), which is a well-recognized and impotant risk factor for CHD and hypertension in men as well as in women (5). Our results agree with other studies which have demonstrated significant correlation between WHR and serum T levels (8,34,35). In the present study the significant correlation between BMI and serum progesterone level may be due to obesity which inhibits ovulation and consequently lowers serum progesterone levels (3). Stepwise multiple regression analysis of data showed that WHR correlated most significantly with serum Chol, LDL, and HDL levels. The result of one study in healthy nonobese women showed that WHR had higher correlation with serum CHOL than BMI and free T/total T ratio (32).

The strong correlation of women's literacy levels with glucose/insulin ratio might be through obesity, because there were significant negative correlations between literacy levels and glucose/insulin ratio with obesity indices. Therefore, since obesity is the main factor in IR and lipids disorders in healthy and hyperandrogenic women, weight loss is very important which is possible with increasing literacy levels. Weight loss causes significant decreases of fasting insulin, T, androstenedione LH, LH/FSH ratio and increases serum SHBG levels (36).

In conclusion, many hirsute women are overweight or obese which exposes them to the risk of CHD and diabetes. These results indicate that metabolic disturbances in these women are mainly due to obesity (especially android obesity), low literacy levels and high serum androstenedione levels.

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