THE RELATIONSHIP BETWEEN SEX STEROIDS, INSULIN RESISTANCE AND BODY COMPOSITIONS IN OBESE WOMEN: A CASE-CONTROL STUDY

ODNOS IZMEĐU POLNIH STEROIDA, INSULINSKE REZISTENCIJE I TELESNE KOMPOZICIJE KOD GOJAZNIH ŽENA: KONTROLISANA STUDIJA SLUČAJA

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Summary

Background: Obesity causes many health problems and affects the quality and duration of life negatively. We aimed to investigate the relationship between sex steroids, insulin resistance and body compositions in obese women.
Methods: This study was carried out on a sample of 150 premenopausal women who were referred to the Outpatient Clinic of Family Medicine between 2014–2015. A survey about their socio-demographic characteristics was carried out, and anthropometric parameters were measured. LDL-C, HDL-C, total cholesterol, triglyceride, glucose, insulin, sex hormone binding globulin (SHBG), estradiol, dehydroepiandrosterone sulfate (DHEA-S), total/free testosterone levels were measured in the blood. Body compositions were assessed with a bioelectrical impedance device. For insulin resistance, Homeostasis Model Assessment (HOMA-IR) was calculated.
Results: In our study, a significant association was found between high glucose, total cholesterol, LDL-C, TG, insulin, insulin resistance and low HDL-C, SHBG, DHEA-S levels with obesity (p<0.05). There was no statistically significant relationship between estradiol, total/free testosterone and obesity (p>0.05).
Conclusions: In our study, high glucose, total cholesterol, LDL-c, TG, insulin, insulin resistance and low HDL-C, SHBG, DHEA-S levels were associated with obesity. This relationship leads to many diseases, especially diabetes mellitus and cardiovascular disease. Therefore, obesity is a disease that needs to be monitored closely, frequently and treated properly.

Keywords: obesity, sex steroids, insulin resistance, female

Kratak sadržaj

Uvod: Gojaznost izaziva mnoge zdravstvene probleme i negativno utiče na kvalitet života i životni vek. Cilj nam je bio da istražimo vezu između polnih steroida, insulinske rezistencije i telesne kompozicije kod gojaznih žena.
Metode: Ova studija je sprovedena na uzorku od 150 žena u perimenopauzi koje su posetile ambulantu porodične medicine u periodu 2014–2015. Primenjeno je istraživanje o njihovim socio-demografskim karakteristikama i izmereni su antropometrijski parametri. Iz krvi su izmereni LDL-C, HDL-C, ukupni holesterol, trigliceridi, glukoza, insulin, globulin koji vezuje polni hormon (SHBG), estradiol, dehidroepiandrosteron sulfat (DHEA-S), i nivoi ukupnog/slobodnog testosterona. Telesne kompozicije su procenjene pomoću uređaja sa bioelektričnom impedansom. Za rezistenciju na insulin, izračunat je Homa model (HOMA-IR, Homeostasis Model Assessment).
Rezultati: U našoj studiji je pronađena značajna povezanost između visoke glukoze, ukupnog holesterola, LDL-C, TG, insulina, rezistencije na insulin i niskog nivoa HDL-C, SHBG, DHEA-S i gojaznosti (p<0,05). Nije bilo statistički značajne veze između estradiola, ukupnog/slobodnog testosterona i gojaznosti (p>0,05).
Zaključak: Naša studija je ukazala da su sledeći faktori bili povezani sa gojaznošću: visoka glukoza, ukupni holesterol, LDL-C, TG, insulin, insulinska rezistencija i niski nivoi HDL-C, SHBG, DHEA-S. Ovaj odnos dovodi do mnogih bolesti, posebno dijabetes melitusa i kardiovaskularnih bolesti. Dakle, gojaznost je bolest koju treba pažljivo pratiti i redovno tretirati na odgovarajući način.

Ključne reči: gojaznost, polni steroidi, rezistencija na insulin, žena

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Introduction

Obesity is a complicated and multifactorial disease which occurs as a result of the interaction of genetic, metabolic, social, behavioural and cultural factors. Obesity provides a basis for many diseases, reduces the quality of life and life's duration and it causes deaths. For this reason, it has become an important public health concern on a global scale (1).

Obesity causes gender-specific issues as well as similar comorbidities in men and women. Gender-specific issues start with early puberty, amenorrhoea and dysovulation, and they go forward with polycystic ovary syndrome (PCOS), infertility, obstetric problems and endometrial and breast cancer incidence which increase after menopause (2).

In premenopausal women, the increase in body fat ratio can cause an imbalance in sex steroids. Estrogen aromatization of androgens increases the amount of estrogen in stromal vascular cells in fatty tissue. While the estrogen/androgen ratio increases in obese individuals, there is a decrease in sex hormone-binding globulin (SHBG). Androgen transition accelerates depending on this and androgen synthesis increases to correspond to this. As a result, free estrogen and testosterone levels increase (3).

In 65% of patients with type 2 diabetes, obesity is responsible for etiology. Type 2 diabetes risk rises with the degree and duration of obesity and the existence of abdominal obesity. Free fatty acids which are extremely secreted by visceral adipocytes cause insulin resistance both in skeletal muscle and in the liver. It is known that the disruption of hormone regulation which is secreted from adipose tissues also affects insulin resistance (4).

In this study, we aimed to investigate the relationship between sex steroids, insulin resistance and body composition in obese and non-obese women who came to our polyclinic.

Materials and Methods

Study design, setting and population

This analytical case-control study was carried out on a sample of women aged 18 and older who came to Family Practise Polyclinic for any reasons between October 1, 2014, and March 1, 2015.

The individuals were classified as normal weight people (BMI<25 kg/m^2), overweight people (BMI 25–29.9 kg/m^2) and obese people (BMI 30 kg/m^2) in terms of their body mass index (BMI). The groups were similar in terms of ages and residences.

In our study, the number of subjects included in the study was calculated using n = $t^2 \cdot p \cdot q/d^2$ formula because the number of individuals in the universe was not known. According to this calculation, 150 women were included in our study.

Exclusion criteria

Those with diabetes mellitus, disorder of thyroid, liver and kidney failure and infertility, and those who were pregnant, lactating women, in the period of menopause, ones who were receiving oral contraceptive and hormone replacement therapy, using medications containing cortisol, ones who had hysterectomy or oophorectomy operations, who had a drug history story to affect SHBG levels and those who did not agree to participate in the study were not included in the research.

Ethical Authorisation of the study

Before the study started, an ethics committee approval was received from Necmettin Erbakan University, Meram Medical Faculty (Number: 2013/31 Date: October 23, 2013).

During the application phase, patients were informed about the objectives of the study, and they gave their oral and written consent.

Collection of data

The survey that questioned sociodemographic characteristics of the participants was carried out through face to face interview technique.

Tall statures, body weights, hip and waist circumferences (WC) of the participants were measured with a standard bascule, and a length meter and BMI was calculated. According to WHO obesity criteria, waist circumference cut-off value was accepted to be 88 cm in women (5). Blood pressure in lower and upper extremities was measured by a sphygmomanometer while patients were lying on their backs.

Bioelectrical impedance device was used to measure and evaluate the body compositions of the individuals. Body fat ratio, water ratio, bone mass, muscle mass, basal metabolism and visceral fat ratio were measured too.

LDL-C, HDL-C, total cholesterol, triglyceride, fasting blood glucose (FBG), fasting insulin, SHGB, total testosterone, free testosterone, estradiol and DHEA-S levels were measured from blood samples of patients after 12-hour fasting. Fasting blood glucose (by the hexokinase method), total cholesterol (by cholesterol esterase method), LDL-C (by Friedewald formula), triglyceride and HDL-C (by enzymatic colourimetric method) were measured using the Abbott Architect c16000 Systems autoanalyser. SHBG, estradiol and insulin (by chemiluminescent microparticle immunoassay method) were measured using Abbott Architect i4000 SR autoanalyser. DHEAS (by competitive chemiluminescent enzyme immunoassay method) was measured using Siemens IMMULITE 2000 XPi autoanalyser. Total testosterone

and free testosterone (by ELISA method) were measured using the Siemens Advia Centaur Immunoassay System.

For insulin resistance, HOMA-IR was calculated with the formula below by using fasting plasma glucose and insulin levels. A cut-off value of HOMA-IR was taken as 2.5 (6).

HOMA-IR=Serum glucose (mmol/L)×plasma insulin (μU/mL)/405.

Statistical analysis

SPSS 20.0 packet program was used to statistically evaluate the results obtained in the study. Descriptive statistics for continuous variables were given in terms of average and standard deviation, and descriptive statistics for categorical data were given in terms of frequency and percentage. To compare quantitative data in doublet groups, the student t-test was used if they corresponded to normal distribution hypothesis and Mann-Whitney U test was used if they did not correspond to normal distribution hypothesis and if they showed a skew distribution. To compare

quantitative data in the triad, one-way ANOVA test was used in the parameters which showed normal distribution. Triads which did not show normal distribution were compared by using the Kruskal-Wallis test. Double comparisons were made by Mann-Whitney U test. Chi-square test was used to compare categorical data. Results were evaluated at a 95% confidence interval, and significance was evaluated in p<0.05 level.

Results

The mean age of 150 women participating in the study was 31.27±8.39. When the women were classified into 3 groups according to BMI, there was not a difference between the groups regarding the average age (p=0.151). There was a significant association between obesity and being low educated (p<0.001). The prevalence of obesity was higher in housewives (p<0.001). The prevalence of being overweight and obesity was higher in married women (p<0.001). The prevalence of obesity in the low-income group was significantly higher (p<0.001) (Table I).

Table I Comparison of sociodemographic characteristics between body mass index groups.

Sociodemographic characteristics	Normal weight		Overweight		Obese		χ^2	p
	n	%	n	%	n	%		
Marital status								
Married	25	24.0	34	32.7	45	43.3	18.875	<0.001
Single	25	54.3	16	34.8	5	10.9		
Working status								
Working	21	38.9	25	46.3	8	14.8	13.715	<0.001
Non-working	29	30.2	25	26.0	42	43.8		
Education level								
≤ Secondary education	7	12.3	14	24.6	36	63.2	38.879	<0.001
≥ High school education	43	46.2	36	38.7	14	15.1		
Income status								
Less than TL 1000	13	28.3	8	17.4	25	54.3	26.832	<0.001
TL 1000-2000	12	21.4	24	42.9	20	35.7		
More than TL 2000	25	52.1	18	37.5	5	10.4		
Residence								
Rural area	4	33.3	3	25.0	5	41.7	0.549	0.760
Urban area	46	33.3	47	34.1	45	32.6		
Smoking								
Yes	6	35.3	6	35.3	5	29.4	0.133	0.936
No	44	33.1	44	33.1	45	33.8		
Doing exercises								
Yes	6	27.3	11	50.0	5	22.7	3.303	0.192
No	44	34.4	39	30.5	45	35.2		
Daily activities								
High	13	35.1	11	29.7	13	35.1	2.105	0.716
Middle	25	30.9	31	38.3	25	30.9		
Low	12	37.5	8	25.0	12	37.5		

Table II Comparison of laboratory parameters between body mass index groups.

	Normal weight (a)	Overweight (b)	Obese (c)		
	Mean±SD	Mean±SD	Mean±SD	F	p
FBG (mmol/L)	4.94±0.47	5.33±0.59	5.39±0.41	12.044	<0.001^{ab} <0.001ac
Total-C (mmol/L)	4.56±0.89	4.68±0.91	5.12±1.03	4.859	0.010^{ac}
LDL-C (mmol/L)	2.73±0.74	2.89±0.75	3.32±0.83	7.731	0.001^{ac} 0.017^{bc}
HDL-C (mmol/L)	1.36±0.25	1.22±0.23	1.18±0.25	7.110	0.018^{ab} 0.001^{ac}
TG (mmol/L)	0.97±0.54	1.20±0.68	1.45±0.79	6.439	0.001^{ac}
	Median (min-max)	Median (min-max)	Median (min-max)	χ^2	p
Insulin (pmol/L)	40.41 (12.29–378.22)	49.30 (13.40–396.14)	54.24 (24.23–201.40)	14.403	0.026^{ab} <0.001^{ac}
*SHBG (nmol/L)	59.8 (15.0–246.0)	40.9 (15.6–321.9)	35.8 (8.1–122.4)	19.000	0.001^{ab} <0.001^{ac}
Estradiol (pmol/L)	381.7 (73.4–1266.4)	436.8 (110.1–3061.6)	295.5 (73.4–1457.3)	1.629	0.443
**DHEA-S (μmol/L)	5.30 (0.14–14.16)	5.00 (0.04–13.20)	3.79 (0.85–11.14)	6.149	0.021^{ac}
T. Testosterone (nmol/L)	1.45 (0.13–2.63)	1.14 (0.34–3.08)	1.04 (0.34–5.69)	1.811	0.404
F. Testosterone (pmol/L)	9.75 (0.52–52.88)	9.61 (2.01–51.46)	7.98 (1.04–49.72)	1.852	0.396

*SHBG= sex hormone-binding globulin, **DHEA-S= dehydroepiandrosterone sulfate, F= One-way ANOVA, χ^2= Kruskal-Wallis
a: Normal weight group, b: Overweight group, c: Obese group

Obesity prevalence in married women was 6.254 times higher than in single women [OR=6.254, %95 CI; (2.287–17.107)], obesity prevalence in non-working women was 4.472 higher than in working women [OR=4.472, %95 CI; (1.907–10.487)], obesity prevalence in the middle school and under-educated women was 9.673 times higher than in high school and highly educated women [OR=9.673, %95 CI; (4.422–21.160)], and these differences were highly statistically significant (p<0.001).

Systolic blood pressures in the obese group were significantly higher than the normal weight (p<0.001) and overweight (p=0.023) group. Diastolic blood pressures in the obese group were significantly higher than in the normal weight group (p=0.014).

FBG, total cholesterol, LDL-C, triglyceride values in the normal weight group were significantly lower than in the overweight (p<0.001) and the obese group (p<0.001); HDL-C values were higher. Whereas insulin values in normal weight group were significantly lower than in overweight (p=0.026) and obese group (p<0.001), their SHBG and DHEA-S values were significantly higher (p<0.001). When BMI and estradiol, total and free testosterone values were compared, no statistically significant relation was found (*Table II*).

In our study, insulin values in the group with WC>88 cm was significantly higher than those with WC 88 cm (p=0.001). Insulin resistance in the group where WC was >88 cm was significantly higher than those with WC 88 cm (χ^2=5.697, p=0.017). When waist circumferences were compared to SHGB, DHEA-S and total testosterone levels, SHBG (p <0.001), DHEA-S (p=0.042) and total testosterone (p=0.037) values were significantly lower in the group with WC>88 cm than those with WC 88 cm. However, estradiol and free testosterone values did not show a significant difference between the groups.

When BMI and body compositions were compared in our study, it was discovered that fat ratio, visceral fat, basal metabolism, metabolic age, muscle and bone ratios in the obese group were significantly higher than the normal weight and overweight groups but the water ratio was significantly lower (p<0.001) (*Table III*).

Table III Comparison of body composition between body mass index groups.

Parameters	Normal weight (a)	Overweight (b)	Obese (c)		
	Mean±SD	Mean±SD	Mean±SD	F	p
Fat ratio (%)	28.31±5.51	36.24±3.49	43.72±4.42	143.252	<0.001[ab.bc.ac]
Basal met. (kcal)	1329±121	1477±98	1758±678	14.678	<0.001[ac] 0.002[bc]
Basal met. (kJ)	5563±508	6183±412	6863±1118	37.730	<0.001[ab.bc.ac]
Metabolic age (year)	27.1±10.0	43.16±8.9	49.1±8.8	74.362	<0.001[ab.ac] 0.005[bc]
Water ratio (%)	52.9±4.1	47.4±2.6	42.2±3.0	129.443	<0.001[ab.bc.ac]
Visceral fat (kg)	2.62±1.3	5.56±1.6	10.4±3.1	163.550	<0.001[ab.bc.ac]
Bone ratio (%)	2.19±0.20	2.42±0.15	2.66±0.28	55.761	<0.001[ab.bc.ac]
Muscle ratio (%)	40.9±3.84	45.3±3.0	50.0±5.5	56.805	<0.001[ab.bc.ac]

a: Normal weight group, b: Overweight group, c: Obese group

Discussion

Obesity is a health problem with gradually increasing prevalence all over the world, particularly in developed countries. When the relationship between obesity and sociodemographic characteristics was investigated in our study, obesity was significantly higher in the middle school and under-educated women, whereas normal weight was higher in the high school and highly educated women. Obesity prevalence was 9.6 times higher in middle school and under-educated women. Various studies have shown that obesity prevalence decreases as the educational status of women increases (7, 8). Knowledge and thinking ability obtained from education seems to be important to prevent the increase in body weight in adulthood.

In our study, there was a significant relationship between marital status and BMI. Obesity was 6.2 times higher in married women than single ones. In long-time monitoring in the USA, it was seen that women used to gain weight after they got married even when they were standardized in terms of their educational status and family income (9). Low prevalence of obesity in single women may result from the fact that women in this group have never been pregnant, their age average is low, and this group may have been more sensitive to weight control.

In our study, obesity was significantly lower in working women. Obesity prevalence in non-working women showed a 4.4-fold increase compared to working women. In TURDEP I study performed in our country, it was found out that obesity prevalence was the highest in the group of housewives (10). Employed women are more conscious about protect-ing their body composition and are more successful than housewives in this respect.

In our study, there was a significant relationship between blood pressures and BMI. Blood pressure averages in the obese group were significantly higher. Epidemiological studies showed that there was a continual and strict correlation between body weight and blood pressure (11, 12). It is thought that hypertension is associated with liquid retention in obesity.

It is known that insulin resistance and hyperinsulinemia in people with type 2 diabetes increase VLDL and LDL-C formation in the liver and this causes hypertriglyceridaemia and low HDL-C levels (13). In studies, dyslipidaemia in obesity, total cholesterol, triglyceride and high LDL-C were defined as low HDL-C (14). In our study, as BMI increased in women, FBG, total cholesterol, LDL-C and TG levels also increased significantly, but the HDL-C level decreased.

It was found out that there was a significant relationship between obesity and HOMA-IR, and HOMA-IR value increased with weight gain as in insulin (15). Obese people need more insulin to keep blood glucose at normal limits than normal individuals. For this reason, a high level of insulin is secreted all the time. However, body fat distribution is a more important risk factor for insulin resistance (16). In our study, a significant relation was found between HOMA-IR and waist circumference which indicates abdominal obesity. Sex hormone-binding globulin (SHBG) is responsible for regulating the biological activities of sex hormones and the main carrier protein for estradiol and testosterone. In our study, while we were investigating the relationship between SHBG level and BMI and waist circumference, we found out that SHBG level

decreased significantly as BMI and waist circumference increased in women. In many studies, the results are found similar to our study (17–19). When the relation between insulin resistance and SHBG was investigated in our study, SHBG levels were significantly lower in the group with insulin resistance. In obesity, the increased insulin levels in the circulation suppress SHBG syntheses in the liver, and this is thought to be the basic mechanism of increased body weight to reduce SHBG levels (20).

The only estrogen source resulting from the stopping of estrogen production in the postmenopausal ovary is a transition of androgen in adipose tissue. Accordingly, it is known that plasma estrogen levels are associated with overweight in postmenopausal women. In the literature, there are different data in the studies performed on premenopausal women (17). In our study, we could not find a relationship between BMI, waist circumference and estradiol level.

In our study, we found out that the level of DHEA-S decreased significantly as BMI and waist circumference increased in women. In many studies, the results are found similar to our study (21–23). Hernandez-Morante et al. (24) presented that DHEA-S treatment increased adiponectin gene expression and that this mechanism was effective in preventing obesity. The same researchers found out that DHEA-S treatment increased lipolysis in subcutaneous fat tissue of women and visceral fat tissue of men.

When we investigated the relationship between total/free testosterone levels and BMI/ waist circumference in our study, the total testosterone level was significantly low in the group with large waist circumference. There was not a significant relationship between the other parameters. In obese people, androgen transition depending on the decrease of sex hormone binding globulin accelerates, and androgen syntheses increase to correspond to this. As a result, the free testosterone level increases (25).

Conclusion

In our study, it was found out that high FBG, total cholesterol, LDL-C, TG, insulin, insulin resistance and low HDL-C, SHBG, DHEA-S levels were associated with obesity. This relationship causes many diseases, particularly diabetes mellitus and cardiovascular diseases. Besides, it is seen that obesity changes overall body metabolism and hormone metabolism in women. Infertility, polycystic ovary syndrome and endometrial cancer prevalence are high in obese women. For this reason, obesity is a disease which needs frequent follow-up and treatment.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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