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The effect of abdominal obesity in patients with polycystic ovary syndrome on metabolic parameters

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Abstract. – OBJECTIVE: Polycystic ovarian syndrome and obesity contribute to the metabolic complications for women of reproductive age. The aim of present study was to analyze the effect of abdominal obesity expressed using waist/hip ratio (WHR) in patients with polycystic ovary syndrome on metabolic parameters.

PATIENTS AND METHODS: The study included 659 women with PCOS with WHR <0.8 and ≥0.8 aged between 17 and 44 years. Patients were tested for follicular stimulating hormone, luteinizing hormone, 17-beta-estradiol, dehydroepiandrosterone sulfate, androstenedione, sex hormone binding globulin, and total lipid profile during the follicular phase (within 3 and 5 days of their menstrual cycle). Also, fasting glucose and insulin concentrations, and after, oral-glucose glucose administration, were determinate. De Ritis and Castelli index I and II were calculated.

RESULTS: Women with WHR ≥0.8 had higher concentration of glucose and insulin (both fasting and after 120 min of oral administration of 75 g glucose), as well as HOMA-IR value, than women with WHR value < 0.8. Also, abdominal obesity disorders hormonal parameters. Higher free androgen index and lower concentration of sex hormone binding globulin and dehydroepiandrosterone sulfate were found in female with WHR ≥ 0.8. Follicular stimulating hormone, luteinizing hormone, androstenedione, and 17-beta-estradiol, were on similar level in both groups. Elevation in triglycerides, total cholesterol, and low-density lipoprotein levels, as well as decrease in high density lipoprotein level in serum of women with WHR value ≥ 0.8, were found when compared to women with WHR < 0.8. A statistically significant correlation was found between WHR value and glucose, insulin, sex hormone binding globulin, free androgen index and lipid profile parameters.

CONCLUSIONS: Abdominal obesity causes additional disorders in metabolic and hormonal parameters in PCOS women, which confirmed changes in analyzed parameters between PCOS women with WHR < 0.8 and WHR ≥ 0.8 and statistically significant correlations between WHR value and analyzed parameters.

Key Words:
Abdominal obesity, Polycystic ovary syndrome, Metabolic parameters, Waist/hip ratio.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders[1,2]. Approximately 7-8% of women in a reproductive age are affected by PCOS, and the syndrome is currently considered the most common cause of female infertility[3,4]. The accumulation of a high number of small antrum follicles in the ovary is characteristic for PCOS. This morphological abnormality is accompanied with hormonal disruption in PCOS, including significant increases in androgens and luteinizing hormone (LH), and reduction in follicle-stimulating hormone (FSH)[5]. The diagnosis of PCOS is still controversial and based on signs, symptoms and laboratory findings that are not unanimously recognized[6,7]. Several concepts of the development of PCOS are considered, including metabolic and hormone disorders. PCOS is characterized by androgen excess and increased risk of diabetes mellitus and cardiovascular disease (CAD)[8]. Also, obesity contributes to the metabolic complications for women in reproductive age[9]. Especially visceral obesity its associated with metabolic disturbances and plays an important role in the development of PCOS[10]. Obesity was the major determinant factor for medical and cardiovascular complications among women with PCOS[11]. Visceral obesi-

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ty is associated with some metabolic disturbances, including insulin resistance, type 2 diabetes mellitus, dyslipidemia and hypertension, and it is also a predictor for the development of CAD and mortality[12,13]. In turn, obesity, type 2 diabetes, dyslipidemia, and the metabolic syndrome, are associated with non-alcoholic fatty liver disease (NAFLD)[1]. The assessment of visceral obesity is a better evaluation, compared to the assessment of overall obesity in predicting CVD than body mass index (BMI; in kg/m^2)[10,14]. Therefore, we investigated the influence of visceral obesity on the metabolic profile in patients with PCOS.

Patients and Methods

This prospective study was conducted in the Department of Endocrinological Gynecology Medical University of Silesia (Katowice, Poland) and was approved by the Bioethical Committee of Medical University of Silesia (Katowice, Poland). Informed consents were obtained from all participants. Visceral obesity was expressed using waist/hip ratio (WHR). The study included 659 women with PCOS: 188 female with WHR <0.8 and 471 patients with WHR ≥ 0.8. All patients were aged between 17 and 44 years. The diagnosis of PCOS was formed on the Rotterdam criteria[12] with at least two of the following three criteria: the existence of oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than 2 menstrual cycles in the past 6 months), clinical or biochemical hyperandrogenism, and polycystic appearance of ovary on ultrasonography. Other causes of hyperandrogenism, such as Cushing's syndrome, congenital adrenal hyperplasia or virilization, were excluded. Subjects taking any drugs or supplementations and who were smoking and alcohol abuse, were also excluded. Hirsutism was defined as FG score > 8. Metabolic syndrome was diagnosed according to the new International Diabetes Federation (IDF) definition. Patients were tested for follicular stimulating hormone (FSH), luteinizing hormone (LH), 17-beta-estradiol (17-β-E2), dehydroepiandrosterone *sulfate* (DHEAS) and androstenedione. Parameters of lipid profile such as: total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride (TG) were assayed. Hepatic enzymes activity such as: aspartate aminotransferase (ASP) and alanine aminotransferase (ALT) were also determined. On the same day, fasting glucose and insulin were determinate as well as an oral glucose tolerance test (OGTT; 75 g) was performed and further blood samples were obtained 120 min later to measure serum glucose and insulin levels. The diagnosis of glucose intolerance was based on World Health Organization criteria: diagnoses of impaired glucose tolerance and type 2 diabetes were made when 2-h plasma glucose levels were 140-199 and 200 mg/dl, respectively[15]. Height (m) and weight (kg) were measured with underwear clothing. Waist circumference (WC) was measured as the minimum size between iliac crest and lateral costal margin. Hip circumference (HC) was measured at the widest point over the buttocks. WHR was calculated as WC divided by HC. Normal WHR was defined < 0.8 and abdominal obesity as ≥ 0.8. BMI was calculated as weight (kg)/height square (m^2). The characteristics of the study groups are presented in Table I and occurrence of PCOS phenotype in analyzed groups are summarized in Table II. Serum was collected during the follicular phase (within 3 and 5 days of her menstrual cycle) according to the routine procedure after an overnight fasting. The samples were stored in deep freeze at -70°C until assays.

Laboratory Analysis

Plasma glucose and lipids were estimated by colorimetric methods using commercially available test kits (Roche Diagnostic, Indianapolis, IN, USA). Serum insulin concentration was determined by ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of sensitivity of 1.76 mIU/ml and intra- and inter-assay coefficient of variation (CV) values of 2.2% and 4.4%, respectively. ALT and AST were measured by photometric assay (Roche, Indianapolis, IN, USA).

Hormone Assay

FSH, LH, 17-β-E2, androstenedione, DHEA-S and SHBG were determined by ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of sensitivity 0.86 mIU/ml, 1.27 mIU/

Table I. Anthropometric parameters of study population.

Studied parameters	WHR < 0.8	WHR ≥ 0.8
Age [years]	24.6 ± 4.9	26.9 ± 6.1
BMI [kg/m^2]	21.6 ± 3.5	26.9 ± 7.3*
WHR	0.76 ± 0.04	0.89 ± 0.07*

*p < 0.05 statistically significant difference when compared to female with WHR < 0.8. BMI: body mass index; WHR: waist/hip ratio.

Table II. PCOS phenotype of study population.

PCOS phenotype	WHR < 0.8	WHR ≥ 0.8
	Percentage %	
1	49.2	55.1
2	18.3	14.2
3	13.6	14.9
4	18.9	15.8

ml, 9.7 pg/ml, 0.083 ng/ml, 0.019 ng/ml, 0.044 mg/ml and 0.2 nmol/l, respectively. The respective intra- and inter-assay CV values were 5.5 and 6.1% for FSH, 5.6 and 6.2% for LH, 4.7 and 7.8% for 17-β-E2, 3.6 and 7.1% for testosterone, 6.5 and 10.2% for androstenedione, 4.8 and 7.5% for DHEA-S and 5.3 and 9.0% for SHBG.

Calculations

Homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated using the standard formula: HOMA-IR = fasting concentration of insulin (μIU/ml) × fasting concentration of glucose (mmol/l)/22.5. The free androgen index (FAI) was calculated according to the standard formula. De Ritis ratio (AST/ALT ratio), Castelli risk index I (TC/HDL ratio) and Castelli risk index II (LDL/HDL ratio) were calculated[16,17].

Statistical Analysis

Data were expressed as mean with standard deviation (X ± SD) values. The normality of the variables was tested using the Shapiro-Wilk W-test. Differences between groups were tested using the Student *t*-test. When a lack of normal distribution and variance uniformity occurred, the differences between groups were analyzed using a non-parametric U Mann-Whitney test. Correlation was expressed by Spearman's rank correlation coefficients (r). In all instances, $p < 0.05$ was considered statistically significant. Statistical calculations were done using the Statistica Software Package, version 10.5 (Polish version: StatSoft, Cracow, Poland).

Results

Values of WHR and BMI were statistically significant different between analyzed groups (Table I). Females with WHR value ≥ 0.8 had higher concentrations of glucose and insulin (both fasting and after 120 min of oral administration of 75 g glucose), as well as HOMA-IR value, than women with WHR value < 0.8. We have also detected disorders in hormonal parameters in serum of women with higher WHR value. Higher free androgen index was found in female with WHR ≥ 0.8, when compared to female with WHR < 0.8, whereas the concentrations of androstenedione and 17-β E2 were similar in both groups (Table III). Lower SHBG and DHEA-S concentrations in serum were observed in women with abdominal obesity. We did not observe any statistically significant differences in LH and FSH between analyzed groups (Table IV). Statistically significant higher ALT activity was detected in serum of women with abdominal obesity, while ASP activity was on similar level in both studied groups. Lower value of de Ritis ratio was observed in the

Table III. Hormonal parameters in studied groups.

Hormonal parameters X ± SD	WHR < 0.8	WHR ≥ 0.8
LH [mIU/ml]	7.9 ± 9.0	6.4 ± 5.9
FSH [mIU/ml]	7.0 ± 1 3.9	6.5 ± 11.2
LH/FSH	1.4 ± 1.3	1.2 ± 0.9
SHBG [nmol/l]	74.6 ± 34.1	57.7 ± 34.6*
Androstenedione [ng/ml]	3.2 ± 1.4	3.4 ± 2.2
FAI	2.4 ±1.6	3.6 ± 2.6*
DHEA-S [μg/ml]	394.7 ± 162.0	362.7 ± 150.0*
17-β-E2 [pg/ml]	57.6 ± 69.0	47.3 ± 41.7

*$p < 0.05$ statistically significant difference when compared to female with WHR < 0.8. LH: luteinizing hormone; FSH: follicular stimulating hormone; SHBG: sex hormone binding globulin; FAI: free androgen index; DHEA-S: dehydroepiandrosterone sulfate; 17 β E2: 17-beta-estradiol.

Table IV. Biochemical and metabolic characteristics of study population

Studied parameters X ± SD	WHR < 0.8	WHR ≥ 0.8
Fasting glucose [mmol/L]	89.5 ± 6.8	91.6 ± 9.9*
Fasting insulin [μIU/ml]	7.5 ± 3.8	11.4 ± 8.9*
Fasting G/I ratio	11.2 ± 7.1	14.8 ± 8.2*
HOMA-IR	1.7 ± 0.9	2.6 ± 2.0*
OGTT 120 [mmol/L]	95.5 ± 22.3	107.8 ± 31.9*
Insulin 120 [μIU/ml]	41.6 ± 35.0	66.8 ± 74.5*

*$p < 0.05$ statistically significant difference when compared to female with WHR < 0.8. OGTT: oral glucose tolerance test; G/I ratio: glucose/insulin ratio; HOMA-IR: homeostatic model assessment of insulin resistance.

group of PCOS women with WHR value ≥ 0.8 when compared to women with WHR < 0.8. We have found increase in TG, TCH and LDL levels as well as decrease in HDL level in serum of women with WHR value ≥ 0.8 when compared to women with WHR < 0.8. Also, women with abdominal obesity had higher Castelli index I and II than women with WHR value within normal range (Table V).

Table V. The characteristics of hepatic enzymes activity and lipid profile parameters in studied population.

Lipid profile parameters X ± SD	WHR < 0.8	WHR ≥ 0.8
ALT [U/l]	17.5 ± 11.0	22.1 ± 16.4*
ASP [U/l]	22.1 ± 9.2	22.9 ± 11.7
De Ritis ratio (ASP/ALT)	1.5 ± 0.6	1.3 ± 0.5*
TC [mg/dl]	179.2 ± 31.7	191. ± 36.5*
TG [mg/dl]	79.6 ± 41.9	104.3 ± 68.6*
HDL [mg/dl]	66.5 ± 13.3	59.0 ± 17.2*
LDL [mg/dl]	97.7 ± 24.9	112.7 ± 31.5*
Castelli index I (LDL/HDL)	1.5 ± 0.4	2.1 ± 0.8*
Castelli index I (CH/HDL)	2.8 ± 0.5	3.4 ± 1.1*

*$p < 0.05$ statistically significant difference when compared to female with WHR < 0.8. ALT: alanine aminotransferase; ASP: aspartate aminotransferase; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein.

Correlations

In both analyzed groups, WHR value was positively correlated with BMI, stronger correlation was found in group with WHR ≥ 0.8 (r = 0.57) than in group with WHR < 0.8 (r = 0.23) (Table VI). In the group of female with abdominal obesity as the WHR value increased, the concentrations of fasting glucose and insulin as well as after post-oral glucose administration (120 min) were higher. In the group of female with WHR value within normal range, positive correlations were found between WHR value and the level of OGTT and insulin. In case of insulin resistance, in both analyzed groups WHR value was correlated with HOMA-IR, but stronger correlation was found in the group of female with higher value of WHR (r = 0.45) than in group with lower

Table VI. Correlation between WHR value and analyzed parameters in studied groups.

Correlation coefficients		Women with PCOS	
		WHR < 0.8	WHR ≥ 0.8
WHR	BMI	r = 0.23; p = 0.002	NS
	Glucose [mmol/L]	NS	r = 0.28; p = 0.000
	OGTT [mmol/L]	r = 0.19; p = 0.009	r = 0.34; p = 0.000
	Insulin [µIU/ml]	r = 0.16; p =0.032	r = 0.46; p = 0.000
	Insulin 120 [µIU/ml]	NS	r = 0.36; p = 0.000
	G/I	r = -0.18; p = 0.016	r = -0.39; p = 0.000
	HOMA-IR	r = 0.15; p = 0.044	r = 0.45; p = 0.000
	LH [mIU/mL]	NS	NS
	FSH [mIU/mL]	NS	NS
	LH/FSH	NS	NS
	SHBG [nmol/L]	NS	r = -0.37; p = 0.00
	DHEA-S [µg/ml]	NS	NS
	17-β-E2 [pg/mL]	NS	NS
	Androstenedione [ng/ml]	NS	NS
	FAI	NS	r = 0.36; p = 0.000
	ALT [U/L]	NS	r = 0.34; p = 0.000
	ASP [U/L]	NS	r = 0.11; p = 0.021
	de Ritis	NS	r = -0.38; p = 0.000
	TG [mg/dL]	NS	r = 0.43; p = 0.000
	TCH [mg/dL]	NS	r = 0.13; p = 0.006
	HDL [mg/dL]	NS	r = -0.40; p = 0.000
	LDL [mg/dL]	NS	r = 0.21; p = 0.000
	Castelli index I	NS	r = 0.40; p = 0.000
	Castelli index II	r = 0.15; p = 0.047	r = 0 .43; p = 0.000

OGTT: oral glucose tolerance test; G/I ratio: glucose/insulin ratio; HOMA-IR: homeostatic model assessment of insulin resistance; LH: luteinizing hormone; FSH: follicular stimulating hormone; SHBG: sex hormone binding globulin; FAI: free androgen index; DHEA-S: dehydroepiandrosterone sulfate; 17 β E2: 17-beta-estradiol; ALT: alanine aminotransferase; ASP: aspartate aminotransferase; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein.

WHR value (r = 0.15). We did not observe statistically significant correlation between WHR value and FSH, LH, SHBG, DHEA-S, estradiol and androstenedione concentrations in both analyzed groups. In the group of PCOS women with abdominal obesity, a positive correlation was found between WHR value and ALT, ASP activities, while a negative correlation was found between WHR value and de Ritis ratio. Only in the group of women with abdominal obesity we have found statistically significant correlation between WHR value and lipid profile parameters: a positive with triglycerides, total cholesterol, LDL levels and a negative with HDL level. In this group, also a positive correlation was found between WHR value and Castelli index I and II. In the group of women with lower WHR value, only a weak positive correlation was observed between WHR value and Castelli index II (LDL/HDL).

Discussion

In our work we have analyzed the influence of WHR value on metabolic profile in PCOS women with WHR < 0.8 and ≥ 0.8. Abdominal obesity plays crucial role in metabolic disorders and it was shown that obesity worsens the presentation of PCOS[18]. The main feature of PCOS is hyperandrogenism[19]. Increased ovarian androgen production in PCOS is due to higher circulating insulin levels and intrinsic upregulation of steroidogenesis[20]. In our investigation we did not observe any statistically significant differences in androstenedione and DHEA-S levels in serum of PCOS women with WHR < 0.8 and ≥ 0.8. However, FAI was higher in the group of women with abdominal obesity than that in the group of women with normal waist circumference. A positive correlation between FAI and WHR value in the group of PCOS women with WHR ≥ 0.8 suggests that higher abdominal circumference increased free androgen in serum. Hyperandrogenism and anovulation in women with PCOS are associated with modest estradiol secretion when compared to women without PCOS[21]. Nevertheless, in present study there were no significant differences in serum concentration of 17-β-E2 between PCOS women with WHR < 0.8 and WHR ≥ 0.8. We did not observe correlation between WHR value and 17-β-E2 concentration in analyzed groups. In PCOS androgen synthesis in ovarian theca, cells could be induced by increased LH level[24]. In turn, hyperandrogenemia induces a decrease sensitivity to both estradiol and progesterone in gonadotropic hypothalamic cells, reinforcing gonadotropin-releasing hormone and LH hypersecretion[22]. It was shown that women with PCOS have higher LH level than women without PCOS[23]. We did not observe any statistically significant differences in LH concentration between PCOS women with WHR < 0.8 and WHR ≥ 0.8. Also, the lack of correlation between WHR value and LH level suggest that abdominal obesity is not mainly cause of LH level disorders in PCOS. FSH is another gonadotropin essential to both follicle maturation and ovarian steroidogenesis[23]. In PCOS, FSH and FSH receptors appear to be up-regulated and the conversion of androgens to estrogens is disorders[24]. Similar to LH, we did not observe any statistically significant difference in this hormone between PCOS women with WHR < 0.8 and WHR ≥ 0.8. Overweight and obese women with PCOS are also characterized by reduced SHBG. Lower SHBG concentration appears to be predominantly due to the excess body fat rather than to the associated insulin resistance and androgen excess. In our work, higher value WHR resulted even lower SHBG concentration. We have found significant negative correlation between WHR value and SHBG concentration in the group of PCOS, which confirmed that lower SHBG in PCOS is associated with overweight or obesity. This is in line with our previous report[25] demonstrating that obese PCOS women had lower SHBG than PCOS women with normal weight. In PCOS women hyperandrogenism induces insulin resistance in skeletal muscle and adipose tissue. These disorders result in high circulating insulin levels[20]. In present study women with WHR ≥ 0.8 had higher fasting and after post-oral glucose administration (75 g.) glucose and insulin concentrations. Also, much stronger correlation coefficient was found between WHR and OGTT, HOMA-IR values in the group of PCOS women with WHR ≥ 0.8 than in the group of PCOS women with WHR < 0.8 PCOS women are known to have various degrees of IR and insulin secretion deficiency[26]. Non-obese PCOS women had similar HOMA-IR level when compared to women without PCOS. Whereas HOMA-IR level was higher in overweight and/or obese PCOS groups, when compared to women without PCOS. Increased prevalence of NAFLD was also reported in patients with PCOS[27]. Cerda et al[28] demonstrated that 41% of PCOS women had concomitant NAFLD as diagnosed by hepatic steatosis and abnormal ALT levels. In our

investigation we have found statistically significant higher ALT and AST activities in serum of PCOS women with WHR ≥ 0.8 when compared to PCOS women with WHR < 0.8. A positive correlation between WHR value and hepatic enzyme activities in the group of PCOS women with abdominal obesity confirmed that higher WHR value is an additional factor affects on liver disorders. Obesity is often accompanied by atherogenic dyslipidemia[29]. An impaired lipid profile is a prevalent finding in women with PCOS. It was recently noted that the TG, LDL-cholesterol, and TC levels are significantly higher in obese PCOS women than in lean/normal-weight PCOS women[30]. Our study confirmed this observation. In the serum of PCOS women with WHR ≥ 0.8 we have detected higher concentrations of TC, TG, LDL, when compared to PCOS women with WHR < 0.8. Durmus et al[10] shown that overweight or obese PCOS women had higher TG levels when compared to overweight or obese control group and non-obese PCOS women. Moreover, lower HDL concentration was found in serum of PCOS women when compared to healthy women and abdominal obesity additionally decreased HDL concentration[10]. According to the results of previously published studies[10,30] we have observed lower HDL concentration in serum of PCOS women with WHR ≥ 0.8 when compared to PCOS women with WHR < 0.8. We have also calculated Castelli index I (TC/HDL) and II (LDL/HDL). The value of LDL/HDL ratio proposed as a useful predictive marker of atherosclerotic changes on the vascular wall[31]. In patients with CAD, a higher LDL/HDL ratio was observed when compared to the control group[31]. We found statistically significant higher Castelli index I and II in the group of PCOS women with abdominal obesity, which could indicate an increased risk of CAD in the future. Also, positive correlations between WHR value and Castelli index I and II, confirmed the close association between these parameters.

Conclusions

Abdominal obesity causes additional disorders in metabolic profile in women with PCOS. Weight management should be proposed as an initial treatment strategy in women with PCOS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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