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ORIGINAL ARTICLE

Metabolic characteristics of women diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria – our own experience

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Abstract

OBJECTIVES: Analysis of metabolic features of women diagnosed with the PCOS among female patients of Department of Endocrinology and Metabolic Diseases, the Polish Mother's Memorial Hospital – Research Institute (DEMD, PMMH-RI). The secondary aim was assessment if diagnosis of PCOS (according to the Rotterdam criteria) may imply any standard treatment.

MATERIAL AND METHODS: The study was retrospective analysis of patients hospitalized in DEMD. 62 females diagnosed with PCOS were compared with women without the syndrome, adjusted according to the age and BMI. The parameters compared comprised insulin resistance assessed by five different methods (HOMA, HOMA2, QUICKI, IRI and Matsuda Index) and lipid concentration (total cholesterol, HDL-cholesterol and triglycerides).

RESULTS: None of analyzed parameters (insulin resistance indices, lipid fractions concentrations) differed significantly between women diagnosed with PCOS and those without PCOS, adjusted according to age and BMI. Insulin resistance indices correlated with the BMI values.

CONCLUSIONS: The metabolic characteristics of women diagnosed with the PCOS according to the Rotterdam criteria can be variant. PCOS is not necessarily connected with insulin resistance and obesity. Diagnosis of PCOS does not determine metabolic state of the individual so it should be postulated that every diagnosis of PCOS should by specified by information about the phenotype. Only precise information about the phenotype allows assessing the metabolic and cardiovascular risk and introducing optimal treatment.

INTRODUCTION

Polycystic ovary syndrome (PCOS) was first described in 1935 by Stein-Leventhal who observed coincidence of menstrual disorders and polycystic ovaries among his patients. He reported the combination of hirsutism, obesity, amenorrhea, and enlarged bilateral polycystic ovaries in seven women. Since then knowledge of syndrome has developed and nowadays hyperandrogenism is considered the main feature of PCOS. Currently PCOS is one of the most frequently diagnosed endocrinopathies in women. Prevalence of the syndrome in women at reproductive age is estimated in the range between 6.5% and 8% (Lujan *et al.* 2008). The diagnosis depends on used criteria. The most widely used are the so-called Rotterdam 2003 criteria that have been consented by the two societies: European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). However, the application of these criteria during the last dozen or so years has raised many doubts and controversies, concerning the terms of PCOS diagnostics. The Rotterdam criteria provide diagnosis of the POCS when two (2) out of the following three (3) are fulfilled:

1. oligo- and/or anovulation;
2. clinical and/or biochemical signs of hyperandrogenism;
3. polycystic ovaries;

while other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome) are excluded (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

The criteria appear simple in practical use. It seems however that diagnosis of the syndrome using the Rotterdam criteria solely, fails to implicate treatment and prognosis. The patients in whom the PCOS has been diagnosed based on the Rotterdam criteria can vary substantially one from another, considering the health risk and treatment options.

AIMS OF THE STUDY

The aim of the study was to analyze metabolic characteristic of women diagnosed with the PCOS among female patients of DEMD, PMMH-RI. The secondary aim was to assess if in women diagnosed with the PCOS according to the Rotterdam criteria any standard treatment could be established.

MATERIAL AND METHODS

The study was retrospective analysis of patients hospitalized in Department of Endocrinology and Metabolic Diseases, PMMH-RI. The medical reports of female patients hospitalized for various reasons in the above mentioned Department were studied. 248 women were enrolled in whom oral glucose tolerance test (OGTT) with parallel insulin concentrations determination had been preformed for insulin resistance assessment. Among the analyzed group, PCOS patients were selected according to the diagnosis present in the medical files. In our Department, PCOS has been diagnosed based on the Rotterdam 2003 criteria.

The oral glucose tolerance test in DEMD is performed - in presence of clinical indications - in the standard manner: the subjects are restricted carbohydrates in diet for 3 days prior to the test. The test is performed in the morning in the fasting state. After obtaining venous blood sample for fasting plasma glucose and insulin levels the patient drinks 150 ml of water solution containing 75 g of glucose. The next venous blood samples are obtained in the 60th and 120th minute of the test.

Plasma insulin was determined by an immunoenzymatic assay (IMMULITE, DPC). Using glucose and insulin concentration HOMA, HOMA 2, IRI, QUICKI and Matsuda indices were calculated.

1. The HOMA index was calculated using the formula (Matthews *et al.* 1985):
   HOMA = fasting plasma insulin (μU/ml) x fasting plasma glucose (mmol/l)/22.5.
2. The HOMA 2-IR was obtained by The HOMA 2 Calculator ©The University of Oxford 2004 downloaded from the site of the Diabetes Trials Unit of The Oxford Centre for Diabetes Endocrinology and Metabolism (Wallace *et al.* 2004).
3. Insulin Resistance Index for glycaemia [IRI(gly)] was calculated according the formula:
   IRI(gly) = 2/[(1/(INSp x GLYp))+1],
   where INSp, GLYp are insulinemic and glycemic areas under the curve during OGTT (75 g glucose) of the person under study (Belfiore *et al.* 1998).
4. Quantitative Insulin Sensitivity Check Index (QUICKI) was derived by calculating the inverse of the sum of logarithmically expressed values of fasting glucose and insulin (Katz *et al.* 2000):
   QUICKI = 1/log (fasting plasma insulin [mIU/ml]) + log(fasting plasma glucose [mg/dl]).
5. Matsuda Index (ISI) was calculated according to formula (Matsuda & DeFronzo, 1999):

$$Matsuda\ \ index = \frac{10000}{\sqrt{\left(\text{fasting plasma insulin}\left[\frac{\text{mIU}}{\text{ml}}\right]\right) \times \left(\text{fasting plasma glucose}\left[\frac{\text{mg}}{\text{dl}}\right]\right) \text{x}\ \left(\text{meanOGTT insulin}\left[\frac{\text{mIU}}{\text{ml}}\right]\right) \text{x}\left(\text{meanOGTT glucose}\left[\frac{\text{mg}}{\text{dl}}\right]\right)}}$$

In every patient lipid profile was also assessed including total cholesterol, HDL cholesterol, triglycerides and LDL-cholesterol, calculated when possible.

In every patient body mass index (BMI) was calculated as body mass [kg]/(body height)[m]^2.

Following initial statistical description of the group without PCOS, the subgroup of females adjusted according to the age and BMI was selected for the further comparison.

Statistical data are presented as the mean ± standard deviation and the median value.

In the entire analyzed group correlations between IR assessed by five above mentioned methods (HOMA, HOMA 2, IRI, Matsuda Index, QUICKI) and anthropometric parameters (age and BMI) have been assessed using simple regression analysis. The comparison between assessed parameters in PCOS subgroup and the subgroup without PCOS has been performed using Mann-Whitney's test and Kolmogorov-Smirnov test due to the lack of normal data distribution.

RESULTS

In the entire study group of 248 female the mean age was 32.58±13.89 years (median – 28 years), BMI – 27.84±7.38 kg/m^2 (median – 26.05 kg/m^2). In this group 62 patients were diagnosed with PCOS. The PCOS subgroup age was 24.27±6.13 years (the median value – 23 years) and BMI – 25.56±5.53 kg/m^2 (median – 25.65 kg/m^2). In the subgroup without PCOS the age was 35.35±16.64 years (median – 32 years), BMI – 28.60±7.77 kg/m^2 (median – 26.5 kg/m^2). The difference of age between the PCOS subgroup and the remaining women was significant. Because of possible influence of age on the metabolic profile there was necessity for adjustment of subgroup without PCOS according to the age. For further comparison the group of women without PCOS was adjusted according to the age. To the final comparison 116 subjects without PCOS were enrolled, aged 25.44±5.88 years (median – 24 years).

Detailed comparisons of the analyzed parameters in the subgroups are presented in Table 1. None of the analyzed parameters differed significantly between subgroups.

In PCOS subgroup, 24 subjects (39%) were overweight (25 kg/m^2≤BMI<30 kg/m^2) and 14 (23%) were obese (BMI>30 kg/m^2) in the comparative subgroup without PCOS – 23 (20%) were overweight and 35 (30%) were obese.

In both subgroups there was found significant correlation between BMI and IR indices (Fig. 1).

Because of such apparent influence of BMI on IR indices, the comparison was performed also after adjustment according to the BMI. 108 subjects from the subgroup without PCOS, adjusted according to BMI, were included to this comparison. In this selected subgroup HOMA was 2.21±2.15 (median – 1.62); HOMA 2 was 1.34±1.20 (median – 1.06), QUICKI 0.36±0.05 (median – 0.36), IRI 0.95±0.38 (median – 0.96) and Matsuda Index 8.02±6.76 (median – 6.22). None of analyzed indices differed significantly from those found in PCOS subgroup. The lipid profiles with total cholesterol – 167.96±40.02 mg/dl (median – 167 mg/dl), HDL-cholesterol – 59.11±16.18 mg/dl (median – 57 mg/dl) and triglycerides – 93.89±72.46 mg/dl (median 68.5 mg/dl) also did not differ significantly from those in PCOS subgroup (Fig. 2). Only tendency to lower HDL-cholesterol appeared in PCOS women.

DISCUSSION

PCOS is considered an important risk factor of atherosclerosis, atherosclerosis related diseases and metabolic disorders, with diabetes mellitus type 2 among them. For that reason PCOS has been recognised an important public health concern (Villa & Pratley, 2011). However, PCOS however appears to be very heterogeneous disorder. The classic PCOS required chronic anovulation and hyperandrogenism for diagnosis. Since introduction of the ESHRE/ASRM Rotterdam

Tab. 1. Selected parameters of metabolic characteristic of PCOS subjects in comparison with women without PCOS

Study subgroup/ Parameters		PCOS n=62 X±SD (median)	Without PCOS n=116	p
BMI [kg/m2]		25.56±5.53 (25.65)	26.70±7.58 (24.7)	Ns (>0.05)
Fasting glycaemia [mg/dl]		80.09±7.96 (80)	81.76±10.81 (82)	Ns (>0.05)
Total cholesterol [mg/dl]		166.35±31.99 (166)	169.5±39.80 (170)	Ns (>0.05)
HDL [mg/dl]		51.85±24.14 (46)	56.55±17.34 (57)	Ns (>0.05)
TG [mg/dl]		93.92±43.10 (95)	100.36±72.87 (80)	Ns (>0.05)
Insulin resistance	HOMA	1.77±1.36 (1.46)	2.38±2.32 (1.71)	Ns (>0.05)
	HOMA2	1.09±0.79 (0.92)	1.42±1.28 (1.12)	Ns (>0.05)
	QUICKI	0.37±0.06 (0.36)	0.35±0.05 (0.35)	Ns (>0.05)
	IRI	0.98±0.36 (0.94)	0.99±0.39 (0.99)	Ns (>0.05)
	Matsuda index	8.12±6.29 (6.72)	7.64±6.69 (5.79)	Ns (>0.05)

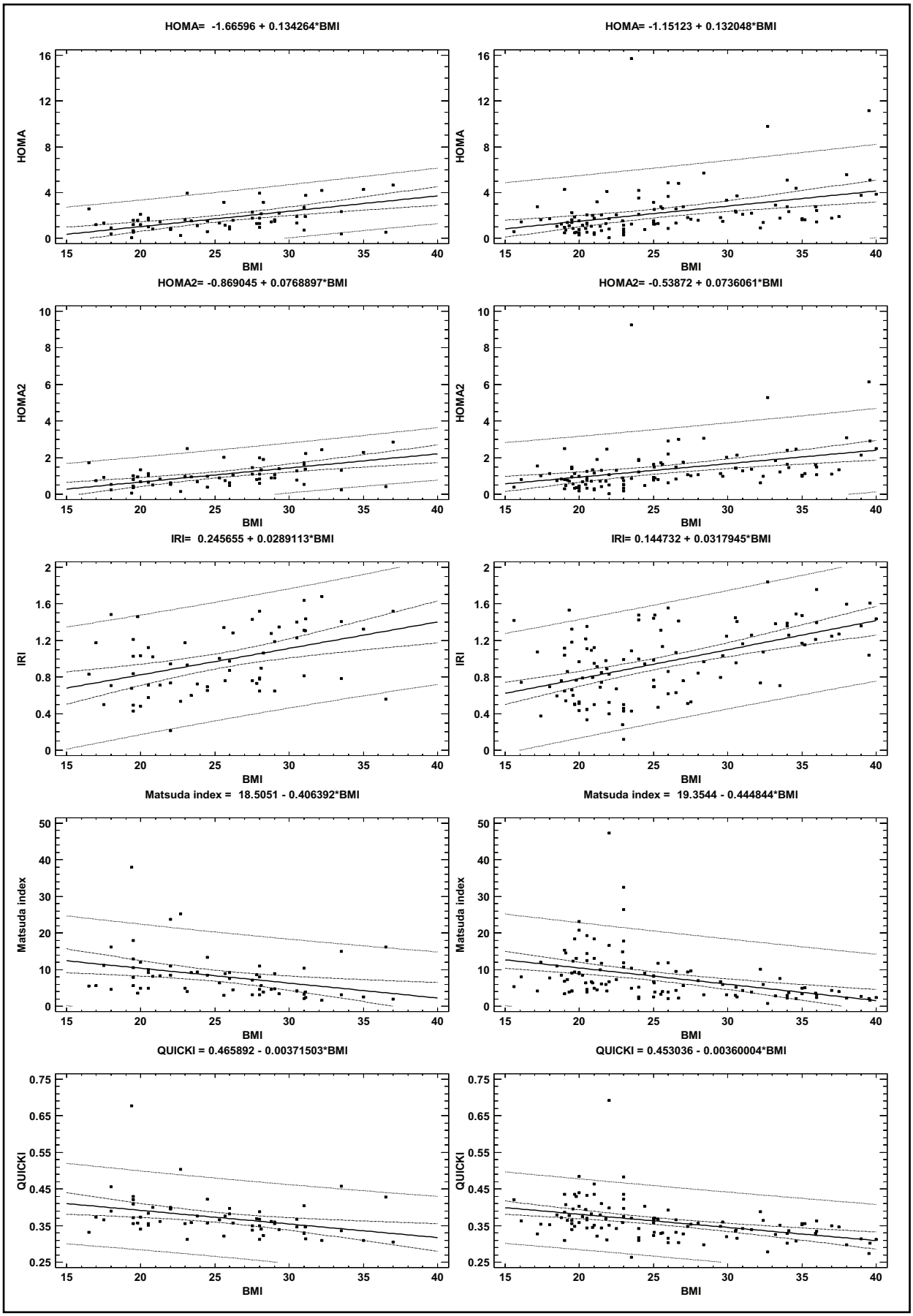

Fig. 1. Relations between BMI and insulin resistance indices in PCOS subjects (left) and women without PCOS (right) group adjusted according to the age.

criteria in 2003, the spectrum of disorder broadened, including patients with wide range of clinical appearances. PCOS according to these criteria includes four different patients' phenotypes:

1) hyperandrogenism, chronic anovulation, and polycystic ovaries;
2) hyperandrogenism and chronic anovulation but normal ovaries;
3) hyperandrogenism and polycystic ovaries but ovulation cycles;
4) chronic anovulation and polycystic ovaries but no clinical or biochemical hyperandrogenism (Guastella *et al.* 2010).

The problem of obesity or overweight is frequently associated with insulin resistance. We discussed these issues in detail in our review paper (Szosland & Lewiński, 2018). Despite the common association of PCOS with obesity, it appears that not all patients with PCOS are obese or overweight. In our study merely 23% women with PCOS were obese and 39% were overweight. Such observation was already reported by others. In study by Głuszak *et al.* (2012) mean BMI varied dependent on the phenotype of PCOS with obesity occurrence in 23% up to 50% of subjects. It is noteworthy that - in their study - insulin resistance was more often found among the obese women (Głuszak *et al.* 2012).

In our study, neither increased insulin resistance nor more expressed features of atherogenic dyslipidemia were found in the PCOS subgroup comparing with the subgroup without PCOS, adjusted according to the age and body mass index. This finding did not meet exactly our expectations. However, there are studies by other authors who also did not confirm insulin resistance in PCOS patients. In study by Tziomalos *et al.* (2013), women with PCOS showed only borderline differences in markers of IR compared with BMI-matched healthy women. Dahan *et al.* (2007) found that American PCOS subjects were more insulin resistant than controls, however the magnitude of IR in PCOS was determined by obesity. The obese PCOS are in their opinion those who have a high probability of IR (Dahan *et al.* 2007).

Interesting is the consideration that obesity is not an essential feature of PCOS, but by aggravating the degree of insulin resistance and hyperinsulinemia, the obesity precipitates the clinical manifestations of the syndrome in predisposed women or aggravates already present signs. Although some women with typical PCOS do not display insulin resistance, what can be explained by a genetic predisposition specific to PCOS, that reveals by the development of insulin resistance and compensatory hyperinsulinemia in most, but not all, women with PCOS (Baptiste *et al.* 2010).

The reports on the subject are however inconsistent. There are authors who claim that PCOS is frequently associated with insulin resistance, the increase prevalence of type 2 diabetes mellitus and greater cardiovascular risk, predominantly in women with higher androgen levels (Cobin, 2013). So, once again it has to be emphasized, that not all women diagnosed PCOS - according to the current criteria - are hyperandrogenic. It seems that accurate for now is the opinion that not all women with PCOS share the same cardiovascular risk profiles (Jovanovic *et al.* 2010). This issue is a subject of controversies and discussion, also considering the treatment. It has been noticed that women with PCO morphology according to the Rotterdam criteria and regular cycles are metabolically normal, although they may have subtle hormonal abnormalities. In such women, confirmation of IR by surrogate methods based on fasting insulin and glucose levels, can be unreliable and should not be indication for pharmacotherapy (Marshall & Dunaif, 2012). Some confirmation of this opinion can be found in our previous study in which it appeared that IR in PCOS women did not correlate with other metabolic features, like adiponectin and resistin concentrations (Lewandowski *et al.* 2005).

Sound criticism of the Rotterdam criteria can be found in current literature. It has been noticed that applying the Rotterdam criteria caused significant increase in the frequency of PCOS diagnosis. The occurrence of obesity and carbohydrate metabolism derangements under this diagnostic approach appeared to be considerably lower and related to the attainment of women with ovarian dysfunction and PCOS at ultrasound scan without the presence of hyperandrogenism (Broekmans *et al.* 2006).

The task force of Androgen Excess Society (AES) claimed that women with oligoamenorrhea and polycystic-appearing ovaries on ultrasonography but no evidence of hyperandrogenism, do not have PCOS. Moreover, the task force stated that not all phenotypes diagnosed as PCOS are associated with the increased risk of metabolic disorders (Azziz *et al.* 2006). It has also been indicated that because of the increase of the phenotypic heterogeneity of the disorder, due to usage of the Rotterdam criteria, the possibility to detect a common underlying abnormality - by means of genetic and other molecular studies - can be decreased. The adoption of ESHRE/ASRM criteria suggests that women with new phenotypes are at the increased risk for metabolic and cardiovascular consequences, as are patients with more classic forms of PCOS what appears not to be true (Azziz, 2006). Moghetti *et al.* (2013) proposed that the so-called normoandrogenic phenotype of PCOS should be considered a separate condition. In their observation insulin resistance appeared to be a specific feature of the classic phenotype and - to a lesser extent - of the ovulatory phenotype, but not of the normoandrogenic phenotype (Moghetti *et al.* 2013).

Among the problems that assemble the difficulty in resolving the PCOS spectrum are the ill defined clinical signs of hyperandrogenism, subjectivity in the diagnosis of hirsutism and polycystic ovary morphology and tendency to assign ovulation status solely on the basis of menstrual cycle history or poorly timed endocrine measurements (Lujan *et al.* 2008).

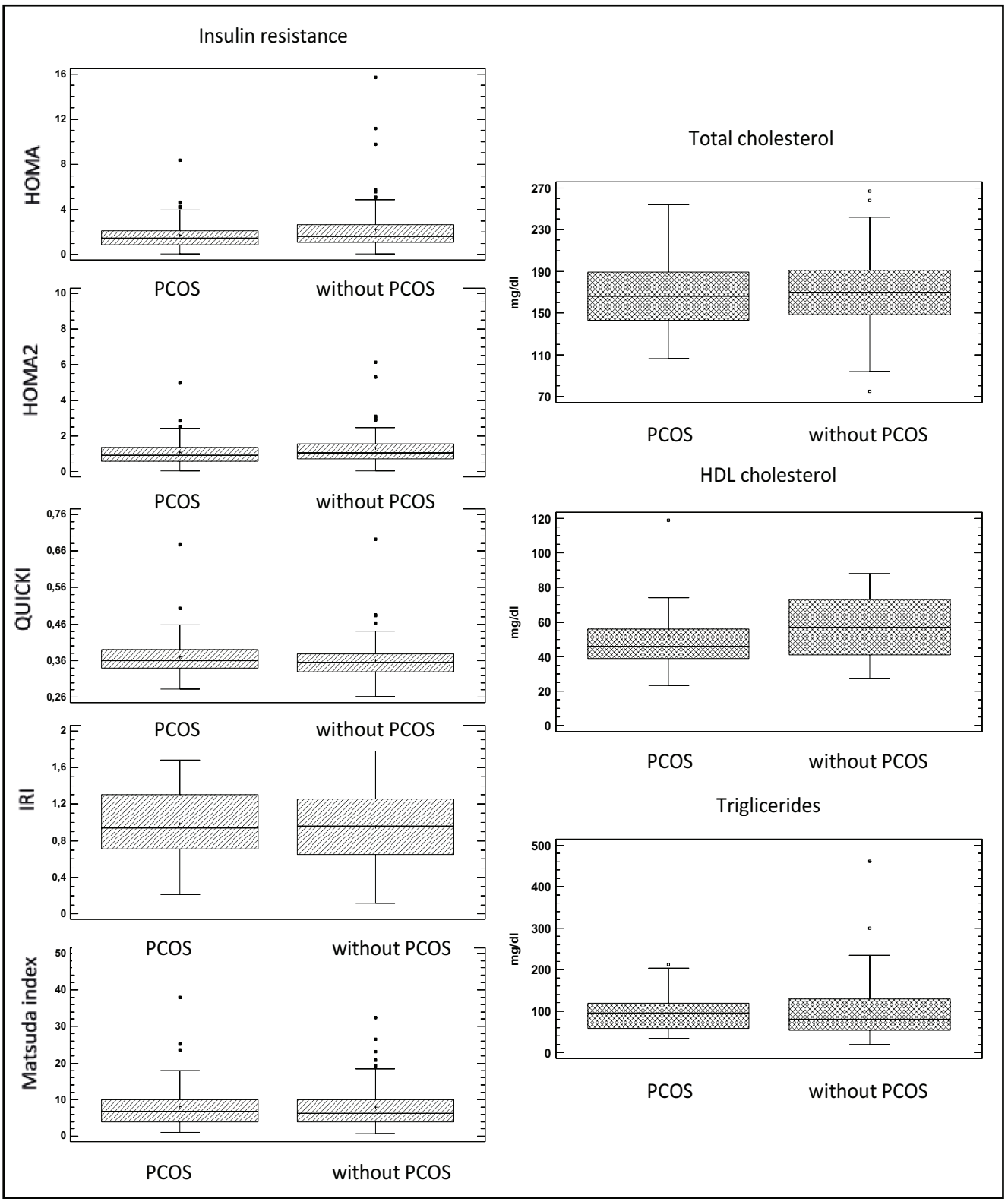

Fig. 2. Comparison of insulin resistance indices and lipid fractions concentrations in PCOS subgroup and subgroup without PCOS adjusted according to age and BMI.

CONCLUSIONS

In conclusion, it can be stated that our observation confirms and supports former findings by other authors indicating heterogeneity of PCOS. Moreover, simple diagnosis of PCOS does not say anything about the metabolic state of the individual - so it is to be postulated that every diagnosis of PCOS should be specified by information about the phenotype. Only precise information about the phenotype allows assessing the metabolic and cardiovascular risk what determines introduction of proper treatment.

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REFERENCES

1 Azziz R (2006). Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab **91**: 781–785.
2 Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF, Androgen Excess Society (2006). Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab **91**: 4237–4245.
3 Baptiste CG, Battista MC, Trottier A, Baillargeon JP (2010). Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol **122**: 42-52.
4 Belfiore F, Iannello S, Volpicelli G (1998). Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab **63**: 134–141.
5 Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC (2006). PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG **113**: 1210-1217.
6 Cobin RH (2013). Cardiovascular and metabolic risks associated with PCOS. Intern Emerg Med **8 (Suppl 1)**: S61–S64.
7 Dahan MH, Abbasi F, Reaven G (2007). Prevalence of insulin resistance among American women with polycystic ovary syndrome (PCOS) as a function of body mass index (BMI). Fertil Steril **88**: S78-S79.
8 Głuszak O, Stopińska-Głuszak U, Glinicki P, Kapuścińska R, Snochowska H, Zgliczyński W, Dębski R (2012). Phenotype and metabolic disorders in polycystic ovary syndrome. ISRN Endocrinol **2012**: 569862.
9 Guastella E, Longo RA, Carmina E (2010). Clinical and endocrine characteristics of the main polycystic ovary syndrome phenotypes. Fertil Steril **94**: 2197–2201.
10 10. Jovanovic VP, Carmina E, Lobo RA (2010). Not all women diagnosed with PCOS share the same cardiovascular risk profiles. Fertil Steril 94: 826-832.
11 Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ (2000). Quantitative insulin sensitivity check index: a simple. accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab **85**: 2402-2410.
12 Lewandowski KC, Szosland K, O'Callaghan C, Tan BK, Randeva HS, Lewinski A (2005). Adiponectin and resistin serum levels in women with polycystic ovary syndrome during oral glucose tolerance test: A significant reciprocal correlation between adiponectin and resistin independent of insulin resistance indices. Mol Genet Metab **85**: 61-69.
13 Lujan ME, Chizen DR, Pierson RA (2008). Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can **30**: 671-679.
14 Lujan ME, Chizen DR, Pierson RA (2008). Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can **30**: 671–679.
15 Marshall JC, Dunaif A (2012). Should all women with PCOS be treated for insulin resistance? Fertil Steril **97**: 18-22.
16 Matsuda M, DeFronzo RA (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care **9**: 1462-1470.
17 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985). Homeostasis model assessment: IR and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**: 412-419.
18 Moghetti P, Tosi F, Bonin C, Di Sarra D, Fiers T, Kaufman JM, Giagulli VA, Signori C, Zambotti F, Dall'Alda M, Spiazzi G, Zanolin ME, Bonora E (2013). Divergences in insulin resistance between the different phenotypes of the polycystic ovary syndrome. J Clin Endocrinol Metab **98**: E628-E637.
19 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004). Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome (PCOS). Hum Reprod **19**: 41-47.
20 Szosland K., Lewiński A (2018). Insulin resistance – "the good or the bad and ugly". Neuroendocrinol Lett **39**: in print
21 Tziomalos K, Katsikis I, Papadakis E, Kandaraki EA, Macut D, Panidis D (2013). Comparison of markers of insulin resistance and circulating androgens between women with polycystic ovary syndrome and women with metabolic syndrome. Hum Reprod **28**: 785-793.
22 Villa J, Pratley RE (2011). Adipose tissue dysfunction in polycystic ovary syndrome. Curr Diab Rep **11**: 179-184.
23 Wallace TM, Levy JC, Mattews DR (2004). Use and abuse of HOMA modeling. Diabetes Care **27**: 1487–1495.