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CLINICAL STUDY

Insulin-like growth factor (IGF) system and hormonal--metabolic profile in women with polycystic ovary syndrome

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ABSTRACT
AIM of the study was to compare serum levels of IGF-1, IGF-2 and insulin-like growth factor-binding protein 3 (IGFBP-3) among non-obese and obese PCOS women, and to assess their relationship to metabolic and hormonal parameters.
METHODS: The study included 64 women diagnosed with PCOS (age 28.9 ± 5 years); 30 of them with BMI ≥ 27 and 34 with BMI lower than 27. All subjects were examined for parameters of glucose and lipid metabolism, steroid hormones and serum IGF-1, IGF-2 and IGFBP-3 levels.
RESULTS: No significant differences in serum IGFBP-3 (p=0.534), IGF-1 (p=0.29) and IGF-2 (p=0.56) between two groups have been detected. IGFBP-3 was in positive correlation with total cholesterol (p=0.026), LDL cholesterol (p=0.03) and triacylglycerols (p=0.022). IGF-1 were negatively correlated with insulin (p=0.022), HOMA IR (p=0.033), triacylglycerols (p=0.0196) and waist circumference (p=0.049).
A positive correlation was detected between IGF-1 and HDL cholesterol (p=0.025). No significant relationship was observed between IGF-1 and steroid hormones.
CONCLUSION: Serum levels of IGF-1, IGF-2 and IGFBP-3 in obese PCOS women do not differ from those detected in non-obese PCOS women. IGF-1 negatively correlated with metabolic parameters, indicating that lower IGF-1 may represent an important predictor of metabolic syndrome (MS) in PCOS women. All peptides seem to have little effect on ovarian steroidogenesis in PCOS *(Tab. 1, Fig. 1, Ref. 30)*. Text in PDF *www.elis.sk*
KEY WORDS: polycystic ovary syndrome, metabolic syndrome, IGF-1, IGF-2, IGFBP-3.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease with a wide phenotypic variability affecting approximately 5–15 % of women in reproductive age (1). Based on Rotterdam criteria, it is defined by two of the following features: chronic oligo/anovulation, hyperandrogenism and ultrasound picture of polycystic ovarian morphology (2). It is well known that PCOS is commonly associated with metabolic syndrome (MS) or its components. An increase in the prevalence of cardiometabolic risk factors in PCOS women has been reported by many researchers (3, 4, 5). Unfortunately, the exact molecular or genetic mechanisms of this relationship are still not fully recognized. Several biomarkers have been identified to be involved in the pathogenesis of obesity and insulin resistance in humans and also in patients with PCOS. Beside various proinflammatory cytokines and adipocytokines, the insulin-like peptides such as insulin growth factor-1 (IGF-1) and insulin growth factor 2 (IGF-2) are commonly studied as well. They are known to regulate a large number of important physiological processes. IGF-1 exerts multiple biological effects, i.e., it promotes cell growth and proliferation and regulates fuel metabolism. Additionally, it has a structural and functional similarities to insulin and play a role in glucose homeostasis along with insulin-like growth factor-binding protein 3 (IGFBP-3), which binds with the majority of circulating IGF-1 (6, 7). A decrease in serum IGF-1 concentrations is associated with reduced insulin sensitivity, glucose intolerance and development of type 2 diabetes, whereas serum IGFBP-3 has been reported to be increased in patients with metabolic syndrome (8, 9).

IGF-2 is a mitogenic peptide widely expressed in humans. It regulates primarily the fetal development and differentiation. However, its role in adults is less determined (10). Evidence suggests that this peptide exerts potent actions in various organs and tissues including ovarian and adipose tissues, skeletal muscles and bones (6). Serum IGF-2 levels have been found to be associated with metabolic parameters such as insulin resistance or body weight (11). Less is known about the role of IGF-2 as well as about the whole IGF system in etiopathogenesis of PCOS and consequentially, the data from the literature are poor.

The aim of this preliminary observational study was primarily to assess the differences in serum IGF-1, IGF-2 and IGFBP-3 concentrations in obese and non-obese PCOS women, and to determine the relationship between serum IGF-1, IGF-2, IGFBP-3

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and metabolic parameters as well as steroid hormones in all PCOS women included in the study.

Subjects and methods

Subjects

This preliminary observational study included 64 Caucasian women diagnosed with polycystic ovary syndrome. Mean age of the patients was 28.9 ± 5 years (range 22–43; median 28 years). The diagnosis of PCOS was postulated according to the Rotterdam criteria (2). Clinical hyperandrogenism was defined as the presence of hirsutism expressed by modified Ferriman-Gallwey score (mFG ≥ 6), acne or androgenic alopecia. Biochemical hyperandrogenism was defined by the serum free testosterone concentration > 1,1 ng/ml, or by FAI > 8 %. Chronic anovulation was defined by menstrual cycle shorter than 21 or longer than 35 days, and co-occurring progesterone levels ≤ 6 ng/ml on days 20–23 of two consecutive menstrual cycles. Polycystic ovarian morphology (PCOM) was postulated as presence of 12 or more ovarian follicles on classic ultrasonography or ovarian volume larger than 10 ml.

The most common manifestations of PCOS were as follows: menstrual cycle irregularities (77 %), PCO morphology (75 %), hirsutism (64 %) and acne (28 %). All patients were divided according to BMI into two groups. The first group consisted of 34 patients with BMI < 27 kg/m^2; the second group contained 30 patients with BMI ≥ 27 kg/m^2.

Exclusion criteria included prolactinomas, congenital adrenal hyperplasia, Cushing´s syndrome, androgen-secreting tumors, and type 2 diabetes mellitus. All patients had normal thyroid, kidney and liver functions and they did not take any drugs that could have affected the hypothalamic-pituitary-ovarian axis during the past six months.

The study was approved by the Ethical Committee of the University Hospital in Kosice, Slovakia and all subjects involved in the study signed a written informed consent.

Methods

Anthropometric parameters such as height, weight and waist circumference were measured in all women. Weight and height were used to calculate body mass index (BMI), which was expressed as kg/m^2. Fasting blood samples were taken in an early follicular phase, or at unspecified point of time in those with amenorrhea. Blood samples were used to analyze serum glucose and insulin concentrations as well as lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triacyclglycerols). Circulating levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), total (TT) and free testosterone (FT), dihydrotestosterone (DHT), estrone (E1) and estradiol (E2) were evaluated from the same blood sample. Free androgen index (FAI) was calculated as TTx100/SHBG. The HOMA-IR was determined by calculation as follows: HOMA-IR= (glucose x insulin)/22.5.

Serum glucose and lipids were analyzed routinely using autoanalyzer (Roche Diagnostics GmbH). Serum concentrations of LH, FSH, SHBG, DHEAS and E2 were measured using chemiluminescent immunoassay (analyzer Architect, module C, Abbott, USA). TT and FT were detected by radio-immunoassay using commercially available kits of DIA Source (Belgium). Serum E1 and DHT were measured by ELISA (Demeditec diagnostics GmbH). Insulin concentrations and the levels of IGF-1and IGFBP-3 were determined using immunoradiometric assays (Beckman Coulter, Inc).

The serum IGF-2 was measured by a commercially available ELISA kit with catalog numbers E30 from Mediagnost (Germany). The analytical sensitivity of the ELISA E30 kit yields 0.02 ng/ml. The inter- and intra-assay variation coefficients are lower than 7.2 % and 6.6 %, respectively.

Statistical analysis

SAS JMP version 13.0.0 (USA) software was used for statistical analysis. Data are presented as mean ± SD regardless of their distribution. For normally distributed variables Student´s t-test was used to compare means between groups, whereas for non-normally distributed data, the non-parametric Mann-Whitney test was used to compare means among two groups. Linear regression analysis was used to detect correlations between variables. Values were considered to be statistically significant at $p \leq 0.05$.

Results

Measured anthropometric and biochemical variables in the group of PCOS women and subgroups according to BMI are presented in Table 1.

Obese PCOS women were significantly older than those with lower BMI (p=0.011). As expected, PCOS women with BMI ≥ 27

Tab. 1. Mean values of measured metabolic and hormonal parameters, and IGF peptides in PCOS women and subgroups depending on BMI.

Parameter	PCOS all group n=64	PCOS BMI < 27 n=34	PCOS BMI ≥ 27 n=30	p
Age (years)	28.9±5	27±5	30.7±5.2	0.011
BMI (kg/m^2)	27.7±7	22.3±2.3	34.2±5.4	0.0001
Glycemia (mmol/l)	5.1±1.5	4.7±0.4	5.5±2.2	0.073
Insulin (mIU/l)	14.4±9.7	9.1±5.1	21.5±9	0.0001
HOMA-IR	3.2±2.5	1.9±1.1	4.9±2.7	0.00026
Cholesterol (mmol/l)	4.9±1.1	4.6±1	5.3±1.26	0.03
TAG (mmol/l)	2.1±4.8	1.02±0.5	3.3±6.9	0.09
HDL-C (mmol/l)	1.5±0.4	1.7±0.3	1.23±0.3	0.0001
LDL-C (mmol/l)	2.7±0.8	2.5±0.75	2.9±0.77	0.03
IGF BP-3 (ng/ml)	**2016±56**	**1989±71**	**2064±95**	**0.534**
IGF-1 (ng(ml)	**190.9±12**	**200.4±15**	**173.6±19.9**	**0.291**
IGF-2 (ng/ml)	**697.7±283**	**678.5±283**	**721.8±291**	**0.56**
E2 (pg/ml)	64.5±40.2	76.12±42.6	58.5±39.7	0.089
E1 (pg/ml)	114.2±122	78.3±73	161±170	0.01
TT (ng/ml)	1.1±0.4	1.03±0.4	1.1±0.3	0.321
FT (pg/ml)	4.3±1.2	3.9±1.1	4.7±1.2	0.014
SHBG (nmol/l)	58.7±65	79.7±80	36.7±36.5	0.016
FAI	11.3±11.1	7.6±7.8	14.8±12.9	0.02

BMI – body mass index, HOMA-IR – homeostasis model assessment of insulin resistance, TAG – triacylglycerols, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, TT – total testosterone, FT – free testosterone, FAI – free androgen index, E2 – estradiol, E1 – estrone, IGF BP-3 – insulin-like growth factor-binding protein, IGF-1 – insulin-like growth factor 1, IGF-2 – insulin-like growth factor 2

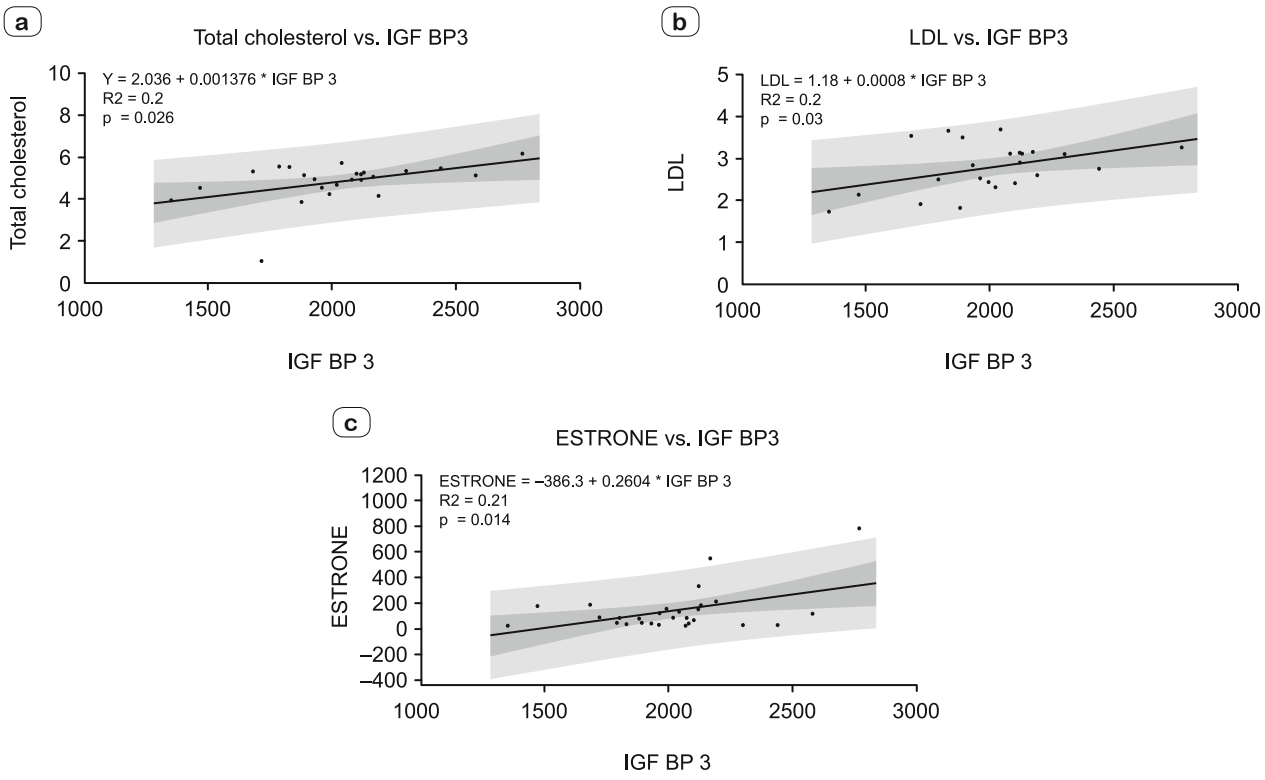

Fig. 1. Relation of serum IGFBP-3 to metabolic parameters and steroid hormones in women with PCOS: (a) positive correlation of total cholesterol and IGFBP-3, (b) positive correlation of LDL-C and IGFBP-3, (c) positive correlation of estrone and IGFBP-3.

kg/m^2 had significantly higher serum insulin concentrations and HOMA- IR (p=0.00001, p=0.00026, respectively). In addition, there was a tendency to higher levels of fasting glycemia (p=0.073) and worse lipid profiles in the obese group (data presented in our previous publication) (30) (Tab. 1).

There were significantly higher FT (p=0.014), FAI (p=0.02), E1 (p=0.01), lower SHBG (p=0.016) and moderately higher serum DHT (p=0.06) with a borderline significance in the group of subjects with higher BMI. No significant differences in TT (p=0.321) levels between the two PCOS groups were detected (Tab. 1). Moreover, no significant differences in serum IGFBP-3 (p=0.534), serum IGF-1 (p=0.29) and IGF-2 (p=0.56) concentrations between non-obese PCOS women and those with higher BMI were observed in this study.

IGFBP-3 was positively correlated with total cholesterol (R^2=0.2, p=0.026), LDL cholesterol (R^2=0.2, p=0.03), TAG (R^2=0.22, p=0.022) and also with E1 (R^2=0.21, p=0.014) and DHT (R^2=0.14, p=0.049). On the other hand, IGF-1 negatively correlated with insulin (R^2=0.25, p=0.022), HOMA-IR (R^2=0.23, p=0.033), TAG (R^2=0.23, p=0.0196) and WC (R^2=0.15, p=0.049). Positive correlation was detected between IGF-1 and HDL cholesterol (R^2=0.21, p=0.025). No significant relationship was demonstrated between serum IGF-1 concentrations and steroid hormones.

IGF-2 and DHT (R^2=0.08, R^2adj=0.07, p=0.0222) were in a significantly negative correlation. However, in the whole PCOS group, no correlation was detected between serum IGF-2 and metabolic variables or between IGF-2 and other steroid hormones.

Discussion

The serum levels of both insulin-like factors, i.e., IGF-1, IGF-2 and IGFBP-3 have not yet been completely studied in PCOS women in relation to metabolic and hormonal parameters, and consequentially, the data from the literature are scarce. The primary aim of the study was to compare serum IGF-1, IGFBP-3 and IGF-2 levels in the group of non-obese PCOS women to those with marked overweight or obesity (cut-off value of BMI was 27 kg/m^2). This study did not demonstrate any significant differences in the serum levels of any of the three parameters between non-obese and obese PCOS women. Secondly, we determined correlations of IGF-1, IGFBP-3 and IGF-2 serum levels with metabolic parameters and markers of ovarian steroidogenesis. In this study, IGF-1 negatively correlated with insulin, HOMA-IR, TAG and WC while a positive correlation was detected between IGF-1 and HDL cholesterol. No significant relationship was observed between serum IGF-1 and steroid hormones. On the other hand, IGFBP-3 was positively correlated with total cholesterol, LDL cholesterol and TAG. Although the data regarding the relationship between IGF-1 and hormonal/metabolic parameters in PCOS women are scarce and conflicting, many authors demonstrated lower levels of IGF-1 in metabolic syndrome in the general population or in some other

selected groups of patients. Jensen et al. showed a strong negative correlation between IGF-1 and insulin sensitivity, which does not seem to be genetically determined (12). Lower levels of IGF-1 were also confirmed in patients with non-alcoholic fatty liver disease (13, 14). Others found positive metabolic effects of IGF-1 in systemic lupus erythematosus patients while in some studies, an anti-apoptotic effect of this peptide was demonstrated (15, 16). On the other hand, as shown in the study of Gonzales, an increase in serum IGF-1 significantly reduced the fat mass (17). Yet, some, albeit few, studies documented increased IGF-1 concentrations in groups of patients with type 2 diabetes (18). According to Aguirre et al., at the initiation of metabolic dysregulation by overfeeding, IGF-1 is decreased. Such deficiency seems to be related to the onset of MS and atherosclerosis (19). In agreement with these previous data, our study confirmed that IGF-1 is inversely related to metabolic parameters of carbohydrates and lipids, suggesting its protective role in the metabolic syndrome associated with PCOS. Conversely, in this study, serum IGFBP-3 positively correlated with serum total cholesterol, LDL cholesterol and TAG, suggesting a probability of opposite effects on metabolism in PCOS women. This finding supports previous data, namely that higher IGFBP-3 is significantly associated with T2DM risk, as was demonstrated in women, and also in general adult population (7). We did not confirm any correlation of IGF-1 with sex steroids or other hormones indicating ovarian function. In an older study, serum IGF-1 levels in PCOS subjects were related solely to the follicle number, not to the markers of ovarian steroidogenesis (20), the fact of which is in agreement with our data. Thus, the elevation of IGF-1 appears to reflect the metabolism of carbohydrates or lipids and have little effect on ovarian steroidogenesis in PCOS.

Also, IGF-2 is a widely expressed polypeptide that has approximately 67 % homology with IGF-1. However, in human serum, it is more abundant in comparison to IGF-1 (6). In the ovary, IGF-2 stimulates the proliferation of granulosa cells and estradiol secretion while seemingly being more important than IGF-1 (10, 11). Altered IGF-2 gene expression has been observed in metabolic disorders, notably in obesity, type 2 diabetes mellitus, and also in PCOS (21, 22, 23). The role of IGF-2 in the pathogenesis of PCOS, especially in patients with metabolic syndrome, has not been yet completely recognized. Because PCOS is highly associated with obesity and other metabolic disturbances, we examined the relationship between IGF-2 and metabolic parameters in PCOS women. No correlation was demonstrated between serum IGF-2 and metabolic variables or between IGF-2 and steroid hormones, except for DHT. The association of IGF-2 and DHT has not been described in the literature, and the clinical impact of this finding is probably uncertain. Albeit, it should be confirmed in further studies. A growing body of recent evidence indicates an association between DM2, IGF-2 and higher risk of breast, colon, endometrial and ovarian cancers, which are also more common in PCOS women (24, 25, 26, 27).

Study of Tian et al. showed that pregestational hyperandrogenism may predispose offspring to disorders of glucose metabolism (28). Another study demonstrated that the expression of IGF-2 in placenta was significantly higher in a group of women with gestational diabetes in comparison to a group without hyperglycemia (25). Others reported that IGF-2 levels were related to insulin resistance and increased susceptibility to DM (26, 27). Fowke et al. found that serum IGF-2 tended to rise with BMI and the lowest IGF-2 serum concentrations were observed in subjects with BMI lower than 20 kg/m^2 (29). Similarly to IGF-1, neither metabolic nor hormonal parameters in the current study were in significant relationship with serum IGF-2. It is possible that the serum concentration of IGF-2 does not reflect the real amount of IGF-2 and its action in organs or tissues (30). Thus, further studies with the expression of IGF-2 in tissues or with measurements of mRNA IGF-2 are needed.

One of the strengths of this study is that we measured a complex IGF system (IGF-1, IGF-2 and IGFBP-3) in the serum of PCOS women with simultaneous measurement of steroid hormones and metabolic profile. From this viewpoint, this is the first study published so far. Unfortunately, the study has also several limitations. The main limitation of the study is a relatively small group of patients enrolled in the study; thus, we could not divide patients into three groups based on BMI. Nevertheless, the results and correlations in the whole group allow us to postulate novel conclusions that have not yet been published.

In conclusion IGF-1, IGF-2 as well as IGFBP-3 serum levels in obese PCOS women do not differ from those detected in women with lower BMI. The serum IGF-1 negatively correlated with the majority of metabolic parameters, indicating that among insulin-like peptides, the most important predictor of metabolic syndrome in PCOS women seems to be the decrease in serum IGF-1 concentration. This IGF-1 deficiency may play a role in the development of MS and cardiovascular events, which poses a higher risk to women with PCOS. Based on the results of the study, IGFBP-3 appears to be in positive relation to metabolic parameters, especially to the lipid profile. On the other hand, the role of IGF-2 in the onset or development of metabolic syndrome is uncertain. Further studies in this field are required. Although related to metabolic parameters, all three peptides appear to have little or no enhancing effect on ovarian steroidogenesis in PCOS.

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