Endokrynologia Polska
DOI: 10.5603/EP.2014.0051
Tom/Volume 65; Numer/Number 5/2014
ISSN 0423–104X

Fetuin-A levels in lean and obese women with polycystic ovary syndrome

Fetuina A u szczupłych i otyłych kobiet z zespołem policystycznych jajników

Jarosław Kozakowski, Wojciech Jeske, Wojciech Zgliczyński

Department of Endocrinology, Medical Centre of Postgraduate Education, Bielański Hospital, Warsaw, Poland

Abstract

Introduction: The aim of this study was to estimate serum fetuin-A levels in lean and obese women with polycystic ovary syndrome (PCOS) and to find possible relationships between fetuin-A, metabolic factors and androgens in these patients.

Material and methods: In 25 lean (18–38 years, BMI 17.5–25.0 kg/m^2) and 15 obese women (20–41 years, BMI 28.1–53.2 kg/m^2) with PCOS, anthropometric indices and body composition were measured. Fasting serum fetuin-A, adiponectin, leptin, glucose, lipids, hsCRP, insulin, androgens and SHGB levels were estimated.

Results: There was no significant difference in serum fetuin-A levels between lean and obese patients: 0.54 ± 0.13 g/L and 0.60 ± 0.14 g/L, respectively. We noted a correlation between BMI and leptin levels ($r = 0.88$; $p < 0.0001$) and a nearly significant negative correlation between BMI and adiponectin levels ($r = –0.53$; $p = 0.11$) in all subjects. In lean patients, we found a correlation between fetuin-A levels and ALT activity ($r = 0.44$; $p < 0.05$). In all participants, fetuin-A correlated directly with DHEA-S levels ($r = 0.44$; $p < 0.03$).

Conclusions: Serum fetuin-A levels were similar in lean and obese women with PCOS. We found an association between fetuin-A levels and ALT activity in lean patients and between fetuin-A levels and DHEA-S in all women. The role of fetuin-A in the mechanisms of insulin resistance, and its potential impact on androgenic hormones production in women with PCOS, need to be tested in further studies.
(Endokrynol Pol 2014; 65 (5): 371–376)

Key words: *polycystic ovary syndrome; fetuin-A; obesity; insulin resistance*

Streszczenie

Wstęp: Celem pracy było porównanie stężenia fetuiny A w surowicy u szczupłych i otyłych kobiet z zespołem policystycznych jajników (PCOS) oraz ocena, czy istnieją zależności między stężeniem tego białka a wskaźnikami metaboliczymi i androgenami w tej grupie chorych.

Materiał i metody: U 25 szczupłych (wiek 18–38 lat, BMI 17,5–25,0 kg/m^2) i 15 otyłych kobiet (wiek 20–41 lat, BMI 28,1–53,2 kg/m^2) z PCOS dokonano pomiarów antropometrycznych i składu ciała, oraz określono na czczo stężenie fetuiny A, adiponektyny, leptyny, glukozy, lipidów, hsCRP, AlAT, insuliny, androgenów i SHBG.

Wyniki: Między grupami kobiet szczupłych i otyłych nie stwierdzono różnicy w zakresie stężenia fetuiny A, które wynosiło odpowiednio 0,54 ± 0,13 g/l i 0,60 ± 0,14 g/l. Wykazano silną korelację między BMI i leptyną ($r = 0,88$; $p < 0,0001$) i niemal znamienną ujemną korelację między BMI a adiponektyną ($r = –0,53$; $p = 0,11$) u wszystkich badanych kobiet. Wśród szczupłych uczestniczek wykazano korelację między stężeniem fetuiny A a aktywnością AlAT ($r = 0,44$; $p < 0,05$), zaś u wszystkich badanych korelację między stężeniem fetuiny A i DHEA-S ($r = 0,44$; $p < 0,03$)

Wnioski: Stężenie fetuiny A u szczupłych i otyłych kobiet było podobne. Wykazano zależność między stężeniem fetuiny A i aktywnością AlAT u szczupłych, oraz między stężeniem fetuiny A i DHEA-S u wszystkich badanych. Wyjaśnienie udziału fetuiny A w mechanizmach powstawania insulinooporności i ewentualnego wpływu na produkcję androgenów u kobiet z PCOS wymaga prowadzenia dalszych badań.
(Endokrynol Pol 2014; 65 (5): 371–376)

Słowa kluczowe: *zespół policystycznych jajników; fetuina A; otyłość; insuliooporność*

This study was supported by a grant from the Medical Centre of Postgraduate Education, Warsaw, Poland, Nº: 501-1-08-11-13.

Introduction

Insulin resistance and hyperinsulinaemia represent substantial metabolic disturbances in women with polycystic ovary syndrome (PCOS) [1]. This syndrome affects 5–10% of women of reproductive age [2]. Liver-derived fetuin-A, also known as alpha2-HS glycoprotein (AHSG) has been found to be one of the important factors involved in the pathogenesis of impaired insulin sensitivity. It is a natural inhibitor of insulin receptor autophosphorylation and tyrosine kinase activity in muscle and the liver, and thereby a blocker of insulin signal transduction [3]. Hence, AHSG is thought to play a significant role in weight gain, fat accumulation and the development of type 2 diabetes [4–6]. Fetuin-A knock-out mice did not exhibit insulin resistance and were protected against obesity on a high-fat diet [7]. Moreover, it has been demonstrated that AHSG may

Jarosław Kozakowski M.D., Ph.D., Department of Endocrinology, Medical Centre of Postgraduate Education, Bielański Hospital, Cegłowska St. 80, 01–809 Warsaw, Poland, tel.: +48 22 834 31 31, fax: +48 22 834 31 31, e-mail: kyaroslaw@tlen.pl

Table I. *Baseline characteristics of lean (group 1) and obese (group 2) women with PCOS*

Tabela I. *Charakterystyka kobiet z zespołem policystycznych jajników z prawidłowym (grupa 1) oraz podwyższonym BMI (grupa 2)*

	Group 1		Group 2		P
	N =	Mean ± SD (range)	N =	Mean ± SD (range)	
Age (years)	25	25.0 ± 5.1 (18.0–38.0)	15	27.3 ± 5.9 (20.0–41.0)	NS
BMI [kg/m^2]	25	20.8 ± 1.9 (17.5–25.0)	15	36.2 ± 7.6 (28.1–53.2)	< 0.0001
FM (%)	9	29.3 ± 8.1 (16.4–39.6)	11	47.5 ± 7.8 (36.4–56.5)	< 0.0001
FMt (%)	9	29.9 ± 9.9 (15.8–42.7)	11	49.7 ± 7.7 (37.5–60.1)	< 0.0001
TC [mmol/L]	24	4.5 ± 0.7 (3.3–6.1)	15	5.4 ± 1.0 (3.9–7.5)	< 0.004
LDL [mmol/L]	24	2.3 ± 0.6 (1.1–3.6)	15	3.4 ± 0.9(2.2–5.3)	< 0.0001
HDL [mmol/L]	24	1.8 ± 0.3 (1.1–2.6)	15	1.2 ± 0.3 (0.8–1.8)	< 0.0001
TG [mmol/L]	24	0.74 ± 0.3 (0.4–1.6)	15	1.7 ± 0.9 (0.7–3.6)	< 0.0001
Glucose [mmol/L]	24	4.8 ± 0.7 (4.1–7.4)	15	5.0 ± 1.0 (4.0–8.4)	NS
hsCRP [μg/L]	24	0.45 ± 0.3 (0.05–1.5)	13	8.07 ± 12.1 (0.4–39.6)	< 0.005
ALT [IU/mL]	24	14.3 ± 4.3 (7.0–25.0)	14	25.9 ± 11.6 (13.0–52.0)	< 0.0002
SBP [mm Hg]	25	115.0 ± 14.2 (90–140)	15	120.7 ± 11.9 (100–140)	NS
DBP [mm Hg]	25	70.0 ± 11.9 (50–100)	15	74.0 ± 11.9 (60–90)	NS

BMI — body mass index; FM — fat mass; FMt — fat mass of the trunk; TC — total cholesterol; LDL — low density lipoprotein cholesterol; HDL — high density lipoprotein cholesterol; TG — triglycerides; hsCRP — high sensitive C-reactive protein; ALT — alanine aminotransferase; SBP — systolic blood pressure; DBP — diastolic blood pressure

act as a proadipogenic factor: *in vitro* studies revealed that fetuin-A stimulates fibroblasts and smooth muscle cell uptake of triglycerides and their incorporation into fatty acids [8]. However, it is still unknown whether similar effects occur *in vivo*. In humans, in a prospective case-cohort study, fetuin-A correlated positively with hs-CRP levels, promoted cytokine expression in monocytes, and suppressed the insulin-sensitising adipokine adiponectin synthesis [9]. In well-functioning, community-living older persons, AHSG levels correlated with the accumulation of visceral adipose tissue, with liver fat accumulation, and rose in patients with insulin resistance [10, 11]. Higher human fetuin-A levels have been found to be strongly associated with metabolic syndrome and atherogenic lipid profile, independently of the BMI [12]. It has been suggested that fetuin-A, similarly to the adipokines secreted from adipose tissue, may represent the first identified factor secreted from the liver (hepatokine) which modulates insulin signalling in target tissues [6].

Approximately 50% of women with polycystic ovary syndrome are overweight or obese and most of them have abdominal obesity that is associated not only with more severe insulin resistance but also with androgen excess and fertility disorders [13–15]. It is speculated that in PCOS, both abdominal adiposity and hyperandrogenism may be specific risk factors for developing atherothrombosis [16, 17]. It is presumed that changes in lifestyle and the use of proper medications could normalise the endocrine system and metabolism through insulin-sensitivity increase and then restore the menses and ovulations [18].

Whether fetuin-A serum levels differ in lean and obese women with PCOS, and if AHSG contributes to insulin resistance in these patients, is so far still unknown.

The aim of our study was to compare serum fetuin-A levels in lean and obese women with PCOS, and to examine whether there are any relationships between serum levels of AHSG, metabolic factors, markers of inflammation and androgens in these patients.

Material and methods

We evaluated 25 lean women aged 18–38 years, mean 25.0 ± 5.1 (x ± SD) with BMI 17.5 – 25.0 kg/m^2 (20.9 ± 1.9), and 15 obese women aged 20-41 years (27.3 ± 5.9) with BMI 28.1-53.2 kg/m^2 (36.2 ± 7.6, see Table I). In all subjects, PCOS was diagnosed according to the Rotterdam consensus criteria: i.e. at least two of the following features: 1) oligo- or anovulation, 2) clinical hyperandrogenaemia or/and elevated levels of androgenic hormones, and 3) polycystic ovaries in ultrasound imaging [19]. Other conditions with similar signs were excluded.

Clinical hyperandrogenaemia was defined as the presence of hirsutism and/or acne. Biochemical hyperandrogenaemia was defined as serum testosterone levels greater than 3.1 nmol/L, dehydroepiandrosterone-sulfate levels (DHEA-S) greater than 2,000–4,100 ng/mL depending on age, or free androgen index (FAI) > 5.

Ovaries in USG were defined as polycystic when they included either ten or more follicles measuring 2–9 mm in diameter or their volume was greater than 10 cm^3. Similar conditions: hyperprolactinemia (defined as serum prolactin levels greater than 25 ng/mL), Cushing's syndrome, nonclassical congenital adrenal hyperplasia (defined as serum 17-hydroxyprogesterone levels greater than 1.2 and 5.2 ng/mL in the follicular and luteal phase, respectively, or greater than 10 ng/mL in synacthen-stimulation test) were excluded. Also current or previous (within the last three months) use of oral contraceptives and other hormonal drugs was an exclusion criterion from the study.

Subjects were studied after an overnight fast. As part of the physical examination, body height and weight mere measured, and then body mass index (BMI) was calculated. Blood was collected at about 8am for glucose, lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides), high sensitive C-reactive protein (hsCRP), alanine aminotransferase (ALT), fetuin-A, leptin, adiponectin, insulin, LH, FSH, oestradiol, testosterone, dehydroepiandrosterone-sulfate, 17-hydroxyprogesterone and sex hormone-binding globulin (SHBG), through an i.v. catheter placed in the forearm. Free androgen index (FAI) was calculated as testosterone (nmol/L)/SHBG (nmol/L) levels. Homeostasis Model of Assessment - Insulin Resistance (HOMA) was calculated by the formula: fasting plasma insulin (microinternational units per millilitre) x fasting plasma glucose (millimoles per litre)/22.4.

Subjects were considered as insulin resistant when HOMA index was > 2.5. All subjects underwent transvaginal ultrasonography (TV-USG) and USG of abdomen (to estimate liver echogenity and to exclude adrenal pathology). At the end of the investigation, body composition by DEXA was determined. The same two operators performed all TV-USG and DEXA measurements, respectively.

The local ethical committee approved the study, and informed consent was obtained from all participants.

Assays

Glucose was measured with a glucose hexokinase reagent set with sensitivity of 2.16 mg/dL. An enzymatic colorimetric method was used to measure total cholesterol in the presence of cholesterol oxidase and esterase. The sensitivity was 0.116 mg/dL. HDL-cholesterol was measured with an enzymatic colorimetric method; sensitivity was 3 mg/dL. Triglycerides were also measured with an enzymatic colorimetric method with sensitivity of 0.85 mg/dL. All mentioned biochemical measurements were performed using a Roche Cobas Integra 400 chemistry analyser (Roche Diagnostics). Insulin was measured by the immunoradiometric method (Insulin IRMA — Immunotech SA, France); sensitivity was 2.0 mIU/mL. Fetuin-A was measured in serum diluted 10,000 times, by Human Fetuin-A ELISA kit, (Epitope Diagnostics Inc, San Diego, CA, USA). Leptin was measured by RIA (Linco Res. Inc, USA), using rabbit antibodies against human leptin. The sensitivity for this assay was 0.5 ng/mL. Adiponectin was measured by RIA method (Millipore, MI, USA, human adiponectin), detection limit 1 ng/mL. LH and FSH were measured by an immunochemiluminescence method with IMMULITE 2000 (Siemens Healthcare Diagnostics, Inc). Oestradiol was measured with the same IMMULITE 2000 analyser, with sensitivity of 15 pg/mL. Total testosterone was measured by an immunochemiluminescence method with Architect iSR 2000 (Abbot Diagnostics Division, Abbot Park, IL, USA); sensitivity was 0.08 ng/mL. Results were then multiplied by a factor of 3.46 to obtain nmol/L. Dehydroepiandrosterone-sulfate was measured by an immunochemiluminescence method with IMMULITE 2000 (Siemens Healthcare Diagnostics, Inc); sensitivity of this method was 30 ng/mL. 17-hydroxyprogesterone was measured by 17OH-RIA-CT Kit (DIAsource ImmunoAssays SA, Belgium); detection limit: 0.02 ng/mL. SHBG was measured by IRMA method (Orion Diagnostics Oy, Finland); detection limit: 1.3 nmol/L.

Body mass index was calculated as body weight (kg)/height (m^2). Subjects with BMI between 25 and 30 kg/m^2 were considered as overweight, whereas subjects with BMI between 30 and 40 kg/m^2 were considered as obese, and with BMI above 40 kg/m^2 as morbidly obese.

To perform measurements of body composition we used a Lunar Prodigy (GE Lunar, Madison, WI, USA) device, which was calibrated each day with a standardised phantom and serviced regularly. The coefficient of variation for measurements with this method is about 2%.

Statistical analysis

All data is presented as the mean ± SD. The normality of the distribution of variables was verified with a Kolmogorov-Smirnov test. To examine bivariate relationships between data, Pearson correlation or Spearman rank analyses were used. Comparisons between groups with normal distribution of the data were performed by unpaired Student's t-test, in other cases comparisons were performed by Kolmogorov-Smirnov test for two samples. For all analyses, a two-tailed $P \leq 0.05$ was considered to indicate statistical significance. All calculations were performed with the Statistica 5.0 software package (StatSoft Inc, Tulsa, OK, USA).

Table II. *Hormonal results of our patients*
Tabela II. *Wyniki badań hormonalnych badanych kobiet*

	Group 1		Group 2		P
	N =	Mean ± SD (range)	N =	Mean ± SD (range)	
Insulin [μIU/mL]	22	3.5 ± 3.1 (1.0–13.0)	14	10.8 ± 8.5 (2.0–27.0)	< 0.0001
HOMA	22	0.8 ± 0.7 (0.2–3.3)	14	2.4 ± 1.8 (0.4–6.2)	< 0.001
Leptin [ng/mL]	17	15.1 ± 7.2 (3.4–27.5)	12	42.3 ± 26.8 (11.4–95.2)	< 0.0001
Adiponectin [μg/mL]	19	14.1 ± 6.8 (3.5–31.8)	9	5.9 ± 2.8 (3.0–11.7)	0.024
Fetuin-A [g/L]	21	0.54 ± 0.13 (0.4–09)	11	0.6 ± 0.14 (0.4–0.9)	NS
Testosterone [mmol/L]	24	2.4 ± 1,3 (0.6–5.6)	15	2.8 ± 1.6 (0.6–5.3)	NS
DHEA-S [ng/mL]	24	3,123.7 ± 1,543 (749–6,740)	15	2,553.1 ± 1,024 (1,180–4,490)	NS
FAI	21	5. 7 ± 5.2 (1.0–253)	14	11.6 ± 6.7 (2.6–26.2)	< 0.0001
LH/FSH	24	2.1 ± 1.1 (0.3–4.0)	15	1.7 ± 0.8 (0.6–3.5)	NS
Oestradiol [pg/mL]	24	49.2 ± 43.4 (21.9–233.0)	15	47.6 ± 22.6 (15.0–84.4)	NS
SHBG [nmol/L]	21	63.3 ± 44.9 (21.4–218.0)	15	29.4 ± 11.2 (17.0–55.0)	< 0.001

HOMA — homeostatic model assessment; DHEA-S — dehydroepiandrosterone-sulfate; FAI — free androgen index; LH — luteinising hormone; FSH — follicle stimulating hormone; TSH — thyroid stimulating hormone; SHBG — sex hormone-binding globulin

Results

Baseline characteristics of lean (group 1) and obese (group 2) subjects are shown in Table I. In group 2, four patients (26.6%) were overweight and 11 were obese, of whom five (33.3%) were considered as morbidly obese. All of the obese subjects had increased fat mass of the trunk. Only one woman (in group 1) was hypertensive, with increased diastolic blood pressure. In 12 women (including five in group 1), hypercholesterolemia , was foundand also in 12 (including two in group 1) hypertriglycerydemia was found. Lean women had lower serum lipids, hsCRP levels and ALP activity than obese patients.

Table II presents hormonal results of our patients. Twenty one subjects (84.0%) in group 1 and 13 (86.6%) in group 2 were hyperandrogenic. Four, all in group 2 (26.6%), had elevated fasting serum insulin levels, and six (including one in group 1) were considered as insulin resistant. Lean patients had lower fasting insulin and leptin levels, HOMA index, and higher adiponectin levels than obese patients. There was no significant difference in serum fetuin-A levels between lean and obese subjects. We found significantly lower FAI and higher SHBG levels in lean compared to obese women.

We noted a strong correlation between BMI and serum leptin levels ($r = 0.88$; $p < 0.0001$; Fig. 1) and a nearly significant negative correlation between BMI and serum adiponectin levels ($r = –0.53$; $p = 0.11$) in all subjects. In both groups estimated separately, similar correlations were found.

Among lean patients (group 1), we found a correlation between serum fetuin-A levels (g/L) and ALT activity (IU/mL), ($r = 0.44$; $p < 0.05$; Fig. 2)

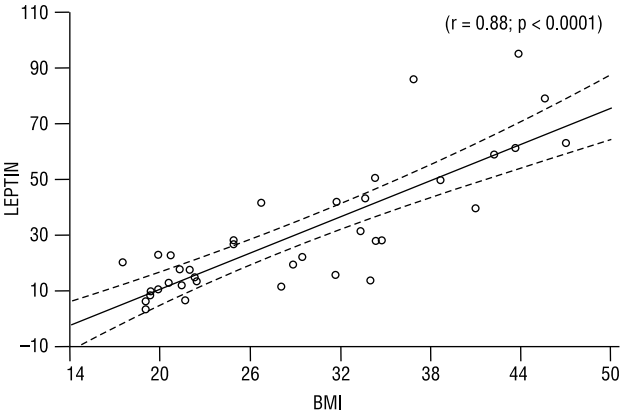

Figure 1. *Correlation between BMI (kg/m²) and serum leptin (μg/mL) levels in all studied women*

Rycina 1. *Korelacja między BMI (kg/m²) a stężeniem leptyny w surowicy (μg/ml) wśród wszystkich badanych kobiet*

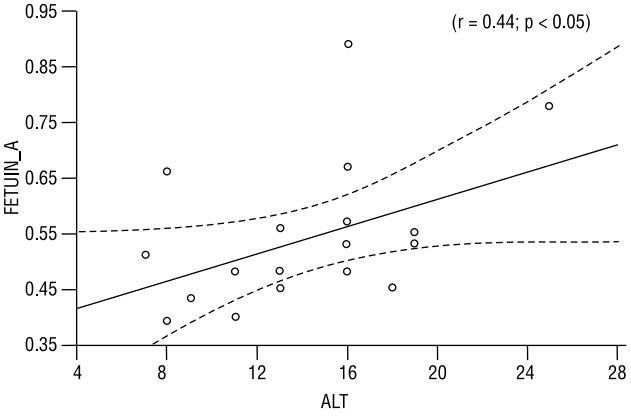

Figure 2. *Correlation between serum fetuin-A levels and ALT activity in lean women with polycystic ovary syndrome*

Rycina 2. *Korelacja między stężeniem fetuiny A i aktywnością AlAT w surowicy w grupie kobiet z prawidłowym BMI*

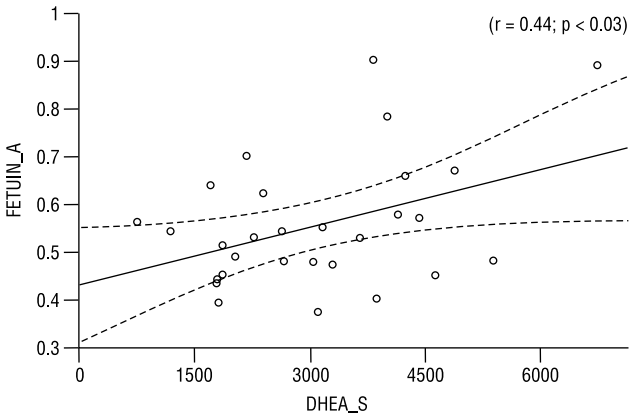

Figure 3. *Correlation between serum fetuin-A and DHEA-S levels in women with PCOS*

Rycina 3. *Korelacja między stężeniem fetuiny A i DHEA-S w surowicy wśród kobiet z zespołem policystycznych jajników*

In all studied women, serum fetuin A levels (g/L) correlated directly with DHEA-S levels (ng/mL), ($r = 0.44$; $p < 0.03$; Fig. 3)

Discussion

To the best of our knowledge, this is the first study to compare fetuin-A levels in lean and obese women with PCOS. We demonstrated that levels of AHSG are similar in both studied groups.

The reason we studied liver-derived fetuin-A in women with PCOS was the previous observation that this protein may play a significant role in mechanisms that regulate postprandial glucose disposal, insulin sensitivity, weight gain and fat accumulation [4–6]. Especially because, as in animal and human studies the inhibitory function of fetuin-A on insulin receptor tyrosine kinase in the muscle and in the liver has been proved [20, 21] AHSG may be considered as an important link between obesity and insulin resistance.

On the other hand, decreased insulin sensitivity and subsequent hyperinsulinaemia, in PCOS more severe than expected on the basis of body weight, represent crucial metabolic disturbances in the majority of obese as well as of lean women with PCOS [22, 23]. Moreover, it is postulated that obesity in women with PCOS is associated not only with more severe insulin resistance but also with hyperandrogenemia and fertility disorders [24]. Also investigations of the genetic aspects of polycystic ovary syndrome have pointed to the significance of metabolic disturbances. It is apparent that some specific insulin and its receptor gene alleles and genotypes may determine the predisposition to anovulatory PCOS and to the concomitant risk of diabetes development. Significant alterations have been found in the expression of genes responsible for androgen production and of oestrogen receptor in granulose and theca cells potentially related to abnormal follicular development [25].

Our finding, that fetuin-A levels in lean and obese women with polycystic ovary syndrome are not different, is rather unexpected. A few other human studies, that did not involve women with PCOS, found higher levels of AHSG in obese subjects with metabolic disturbances compared to lean individuals. In obese children, initially elevated fetuin-A levels decreased during exercise- and diet-induced weight loss [27]. In patients with morbid obesity, fetuin-A was markedly increased and significantly declined after weight loss resulting from bariatric surgery. This fall was related to changes in insulin resistance but not directly to BMI [27]. Our lean and obese patients did not differ in insulin resistance estimated by HOMA. Our results should be re-evaluated in future studies. In two recently published independent trials, there was divergent data on serum fetuin-A levels in women with PCOS. In the paper by Abali et al. [28], mean serum fetuin-A concentrations were considerably elevated compared to healthy controls, whereas in the study by Gulhan et al. [29], there was no difference between women with PCOS and healthy subjects with regard to fetuin-A levels. Probably, all these discrepancies may be related to differences in age, BMI, liver fatness, level of insulin resistance and other yet undefined metabolic factors.

In our lean patients, we found an association between serum fetuin-A levels and alanine aminotransferase activity. ALS is considered to be a weak surrogate marker of liver fatness, and in combination with ultrasound imaging enables the diagnosis of non-alcoholic fatty liver disease (NAFLD) [30]. We did not measure directly fat content in the liver in this study. However, our finding may be intelligible because NAFLD is known to be strongly associated with insulin resistance and is regarded as a hepatic manifestation of metabolic syndrome [31]. Similarly, one may consider polycystic ovary syndrome as the ovarian manifestation of metabolic syndrome. Our findings are in accordance with the observations of Stefan et al. [5] in healthy Caucasians, and may support the hypothesis that fat accumulation in the liver may result in an increased secretion of AHSG.

We noted a significant correlation between serum fetuin-A and DHEA-S levels in our subjects. DHEA-S, the main adrenal androgen, is the most abundant among circulating androgen hormones. On the other hand, in women with PCOS, obesity and subsequent hyperinsulinaemia are regarded as meaningful factors that contribute to androgen excess [32]. It could be that fetuin-A is a factor that promotes insulin resistance, and

in consequence hyperinsulinaemia may be associated with increased androgen production in women with PCOS, at least in adrenals. We could not demonstrate a similar correlation for testosterone and FAI. In the case of FAI, the impact of obesity on hepatic SHBG production and therefore on its serum levels should be taken into account additionally.

Several limitations should be considered when our results are interpreted. Firstly, it includes a relatively small number of studied patients, especially in the group of obese women. Secondly, we did not adjust for additional factors and biochemical variables, so we cannot be sure that any unmeasured covariates may have influenced our observations. Thirdly, our results are based on single measurements of fetuin-A. This might have introduced random measurement errors in determining biochemical variables. However, if anything, such a random error would bias results toward the null. As already discussed, the relationships between fetuin-A and ALS activity were surprisingly evident only in lean patients. Future prospective studies should evaluate whether these results could refer also to obese women with PCOS. Finally, our study subjects were mostly young women, and so our results may not be generalisable to older patients with PCOS.

In conclusion, we demonstrated that serum fetuin-A levels are similar in lean and obese women with PCOS. We found an association between fetuin-A levels and ALS activity in lean patients, and between fetuin-A levels and DHEA-S in all women. The role of fetuin-A in the mechanisms of insulin resistance and its potential impact on androgenic hormones production in women with PCOS need to be tested in further studies.

Acknowledgment

This study was supported by a grant from the Medical Centre of Postgraduate Education, Warsaw, Poland, N°: 501-1-08-11-13.

References

1. Nestler JE, Clore JN, Blackard WG. The central role of obesity (hyperinsulinaemia) in the pathogenesis of the polycystic ovary syndrome. Am J Obstet Gynecol 1989; 161: 1095–1097.
2. Carmina E. PCOS: metabolic impact and long-term management. Minerva Ginecol 2012; 64: 501–505.
3. Auberger P, Falquerho L, Contreres JO et al. Characterisation of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. Cell 1989; 58: 631–640.
4. Mori K, Emoto M, Yokohama H et al. Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. Diabetes Care 2006; 29: 468.
5. Stefan N, Hennige AM, Staiger H et al. Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care 2006; 29: 853–857.
6. Stefan N, Fritsche A, Weikert C et al. Plasma fetuin-A levels and the risk of type 2 diabetes. Diabetes 2008; 57: 2762–2767.
7. Mathews ST, Singh GP, Ranalletta M et al. Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene. Diabetes 2002; 51: 2450–2458.
8. Cayatte AJ, Kumbla L, Subbiah MT. Marked acceleration of exogenous fatty acid incorporation into cellular triglycerides by fetuin. J Biol Chem 1990; 265: 5883–5888.
9. Hennige AM, Staiger H, Wicke C et al. Fetuin-A induces cytokine expression and suppresses adiponectin production. PLoS ONE 2008; 3: e1765.
10. Ix JH, Wassel CL, Kanaya A et al. Fetuin-A and incident diabetes mellitus in older persons. JAMA 2008; 300: 182–188.
11. Ix JH, Wassel CL, Chertow GM et al. Fetuin-A and Change in Body Composition in Older Persons. J Clin Endocrinol Metab 2009; 94: 4492–4498.
12. Ix JH, Shlipak MG, Brandenburg VM et al. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. Circulation 2006; 113: 1760–1767.
13. Lim SS, Norman RJ, Davies MJ et al. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev 2013; 14: 95–109.
14. Kozakowski J, Zgliczyński W. Body composition, glucose metabolism markers and serum androgens — associations in woman with polycystic ovary syndrome. Endokrynol Pol 2013; 64: 94–100.
15. Balen AH, Conway GS, Kaltsas G et al. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod 1995; 10: 2107–2111.
16. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Ann Intern Med 1997; 126: 32–35.
17. Dahlgren E, Janson PO, Johansson S et al. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992; 71: 599–604.
18. Skałba P, Dąbkowska-Huć A. The metabolic aspects of polycystic ovarian syndrome. Endokrynol Pol 2005; 6: 960–963.
19. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004 Revised 2003 consensus on diagnostic criteria and long-term health risk related to polycystic ovary syndrome Fertil Steril 2004; 81: 19–25.
20. Srinivas PR, Goustin AS, Grunberger G. Baculoviral expression of a natural inhibitor of the human insulin receptor tyrosine kinase. Biochem Biophys Res Commun 1995; 208: 879–885.
21. Srinivas PR, Wagner AS, Reddy LV et al. Serum alpha 2-HS-glycoprotein is an inhibitor of the human insulin receptor at the tyrosine kinase level. Mol Endocrinol 1993; 7: 1445–1455.
22. Carmina E, Lobo RA. Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome. Fertil Steril 2004; 82: 661–665.
23. Olszanecka-Glinianowicz M, Banaś M, Zahorska-Markiewicz B et al. Insulin resistance and serum concentrations of ovarian and adrenal androgen in obese women without additional disease and with policystic ovary syndrome. Endokrynol Pol 2005; 6: 921–926.
24. Hamilton-Fairley D, Kiddy D, Watson H et al. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynaecol 1992; 99: 128–131.
25. Jakubowski L. Genetic aspects of Polycystic Ovary Syndrome. Endokrynol Pol 2005; 56: 285–293.
26. Reinehr T, Roth CL. Fetuin-A and its relation to metabolic syndrome and fatty liver disease in obese children before and after weight loss. J Clin Endocrinol Metab 2008; 93: 4479–4485.
27. Brix JM, Stingl H, Höller F et al. Elevated Fetuin-A Concentrations in Morbid Obesity Decrease after Dramatic Weight Loss. J Clin Endocrinol Metab 2010; 95: 4877–4881.
28. Abali R, Celik C, Tasdemir N et al. The serum protein 2-Heremans-Schmid glycoprotein/fetuin-A concentration and caroid intima-media thickness in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2013; 169: 45–49.
29. Gulhan I, Bozkaya G, Ozetkin D et al. Serum Fetuin-A levels in women with polycystic ovary syndrome. Arch Gynecol Obstet 2012; 286: 1473–1476.
30. Chalasani N, Younossi Z, Lavine JE et al. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012; 55: 2005–2018.
31. Baranova A, Tran TP, Birerdinc A et al. Systemic review: association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2011; 33: 801–814.
32. Singh KB, Mahajan DK, Wortsman J. Effect of obesity on the hormonal characteristics of the polycystic ovary syndrome. Reprod Med 1990; 39: 805–808.