Differences in the psychological and hormonal presentation of lean and obese patients with polycystic ovary syndrome

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Abstract

BACKGROUND: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders found in women of reproductive age. Differences in hormonal and metabolic profiles are observed in groups of patients with normal and elevated BMI. Cause of disturbances observed in the two groups of patients with PCOS is analyzed. The aim of the study is to assess whether psychological parameters of lean and obese patients with PCOS are comparably significantly different and whether there is a correlation between these characteristics and the concentration of various hormones.

PARTICIPANTS AND PROCEDURES: The study consisted of 20 patients with diagnosed polycystic ovary syndrome and 20 healthy women of similar age. Both groups were stratified according to BMI. Specific psychological parameters and hormones were estimated in all patients.

RESULTS: In our study, we found that patients with BMI <25 represented personality traits associated with lower resistance to stress. We also observed significantly higher ACTH levels in the same group as compared to patients with BMI >25. A correlation between plasma ghrelin and the severity of anxiety experienced by test subjects was also observed.

CONCLUSION: The type of personality and emotional disorders in lean PCOS patients may lead to the activation of the hypothalamic-pituitary-adrenal (HPA) axis and disturbences in hypothalamic-pituitary-ovary (HPO) axis. The results suggest participation of primary hypothalamic dysfunction in the pathogenesis of PCOS in patients with specific fenotype. Ghrelin is a hormone that may affect the symptoms of PCOS in lean patients. Psychological therapy should be considered as a permanent element in the therapeutic plan provided to PCOS patients.

ORIGINAL ARTICLE

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. Depending on the accepted diagnostic criteria and overall prevalence, it is estimated to be at 2–20% (Knochenhauer *et al.* 1998; Franks 1995; Solomon 1999; Asunción *et al.* 2000; Diamanti – Kandarakis*et al.* 1999, Azziz *et al.* 2004; March *et al.* 2009). Percentage of patients with this syndrome has increased significantly. Currently, diagnosis of PCOS is based on the criteria established at a conference in Rotterdam in May 2003 (ESHRE/ASRM Sponsored PCOS Consensus Workshop Group) published in Fertility and Sterility in 2004.

Women with PCOS are a very heterogeneous group. We can observe several phenotypes of this syndrome. Patients differ in terms of visible features on examination, as well as in laboratory studies. The most visible distinction is between lean and obese patients. It seems that the basis of the disturbances observed in these two groups of PCOS patients is different. It also seems that these differences relate to the psychological profile of these patients. Often anxiety and depressive disorders are described in PCOS patients, which previous literature propose to be attributed to personal psychological interpretation of their physically manifested symptoms of infertility, hirsutism and obesity.

Ghrelin is an endogenous receptor ligand (GHS-R) for the substance that stimulates the secretion of growth hormone (GHSs) (Kojima *et al.* 1999). Ghrelin is a peptide affecting the body's energy balance and additionally, the secretion of various hormones (Tschőp 2001). It also has the possibility of having effects on mood and behavior. Ghrelin has been proven to have an antidepressant effect on GHS-R antagonists. Additionally, it has been confirmed that ghrelin improves memory and spatial orientation. Based upon such findings, it is suspected that mood disorders and the regulation of the body's energy can be related to substances such as leptin and ghrelin (Lutter & Elmquist 2009). Ghrelin affects the hypothalamus-pituitary-adrenal axis, whose functioning is regulated by emotional, metabolic, as well as hormonal factors. Further studies have shown that ghrelin plays a significant role in the entire reproductive system (Giordano *et al.* 2009).

During our long-term observations of patients with PCOS, we noticed that lean patients with this syndrome usually present with some common features of behavior that are different from obese PCOS patients. In our earlier work, we found that in comparison to obese PCOS patients, lean PCOS patients scored lower in the scale of emotional intelligence. This would suggest that lean patients are less prepared and able to cope with situational stress than obese patients with the same syndrome. However, in contrast to other authors, in our work assessing the levels of ghrelin in PCOS patients, elevated levels of this peptide were found in patients with PCOS in comparison to the control group (Waśko *et al.* 2004). Previous literature reported ghrelin to be markedly lower in PCOS individuals than in healthy control groups. However, during our studies, we observed a marked elevation in ghrelin levels in our lean PCOS patient study group when compared to the BMI-matched controls. Such findings can be potentially explained by the fact that previous papers focused on the stereotypically presented obese PCOS patients, while we attempted to separate the two PCOS phenotypes in our study. Causes of higher ghrelin level concentrations in PCOS patients, as compared to BMI-matched counterparts, were not fully explained.

The aim of this study is to assess whether psychological parameters of lean and obese PCOS patients differ significantly and whether there is a correlation between these characteristics with the concentration levels of ghrelin and other hormones.

PARTICIPANTS AND PROCEDURES

The study was comprised of 20 patients with previously diagnosed polycystic ovarian syndrome and 20 healthy women. Both the study group and control group were matched according to age, BMI and education. All the studied women had at least a completed secondary education and were unmarried. All the women in the control group had regular menstrual cycles and did not show any features of an endocrine disorder. Any history of psychiatric disorders was also excluded. The participating women did not take any medications for at least 12 weeks prior to the conducted study and continued refraining from the use of any medications during the study's entirety. Both groups were stratified in accordance to BMI. The adopted limit for the groups was a BMI of 25. Each BMI group consisted of 10 women. The Rotterdam criteria were used for the diagnosis of PCOS. The patient's severity of hirsutism was rated using the Ferriman-Gallewey scale. In all the studied women, a psychometric evaluation was conducted to assess: psychological sex-role, temperament, level of situational anxiety and anxiety traits, as well as symptoms of depression. Standardized psychometric questionnaires were administered to PCOS patients at the endocrine clinic to assess temperament (EAS-D), level of anxiety state and anxiety trait (STAI), sex-role (IPP) and subjective level of depression (Beck's Scale).

The Charles D. Spielberger State-Trait Anxiety Inventory (STAI) for Adults (Wrześniewski & Sosnowski 1987) was modified to a Polish version (ISCL). This questionnaire comprises of forty questions and each with a range of four possible answers. It clearly differentiates the temporary condition of "state anxiety" (X1) from the more general and long-standing quality of "trait anxiety" (X2).

Polish adaptation of the Emotionality, Activity and Sociability Temperament Survey (EAS-D) for Adults (Oniszczenko *et al.* 1997) is a questionnaire assessing the three dimensions of personality: 1. Emotionality (E)

(N-emotionality-distress, S-emotionality-fear, Z-emotionality-anger), 2. Activity (A) and 3. Sociability (S). It comprises of twenty items ranging from 1 (non-characteristic or atypical) to 5 (very characteristic or typical). Activity was defined as the sheer expenditure of physical energy. Sociability was defined as preference for being with others and Emotionality was defined as distress differentiated into fear and anger.

The Polish IPP scale (Kuczyńska 1992) is based on the Bem Sex Role Inventory (BSRI) (Bem 1981). The thirty-five-item questionnaire measures sex-typed (masculinity, femininity), androgynous, cross-sexed or undifferentiated sex-role.

The modified version of Beck Depression Scale (BDI) measures the presence and subjective level of depression symptoms. It consists of twenty-one items to assess the intensity of physical and physiological depressive symptoms including: mood, sense of failure, pessimism, self-dissatisfaction, punishment, guilt, self-dislike, suicidal ideas, crying, self-accusation, irritability, body image, social withdrawal, work difficulties, insomnia, appetite, fatigue, weight loss, loss of libido and bodily preoccupation.

Blood samples were collected from PCOS patients in order to determine serum ghrelin, LH, FSH, free testosterone, androstenedione, ACTH, cortisol and DHEAs. Venous blood was collected at 7:00 am on an empty stomach. Aprotinin was added in samples evaluating ghrelin. Blood serum was obtained through centrifugation and kept frozen at –70 °C until the time of hormonal determinations. Ghrelin was measured by radioimmunoassay using a kit from Phoenix Pharmaceuticals (Cat. No. RK-031-30). The kit contained ^{125}I-labeled bioactive ghrelin as a tracer and rabbit polyclonal antibodies directed against the C-terminus of human ghrelin, which recognized both acylated and nonacylated forms of the peptide. Other hormonal assays were performed by electrochemiluminescence (ECL) using A Roche Diagnostics ECL.

Statistical calculations were performed using Statistica (version 6.0). Besides N, S and T, a two-tailed t-test was used for the comparison of all data between study groups. As the analyzed groups of patients were rather small, statistical analyses were performed using the Mann-Whitney test for N, S and T. Pearson's correlation was used to measure the strength of association between variables. In all the groups, Spearman rank correlation was used for N, S and X1.

RESULTS

The results of the PCOS patients' hormonal tests and assessment of hirsutism severity are shown in Table 1. Significantly higher concentration levels of ghrelin and ACTH were observed in the group of lean PCOS women. This group also demonstrated higher levels of androstenedione, but the difference was not deemed statistically significant. The PCOS patients with >25 BMI were observed to have a greater severity of hirsutism than other groups.

In comparison to PCOS patients with a BMI greater than 25 kg/m^2, PCOS patients with <25 BMI were less commonly found to have an androgynous(A) sex-role (IPP) (p=0.012). However, one patient in the group of lean PCOS patients has her psychological sex-role established as androgynous. It is worth noting that this patient had the highest BMI of the entire lean PCOS women study group. Additionally, it is worth to consider, that one patient in the group of lean PCOS women, whose psychological sex-role was established

Tab. 1. The results of the PCOS patients' hormonal tests and assessment of hirsutism severity.

	ALL PATIENTS		LEAN-PCOS		OBESE-PCOS		*p*-value
	MEAN	SD	MEAN	SD	MEAN	SD	
AGE	25.05	4.35	24	4.38	26	4.32	0.33
BMI	26.16	5.89	21.47	1.2	30	5.13	**0.0007**
TOTAL GHRELIN	249.28	142.76	337.34	139.74	168.04	109.35	**0.033**
LH	17.79	24.61	19.19	24.48	16.54	25.98	0.82
FSH	6.1	3.68	6.38	3.07	5.85	4.31	0.76
LH/FSH	2.36	1.56	2.4	1.8	2.33	1.4	0.93
free testosteron	2.07	0.77	2.2	0.8	1.89	0.75	0.38
DHEA-S	340.26	124.28	348.45	91.87	332.89	152.52	0.79
androstendion	3.79	1.38	4.38	1.4	3.26	1.2	0.07
PRL	523.95	423.21	447.1	236.47	396.61	156.61	0.6
F-G score	13.15	9.36	9.6	6.27	15.37	10.63	**0.04**
cortisol	514.66	194.87	533.24	190.26	497.94	207.65	0.7
ACTH	48.30	29.53	68.14	26.27	34.13	24	**0.04**

as androgynous, had the highest BMI of her whole group. Other measured psychological parameters amongst the two BMI-differentiated groups of PCOS patients were not significantly different.

Correlations between different parameters were studied in all groups of women. A correlation observed between total ghrelin levels and X2 (*anxiety-trait)* (p=0.034; r=0.515) in the entire group of patients. In the group of lean PCOS patients, a correlation was found between N (*emotionality-distress*) and BMI (p=0.026; r=0.726), as well as between T (*sociability*) and BMI (p=0.004; r=–0.843).

When comparing psychological parameters between lean and obese controls groups, obese controls scored significantly higher in depression (D) than the group of lean controls (11 vs. 5.27; p<0.001). We also found that the lean controls were more likely to have their sex-role established as androgynous (A) than the obese controls (6/10 vs. 4/10). Other determined psychological parameters did not statistically differ.

Psychological parameters were also compared between both subdivided BMI PCOS patient groups with their similarly divided control counterparts. PCOS patients were found to have a higher level of anxiety-trait (X2) in comparison to controls (48 vs. 40, p=0.01). Despite the lack of any statistical significance in difference (p=0.08), PCOS patients were found to have slightly higher levels of depression (D).

When comparing >25 BMI women, no differences were observed between PCOS patients and controls. Androgyny (A) was more frequently observed in lean controls than in lean PCOS patients (6/10 vs. 1/10, p<0.0).

DISCUSSION

There is an ongoing discussion in regards to the criteria for the diagnosis of PCOS. Since the introduction of the Rotterdam Criteria, a significant increase in diagnosis of PCOS has been observed (Franks 1995; Solomon 1999; Azziz *et al.* 2004; March *et al.* 2009). The Rotterdam Criteria leaves quite a large range of freedom, which include women with different profiles of hormones, metabolism, varying intensity of androgen effects, and varying visual profiles of ovaries. Our study consists of PCOS patients taken from two very divergent phenotypes: lean and obese. Lean patients resulted having statistically significant higher levels of ACTH and ghrelin. It was also noted, that these patients, additionally, had higher concentrations of androstenedione, testosterone, cortisol and DHEAs. Despite these findings, the differences were not statistically significant. However, the difference in the severity of hirsutism was significant. In obese patients, the F-G score was higher than in their lean counterparts.

Interesting results were obtained in the psychological analysis. Several previous psychological studies demonstrated generally higher levels of depression, psychological and psychosexual morbidity rates and an increased response to stress in women with PCOS (Coffey & Mason 2003). Based upon our observations and experience with this group of patients, we are inclined to suppose that many of these symptoms are a result of an innate, individual predispositions connected with personality traits. Experienced distress among PCOS females can be caused by a variety of factors including: changes in appearance, menstrual irregularities, infertility and adverse influences on the feminine body identity (Kerchner *et al.* 2009; Hollinrake *et al.* 2007; Mansson *et al.* 2008; Elsenbruch *et al.* 2006) but psychological predispositions and coping tools also seem to be a significant but underestimated factor.

There is no doubt that personal predispositions and situational experiences play an important role in genesis and symptoms of the disease. Every day stress is impossible to avoid, but is possible to copy. Coping is defined as a process through which individuals try to understand and deal with significant demands in their lives, which may greatly impact patients' perceptions about illness. Person using constructive coping, presents lower anxiety, less of depressive symptoms, better self-esteem and tend to create less of distress for themselves. Constructive style of coping means better physical, cognitive, emotional and social existence in spite of the disease. In opposite situation, when copying is destructive individual existence is disturbed and the illness can be real cost of that. Though the disease is an origin which may significantly complicate personal situation and activity, proper organization of the personality structures will results in better functioning of whole the organism.

The two of psychological components: emotional intelligence and androgyny considerably influence on various social interactions, coping with stressful situations and adjustment to illness. S. Bem in her gender type theory classified individuals as a particular gender-role orientation: typical (masculine, feminine) or crossed, androgynous, and undifferentiated. She claimed, that androgynous individuals as more mentally fit than either masculine or feminine people, while undifferentiated type showed lower levels of competency, and it was best to be androgynous (with complementary masculinity and feminism) (Kuczyńska 1992). According to her theory androgynous people are more flexible with diversity of behavior, exhibit higher levels of self-esteem and psychological well-being, stronger personality and better possibility for constructive reactions, they are also less submissive.

Among all of the examined PCOS patients in the study, not many were found to be androgynous. Most of patients in the study were sex-typed or undifferentiated, what means that they seem to exhibit worse abilities to solve different problems and cope with stressful demands. These decreased abilities were found more often in the group with lower BMI. The results of study group of PCOS females showed that

body mass appeared a significant dimension related to personal traits and abilities. Despite the absence of statistical significance between the different BMI study groups, results did indicate different tendencies. Next to the lack of androgyny the group with BMI below 25 showed tendencies of lower temperamental sociability, higher anxiety traits and distress. Biologically based personality origins connected with body mass are suggested through the inconsiderably enlarged quantity of anxiety traits observed in the <25 BMI group. All of estimated psychological parameters: the gender (IPP), temperament (EAS-D) and emotional characteristics (STAI) of the "leaner" group indicated tendency to decreased social abilities, less behavioral flexibility, less stress resistance and the avoidance of stress. This may result in problems with adaptation, social relations and communication. Ultimately, psychological barriers in medical therapy may be generated and complicate their coping with illness.

The exact causes of PCOS are still unknown. Considerations include: primary ovarian defects, hypothalamic and metabolic disturbances. In some PCOS patients, adrenal hyperandrogenism is also observed.

Both PCOS and hypothalamic menstrual disorders (HD) are diagnoses of exclusion. This diagnosis is made through the process of elimination because despite the ability to identify the probable cause, there is no way of checking or controlling hypothalamic function to confirm the diagnosis. In 30% of patients with HD, there were no abnormalities in the secretion of gonadotropins observed (Perkins *et al.* 2001). It seems that the borders between hypothalamic dysfunction and PCOS are undefined.

The 2008 work of Wang and Lobo described patients who were initially diagnosed with hypothalamic dysfunction, but when the hypothalamic function returned to normal, PCOS was diagnosed. The authors propose that some of the patients with (hyperandrogenism) HA have what is so called hyperandrogenic ovaries, whose activity is dormant during low production of gonadotropins. At the time of normal hypothalamic stimulation, there is an overproduction of androgens and the patient then meets the diagnostic criteria for PCOS.

Elevated levels of adrenal androgens are observed in 20–60% of patients with PCOS (Azziz *et al.* 2004; Kumar 2005). Opinions on the causes of this manifestation are opposing. Some researchers claim that the increase in adrenal steroidogenesis is responsible for the over-stimulation of the HPA axis and others suppose that the adrenal glands in these patients are more sensitive to the stimulant effect of ACTH. While other researchers think that a defect in the steroidogenic enzyme causes this condition.

In their work, Milutinović *et al.* (2011), failed to prove that the cause of excessive production of adrenal hormones in PCOS patients is due to the HPA axis sensitivity change or due to a change in the GR receptor. These authors also divided the patients into the two separate categories of lean and obese. The mean concentration of DHEAS was found to be higher in lean patients than in obese patients, therefore, the concentration of cortisol was slightly higher in lean women with PCOS. These results may seem surprising because hypercortisolemia is often observed in obese individuals. Therefore, there must be another cause for the excess stimulation of steroidogenesis in lean PCOS females. Possible that psychological features play an important role in pathogenesis.

In our study, we found that patients with <25 BMI present with personality traits associated with lower resistance to stress and decreased adaptability. In the same group, we observed a significantly higher level of ACTH than in patients with >25 BMI. These findings may suggest that emotional disorders in these patients are associated with stimulation of the HPA axis.

The axis of the hypothalamic-pituitary-adrenal system is what regulates and controls body functioning. The HPA axis connects the CNS with the endocrine system. This axis may be stimulated by stress, depression or physical activity. Stress often causes the activation of the HPA axis and suppression of the HPG axis.

Elevated levels of ACTH in our subjects may increase the production and secretion of not only cortisol, but also adrenal androgens. Stimulation of the HPA axis often leads to menstrual dysfunction. It may also cause a soft androgenization observed in these women.

Rouach *et al.* (2007) demonstrated that stress causes an increase in ghrelin and a proportional increase in cortisol levels. It has been shown that ghrelin has a stimulatory effect on ACTH secretion. This effect is probably exerted at the level of the hypothalamus through AVP, NPY and CRH (Korbonits *et al.* 1999). Perhaps ghrelin is an additional factor, which stimulates the HPA axis in lean PCOS patients.

In comparison to obese PCOS patients, it is not surprising that lean PCOS patients have higher levels of ghrelin. However, higher ghrelin levels observed in lean PCOS women compared with the healthy lean women control group remains unexplained. It was found that ghrelin levels are elevated in conditions of chronic stress. Due to the anxiolytic and antidepressant effects of ghrelin, it is proposed that this helps the body deal with stress and anxiety associated with it. Perhaps only caloric restriction and a negative energy balance exert this beneficial effect of ghrelin on the psyche. While assuming the "beneficial" effects of ghrelin on the psyche, we assume that higher ghrelin levels observed in lean PCOS patients, as compared to their BMI matched control group counterparts, may be due to a compensation mechanism. Theoretically, higher levels of ghrelin should improve the emotional state of these patients. Such a relationship will confirm a positive correlation between ghrelin and anxiety-trait (X2).

CONCLUSIONS

1. Psychological parameters and emotional disturbances observed among patients with diagnosed Policystic Ovarian Syndrome and low BMI may result from chronic stimulation of HPA axis and HPG axis disturbances.
2. It seems that there is a group of PCOS women, in whom the occurrence of specific symptoms is associated with a dysfunction of the hypothalamus.
3. The influence of ACTH, ghrelin and other neuropeptides in pulsative production of gonadotropins in this group of individuals needs further evaluation.
4. Consideration should be given to the addition of psychological therapy as a permanent element in conjunction with hormonal therapy in the treatment plan of PCOS patients with this phenotype.

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