Insulin resistance in women with hirsutism

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Submitted: 1 August 2010
Accepted: 20 October 2010

Arch Med Sci 2012; 8, 2: 342-346
DOI: 10.5114/aoms.2012.28563

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Abstract

Introduction: There are still not enough data showing whether patients with idiopathic hirsutism (IH) also have insulin resistance. The association between polycystic ovary syndrome (PCOS) and insulin resistance is well documented in the literature, but the Rotterdam Consensus has concluded that principally obese women with PCOS should be screened for the metabolic syndrome. We intended to investigate the presence/absence of insulin resistance in non-obese women with hirsutism.
Material and methods: Twenty-eight women with PCOS (14 non-obese and 14 obese), 12 non-obese with IH, and 16 non-obese healthy women were included in the study. The presence of insulin resistance was investigated by using basal insulin levels and the homeostasis model assessment (HOMA) score in the study group.
Results: Patients with obese and nonobese PCOS had significantly ($p < 0.05$) higher basal insulin levels and HOMA scores than IH and control subjects. Insulin levels and HOMA scores did not differ between obese and non-obese PCOS patients. Patients with IH did not show any difference from the control group.
Conclusions: Insulin resistance exists in non-obese women with PCOS as well as obese women with PCOS. The PCOS is associated with insulin resistance independent of obesity. Insulin resistance should be assessed in all hirsute women with PCOS regardless of their body mass index. More studies in larger numbers of patients should be performed to investigate the role of insulin resistance in women with IH.

Key words: insulin resistance, idiopathic hirsutism, non-obese women.

Introduction

Hirsutism is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions. It may result from various causes including polycystic ovary syndrome, non-classic adrenal hyperplasia, adrenal or ovarian tumors, or it may be idiopathic. Idiopathic hirsutism (IH) is the second most common cause of hirsutism, after polycystic ovary syndrome [1]. Idiopathic hirsutism is defined as hirsutism associated with normal ovulatory function and normal circulating serum androgen concentrations [2]. In these patients mild forms of ovarian and adrenal functional hyperandrogenism may be present [3]. Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation, obesity and hyperandrogenism. The Rotterdam Consensus Conference [4] proposed that the syndrome can be diagnosed after the exclusion of other disorders (non-classical adrenal hyperplasia, Cushing's syndrome, hyperprolactinaemia, hypothyroidism,

virilizing adrenal or ovarian neoplasm), and the determination that at least two of the following are present: oligoovulation or anovulation, elevated levels of circulating androgens and/or clinical hyperandrogenism, and polycystic ovaries as defined by ultrasonography. Moreover, the Rotterdam Consensus has concluded that principally obese women with PCOS should be evaluated for the metabolic syndrome. It is well known that hyperandrogenism and insulin resistance are now closely associated. However, there are not enough data showing whether patients with IH also have insulin resistance.

Our aim was to investigate the presence/absence of insulin resistance and hyperinsulinaemia in especially non-obese women presenting with hirsutism.

Material and methods

Four groups of subjects were recruited: 14 obese (body mass index [BMI] > 27 kg/m^2) women with PCOS, 14 non-obese (BMI < 25 kg/m^2) women with PCOS, 12 non-obese women with IH, and 16 non-obese controls. The study group comprised patients who attended the dermatology outpatient clinic. All patients were consulted by the Department of Endocrinology. The control subjects were matched for age and weight to the women with PCOS and IH.

Obesity was defined as BMI > 27 kg/m^2. The diagnosis of PCOS was performed according to the Rotterdam 2003 criteria [4]. Rotterdam diagnostic criteria are shown in Table I. Patients with PCOS fulfilled all three Rotterdam criteria. The group with PCOS had oligomenorrhoea, polycystic ovarian morphology on ultrasonography and hyperandrogenemia estimated by laboratory measurements. Hyperandrogenemia was defined as a serum free testosterone level greater than 3.9 pg/ml (normal: 0.04-3.9 pg/ml). Oligomenorrhoea was defined as bleeding at intervals of greater than 35 days. Amenorrhea was defined as absence of menstruation for 6 months or more. Transabdominal or transvaginal ovary ultrasound was performed for all patients in the early follicular phase (days 3-9 of the menstrual cycle). Ovaries were classified as polycystic based on the presence of 12 or more follicles in each ovary measuring 2-8 mm in diameter, and/or increased ovarian volume (> 10 ml) [4]. Thyroid dysfunction, hyperprolactinaemia, non-classic congenital adrenal hyperplasia, and adrenal/ovarian tumors were excluded by appropriate tests and ultrasonography of the ovaries and the adrenal glands. In the confirmed PCOS group, any patient with a 17α-hydroxyprogesterone level of > 2 ng/ml (normal: 0.2-2.6 ng/ml) was subjected to an adrenocorticotropic hormone stimulation test (250 μg IV, Synachten; Ciba-Geigy, Basel, Switzerland) to rule out non-classic congenital adrenal hyperplasia. Hirsutism was defined as Ferriman-Gallwey (FG) score > 8 [5]. The diagnosis of IH was based on the presence of hirsutism, regular ovulatory menstrual cycles, and a normal serum androgen profile including free testosterone (normal: 0.04-3.9 pg/ml) and dehydroepiandrosterone sulfate (normal: 35-430 μg/dl). All controls had a regular cycle and no clinical or laboratory features of PCOS. There was no history of diabetes mellitus in the study group. All participants had not used any medication or oral contraceptives for the last three months.

In the study group, blood sampling was done in the early follicular phase of spontaneous or induced (by medroxyprogesterone acetate 10 mg/day for 7 days) menstrual cycles. After an overnight fast, blood samples were collected around 8-10 a.m. to measure serum levels of free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL), 17α-hydroxyprogesterone (17-OHP), fasting plasma glucose and insulin. Serum levels of DHEAS and PRL were measured by electrochemiluminescence immunoassays (Elecsys, Roche Diagnostic Corporation, Germany). Serum levels of FT and 17-OHP were measured by a radioimmunoassay kit (DPC, CA, USA). Plasma glucose levels were determined by the glucose oxidase technique with a glucose analyser (Dimension, Dade Behring, Germany). Plasma insulin concentrations were measured by an insulin radioimmunoassay kit (DPC, CA, USA); normal range 0-30 μIU/ml; inter-assay CV < 5%; intra-assay CV < 8.5%. Insulin resistance was calculated with homeostasis model assessment of insulin resistance (HOMA-IR), using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose mmol/l)/22.5 [6].

Statistical analysis

Data analysis was performed using the SPSS 11 software (Chicago, IL, USA). The distribution of variables was tested for normality. The results are report-

Table I. 2003 Consensus Conference diagnostic criteria

1. Oligo- or anovulation
2. Clinical and/or biochemical hyperandrogenism findings
3. With polycystic ovarian appearance with exclusion of other causes
The presence of at least two of three diagnostic criteria is essential

ed as means ± SD, ranges (min-max), median values and interquartile range (IQR). The results of women with PCOS, obese and non-obese, were compared using the Mann-Whitney *U* test. As continuous variables were without normal distribution, we used non-parametric tests. The comparisons of the non-obese groups were made by the Kruskal-Wallis test. Value of $p < 0.05$ was regarded as statistically significant.

Results

Non-obese patients (PCOS, IH) and non-obese control subjects did not differ in mean age (22.6 ±4.1, 26.2 ±7.7, and 28.0 ±6.5 years, respectively $p > 0.05$; range: 18-30 for non-obese PCOS, 18-40 for non-obese IH and 18-39 for control subjects) and BMI (22.9 ±2.1, 22.6 ±2.7, and 21.6 ±2.3 kg/m^2, respectively $p > 0.05$) values. The Ferriman-Gallwey score was significantly higher in both women with PCOS and women with IH compared with controls (16.7 ±10.2, 11.4 ±2.7, 4.3 ±1.2, respectively $p < 0.05$).

Fasting glucose levels were similar in all groups and there were no statistically significant differences. However, patients with non-obese PCOS had significantly higher basal insulin levels and HOMA scores than patients with IH and control subjects ($p < 0.05$). Insulin levels and HOMA scores in patients with IH did not show any differences from the control subjects ($p > 0.05$). Age, BMI, fasting glucose, insulin, and HOMA values of the nonobese study group are shown in Table II. The women with non-obese PCOS had higher levels of insulin as well as women with obese PCOS and HOMA values were similar in both groups ($p > 0.05$). Age, BMI, fasting glucose, insulin, and HOMA values of groups of obese and non-obese with PCOS are shown in Table III.

Discussion

Polycystic ovary syndrome and IH account for most cases of hirsutism [1]. Not all hirsute patients have evidence of detectable androgen excess or endocrine imbalance, as in women with IH. The association of carbohydrate metabolism abnormalities with androgen excess disorders, particularly PCOS, is a well-defined entity. Recognition of the relationship between PCOS and insulin excess dates to 1980 [7, 8]. Insulin resistance and hyperinsulinism are now recognized as important features of PCOS, stimulating ovarian androgen secretion and suppressing sex hormone-binding globulin production [8, 9]. Insulin resistance and hyperinsulinaemia contribute to ovarian and adrenal cytochrome $P450_c17_\alpha$ activity in women with PCOS. Dysregulation of cytochrome $P450_c17_\alpha$ enzyme causes the exaggerated secretion of adrenal and ovarian androgens in these women [9, 10].

Obesity is encountered in 30-70% of PCOS-affected women, and its presence significantly modifies both clinical and laboratory expression of the syndrome. Obesity increases the risk of co-morbidities associated with PCOS, such as impaired glucose tolerance and type 2 diabetes mellitus, hyperlipidaemia and arterial hypertension [11]. Weight loss is the first choice recommendation for the

Table II. General features of the non-obese study group

	Age [years]	BMI [kg/m^2]	Insulin (0-30) [µU/ml]	Glucose (70-110) [g/dl]	HOMA
Non-obese PCOS (n = 14)					
Mean ± SD	22.64 ±4.16	22.96 ±2.14	20.79 ±20.57	88.57 ±7.86	4.49 ±4.17
Median (IQR)	23 (3.63)	22.9 (1.78)	12.05 (8.94)	86.5 (6.88)	2.76 (2.22)
Min-max	18-30	20.0-26.66	4.0-77.8	75-99	0.85-14.41
Non-obese IH (n = 12)					
Mean ± SD	26.25 ±7.70	22.64 ±2.73	9.27 ±5.17	85.17 ±9.13	1.96 ±1.19
Median (IQR)	25.0 (7.25)	22.78 (2.66)	8.2 (5.1)	85.5 (3.75)	1.8 (1.01)
Min-max	18-40	17.91-26.42	3.0-18.4	61-100	0.61-4.54
Non-obese control (n = 16)					
Mean ± SD	28.0 ±6.51	21.60 ±2.38	8.78 ±2.13	81.63 ±10.12	1.77 ±0.49
Median (IQR)	29.0 (4.75)	21.89 (1.75)	9.1 (1.93)	85.0 (9.0)	1.79 (0.40)
Min-max	18-39	17.26-24.97	5.4-12.0	62-94	0.92-2.56
Kruskal-Wallis test					
χ^2	5.074	2.035	6.034	2.700	7.853
p	0.079	0.361	0.049*	0.259	0.020*

*$p < 0.05$

Table III. General features of obese and non-obese groups with PCOS

	Age [years]	BMI [kg/m²]	Insulin (0-30) [µU/ml]	Glucose (70-110) [g/dl]	HOMA
Obese PCOS (*n* = 14)					
Mean ± SD	24.36 ±5.99	30.86 ±2.3	20.72 ±1.55	90.29 ±8.19	4.71 ±3.99
Median (IQR)	23 (4.63)	30.11 (1.75)	17.2 (5.5)	90.5 (5.63)	3.68 (1.44)
Min-max	18-40	28.80-36.39	7.3-69	77-103	1.62-17.55
Non-obese PCOS (*n* = 14)					
Mean ± SD	22.64 ±4.16	22.96 ±2.14	20.79 ±20.57	88.57 ±7.86	4.49 ±4.17
Median (IQR)	23 (3.63)	22.9 (1.78)	12.05 (8.94)	86.5 (6.88)	2.76 (2.22)
Min-max	18-30	20-26.66	4-7.8	75-99	0.85-14.41
Mann-Whitney *U* test					
Z	0.487	4.521	0.851	0.621	0.965
p	0.626	0.0001*	0.395	0.534	0.335

**p < 0.001*

treatment of clinical manifestations of PCOS, such as menstrual cycle irregularities, infertility or hirsutism [11, 12].

Ehrmann *et al*. [13] showed that women with PCOS have a substantially higher impaired glucose tolerance and diabetes mellitus than age- and body weight-matched healthy women. The Rotterdam Consensus has concluded that principally obese women with PCOS should be evaluated for the metabolic syndrome. Obesity itself is usually accompanied by insulin resistance. Therefore, we intended to investigate the presence/absence of insulin resistance in women with especially non-obese PCOS and non-obese IH. In the present study, significantly higher insulin levels and an insulin-resistant state were found in obese and non-obese women with PCOS. Studies on the relationship between obesity and hyperinsulinism in PCOS have yielded conflicting results. Chang *et al*. [14] and Dunaif *et al*. [15, 16] have demonstrated a degree of decreased insulin sensitivity in both obese and non-obese women by different methods. But others have not been able to find any degree of insulin resistance in non-obese women with PCOS [17-19]. In a recent study, it was demonstrated that non-obese women with PCOS have insulin resistance [20]. In our study, non-obese women with PCOS had significantly higher basal insulin levels and HOMA scores than non-obese women with IH and controls. However, there was no statistically significant difference with regard to insulin levels and HOMA scores between obese and non-obese women. On the other hand, we did not find any differences between obese women and non-obese women with respect to insulin levels and HOMA scores. Insulin levels were significantly higher in non-obese PCOS. Our findings showed that insulin resistance develops independently from obesity in all hirsute women with PCOS. More recently, some studies have suggested that there may be a link between insulin resistance and hirsutism rather than body weight in women with PCOS [21, 22].

Insulin also seems to be one of the factors that interact with androgen to regulate pilosebaceous unit development [8]. The effect of insulin and the IGF system have been investigated by an *in vitro* study [23]. Some authors have shown that insulin/IGF plays a role in stimulating hair follicle growth acting together with androgens [24]. The pathophysiology of IH is presumed to involve a primary increase in skin 5α-reductase activity and possibly an alteration in androgen receptor function [2]. In these patients there may be present mild forms of ovarian and adrenal functional hyperandrogenism [3]. In the light of this information, we investigated whether this peripheral increased androgen activity is associated with insulin metabolism. In contrast, there are not enough data showing whether patients with IH also have insulin resistance. Paoletti *et al*. [25] suggested that peripheral activity of androgens is related to hyperinsulinaemia and that anti-androgen treatment improves hyperinsulinaemia. Unlühizarci *et al*. [26] found a higher prevalence (18.7%) of impaired glucose tolerance among women with IH, and these authors also suggested that IH is associated with insulin resistance. Recently, insulin resistance was shown in obese patients with IH in another study [27]. In our study, the insulin levels and insulin-resistant state of women with non-obese IH and the non-obese control group did not show any differences. This might have been due to the small number of women with IH.

In conclusion, insulin resistance should be assessed in all hirsute women with PCOS regard-

less of their body mass index. More studies in larger numbers of patients should be performed to investigate the role of insulin resistance in women with IH.

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