Clinical and Biochemical Characterization of Women with Polycystic Ovary Syndrome in North Rhine-Westphalia

S. Hahn[1]
S. Tan[1]
S. Elsenbruch[2]
B. Quadbeck[1]
B. L. Herrmann[1]
K. Mann[1]
O. E. Janssen[1]

Abstract

Polycystic ovary syndrome (PCOS), defined as the combination of oligoanovulation and hyperandrogenism, affects more than 5% of women of reproductive age. Insulin resistance and hyperinsulinemia appear to play an important role in its pathogenesis. Here, we will present a characterization of a PCOS cohort from North Rhine-Westphalia in Germany. Clinical features, family history as well as endocrine and metabolic parameters were prospectively recorded from 200 successive patients. All patients were evaluated for insulin resistance and β-cell-function by oral glucose tolerance test. Patient data were compared with those of 98 age-matched control women. PCOS patients showed significantly higher BMI, body fat mass and androgen levels as well as impaired glucose and insulin metabolism. A positive family history of PCOS and diabetes was more frequent in PCOS patients. Insulin resistance (71%) was the most common metabolic abnormality in PCOS patients followed by obesity (52%) and dyslipidemia (46.3%), with an incidence of 31.5% for the metabolic syndrome. C-reactive protein and other cardiovascular risk factors were frequently elevated even in young PCOS patients. While the clinical characteristics and endocrine parameters of this German PCOS cohort were heterogeneous, they were comparable to those from other Caucasian populations.

Key words
PCOS · Infertility · Hirsutism · Obesity · Hyperandrogenism · Ethnic diversity

Introduction

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders, affecting more than 5% of women of reproductive age [1–3]. A National Institutes of Health (NIH) conference in 1990 has defined PCOS as the presence of chronic anovulation in combination with clinical and/or biochemical signs of hyperandrogenism and the exclusion of pituitary, adrenal or ovarian diseases [4,5]. By this definition, the typical clinical appearances (hirsutism, acne, alopecia, obesity) and biochemical features are highly variable in affected women. The originally eponymous polycystic ovaries (PCO) [6] are not required for the NIH definition of PCOS and are found only in 70% of affected women. PCO by itself is not consistently defined [7,8] and, at least in clinical practice, may suffer from a high variation among observers and within the same observer's record [9]. The 2003 revision of the PCOS definition from the consensus meeting of the American Society for Reproductive Medicine (ASRM) and the European Society for Human Reproduction (ESHRE) in Rotterdam as two out of three of oligoovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism and PCO further increases heterogeneity and expands the number of affected women [5,8].

An association of PCOS with peripheral insulin resistance and alterations in β-cell function as the cause of its predisposition to

Affiliation
[1] Div. of Endocrinology, Dept. of Medicine, University of Duisburg and Essen, Essen, Germany
[2] Dept. of Medical Psychology, University of Duisburg-Essen, Essen, Germany

Correspondence
O. E. Janssen, M.D. · Div. of Endocrinology, Dept. of Medicine, University of Duisburg-Essen · Hufelandstraße 55 · 45122 Essen · Germany · Phone: +49(201)7232854 · Fax: +49(201)7235976 · E-Mail: onno.janssen@uni-essen.de

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develop a metabolic syndrome (type 2 diabetes mellitus, hypertension, lipid disorders, and obesity) has been established [10]. Most relevant risk factors of cardiovascular disease are elevated in PCOS [11,12], possibly putting the patients at an increased risk to suffer from coronary artery disease, myocardial infarction, stroke and peripheral arterial occlusion in later years. Due to the lack of prospective studies, whether PCOS patients only have an increased incidence of risk factors or also have an increased rate of cardiovascular events remains unclear [13,14]. However, there is clear evidence that insulin resistance and hyperinsulinemia aggravate ovarian androgen overproduction and enhance skin manifestations.

An increased prevalence of PCOS has been described in Hispanic Caribbeans [15], suggesting a predisposition for PCOS in this population. A case control cross sectional study of South Asian and Caucasian PCOS women [16] revealed ethnic differences, presenting more severe clinical manifestations (hirsutism, acne) and a higher insulin resistance in young Asian women, supporting the hypothesis of ethnic variations in clinical and biochemical features of PCOS. A population of Indian women with PCOS also showed a higher insulin response to a glucose load than age-matched Caucasian PCOS patients [17]. Significant differences related to ethnicity were also found in Hispanic Caribbean and non-Hispanic white PCOS women [18]. Hispanic women showed increased insulin resistance and reduced metabolic insulin clearance rates compared to non-Hispanics in euglycemic clamp tests. Mexican American women were also shown to be more insulin resistant than women of northern European ethnic background [19]. Another study comparing Maori, Pacific Island and Europeans found that European PCOS women were less obese, less insulin-resistant and less prone to present with lipid abnormalities than the two other ethnic groups [20]. In addition, Pacific Island women only had little or no acne. The determination of clinical features, metabolic and endocrine abnormalities in different ethnic cohorts is thought to allow a better correlation of PCOS phenotype and genotype. To this end we designed an observational study to characterize a large PCOS sample of North Rhine-Westphalia in Germany.

Material and Methods

Study population

PCOS patients (n = 200) were recruited from the outpatient clinics of the Division of Endocrinology, Department of Medicine and the Department of Gynecology at the University of Essen. Some patients were also attracted by the clinic's PCOS homepage (www.pco-syndrom.de). Based on the criteria derived from the 1990 NIH conference [4], PCOS was diagnosed where either oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than two menstrual cycles in the past 6 months) and either clinical signs of hyperandrogenism (hirsutism with a Ferriman/Gallwey score of more than 7 [21] or obvious acne or alopecia and/or an elevated total testosterone (normal range < 2.0 nmol/l)) were found. Other pituitary, adrenal or ovarian diseases were excluded by history and by documentation of normal values for prolactin, gonadotropins, TSH, free thyroxin, IGF-1, cortisol (basal and after 1 mg dexamethasone suppression test), 17-OH-pregnenolone and 11-desoxycorticosterone. Basal and ACTH-stimulated 17-OH-progesterone was either normal or, when elevated, mutations of 21-hydroxylase were excluded by genetic testing in all PCOS patients. Age-matched healthy controls (n = 98) were recruited from a mandatory screening program for employees instituted at the University of Essen. Control women were required to have a normal menstrual cycle (shorter than 35 days), testosterone lower than 2.0 nmol/l and no hirsutism, acne or alopecia, thus all NIH-criteria of PCOS were excluded. All PCOS and control women were Caucasians and of German descent.

Data collection

In PCOS subjects clinical parameters were verified by physical examination, including the degree of hirsutism and the presence of acne, alopecia, acanthosis nigricans and the measurement of waist circumference. Sitting blood pressure was measured after a 15-minute rest from the right arm using a standard sphygmomanometer, while the appearance of the first sound (Korotkoff sound, phase I) was used to define systolic blood pressure and the disappearance of sound (phase V)-defined diastolic blood pressure. Body fat was measured using the bioimpedance method using the Body FAT Watcher (NAIS Wellnesslife GmbH, Düsseldorf, Germany), and body mass index (BMI) was calculated as weight/(height)^2 (kg/m^2). Parameters of insulin resistance and beta-cell function were evaluated using a three-hour oral glucose tolerance test (OGTT). After an overnight fast of twelve hours, patients ingested 75 g glucose and had their glucose and insulin levels determined at baseline and at 30, 60, 90, 120 and 180 min. Insulin resistance and β-cell function were defined by the HOMA-model [22], hyperinsulinemia by calculating the area under the insulin response curve (AUC-insulin) and insulin secretion by the 30 min increment in insulin concentration over the 30 min increment in glucose concentration (dI/dG) [23]. In addition, whole-body insulin sensitivity (WBIS or Matsuda index) [24], which combines hepatic and peripheral insulin sensitivity, was measured by the formula: 10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin during OGTT (times 0, 30, 60, 90, 120 min)]. According to the third report of the National Cholesterol Education Program (NCEP) on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III, ATP III) [25], a women had the metabolic syndrome if she had three or more of the following criteria: waist circumference above 88 cm, triglycerides at least 150 mg/dl, HDL cholesterol less than 50 mg/dl, blood pressure at least 130/85 mm Hg, fasting glucose at least 110 mg/dl. Impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2 DM) were defined by the classification from the German Diabetes Association, which is identical to that of the American Diabetes Association [26]. Menstrual disturbances, family history of T2 DM, PCOS in female and premature balding in male relatives, age at menarche, unfulfilled wish to conceive and number of children were evaluated in each patient by a personal interview.

Biochemical assays

Automated chemiluminescence immunoassay systems were used for the determination of LH, FSH, testosterone, estradiol, cortisol, cholesterol (CHOL), LDL-cholesterol (LDL), HDL-cholesterol (HDL), triglycerides (TGL), C-reactive protein (CRP) (ADVIA Centaur, Bayer Vital, Fernwald, Germany), dehydroepiandrosterone sulfate (DHEAS), androstendione, insulin and SHBG (IMMULITE 2000, DPC Biermann, Bad Nauheim, Germany) and IGF-1

Tab. **2** Parameters of insulin resistance and secretion in PCOS patients according to their glucose metabolism: NGT (n = 174) *vs.* IGT (n = 16) *vs.* T2 DM (n = 7)

Variable	*NGT*	*IGT*	*T2 DM*
BMI (kg/m²)	29.9 ± 8.6	34.6 ± 10.4	36.3 ± 7.1
Fasting insulin (pmol/l)	86.2 ± 75.9	135.3 ± 101.4	181.8 ± 166.5
HOMA-IR (mU.mM/l)	3.7 ± 3.3	5.7 ± 4.6	9.1 ± 3.4
WBIS (Matsuda index)	5.01 ± 4.24	2.43 ± 2.26	1.14 ± 0.42
AUC-insulin (uU/ml/h)	291.0 ± 221.5	591.0 ± 670.9	436.0 ± 348.6
dI/dG (uU.dl/ml/mg)	271.0 ± 251.4	193.0 ± 176.8	84.0 ± 94.5
Fasting glucose (mg/dl)	88.4 ± 9.5	94.9 ± 16.3	110.7 ± 22.0

Values are mean ± SD.

Tab. **3** Prevalence of pathological findings of endocrine parameters and family history of PCOS patients

Variable	*Number (of total)*	*%*
Amenorrhea	54 (200)	27.0
Oligomenorrhea	146 (200)	73.0
Menarche ≤ 11 years	25 (200)	12.5
Acne	70 (200)	35.0
Alopecia	62 (200)	31.0
Hirsutism	129 (200)	64.5
Hyperandrogenemia (testosterone)	162 (200)	81.0
Unfulfilled wish to conceive	60 (200)	30.0
PCOS women with children	15 (200)	7.5
Mother with PCOS	15 (109)	13.8
Sister with PCOS	20 (109)	18.3
First degree male relative with premature balding	15 (109)	12.8

Values are number of total or percent.

Endocrine parameters and family history of PCOS

The endocrine characteristics of PCOS subjects are summarized in Table **3**. Most of the patients suffered from oligomenorrhea rather than amenorrhea. The mean age at menarche was 12.9 ± 1.7 years. In twenty-five women (12.5%), menarche commenced before the age of eleven. Hirsutism was diagnosed in one hundred and twenty-nine patients with a mean hirsutism score of 13.1 ± 5.3, while the mean score of all PCOS patients was 9.4 ± 6.4. Elevated testosterone-levels were found in one hundred and sixty-two patients with a mean value of 3.0 ± 0.8 nmol/l. Only a hundred and nine PCOS women knew whether their mothers or sisters were also affected by PCOS and whether their fathers or brothers were affected by premature balding.

Adrenal hyperandrogenism

Compared to controls, PCOS women showed significantly elevated DHEAS levels (Table **1**). Compared to the normal range (1.1 – 3.6 µg/l), the PCOS cohort had elevated mean androstendione levels (4.0 ± 1.7 µg/l). In 38% of PCOS patients elevated DHEA levels were detected, while the mean DHEA level of 4.6 ± 2.9 µg/l of our study population remained within the normal range (0.55 – 5.0 µg/l).

Parameters of inflammation

High sensitive C-reactive protein (HS-CRP) was elevated in 46.4% of PCOS women with a mean concentration of 0.6 ± 0.6 mg/dl (normal range is less than 0.2 mg/dl). Fibrinogen levels were available in a subgroup of fifty-eight from two hundred PCOS women with a mean level of 339.2 ± 88.9 mg/dl (normal range, 180 – 350 mg/dl). Elevated fibrinogen levels more than 350 mg/dl were found in twenty-three of fifty-eight patients (39.6%).

Discussion

This study was designed to characterize a PCOS cohort from North Rhine-Westphalia and to compare its phenotype, likely to represent German PCOS women, with recently published data from other ethnic cohorts. A word of caution is needed for the comparison presented, as the cohorts from other studies varied according to their definition of PCOS and IR, the study population and the classification of hyperandrogenemia.

The age at menarche in the German PCOS group was similar to data from a South Asian (12.9 ± 0.21 years) and a Caucasian group (12.8 ± 0.29 years) published in 2002 [16]. Twelve and a half percent of German PCOS women were younger than twelve at menarche compared to 15.5% of PCOS women from the Netherlands [28]. The difference is most likely due to different diagnostic criteria of PCOS in the two cohorts. The majority of PCOS women in this study presented with oligomenorrhea, while amenorrhea (up to 54%) was more frequent in studies from the US [29]. No data are available from other European cohorts.

Most of the dermatological features of German PCOS women were similar to those of recent published data. Of the PCOS women participating in this study, 35% suffered from acne and 64.5% from hirsutism. Other studies had found acne in about 30% and hirsutism in 60 to 70% of PCOS women [30]. The hirsutism score was quite variable between different cohorts, from 7.5 in Caucasians [16], 8 in Finland [31], 9.4 in this German PCOS group, 12 in Turkey [32], 17.7 in the UK [33] to 18 in South Asians [16]. The very high hirsutism score found in the UK-cohort was probably influenced by a large proportion of South Asian immigrants studied. The differences in the incidence of alopecia (31% of German PCOS patients *vs.* 8% in other study-groups) were due to our use of patient perception rather than an objective measurement scale such as the Ludwig classification [34]. No significant differences were found in the incidence of acanthosis nigricans in this study compared to others (3.5% *vs.* 1 – 2.5%) [30].

Ovarian steroidogenesis of German PCOS women was comparable to those of other cohorts. Testosterone levels were 2.7 ± 1.0 nmol/l in our study-group, similar to cohorts from South Asia at 2.69 ± 0.11 nmol/l, Caucasians at 2.64 ± 0.13 nmol/l [16], and Turks at 2.76 nmol/l [32] and Finns at 2.7 nmol/l [31]. In German patients, the LH/FSH ratio was elevated with 2.5 ± 1.8. An increased LH/FSH ratio was also evident in South Asians (2.6 ± 0.4) and in another Caucasian group (2.59 ± 0.3) [16]. Elevated adrenal androgens have been detected in 20 to 30% of PCOS women [35]. These androgens, primarily DHEAS, are thought to contribute to the development of the PCOS phenotype, especially hirsut-

(Nichols Advantage, Nichols Institute Diagnostics, Bad Vilbel, Germany). Blood glucose was measured by an automated hexokinase method on a Dimension RXL, fibrinogen was determined with the Multifibren-U test on a BCS coagulation analyzer, high-sensitivity CRP (HS-CRP) was determined by particle enhanced immunonephelometry on a BNII-system (Dade Behring Marburg GmbH, Marburg, Germany). Radioimmunoassays were used to determine 11-desoxycorticosterone (DRG Instruments GmbH, Marburg, Germany), dehydroepiandrosterone (DHEA) (Diagnostic Systems Laboratories Germany GmbH, Sinsheim, Germany) and 17-hydroxypregnenolone (ICN Biomedicals GmbH, Eschwege, Germany). The glycosylated fraction of hemoglobin-A1c (HbA_{1c}) was determined by an automated HPLC method on an A1C 2.2 glycohemoglobin analyzer, TOSOH-Eurogenetics, Cologne, Germany. Intraassay variation was less than 5% and interassay variation was less than 8% for all parameters.

Ethical approval

The study protocol was approved by the Ethics Committee of the University of Duisburg and Essen. All participants gave written informed consent before entering the study.

Statistical analysis

Data are presented as mean ± standard deviation (SD) and median or as number and percent affected. Although most parameters were not normally distributed, the sample size was large enough to allow evaluation by unpaired *t*-test [27]. In addition, significance was also tested by Wilcoxon rank-sum test for non-normally distributed parameters and/or by Chi-square test, as appropriate. Values of $p < 0.05$ were considered significant.

Tab. **1** Characteristics of healthy controls (n = 98) and PCOS patients (n = 200)

Variable	*Controls*	*PCOS*	*Value of p*
Age (years)	28.0 ± 5.4 (28.0)	27.0 ± 5.7 (27.0)	NS
BMI (kg/m²)	24.0 ± 7.0 (23.0)	31.0 ± 8.8 (30.0)	< 0.0001 (< 0.0001)
Body fat (%)	31.0 ± 7.0 (27.9)	38.1 ± 9.0 (35.1)	< 0.0001 (< 0.0001)
Fasting insulin (pmol/l)	57.3 ± 24.9 (48.6)	92.7 ± 84.8 (72.3)	< 0.0001 (0.005)
HOMA-IR (mU.mM/l)	2.2 ± 1.3 (1.7)	4.0 ± 3.5 (2.9)	< 0.0001 (0.0004)
WBIS (Matsuda index)	7.2 ± 2.8 (7.0)	4.7 ± 4.2 (3.3)	< 0.0001 (< 0.0001)
HOMA-β (%)	126.0 ± 260.0 (130.0)	239.0 ± 168.9 (197.0)	< 0.0001 (0.0007)
dI/dG (uU.dl/ml/mg)	291.0 ± 232.0 (200.0)	259.0 ± 245.6 (190.0)	NS
AUC-insulin (uU/ml/h)	160.0 ± 101.0 (126.1)	317.0 ± 295.6 (237.0)	< 0.0001 (< 0.0001)
2-h glucose (mg/dl)	87.0 ± 19.0 (86.0)	108.0 ± 40.0 (99.0)	< 0.0001 (0.005)
HbA1c (%)	4.8 ± 0.4 (4.8)	5.2 ± 0.9 (5.1)	< 0.0001 (< 0.0001)
LH-to-FSH ratio	1.0 ± 0.7 (0.9)	2.5 ± 1.8 (2.0)	< 0.0001 (< 0.0001)
Testosterone (nmol/l)	1.0 ± 0.5 (1.0)	2.7 ± 1.0 (2.5)	< 0.0001 (< 0.0001)
Estradiol (ng/dl)	6.7 ± 5.9 (6.7)	6.3 ± 4.4 (6.2)	NS
DHEAS (µg/dl)	188.0 ± 98.1 (154.0)	214.4 ± 106.1 (211.0)	< 0.05 (0.0081)
Cortisol (nmol/l)	384.0 ± 161.0 (349.0)	420.0 ± 184.4 (385.0)	NS
IGF-1 (ng/ml)	180.0 ± 63.0 (160.5)	174.6 ± 60.0 (174.0)	NS

Values are mean ± SD and (median); p-values by *t*-test and (Wilcoxon rank sum test). NS, not significant.

Results

Baseline characteristics

A total of 200 women with PCOS and 98 aged-matched, healthy women were recruited. Most of the individuals in both groups were non-smokers, drank alcohol infrequently, and rated their general health as being "good" or "very good". PCOS patients showed significantly higher BMI, percentage of body fat and degree of insulin resistance (HOMA-IR, Matsuda) than controls (Table **1**). However, when corrected for BMI, no differences in insulin resistance (HOMA-IR in PCOS patients corrected for BMI: 2.1 ± 1.2) or insulin sensitivity (Matsuda index in PCOS patients corrected for BMI: 7.86 ± 4.5) were found. In addition, compensatory hyperinsulinemia (AUC-I) as well as higher HbA_{1c} and 2 h glucose-levels were detected in PCOS patients. Furthermore, significantly higher levels of ovarian and adrenal androgens were found in PCOS patients, while their estradiol, cortisol and IGF-1 levels did not differ from controls (Table **1**).

Metabolic parameters and family history of type 2 diabetes mellitus in PCOS women

Sixty-three out of two hundred PCOS subjects (31.5%) were lean. Thirty-three patients (16.5%) were overweight with a BMI between 25 and 29.9 kg/m², and one hundred and four women (52%) were obese. In the obese group, forty-two women (21% of the total study population) had a BMI between 30.0 and 34.9 kg/m², twenty-nine patients (14.5%) had a BMI between 35.0 and 39.0 kg/m², and thirty-three women (16.5%) had a BMI of over 40 kg/m². Insulin resistance (HOMA-IR > 2.5) was diagnosed in a hundred and forty-two women (71%). Only 3.5% of lean women were insulin-resistant as determined by an elevated HOMA-IR. Acanthosis nigricans, a common sign of severe insulin resistance, was found in seven patients (3.5%). In the PCOS cohort, sixteen women had IGT, seven had manifest T2 DM and three suffered from type 1 diabetes mellitus. The OGTT revealed no alterations in glucose metabolism in the control group. According to the NCEP ATP III criteria, 31.4% of PCOS women had the metabolic syndrome, with a high incidence of a waist circumference of above 88 cm as a sign of abdominal obesity in 55.6% of women, followed by low HDL levels in 46.3%, high triglycerides in 24.1%, elevated blood pressure in 21.9% and elevated fasting blood glucose in 5% of PCOS subjects. Total cholesterol greater than 200 mg/dl was found in 32.5% of women, while a mean cholesterol level of 193.0 ± 36.6 mg/dl (normal range is lower than 200 mg/dl) and a mean LDL cholesterol level of 128.0 ± 38.0 mg/dl (normal range is lower than 155 mg/dl) was found in the entire PCOS cohort. LDL cholesterol levels of more than 115 mg/dl were measured in 63.5% and levels of more than 155 mg/dl in 22% of study subjects. Subgroup analysis of PCOS patients with IGT, T2 DM and normal glucose tolerance (NGT) revealed significant differences in insulin resistance and secretion (Table **2**). In the entire PCOS cohort, 70.5% of women had first-degree relatives with T2 DM.

ism. DHEAS levels in our study were significantly higher in PCOS than in control women. Subgroup analysis of hirsute and non-hirsute patients revealed no significant difference in DHEAS levels (non-hirsute: 193.2 ± 94.4 *vs.* hirsute: 214.4 ± 106.1 µg/dl). Hyperinsulinemia appears to be involved in the secretion of adrenal androgens. Buffington [36] demonstrated increased basic and ACTH-stimulated adrenal androgens in PCOS patients with T2 DM compared to NGT-PCOS women and controls. *In vitro* studies have suggested that insulin increases the sulfotransferase activity, stimulating DHEAS secretion [35]. In our German study, no significant differences in DHEAS levels between NGT (212.2 ± 104.3 µg/dl) and IGT/T2 DM (241.9 ± 149.0/ 226.2 ± 66.8 µg/dl) patients or non-insulin-resistant (202.4 ± 95.6 µg/dl) *vs.* insulin-resistant PCOS women (220.8 ± 115.0 µg/dl) were found.

Due to the variability of symptoms, PCOS is thought to have an oligogenetic pattern of inheritance. In our German cohort, 13.8% of PCOS women reported affected mothers and 18.3% reported affected sisters. In 1998, Legro et al. examined one hundred and fifty-five sisters of eighty PCOS women and found 22% of the sisters suffered from oligomenorrhea and elevated androgens, and that 24% had hyperandrogenemia but regular menses [37]. In an evaluation of British women, the rates of PCOS in mothers and sisters were 24% and 32% [38], while in another British study [39], four out of eighteen (22%) were assigned affected status. The higher prevalence of PCOS in female first-degree relatives of the British PCOS study group may be due to their complete biochemical and clinical evaluation; in our study, affected relatives were only assessed by an interview. Premature balding in men is discussed to be the primary male phenotype. In our study, 12.8% of PCOS subjects evaluated had one ore more male relative with premature balding. A survey of PCOS in the Greek Island of Lesbos [40] showed a positive family history concerning male relatives with premature balding in 7.6% of PCOS women. Taken together, cumulative data provides a strong argument for oligogenetic inheritance of PCOS.

In addition to endocrine disturbances, obesity has a high prevalence in PCOS. Several studies have reported 30 – 50% obese PCOS women [30]. The mean BMI of all 200 subjects in our study was 31.0 ± 8.8 kg/m^2, similar to that of South Asians [16] and patients from Venezuela [41], but lower than the BMI in two US cohorts [29, 42] or in Greek women [43] and higher than the mean BMI in patients from Italy [44, 45], Finland [31], India [46] or Turkey [32].

Since the first description of the *diabète des femmes à barbe*, the bearded diabetic, by Achad and Thiers in 1921 [47], attention of PCOS has focused on its association with insulin resistance and hyperinsulinemia. However, it took sixty years for Burghen and colleagues [48] to demonstrate basal and glucose stimulated hyperinsulinemia in PCOS women compared to weight-matched controls. Subsequently, several studies have confirmed insulin resistance and characteristics of the metabolic syndrome in PCOS. In our PCOS population, the majority of women including a few lean PCOS patients were insulin-resistant. Furthermore, we found an increased insulin response to an oral glucose load in obese and in a small number of lean PCOS patients as shown by increased AUC-I. PCOS women are at an increased risk of developing IGT and T2 DM [49, 50]. Conway et al. [51] showed that 8% of lean and 11% of obese PCOS women had impaired glucose tolerance. We found a similar prevalence (11.5%) of IGT in obese PCOS women.

The key factors in the pathogenesis of T2 DM are insulin resistance and β-cell failure. In our PCOS cohort, subgroup analysis of metabolic parameters demonstrated a higher degree of insulin resistance in IGT and T2 DM patients compared to NGT women. Furthermore, secondary β-cell failure was present in PCOS patients with overt T2 DM, as evidenced by a lower AUC-I and dI/dG as compared to NGT and IGT patients.

Dyslipidemia, characteristic of the metabolic syndrome with low HDL and elevated triglyceride levels, is common in PCOS patients [11, 51, 52]. We also found elevated total cholesterol and increased triglyceride levels in German PCOS women, which is comparable to data from Christian and co-workers [53] also showing higher total cholesterol and LDL cholesterol levels in PCOS patients than in controls. Interestingly, Christian et al. demonstrated three times the prevalence of coronary artery calcium detected by electron beam computed tomography in PCOS women compared to BMI-matched controls, suggesting that LDL cholesterol is a strong predictor of atherosclerosis, as this lipid abnormality distinguished PCOS patients from controls. According to the NCEP ATP III criteria, 31.5% of PCOS women in our cohort from North Rhine-Westphalia had the metabolic syndrome, comparable to 37% obese PCOS women in an Italian cohort suffering from the metabolic syndrome [54].

Several studies have correlated low-grade chronic inflammation with myocardial infarction as well as ischemic stroke (reviewed in: [55]). In PCOS women, an increased prevalence of chronic inflammation, as evidenced by elevated C-reactive protein (CRP) levels, has also been found [56]. Our study population was also found to have elevated high sensitivity CRP (hS-CRP) levels.

In summary, our data confirm a high incidence of the metabolic syndrome and other cardiovascular risk factors in a German PCOS cohort from North Rhine-Westphalia. Therefore, metabolic screening is advisable even in young PCOS women to establish pharmacological therapies and lifestyle changes in order to prevent cardiovascular complications in later years. While the clinical characteristics and endocrine parameters of our German PCOS women were heterogeneous, they were comparable to those from other Caucasian populations. However, even when defined by similar PCOS criteria, some clinical features apparently vary from population to population, suggesting ethnic specific differences in the PCOS phenotype.

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Footnotes

Abbreviations: ASRM, American Society of Reproductive Medicine; ATP III, Adult Treatment Panel III; AUC, area-under-the-curve; BMI, body mass index; CHOL, cholesterol; CRP, C-reactive protein; dI/dG, ratio of delta insulin to delta glucose at baseline and 30 minutes; T2 DM, type 2 diabetes mellitus; ESHRE, European Society for Human Reproduction; HDL, HDL-cholesterol; HOMA, homology model assessment; HOMA-IR, HOMA-insulin resistance; HOMA-β, HOMA-β-cell function; HS-CRP, high sensitivity CRP; IGT, impaired glucose tolerance; IVF, *in vitro* fertilization; LDL, LDL-cholesterol; NCEP, National Cholesterol Education Program; NGT, normal glucose tolerance; NIH, National Institute of Health; NRW, North Rhine-Westphalia; OGTT, oral glucose tolerance test; PCO, polycystic ovaries; PCOS, polycystic ovary syndrome; TGL, triglycerides, WBIS, whole body insulin sensitivity.

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