C-Peptide, Baseline and Postprandial Insulin Resistance after a Carbohydrate-Rich Test Meal – Evidence for an Increased Insulin Clearance in PCOS Patients?

C-Peptid, basale und postprandiale Insulinresistenz nach kohlenhydratreicher Testmahlzeit – Hinweis auf eine erhöhte Insulinclearance bei PCOS-Patientinnen?

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ABSTRACT

Introduction Known characteristics of patients with PCOS include infertility, menstrual disorders, hirsutism and also often insulin resistance. These symptoms increase with increasing body weight. In the LIPCOS study (**L**ifestyle **I**ntervention for **P**atients with **P**olycystic **O**vary **S**yndrome [**PCOS**]) long-term changes of the PCOS in dependence on pregnancy and parenthood were systematically assessed. In the framework of the LIPCOS study, PCOS patients were given a standardised carbohydrate-rich test meal in order to examine glucose homeostasis and insulin secretion. The results were compared with those of a eumenorrhoeic control group who all had corresponding BMI values and corresponding ages.

Methods and Patients 41 PCOS patients (without diabetes) and 68 controls received a standardised carbohydrate-rich test meal (260 kcal, 62% carbohydrates, 32% fat, 6% proteins) in order to generate a submaximal insulin and glucose stimulation. The values were determined at baseline and postprandial after 60, 120 and 180 minutes. In addition, the corresponding C-peptide levels were recorded.

Results In the PCOS patients (n = 41), the insulin secretion test after a standardised test meal showed almost identical baseline and postprandial insulin levels when compared with those of the age- and BMI-matched eumenorrhoeic controls (n = 68). In the PCOS patients, the baseline and postprandial glucose levels were significantly elevated (92.88 ± 10.28 [PCOS] vs. 85.07 ± 9.42 mg/dL [controls]; $p < 0.001$) so was C-peptide ($p < 0.025$).

Conclusions In the present study we have shown for the first time that, after consumption of a standardised test meal, PCOS patients formally exhibit a higher fasting insulin resistance than controls. In spite of the higher stimulated C-peptide levels, the insulin levels did not increase more strongly with increasing glucose levels than in controls which may be indicative of a higher insulin clearance in PCOS patients.

ZUSAMMENFASSUNG

Einleitung Als bekannte Charakteristika von Patientinnen mit PCOS gelten Infertilität, Zyklusstörungen, Hirsutismus sowie auch häufig eine Insulinresistenz. Sie nimmt mit steigendem Körpergewicht zu. In der LIPCOS-Studie (**L**ebensstil-**I**ntervention bei polyzystischem Ovarsyndrom [**PCOS**]) werden systematisch Langzeitveränderungen des PCOS in Abhängigkeit von Schwangerschaft und Elternschaft betrachtet. Im Rahmen der LIPCOS-Studie wurde PCOS-Patientinnen eine standardisierte kohlenhydratreiche Testmahlzeit verabreicht, um die Glukosehomöostase und die Insulinsekretion zu untersuchen. Die Ergebnisse wurden mit eumenorrhöischen Kontrollen verglichen, die jeweils einen entsprechenden BMI und ein entsprechendes Alter hatten.

Methoden und Patientinnen 41 PCOS-Patientinnen (ohne Diabetes) und 68 Kontrollen bekamen eine standardisierte kohlenhydratreiche Testmahlzeit (260 kcal, 62% Kohlenhydrate, 32% Fett, 6% Proteine) verabreicht, um eine submaximale Insulin- und Glukosestimulation zu erzeugen. Die Werte wurden basal, nach 60, 120 und 180 Minuten postprandial gemessen. Außerdem wurden jeweils die C-Peptid-Werte bestimmt.

Ergebnisse Der Insulinsekretionstest nach standardisierter Testmahlzeit zeigte bei PCOS-Patientinnen (n = 41) nahezu gleiche basale und postprandiale Insulinwerte verglichen mit jeweils zu Alter und BMI entsprechenden eumenorrhöischen Kontrollen (n = 68). Die basalen und postprandialen Glukosespiegel waren bei PCOS-Patientinnen signifikant erhöht ($92,88 \pm 10,28$ [PCOS] vs. $85,07 \pm 9,42$ mg/dl [Kontrollen]; $p < 0,001$), ebenso die C-Peptid-Werte ($p < 0,025$).

Schlussfolgerung In der vorliegenden Arbeit konnte erstmals gezeigt werden, dass Patientinnen mit PCOS unter Gabe einer standardisierten Testmahlzeit eine formal größere Nüchtern-Insulinresistenz als Kontrollen hatten. Trotz höher stimulierter C-Peptid-Werte stiegen die Insulinwerte mit erhöhten Glukosewerten bei PCOS-Patientinnen nicht stärker an als bei Kontrollen, was auf eine erhöhte Insulinclearance bei PCOS hindeuten könnte.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinological cause of infertility, menstrual disorders and hirsutism in women of child-bearing age [1]. Hyperandrogenaemia as well as insulin resistance with a compensatory hyperinsulinaemia that can develop into type 2 diabetes mellitus (DM) [2, 3] are the central pathomechanisms of PCOS. Although the presence of insulin resistance is not necessary for a diagnosis of PCOS, it is clearly apparent that insulin resistance plays a significant role in PCO syndrome [4]. The prevalence of insulin resistance in PCOS lies in the range of 50–70% [2, 5–7] and occurs independently of obesity [8]. Slim women [9] and women for whom PCOS has been diagnosed according to the Rotterdam criteria, appear to have less pronounced insulin resistance [10].

Women with PCOS carry a higher risk to develop an impaired glucose tolerance [IGT] and also type 2 DM [4]. Impaired glucose tolerance is defined by 2-hour values of > 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.0 mmol/L) in the oral glucose tolerance test (OGTT) with 75 g glucose [11]. In an American study up to 31.3% of patients with PCOS had impaired glucose tolerance and 7.5% had type 2 DM, compared with 14% and 0% in an age- and weight-matched control group without PCOS [12]. In addition, women with PCOS develop an impaired glucose metabolism earlier, and their IGT also appears to progress more rapidly to type 2 DM [13].

IGT is also clinically relevant and its early detection and therapy improves the long-term outcome [14]. It has been demonstrated in one study that IGT increases the risk for cardiovascular diseases, mortality and type 2 DM [15].

The International Diabetes Federation has classified PCOS as a significant but immutable risk factor that is associated with type 2 DM [16]. To date there are no long-term studies with robust results on IGT, type 2 DM and cardiovascular diseases in PCOS but rather only studies with surrogate parameters.

There are hardly any longitudinal data on how the clinical and endocrinological symptoms of PCO syndrome change over a longer time period. Also no studies have yet addressed how pronounced the pre-diabetic metabolic situation is under everyday conditions in women with PCOS compared to a control group. This was the aim of the present analysis.

Study Participants and Methods

Study collective

In the framework of the LIPCOS pilot study (**L**ifestyle **I**ntervention for **P**atients with Poly**c**ystic **O**vary **S**yndrome [**PCOS**]), 403 patients with oligo-amenorrhoea and/or hyperandrogenaemia were identified from a large infertility database and requested to complete and return a questionnaire. At the same time they were invited to participate in the prospective LIPCOS main study. Further recruitment for the prospective LIPCOS main study took place through the outpatient unit of the gynaecology department of Munich Technical University (director: Prof. Marion Kiechle) in the "Klinikum rechts der Isar", referring gynaecologists in the Munich urban area, and the PCOS self-help groups in Munich.

The study was approved by the ethics committee of Munich Technical University (TUM). Details of the conduct of the study have already been published [17], and are briefly delineated below.

Inclusion criteria

Patients with spontaneous (not post-pill) oligo-/amenorrhoea and/or clinical or biochemical hyperandrogenemia (acne, hirsutism) were eligible if they fulfilled two of the following three criteria according to the Rotterdam criteria of 2003 [5]:
1. anovulation,
2. hyperandrogenaemia, and
3. polycystic ovaries.

Oligomenorrhoea was defined as cycle duration of > 35 days and amenorrhoea as > 90 days. Eumenorrhoeic women with corresponding age and BMI from a cohort of the Institute for Nutritional Medicine (director: Prof. Dr. Hans Hauner) served as control group.

Exclusion criteria

Patients on any medications that act on the hypothalamic-pituitary-gonadal axis, such as hormonal contraceptives, oestrogens or progestins for hormone therapy, endocrine therapy after breast cancer or GnRH analogues for endometriosis were excluded as well as pregnant or breast-feeding women. Patients with hyperandrogenemia or oligomenorrhoea due to other known endocrine diseases such as androgen-producing tumours, adrenal hyperplasia, primary hypothalamic amenorrhoea or premature ovarian failure as well as prolactinomas were also excluded from participation in the study.

Course of the study

After signing informed consent, a structured interview was carried out with all participants, blood samples were taken and a vaginal ultrasound scan with ovary score was performed [18]. All participants were also offered the standardised test meal study on a subsequent study day.

Standardised test meal

For this part of the study, the participants presented for the 3-hour test in the morning after a 10-hour fasting period. After placement of an indwelling venous cannula in an antecubital vein, a blood sample was taken to determine the baseline values of haemoglobin A1c (HbA_{1c}), glucose, insulin and C-peptide. The test consisted of four blood samplings at the time points 0, 60, 120 and 180 minutes.

Test meal

Following the baseline blood sampling, each participant received a standardised, carbohydrate-rich test meal. The meal was to be consumed within 10 minutes. It consisted of a 50 g white flour bread roll, 25 g of jam as well as 10 g of butter and comprised 62% carbohydrates, 32% fat and 6% protein or, respectively, 42 g of carbohydrates, 9 g of fat and 3.8 g of protein, amounting to a total calorie count of 267 kcal.

Analyses

The samples for insulin and C-peptide (each 4.5 mL whole blood) were placed in small plastic tubes that contained 500 μL of a mixture of 1.5 g of ethylenediamine tetraacetate (EDTA) in 100 mL NaCl. They were stored at 4 °C. The samples for glucose were placed in blood sampling tubes containing EDTA/sodium fluoride (NaF) and also stored in the cold until centrifugation. HbA_{1c} was taken up from EDTA-haemogram tubes and analysed by the Institute of Clinical Chemistry at the "Klinikum rechts der Isar".

After the test, the cooled samples were centrifuged at 3000 rpm for 15 minutes at 4 °C (Hettich Rotixa/P centrifuge, Tuttlingen, Germany). The separated plasma was stored at −26 °C until analysis. All samples from each patient were analysed at least twice.

Insulin measurement

Insulin was measured using a radioimmunoassay (RIA) from Siemens Medical Solutions Diagnostics (Los Angeles, California, USA) with < 20% cross-reactivity to proinsulin and subsequently with a gamma counter (type 1470 Wizard, Wallac, Freiburg, Germany). The emitted radioactivity was recorded in counts per minute (cpm). Measured cpm values were read as percentage binding and the hormone concentration originally present in the plasma was calculated on the basis of the calibration values.

C-peptide measurement

The concentration of C-peptide in plasma was determined with the IRMA-CPEP test (CIS Biointernational, Gif-sur-Yvette Cedex, France).

The C-peptide values of the samples were directly read off the standard curve. The intra- and interassay variation coefficients amounted to 4.5 and 6.4%.

Glucose measurement

Glucose was determined photometrically by means of the hexokinase method (Glucose-HK-Test [100 + 1], Greiner Diagnostic GmbH, Bahlingen, Germany).

Calculations

The baseline insulin sensitivity was determined by the Homeostasis Model Assessment Insulin Resistance (HOMA-IR) Index [19]. HOMA-IR was calculated as [fasting glucose (mg/dL) × fasting insulin (μU/mL)] ÷ 405.

The area under the curve (AUC) was calculated as Δ-AUC according to the trapezoid method [20].

Statistics

Data analyses were carried out with the programmes SPSS and Microsoft Office Excel for Windows in cooperation with the Institute for Medicinal Statistics and Epidemiology (IMSE) of the TU Munich. Continuous variables are described with mean values (MV) and standard deviation (± SD). Significance was tested by means of the Mann-Whitney U test. Categorial values are described with absolute and relative frequencies and were tested for significance by means of Fisher's exact test. The level of significance was set at $p < 0.05$ [17, 21].

Results

Altogether 72 participants were recruited into the LIPCOS main study in the period from 15.12.2008 to 24.03.2011 and invited to the test. 41 of the participants (PCOS) and 68 BMI- and age-matched eumenorrhoeic controls (C) consumed the standardised, carbohydrate-rich test meal and completed the 3-hour test.

Baseline characteristics

The baseline characteristics of both groups are listed in ▶ **Table 1**. HOMA-IR in the participants with PCOS was higher than that in controls but the difference was not statistically significant (0.67 ± 0.95 vs. 0.45 ± 0.66; p = 0.144). The HbA_{1c} value in participants with PCOS was significantly higher compared to that in controls (5.20 ± 0.29 [n = 40] vs. 4.98 ± 0.49% [n = 58]; p = 0.016).

Baseline values and AUC

Baseline glucose of participants with PCOS was significantly elevated compared to controls (92.9 ± 10.3 [PCOS] vs. 85.1 ± 9.4 mg/dl [C]; p < 0.001).
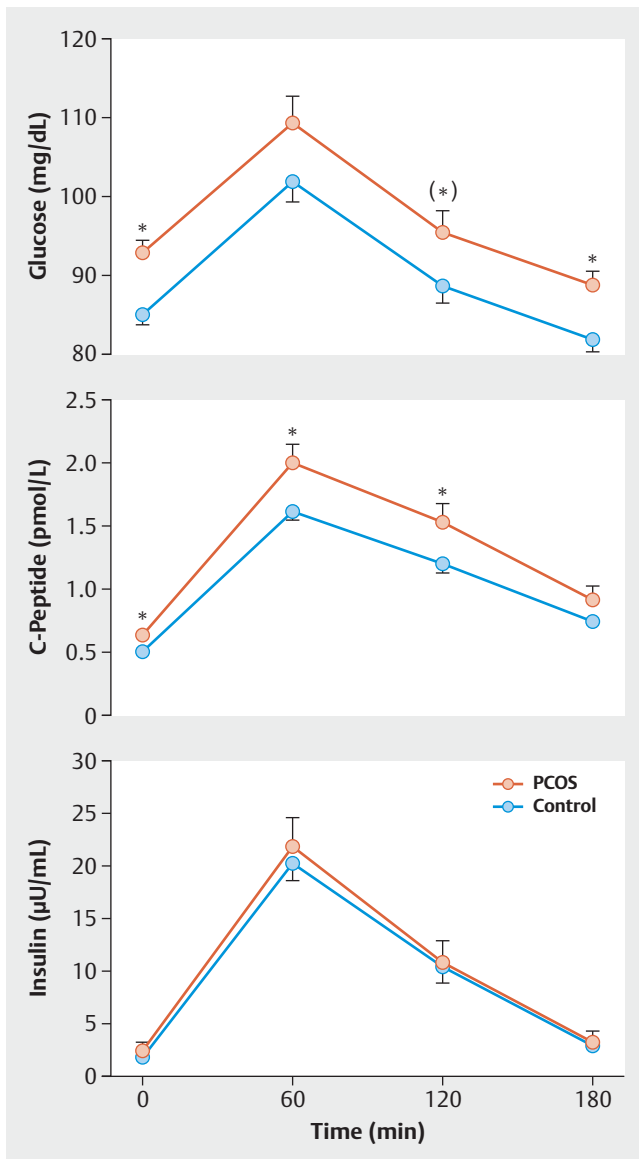
The area under the curve (Δ-AUC) for glucose in the controls was not significantly higher than that for the participants with PCOS (1005.1 ± 2028.6 [PCOS] vs. 1127.7 ± 1956.0 mg/dL × 180 min [C]; p = 0.755) (▶ **Figs. 1** and **2**).

Baseline C-peptide in participants with PCOS amounted to 0.6 ± 0.3 pmol/L whereas that of the controls were significantly lower with 0.5 ± 0.2 pmol/L (p = 0.019).

The average Δ-AUC for C-peptide in the participants with PCOS was significantly higher than that for the control group (145.5 ± 68.4 [PCOS] vs. 115.3 ± 65.2 pmol/L × 180 min [C]; p = 0.023) (▶ **Figs. 1** and **2**).

Baseline values for the two groups were almost identical (2.8 ± 3.7 [PCOS] vs. 2.1 ± 2.9 μU/mL [C]; p = 0.237).

Accordingly, the Δ-AUCs for insulin in both groups were almost the same (1685.8 ± 1248.3 [PCOS] vs. 1657.0 ± 1458.3 μU/mL × 180 min [C]; p = 0.916) (▶ **Figs. 1** and **2**).

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► **Fig. 1** Glucose, C-peptide and insulin courses after the carbo-hydrate-rich standardised test meal in PCOS patients and age- and BMI-matched controls. * p = 0.055
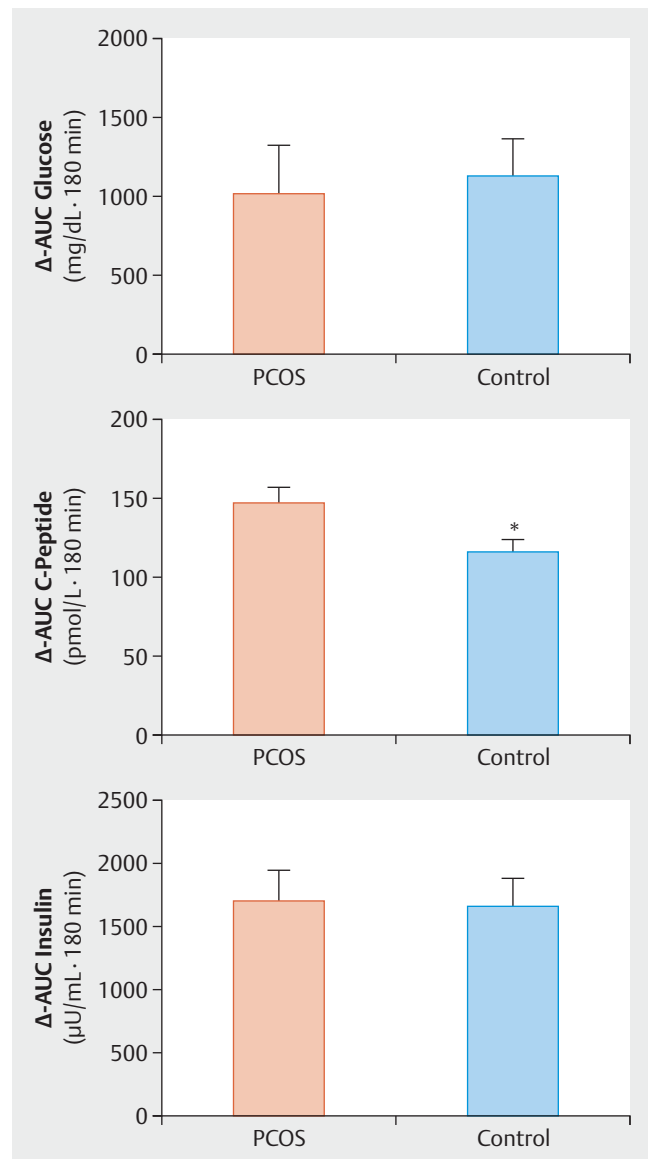
► **Fig. 2** AUC for glucose, C-peptide and insulin for participants with PCOS and the age- and BMI-matched controls. * p < 0.05

► **Table 1** Baseline characteristics of the participants (PCOS) and the control collective (C).

	PCOS	C	P
Age (years)	33.61 ± 8.79	34.77 ± 9.49	n. s.
Weight (kg)	72.80 ± 17.18	71.01 ± 15.80	n. s.
BMI (kg/m^2)	25.68 ± 6.31	25.06 ± 5.38	n. s.
HOMA-IR	0.67 ± 0.95	0.45 ± 0.66	n. s.
HbA$_{1c}$ (%)	5.20 ± 0.29	4.98 ± 0.49	0.016

Postprandial values

The postprandial 60-minute glucose values for both groups were not significantly different (109.2 ± 22.2 [PCOS] vs. 101.9 ± 21.0 mg/dL [C]; p = 0.089). The 120-minute elevation for the PCOS patients was of borderline significance (95.4 ± 18.4 [PCOS] vs. 88.7 ± 17.0 mg/dL [C]; p = 0.055). After 180 minutes the glucose in the PCOS participants was significantly higher with 88.7 ± 12,5 mg/dL vs. controls (81.8 ± 11.8 mg/dL, p = 0.005) (▸ **Fig. 1**).

In the postprandial period, after 60 minutes C-peptide increased to 2.0 ± 0.8 pmol/L in the PCOS group and to 1.6 ± 0.7 pmol/L (p = 0.007) in controls. The increase in the PCOS group was still statistically significant after 2 hours (1.6 ± 0.8 [PCOS] vs. 1.2 ± 0.7 pmol/L [C]; p = 0.022). After 3 hours the higher C-peptide value for the participants with PCOS was no longer statistically significant compared to controls (0.9 ± 0.6 [PCOS] vs. 0.8 ± 0.5 pmol/L [C]; p = 0.093) (▸ **Fig. 1**).

The postprandial insulin values increased almost in parallel up to the time point 60 minutes (22.1 ± 15.8 [PCOS] vs. 20.5 ± 16.6 µU/mL [C]; p = 0.607), and then declined almost identically (120 minutes: 11.2 ± 11.2 [PCOS] vs. 10.7 ± 14.6 µU/mL [C]; p = 0.836). Also after 180 minutes, the insulin values of both groups had declined further but still almost identically (3.6 ± 4.9 [PCOS] vs. 3.2 ± 5.7 µU/mL [C]; p = 0.735) (▸ **Fig. 1**).

IFG und DM

An impaired fasting glucose [IFG] with baseline glucose values > 100 mg/dL was detected in 17.07 % (7/41) of the PCOS patients and 5.88 % (4/68) of the controls. None of the patients had baseline glucose levels > 126 mg/dL and thus there was no evidence for diabetes mellitus (DM) [21].

Discussion

Previous studies that examined diabetological parameters in PCOS patients used either the euglycaemic hyperinsulinaemic clamp method, that represents the gold standard test for determining insulin sensitivity [22], or the OGTT [23–25]. In this study we specifically decided in favour of the standardised carbohydrate test meal [26] in order to generate a submaximal, "more physiological" insulin stimulation, similar to that to be expected also in everyday conditions. The 75 g glucose in the OGTT leads to a maximal insulin stimulation whereas, by comparison, the standardised carbohydrate-rich test meal contains 42 g carbohydrates that still have to be degraded.

Due to test duration of three hours instead of the two hours in the OGTT, we were able to verify the decline in the measured values more precisely with our test procedure. Because of this strategy, the results presented here can only be compared to a limited extent with those from studies based on the OGTT. However, there are studies with similar objectives that can be compared with our work [2,27,28]. For the participants, the nutritional medicine part of the study meant an additional time load of about four hours for the visit on a subsequent day. This could not be arranged in any other way for the participants. For this reason only 41 of the total of 72 participants did in fact partake in the standardised, carbohydrate-rich test meal study.

In this study, patients with PCOS exhibited higher baseline glucose values and identical peripheral insulin concentrations compared to controls. We also detected a formally higher insulin resistance in the patients with PCOS. Strikingly in patients with PCOS, higher C-peptide concentrations both at baseline and postprandial existed as indication for an increased insulin secretion. This could mean that the insulin clearance in these patients (uptake of insulin by the liver from the portal vein system) is higher than in controls.

Glucose tolerance in patients with PCOS was first investigated systematically in 1987 by Dunaif et al. [2,27]. Obese and slim patients with PCOS were compared both with obese and slim ovulatory hyperandrogenic patients and with age- and weight-matched control subjects of the same gender. After administration of 40 g/m² glucose orally, insulin values in obese PCOS patients increased significantly over a period of 120 minutes compared with those of obese ovulatory hyperandrogenic women and controls. Also, in the groups of slim patients those with PCOS exhibited significantly higher insulin values in comparison to the other two groups. The glucose levels were significantly increased only in the obese PCOS patients from 30 minutes onward after administration of the glucose. The conclusion from these results was that hyperinsulinaemia is a feature of PCOS and is not dependent on hyperandrogenaemia.

In our studies the glucose levels were already elevated in the fasting state and also remained significantly elevated in the postprandial phase. Worthy of note is that the glucose values in the study of Dunaif et al. [2,27] increased to about 150 mg/dL in obese patients with PCOS and to about 125 mg/dL in controls. In our study, however, the glucose levels rose to 109 mg/dL in the patients with PCOS and to 101 mg/dL in the controls. This could be explained by the lower amount of glucose administered in our study since with a glucose dose of 40 g/m² most of the patients probably received over 60 g glucose whereas in our study merely 42 g carbohydrate were administered.

Compared to the study of Dunaif et al. [2,27], the insulin values in our PCOS patients were not significantly increased. Due to its higher glucose load in comparison to the standardised carbohydrate-rich test meal used in the present study, the OGTT exerts a stronger effect with regard to the insulin increase. This is useful for an interpretation of the results. However, the test meal has a higher everyday relevance since a meal consisting of a bread roll with butter and jam would be taken by a great many more patients in comparison to a drink with 75 g glucose.

An Indian case-control study by Kulshreshtha et al. [24] examined the glucose and insulin values after administration of an OGTT in 285 patients with PCOS and in 27 slim controls (C) without diabetes in the family history. 62 % of the PCOS patients had a normal glucose tolerance (NGT), 14 % elevated fasting glucose values (impaired fasting glucose [IFG]), 17 % had IGT and 7 % type 2 DM. In this study the glucose values of those PCOS patients with NGT were not significantly increased in comparison to the values of controls (glucose 0 h: 84.8 ± 10.9 mg/dL [NGT-PCOS] vs. 88.2 ± 7.2 [C]; glucose 1 h: 116.9 ± 26.2 mg/dL [NGT-PCOS] vs. 115.5 ± 27.5 [C]; glucose 2 h: 102.0 ± 18.2 mg/dL [NGT-PCOS] vs.

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91.8 ± 20.5 [C]). However, baseline and postprandial insulin values were significantly elevated compared to controls (insulin 0 h: 5.8 ± 11 [NGT-PCOS] vs. 15.0 ± 15.4 mIU/L [C]; insulin 1 h: 32.7 ± 26.5 [NGT-PCOS] vs. 98.8 ± 81.8 mIU/L [C]; insulin 2 h: 14.6 ± 9.6 [NGT-PCOS] vs. 62.9 ± 49.3 mIU/L [C]). Also the HOMA-IR values were significantly elevated in the PCOS patients with normal glucose tolerance (3.1 ± 3.0 [NGT PCOS] vs. 1.2 ± 0.2 [C]).

Since the majority of our PCOS patients had a normal glucose tolerance, our results can be compared with the results of the patients with normal glucose tolerance and of the controls from the study of Kulshreshtha et al. [24]. With regard to BMI, the LIPCOS patients are comparable with the patients in the Indian study (25.68 ± 6.31 [LIPCOS] vs. 26.5 ± 5.7 kg/m^2 [Kulshreshtha et al.]), however, our patients are markedly older (34.77 ± 9.49 [LIPCOS] vs. 22.6 ± 5.6 years [Kulshreshtha et al.]). In the Indian study the controls were not matched for BMI and age as was done in LIPCOS, thus their characteristics are markedly different (BMI 25.06 ± 5.38 [LIPCOS] vs. 19.7 ± 2.6 kg/m^2 [Kulshreshtha et al.] and age 34.77 ± 9.49 [LIPCOS] vs. 22.8 ± 4.5 years [Kulshreshtha et al.]).

In the Indian study fewer PCOS patients had impaired fasting glucose [IFG] than in LIPCOS (14 vs. 17.07%). Whereas in the Indian study the glucose values of PCOS and control were almost identical, in the present work the glucose values of the PCOS patients are significantly increased compared with controls. The baseline glucose values of PCOS patients with normal glucose tolerance (NGT) in the study of Kulshreshtha et al. [24] were even lower than that of the controls. The glucose values of PCOS patients with IFG were, however, also significantly increased vs. controls, similar to LIPCOS. Comparability is, however, limited since the baseline glucose value of the Indian controls already shows that this was a group with impaired glucose tolerance [IGT] (108.3 mg/dL [Kulshreshtha et al.]; 92.88 mg/dL [LIPCOS]). Accordingly, all postprandial glucose values were markedly higher than those in LIPCOS. In the Indian study the insulin values were significantly different between the PCOS patients and controls whereas in our investigation there were no differences between the two groups in this regard. It is also striking that the baseline insulin values in the present study are markedly lower both for the patients with PCOS and for the controls (2.80 ± 3.66 [PCOS] and 2.05 ± 2.87 μU/mL [C] in LIPCOS vs. 5.8 ± 1.1 [PCOS] vs. 15.0 ± 15.4 mIU/L [C] in Kulshreshtha et al.). Since the BMI values of both PCOS collectives are comparable, other reasons must be taken into consideration. Beside methodical reasons like using a different kind of insulin-assay a possible cause for these different insulin values could be the ethnic differences between the two patient collectives. Verification of this possible ethnic difference was the aim of the study by Mohan et al. [29], who compared the insulin values of Indians and Europeans with type 2 DM and controls. It was noticed that not only in Indian patients with type 2 DM but also in Indian controls both the baseline insulin value and the insulin response were significantly higher in comparison to those of European patients and the European controls. The authors concluded that ethnic differences could have contributed to the differing values for the control groups.

The majority of insulin secreted from the pancreas is absorbed by the liver (insulin clearance). Peripheral insulin concentrations are thus not suitable to evaluate the secretion. C-peptide, consist-

ing of 31 amino acids, as a polypeptide binds the two chains of proinsulin and is enzymatically cleaved during transformation to insulin. Together with insulin, C-peptide is emitted into the blood from the pancreas and can be measured as a diabetic parameter [30]. Studies in the past few years have shown that C-peptide possesses specific binding to cell membranes, influences numerous cell signalling pathways and has a protective role in diabetic complications [31]. So far there are only few studies that included C-peptide in the investigation of diabetic parameters in cases of PCOS. In our study not only baseline but also postprandial C-peptide values were significantly higher in PCOS patients than in the controls.

In a study by Maciejewska-Jeske et al. [32] the baseline glucose and C-peptide levels of 5 overweight (27.2 years, BMI 27.3 kg/m^2) and 60 obese patients with PCOS (26.2 years, BMI 35 kg/m^2) were compared with those of 10 controls (28.8 years, BMI 21.2 kg/m^2). In the group of overweight women with PCOS, the C-peptide concentration was somewhat higher than that in the obese women with PCOS (1.39 and 1.31 nmol/L), but lower than that in the controls (1.62 nmol/L). In the control group, C-peptide concentration correlated negatively with glucose (R = − 0.71; p < 0.05), whereas in the group of overweight women with PCOS there was a positive correlation between these two values (R = 0.90; p < 0.05). Increased insulin clearance may explain these divergent correlations.

Due to the use of different assays and standard curves, the absolute values from the study by Maciejewska-Jeske et al. [32] probably cannot be compared with the results of the LIPCOS study. However, on the basis of the relative values, a trend can be seen that in patients with PCOS higher glucose levels are associated with higher C-peptide concentrations.

In agreement with the present work, several studies have found significantly elevated glucose values in patients with PCOS in comparison to weight- and age-matched controls. Elevated insulin values, as have been found in a few studies on patients with PCOS, could not be detected in our study. However, we did find significantly increased baseline and postprandial C-peptide and HbA$_{1c}$ levels in patients with PCOS in comparison to controls.

In the present work we have shown for the first time that patients with PCOS have a higher fasting insulin resistance than controls, not only with an OGTT as previously published [2, 27], but also after administration of a standardised test meal. This insulin resistance did not increase further in the postprandial phase despite of higher stimulated C-peptide levels. This suggests a mechanism that is linked to a higher hepatic clearance in PCOS patients [33–35]. However, the small number in our study is a limitation and our results need to be replicated.

Petersen et al. [36] have shown that the insulin sensitivity in patients with coronary artery disease could be improved by dieting in contrast to only physical training. Improved insulin sensitivity was associated with a reduction in abdominal fat, hip circumference and body weight. Whether a diet can affect the insulin sensitivity or the insulin clearance in PCOS patients or whether there are differences in this clinical entity is, as far as we are aware, not known and has not yet been investigated.

Conflict of Interest

None.

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