Dyslipidaemia in polycystic ovarian syndrome: different groups, different aetiologies?

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The objective was to study the pathophysiology of the dyslipidaemia in polycystic ovarian syndrome (PCOS) patients, and to determine how it is related to hyperinsulinaemia, hyperandrogenism and dehydroepiandrosterone sulphate (DHEA-S) concentrations. The lipoprotein lipid profile, anthropometric measurements, endocrine profile and the presence of insulin resistance were evaluated in 31 PCOS patients and 20 age-matched healthy women, who served as controls. PCOS patients had higher fasting insulin concentrations, higher body mass indexes (BMI) and were hyperlipidaemic, with higher total cholesterol, low density lipoprotein (LDL) and triglyceride (TG) concentrations. There were no relationships between plasma lipids and anthropometric variables in the patient group as a whole. Insulin-resistant (IR) and non-IR (NIR) PCOS patients were then evaluated separately. Obesity with marked hyperandrogenism were the predominant features in patients with IR. NIR patients were not obese and had significantly less hyperandrogenism. The adrenal androgen DHEA-S was at the upper limit of its normal range in both groups. However, both PCOS subgroups exhibited similar significant abnormalities in terms of their lipid parameters. Insulin and DHEA-S concentrations were positively correlated with total cholesterol, LDL and TG, and negatively correlated with high density lipoprotein, in IR patients. In NIR subjects, insulin was not correlated with any of the lipids and DHEA-S was negatively related to cholesterol and LDL. Anthropometric variables were related to lipids in only the NIR patients. Thus PCOS subjects as a group exhibit dyslipidaemia, characterized by increased total cholesterol, LDL and TG concentrations. When divided into IR and NIR subjects, there were no differences in the degree of lipid abnormalities, despite significant variations in the BMI and androgen status. Thus, in PCOS subjects, dyslipidaemia may occur irrespective of insulin resistance. Insulin and DHEA-S concentrations were positively correlated with an atherogenic lipid profile in the IR group only. As distinct from syndrome X when IR was present, dyslipidaemia was not related to body weight or the waist:hip ratio. In the NIR group there was no relationship between lipids and insulin; DHEA-S, on the other hand, was negatively related to cholesterol and LDL concentrations. Thus, dyslipidaemia in PCOS patients may occur irrespective of insulin resistance, and may have different metabolic aetiologies depending on DHEA-S metabolism. It remains to be seen whether the two types of PCOS are associated with different risks for ischaemic heart disease.

Key words: androgens/DHEA-S/hyperinsulinaemia/plasma lipids/polycystic ovarian syndrome

Introduction

Women with polycystic ovarian syndrome (PCOS) have disturbed lipoprotein lipid profiles (Wild et al., 1985; Lithell et al., 1987). Android-type obesity is present in 40–50% of the patients (Kiddy et al., 1990; Meirow et al., 1995) and is closely related to these disturbances (Lapidus et al., 1984; Wild and Bartholomew, 1988). Hyperandrogenism with higher circulating concentrations of testosterone, androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEA-S) are common features and result phenotypically in hirsutism, acne and oily skin (Goldzieher and Axelrod, 1963; Laatikainen et al., 1980; Yen, 1980). Circulating blood concentrations of the adrenal androgen DHEA-S are raised in 50% of PCOS patients (Hoffman et al., 1984). Metabolic tests have shown that testosterone in men is closely involved in high density lipoprotein (HDL) regulation (Goldberg et al., 1985), while women with an excess of androgen have an atherogenic lipoprotein profile (Stuart et al., 1987; Wild, 1991; Sowers, 1992). Low DHEA-S concentrations are associated with high lipid concentrations (Leszczynski et al., 1989; Nestler et al., 1992), and epidemiological studies have shown an inverse relationship between DHEA-S and ischaemic heart disease (Barrett-Connor et al., 1986; Mitchell et al., 1994).

Hyperinsulinaemia with insulin resistance (IR) is present in at least 50% of PCOS patients (Barbieri et al., 1988; Franks et al., 1989; Dunai et al., 1990). Hyperandrogenism and IR are closely related (Burghen et al., 1980; Pasquali et al., 1983; Stuart et al., 1987; Nader, 1991) and when present in PCOS patients may be the primary reason for dyslipidaemia, which is more pronounced in overt diabetes (Reaven, 1988). Insulin lowers DHEA-S blood concentrations by inhibiting synthesis and increasing catabolism (Nestler et al., 1992).

This study reports on the interrelationships between IR, hyperandrogenism, DHEA-S concentrations and obesity in the pathophysiology of the dyslipidaemia of PCOS. Our results suggest that DHEA-S may be an important modifier of the lipid profile in these patients depending on the existence of
IR. Furthermore, dyslipidaemia in PCOS may be present in the absence of IR.

Materials and methods

Patient population

A group of 31 patients who presented with anovulatory infertility associated with PCOS were selected for study. Of these, six patients had amenorrhoea and 25 had oligoamenorrhoea. The diagnosis of PCOS was established initially by pathognomonic ultrasound, and characteristic clinical and hormonal features. All patients had typical PCOS ovaries on sonography, i.e. enlarged with multiple small cysts (necklace-like pattern) and thickened ovarian stroma, as demonstrated previously (Adams et al., 1986; Ardaens et al., 1991). Of these 31 patients, 12 underwent diagnostic laparoscopy which showed enlarged ovaries (>4 cm) with smooth white capsules. Hirsutism (Ferriman Galloway score >10) was present in 14 of the patients, and 20 patients were obese [body mass index (BMI) >25 kg/m²]. An endocrine profile showed a high luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio (>2.0) in 13 patients. A high testosterone concentration was measured in 11 patients (upper normal limit of 3.0 nmol/l), and the androstenedione concentration was high in all but six patients (upper normal limit 4.9 nmol/l). All patients had normal thyroid function tests, did not consume excessive amounts of alcohol and were not on a hypocaloric diet. A group of 20 healthy women with regular ovulatory cycles were evaluated as controls. All control patients were of normal weight and did not have glucose intolerance or hyperinsulinemia. All subjects and controls gave informed consent according to the Helsinki Committee requirements.

Lipoprotein profiles

Venous blood was obtained after a 12 h fast and the serum was separated immediately. Total cholesterol concentrations were determined by an enzymatic assay (cholesterol enzymatic color II, Bristol, Paris, France). HDL cholesterol concentrations were determined after the precipitation of chylomicrons, very low density lipoproteins (LDL) and LDL cholesterol (Boehringer-Mannheim GmbH, Mannheim, Germany). Triglyceride (TG) concentrations were determined by an enzymatic assay (Triglycerides Enzymaticues, VuHp; Bristol). The amount of LDL was calculated according to the equation proposed by Friedwald et al. (1972): LDL = [(total cholesterol) - [HDL] - [TG]]/5

Anthropometric measurements

The subjects wore light indoor clothes and no shoes when the anthropometric measurements were performed by the same investigator in every case. These measurements included weight (kg), height (cm), waist circumference at the umbilical level (cm) and hip circumference at the level of the widest femoral girth (cm). Quetelet's index, i.e BMI = weight (in kg) divided by the square height (in m), was calculated as a measure of the total fatness, and the waist to hip girth ratio (W/H ratio) as a measure of body fat distribution. The body composition, i.e. lean body mass and fat mass, were measured using a Futrex 5000 machine (Futrex Inc., Gaithersburg, MD, USA). This is a hand-held device that estimates body composition by 'infrared interactance'. This technique uses a light beam that enters the body and determines the presence of fat by the spectrum of that beam. By measuring the spectrum shift in the glow emitted from the body, the percentage of body fat (BCF) can be determined accurately (Conway et al., 1984; Elia et al., 1990).

Oral glucose tolerance test (OGTT) and evaluation of IR

Patients were instructed to eat meals containing at least 150 g carbohydrates per day for 3 days prior to the study. On the day of the study, subjects were instructed to report after a 12 h fast. Venous blood samples were obtained before, and 1 and 2 h after, a load of 75 g glucose in 250 ml water. The glucose was ingested within 3 min under the supervision of the investigator. All blood samples were placed immediately in ice. Blood was separated and the serum kept at -20°C until analysed. Glucose concentrations were measured by a glucose dehydrogenase ultraviolet test (MA-ki 100; Roche, Basel, Switzerland) and insulin by a radioimmunoassay after polyethylene glycol separation. Human insulin standards were used.

All but four of the PCOS subjects had normal fasting tests and OGTT. These four subjects were not diabetic (1 h post-glucose 160–250 mg%, and/or 2 h post-glucose 140–200 mg%). IR was characterized by a fasting insulin concentration >20 mIU/ml accompanied by one or both of the following: a 1 h post-glucose insulin concentration >200 mIU/ml and a 2 h post-glucose insulin concentration >150 mIU/ml, or 2 h insulin concentrations higher than 1 h concentrations. Fasting insulin concentrations >30 mIU/ml were also considered as IR even if 1 and/or 2 h postprandial insulin concentrations were lower than the standard for IR. Hyperinsulinaemia in the presence of a normal glucose response is a characteristic marker of, and (presumably) a compensatory mechanism for, IR (Bonadonna and DeFronzo, 1992). Insulin response following the OGTT was correlated with the response of 20 healthy, normally ovulating female subjects.

All clinical parameters and the endocrine profiles were determined before the OGTT results were obtained.

Biochemical and endocrine measurements

Hormone serum concentrations were determined from blood withdrawn on days 2–4 of a spontaneous cycle or following progesterone withdrawal bleeding. Sensitive and specific radioimmunoassay methods described previously (Eldar-Geva et al., 1990) were used to measure the concentrations of LH, FSH, oestradiol, DHEA-S, androstenedione, testosterone and cortisol. Sex hormone binding globulin (SHBG) concentrations were determined using a kit from Diagnostic System Laboratories (Los Angeles, CA, USA). The fraction of free testosterone was shown by the testosterone index (=[(testosterone]×100)/[SHBG]).

Statistics

All values are expressed as means ± SEM. Significance was tested using the non-parametric two-sample Mann-Whitney test. Correlations were calculated using the non-parametric two-sample Mann-Whitney test. Differences with a P value <0.05 were considered significant. Relationships between the different variables were calculated by Spearman's rank correlation method. Possible type I errors due to multiple comparisons may be assessed using more stringent P values of <0.05.

Results

The mean ages of the PCOS group and the control group were similar (29.6 and 29.3 years respectively). Most PCOS patients showed normal glucose concentrations following an OGTT, except for four patients who had intolerance to glucose but were not diabetic (1 h postprandial 160–250 mg/100 ml and/or 2 h postprandial 140–200 mg/100 ml). As a group, PCOS patients had higher fasting insulin concentrations (31.8 versus 18.5 mIU/ml) and higher BMI (30.6 versus 22.4 kg/m²) than
controls. PCOS patients were hyperlipidaemic with significantly higher cholesterol, LDL and TG concentrations and nonsignificantly lower HDL concentrations (Table I). However, there were no significant relationships between plasma lipids and anthropometric variables (BMI, W/H ratio, BCF) in the whole PCOS group of patients.

On the basis of the OGTT, PCOS patients could be separated into two groups. The first group has high fasting insulin concentrations which responded to the OGTT with an exaggerated insulin secretion; these patients had IR. The second group consisted of PCOS patients with normal fasting insulin concentrations and a normal insulin secretion response following the OGTT. Insulin secretion in this group was similar to the controls. PCOS patients were hyperinsulinaemic with significantly higher insulin concentrations following the OGTT in the 20 healthy, normally ovulating control group (Figure 1). This difference could be clearly shown when the sums of the insulin concentrations following the OGTT were compared (sum [insulin] = [insulin] at 0 min + [insulin] at 60 min + [insulin] at 120 min) 167 ± 39 for NIR patients versus 376 ± 104 for IR patients (P < 0.001). Of the PCOS patients, 16 had high fasting and post-glucose load insulin concentrations, while 15 had normal values (Figure 1 and Table II).

Body composition was assessed by the three different parameters described above. Both BCF and BMI were found to be significantly higher in the IR group compared with the NIR group (Table II; P < 0.008 and P < 0.0001 respectively). Fat distribution, as measured by the W/H ratio, was mostly in the upper body segment (android type) in IR PCOS patients compared with the other 15 patients and 20 healthy normally ovulating female subjects. Thus, two distinct subgroups were defined: insulin resistant (IR) and non-IR (NIR).

Figure 1. Mean (SEM) glucose (left) and insulin (right) concentrations at time 0 and every hour for 2 h following the administration of 75 g glucose per os in polycystic ovarian syndrome (PCOS) patients. In all patients, glucose concentrations were within normal limits; hence none of the patients was diabetic. Fasting insulin concentrations and insulin concentrations in response to glucose administration were found to be significantly higher in 16 PCOS patients compared with the other 15 patients and 20 healthy normally ovulating female subjects. Thus, two distinct subgroups were defined: insulin resistant (IR) and non-IR (NIR).

Table I. Plasma lipids and insulin concentrations in polycystic ovarian syndrome (PCOS) patients and controls

<table>
<thead>
<tr>
<th></th>
<th>PCOS (n = 31)</th>
<th>Controls (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.6 ± 1.7</td>
<td>29.3 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.6 ± 6.0</td>
<td>22.4 ± 2.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Insulin (mIU/ml)</td>
<td>31.8 ± 17.3</td>
<td>18.5 ± 2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Sum insulin (mIU/ml)</td>
<td>264 ± 25</td>
<td>170 ± 12</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.0 ± 1.06</td>
<td>4.34 ± 0.94</td>
<td>0.025</td>
</tr>
<tr>
<td>Low density lipids (mmol/l)</td>
<td>3.80 ± 0.96</td>
<td>2.84 ± 0.74</td>
<td>0.001</td>
</tr>
<tr>
<td>High density lipids (mmol/l)</td>
<td>1.17 ± 0.37</td>
<td>1.23 ± 0.48</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.94 ± 0.93</td>
<td>1.33 ± 0.75</td>
<td>0.018</td>
</tr>
</tbody>
</table>

NS = not significant

Table II. Lipid and insulin concentrations in the two polycystic ovarian syndrome groups, insulin resistant (IR) and non-IR (NIR)

<table>
<thead>
<tr>
<th></th>
<th>IR (n = 16)</th>
<th>NIR (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (BMI, kg/m²)</td>
<td>34.5 ± 5.2</td>
<td>26.2 ± 3.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Waist/hip (W/H) ratio</td>
<td>0.89 ± 0.07</td>
<td>0.83 ± 0.05</td>
<td>0.005</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>37.0 ± 1.6</td>
<td>31.0 ± 2.0</td>
<td>0.008</td>
</tr>
<tr>
<td>(BCF, % fat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin concentration (mIU/ml)</td>
<td>44.9 ± 9.3</td>
<td>23.0 ± 2.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Sum insulin concentration (mIU/ml)</td>
<td>376 ± 104</td>
<td>167 ± 39</td>
<td>0.000</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.8 ± 1.8</td>
<td>5.20 ± 1.14</td>
<td>NS</td>
</tr>
<tr>
<td>Low density lipids (mmol/l)</td>
<td>3.8 ± 1.0</td>
<td>3.80 ± 1.04</td>
<td>NS</td>
</tr>
<tr>
<td>High density lipids (mmol/l)</td>
<td>1.2 ± 0.5</td>
<td>1.20 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>2.29 ± 1.01</td>
<td>1.57 ± 0.67</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant

*Sum insulin = Σ[insulin] = total insulin at 0, 60 and 120 min.
Lipids, insulin and DHEA-S in PCOS

Table III. Spearman rank correlations between plasma lipids and anthropometric and hormonal parameters in polycystic ovarian syndrome

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol</th>
<th>Low density lipid</th>
<th>High density lipid</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IR</td>
<td>NIR</td>
<td>IR</td>
<td>NIR</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.68 (0.01)</td>
<td>0.50 (0.03)</td>
<td>-0.63 (0.04)</td>
<td>-0.71 (0.003)</td>
</tr>
<tr>
<td>Sum insulin</td>
<td>0.86 (0.00)</td>
<td>0.70 (0.01)</td>
<td>-0.74 (0.006)</td>
<td>0.86 (0.00)</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>0.56 (0.03)</td>
<td>-0.57 (0.049)</td>
<td>-0.70 (0.003)</td>
<td>0.71 (0.003)</td>
</tr>
<tr>
<td>DHEA-S/testosterone</td>
<td>0.60 (0.019)</td>
<td>0.49 (0.06)</td>
<td>-0.48 (0.07)</td>
<td>0.56 (0.03)</td>
</tr>
</tbody>
</table>

DHEA-S = dehydroepiandrosterone sulphate, IR = insulin resistant, NIR = non-insulin resistant.

Figure 2. Summary of the different parameters that influence plasma lipid concentrations in polycystic ovarian syndrome patients with and without insulin resistance (IR and NIR respectively). CHOL = cholesterol; DHEA-S = dehydroepiandrosterone sulphate; T = testosterone; LDL = low density lipid; HDL = high density lipid; TG = triglyceride; W/H = waist/hip ratio; BCF = percentage of body fat.

In PCOS patients as a group, there was no correlation between the lipid profiles. With regard to body composition, there were no correlations except for TG with BCF, and W/H ratio with HDL in the NIR group. There were no relationships between plasma lipids and anthropometric variables in any of the IR patients. There were no correlations between insulin and plasma lipids in the NIR patients, but significant relationships for all the lipids in the IR group, independent of the BMI (Figure 2 and Table III).

A comparison between these two groups of PCOS patients with and without IR shows that IR subjects had significantly higher androgen concentrations: higher testosterone and lower SHBG concentrations, and therefore a lower testosterone index ([testosterone]/[SHBG]). The adrenal secretion of cortisol and DHEA-S (standard in our laboratory <5.7 ± 2.7 mmol/l; Elia et al., 1990) was similar in both groups. However, DHEA-S/testosterone ratios were significantly different between these two groups. LH concentrations and the gonadotrophin ratio were elevated in NIR PCOS patients, while normal gonadotrophin blood concentrations and normal LH/FSH ratios were measured in IR PCOS patients (Table IV).

The relationships between endocrine profiles and lipids are shown in Table III. In IR patients, insulin and DHEA-S concentrations and the DHEA-S/testosterone ratio were positively correlated with cholesterol, LDL and TG concentrations and negatively correlated with HDL concentrations. In NIR subjects, the DHEA-S concentration was negatively correlated with cholesterol and LDL concentrations. The HDL concentration was negatively related to the W/H ratio, and the TG concentration was positively related to BCF. There were no correlations between insulin and plasma lipids in NIR patients.

In PCOS patients as a group, there was no correlation between DHEA-S and fasting insulin concentrations ($r = 0.29$, $P = 0.18$).

Discussion

The present series, in agreement with other reports (Wild et al., 1985; Lithell et al., 1987; Wild and Bartholomew, 1988), shows that PCOS patients have abnormal lipid profiles compared with age-matched controls. However, their plasma lipids were not related to anthropometric variables. The PCOS group was divided according to insulin sensitivity rather than obesity because they formed better defined groups with similar hormonal characteristics. When our patients were so divided (Table II), both groups exhibited similar significant abnormalities in lipid parameters in comparison with the controls. However, a subsequent analysis has shown that the metabolic factors relating to lipids, such as body weight and insulin and androgen concentrations, show very different relationships within the two groups.
Obesity is related to increased TG and decreased HDL concentrations (Bonadonna and DeFronzo, 1992). However, the IR PCOS patients in this series showed no relationship between BMI, BCF, the W/H ratio and lipid values. This is in distinct contrast to the findings in patients with IR in type II diabetes and syndrome X (upper body obesity, IR, diabetes, hyperlipidaemia, hypertension; Reaven, 1988; McKeigue et al., 1992; Young et al., 1993). In the NIR patient group who were not obese, there were relationships between anthropometric parameters and lipids: BCF was positively correlated with TG concentration \( (r = 0.528, P = 0.04) \), and there was a negative correlation between the W/H ratio and HDL concentration \( (r = -0.608, P = 0.02) \). Furthermore, in the NIR patients with comparable insulin kinetics and BMI with the control group, there were significant differences in the lipid profiles. It is also interesting to contrast the effects of IR between IR obese patients and IR PCOS subjects. In the former there is a strong correlation between obesity and all the lipid parameters, whereas in the IR PCOS patients, despite a mean BMI of 34.5 kg/m\(^2\), no correlation whatsoever was found. Therefore the lipid abnormalities in this group were not related to obesity.

The degree of IR, as demonstrated by an increased \( \Sigma[\text{insulin}] \), was strongly correlated in the IR group with the cholesterol \( (r = 0.862, P < 0.0001) \), LDL \( (r = 0.695, P = 0.012) \), and TG \( (r = 0.856, P < 0.0001) \) concentrations, and negatively correlated with the HDL concentration \( (r = -0.735, P = 0.006) \). No correlation was found in the NIR patients. These relationships held similarly for fasting insulin concentrations. These data suggest that in PCOS patients with IR, dyslipidaemia is not related to the degree of obesity. To verify this point, it will be necessary to study a weight-matched control group of subjects.

Furthermore, there were no correlations between lipid values in all the patients with PCOS and any of the gonadotrophic hormones, their ratio or total testosterone concentration. These data are also supported by a recent study by Norman et al. (1995), who showed that in polycystic ovaries and PCOS patients there were no correlations between lipid profiles and androgens. Despite the fact that the PCOS group as a whole showed anthropometric, endocrine and lipid disturbances, their interrelationships were complex and could not be explained by obesity. With regard to adrenal function, all patients had normal plasma cortisol concentrations and there was no significant difference between DHEA-S concentrations in the two PCOS groups, despite a small increase observed in the NIR patients (12.1 versus 7.9 mmol/l). Nevertheless, there were completely opposite significant relationships between DHEA-S and lipid concentrations in each of the groups. In the IR group, the DHEA-S concentration was related to cholesterol, LDL and TG concentrations and negatively related to HDL concentration — all increasing the atherogenic risk profile. This is in contrast to findings in other situations where the DHEA-S concentration is considered to be protective (Barrett-Connor et al., 1986; Nestler et al., 1992). However, in the NIR group, there was a negative relationship between cholesterol and LDL concentrations. The reason for these differences is not entirely clear. DHEA-S concentrations did not correlate with the BMI or basal insulin or testosterone concentrations in any of the patients; in the IR group there was a significant correlation with \( \Sigma[\text{insulin}] \) \( (r = 0.701, P = 0.016) \). The various interactions between the metabolic and anthropometric parameters on plasma lipids in IR and NIR patients are summarized and shown schematically in Figure 2.

The relevance of DHEA-S concentration in the pathogenesis of atherosclerosis in general and of dyslipidaemia in particular has received much attention recently (Leszczynski et al., 1989; Mortola and Yen, 1990). In epidemiological studies, DHEA-S concentrations are inversely correlated with the development of myocardial infarction and hyperlipidaemia (Barrett-Connor et al., 1986; Mitchell et al., 1994). There is also an indication that low DHEA-S concentrations are an independent risk factor after accounting for other known risk factors, including plasma lipid concentrations. There are differences of opinion regarding the connection between insulin and DHEA-S concentrations. Nestler et al. (1992) maintain that insulin decreases the production of DHEA-S and increases its metabolic clearance rate, and even considers that DHEA-S is the ‘missing link’ between hyperinsulinaemia and atherosclerosis. Buffington et al. (1991) have shown that DHEA concentration is positively correlated with insulin binding and is inversely related to basal insulin and \( \Sigma[\text{insulin}] \). On the other hand, Yen’s group (Mortola and Yen, 1990) found that pharmacological doses of DHEA (1600 mg/day) induced IR yet lowered cholesterol and HDL concentrations. This suggests that DHEA affects insulin and not vice versa. These contradictory results may relate to differences in exogenous versus endogenous hormones, differences in the age and sex of the populations, and the presence of existing IR.

In our group, the interaction between DHEA-S, insulin and plasma lipids was complex and markedly influenced by the state of insulin sensitivity. Our results suggest that dyslipidaemia in PCOS patients may have different metabolic aetiologies depending on insulin sensitivity and DHEA-S metabolism. Therefore the investigation of PCOS should include an assessment of IR in the future. Furthermore, dyslipidaemia may occur in PCOS in the absence of IR.

It remains to be seen whether the two types of PCOS with similar degrees of dyslipidaemia are associated with an increased risk of coronary heart disease (Mattson et al., 1984).

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