Published in final edited form as:

Clin Endocrinol (Oxf). 2011 June ; 74(6): 714–719. doi:10.1111/j.1365-2265.2011.03983.x.

Determinants of dyslipidaemia in probands with polycystic ovary syndrome and their sisters

Jalini Joharatnam^{*}, Thomas M. Barber[†], Lisa Webber[‡], Gerard S. Conway[§], Mark I. McCarthy[†], and Stephen Franks^{*}

^{*}Institute of Reproductive and Developmental Biology, Imperial College London, London

[†]Diabetes and Endocrinology, University of Oxford, Oxford

[‡]Obstetrics and Gynaecology, Imperial College NHS Healthcare Trust, London, UK

[§]Reproductive Endocrinology, University College Hospital, London, UK

Summary

Objective—Polycystic ovary syndrome (PCOS) is associated with dyslipidaemia and obesity. It is not clear whether the dyslipidaemia of PCOS is attributable to PCOS itself, obesity, or a combination of both. Our objective was to assess the importance of familial dyslipidaemia in PCOS by comparing fasting lipids between probands and their (affected and nonaffected) sisters.

Design—Retrospective data set analyses.

Patients—Family study; 157 probands, 214 sisters and 76 control women (normal ovaries and regular cycles). All probands had PCOS, defined by symptoms of anovulation and/or hyperandrogenism with polycystic ovaries on ultrasound. Affected or unaffected status of sisters was defined by ovarian morphology.

Measurements—Serum concentrations of triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol.

Results—Triglyceride levels and body mass index (BMI) were higher and HDL cholesterol levels were lower in the probands than affected sisters, unaffected sisters and controls. These differences in lipid profiles between the groups disappeared after adjustment for BMI. No differences in lipids were seen between affected and unaffected sisters.

Conclusions—These data are consistent with heritability of lipid levels in sisters but strongly suggest that the predominant influence on the manifestation of dyslipidaemia in PCOS is body weight.

Introduction

Polycystic ovary syndrome (PCOS) is most typically characterized by hyperandrogenaemia and chronic anovulation¹ but is also a metabolic disorder associated with insulin resistance

Correspondence: Stephen Franks, Institute of Reproductive and Developmental Biology, Imperial College London, 5th Floor IRDB Hammersmith Hospital Du Cane Rd London W12 0NN, UK. Tel.: +44 (0)207 594 2109; Fax: +44 (0)207 594 2184; s.franks@imperial.ac.uk.

(IR) and dyslipidaemia, and often co exists with obesity. Women with PCOS and impaired glucose tolerance or type 2 diabetes have a significantly greater prevalence of lipid abnormalities (88%) than women with normal glucose tolerance and PCOS (58%).² Obesity appears to have an important role in the aetiology and development of PCOS and the degree of obesity often determines the severity of both reproductive and metabolic disturbances. There is a well-established link between obesity and dyslipidaemia, and it remains unclear whether the dyslipidaemia of PCOS is attributed to PCOS itself, obesity or (perhaps most likely) a combination of both these factors.

Polycystic ovary syndrome is a heterogeneous condition which is reflected in the 2003 Rotterdam diagnostic criteria.³ This requires the presence of two of the following three features for the diagnosis of PCOS: oligomenorrhoea, hyperandrogenism (defined clinically and/or biochemically) and polycystic ovarian morphology on ultrasonography. This creates several different subgroups of PCOS patients with differences between the subgroups in metabolic profiles, including lipid levels.^{4–6} The aetiology of PCOS is complex but heritability studies suggest a strong genetic susceptibility.⁷ Familial clustering has been noted⁸ and also greater concordance is seen in monozygotic twins compared to dizygotic twins.⁹ Although there is good evidence for heritability of hyperandrogenaemia and hyperinsulinaemia in sisters of women with PCOS,^{7,10,11} the heritability of lipid abnormalities is less clear. There is some evidence that dyslipidaemia is prevalent amongst relatives of women with PCOS,¹² although there have been very few large cohort studies investigating this.¹³

Dyslipidaemia has been reported in up to 70% of patients with PCOS,¹⁴ in both lean¹⁵ and obese^{16,17} subjects. It is important to identify such abnormalities early and to consider management of dyslipidaemia in women with PCOS to reduce cardiovascular risk. Given the potential significance of finding dyslipidaemia in young women and the fact that PCOS is a familial condition, the question arises as to whether to screen families of women with PCOS for lipid abnormalities. There are a few studies that address this question, and the principal objective of the current study was to compare fasting lipid profiles between PCOS probands and their (affected and unaffected) sisters.

Materials and methods

Subjects

The subjects studied included 157 probands, 214 sisters and 76 control women. Probands were recruited from reproductive endocrine, general endocrine or infertility clinics at one of two centres: St Mary's Hospital (Imperial College Healthcare Trust) and University College Hospitals, London as previously described.⁷ All probands had polycystic ovarian morphology on ultrasound scan. Clinical and biochemical features included menstrual irregularities (oligo-amenorrhoea $n = 42$), hyperandrogenism (defined clinically $n = 8$) or both ($n = 108$) i.e. 69% also met the "classic" NIH criteria for diagnosis of PCOS.¹⁸ Clinical hyperandrogenism was defined as the presence of acne, hirsutism (Ferriman-Gallwey score 8) or alopecia. All probands therefore satisfied the Rotterdam criteria for the diagnosis of PCOS.³ Sisters were defined as 'affected' (according to the presence of polycystic ovarian morphology, $n = 153$) or 'unaffected' (normal ovarian morphology, $n = 61$) according to the

images obtained using trans-vaginal ultrasonography. The unaffected sister group is arguably the most appropriate control group for comparison with the probands as they share similar genetic and environmental exposure but not the ultrasonographic features of PCOS.⁷ Of the affected sisters, 22 had oligomenorrhea, 36 had hyperandrogenism and 47 had both oligomenorrhea and clinical hyperandrogenism. In the unaffected group, four had irregular menses and clinical hyperandrogenism. Therefore, using the Rotterdam criteria for diagnosis, 105 of the 153 'affected' sisters had PCOS, and only four of the 61 'unaffected' sisters had PCOS. It is unknown whether any of the sisters with symptoms of PCOS themselves presented to a physician. All the control women had ultrasound-proven normal ovarian morphology, all had regular menstrual cycles and none had any hyperandrogenic features. Therefore, none of the control women fulfilled any of the Rotterdam-defined diagnostic criteria for PCOS.³

The subjects were of multiple ethnicities, within the proband group 136 European, seven Afro-Caribbean, six South Asian, one Middle Eastern and seven other. The ethnicities of the 214 sisters were as follows: 183 European, 11 Afro-Caribbean, 11 South Asian, four Middle Eastern and five other. Of the controls, 76 were European. All subjects were postmenarchal and premenopausal. None of the subjects was pregnant at the time of inclusion in the study.

The relevant UK Ethics Committees approved this study. All subjects gave fully informed consent. The study was conducted in accordance with the guidelines in the Declaration of Helsinki.

Biochemical measurements

Blood samples were taken from each subject in a fasting state. These samples were used to measure serum insulin, high-density lipoprotein (HDL)-cholesterol, total cholesterol and triglycerides, and plasma glucose. Samples were assayed for insulin using an in-house insulin ELISA kit.¹⁹ This assay specifically measures insulin, and there is no specific cross-reactivity with proinsulin and split proinsulin. Insulin resistance was calculated from fasting plasma glucose and fasting serum insulin levels by means of the Homeostatic Model Assessment (HOMA) algorithm.²⁰ For this purpose, where possible, an average of two fasting glucose samples, obtained with a 30-min collection interval, was used. Triglycerides, HDL cholesterol and total cholesterol were measured as previously described.²¹ LDL cholesterol was calculated using the Friedewald equation [Total cholesterol-HDL cholesterol-(Triglycerides/2.19)]. Testosterone was measured by RIA after extraction as previously described.²²

Statistical analysis

All data were log transformed and checked for normal distribution. Data are presented as geometric mean [Standard Deviation (SD) range]. Statistical analyses were performed using InStat 3.0a for Macintosh (Graph Pad, San Diego, CA, USA). Comparisons between three groups (Table 2) were made using one-way ANOVA (independent-sample *t*-test) if data were normally distributed and by the Kruskal–Wallis test if not. Comparisons between two different groups (Table 3) were performed using unpaired *t* testing on normally distributed data or Mann–Whitney testing if data were not normally distributed (nonparametric testing

indicated by * on graphs). Multiple linear regression was used to adjust for body mass index (BMI).

Results

Comparison of lipid profiles between probands and sisters

The clinical and biochemical data of the probands, sisters and controls are summarized in Table 1. Serum triglyceride levels in probands were significantly higher than in either affected sisters or unaffected sisters. Serum triglyceride levels in affected and unaffected sisters were not significantly different. Serum HDL-cholesterol levels in probands were lower than in either affected sisters or unaffected sisters. HDL-cholesterol levels in affected and unaffected sisters were not statistically different. Total cholesterol and LDL cholesterol levels were similar between the groups. Probands had a higher BMI and waist-to-hip ratio (WHR) than both affected sisters and unaffected sisters. BMI and WHR were similar in affected and unaffected sisters.

The analyses of probands and affected sisters, and probands and unaffected sisters were then repeated using adjustments for differences in BMI between the groups, to determine whether the differences in triglycerides and HDL between probands and the sister groups, between the groups remained significant. After correction for BMI, the difference between probands and affected sisters in levels of LDL between the two groups just reached significance ($P = 0.05$) but the differences between the groups in triglyceride and HDL levels were no longer present. However, the difference in HDL levels remained after correction for BMI, although the degree of significance changed from $P = 0.01$ to <0.05 (Table 2). There were no significant differences between the lipid profiles of affected and unaffected sisters, or unaffected sisters and controls. After correction for BMI, neither the probands nor unaffected sisters showed any significant differences in lipid profile from the control group.

Many of the affected sisters fulfilled the Rotterdam diagnostic criteria for PCOS (105/153). To assess whether there were any androgen or lipid differences within this affected sister subgroup, the affected sisters with symptoms ($n = 105$) were compared to affected sisters without symptoms ($n = 48$). Significant differences were seen in their fasting insulin ($P = 0.05$) and HOMA-IR levels (<0.05) as well as testosterone ($P = 0.05$) and triglyceride levels ($P = 0.05$; Table 3). The BMI of affected sisters with symptoms was 1.2 kg/m^2 higher than affected sisters without symptoms, although this was not significant. However, after correction for BMI the differences in fasting insulin, HOMA-IR, triglycerides and testosterone disappeared. The triglyceride levels of all the groups are summarized in Fig. 1.

To investigate the effect of PCO phenotype itself on lipid profiles, the affected sisters without symptoms were compared to unaffected sisters (Table 3). Significant differences were seen in androstenedione levels. The difference in testosterone levels approached significance with a P value of 0.06 . No significant differences were seen in any of the lipid parameters.

Discussion

Our initial analysis demonstrated that serum triglyceride and HDL-cholesterol concentrations in PCOS probands were significantly different from those in their sisters (regardless of whether or not those sisters had polycystic ovarian morphology). Triglyceride levels were higher in the probands than either of the sister groups whilst HDL cholesterol levels were lower in the probands than both affected and unaffected sisters. However, probands in our study had a higher WHR and BMI compared to their sisters and controls, and the differences in lipid profiles between the groups were no longer present after adjustment for BMI. There were no significant differences in lipid profiles between affected and unaffected sisters. These data are consistent with the heritability of lipid levels in sisters (with or without PCOS), but also strongly suggest that obesity has a predominant influence in the manifestation of dyslipidaemia in PCOS.

A similar result was seen when comparing affected sisters with and without symptoms of PCOS. Affected sisters with PCO symptoms had significantly higher triglyceride levels, testosterone, fasting insulin and HOMA-IR than affected sisters without symptoms. The BMI of affected sisters with PCO symptoms was 1.2 kg/m² higher than the affected sisters without PCO symptoms. When adjusted for this BMI difference, both the affected sisters with and without PCO symptoms showed no significant differences.

Sam *et al.*¹³ have shown that probands and affected sisters had similar and elevated total and LDL cholesterol levels compared to unaffected sisters, and also showed higher triglycerides and lower HDL cholesterol in their probands compared to affected and unaffected sisters, but did not correct for BMI in their analysis. High triglyceride levels and low HDL levels are more commonly seen in obese women with PCOS.^{2,17,23} Evidence supporting a role for environmental factors on lipid profiles includes those studies examining the effect of diet on lipid composition. Hypocaloric diets, regardless of their composition in obese women with PCOS, have been shown to reduce weight and leptin levels as well as total cholesterol, LDL and triglycerides.^{23,24,25} On the other hand, high fructose diets are known to up-regulate the lipogenesis pathway leading to an increase in triglycerides.²⁶

Although probands had higher triglyceride levels than their sisters the mean, 1.14 mM (1.07, 1.27) was below the 1.7 mM (150 mg/dl) threshold to fulfil a key component of the metabolic syndrome.³ This highlights the problem of if or when strategies for lipid-lowering intervention are necessary in this young group of patients. Limited epidemiological studies have shown no direct evidence of an increase in coronary heart disease in middle aged women with a history of PCOS.²⁷ There are, as yet, no data from long-term prospectively designed studies looking at cardiovascular events in PCOS patients and therefore no good evidence that lipid-lowering intervention would actually lower the cardiovascular event rate in PCOS.

Limitations of this study include the fact that the data here are cross-sectional rather than longitudinal. It would be interesting to see if the lipid profiles of particular patients change over time as their BMI changes. It is also not possible to infer definite causality from the data presented; we can only present associations. There are also other factors such as alcohol

intake, smoking, diet, exercise and medications that the patients may be taking that we have not been able to account for.

In conclusion, we found no concordance of serum concentrations of triglycerides and high-density lipoprotein cholesterol between probands and affected sisters. Both indices were independently associated with body mass index and after adjustment for body mass index, the differences between probands and their sisters were no longer evident. Adjustment for polycystic ovarian appearance itself using comparison of the affected sisters without symptoms and unaffected sisters showed no differences in lipid profiles. It may be inferred from this that obese women with polycystic ovary syndrome have an exaggerated metabolic insult with dyslipidaemia being influenced by the effects of obesity. Our data suggest that any genetic predisposition to dyslipidaemia in women with polycystic ovary syndrome could be considerably amplified by weight gain. Sisters with minimal clinical or biochemical effects of polycystic ovary syndrome should therefore be advised about the hazards of weight gain.

Acknowledgements

This study was funded in part by the Medical Research Council (G9710020). JJ was funded by a Project Grant from Wellbeing of Women (RG944).

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Fig. 1. Serum triglyceride levels (mm, arithmetic means denoted by a black line) of probands ($n = 157$), affected sisters with symptoms (affected sisters +, $n = 105$), affected sisters without symptoms (affected sisters -, $n = 48$), unaffected sisters ($n = 61$) and controls ($n = 76$).

Table 1

Clinical and biochemical data [geometric means (SD range)] in probands, sisters and controls

	Probands (<i>n</i> = 157)	Affected sister (<i>n</i> = 153)	Unaffected sister (<i>n</i> = 61)	Controls (<i>n</i> = 76)
Age	32.9 (26.4, 39.3)	31.3 (25.3, 37.3)	37.8 (30.1, 45.5)	36.9 (31.9, 41.8)
BMI (kg/m ²)	28.3 (26.9, 29.5)	25.1 (24.5, 25.7)	24.5 (23.4, 25.7)	24 (19.9, 28.8)
Triglycerides (mm)	1.14 (1.07, 1.27)	0.98 (0.93, 1.05)	0.92 (0.83, 1.02)	0.91 (0.60, 1.37)
HDL (mm)	1.23 (1.17, 1.30)	1.35 (1.29, 1.40)	1.43 (1.35, 1.53)	1.33 (1.08, 1.64)
LDL (mm)	2.88 (2.69, 3.05)	3.00 (2.86, 3.14)	2.87 (2.66, 3.08)	2.7 (2.12, 3.53)
Waist/Hip Ratio	0.81 (0.79, 0.83)	0.78 (0.77, 0.79)	0.78 (0.76, 0.79)	0.78 (0.7, 0.86)
Total cholesterol (mm)	4.79 (4.67, 4.99)	4.9 (4.67, 5.01)	4.85 (4.65, 5.01)	4.6 (3.88, 5.47)
Fasting insulin (pm)	24.2 (18.6, 30.9)	20.8 (16.2, 26.3)	12.5 (8.1, 19.1)	9.8 (2.88, 33.11)
HOMA-IR	0.58 (0.45, 2.21)	0.45 (0.10, 1.82)	0.28 (0.06, 1.41)	0.21 (0.06, 0.72)
SHBG (nm)	40.6 (34.5, 45.7)	46.8 (41.6, 52.5)	52.5 (45.7, 61.7)	60.3 (39.2, 92.8)
Testosterone (nm)	2.14 (1.95, 2.29)	2.01 (1.82, 2.17)	1.56 (1.41, 1.74)	1.5 (1.01, 2.21)
Androstenedione (nm)	6.61 (6.17, 7.23)	6.75 (6.17, 7.34)	5.01 (4.57, 5.49)	4.95 (3.36, 7.08)

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance.

Table 2

Comparison of the endocrine and metabolic indices between groups (probands, affected and unaffected sisters) using one-way ANOVA (independent-sample *t*-test) when data normally distributed and Kruskal–Wallis testing (indicated by *) if data were not normally distributed

	Probands <i>n</i> = 157 vs. affected <i>n</i> = 153 <i>P</i> -value	Probands <i>n</i> = 157 vs. affected <i>n</i> = 153 adjusted for BMI <i>P</i> -value	Probands <i>n</i> = 157 vs. unaffected <i>n</i> = 61 <i>P</i> -value	Probands vs. unaffected adjusted for BMI <i>P</i> -value	Affected vs. unaffected <i>P</i> -value	Unaffected vs. controls <i>P</i> -value	Probands <i>n</i> = 157 vs. controls <i>n</i> = 76 adjusted for BMI
BMI (kg/m ²)*	<0.001	–	<0.01	–	ns	–	–
Triglyceride (mmol)*	<0.01	ns	<0.01	ns	ns	ns	ns
HDL cholesterol (mmol)	<0.05	ns	<0.01	<0.05	ns	<0.05	ns
LDL cholesterol (mmol)*	ns	0.05	ns	ns	ns	ns	ns
Waist/Hip ratio	<0.01	–	<0.01	–	ns	–	–
Total cholesterol (mmol)	ns	ns	ns	ns	ns	ns	ns
Fasting insulin (pmol)*	ns	ns	<0.05	<0.01	ns	ns	<0.05
HOMA-IR*	ns	ns	<0.05	<0.01	ns	ns	<0.01
SHBG (nmol)	ns	ns	<0.05	ns	ns	ns	<0.01
Testosterone (nmol)*	ns	ns	<0.001	<0.0001	<0.001	ns	<0.0001
Androstenedione (nmol)	ns	ns	<0.001	<0.0001	<0.001	ns	<0.0001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance.

Adjustment for BMI made using multiple regression analysis; ns, nonsignificant.

Table 3

Table showing affected sisters with symptoms of PCOS (affected sisters +), affected sisters without symptoms (affected sisters –) and unaffected sisters. Students *t* test used to compare normally distributed data and Mann–Whitney test used (indicated by *) if data were not normally distributed

	Affected sisters + <i>n</i> = 105	Affected sisters – <i>n</i> = 48	Unaffected sisters <i>n</i> = 61	Comparing affected sisters + and affected sisters – (<i>P</i> value)	Comparing affected sisters + and affected sisters – adjusted for BMI	Comparing affected sisters – to unaffected sisters (<i>P</i> value)
BMI (kg/m ²)	25.7 (20.4–32.3)	24.5 (20.8–29.5)	24.5 (20.9–28.8)	ns*	–	ns
Triglycerides (mm)	1.03 (0.65–1.63)	0.89 (0.60–1.31)	0.92 (0.62–1.09)	<0.05	ns	ns*
HDL (mm)	1.39 (0.95–2.05)	1.32 (1.02–1.7)	1.43 (1.12–1.84)	ns*	ns	ns
LDL (mm)	3.04 (2.29–4.06)	2.9 (2.25–3.8)	2.86 (2.15–3.81)	ns	ns	ns
Waist/Hip Ratio	0.78 (0.71–0.86)	0.78 (0.73–0.85)	0.78 (0.72–.83)	ns*	ns	ns
Total cholesterol (mm)	4.97 (4.13–5.89)	4.72 (3.93–5.62)	4.85 (4.13–5.7)	ns	ns	ns
Fasting insulin (pm)	23.8 (5.75–97)	16.2 (11.2–61.3)	12.6 (2.51–64.4)	<0.05*	ns	ns*
HOMA-IR	0.51 (0.12–2.13))	0.34 (0.09–1.27)	0.28 (0.06–1.43)	<0.05 *	ns	ns*
SHBG (nm)	46.8 (24.5–89.1)	46.7 (28.2–78.7)	53.2 (32.8–86.1)	ns	ns	ns
Testosterone (nm)	2.1 (1.35–3.29)	1.82 (1.25–2.63)	1.57 (1.1–2.23)	<0.05 *	ns	0.06
Androstenedione (nm)	6.97 (4.47–10.7)	6.3 (4.17–9.53)	5.06 (3.74–6.4)	ns	ns	<0.01

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance. Clinical and biochemical data [geometric means (SD range)]; ns, nonsignificant. Adjustment for BMI made using multiple regression analysis.