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Evidence for pancreatic β-cell dysfunction in brothers of women with polycystic ovary syndrome

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Abstract

Hyperandrogenemia and insulin resistance are heritable traits in sisters of women with polycystic ovary syndrome (PCOS). Hyperandrogenemia also appears to be the male reproductive phenotype; however, it is less clear whether male relatives are at risk for the metabolic disorders associated with PCOS. In this study, we tested the hypothesis that brothers of women with PCOS have defects in insulin action and/or secretion. Twenty-three non-Hispanic white brothers of women with PCOS and 23 non-Hispanic white control men of comparable age matched for body mass index underwent a modified frequently sampled intravenous glucose tolerance test. Parameters of insulin sensitivity and secretion were determined using minimal-model Bergman protocol. Disposition index was significantly decreased (2540 [1080, 3172] vs 2901 [2096, 4487], $P = .009$) independent of a family history of diabetes mellitus, and glucose effectiveness was significantly increased (2.4 [1.9, 2.7] vs 2.0 [1.8, 2.2], $P = .02$) in brothers compared with control men. We conclude that brothers of women with PCOS have evidence for pancreatic β-cell dysfunction and may be at increased risk for type 2 diabetes mellitus.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common disorder of premenopausal women, affecting approximately 7% of this population [1]. The reproductive phenotype is characterized by hyperandrogenemia, disordered gonadotropin secretion, and polycystic ovaries [2]. Women with PCOS frequently have profound insulin resistance [3], pancreatic β-cell dysfunction [4,5], dyslipidemia [6], obesity, and other features of the metabolic syndrome [7]. Indeed, PCOS is likely the leading risk factor for type 2 diabetes mellitus (DM) in adolescent girls and young adult women [8,9].

Familial aggregation of PCOS has been well established consistent with a genetic susceptibility to the disorder, and up to approximately 40% of premenopausal sisters have the reproductive phenotype of hyperandrogenemia [10-12]. Sisters with this reproductive phenotype also have the characteristic metabolic defects of PCOS [13,14]. These observations have led to a search for male phenotypes in PCOS families, and we have found that hyperandrogenemia is the reproductive phenotype in the brothers of women with PCOS [15]. Several studies have suggested that male relatives may also have metabolic abnormalities, such as dyslipidemia [16], glucose intolerance [17], and insulin resistance [12,17,18]. However, the underlying defects in glucose homeostasis have not been defined in male relatives compared with control men. We performed this study to test the hypothesis that male first-degree relatives of women with PCOS have defects in insulin action and/or secretion.

2. Methods

2.1. Subjects

We studied 23 brothers of the 19 non-Hispanic white women with PCOS. The diagnosis of PCOS was made in the probands by an elevation of circulating testosterone (T) and/or non–sex hormone binding globulin-bound (unbound) T

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Table 1
Clinical features and reproductive hormone levels in PCOS brothers and control men

Variables	Brothers (n = 23)	Control (n = 23)	*P*
Age (y)	30 (21, 34)	31 (25, 37)	.21
BMI (kg/m^2)	28.1 (22.9, 32.3)	26.7 (23.4, 30.3)	.81
Systolic blood pressure (mm Hg)	118 (110, 130)	115 (110, 126)	.64
Diastolic blood pressure (mm Hg)	72 (62, 82)	72 (70, 78)	.95
T (ng/dL)[a]	522 (419, 616)	512 (433, 593)	.39
uT (ng/dL)[a]	241 (219, 302)	255 (166, 310)	.64
DHEAS (ng/mL)[b]	2820 (1704, 3697)	2827 (2405, 3090)	.47
Fasting glucose (mg/dL)[c]	87 (81, 97)	88 (82, 92)	.88
2-h postchallenge glucose (mg/dL)[c]	115 (72, 123)	92 (77, 111)	.26
Fasting insulin (μU/mL)[d]	13 (10, 17)	11 (8, 19)	.40
2-h postchallenge insulin (μU/mL)[d]	40 (21, 79)	28 (22, 47)	.51

Values are the median (25%, 75% interquartile range); *P* value by Wilcoxon signed ranks test.
[a] To convert to nanomoles per liter, multiply by 0.00347.
[b] To convert to micromoles, multiply by 0.002714.
[c] n = 17; to convert to millimoles per liter, multiply by 5.55.
[d] n = 17; to convert to picomoles per liter, multiply by 7.175.

(uT) levels associated with chronic oligomenorrhea (≤6 menses per year) [10,13,15]. Women with nonclassic 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate tests [10,13,15]. One family had 3 brothers, 2 families had 2 brothers, and 16 families had a single brother. The clinical and biochemical features on the probands have been reported as part of previous studies [10,13,15]. Twenty-three unrelated non-Hispanic white control men were matched to each brother for BMI. All subjects were aged 16 to 48 years, were in good health, and had no history of hypertension or dyslipidemia. Subjects were not taking any medications known to alter sex hormones, or insulin sensitivity or secretion for at least 1 month before the study. None of the control men had a history of DM personally or in a first-degree relative. None of the brothers had a personal history of DM; however, 5 families had a first-degree relative with DM. Of these families, one had 3 brothers, one had 2 brothers, and 3 had a single brother. The Institutional Review Boards of the Pennsylvania State University College of Medicine, Brigham and Women's Hospital, and Northwestern University's Feinberg School of Medicine approved this study; and all subjects gave written informed consent.

Height, weight, and blood pressure were obtained; and body mass index (BMI) was determined in all subjects. A 75-g oral glucose tolerance test (OGTT) with glucose and insulin levels obtained at 0 and 2 hours postchallenge was performed after a 300-g carbohydrate preparatory diet and an overnight fast in 17 brothers and all control subjects; the control subjects were required to have normal glucose tolerance as a selection criterion [19]. A baseline blood sample was obtained for T, uT, and dehydroepiandrosterone sulfate (DHEAS) measurements.

A frequently sampled intravenous glucose tolerance test (FSIGT) was performed in the morning after a 300-g carbohydrate preparatory diet and a standard overnight fasting period of 10 hours as reported [5]. All subjects had 2 intravenous catheters inserted, one in each arm, and were then allowed to rest for 30 minutes. At 0 minute, glucose (0.3 g/kg) was injected over 1 minute; at 20 minutes, 500 mg of tolbutamide was injected over 20 seconds. Blood samples were drawn at −15, −10, −5, −1, 0, 2, 3, 4, 5, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, and 100 minutes and every 20 minutes thereafter until 180 minutes. The insulin sensitivity index (SI) and glucose effectiveness (SG) were calculated by application of the minimal model of glucose kinetics (MINMOD computer program Millennium version; copyright, RN Bergman) to the dynamics of plasma glucose and insulin during the FSIGT [20,21]. The acute insulin response to glucose (AIRg) was calculated as the increment area under curve from basal of insulin values measured at 2 to 10 minutes and disposition index (DI; β-cell compensation index) as the product of SI and AIRg [21-23]. Glucose clearance (KG), a parameter of glucose tolerance, was calculated from the FSIGT as the slope of the least square regression line to the natural log of the glucose concentration vs time from 10 to 19 minutes after the glucose injection [5,24].

2.2. Assays

Plasma glucose levels were determined by glucose oxidase method. Assays for insulin, T, uT, and DHEAS were performed as previously reported [10,13,15].

2.3. Data analyses

For analysis of the data, the family unit was the case; in families with multiple brothers, brothers' and their matched controls' data were averaged to yield one mean value per family for brothers and their matched controls [15].

Table 2
Measures of glucose regulation in PCOS brothers and control men

	Brothers (n = 19[a])	Control (n = 19)	*P*
AIRg (μU/[mL.min])[b]	468 (285, 1200)	569 (319, 892)	1.00
SI ([×10^{-4}/min]/[μU/mL])[c]	4.5 (1.7, 7.4)	5.2 (4.0, 7.7)	.47
DI	2540 (1080, 3172)	2901 (2096, 4487)	.009
SG (10^{-2}/min)	2.4 (1.9, 2.7)	2.0 (1.8, 2.2)	.02
Peak insulin after glucose infusion (μU/mL)[b]	89 (51, 225)	116 (64, 171)	.83
Peak insulin after tolbutamide (μU/mL)[b]	153 (84, 296)	161 (104, 297)	.95
KG (/min)	2.16 (1.73, 3.01)	2.16 (1.55, 3.01)	.72

Values are the median (25%, 75% interquartile range); *P* value by Wilcoxon signed ranks test.
[a] Multiple brothers and control men for a single family are averaged to yield one mean value per family.
[b] To convert to picomoles per liter, multiply by 7.175.
[c] To convert to 10^{-5} per minute per picomole per liter, multiply by 1.67.

However, we repeated the analysis without adjusting for multiple brothers by using data from all of the individual brothers and their matched control subjects. All parameters were compared using Wilcoxon signed ranks test because data were not normally distributed. Analyses were repeated after exclusion of brothers with impaired glucose tolerance (IGT) (n = 3) and after exclusion of brothers (n = 8) with family history of DM. Analyses were performed using the 11.0 PC package of SPSS statistical software (SPSS, Chicago, IL). A $P < .05$ was considered significant. Data are reported as the untransformed mean ± SD.

3. Results

3.1. Clinical and biochemical features

The ages of PCOS brothers and control men were comparable, and the BMIs were well matched by design (Table 1). Blood pressure was similar in the 2 groups (Table 1). There were no differences between the 2 groups in T, uT, and DHEAS levels (Table 1). There were no significant differences between fasting or 2-hour post–glucose challenge glucose and insulin levels; however, 3 of 17 brothers (18%) had IGT (Table 1). All of the 6 brothers who did not have an OGTT had fasting glucose levels less than 100 mg/dL, and these levels did not differ from those in the brothers with normal glucose tolerance by OGTT.

3.2. Parameters of insulin action and secretion

There were no significant differences in SI or in AIRg in brothers compared with control men (Table 2). However, the DI, the product of SI and AIRg, was significantly decreased ($P = .009$) in brothers compared with control men (Table 2, Fig. 1). The differences in DI remained significant after exclusion of the 3 brothers with IGT (2309 [1010, 3120] brothers vs 2729 [2033, 4005] control, $P = .03$). These results were also not changed by the removal of the 5 PCOS families (8 brothers) who had history of type 2 DM in their first-degree relatives (DI 2513 [1056, 3194] brothers vs DI 2958 [2075, 4630] control, $P = .03$). The difference in DI remained significant when all individual brothers were compared with their matched control subjects. The SG was higher in brothers than in control men ($P = .02$) (Table 2). The glucose disappearance, KG, did not differ in the 2 groups (Table 2). Brothers who did not have an OGTT had a trend toward higher KG compared with those with normal glucose tolerance on OGTT (2.97/min ± 0.97/min for brothers who did not undergo an OGTT vs 2.06/min ± 0.97/min for brothers with normal glucose tolerance on OGTT, $P = .06$).

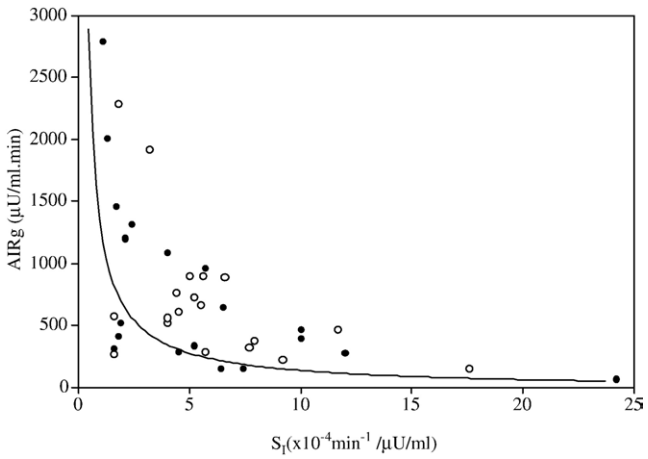

Fig. 1. The relationship between insulin secretion and insulin sensitivity in the brothers (●) and control men (○). The line depicts 50th percentile for this relationship from a large study (n = 93) of normal men and women, where SI × AIRg = 0.02237 [25]. Values below the 50th percentile are associated with an increased risk for type 2 DM [23].

4. Discussion

We found that the brothers of women with PCOS have a significantly decreased DI compared with control men regardless of glucose tolerance. Disposition index is the product of insulin sensitivity and insulin secretion [21-23]. When pancreatic β-cell function is normal, DI is a constant hyperbolic relationship; that is, if insulin sensitivity decreases, insulin secretion increases in a compensatory fashion and vice versa [23]. The finding of a decreased DI suggests that insulin secretion was inappropriately low when corrected for peripheral insulin sensitivity [5,21-23]. Therefore, one male metabolic phenotype in PCOS families appears to be pancreatic β-cell dysfunction. The SG was also significantly increased in brothers compared with control men [5,21]. This parameter has been suggested to be a measure of insulin-independent glucose-mediated glucose clearance known as *glucose effectiveness* [26], which is an important component of glucose tolerance [20,21,26,27]. There is concern about accuracy of minimal-model estimates of this parameter [28]. However, the finding of increased SG in first-degree relatives of patients with type 2 DM was confirmed by direct measurement [29].

First-degree relatives of individuals with type 2 DM also have insulin resistance [30] and decreased DI [29,31]; the latter predicts their risk for progression to type 2 DM [23,32,33]. There appears to be an increased prevalence of type 2 DM in the first-degree relatives of women with PCOS [12,17]. Nevertheless, DI was significantly decreased even in the PCOS brothers without a first-degree relative with type 2 DM. This finding suggests that abnormalities in insulin secretion in PCOS families were due to more than the coexistence of two common diseases: type 2 DM and PCOS. However, it remains possible that some of these first-degree relatives will develop type 2 DM. Furthermore, DI was still significantly decreased after exclusion of brothers with IGT. A limitation of this study is that we cannot exclude the presence of IGT in the brothers who did not undergo an

OGTT. However, none of these brothers had impaired fasting glucose according to the new, more stringent American Diabetes Association criteria [34]. Furthermore, mean KG tended to be higher in brothers who did not undergo an OGTT compared with those who had normal glucose tolerance based on OGTT. The KG decreases as glucose tolerance declines; KG <1.5/min indicates poor glucose tolerance [22], and KG <1/min is usually observed in diabetes [21]. Taken together, these findings suggest that the untested brothers had normal glucose tolerance. Another limitation of this study is that the groups were pair-matched for BMI but not for age. Nevertheless, the age range in both the brothers and control men was similar; and the age difference was within 2 years for most pairs. In those pairs where age differed by more than 10 years (n = 2), the control was older than the brother, which would favor the null hypothesis if insulin sensitivity or secretion decreased with age. Furthermore, there have been no changes in these metabolic parameters with age in previous studies using FSIGT [35] or euglycemic hyperinsulinemic clamp [36] techniques across a similar age range. Therefore, it is unlikely that differences in age between brothers and control men biased our findings. Increased glucose effectiveness [29] has also been reported in first-degree relatives of individuals with type 2 DM and may represent a compensatory mechanism for abnormalities in insulin action [21,27,29]. We have not found changes in SG in women with PCOS [5], whereas other investigators have reported decreases [37,38].

Metabolic abnormalities, such as dyslipidemia [16] and hyperinsulinemia [39], have been reported anecdotally in the male first-degree relatives of women with PCOS. The prevalence of type 2 DM is increased in parents of women with PCOS [12,17]. Eighteen percent of the 17 brothers tested had newly diagnosed glucose intolerance, which appears to be increased compared with rates in the general population of non-Hispanic white men of similar age [40]. However, this finding is constrained by the small sample of brothers who had glucose tolerance testing. Furthermore, there were no differences in KG, another parameter of glucose tolerance [24], in brothers and control men. Previous studies of the male metabolic phenotype have found evidence for insulin resistance in male first-degree relatives of women with PCOS or polycystic ovary morphology compared with control men by OGTTs [12,18]. To our knowledge, the mechanisms of such defects in glucose homeostasis have not been investigated. There is evidence to suggest that both insulin secretion and DI are heritable in the siblings of women with PCOS [12]. However, that study contained sisters as well as brothers and did not compare the findings in the siblings to a normal control group to define a metabolic phenotype. Disposition index has been found to be highly heritable in several populations [41-43]. In addition, prospective studies have shown that DI is the best predictor of risk for progression to diabetes [23]. Women with PCOS are at substantially increased risk for development of type 2 DM [8,9] because of defects in insulin action and secretion. Such abnormalities precede the development of glucose intolerance in these women [5]. The present study suggests that defects in insulin secretion are present in brothers of affected women and thus may confer an increased risk for type 2 DM in this population.

Although defects in insulin action and secretion are heritable in PCOS families [12,13,44], the precise pathogenesis of these abnormalities is unknown. Recent studies in adult male rhesus monkeys exposed to exogenous T in utero have found both insulin resistance and impaired insulin secretion, analogous to changes in similarly exposed female monkeys [45]. These observations suggest that intrauterine exposure to androgens may contribute to the putative defects in pancreatic β-cell function in brothers of women with PCOS. Our studies in the sisters of women with PCOS provide strong evidence that hyperandrogenemia secondary to variation in a gene regulating ovarian and adrenal steroidogenesis is the major reproductive phenotype [10,46]. Furthermore, metabolic abnormalities track with hyperandrogenemia in affected sisters, suggesting that these abnormalities have a common pathogenesis [13,14]. We have also found evidence for a similar defect in androgen biosynthesis in brothers of women with PCOS, who have significant elevations in DHEAS levels [15]. In the present study, mean DHEAS did not differ in brothers compared with control men, which was likely the result of a type 2 error due to the relatively small sample size. Nevertheless, it remains plausible that there may also be increased androgen production by affected male as well as female fetuses in PCOS families that programs abnormalities in glucose homeostasis in the adult [2,47,48].

In summary, we have found evidence for impaired insulin secretion in brothers of women with PCOS. The increase in SG in brothers may be due to a compensatory increase in insulin-independent KG. Prospective studies will be needed to determine whether such defects are predictive of development of type 2 DM in brothers of women with PCOS.

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