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PANCREATIC β -CELL DYSFUNCTION IN POLYCYSTIC OVARY SYNDROME: THE ROLE OF METFORMIN

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Abstract

Objective—To determine whether the administration of 6 months of daily metformin treatment in women with polycystic ovary syndrome (PCOS) would significantly improve pancreatic β -cell function as measured by an increase in the disposition index.

Methods—We enrolled women with PCOS from a private practice and from the Mount Sinai Hospital Endocrinology Clinic. All patients underwent frequently sampled intravenous glucose tolerance tests both on and off 500 to 1000 mg of twice daily metformin. Values of insulin sensitivity, glucose effectiveness, acute insulin response to glucose, and disposition index were calculated for each test. The product of acute insulin response to glucose and insulin sensitivity yielded the disposition index and estimated the degree of β -cell compensation for insulin resistance.

Results—We enrolled 14 women. We observed no significant changes in insulin sensitivity, glucose effectiveness, or acute insulin response to glucose, disposition index, or distributed glucose at time 0 before or after metformin treatment. Patients with PCOS treated with metformin remained statistically on the same hyperbolic curve, which is consistent with previously reported results of the effect of metformin on β -cell function. In contrast, the proportional change in disposition index correlated significantly with the proportional change in insulin sensitivity. Patients whose insulin sensitivity decreased after treatment showed a proportional decrease in disposition index, while patients whose insulin sensitivity increased showed a proportional increase in disposition index.

Conclusions—Our findings suggest that acute insulin response to glucose does not proportionately change to match change in insulin sensitivity. Thus, there may be a β -cell defect in women with PCOS.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

INTRODUCTION

Polycystic ovary syndrome (PCOS) occurs in approximately 6% to 7% of women of reproductive age (1) and is arguably the most common endocrine disorder in women (2-4). The syndrome is defined by 2 of the following 3 features: (a) oligo-ovulation or anovulation, (b) clinical and/or biochemical signs of hyperandrogenism, and (c) polycystic ovaries (5). This definition assumes the exclusion of other disorders that might present in a similar fashion (5). Studies show that up to 90% of women with PCOS have insulin resistance (3,6,7), and it is increasingly recognized that even lean women with PCOS have elevated insulin resistance when compared with findings in body mass index-matched controls (6). The prevalence of both impaired glucose tolerance (IGT) and type 2 diabetes mellitus in patients with PCOS significantly exceeds normal population estimates (8,9). In view of the metabolic burden of insulin resistance in PCOS, women with PCOS frequently have concurrent dyslipidemia and other features of metabolic syndrome (8,10). In the presence of peripheral insulin resistance, pancreatic β -cell insulin secretion increases in a compensatory manner in both obese and nonobese women with PCOS (11). Type 2 diabetes mellitus only develops when the β cells become “exhausted” and are unable to produce sufficient levels of insulin to maintain euglycemia against lower sensitivity. In PCOS, only a portion of women with insulin resistance eventually develops diabetes. This suggests that such patients may also have potential defects in insulin secretion (12).

Until now, no studies have analyzed the effect of metformin on β -cell function in women with PCOS. In view of the known anti-insulin therapeutic effect of metformin in most women with PCOS and the differing conclusions regarding insulin secretion in PCOS, our purpose in initiating this study was to correlate insulin secretion with insulin sensitivity in our cohort of women with PCOS. Our hypothesis was that the administration of daily metformin for 6 months in women with PCOS would significantly improve pancreatic β -cell function as measured by an increase in the disposition index. The disposition index is the product of the measures of insulin sensitivity and first-phase insulin secretion (acute insulin response to glucose [AIR_g]) and represents the ability of pancreatic β cells to compensate for peripheral insulin resistance. Disposition index defines a hyperbolic curve in which an increase in insulin sensitivity leads to a compensatory decrease in AIR_g and vice versa. Therefore, the disposition index is low when first-phase insulin secretion is insufficient relative to the prevailing level of peripheral insulin resistance. The disposition index decreases as glucose tolerance declines and has been shown to predict conversion to diabetes (13,14). Conversely, a high disposition index suggests elevated first-phase insulin secretion relative to the corresponding degree of peripheral insulin resistance.

METHODS

We prospectively enrolled women with PCOS from a private practice and from the Mount Sinai Hospital Endocrinology Clinic from January 2009 until June 2010. We documented age, self-reported race/ethnicity, body mass index, and testosterone concentration. Family history of type 2 diabetes mellitus was noted. All study participants met 2 of the 3 revised 2003 Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine PCOS Consensus Workshop Group diagnostic criteria, ie, (a) oligo-ovulation or anovulation, (b) clinical and/or biochemical signs of hyperandrogenism, and (c) polycystic ovaries (5). A pregnancy test was performed on all study participants. Other endocrinopathies were excluded by measuring thyrotropin, basal serum 17-hydroxyprogesterone, prolactin, and 24-hour urinary free cortisol levels. Exclusion criteria included age older than 50 years, known cardiovascular disease, thyroid disease, neoplasm, current smoking, diabetes mellitus, hypertension (blood pressure greater than 135/85 mm Hg), liver dysfunction, and renal impairment (serum creatinine concentration >1.4 mg/dL).

None of the patients had taken any of the following medications for at least 6 months before study enrollment: hormonal contraceptives; glucocorticoids; ovulation induction agents; antidiabetes or antiobesity drugs; or estrogenic, antiandrogenic, or antihypertensive medications.

All participants provided written informed consent before study participation. The Mount Sinai Medical Center Institutional Review Board approved the study protocol.

Study Design

Metformin Administration—After the initial frequently sampled intravenous glucose tolerance tests, participants who had been taking metformin for longer than 6 months were asked to hold metformin for a 6-week “washout” period before returning for the second round of frequently sampled intravenous glucose tolerance tests. For metformin-naïve participants, after the first round of frequently sampled intravenous glucose tolerance tests, metformin, 500 to 1000 mg twice daily, was initiated and taken for at least 6 months before the patients returned for the second round of tests. All patients were prescribed 1000 mg twice daily unless they were unable to tolerate the full dosage because of adverse effects; in those instances, patients were prescribed 500 mg twice daily.

Frequently Sampled Intravenous Glucose Tolerance Tests—All participants underwent frequently sampled intravenous glucose tolerance tests at the Mount Sinai Clinical Research Center both on and off the metformin regimen of 500 to 1000 mg twice daily as follows: patients fasted overnight and were admitted to the Mount Sinai General Clinical Research Center between 8 AM and 10 AM. Weight and height were measured to establish body mass index and to determine the glucose dosage for the frequently sampled intravenous glucose tolerance tests. An indwelling catheter was inserted in the right arm. Patients remained incumbent for the study period. A glucose injection (0.3 g/kg) was administered over 1 minute at time = 0 minutes followed by an insulin injection (0.05 units/kg) at time = 20 minutes. Twenty-three 4-mL blood samples were obtained for glucose and insulin concentrations corresponding to the following sample times: −10, −5, 0, 2, 4, 6, 8, 14, 19, 20, 22, 24, 30, 40, 60, 80, 100, 120, 140, 160, 180, 210, and 240 minutes (Fig. 1).

Laboratory Testing—Fasting insulin and glucose were measured in all patients. Serum was frozen at −80°C. Each patient’s samples were run in the same assay and in duplicate.

Assays—Insulin was measured by an Immulite assay (Diagnostic Products Corp, Los Angeles, California). The intra-assay coefficient of variation was 5.3% and the interassay coefficient of variation was 6.0%. Sensitivity was 2 μ IU/mL. Glucose was measured by the hexokinase method.

Minimal Model Analysis—Values of insulin sensitivity, glucose effectiveness, AIR_g , and disposition index were calculated for each frequently sampled intravenous glucose tolerance test on the basis of the Bergman minimal model using MINMOD Millenium software, Los Angeles, California (15,16). Insulin sensitivity measures the capacity for insulin-stimulated glucose uptake, while glucose effectiveness is the capacity for glucose-facilitated (insulin-independent) glucose uptake. AIR_g represents the responsiveness of β cells to a glucose load and is equal to the area under the curve for circulating insulin above basal level for the first 10 minutes after glucose injection. The product of AIR_g and insulin sensitivity yields the disposition index, which is an estimate of the degree of β -cell compensation for insulin resistance (15,17,18).

Statistical Analysis—All nonnormal data were log-transformed before analysis. The *P* values were computed with paired *t* tests.

Results

The study cohort included 12 white patients, 1 African American patient, and 1 Hispanic patient. The mean age at entry was 32 years (range 20–49 years), mean body mass index was 26.1 kg/m² (± 6.7 kg/m²), and mean total testosterone concentration was 49.5 ng/dL (± 26.3 ng/dL). Three patients had a family history of type 2 diabetes mellitus (Table 1). The patients' baseline glucose minimal model characteristics, as well as typical normal values and normal ranges (15), are shown in Table 2. Most patients were within the reference range for insulin sensitivity. Three patients had a family history of type 2 diabetes (Table 1). Pregnancy test was negative in all participants.

Intravenous glucose tolerance tests were performed before and after metformin treatment. There were no significant changes in insulin sensitivity, glucose effectiveness, AIR_g, disposition index, or distributed glucose at time 0 before or after metformin treatment (Table 3). The average glucose and insulin values during the intravenous glucose tolerance testing before and after metformin treatment are shown in Figure 2.

Despite the fact that the disposition index and insulin sensitivity showed no significant changes over the course of the study, the proportionate change in disposition index correlated significantly with the proportional change in insulin sensitivity. Those patients whose insulin sensitivity decreased after treatment showed a proportionate decrease in the disposition index, while those patients whose insulin sensitivity increased showed a proportionate increase in the disposition index (Fig. 3A). There were 2 obvious outliers, as shown in Figure 3, but the result was the same even after those were removed (Fig. 3B).

There was no obvious significant correlation between body mass index, testosterone levels, family history of diabetes, or metformin naïveté vs metformin washout and the propensity to have a positive vs negative change in the relationship of the disposition index and insulin sensitivity.

DISCUSSION

Many studies have examined β -cell function in PCOS, and thus far, the results are equivocal. Several studies have shown that there is a defect in glucose-stimulated insulin secretion (11,19,20). However, other studies have shown that patients with PCOS have an increased insulin response, probably as compensation for peripheral insulin resistance (21–24). Finally, some investigators have demonstrated entirely normal first-phase insulin secretion in patients with PCOS (25,26). This discrepancy can be explained by noting that many of the studies fail to adjust insulin secretion to the degree of insulin resistance. Although the insulin response may be enhanced (ie, as measured by increased AIR_g), it may not be appropriately elevated to match the degree of insulin resistance. The use of a disposition index avoids this potential pitfall by providing an estimate of β -cell functionality relative to the prevailing level of insulin resistance.

The insulin-sensitizing drug metformin has multiple known mechanisms of action including the augmentation of peripheral glucose uptake and inhibition of hepatic glucose production and intestinal absorption of glucose (27). Insulin resistance usually occurs at the postinsulin receptor site in obese individuals, where there is an apparent failure to activate the postreceptor tyrosine kinase (28). Metformin facilitates postreceptor transport of insulin. In addition, metformin increases serum sex hormone-binding globulin, decreases serum free testosterone, and improves the frequency of ovulation in women with PCOS (29). Results

from the Diabetes Prevention Program suggest that metformin reduces the risk for type 2 diabetes and metabolic syndrome in women with PCOS who have both impaired fasting blood glucose and IGT (30,31). However, it is unclear what role metformin has regarding pancreatic β -cell function. It is well known that metformin's action on liver and muscle cells is mediated via activation of adenosine monophosphate-activated protein kinase. In 2004, Leclerc and Rutter showed that adenosine monophosphate-activated protein kinase also regulates glucose-stimulated insulin secretion in β cells (32). Findings from in vitro studies suggest a protective role for metformin on pancreatic β cells. In 2004, Marchetti et al showed that the 24-hour incubation of pancreatic islet cells isolated from patients with type 2 diabetic patients with metformin led to increased insulin content, increased number and density of mature insulin granules, increased insulin messenger RNA expression, and improved glucose-stimulated insulin release (33). In 2005, Hull et al demonstrated decreased amyloid deposition and preservation of β -cell mass after metformin treatment (34). However, in vivo studies thus far have not confirmed the results of the aforementioned in vitro studies. In 2007, Rasouli et al evaluated the effect of metformin on β -cell function in participants with impaired glucose tolerance or a history of gestational diabetes and found that metformin did not significantly improve β -cell compensation for insulin resistance (35).

Since PCOS may be associated with defects in pancreatic β cells, we sought to determine the effect of metformin on pancreatic β -cells in patients with PCOS. To address this question, we performed frequently sampled intravenous glucose tolerance tests in women with PCOS while on and off metformin to compare the disposition index in each situation. The relationship between measures of insulin secretion and insulin action describes a hyperbolic curve when insulin sensitivity is graphed on the abscissa and insulin secretion (AIR_g) is graphed on the ordinate axis (18). Insulin sensitivity is the capacity of insulin to stimulate glucose uptake in the tissues, while AIR_g is the responsiveness of β cells to a glucose load (16). The product of insulin sensitivity and AIR_g is the disposition index, which describes the appropriateness of the β -cell response with respect to the prevailing degree of insulin resistance in the tissues (16). When insulin secretion compensates appropriately for changes in insulin sensitivity, the disposition index remains constant.

Our study demonstrates that the administration of 6 months of metformin to patients with PCOS does not significantly change the disposition index, insulin sensitivity, or AIR_g . These findings are in agreement with previously reported results of the effect of metformin on β -cell function (35). However, the lack of a significant change in AIR_g does not, by itself, demonstrate insufficient β -cell responsiveness to the prevailing level of peripheral insulin resistance. To measure such responsiveness, one must examine the proportionate change in AIR_g relative to the proportionate change in insulin sensitivity. When these parameters were analyzed, it became apparent that AIR_g did not proportionately change to match changes in insulin sensitivity, as evidenced by Figures 3A and 3B. If β cells had been responding appropriately to changes in insulin resistance, the proportionate change in the disposition index would not have correlated significantly with the proportionate change in insulin sensitivity. In fact, however, the proportionate change in the disposition index did correlate significantly with the proportionate change in insulin sensitivity with a P value less than .001. This implies that there may, in fact, be insufficient β -cell responsiveness in patients with PCOS.

In retrospect, it would have been helpful to have performed frequently sampled intravenous glucose tolerance tests 6 months apart in patients with PCOS before and after placebo to see if the same results might have occurred without the metformin intervention. In addition, the study enrolled patients with a very wide demographic profile in terms of body mass index, age, and testosterone levels. Similarly, some of the patients were taking metformin before study initiation, while others were prescribed metformin as part of the research. A more

homogenous group of patients would have allowed the study's results to be interpreted with more confidence. Further limitations of this study include the small sample number, the limited study duration, and the difficulty of accurately defining a patient with PCOS.

CONCLUSION

We determined that metformin does not lead to a significant change in AIR_g , insulin sensitivity, or disposition index in patients with PCOS. However, the proportionate change in disposition index after metformin treatment correlated significantly with the proportionate change in insulin sensitivity. These data suggest that AIR_g did not respond appropriately to changes in insulin sensitivity and may indicate a β -cell defect in patients with PCOS. Further research is needed to define the magnitude of the effect and whether it occurred as a result of or independent from metformin treatment.

Acknowledgments

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Abbreviations

AIR_g	acute insulin response to glucose
IGT	impaired glucose tolerance
PCOS	polycystic ovary syndrome

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Fig. 1.
Times of blood sample collection, glucose injections, and insulin injections.

Fig. 2.
Panel A, Average glucose values during intravenous glucose tolerance testing before and after metformin treatment. *Panel B*, Average insulin values during intravenous glucose tolerance testing before and after metformin treatment.

Fig. 3. *Panel A*, Change in the disposition index (DI) correlated significantly with change in insulin sensitivity (SI). *Panel B*, Change in the DI correlated significantly with change in SI with outliers removed.

Table 1
Demographic and Endocrinologic Characteristics of 14 Women With Polycystic Ovary Syndrome

Patient	Age ^a , y	Ethnicity	BMI ^b , kg/m ²	Total Testosterone ^c , ng/dL	Family history of diabetes	Metformin naïve?
1	22	White	32.7	77	Yes	No
2	32	White	25.8	65	No	No
3	33	Hispanic	40.5	101	No	Yes
4	20	White	21.1	29	No	No
5	24	White	25.3	75	No	Yes
6	39	White	21.0	32	No	Yes
7	48	White	23.0	15	No	No
8	23	White	25.2	68	No	Yes
9	34	Black	23.6	45	Yes	Yes
10	32	White	21.0	59	No	Yes
11	49	White	21.0	59	No	No
12	36	White	26.5	28	No	No
13	27	White	39.2	25	Yes	Yes
14	27	White	19.3	15	No	Yes

Abbreviation: BMI, body mass index.

^aMean (±standard deviation) age was 32 (±9.0) years.

^bMean (±standard deviation) BMI was 26.1 (±6.7) kg/m².

^cMean (±standard deviation) testosterone concentration was 50 (±26.3) ng/dL.

Table 2
Baseline Glucose Minimal Model Characteristics for 14 Women With Polycystic Ovary Syndrome

Patient	Glucose effectiveness ^a , min ⁻¹	Insulin sensitivity ^b , min ⁻¹ • (μ/L) ⁻¹ • 10 ⁻⁴	AIR _g ^c , min • (μ/L)	Disposition index ^d
1	0.041	11.46	365	4187
2	0.034	5.41	191	1035
3	0.000	2.19	685	1502
4	0.019	20.14	214	4313
5	0.055	94.04	52	4920
6	0.152	19.28	670	12 909
7	0.015	6.07	139	843
8	0.027	5.53	147	811
9	0.004	1.23	1914	2361
10	0.014	6.95	122	845
11	0.002	2.19	506	1110
12	0.059	16.35	491	8030
13	0.006	1.80	343	617
14	0.021	6.79	173	1172

Abbreviation: AIR_g, acute insulin response to glucose.

^aMean (±standard deviation) glucose effectiveness was 0.032 (±0.039) min⁻¹. Reference range: 1.2e-3 to 4.5e-2.

^bMean (±standard deviation) insulin sensitivity was 14.24 (±23.83) min⁻¹ • (μ/L)⁻¹ • 10⁻⁴. Reference range: 0.5-22.

^cMean (±standard deviation) AIR_g was 429 (±474) min • (μ/L). Reference range: 45-3700.

^dMean (±standard deviation) disposition index was 3190 (±3541). Reference range: 160-10 000.

Table 3
Baseline Characteristics and Changes After Metformin Administration
in 14 Women With Polycystic Ovary Syndrome^a

Assessments	Baseline	Change after metformin	Time effect <i>P</i> value
Insulin sensitivity, min ⁻¹ • (μ/L) ⁻¹ • 10 ⁻⁴	14.24 (±23.83)	-2.20 (±32.43)	.80
Glucose effectiveness, min ⁻¹	0.032 (±0.039)	-0.01 (±0.03)	.23
AIRG, min • (μ/L)	429 (±474)	34 (±177)	.48
Disposition index	3190 (±3541)	2791 (±15 302)	.51
Distributed glucose at time 0 (G0) ¹⁴ , kg/dL	2.33 (±0.86)	-0.12 (±0.98)	.65

^aData are presented as mean (±standard deviation).