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An observational study of reduction of insulin resistance and prevention of development of type 2 diabetes mellitus in women with polycystic ovary syndrome treated with metformin and diet

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Abstract

Our first specific aim in an observational study of 431 nondiabetic women with polycystic ovary syndrome (PCOS), aged ≥20 years and with ≥11 months follow-up on metformin diet, was to prospectively assess relationships between pretreatment glucose and insulin resistance (IR) and the development of type 2 diabetes mellitus (T2DM) or gestational diabetes (GD). Our second specific aim was to determine whether development of T2DM and GD was independently associated with lesser reduction of IR on metformin diet when compared with women who remained free of T2DM and GD. Women with body mass index <25 kg/m^2 and those with body mass index ≥25 kg/m^2 were, respectively, instructed in a 2000- or 1500-cal/d, high-protein (26% of calories), low-carbohydrate (44%) diet, with 30% of calories as fat and a polyunsaturate-saturate ratio of 2:1. Three groups of women with PCOS were categorized: (*a*) 17 with no previous GD, who developed T2DM on metformin diet (mean ± SD follow-up, 49 ± 33 months), (*b*) 401 with no previous GD and free of T2DM on metformin diet (follow-up, 38 ± 25 months), and (*c*) 13 with either previous GD or GD on metformin diet (follow-up, 38 ± 25 months). On metformin diet, women who developed T2DM vs those who remained free of T2DM had higher pretreatment glucose (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.03-1.16; P = .003) and homeostasis model assessment of insulin resistance (HOMA-IR) (OR, 1.22; 95% CI, 1.04-1.42; P = .01), and less reduction of HOMA-IR (OR, 0.82; 95% CI, 0.72-0.92; P = .0008). On metformin diet, women either with previous GD or who developed GD vs those who remained free of T2DM had less reduction of HOMA-IR (OR, 0.88; 95% CI, 0.78-0.99; P = .03). By repeated-measures analysis, on metformin diet, women who did not develop T2DM had reduction in HOMA-IR (P < .0001), with the slope of this curve different (P = .002) from the unchanged IR exhibited by women who developed T2DM and different (P = .017) from an increased IR slope (P = .049) in women who had GD. In women with PCOS, pretreatment glucose and IR, and lesser reduction in IR on metformin diet were associated with T2DM and GD.

1. Introduction

By the mid-1990s, it was realized that a central pathophysiology of polycystic ovary syndrome (PCOS) was insulin resistance (IR) with compensatory hyperinsulinemia [1,2], associated with increased ovarian androgen production by theca cells and clinical-biochemical hyperandrogenism. In 1994 [3] and in 1997 [4], Velazquez et al reported that metformin (1.5-2.55 g/d), a biguanide compound that lowers IR and insulin levels, reduced hyperinsulinemia, reduced weight and centripetal obesity, ameliorated hyperlipidemia and hypertension, lowered levels of hypofibrinolytic plasminogen activator inhibitor activity, decreased ovarian androgen production, and increased ovulatory cycles in oligoamenorrheic women with PCOS.

In PCOS, metformin may protect against development of gestational diabetes (GD) and, speculatively, reduce later development of type 2 diabetes mellitus (T2DM) by reducing IR and protecting pancreatic β-cell reserve during pregnancy, when both IR and insulin secretion are increased

This study was carried out following a protocol approved by the Jewish Hospital Institutional Review Board, with signed informed consent.

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Table 1
Distribution of duration of metformin diet treatment and live birth pregnancies in 3 groups of 431 patients with PCOS, nondiabetic, aged ≥20 years at pretreatment study entry, and with ≥11 months follow-up

Groups	n	Duration of treatment (mo)					
Previous — on metformin diet		Mean ± SD	11-24 mo	24-36 mo	36-48 mo	48-60 mo	≥60 mo
A: No GD — developed T2DM on metformin diet	17	49 ± 33	6 (35%)	2 (12%)	0 (0%)	3 (18%)	6 (35%)
B: No GD — no DM on metformin diet	401	38 ± 25	159 (40%)	67 (17%)	51 (13%)	33 (8%)	91 (23%)
C: GD and/or developed GD on metformin diet	13	38 ± 25	5 (38%)	1 (8%)	3 (23%)	1 (8%)	3 (23%)
			Cochran-Mantel-Haenszel $\chi^2 = 1.51$, $df = 2$, $P = .47$				

Groups	n	No. (%) of women with live birth pregnancies during treatment	No. of live birth pregnancies					Mean ± SD weight change per pregnancy
Previous — on metformin diet			1	2	3	4	Total	
A: No GD — developed T2DM on metformin diet	17	4 (24%)	4	0	0	0	4	3.48 ± 9.32 kg
B: No GD — no DM on metformin diet	401	90 (22%)	73	12	4	1	113	5.25 ± 6.46 kg
C: GD and/or developed GD on metformin diet	13	10 (77%)	9	1	0	0	11	3.18 ± 2.76 kg
		Groups A, B did not differ for % of women with live birth pregnancies, Fisher $P = 1.0$						No group difference, Kruskal-Wallis $P = .79$

[5-9]. As noted by Buchanan et al [10] "Type 2 diabetes frequently results from progressive failure of pancreatic beta-cell function in the presence of chronic IR." Buchanan et al randomized women with previous GD to placebo or the insulin-sensitizing peroxisome proliferator–activated receptor α agonist troglitazone with 30-month follow-up. Average annual diabetes incidence rates in women who returned for at least 1 follow-up visit were 12.1% in women on placebo and 5.4% in those on troglitazone ($P < .01$). Protection from diabetes in the troglitazone group was related to reduced IR and preservation of β-cell compensation for IR. A subsequent study by Xiang et al [11], using pioglitazone, revealed that the risk of developing T2DM was lowest in those women who had the greatest reduction in IR after 1 year of treatment.

In population studies of adults, impaired fasting glucose, obesity, IR, and impaired insulin response to glucose are independent predictors of T2DM [12], along with family history of T2DM [13]. In adult offspring of 2 parents with T2DM, IR is robustly associated with development of T2DM; but IR is not associated with T2DM in young adults whose parents did not have T2DM [13]. Development of T2DM is related to number of pregnancies [14] and to high body mass index (BMI) at first pregnancy, weight gain after pregnancy, and BMI later in life [15].

Our first specific aim in an observational study of 431 nondiabetic women with PCOS, aged ≥20 years and with ≥11 months follow-up on metformin diet, was to prospectively assess relationships between pretreatment glucose and IR and the development of T2DM or GD. Our second specific aim was to determine whether development of T2DM and GD was independently associated with lesser reduction of IR on metformin diet when compared with women who remained free of T2DM and GD.

2. Patients and methods

This study was carried out following a protocol approved by the Jewish Hospital Institutional Review Board, with signed informed consent.

2.1. Study design, women with PCOS

From July 17, 1995, to April 19, 2007, 1382 women with a presumptive diagnosis of PCOS were referred for diagnosis and treatment to the Jewish Hospital Cholesterol Center. Of these 1382 women, 1119 met the diagnostic criteria for PCOS established by the 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine consensus conference [16]. Exclusionary criteria included serum creatinine >1.5 mg/dL, type 1 DM, pituitary insufficiency, persistent hyperprolactinemia, and congenital adrenal hyperplasia [7]. Of the 1119 women, 1006 were aged ≥20 years at study entry, 60 (5.4%) had T2DM at pretreatment study entry, and 946 did not.

At study entry and every 3 months during follow-up, after an overnight fast, women with PCOS had measures of total and free testosterone, insulin, glucose, cholesterol, triglyceride, high- and low-density lipoprotein cholesterol, and systolic and diastolic blood pressure, with calculation of homeostasis model assessment of insulin resistance (HOMA-IR), as previously described [17]. We did not systematically carry out 2-hour postglucose tests. At each follow-up visit, the amount of metformin taken in the

Table 2
Differences at the initial pretreatment visit in age, BMI, insulin, glucose, and HOMA-IR among 3 groups of women with PCOS, nondiabetic at pretreatment, aged ≥20 years at initial visit, and with ≥11 months follow-up (mean ± SD)

Groups Previous — on metformin diet	n	Age (y)	BMI (kg/m^2)	Insulin (μU/mL)	Glucose (mg/dL)	HOMA-IR
A: No GD — developed T2DM on metformin diet	17	35.6 ± 8.5	38.6 ± 8.6	26 ± 17	96 ± 15	6.44 ± 4.83
B: No GD — no DM on metformin diet	401	31.6 ± 7.1	35.2 ± 7.8	19 ± 14	88 ± 10	4.11 ± 3.53
C: GD and/or developed GD on metformin diet	13	32.1 ± 4.4	36.5 ± 7.4	20 ± 12	90 ± 7	4.57 ± 2.85
Group significant difference ($P \leq .05$)		A > B		A > B	A > B	A > B
Group significant difference ($P \leq .05$), adjusted for race, age, BMI, and parental T2DM					A > B	

antecedent 3-month period was recorded by the investigators to assess metformin adherence. Dietary adherence was assessed by review with dietitians every 6 months. Development of T2DM [18] and GD [9] during follow-up on metformin was documented as previously described. Parental history of T2DM was obtained by investigator-directed interviews [19].

Women with BMI <25 kg/m^2 and those with BMI ≥25 kg/m^2 [20] were, respectively, instructed in a 2000- or 1500-cal/d, high-protein (26% of calories), low-carbohydrate (44%) diet (42% of carbohydrate complex), with 30% of the calories as fat and a polyunsaturate-saturate ratio of 2:1 [7]. At the first visit, Glucophage (Bristol-Myers-Squibb, Princeton, NJ) was started, 2.55 g, given as 850 mg 3 times per day with meals [17]. When pregnancy occurred during the follow-up period (Table 2), dietary caloric restrictions were dropped; but caloric composition was maintained and Glucophage (2.55 g/d) was continued throughout pregnancy.

Of the 946 nondiabetic women (aged ≥20 years) with PCOS, 431 had ≥11 months follow-up on metformin diet (Tables 1-5, Fig. 1). During the ≥11-month follow-up period, 104 women had 128 live birth pregnancies (Table 1). Using the 431 women's history, entry, pretreatment information, and subsequent follow-up data on metformin diet, 3 groups of women were categorized, as follows:

Group A, no previous GD–developed T2DM on metformin diet: 17 women with no previous GD who then developed T2DM on metformin diet therapy (mean ± SD metformin dose, 2224 ± 690 mg/d; mean ± SD follow-up, 49 ± 33 months) (Tables 1-5, Fig. 1).

Group B, no previous GD–did not develop T2DM on metformin diet: 401 women with no previous GD who did not develop T2DM on metformin diet (mean ± SD metformin dose, 2247 ± 635 mg/d; mean ± SD follow-up, 38 ± 25 months) (Tables 1-5, Fig. 1).

Group C, previous GD or developed GD on metformin diet: 13 women with either previous GD (n = 3) or both previous GD and GD on metformin diet (n = 1), or developed GD on metformin diet (n = 9) (mean ± SD metformin dose, 2342 ± 390 mg/d; mean ± SD follow-up, 38 ± 25 months) (Tables 1-5, Fig. 1).

2.2. Statistical methods

All statistical evaluations were done using SAS (SAS/STAT software, 9.1; SAS Institute, Cary NC). Of the 946 nondiabetic women with PCOS at pretreatment study entry, 431 women were selected by ≥11 months follow-up on metformin diet and were then separated into 3 groups—A, B, and C—as summarized above (Tables 1-5, Fig. 1). Comparisons of the duration of metformin diet therapy among these 3 groups were made by the Cochran-Mantel-Haenszel test (Table 1). Comparisons of weight gain during pregnancy were made by the Kruskal-Wallis nonparametric test (Table 1). At the initial pretreatment visit (Table 2) and at the last follow-up visit (Table 3), variables were compared among these 3 groups without adjustment and after

Table 3
At last follow-up on metformin diet, differences in age, BMI, insulin, glucose, and HOMA-IR among 3 groups of women with PCOS, nondiabetic at pretreatment, aged ≥20 years at initial visit, and with ≥11 months follow-up (mean ± SD)

Groups Previous — on metformin diet	n	Age (y)	BMI (kg/m^2)	Rx duration (mo)	Insulin (μU/mL)	Glucose (mg/dL)	HOMA-IR
A: No GD — developed T2DM on metformin diet	17	38.9 ± 9.0	38.0 ± 9.5	49 ± 33	27 ± 34	116 ± 41	7.43 ± 10.24
B: No GD — no DM on metformin diet	401	34.6 ± 7.5	33.8 ± 7.8	38 ± 25	11 ± 8.9	87 ± 9	2.51 ± 2.21
C: GD and/or developed GD on metformin diet	13	34.7 ± 5.7	36.9 ± 11.1	38 ± 25	24 ± 28	95 ± 39	6.86 ± 12.80
Group significant difference ($P \leq .05$)		A > B			A > B B < C	A > B, C B < C	A > B B < C
Group significant difference ($P \leq .05$) Adjusted for race, on-treatment age and BMI, duration on Rx, parental T2DM, live birth pregnancies on Rx (yes/no), number of live birth pregnancies on Rx, weight gain during pregnancies, and an interaction term (number of pregnancies × weight gain during pregnancies)					A > B B < C	A > B, C B < C	A > B B < C

Table 4
Significant explanatory variables for group differences

Response variable	Significant explanatory variables	P
A: No GD, developed T2DM on metformin diet vs B: no GD, no T2DM on metformin diet	Baseline glucose (OR, 1.09; 95% CI, 1.03-1.16)	.003
	Reduction in IR (OR, 0.82; 95% CI, 0.72-0.92)	.0008
	Baseline IR (OR, 1.22; 95% CI, 1.04-1.42)	.01
C: GD and/or developed GD on metformin diet vs B: no GD, no T2DM on metformin diet	Reduction in IR (OR, 0.88; 95% CI, 0.78-0.99)	.03
A + C vs B: no GD, no T2DM on metformin diet	Baseline glucose (OR, 1.07; 95% CI, 1.02-1.13)	.01
	Reduction in IR (OR, 0.84; 95% CI, 0.76-0.93)	.001
	Baseline IR (OR, 1.18; 95% CI, 1.03-1.35)	.02

Stepwise logistic regression. Dependent variables group A vs B, group C vs B, groups A + C vs B. Explanatory variables include baseline age, race, BMI, glucose, IR, duration of treatment with metformin diet, change in weight and IR on treatment, live birth pregnancies during treatment (yes, no), number of live birth pregnancies during treatment, weight change during pregnancies, interaction term (number of live birth pregnancies × weight change during pregnancies), and parental T2DM. Odds ratios and 95% CIs are displayed.

adjustment using the general linear model analysis of variance. At the initial pretreatment visit, adjusting variables included entry age, race, BMI, and parental history of T2DM (Table 2). At the last follow-up visit (Table 3), adjusting variables included race, on-treatment age and BMI, duration on therapy, parental history of T2DM, live birth pregnancies during follow-up (yes/no), number of pregnancies, change in weight during pregnancies, and an interaction term (live birth pregnancies × change in weight during pregnancies).

Table 5
Significant explanatory variables for group differences

Dependent variable	Significant explanatory variables	P
A + C: Developed T2DM/GD on metformin diet vs B: no GD, no T2DM on metformin diet	Age at baseline (OR, 1.69; 95% CI, 1.12-2.54)	.013
	Age at last follow-up (OR, 0.63; 95% CI, 0.42-0.94)	.023
	Baseline glucose (OR, 1.06; 95% CI, 1.01-1.12)	.026
	Reduction in IR (OR, 0.82; 95% CI, 0.73-0.92)	.0008
	Baseline IR (OR, 1.25; 95% CI, 1.05-1.48)	.011
	Duration of treatment (OR, 1.05; 95% CI, 1.01-1.08)	.011

Logistic regression with all explanatory variables forced into the model: baseline age, race, BMI, glucose, IR, duration (months) of treatment with metformin diet, age at last follow-up, change in weight and IR on treatment, live birth pregnancies during treatment (yes, no), number of live birth pregnancies during treatment, weight change during pregnancies, interaction term (number of live birth pregnancies × weight change during pregnancies), and parental T2DM. Odds ratios and 95% CIs are displayed.

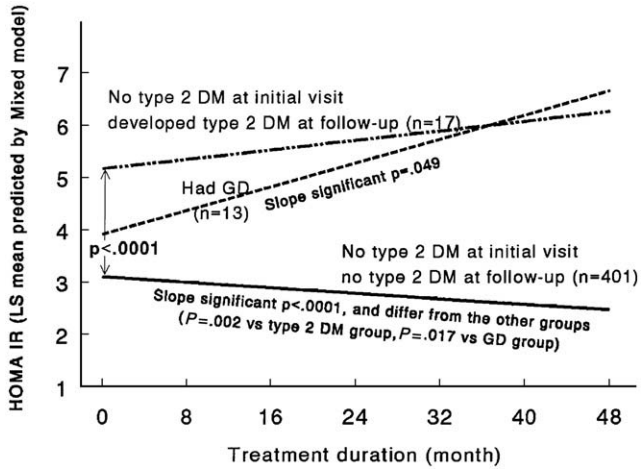

Fig. 1. Using the mixed model, HOMA-IR at baseline and means at each 6-month follow-up along the treatment course for each patient were the dependent variables. For explanatory variables, fixed effects included diabetes group, time, group × time, race, age and BMI at baseline, change in weight on therapy, pregnancy (yes, no), number of live birth pregnancies during the follow-up period, weight change during pregnancies during the follow-up period, an interaction term (number of live birth pregnancies during treatment × change in weight during pregnancies), and parental T2DM history. The random effect was patients with first-order autoregressive covariance structure for each patient. Least square means of HOMA-IR are displayed in 17 women who developed T2DM during mean ± SD follow-up of 49 ± 33 months on metformin diet, in 401 women who did not develop T2DM during 38 ± 25 months of follow-up, and in 13 women with previous GD without metformin diet or GD on metformin diet during 38 ± 25 months of follow-up. LS indicates least square.

Three stepwise logistic regression models were fit, with the groups as response variables (group A [n = 17] vs group B [n = 401], C [n = 13] vs B [n = 401], A and C [n = 30] vs B [n = 401]) (Table 4). Explanatory variables included race; age, glucose, HOMA-IR, and BMI at study entry; duration of treatment; changes in body weight and HOMA-IR during treatment; live birth pregnancies (yes, no); number of live birth pregnancies during treatment; change in weight during pregnancies; an interaction term (number of live birth pregnancies during treatment × change in weight during pregnancies); and history of parental T2DM (Table 4). A separate logistic regression model was fit, forcing all the above explanatory variables into the model (Table 5).

To investigate group differences and changes in HOMA-IR throughout treatment, PROC MIXED with repeated-measures analysis was used for the 3 groups of women (Fig. 1). The HOMA-IR at baseline and the means at each 6-month follow-up along the treatment course for each patient were the dependent variables. For explanatory variables, fixed effects included diabetes group, time, group × time, race, age and BMI at baseline, change in weight during therapy, pregnancy (yes, no), number of live birth pregnancies during the follow-up period, weight change during pregnancies during the follow-up period, an interaction term (number of live birth pregnancies during treatment × change in weight during pregnancies), and

parental T2DM history. The random effect was patients, with first-order autoregressive covariance structure for each patient (Fig. 1).

3. Results

Of the 17 women in group A (no previous GD, developed T2DM on metformin diet), 4 (24%) had live birth pregnancies on metformin diet, all free of GD (Table 2). Mean ± SD weight gain during these live birth pregnancies was 3.48 ± 9.32 kg (Table 1). Of the 401 women in group B (no previous GD, no development of T2DM on metformin diet), 90 (22%) had live birth pregnancies on metformin diet, all free of GD (Table 2). Mean ± SD weight gain during these live birth pregnancies was 5.25 ± 6.46 kg (Table 1). Of the 13 women in group C (previous GD or GD on metformin diet), 10 (77%) had live birth pregnancies on metformin diet and developed GD (1 of the 10 women also had previous GD); the other 3 women had GD before entering the study. Mean ± SD weight gain during pregnancies was 3.18 ± 2.76 kg (Table 1). The percentage of women in groups A (24%) and B (22%) having live birth pregnancies during the metformin diet treatment period did not differ (Fisher $P = 1.0$). Weight gain during pregnancy did not differ among the 3 groups ($P = .79$, Table 1).

Duration of treatment on metformin diet did not differ among the 3 groups of women with PCOS (Cochran-Mantel-Haenszel $\chi^2 = 1.51$, $df = 2$, $P = .47$; Table 1).

At pretreatment study entry, BMI did not differ among the 3 groups of women (Table 2). The 17 women who developed T2DM on follow-up were older and had higher pretreatment insulin, glucose, and HOMA-IR than the 401 women who did not develop T2DM. After adjusting for race, age, BMI, and parental history of T2DM, the 17 women who developed T2DM on follow-up had higher pretreatment glucose than the 401 women who did not develop T2DM (Table 2). With and without adjusting for race, age, BMI, and parental history of T2DM, the 13 women with previous GD or who developed GD on metformin diet did not differ in pretreatment insulin, glucose, and HOMA-IR from the 17 women who developed DM or the 401 who did not (Table 2).

At the last follow-up visit on metformin diet, the 3 groups of women did not differ by BMI (Table 3) or duration of treatment, with mean ± SD duration of treatment being 49 ± 33 months for group A, 38 ± 25 months for group B, and 38 ± 25 months for group C (Table 1). With and without adjusting at their last follow-up visit on metformin diet, the 17 women who developed T2DM on metformin diet had higher insulin, glucose, and HOMA-IR than the 401 women who did not develop T2DM on follow-up, and had higher glucose than the 13 women who previously had GD or developed GD on follow-up (Table 3). With and without adjusting at their last follow-up visit, the 13 women with a previous history of GD or GD on metformin diet had higher insulin, glucose, and HOMA-IR than the 401 women who did not develop T2DM on follow-up (Table 3).

Higher pretreatment glucose (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.03-1.16; $P = .003$), higher pretreatment HOMA-IR (OR, 1.22; 95% CI, 1.04-1.42; $P = .01$), and less reduction of HOMA-IR on metformin diet (OR, 0.82; 95% CI, 0.72-0.92; $P = .0008$) were associated with group A, 17 women who developed T2DM, rather than group B (Table 4). Less reduction of HOMA-IR on metformin diet (OR, 0.88; 95% CI, 0.78-0.99; $P = .03$) was associated with group C, 13 with either previous GD or GD on metformin diet, rather than group B. Less reduction of HOMA-IR on metformin diet (OR, 0.84; 95% CI, 0.76-0.93; $P = .001$), higher pretreatment HOMA-IR (OR, 1.18; 95% CI, 1.03-1.35; $P = .02$), and higher pretreatment glucose (OR, 1.07; 95% CI, 1.02-1.13; $P = .01$) were associated with groups A + C (T2DM + GD) rather than group B (Table 4).

As displayed in Table 5, by logistic regression, with all explanatory variables forced into the model, group A + C (developed T2DM/GD) vs group B (no GD, no T2DM) was positively associated with baseline glucose and baseline IR, and negatively associated with reduction in IR by metformin diet. These were the same significant explanatory variables identified by the stepwise logistic regression model (Table 4). Additional significant variables for group A + C vs B included age at baseline and last follow-up, and duration of follow-up (Table 5).

Using the mixed model, as displayed in Fig. 1, at pretreatment study entry, the 17 women who developed T2DM had higher IR than the 401 women who did not develop T2DM on follow-up ($P < .0001$). During metformin diet treatment for a mean of 38 months, HOMA-IR fell ($P < .0001$) in the 401 women who did not develop T2DM (Fig. 1). The slope of this IR curve differed ($P = .002$) from insignificant changes in IR exhibited by the 17 women who developed T2DM and differed ($P = .017$) from the increasing IR slope ($P = .049$) exhibited by the 13 women who had GD (Fig. 1).

4. Discussion

A major finding in the current observational study was that women who developed T2DM vs those who remained free of T2DM had higher pretreatment glucose and IR, and less reduction of HOMA-IR on metformin diet. Moreover, on metformin diet, women with previous GD or who developed GD vs those who remained free of T2DM and GD had less reduction of HOMA-IR. By repeated-measures analysis, on metformin diet, women who did not develop T2DM had reduction in HOMA-IR, with the slope of this curve different from the unchanged IR exhibited by women who developed T2DM and different from an increased IR slope in women who had GD. The associations of change in IR with development of T2DM on metformin diet were

independent of duration of therapy, change in weight, age, race, parental history of T2DM, number of pregnancies, and change of weight during pregnancy. Hyperinsulinemia, a pathoetiologic hallmark of PCOS [1], probably accounts for the high prevalence of hyperinsulinemic T2DM in women with PCOS [21].

Our study was observational, delineating predictors of T2DM in a large group of relatively young women with PCOS who had metformin diet intervention. We cannot measure the unknown biases associated with those subjects who remained for long-term follow-up. Without a double-blind, placebo-controlled design, we cannot assess the role of metformin, independent of diet, in the prevention of T2DM.

In the presence of persistent IR, progressive failure of pancreatic β-cell function leads to development of T2DM [10,11,22]; and when the IR of pregnancy is superimposed on chronic IR in PCOS, β-cell failure leads to GD [5-9]. By reducing IR during pregnancy in women with PCOS, metformin diet reduces development of GD from 30% (without metformin diet) to 12% [9].

Exhaustion of β-cell reserves [9,11,23] during development of GD has downstream adverse effects, associated with a 50% chance of developing T2DM in the next 10 years after GD [24]. It has been suggested that reducing the secretory demands imposed by chronic IR can preserve β-cell function and that this could slow or stop progression of subsequent T2DM [10,11]. In women who had previous GD, subsequent treatment with troglitazone reduced IR, improved insulin sensitivity, and reduced the incidence of T2DM [10,23]. Women who were protected from DM while taking troglitazone had stable β-cell function for nearly 5 years [10,23]. Women who had completed the troglitazone study [10,23] were subsequently given pioglitazone for 3 years [11]. Pioglitazone stopped the decline in β-cell function seen in the placebo group of the troglitazone study [10,23] and maintained the stability of β-cell function in the troglitazone group [11].

During treatment of women with PCOS with metformin diet, if failure to reduce IR is observed longitudinally, then it might be reasonable to add additional insulin-sensitizing agents such as pioglitazone [25] to further reduce IR as a primary approach to prevention of T2DM. We speculate that failure to reduce IR with metformin diet increases the likelihood over time that the pancreatic β cells will fail, leading to development of T2DM and GD [9], because peripheral IR remains high but the β cells can no longer compensate by increasing insulin secretion enough to normalize blood glucose.

In a 6.2-year longitudinal study by Norman et al [26] of 67 women with PCOS without diet-drug intervention, there was an overall conversion rate to T2DM of 2.6% per year. Boudreaux et al [21] reported that the 8-year incidence rate of developing T2DM in women with PCOS without diet-drug intervention was 13.4%. In our current study, over a mean 4-year follow-up on metformin diet, only 17 of 431 (3.9%) women with PCOS developed T2DM. Within this frame of reference, we speculate that metformin diet delays or prevents the development of T2DM in women with PCOS, congruent with the retrospective study of Sharma et al [27].

In nondiabetic subjects with impaired glucose tolerance, a variety of lifestyle modification and pharmacological interventions can prevent or delay progression to T2DM [28]. In patients with impaired fasting glucose, intensive lifestyle modification reduced risk of developing T2DM by 58%, whereas metformin reduced risk of developing T2DM by 31% [29]. In the Stop Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial [30] in a population with impaired glucose tolerance, acarbose decreased the risk of T2DM by 36%. In the Xenical in the Prevention of Diabetes in Obese Subjects study [31], intensive lifestyle modification coupled with Xenical (Roche Labs, Nutley, NJ) was associated with a 37% reduction in development of T2DM. In nondiabetic subjects with impaired glucose tolerance in the diabetes prevention study, there was a 32% reduction in risk of developing T2DM for those adherent to metformin vs those adherent to placebo [32].

Because of preponderant obesity [33], increased age at conception, preconception IR [1], and a low frequency of the wild-type normal 5G PAI-1 gene allele [34], women with PCOS are at increased risk for development of GD [5-9, 34-41] and subsequently are at increased risk for development of T2DM [42,43]. Reduction of IR with metformin diet in the current and other [29] studies, or reduction of IR by metformin diet, pioglitazone [25], acarbose [30], or Xenical [31] may provide primary prevention [28] of T2DM.

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