Incidence and Treatment of Metabolic Syndrome in Newly Referred Women With Confirmed Polycystic Ovarian Syndrome

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In 138 oligo-amenorrheic white women with polycystic ovary syndrome (PCOS) (31 ± 9-years-old), our first specific aim was to assess the incidence of the metabolic syndrome and to compare metabolic syndrome abnormalities in women with PCOS to those in the National Health and Nutrition Examination Survey (NHANES) III cohort of 1,887 white women. Our second aim was to determine whether metformin (2.55 g/d) and a diet of 1,500 calories, 26% protein, 44% carbohydrate (42% of carbohydrate complex), 30% fat (polyunsaturate/saturate ratio [P/S] = 2/1), would ameliorate metabolic syndrome abnormalities in women with both PCOS and metabolic syndrome. The metabolic syndrome was present in 64 (46%) of the women with PCOS. In these 64 women, there were abnormalities in waist circumference (98%), high-density lipoprotein cholesterol (HDL-C) (95%), blood pressure (70%), triglycerides (56%), and glucose (11%). In these 64 women, mean ± SD waist circumference was 116 ± 15 cm, triglyceride 192 ± 152 mg/dL, HDL-C 39 ± 7 mg/dL, systolic blood pressure 131 ± 13 mm Hg, diastolic blood pressure 83 ± 7 mm Hg, and serum glucose 94 ± 22 mg/dL. Serum insulin was high (>17 μU/mL) in 42 of the 64 women (66%). After age adjustment, 46.4% ± 4.2% of women with PCOS had the metabolic syndrome (≥3 abnormalities) versus 22.8% ± 1.1% of NHANES III women, $P < .0001$ versus 6% of 20 to 29-year-old and 15% of 30 to 39-year-old NHANES III women. Of the 64 women with both PCOS and the metabolic syndrome, 50 had follow-up studies after an average of 6 months on metformin and diet. At 6 months follow-up, mean percent reductions were as follows: body weight 4.7% (111 to 106 kg, $P < .0001$), triglycerides 14% (197 to 136 mg/dL, $P = .0001$), systolic blood pressure 5.2% (131 to 124 mm Hg, $P = .0002$), diastolic blood pressure 6% (83 to 77 mm Hg, $P = .0007$), and insulin 31% (25 to 17 μU/mL, $P < .0001$); mean percent HDL-C increased 6% (39 to 41 mg/dL, $P = .013$). Of these 50 women, 29 had pretreatment baseline abnormal triglycerides (≥150 mg/dL), 47 had low HDL-C (<50 mg/dL), 26 had high systolic blood pressure (≥130 mm Hg), 16 had high diastolic blood pressure (≥85 mm Hg), and 5 had glucose ≥ 110 mg/dL. On metformin plus diet at 6 months, triglycerides moved within guidelines in 10 of 29 (34%) women, HDL-C in 6 of 47 (13%), systolic blood pressure in 16 of 26 (62%), diastolic blood pressure in 10 of 16 (63%), and glucose in 3 of 5 (60%). Metformin and diet ameliorate many of the features of the metabolic syndrome, present in 46% of women with PCOS in the current study, and should reduce risk for atherothrombosis and type 2 diabetes mellitus (DM) in PCOS.
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AS DEFINED BY the recent Adult Treatment Panel (ATP) III guidelines,[1] women with ≥ 3 of the following abnormalities have the metabolic syndrome: waist circumference > 88 cm, fasting serum triglycerides ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL, blood pressure ≥ 130/85 mm Hg, or serum glucose ≥ 110 mg/dL. The metabolic syndrome[1] is associated with increased risk for developing diabetes mellitus (DM)[2] and cardiovascular disease[3] and is associated with increased cardiovascular and all-cause mortality.[4] Recently, the prevalence of the metabolic syndrome as defined by ATP III[1] was assessed in 4,265 men and 4,549 women (1,887 white) ≥ age 20 years in the third National Health and Nutrition Examination Survey (NHANES III) (1988 to 1994), a cross-sectional health survey of a nationally representative sample of the noninstitutionalized civilian US population.[5] In the total NHANES III cohort, the unadjusted and age-adjusted prevalences of the metabolic syndrome were 21.8% and 23.7%, respectively.[5] The age-adjusted prevalence of the metabolic syndrome in the total NHANES III cohort was similar for men (24%) and women (23.4%). The prevalence of the metabolic syndrome in women ages 20 to 29 years was 6% and 15% for those 30 to 39.[5]

Insulin resistance with resultant hyperinsulinemia appears to be a major determinant of the metabolic syndrome.[6] Treatment includes diet, physical activity, and perhaps metformin, with a goal of reducing the risk of developing type 2 DM, and reducing weight, dyslipidemia, hypertension, and hyperinsulinemia.[7-10]

Similar to its role in the metabolic syndrome,[2,5,6] insulin resistance appears to be a major determinant of the polycystic ovary syndrome (PCOS), an endocrine disorder affecting ~7% of American women, characterized by oligo-amenorrhea and clinical and/or chemical hyperandrogenism, accompanied by infertility, obesity, dyslipidemias, hypertension, and impaired glucose tolerance.[11-15] Many patients with PCOS[10,11,13,14] have metabolic abnormalities, which would meet the recently defined ATP III criteria[1,5] for the metabolic syndrome.

In 138 oligo-amenorrheic white women with well-defined PCOS (31 ± 9-years-old), our first specific aim was to assess the incidence of the metabolic syndrome.[1,5] Our second aim was to compare metabolic syndrome abnormalities in the women with PCOS to those recently described in the NHANES III cohort of 1,887 white women.[5] Our third specific aim was to determine whether metformin (2.55 g/d) and a 1,500-calorie, 26% protein, 44% carbohydrate (42% of carbohydrate complex), 30% fat (polyunsaturate/saturate ratio [P/S] 2/1) diet would ameliorate metabolic syndrome abnormalities in those women who had both PCOS and metabolic syndrome.

MATERIALS AND METHODS

Design and Participants With PCOS

This work was performed after obtaining signed informed consent from all participants according to a protocol approved by the Jewish Hospital Institutional Review Board.

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Table 1. Diagnostic Characteristics for PCOS at Study Entry in 138 Oligo-Amenorrheic Women

T1	No.	(%)
Ferriman-Gallwey [20] (FG) scores ≥7	131	(96)
Total testosterone (>70 ng/dL)	26	(19)
Free testosterone (>6.8 pg/mL)	28	(20)
Androstenedione (>270 ng/dL)	33	(24)
DHEAS (>240 μg/dL)	36	(26)
At least 1 positive of above	138	(100)

In the consecutive order of their referral for diagnosis and therapy of PCOS, at study entry after an overnight fast, blood was obtained in women for measurement of lipid profile, Lp(a), serum glucose, hemoglobin A_{1C}, thyroxine (T_4), thyroid-stimulating hormone (TSH), blood urea nitrogen (BUN), creatinine, liver function tests, insulin and C-peptide, as previously described.[11,16-18] Enzymatic measurements of serum glucose and triglycerides were performed by the same methods as Ford et al.[5] High-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of other lipoproteins by heparin-MnCl2 by the same method as per Ford et al.[5] Our lipid-analysis laboratory and that of Ford et al[5] follow the same laboratory certification program. Two blood pressure readings were obtained in seated subjects; the second blood pressure, taken 5 minutes after the first, was used in the analysis. Waist circumference was measured by tape measure resting on the ischial tuberosities.

The women were referred predominantly because of amenorrhea (45%), oligomenorrhea (55%), and hirsutism (96%).

At study entry, after an overnight fast, measurements were made[11,16-18] of estradiol, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), androstenedione, dehydroepiandrosterone sulfate (DHEAS), testosterone (total and free), sex hormone-binding globulin, and serum insulin. Prolactin, 17-hydroxyprogesterone, T_4, TSH, and cortisol were measured to rule out diseases that can mimic PCOS or effect its presentation.

The diagnosis of PCOS[11,16-18] was based on 1990 National Institutes of Health[19] guidelines, which included oligomenorrhea or amenorrhea and clinical (hirsutism, Ferriman-Gallwey score ≥7)[20] and/or biochemical hyperandrogenism (≥1 high DHEAS, androstenedione, total testosterone, free testosterone), and exclusion of disorders (congenital adrenal hyperplasia, prolactinemia) that can mimic PCOS. Exclusion criteria included serum creatinine > 1.5 mg/dL, other virilizing endocrinopathies, hypothyroidism, and pituitary insufficiency. Women taking drugs known to affect endogenous sex hormones or lipids and those taking valproic acid in the 2 prestudy months were also excluded.

After documentation of PCOS (Table 1), all 138 women were given metformin (2.55 g/d), accompanied by a 1,500-calorie diet, 26% protein, 30% fat (P/S 2/1) and 44% carbohydrate (42% of carbohydrate calories complex). Follow-up visits were conducted every 2 months for 6 to 8 months.

Diagnosis of the Metabolic Syndrome

The metabolic syndrome was defined using the ATP III guidelines[1,5] as follows: ≥ 3 of the following abnormalities (waist circumference >88 cm, serum triglycerides ≥150 mg/dL, HDL-C <50 mg/dL, blood pressure 130/85 mm Hg, serum glucose ≥110 mg/dL). All blood samples were obtained after an overnight fast.[1,5]

The metabolic syndrome as diagnosed in 1,887 white women from NHANES III was compared with that in the 138 white women with PCOS, using identical diagnostic criteria.[5] As was the case for women in NHANES III,[5] diabetes and/or hypertension were not exclusionary criteria in the 138 women with PCOS.

Statistical Analysis

The age adjusted (analysis of variance)[21] prevalence of 1 or more abnormalities of the metabolic syndrome was compared between the 138 white women in our study and the 1,887 general population white women from NHANES III[5] (Tables 2 and 3).

Changes in components of the metabolic syndrome from pretreatment baseline to levels on metformin (2.55 g/d) and diet at an average of 2 and 6 months of follow-up were compared by paired Wilcoxon tests[21] (Tables 4 and 5). Percentage changes for components of the metabolic syndrome were calculated for each patient, along with the mean ± SD of these percentage changes (Table 4). In those women with PCOS and the metabolic syndrome whose pretreatment metabolic syndrome components were abnormal by ATPIII[1]-metabolic syndrome[5] guidelines (triglyceride ≥150 mg/dL, HDL-C <50 mg/dL, systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, glucose ≥110 mg/dL), the percentage of patients moving within the guideline on treatment at 2 and 6 months was assessed (Table 5, Fig 1).

Pretreatment baseline and follow-up (on treatment) weights were measured by a single staff member, as were blood pressures. However, although a single staff member measured all baseline waist circumferences, the same observer did not do all follow-up waist measurements. There was substantial between-observer measurement variance for follow-up waist measures in the same subject. Hence, in the 64 women with PCOS also identified as having the metabolic syndrome, rather than compare baseline and follow-up (on treatment) waist circumferences, baseline and follow-up weights (Table 4) and baseline and follow-up weights in those women with baseline waist circumference > 88 cm (Table 5) were compared by paired Wilcoxon tests.[21]

Spearman correlations[21] were calculated between absolute changes in components of the metabolic syndrome, as well as fasting serum insulin from pretreatment baseline to 6 months follow-up on metformin and diet.

RESULTS

PCOS

The 138 white women with PCOS were 31 ± 9-years-old. By selection, they all had both oligo-amenorrhea and at least 1

Table 2. Age-Adjusted Prevalence (%, SE) of ≥1 Abnormalities of the Metabolic Syndrome Among 138 White Women With PCOS Compared With 1,887 White Women in the NHANES III

	No. of Metabolic Abnormalities				
	≥1	≥2	≥3	≥4	=5
PCOS women (n = 138)	94.2% (2.0%)	77.5% (3.5%)	46.4% (4.2%)	13.8% (2.9%)	0.7% (0.7%)
NHANES women (n = 1,887)	68.4% (1.5%)	40.7% (1.5%)	22.8% (1.1%)	9.2% (0.6%)	3.0% (0.3%)
NHANES *v* PCOS, *P*	<.0001	<.0001	<.0001	.13	.004

NOTE. Data from National Institutes of Health[1] and Ford et al.[5]

Table 3. Age-Adjusted Prevalence (%, SE) of Individual Abnormalities of the Metabolic Syndrome Among 138 White Women With PCOS Compared With 1,887 White Women in the NHANES III

	Waist Circumference (>88cm)	Triglycerides (≥150 mg/dL)	HDL-C (<50 mg/dL)	Blood Pressure (≥130/85 mm Hg)	Glucose (≥110 mg/dL)
PCOS women (n = 138)	85.5% (3.0%)	32.6% (4.0%)	64.5% (4.1%)	44.9% (4.1%)	5.1% (1.9%)
NHANES women (n = 1887)	43.5% (1.4%)	25.0% (1.1%)	39.3% (1.9%)	27.8% (0.9%)	8.5% (0.6%)
NHANES *v* PCOS, *P*	<.0001	.067	<.0001	<.0001	.082

NOTE. Data from National Institutes of Health[1] and Ford et al.

manifestation of clinical hyperandrogenism (hirsutism with Ferriman-Galwey[20] scores ≥7) and/or biochemical hyperandrogenism (Table 1). Of the 138 women, 62 (45%) were amenorrheic and 76 (55%) were oligomenorrheic, with 33 having 1 to 3 menses per year, 24 having 4 to 6, and 19 having 7 to 8 menses per year. Three women (2%) had well-controlled, diet-treated type 2 DM at study entry.

The Metabolic Syndrome in Women With PCOS and in Women in NHANES III

The 138 women with PCOS had more age-adjusted metabolic syndrome abnormalities than 1,887 NHANES III women (Table 2). After age adjustment, 46.4% ± 4.2% of women with PCOS had the metabolic syndrome (≥3 abnormalities) versus 22.8% ± 1.1% of NHANES III women, $P < .0001$, (Table 2). The 46% incidence of the metabolic syndrome in the women with PCOS was much higher than in 20 to 29 and 30 to 39-year-old women in NHANES III5 (6% and 15%, respectively). Women with PCOS were much more likely than those in NHANES III to have abdominal obesity ($P < .0001$), low HDL-C ($P < .0001$), and high blood pressure ($P < .0001$) (Table 3).

In the 64 women with both PCOS and the metabolic syndrome, there were abnormalities in the following metabolic syndrome categories: waist circumference (98%), HDL-C (95%), blood pressure (70%), triglycerides (56%), and glucose (11%). In these 64 women, mean ± SD waist circumference was 116 ± 15 cm, triglyceride 192 ± 152 mg/dL, HDL-C 38.9 ± 7.3 mg/dL, systolic blood pressure 131 ± 13 mm Hg, diastolic blood pressure 83 ± 7 mm Hg, and glucose 94 ± 22 mg/dL. Fasting serum insulin was high (>17 μU/mL) in 42 of the 64 women (66%). In the 64 PCOS women with ≥3 metabolic abnormalities, the most common aggregates of variables were waist circumference >88 cm + HDL-C <50 mg/dL + blood pressure ≥130/85 mm Hg (n = 41, 64%), and waist + HDL-C + triglycerides ≥150 mg/dL (n = 33, 52%).

Amelioration of the Metabolic Syndrome by Diet and Metformin for 2 Months

Of the 64 women with PCOS who were identified at baseline as also having the metabolic syndrome, 4 had follow-up outside of our standardized laboratory and are not included in calculations of changes produced by combined metformin-diet therapy, leaving 60 cases followed directly by us. Abnormalities of the metabolic syndrome were improved by therapy with met-

Table 4. Changes From Pretreatment Baseline in Measures of the Metabolic Syndrome on Metformin and Diet Therapy in 5 III Women With Both PCOS and the Metabolic Syndrome

		Baseline		On Metformin + Diet		Percent Change	
	No.	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	*P*
2 mo (2.1 ± 0.5)							
Body weight (kg)	56	111 ± 21	107	108 ± 21	105	−2.7 ± 3.6	< .0001
Cholesterol (mg/dL)	54	192 ± 29	188	179 ± 32	175	−6.0 ± 13.1	.0011
Triglyceride (mg/dL)	55	203 ± 160	164	154 ± 77	134	−9.4 ± 39.1	.0018
HDL-C (mg/dL)	55	38.9 ± 7.6	40.0	38.9 ± 6.6	38.0	1.5 ± 13.3	NS
LDL-C (mg/dL)	53	115 ± 26	119	111 ± 29	110	−0.7 ± 28.0	NS
Systolic BP (mm Hg)	42	131 ± 12	135	126 ± 11	124	−3.4 ± 10.5	.014
Diastolic BP (mm Hg)	42	83 ± 7	84	80 ± 8	78	−4.0 ± 8.9	.0017
Glucose (mg/dL)	55	93 ± 20	90	96 ± 29	90	3.9 ± 24.7	NS
Insulin (μU/mL)	51	25 ± 14	24	20 ± 12	18	−14.5 ± 39.8	< .0001
6 mo (5.2 ± 0.9)							
Body weight (kg)	50	111 ± 21	107	106 ± 22	101	−4.7 ± 5.5	< .0001
Cholesterol (mg/dL)	49	194 ± 28	189	175 ± 27	169	−8.6 ± 12.6	< .0001
Triglyceride (mg/dL)	50	197 ± 164	163	136 ± 57	132	−13.9 ± 36.4	.0001
HDL-C (mg/dL)	50	39.4 ± 7.5	40.0	41.3 ± 8.1	40.5	6.0 ± 16.0	.013
LDL-C (mg/dL)	48	118 ± 23	120	108 ± 24	106	−6.1 ± 20.5	.011
Systolic BP (mm Hg)	39	131 ± 12	134	124 ± 12	125	−5.2 ± 9.8	.0002
Diastolic BP (mm Hg)	39	83 ± 7	84	77 ± 8	76	−6.0 ± 10.7	.0007
Glucose (mg/dL)	49	93 ± 21	89	94 ± 32	88	1.5 ± 21.4	NS
Insulin (μU/mL)	50	25 ± 15	24	17 ± 11	13	−25.2 ± 35.9	< .0001

Abbreviation: NS, not significant.

Table 5. Metformin and Diet Therapy for an Average of 2 mo (2.1 ± 0.5 mo) and 6 mo (5.2 ± 0.9): Changes From Pretreatment Baseline Abnormal Components of the Metabolic Syndrome in 5 III Women With Both PCOS and the Metabolic Syndrome

Abnormality at Baseline	No.	Baseline		On Metformin + Diet		P	Components of the Metabolic Syndrome Moving Within Guidelines on Metformin + Diet
		Mean ± SD	Median	Mean ± SD	Median		
2 mo							
Triglyceride ≥ 150 mg/dL	33	271 ± 174	232	192 ± 76	191	.0008	Triglyceride < 150 mg/dL in 8 (24%)
HDL-C < 50 mg/dL	52	38.1 ± 6.9	39.0	38.3 ± 6.1	37.5	NS	HDL-C ≥ 50 mg/dL in 2 (4%)
Systolic BP ≥ 130 mm Hg	28	139 ± 5	138	128 ± 10	125	< .0001	Systolic BP < 130 mm Hg in 17 (61%)
Diastolic BP ≥ 85 mm Hg	17	89 ± 2	88	84 ± 6	86	.0077	Diastolic BP < 85 mm Hg in 7 (41%)
Glucose ≥ 110 mg/dL	5	132 ± 46	111	121 ± 40	108	NS	Glucose < 110 mg/dL in 3 (60%)
Weight (kg) in women with waist > 88 cm	55	112 ± 21	108	108 ± 21	105	< .0001	
6 mo							
Triglyceride ≥ 150 mg/dL	29	271 ± 182	232	167 ± 51	160	< .0001	Triglyceride < 150 mg/dL in 10 (34%)
HDL-C < 50 mg/dL	47	38.5 ± 6.8	40.0	40.3 ± 7.1	40.0	.016	HDL-C ≥ 50 mg/dL in 6 (13%)
Systolic BP ≥ 130 mm Hg	26	138 ± 5	137	125 ± 10	128	< .0001	Systolic BP < 130 mm Hg in 16 (62%)
Diastolic BP ≥ 85 mm Hg	16	89 ± 2	88	81 ± 7	84	< .0001	Diastolic BP < 85 mm Hg in 10 (63%)
Glucose ≥ 110 mg/dL)	5	132 ± 46	111	133 ± 73	93	NS	Glucose < 110 mg/dL in 3 (60%)
Weight (kg) in women with waist > 88 cm	50	111 ± 21	107	106 ± 22	101	< .0001	

formin (2.55 g/d), accompanied by a diet of 1,500 calories, 26% protein, 44% carbohydrate (42% of carbohydrate complex), 30% fat (P/S = 2/1) (Table 4). In 56 of the 60 women with both PCOS and the metabolic syndrome who have, to date, completed an average of 2 months (2.1 ± 0.5 months) on metformin and diet, mean percent reduction in body weight was 2.7% ($P < .0001$), triglycerides decreased 9.4% ($P = .0018$), systolic blood pressure decreased 3.4% ($P = .014$), diastolic blood pressure decreased 4% ($P = .0017$), total cholesterol decreased 6% ($P = .0011$), and insulin decreased 14.5% ($P < .0001$) (Table 4).

There were 56 women with metabolic syndrome and subsequent follow-up at 2 months on therapy (Table 5, Fig 1). Of these 56 women, 33 had abnormal[1,5] high pretreatment-baseline triglycerides (≥150 mg/dL), 52 had low HDL-C (<50 mg/dL), 28 had high systolic blood pressure (≥130 mm Hg), 17 had high diastolic blood pressure (≥85 mm Hg), and 5 had glucose ≥110 mg/dL (Table 5, Fig 1). Of these women with pretreatment metabolic syndrome abnormalities, on metformin plus diet at 2 months, triglycerides moved within guidelines[1,5] in 8 of 33 (24%), HDL-C in 2 of 52 (4%), systolic blood pressure in 17 of 28 (61%), diastolic blood pressure in 7 of 17 (41%), and glucose in 3 of 5 (60%) (Table 5, Fig 1). By paired Wilcoxon tests, in those women with pretreatment baseline abnormal components of the metabolic syndrome, after 2 months on metformin plus diet, reductions in triglycerides ($P = .0008$) and systolic ($P < .0001$) and diastolic blood pressure ($P = .0077$) were significant (Table 5). Of those 56 women with metabolic syndrome and subsequent follow-up at 2 months on therapy, 55 had baseline waist circumference > 88 cm. These 55 women had a mean baseline weight of 112 kg, which decreased after 2 months on therapy to 108 kg ($P < .0001$), Table 5.

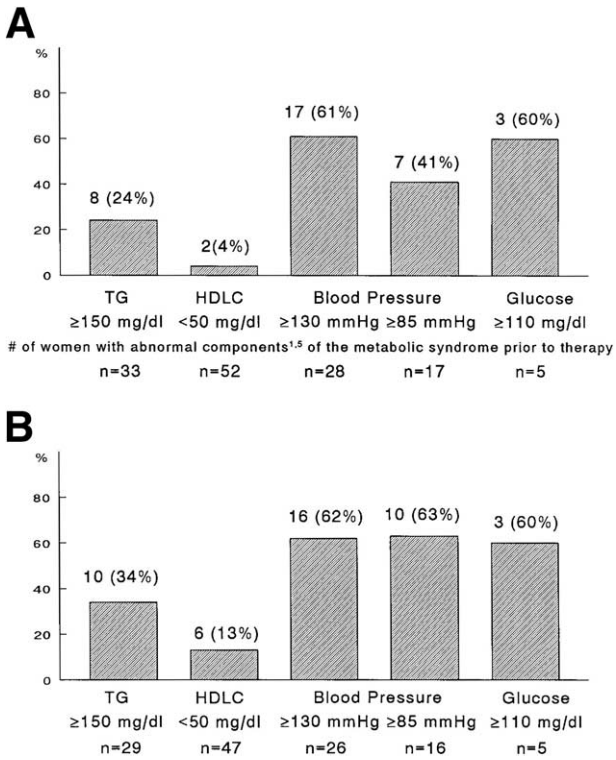

Fig 1. Number and percentage of women with both PCOS and the metabolic syndrome with abnormal, above guideline, pretreatment components[1,5] of the metabolic syndrome moving within guidelines on metformin and diet therapy for 2 (56 women) and 6 (50 women) months.

Amelioration of the Metabolic Syndrome by Diet and Metformin for 6 Months

In those 50 (of 60) women with both PCOS and the metabolic syndrome who have, to date, completed 6 months (5.2 ± 0.9 months) on metformin and diet at our center, mean percent reduction in body weight was 4.7% (111 to 106 kg, $P < .0001$), triglycerides decreased 13.9% (197 to 136 mg/dL, $P = .0001$), HDL-C increased 6% (39.4 to 41.3 mg/dL, $P = .013$), total cholesterol decreased 8.6% (194 to 175 mg/dL, $P < .0001$), low-density lipoprotein-cholesterol (LDL-C) decreased 6% (118 to 108 mg/dL, $P = .011$), systolic blood pressure decreased 5.2% from 131 to 124 mm Hg ($P = .0002$), diastolic blood pressure decreased 6% from 83 to 77 mm Hg ($P = .0007$), and insulin decreased 25.2% (25 to 17 μU/mL, $P < .0001$) (Table 4). For almost all categories of the metabolic syndrome, changes from baseline to 6 months were greater than at 2 months (Table 4).

There were 50 women with metabolic syndrome and subsequent follow-up at 6 months on therapy. Of these 50 women, 29 had abnormal[1,5] high pretreatment-baseline triglycerides (≥150 mg/dL), 47 had low HDL-C (<50 mg/dL), 26 had high systolic blood pressure (≥ 130 mm Hg), 16 had high diastolic blood pressure (≥85 mm Hg), and 5 had glucose ≥ 110 mg/dL (Table 5, Fig 1). Of these women with pretreatment metabolic syndrome abnormalities, on metformin plus diet at 6 months, triglycerides moved within guidelines in 10 of 29 (34%), HDL-C in 6 of 47 (13%), systolic blood pressure in 16 of 26 (62%), diastolic blood pressure in 10 of 16 (63%), and glucose in 3 of 5 (60%) (Table 5, Fig 1). By paired Wilcoxon tests, in those women with pretreatment baseline abnormal components of the metabolic syndrome, after 6 months on metformin plus diet, reductions in triglycerides ($P < .0001$), systolic ($P < .0001$) and diastolic blood pressure ($P < .0001$), and increments in HDL-C ($P = .016$) were significant (Table 5). Of those 50 women with metabolic syndrome and subsequent follow-up at 6 months on therapy, all 50 had pretreatment-baseline waist circumference > 88 cm. Their pretreatment mean weight was 111 kg, which decreased after 6 months on therapy to 106 kg ($P < .0001$), Table 5. At 6 months follow-up on metformin and diet, changes from pretreatment baseline in weight were positively correlated with changes in fasting serum insulin, $r = .40$, $P = .004$.

DISCUSSION

The metabolic syndrome[1-10,22] has been defined by a constellation of risk factors for cardiovascular disease, including centripetal obesity, hypertriglyceridemia, low levels of HDL-C, hypertension, and abnormal glucose metabolism. Hypofibrinolysis is often present. The risk factors of the metabolic syndrome are related to and augmented by insulin resistance.[22] PCOS is characterized by most of the risk factors, which define the metabolic syndrome,[1,5,22] including centripetal obesity, high triglycerides, low HDL-C, hypertension, impaired glucose tolerance, type 2 DM, insulin resistance, and hypofibrinolysis mediated by high levels of plasminogen activator inhibitor activity.[10,11,13-15,17,19,23-28] In the current study of 138 white women with PCOS, using the ATP III diagnostic criteria for metabolic syndrome characteristics,[1,5] the metabolic syndrome was present in 64 (46%) of women, much higher ($P < .0001$) than in 1,887 white women in NHANES III (23%), and much higher than in 20 to 29 and 30 to 39-year-old women in NHANES III (6% and 15%, respectively).[5] We did not match the 138 white women with PCOS to those 1,887 white women in NHANES III by body mass index (BMI), because we wanted to compare components of the metabolic syndrome in PCOS with the general white female population. A future study might match women with PCOS to those in NHANES III[5] by BMI to determine whether the components of the metabolic syndrome are predominantly driven by obesity, irrespective of the presence or absence of PCOS.

Within the frame of reference of 46% of women with PCOS in the current report having the metabolic syndrome, it is not surprising that PCOS is associated with endothelial and cardiac dysfunction,[28-30] and with atherosclerosis.[25-27,31-33] Beyond improving the coronary artery disease-linked components of the metabolic syndrome, metformin therapy in women with PCOS reduces the levels of endothelin-1, a marker of vasculopathy,[28,30] concurrent with improvement in hyperandrogenemia and hyperinsulinemia.[30] Polycystic ovaries are associated with the extent of coronary artery disease in women having cardiac catheterization.[32] Women with PCOS have an estimated 7-fold increased risk for myocardial infarction,[33] probably related to commonly having the metabolic syndrome, hyperinsulinemia, and hypofibrinolysis.

Legro et al[34] recently compared metabolic abnormalities and cardiovascular risk factors in 45 self-selected women with PCOS with 80 controls. The self-selected women with PCOS differed from controls, having higher blood pressure, waist-hip ratio, fasting insulin, total and LDL-C, and lower fasting glucose/insulin ratios and HDL-C levels. Legro et al[34] concluded that self-selected women with PCOS had multiple metabolic abnormalities and received inadequate treatment for risk factors for diabetes, heart disease, and endometrial cancer. Pasquali et al[10] evaluated 37 women with PCOS 6 to 18 years after their first assessment (original age 19.8 ± 4.9 years, follow-up 29 ± 4.4 years). Hyperinsulinemia and insulin resistance appeared to worsen spontaneously over time without any worsening of hyperandrogenism.

Recently Korhonen et al[35] conducted a cross-sectional population-based study of the relationship of the metabolic syndrome and obesity (albeit defined differently than ATP III[1]) to PCOS-compatible gynecologic disorders. Two hundred and four participants were recruited from a random sample of women in 5 age groups (ages 35 to 54 years). The metabolic syndrome was considered present if 3 of the following 8 criteria were present: first-degree relative with type 2 DM, BMI > 30 kg/m^2, waist/hip ratio > 0.88, blood pressure ≥ 160/95 mm Hg or drug treatment for hypertension, fasting triglyceride levels 1.7 nmol/L, HDL-C < 1.20 nmol/L abnormal glucose metabolism, and fasting serum insulin 13 μU/mL. The frequency of the metabolic syndrome as defined by Korhonen et al[35] was 106 of 543 cases (19.5 %). Two control groups were considered, 62 overweight women without central obesity or metabolic syndrome and 53 healthy lean women (BMI <27). The group with the metabolic syndrome had the highest serum free testosterone concentration. Oligomenorrhea was more prominent in women with the metabolic syndrome (46.2%), especially in those with

more severe symptoms, and was less common in the obese (25.4%) and lean (15.1%) control subjects. The investigators concluded that PCOS accounted for a distinct subgroup of a much wider problem, metabolic syndrome.[35]

As emphasized by Ford et al[5] in their assessment of the glycemic component of the metabolic syndrome in NHANES III, ". . . the cornerstones of treatment are management of weight and ensuring appropriate levels of physical activity." Lifestyle modification (diet and increased physical activity) may delay or prevent the development of type 2 diabetes,[36-39] and as emphasized by Ford et al,[5] ". . . provide relevant treatment paradigms for patients with the metabolic syndrome." Similarly, the insulin sensitizing drugs metformin[40,41] and troglitazone[42] have the potential to sharply reduce the likelihood of development of type 2 DM. Metformin provides a significant anti-obesity effect in hyperinsulinemic obese adolescents compared with a low calorie diet alone.[43] Within this frame of reference, in the current study, after an average of 6 months on metformin (2.55 g/d) and a 1,500 calorie, 26% protein, 44% carbohydrate diet, in women with both PCOS and the metabolic syndrome, mean percent reduction in body weight was 4.7% ($P < .0001$), triglycerides decreased 14% ($P < .0001$), HDL-C increased 6% ($P = .013$), total cholesterol decreased 8.6% ($P < .0001$), LDL-C decreased 6% ($P = .011$), and insulin decreased 25% ($P < .0001$). Changes from pretreatment baseline to levels after 6 months on metformin and diet in weight were positively associated with changes in fasting serum insulin, $r = .40$, $P = .004$.

In those women with PCOS and the metabolic syndrome whose pretreatment metabolic syndrome components were abnormal by ATPIII[1]-metabolic syndrome[5] guidelines, having follow-up on metformin plus diet at 2 months, triglycerides moved within guidelines[1,5] in 24%, HDL-C in 4%, systolic blood pressure in 61%, diastolic blood pressure in 41%, and glucose in 60%. Of those women with pretreatment metabolic syndrome component abnormalities[1,5] having follow-up on metformin plus diet at 6 months, triglycerides moved within guidelines in 34%, HDL-C in 13%, systolic blood pressure in 62%, diastolic blood pressure in 63%, and glucose in 60%. Metformin and diet ameliorated many of the cardiovascular risk factors that characterized women with both PCOS and the metabolic syndrome and should, speculatively, reduce risk for atherothrombosis.[5] However, without a placebo-diet group for comparison with a metformin-diet group, we cannot attribute the reduction of coronary heart disease (CHD) risk factors to diet alone or to drug alone, or, more likely, to a diet-drug interaction. However, before our metformin and diet program, the 138 women with PCOS in the current study had previously participated in many different weight-lowering programs without lasting success in improving either their weight or their endocrinopathy. When they were given metformin, similar to previous reports,[11,13,17,18,44] many women noticed that their craving for food and carbohydrates decreased dramatically,[11,13,17,18,44] so they were able to comply better with the diet.

Impaired fasting glucose (serum glucose ≥110 mg/dL) is only the tip of the iceberg of impaired glucose metabolism.[45] In the current study, 5.1% of 138 women with PCOS had fasting glucose ≥ 110 mg/dL, versus 85.5% with waist circumference > 88 cm, 64.5% with HDL-C < 50 mg/dL, 44.9% with blood pressure ≥ 130/85 mm Hg, and 32.6% with triglycerides ≥ 150 mg/dL. In women with PCOS and the metabolic syndrome who have fasting serum glucose ≥ 110 mg/dL, it may be useful to perform an oral glucose tolerance test, since the diagnostic yield[45] for the diagnosis of type 2 DM may be much higher than in the general population. Perry et al[45] have reported that nearly 50% of subjects with fasting plasma glucose 110 to 125 mg/dL had DM detected by an oral glucose tolerance test.

In aggregate, the diagnosis of PCOS offers a very good opportunity to begin primary prevention, not only of CHD, but also type 2 DM.[11,13-18,23-26,34,44] Diet plus metformin facilitate weight loss, increase HDL-C, reduce triglycerides, total cholesterol, and LDL-C, as recently reviewed,[44] and as in the current report. The metabolic syndrome is associated with increased cardiovascular and all-cause mortality.[4,46] Diet plus metfomin lower fasting serum insulin, itself an independent risk factor for CHD.[47-50] Moreover, because metformin plus diet reduces the development of gestational DM in women with PCOS from 31% to 3%,[18] and delays or prevents the development of type 2 DM in high-risk populations,[40,41] we speculate that metformin plus diet should prevent or delay the onset of type 2 DM in women with both PCOS and the metabolic syndrome.

In women with PCOS, metformin plus diet may be insufficient to optimally improve all of the components of the metabolic syndrome, as was the case for HDL-C < 50 mg/dL in the current study in which 2 of 52 (4%) and 6 of 47 (13%) women with pretreatment HDL-C < 50 mg/dL had HDL-C move within guidelines[5] (≥50 mg/dL) after 2 and 6 months on therapy, respectively. Beyond metformin and diet, specific, case-by-case, diet-drug-exercise therapies may be needed to further normalize components of the metabolic syndrome, such as HDL-C <50 mg/dL, in women with PCOS.

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