Short-term therapy with combination dipeptidyl peptidase-4 inhibitor saxagliptin/metformin extended release (XR) is superior to saxagliptin or metformin XR monotherapy in prediabetic women with polycystic ovary syndrome: a single-blind, randomized, pilot study

Karen E. Elkind-Hirsch, Ph.D., Martha S. Paterson, M.D., Ericka L. Seidemann, M.S., and Hanh C. Gutowski, R.N.

Woman's Metabolic Health and Research Services, Woman's Hospital, Baton Rouge, Louisiana

Objective: To evaluate efficacy with the dipeptidyl peptidase-4 inhibitor saxagliptin (SAXA), metformin extended release (MET), and combination (SAXA-MET) in patients with polycystic ovary syndrome (PCOS) and impaired glucose regulation.
Design: Prospective, randomized, single-blind drug study.
Setting: Outpatient clinic.
Patient(s): Patients (n = 38) with PCOS (aged 18–42 years) and prediabetic hyperglycemia determined by a 75-gram oral glucose tolerance test.
Intervention(s): Patients were randomized to SAXA-MET (5 mg/2,000 mg), SAXA (5 mg), or MET (2,000 mg) for 16 weeks.
Main Outcome Measure(s): Fasting and mean blood glucose, insulin sensitivity, insulin secretion, and insulin secretion-sensitivity index (IS-SI) by oral glucose tolerance tests. Free androgen index and lipid levels, average menstrual interval, and anthropometric measurements (body mass index, waist circumference, and waist/height ratio).
Result(s): The study was completed by 34 patients. Nineteen patients had normal glucose tolerance: 3 of 12 (25%) on MET; 6 of 11 (55%) on SAXA; and 10 of 11 (91%) on SAXA-MET (SAXA-MET statistically superior to MET) at study completion. Body mass index, waist circumference, waist/height ratio, free androgen index, insulin sensitivity, IS-SI, and menses improved in all groups; however, IS-SI and menstrual regularity were significantly better with SAXA-MET vs. MET treatment. Triglyceride, triglyceride/high-density lipoprotein cholesterol ratio and mean blood glucose significantly declined in the SAXA-MET and SAXA groups only.
Conclusion(s): This pilot work provides the first evidence regarding the effects of a dipeptidyl peptidase-4 inhibitor alone and in combination with MET in this patient population. Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.
Clinical Trial Registration Number: NCT02022007. (Fertil Steril® 2017;107:253–60. ©2016 by American Society for Reproductive Medicine.)
Key Words: Dipeptidyl peptidase-4 inhibitor, polycystic ovary syndrome, prediabetic hyperglycemia, saxagliptin

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/12077-22740

Received July 7, 2016; revised September 8, 2016; accepted September 12, 2016; published online October 27, 2016.
K.E.E.-H. served on an advisory board for AstraZeneca and has received research grant support from Novo Nordisk, Bayer, and Merck, Sharp and Dohme. M.S.P. has nothing to disclose. E.L.S. has nothing to disclose. H.C.G. has nothing to disclose.
This study is an investigator-initiated clinical trial supported by a research grant from AstraZeneca Pharmaceuticals (awarded to K.E.E.-H.).
Parts of this study were presented at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, June 10–14, 2016.
Reprint requests: Karen E. Elkind-Hirsch, Ph.D., Woman's Metabolic Health and Research Services, 100 Woman's Way – Support Services Building, Baton Rouge, Louisiana 70817 (E-mail: karen.elkind-hirsch@womans.org).

Fertility and Sterility® Vol. 107, No. 1, January 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.09.023

Up to 10% of women of reproductive age are affected by polycystic ovary syndrome (PCOS), an endocrinopathy characterized by excessive androgen production and reproductive dysfunction (1–4). Obesity is highly prevalent in PCOS and significantly exacerbates all metabolic and reproductive disturbances of the syndrome. Excess adiposity is associated with insulin resistance (IR) and compensatory hyperinsulinemia, and leads to decreased sex hormone–binding globulin (SHBG) synthesis and excessive ovarian androgen production (5). This syndrome is associated with metabolic dysfunction, including type 2 diabetes (T2D) and cardiovascular morbidity (6–8). Patients with PCOS have been found to have an abnormal metabolic profile that is independent of obesity and apparent at a young age (8, 9). Metabolic syndrome prevalence was found to be twice as high in patients with PCOS compared with the general population (10). Up to 20% of patients with PCOS exhibit impaired glucose tolerance (IGT) and increased risk of developing T2D (7, 11). Moreover, the incidence of IGT and T2D in PCOS significantly exceeds normal population estimates (7, 8, 11).

Insulin resistance plays a key role in the increased risk of T2D in PCOS patients (12). In the presence of IR, pancreatic β-cell insulin secretion increases in both obese and nonobese patients with PCOS (13). Despite an enhanced insulin response, several studies have shown that there is a defect in glucose-stimulated insulin secretion, with an imbalance between insulin secretion and IR in patients with PCOS (14–16). Ehrmann et al. (16) reported that 25%–35% of obese patients with PCOS will have either IGT or T2D by 30 years of age, and that the history of T2D in a first-degree relative defines a subset of PCOS patients with a greater prevalence of insulin secretory defects. Currently it is accepted that disorders of glucose tolerance and T2D are more frequent in patients with PCOS compared with the general population, and that these metabolic derangements result from a combination of increased IR and pancreatic β-cell dysfunction (7, 11, 12).

Incretin-based therapies represent a new class of antihyperglycemic drugs for the treatment of T2D. The gut-derived incretin hormone glucagon-like peptide 1 (GLP-1) enhances glucose-stimulated insulin secretion after a meal and lowers glucagon secretion (17, 18). Rapid degradation by dipeptidyl peptidase-4 (DPP-4) and renal clearance of GLP-1 levels result in a short half-life of 1 to 2 minutes (18). Incretin mimetics and inhibitors of the protease DPP-4 use the antihyperglycemic properties of GLP-1 (19) to augment pancreatic insulin secretion and inhibit glucagon in a highly glucose-dependent manner (20). Long-acting GLP-1 mimetics bind to the GLP-1 receptor and mimic the action of GLP-1 (19, 20). Dipeptidyl peptidase-4 inhibitors (DPP-4is) extend the half-life of endogenous gastrointestinal GLP-1, thereby prolonging its effects. Concurrent treatment with the GLP-1 receptor agonist exenatide and metformin for 24 weeks was reported to be superior to single-agent therapy in improving glycemia and reducing body weight and hyperandrogenism in overweight patients with PCOS (21). Furthermore, concomitant exenatide–metformin therapy significantly reduced fasting insulin levels as well as improved first-phase insulin responses to oral glucose administration (21). Saxagliptin is a selective oral DPP-4i that prolongs endogenously produced GLP-1 activity. The benefits of a DPP-4i alone or in combination with metformin have not been evaluated in the prediabetic PCOS population. Because aberrant first-phase insulin secretion and impaired suppression of endogenous glucose production are major contributors to postprandial hyperglycemia (22), the effects of saxagliptin to target these defects and normalize glucose excursions are likely to be clinically significant in patients with PCOS and prediabetic hyperglycemia. The present study was designed to directly compare the effects of saxagliptin and metformin and to determine whether treatment with saxagliptin/metformin combination is superior to monotherapy with the individual components in patients with PCOS and impaired glucose regulation (IGR).

MATERIALS AND METHODS

Participants

Healthy, premenopausal patients (n = 38) with PCOS, aged between 18 and 42 years inclusive, and with IGR were enrolled in the study from March 2014 to January 2016. Polycystic ovary syndrome was defined according to modified National Institutes of Health 1990 criteria (4). Eligible patients were required to have the combination of irregular periods (cycle length outside 21–35 days or fewer than eight cycles per year) together with biochemical evidence of hyperandrogenism (total T >50 ng/dL or free androgen index [FAI] >3.87 [23]) and exclusion of known disorders (nonclassic congenital adrenal hyperplasia, androgen-secreting tumors, elevated prolactin, thyroid dysfunction, and primary ovarian insufficiency). Prediabetic hyperglycemia was determined by a 75-g oral glucose tolerance test (OGTT) and included PCOS patients with impaired fasting glucose, IGT, or both (impaired fasting glucose/IGT) (24). The study excluded diabetic subjects, smokers, suspected pregnancy, desiring pregnancy, or injectable hormonal contraceptive use within 6 months; and use of oral contraceptives, other steroid hormones, drugs that affect gastrointestinal motility or carbohydrate metabolism, and/or antiobesity drugs within 3 months before study entry. The institutional review board of the Woman's Hospital Foundation approved the study, and all participants gave written informed consent.

Treatment Protocol

Thirty-eight patients with PCOS and IGR provided consent and were randomly assigned to 1 of 3 treatment groups: MET (metformin extended release [XR], 2,000 mg orally once daily); SAXA (saxagliptin 5 mg orally once daily); or SAXA-MET (5 mg saxagliptin/2,000 mg metformin XR orally once daily) for 16 weeks. All patients were allocated to 1 of these 3 groups according to computer-generated random numbers using a block randomization method. The primary investigator was blinded to all treatment arms. The research coordinator filled color-coded bags (A, B, C) with 1 of 3 medications—A, MET; B, SAXA; and C, SAXA-MET—and dispensed open-label medications to study patients in color-coded bags with instructions. Saxagliptin (ONGLYZA), metformin XR (GLUCOPHAGE XR), and combination saxagliptin/metformin XR (KOMBIGLYZE XR) were provided by AstraZeneca Pharmaceuticals.

Oral glucose tolerance tests were performed in the morning (starting at 7:00–9:30 AM) after a 12-hour overnight fast. After the collection of a baseline blood sample, a 75-g oral glucose load was administered; additional blood samples were drawn 30, 60, and 120 minutes later for analysis of glucose and insulin levels. Fasting baseline blood specimens were also used for measures of an androgen profile: total T, DHEAS, SHBG, and a lipid panel (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TRG]). All patients were screened with a qualitative β-hCG level to exclude pregnancy and use of adequate barrier contraception recorded. A TRG/HDL-C ratio >3.0 was used as an indirect measure of IR (25).

At the initial clinic visit, body weight, height, waist circumference (WC), and blood pressure (BP) were determined. Height and weight measurements were used to calculate body mass index (BMI), defined as kg/m^2. The waist/height ratio (WHtR) was calculated, and WC >88 cm and WHtR >0.5 were considered to be elevated, indicating abdominal adiposity (26). At clinic visit completion, patients were dispensed a 1-month supply of medication. Patients were asked about the number of menses in the previous 12 months, and menstrual frequency was recorded. Study patients were instructed to record the presence/absence of menstrual bleeding daily in a menstrual diary distributed at the time medication was provided. At 4 weeks, patients returned for a clinic evaluation that included vital signs, anthropometric measurements, and a safety assessment. Medication for the remainder of the study was dispensed to the patients.

Laboratory testing and anthropometric measures described for the baseline evaluation were repeated at the final 16-week visit. All patients' complete menstrual diaries were reviewed. At study completion, medications were stopped and patients given a prescription for the same or other medications if needed. Adverse events and reason for any withdraws from the study were recorded throughout the study from patients' self-reporting and results of physical examinations and laboratory tests. A summary of participant flow can be found in Supplemental Figure 1 (available online).

Study Measurements and Analyses

Anthropometric and menstrual frequency. Anthropometric measurements were collected (height, weight, WC) at baseline, 4 weeks, and at the 16th week of treatment. The BMI, waist/hip ratio, and WHtR were calculated using standard formulas.

The number of menstrual cycles during the previous year was recorded. An average menstrual interval was defined as 365 divided by the number of menstrual cycles in the previous year. During the study period the patients recorded vaginal bleeding in a menstrual diary. The effects of treatment intervention on menses was evaluated by assessing posttreatment changes in the menstrual cycle interval over 16 weeks from each patient's menstrual cycle diary. Average menstrual interval before and after drug treatment was also included as a secondary endpoint.

On each visit, compliance with treatment was checked by asking the patients about incidental missed administrations and whether they had correctly followed the scheduled treatment.

Laboratory measures. Glucose concentrations were measured by the glucose oxidase method using the Vitros Chemistry System (Ortho Vitros 5600 System; Ortho-Clinical Diagnostics), and insulin levels were analyzed by paramagnetic particle chemiluminescent immunoassay using a Beckman Coulter Access 2 Analyzer. Levels of T, DHEAS, SHBG, total cholesterol, HDL-C, TRG, calculated LDL-C, and quantitative β-hCG were determined using an automated clinical chemistry analyzer, as previously described (21).

Calculations. The FAI was calculated as the quotient 100 × T/SHBG; hyperandrogenism was defined by a value ≥3.85 (23). Mean blood glucose concentrations were calculated by summing glucose values obtained at 0, 30, 60, and 120 minutes during the OGTT and dividing by 4. Hyperinsulinemia was considered when fasting levels were >71.75 pmol/L and 2-hour postload levels were >287 pmol/L. Fasting insulin sensitivity was estimated by homeostasis model assessment of IR (HOMA-IR) (27). Oral glucose tolerance test–derived insulin sensitivity was measured using the Matsuda index (SI_{OGTT}) (28). Estimation of acute pancreatic β-cell response to glucose was calculated using the insulinogenic index (IGI = ΔI30/ΔG30) (29) corrected with the relative level of IR (IGI/HOMA-IR) (30). The insulin secretion–sensitivity index (IS-SI) was derived by applying the concept of the disposition index to measurements obtained during the 2-hour OGTT (31). The IS-SI, a surrogate measure of the disposition index derived from the OGTT (IGI multiplied by the SI_{OGTT}), was calculated as the product of acute β-cell response (IGI) and Matsuda index (SI_{OGTT}) based on the existence of the predicted hyperbolic relationship between these two measures and provides an estimate of β-cell compensation relative to the prevailing IR, not absolute insulin secretion (32).

Statistical Methods

The primary trial endpoint was improvement in β-cell compensatory function (IS-SI) with drug treatment. A priori sample size analysis was performed using an online calculator. Given there were no previous studies utilizing DPP-4i treatment in PCOS patients with dysglycemia, power calculations were based on the assumption of an estimated mean difference between treatment groups of 30%, with an average SD of 12%, which would require 11 completers per treatment group to give a power of 80% to detect a statistically significant difference ($\alpha = 0.05$). The study was designed to recruit 12 patients in each arm to ensure that the number of patients completing the study as derived by the sample size calculation was met.

All other analyses were conducted using SPSS for Windows statistical software (version 15.1; IBM). Descriptive information was reported as mean ± SD for continuous variables. Categorical variables were presented as numbers and percentages (proportions) unless otherwise indicated. All P values were two-tailed; with statistical significance set at α level of $P \leq .05$. Data were assessed for normality using the Kolmogorov-Smirov test. When necessary, nonnormally distributed data were subjected to logarithmic or square-root transformation to obtain a normal distribution before group comparison.

The primary outcome measure was IS-SI, and secondary outcome measures included insulin sensitivity and secretion,

TABLE 1

Baseline characteristics of PCOS study groups at the time of randomization.

Parameters	MET (n = 12)	SAXA (n = 11)	SAXA-MET (n = 11)	ANOVA *P* values[a]
Age (y)	29.9 ± 7	28.6 ± 6.6	29.6 ± 8	.9
Menstrual cycles (no./y)	4 ± 2.8	4 ± 2.6	5.3 ± 2	.4
BMI (kg/m^2)	42.1 ± 7.3	37.2 ± 6.8	43.8 ± 10.5	.17
WC (cm)	111 ± 11	100 ± 17	111 ± 15	.14
WHt ratio	0.67 ± 0.06	0.61 ± 0.1	0.68 ± 0.09	.1
SBP (mm Hg)	135.7 ± 7.1	134.6 ± 11	131.6 ± 12	.61
DBP (mm Hg)	88.6 ± 8.5	82.7 ± 10.9	82.5 ± 13	.32
Testosterone (nmol/L)	1.46 ± 0.58	1.84 ± 0.58	1.46 ± 0.64	.23
SHBG (nmol/L)	23.4 ± 11.4	29.3 ± 11.9	28.8 ± 12.8	.42
FAI (U)	6.7 ± 2.1	7.4 ± 4.4	6.8 ± 4.4	.89
DHEAS (μmol/L)	4.78 ± 1.5	6.26 ± 2.9	3.98 ± 2.2	.07
FBG (mmol/L)	5.6 ± 0.57	5.6 ± 0.37	5.6 ± 0.55	.93
Mean BG (mmol/L)	8.3 ± 0.85	7.5 ± 1.18	7.7 ± 1.42	.27
HOMA-IR	6.8 ± 3.6	4.9 ± 3.3	5.0 ± 2	.44
SI_{ogtt}	2.1 ± 1.4	2.6 ± 1.8	2.2 ± 1.3	.67
IGI	1.5 ± 1.05	1.8 ± 0.86	2.1 ± 1.9	.5
IS-SI	130 ± 60	258 ± 217	213 ± 141	.13
IGI/HOMA	0.28 ± 0.15	0.57 ± 0.48	0.43 ± 0.35	.16
Cholesterol (mmol/L)	4.9 ± 0.7	5.3 ± 1.68	4.9 ± 0.76	.62
HDL-C (mmol/L)	1.12 ± 0.35	1.05 ± 0.2	1.04 ± 0.25	.76
LDL-C (mmol/L)	3.06 ± 0.6	3.42 ± 1.0	3.16 ± 0.56	.43
TRG (mmol/L)	1.52 ± 0.64	1.98 ± 0.88	1.61 ± 0.56	.39
TRG/HDL ratio	3.4 ± 1.9	4.5 ± 2.3	3.6 ± 1.4	.49

Note: Each value represents mean ± SD. BG = blood glucose; FBG = fasting blood glucose.
[a] All *P* values not significant.

Elkind-Hirsch. Saxagliptin/metformin therapy in PCOS. Fertil Steril 2016.

glycemic parameters, sex steroids, FAI, lipid profiles, menstrual cycle interval, BP, and anthropometric measurements, which were considered as dependent variables. Baseline characteristics in the three treatment groups were compared using one-way analyses of variance (ANOVAs). For all analyses in which the measures were continuous, data were analyzed using a factorial repeated-measures ANOVA model (subjects/drug treatments × study visit) with drug treatment as the between-subjects effect and the visit (baseline and 16 weeks) as the within-subjects effect. To evaluate the differences in the response to different treatments over visits, the interaction effect was calculated. Only where a statistically significant interaction effect was found ($P \leq .05$) was the Bonferroni contrast test applied to locate the differences among the three medication groups. Dysglycemia occurrence before and after treatments was compared with the McNemar test (complex χ^2 for paired data), which formally tests for a change between the observed proportions of k-related samples.

RESULTS

Baseline Characteristics

Table 1 presents baseline characteristics of all patients who completed the study. Twenty-eight Caucasian and 10 African American women were randomized and received treatment, and 34 (89%) completed the study per protocol. Race was equally distributed across treatment arms. Baseline comparisons revealed that basal and glucose-stimulated metabolic, anthropometric, and hormonal measures were comparable between groups (Table 1).

Changes with Drug Treatment

Effects of 16 weeks of treatment on metabolic, hormonal, and anthropometric parameters and indices of body fat distribution are summarized in Tables 2 and 3.

Metabolic changes. All study patients had dysglycemia at the start of the study. Nineteen of 34 patients (56%) had normal glucose tolerance at completion of 16 weeks of therapy: 3 of 12 patients taking MET (25%); 6 of 11 patients taking SAXA (55%); and 10 of 11 patients taking SAXA-MET (91%). The combination therapy was statistically superior to metformin alone in normalizing fasting and postchallenge glucose concentrations ($P = .007$).

Fasting blood glucose levels were significantly reduced in all three treatment groups ($P = .0001$; Table 2). In contrast, OGTT mean blood glucose concentrations were significantly improved only in patients who received saxagliptin, either alone or in combination with metformin (Table 2). Both SAXA-MET ($P = .02$) and SAXA ($P = .04$) therapy were superior to MET therapy in significantly lowering blood glucose levels during OGTT.

The HOMA-IR, a measure of basal insulin sensitivity, was significantly better with all drug treatments ($P = .004$; Table 2). Likewise, the OGTT-derived insulin sensitivity index (SI_{OGTT}), a measure of basal and stimulated insulin sensitivity, was significantly improved after 16 weeks in all groups ($P = .003$). Insulinogenic index, reflecting the early insulin response, and corrected early phase insulin secretion index (IGI/HOMA) were significantly improved in all groups ($P = .006$ and $P = .025$, respectively). As to the primary

TABLE 2

Effect of saxagliptin and metformin, alone and in combination, on glucose levels, insulin secretion, and sensitivity parameters and lipid profiles.

	MET		SAXA		SAXA-MET		
Parameter	Baseline (n = 12)	Posttherapy (n = 12)	Baseline (n = 11)	Posttherapy (n = 11)	Baseline (n = 11)	Posttherapy (n = 11)	ANOVA *P* values
Plasma glucose							
FBG (mmol/L)	5.6 ± 0.57	5.4 ± 0.7	5.6 ± 0.37	5.3 ± .51	5.6 ± 0.55	5.0 ± .36	T = .0001
Mean BG (mmol/L)	8.3 ± 0.85	7.9 ± 1.4	7.5 ± 1.18	7.1 ± 1.64	7.7 ± 1.42	6.2 ± 1.2	T = .0001, I = .038; C vs. M = .02, S vs. M = .04
Insulin measures							
HOMA-IR	6.8 ± 3.6	5.9 ± 3.7	4.9 ± 3.3	4.4 ± 2.9	5.0 ± 2	3.6 ± 2.1	T = .004
SI_{ogtt}	2.1 ± 1.4	2.5 ± 1.6	2.6 ± 1.8	3.5 ± 3.4	2.2 ± 1.3	4.1 ± 2.6	T = .003
IGI	1.5 ± 1.05	1.6 ± 0.7	1.8 ± 0.86	3.0 ± 2.3	2.1 ± 1.9	3.2 ± 2.3	T = .006
IS-SI	130 ± 60	208 ± 126	258 ± 217	359 ± 295	213 ± 141	532 ± 347	T = .0001, I = .012; C vs. M = .02, S vs. M = .29
IGI/HOMA	0.28 ± 0.15	0.46 ± 0.3	0.57 ± 0.4	1.4 ± 17	0.43 ± 0.35	1.03 ± 0.7	T = .025
Metabolic features							
Cholesterol (mmol/L)	4.9 ± 0.7	4.7 ± 0.62	5.3 ± 1.68	5.0 ± 1.7	4.9 ± 0.76	4.6 ± 0.54	T = .014
HDL-C (mmol/L)	1.12 ± 0.35	1.06 ± 0.3	1.05 ± 0.2	1.06 ± 0.2	1.04 ± 0.25	1.06 ± 0.2	NS
LDL-C (mmol/L)	3.06 ± 0.6	2.82 ± 0.6	3.42 ± 1.0	3.21 ± 1.3	3.16 ± 0.56	2.95 ± 0.5	T = .015
TRG (mmol/L)	1.52 ± 0.64	1.86 ± 0.7	1.98 ± 0.9	1.54 ± 0.7	1.61 ± 0.6	1.33 ± 0.4	I = .003; C vs. M = .004, S vs. M = .001
TRG/HDL ratio	3.4 ± 1.9	4.2 ± 2.4	4.5 ± 2.3	2.9 ± 1.3	3.6 ± 1.4	3.0 ± 0.9	I = .006; C vs. M = .009, S vs. M = .004

Note: Each value represents mean ± SD. BG = blood glucose; C = combined SAXA-MET; FBG = fasting blood glucose; I = interaction differences between treatment over trials; M = metformin; NS = not significant; S = saxagliptin; T = main effect after all treatments.

Elkind-Hirsch. Saxagliptin/metformin therapy in PCOS. Fertil Steril 2016.

endpoint, the IS-SI, there was a tendency to an increased mean score from baseline with all therapies, indicative of improved β-cell function with enhanced insulin sensitivity (P=.0001; Table 2). Changes in the IS-SI, derived from the product of the IGI and IS_{OGTT}, with drug treatment are illustrated in Figure 1. The IS-SI showed a progressive increasing mean score from MET (208 ± 126) to (359 ± 295) to SAXA-MET (532 ± 347; Fig. 1). Patients' mean IS-SI in the SAXA-MET treatment group was significantly higher than the mean value with MET alone (P=.02; Table 2).

Total cholesterol (P=.014) and LDL-C (P=.014) concentrations were significantly decreased, whereas HDL-C levels did not change significantly with all treatments (Table 2). In contrast, TRG levels were lowered significantly with SAXA-MET (P=.004) and SAXA (P=.001) therapy compared with MET treatment, in which TRG levels slightly increased (Table 2). The TRG/HDL-C ratio was significantly reduced with both SAXA-MET (P=.009) and SAXA (P=.004) treatment compared with no improvement with MET monotherapy (Table 2).

TABLE 3

Effect of saxagliptin and metformin, alone and in combination, on clinical, anthropometric, and endocrine parameters and indices of body fat distribution.

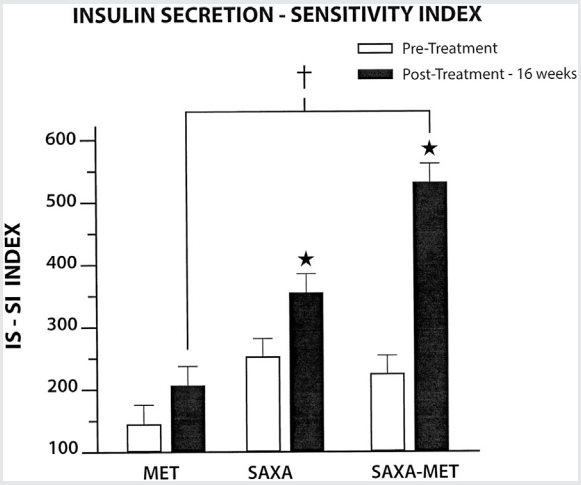
	MET		SAXA		SAX-MET		
Parameter	Baseline (n = 12)	Posttherapy (n = 12)	Baseline (n = 11)	Posttherapy (n = 11)	Baseline (n = 11)	Posttherapy (n = 11)	ANOVA *P* values
Anthropomorphic characteristics							
Menstrual interval (d)[a]	121 ± 68	81 ± 44	121 ± 52	58 ± 29	98 ± 48	36 ± 11	T = .001; I = .026; C vs. M = .03, S vs. M = .18
BMI (kg/m^2)	42.1 ± 7.3	42 ± 7.7	37.2 ± 6.8	36.7 ± 7.4	43.8 ± 10.5	42 ± 10.2	T = .006
WC (cm)	111 ± 11	109 ± 13	100 ± 17	99.6 ± 17	111 ± 15	106 ± 16	T = .006
WHtR	0.67 ± .06	0.66 ± .07	0.6 ± 0.1	0.6 ± 0.1	0.68 ± .09	0.65 ± .08	T = .0001
SBP (mm Hg)	135.7 ± 7	133 ± 11	135 ± 11	130 ± 11.7	131.6 ± 12	131 ± 13	NS
DBP (mm Hg)	88.6 ± 8	85.4 ± 9.8	82.7 ± 11	82.7 ± 6.5	82.5 ± 13	83.5 ± 8.9	NS
Hormonal levels							
T (nmol/L)	1.46 ± 0.6	1.1 ± 0.42	1.84 ± 0.58	1.5 ± 0.52	1.46 ± 0.64	1.1 ± 0.73	T = .006
SHBG (nmol/L)	23.4 ± 11.4	20 ± 11	29.3 ± 11.9	32 ± 14	28.8 ± 12.8	31 ± 10	NS
FAI (U)	6.7 ± 2.1	6.3 ± 2.8	7.4 ± 4.4	5.5 ± 3.4	6.8 ± 4.4	4.3 ± 3.5	T = .006
DHEAS (umol/L)	4.78 ± 1.5	4.7 ± 1.5	6.3 ± 2.9	5.35 ± 2.3	3.98 ± 2.2	3.83 ± 1.8	T = .006

Note: Each value represents mean ± SD. C = combined SAXA-MET; I = interaction differences between treatment over trials; M = metformin; NS = not significant; S = saxagliptin; T = main effect after all treatments.

[a] Menstrual interval reflects the number of days between menstrual cycles.

Elkind-Hirsch. Saxagliptin/metformin therapy in PCOS. Fertil Steril 2016.

FIGURE 1



Changes in insulin secretion-sensitivity indices (IS-SI) obtained from an oral glucose tolerance test at baseline and after 16 weeks of therapy in patients with PCOS and prediabetic hyperglycemia. The IS-SI significantly increased after 16 weeks with SAXA-MET treatment in contrast to MET therapy (*P=.0001 main pre- vs. post-treatment effect); † = P=.02 specific treatment effect (SAXA-MET vs. MET).

Elkind-Hirsch. Saxagliptin/metformin therapy in PCOS. Fertil Steril 2016.

Cycle changes. Menses occurrence was significantly increased in all groups after treatment (P=.0001). Return of menses was reported at a significantly higher rate with SAXA-MET therapy compared with single-agent therapy with MET (P=.03). In the SAXA-MET group, menses were more regular, with average menstrual interval decreased from baseline of 98 ± 48 days to 36 ± 11 days, compared with 121 ± 68 days to 81 ± 44 in the MET group (Table 3).

Endocrine changes. Levels of DHEAS (P=.02) and T (P=.0001) and FAI (P=.001) were significantly lower after 16 weeks of treatment in all groups, whereas SHBG levels were increased, but not significantly, with SAXA and SAXA-MET but not MET treatment (Table 3).

Anthropometric changes. Body mass index declined with all treatments (P=.035; Table 3). Comparable results were shown for WC and WHtR, with a significant reduction in mean WC (P=.004) and mean WHtR (P=.008) in all groups after 16 weeks (Table 3). Although not statistically significant, SAXA-MET therapy was more effective in reducing WC and WHtR compared with either single-agent treatment (Table 3). Systolic and diastolic BP were not affected by drug treatment (Table 3).

DISCUSSION

This study presents the results of the first analysis comparing the effects of combination DPP-4i saxagliptin and metformin XR (SAXA-MET) with single-agent saxagliptin (SAXA) or metformin XR (MET) on clinical, hormonal, and metabolic characteristics in patients with PCOS and IGR. We have demonstrated superior efficacy (normalization of glucose tolerance, mean OGTT blood glucose levels, insulin action, TRG concentrations and TRG/HDL-C ratio, and menstrual cyclicity) of SAXA-MET over either agent alone in the management of prediabetic patients with PCOS.

Dysglycemia was evident in all patients at baseline. The most striking finding in this study is that more than 90% of patients in the SAXA-MET group achieved normal glucose tolerance after 16 weeks of therapy. Although the improvement in HOMA-IR was greater with SAXA-MET therapy, the lack of statistically significant differences between treatments in the present study may be due to the large variability in IR calculated using the HOMA method in patients with PCOS, as previously described (33). An apparently unique form of IR characterizes PCOS. Even in the absence of changes in fasting glucose and insulin levels, the results of dynamic studies indicate that glucose utilization is variable in overweight women with PCOS. These abnormalities are not detected using the HOMA indices that are calculated from fasting values. The SI_{OGTT} was significantly improved with all treatments, with SAXA-MET treatment superior to single-agent therapy. Subtle alterations in insulin secretion were also demonstrable. Beneficial effects on insulin secretion were seen with SAXA and SAXA-MET, suggesting more efficient insulin secretion, which was not observed with MET treatment. In the setting of normal β-cell function, as insulin sensitivity decreases, insulin secretion increases in a compensatory manner to maintain a constant hyperbolic relationship (30). As glucose tolerance declines, the IS-SI decreases, which has been shown to predict conversion to diabetes (32). Conversely, higher IS-SI suggests elevated first phase insulin secretion relative to the corresponding degree of IR. An increase in IS-SI is exhibited in individuals who progress from IGT to normoglycemia, indicating appropriate β-cell function relative to their prevailing insulin sensitivity and a positive shift on the hyperbolic curve. We observed after 16 weeks that the mean IS-SI in the SAXA-MET group increased to the greatest extent, followed by SAXA, and was statistically greater than MET. The minimal effect of metformin in our study may result from many of the research participants having moderate to extreme obesity (34). Similarly, other studies evaluating the effects of metformin alone in comparably overweight patients with PCOS noted a similar lack of beneficial effects on these aspects of PCOS with metformin (35, 36). The improvement in the mean TRG/HDL ratio, a marker of IR, further confirms the beneficial effect on insulin action with saxagliptin–metformin treatment but not metformin (25).

A significant reduction in mean BMI was observed across all treatment groups. This was not expected, given that DPP-4is are considered weight neutral medications (37). Therapy with DPP-4i has been shown to have little effect on weight in most clinical trials to date, but patients evaluated in prior studies all had T2D (38). Bruno et al. (39) reported modest weight reduction in patients with PCOS taking metformin, with more consistent effects with higher doses of metformin. The improvement in central adiposity was most dramatic with saxagliptin–metformin therapy, whereas mean WC and mean WHtR measurements were not as reduced at 16 weeks on metformin. This finding is in agreement with Lord et al. (40) who showed that metformin had no clinically significant effect on decreasing visceral fat in patients with PCOS.

The present report indicates that all treatments improved T and DHEAS levels. A greater reduction in mean FAI was observed in the SAXA-MET group compared with MET alone. Although not significant, this trend could be the result of increased levels of SHBG with both SAXA-MET and SAXA therapy but not MET, further lessening the bioavailability of circulating androgens. Comparable findings documenting the failure of metformin to influence circulating SHBG has been reported previously (21, 34).

Clinical improvement in the time interval between menses was observed with all treatment regimens. Significantly more patients experienced regular menstrual periods on SAXA-MET therapy than MET during the 16-week trial. We reported similar findings with concomitant use of exenatide and metformin, in which clinical improvement in menstrual cycle regularity was apparent with all treatment regimens, with significantly more patients experiencing menstrual periods on concomitant therapy than with metformin (21).

Saxagliptin was well tolerated in this trial. The addition of SAXA to MET therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone. No clinically meaningful differences between treatment groups in the overall incidence of clinical adverse experiences, serious clinical adverse experiences, or laboratory adverse experiences were observed. The incidence of study discontinuation due to adverse events over 16 weeks was similar across arms.

Important limitations of the present study were the small number of patients in the treatment groups and the short interval (16 weeks) of drug treatment. Second, surrogate measures were used to estimate insulin sensitivity and secretion. For the patients in the present study, we used measures derived from the OGTT. Although the OGTT is less precise than intravenous tests, the OGTT is a practical test in clinical trials and is much more physiologic than intravenous testing, particularly because glucose sensors widespread through gastrointestinal tract may actively participate in insulin secretion and action.

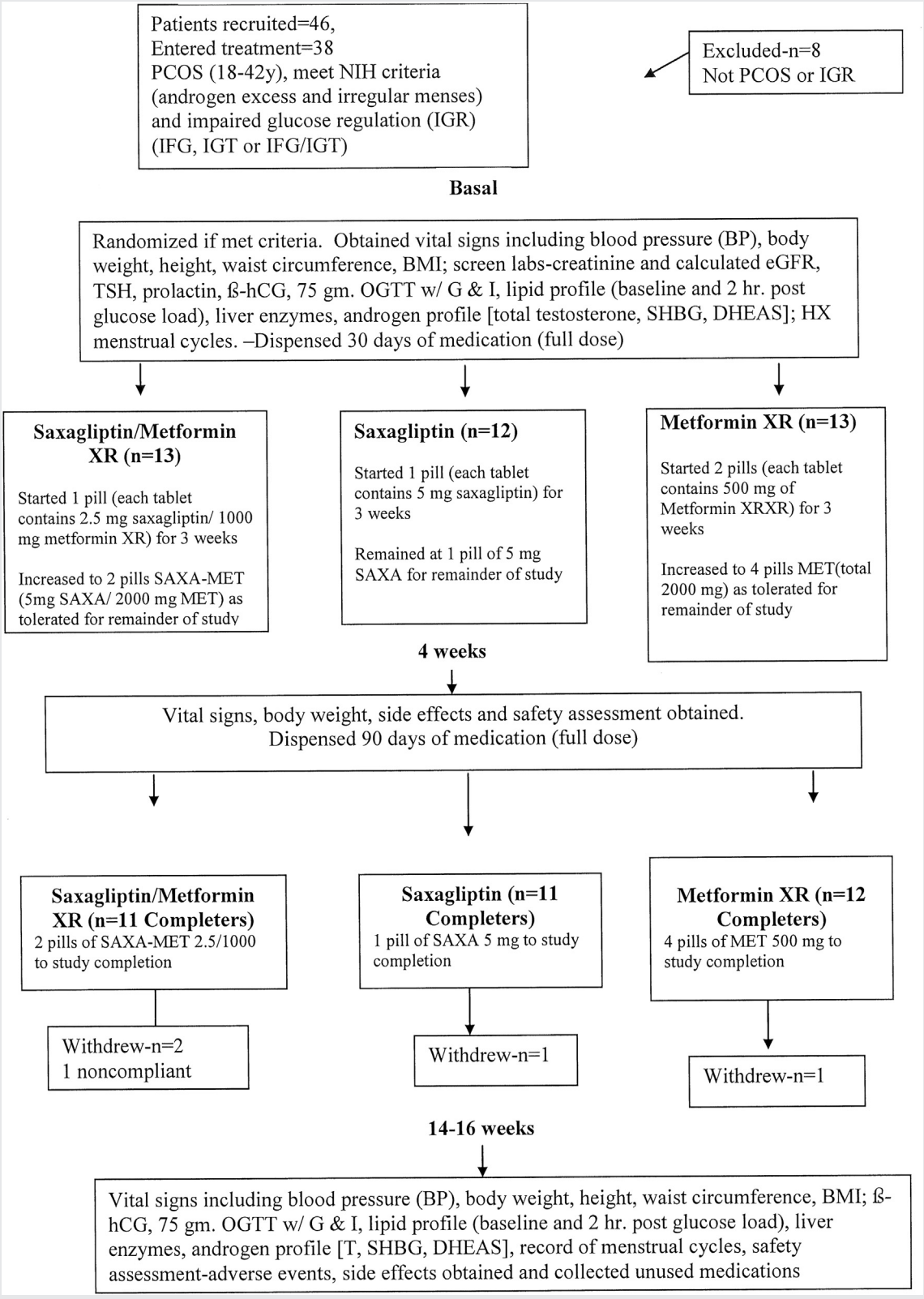
In summary, the results provide the first evidence regarding the efficacy of DPP-4i monotherapy and in combination with metformin in a PCOS patient population. Overall, 16 weeks of combination saxagliptin/metformin XR administration among prediabetic patients diagnosed with PCOS had greater beneficial effects on central adiposity, insulin levels, glucose control, androgen levels, and menstrual cyclicity. Further large, long-term, double-blinded, randomized studies are warranted to examine the long-term efficacy and safety of combination therapy with saxagliptin and metformin XR in PCOS patients.

REFERENCES

1. Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. Gynecol Endocrinol 1987;1:235–45.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998;83:3078–82.
3. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–9.
4. National Institutes of Health. National Institutes of Health Evidence-based Methodology Workshop on Polycystic Ovary Syndrome, December 3-5 2012. Available at: https://prevention.nih.gov/docs/programs/pcos/finalreport.pdf. Accessed June 1, 2016.
5. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord 2002;26:883–96.
6. Morgan C, Jenkins-Jones S, Currie C, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched reference controls: a retrospective, observational study. J Clin Endocrinol Metab 2012;97:3251–60.
7. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141–6.
8. Cibula D, Cífková R, Fanta M, Poledne R, Zivny J, Skibová J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. Hum Reprod 2000;15:785–9.
9. Diamanti Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. Trends Endocrinol Metab 2007;18:280–5.
10. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism 2003;52:908–15.
11. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–9.
12. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implication for pathogenesis. Endocr Rev 1997;18:774–800.
13. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989;38:1165–74.
14. Dunaif A, Finegood DT. Beta-cell dysfunction independent of obesity and glucose tolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 1996;81:942–7.
15. O'Meara NM, Blackman JD, Ehrmann DA, Barnes RB, Jaspan JB, Rosenfield RL, et al. Defects in beta-cell function in functional ovarian hyperandrogenism. J Clin Endocrinol Metab 1993;76:1241–7.
16. Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS. Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 1995;96:520–7.
17. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013;17:819–37.
18. Janardhan S, Sastry GN. Dipeptidyl peptidase IV inhibitors: a new paradigm in type 2 diabetes treatment. Curr Drug Targets 2014;15:600–21.
19. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–705.
20. Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 2002;87:1239–46.
21. Elkind-Hirsch KE, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endo Metab 2008;93:2670–8.
22. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130–9.
23. Mathur RS, Moody LO, Landgrebbe S, Williamson HO. Plasma androgens and sex hormone binding globulin in the evaluation of hirsute patients. Fertil Steril 1981;35:29–35.
24. American Diabetes Association. Position statement. Standards of medical care in diabetes-2013. Diabetes Care 2013;36(Suppl 1):4–10.
25. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003;139:802–9.

26. Ashwell M, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. Br Med J 1996; 313:559–60.
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and ß-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
28. Matsuda M, DeFronzo R. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–70.
29. Wareham NJ, Phillips DI, Byrne CD, Hales CN. The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. Diabet Med 1995;12:931.
30. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects: evidence for a hyperbolic function. Diabetes 1993;42:1663–72.
31. Ahren B, Pacini G. Importance of quantifying insulin secretion in relation to insulin sensitivity to accurately assess β cell function in clinical studies. Eur J Endocrinol 2004;150:97–104.
32. Retnakaran R, Shen S, Hanley AJ, Vuksan V, Hamilton JK, Zinman B. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. Obesity (Silver Spring) 2008;16:1901–7.
33. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril 2005;83:1454–60.
34. Crave JC, Fimbel S, Lejeune H, Cugnardey N, Déchaud H, Pugeat M. Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. J Clin Endocrinol Metab 1995;80:2057–62.
35. Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS. Effects of metformin on insulin secretion, insulin action, and ovarian steroidogenesis in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1997;82:524–30.
36. Messer C, Boston R, Leroith D, Geer E, Miller J, Messer M, et al. Pancreatic ß-cell dysfunction in polycystic ovary syndrome: the role of metformin. Endocrin Pract 2012;18:685–93.
37. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369.
38. Rosenstock J, Baron MA, Camisasca RP, Cressier F, Couturier A, Dejager S. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:175–85.
39. Bruno RV, de Avila MA, Neves FB, Nardi AE, Crespo CM, Sobrinho AT. Comparison of two doses of metformin (2.5 and 1.5 g/day) for the treatment of polycystic ovary syndrome and their effect on body mass index and waist circumference. Fertil Steril 2007;88:510–2.
40. Lord J, Thomas R, Fox B, Acharya U, Wilkin T. The effect of metformin on fat distribution and the metabolic syndrome in women with polycystic ovary syndrome—a randomised, double-blind, placebo-controlled trial. Br J Ob Gyn 2006;113:817–24.

SUPPLEMENTAL FIGURE 1



Patient flow chart. A total of 38 patients who met eligibility criteria were recruited and consented. In all, 34 of the 38 patients completed the 16-week study. The remaining 4 patients dropped out for incomplete data or non-compliance with medication.

Elkind-Hirsch. Saxagliptin/metformin therapy in PCOS. Fertil Steril 2016.