Alterations in nonesterified free fatty acid trafficking rather than hyperandrogenism contribute to metabolic health in obese women with polycystic ovary syndrome

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Objective: To determine whether alterations in nonesterified fatty acid (NEFA) dynamics or degree of hyperandrogenism (HA) contribute to the difference in insulin sensitivity between women with metabolically healthy obese polycystic ovary syndrome (PCOS) (MHO-PCOS) and women with metabolically unhealthy obese PCOS (MUO-PCOS).
Design: Prospective cross-sectional study.
Setting: Tertiary-care academic center.
Patients: One hundred twenty-five obese women with PCOS.
Intervention: Consecutive obese (body mass index [BMI] $\geq$ 30 kg/m^2) oligo-ovulatory women (n = 125) with PCOS underwent an oral glucose tolerance test and a subgroup of 16 participants underwent a modified frequently sampled intravenous glucose tolerance test to determine insulin-glucose and -NEFA dynamics.
Main Outcome Measures: Degree of insulin resistance (IR) in adipose tissue (AT) basally (Adipo-IR) and dynamically (the nadir in NEFA levels observed [$NEFA_{nadir}$], the time it took for NEFA levels to reach nadir [$TIME_{nadir}$], and the percent suppression in plasma NEFA levels from baseline to nadir [$\%NEFA_{supp}$]); peak lipolysis rate (S_{NEFA}) and peak rate of NEFA disposal from plasma pool (K_{NEFA}); whole-body insulin-glucose interaction (acute response of insulin to glucose [AIRg], insulin sensitivity index [Si], glucose effectiveness [Sg], and disposition index [Di]); and HA (hirsutism score, total and free testosterone levels, and dehydroepiandrosterone sulfate levels).
Results: A total of 85 (68%) women were MUO-PCOS and 40 (32%) were MHO-PCOS using the homeostasis model of assessment of IR. Subjects with MUO-PCOS and MHO-PCOS did not differ in mean age, BMI, waist-to-hip ratio, HA, and lipoprotein levels. By a modified frequently sampled intravenous glucose tolerance test, eight women with MUO-PCOS had lesser Si, K_{NEFA}, and the percent suppression in plasma NEFA levels from baseline to nadir ($\%NEFA_{supp}$) and greater $TIME_{nadir}$, $NEFA_{nadir}$, and baseline adipose tissue IR index (Adipo-IR) than eight subjects with MHO-PCOS, but similar fasting NEFA levels and S_{NEFA}. Women with MUO-PCOS had a higher homeostasis model of assessment-β% and fasting insulin levels than women with MHO-PCOS. In bivalent analysis, Si correlated strongly and negatively with Adipo-IR and $NEFA_{nadir}$, weakly and negatively with $TIME_{nadir}$, and positively with K_{NEFA} and % $NEFA_{supp}$, in women with MUO-PCOS only.

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Conclusion: Independent of age and BMI, women with MUO-PCOS have reduced NEFA uptake and altered insulin-mediated NEFA suppression, but no difference in HA, compared with women with MHO-PCOS. Altered insulin-mediated NEFA suppression, rather than HA or lipolysis rate, contributes to variations in insulin sensitivity among obese women with PCOS. (Fertil Steril® 2024;121: 1040–52. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: PCOS, nonesterified free fatty acids, insulin resistance, obesity, metabolic dysfunction

Polycystic ovary syndrome (PCOS) affects 7%–10% of reproductive-aged women (1), making it the most common endocrine-metabolic disorder in women, and a significant economic and public health burden (2). Polycystic ovary syndrome is characterized by hyperandrogenism (HA), chronic oligo-ovulation, and polycystic ovary morphology, and is frequently associated with insulin resistance (IR) and compensatory hyperinsulinemia (3–5), which increase the risks of type 2 diabetes mellitus (T2DM) (6) and metabolic syndrome (MetS) (7), both of which are risk factors for cardiovascular disease (CVD) (8).

The prevalence and burden of obesity continue to increase globally, despite the availability of preventive lifestyle modifications and novel therapeutic measures for obesity (9). Polycystic ovary syndrome is associated with obesity, at least in patients seen in clinical populations (10). Some adults with obesity among both the PCOS (4–6, 8, 11) and the general population (12, 13) develop obesity-related metabolic abnormalities such as IR or hyperinsulinemia (i.e., metabolically unhealthy obese [MUO]), whereas others do not (i.e., metabolically healthy obese [MUO]) (4, 11, 14–22), even when they have a similar degree of adiposity. However, the definition or the underlying cause of MUO or MHO remain challenging. Some studies have indicated that the heterogeneity in the metabolic phenotype in PCOS and general population can be better defined by measures of intraabdominal adiposity including waist circumference (WC), waist:hip ratio (WHR), computed tomography (CT) and magnetic resonance imaging (MRI), although the results have been inconsistent (4, 18, 22–28).

In adipose tissue (AT), insulin suppresses the intracellular lipolysis resulting in the suppression of circulating nonesterified fatty acid (NEFA) levels and an increase in systemic glucose utilization (29–37). Elevated circulating NEFA levels promote ectopic lipid deposition in the liver and muscle, IR, and vascular and cardiac dysfunction (29–37). Additionally, circulating NEFA provides energy for β-oxidation, and may reduce systemic glucose uptake through its role as an alternative fuel (29–37). Data concerning the contribution of abnormalities in circulating NEFA to the IR of PCOS are limited, even though impaired insulin-mediated suppression of lipolysis and increased circulatory NEFA, also known as free fatty acids, are also associated with IR (14, 29–37). Consequently, aberrant NEFA metabolism (14, 29, 30, 33, 34, 38), IR (12), and hyperinsulinemia (13) may underlie the development of cardiometabolic diseases.

Additionally, HA is often associated with obesity, partly because of hyperinsulinemia-induced suppresses of sex hormone–binding globulin. In addition, androgens have been shown to modify adipocyte function (38–41) and may therefore contribute to heterogeneity in obesity-related metabolic abnormalities. In previous studies, we observed that measures of HA (4, 28, 33, 34), NEFA kinetics (33), and insulin resistance in adipose tissue (IR in AT) (34) differ in obese patients with PCOS vs. obese controls without PCOS, whereas nonobese subjects did not differ in any of the NEFA kinetic parameters assessed (33).

In the present study, we hypothesized that, independent of obesity and age, alterations in NEFA trafficking in response to hyperinsulinemia and HA contribute to heterogeneity in insulin sensitivity among obese women with PCOS. To test this hypothesis, we first determined the prevalence of women with metabolically healthy obese PCOS (MHO-PCOS) and women with metabolically unhealthy obese PCOS (MUO-PCOS) in a consecutive referral population categorized on the basis of basal and dynamic state insulin sensitivity. We then compared women with MHO-PCOS and women with MUO-PCOS to determine whether alterations in NEFA dynamics or HA contributed to the differences in insulin sensitivity between these cohorts.

MATERIALS AND METHODS

Study population

Definition of PCOS. Because we were interested in studying metabolic dysfunction, the diagnosis of PCOS was made using the 1990 National Institutes of Health consensus criteria (i.e., phenotypes A and B of the Rotterdam criteria [42]), namely the presence of oligo-ovulation and biochemical and/or clinical HA, including a modified Ferriman-Gallwey (mF-G) hirsutism score of $\geq$6 and/or hyperandrogenemia (i.e., total testosterone [T], free T, or dehydroepiandrosterone sulfate [DHEAS] levels above normal level), and excluding other known endocrinopathies, as previously described (43–45). This study included women who presented for evaluation of androgen excess at Cedars-Sinai Medical Center (CSMC) in Los Angeles, California. This study was approved by the Institutional Review Board at CSMC, and written informed consent was obtained from each subject.

Subject recruitment. Research participants were recruited as previously described (4, 33, 34). Briefly, research participants were recruited through advertisements or the clinical and research practice of the Center for Androgen-Related Disorder at CSMC, Los Angeles. The study population for this study was therefore recruited consecutively and prospectively. An attempt was made to closely match participants with MUO-PCOS and participants with MHO-PCOS within narrow ranges (i.e., BMI $\pm$ 3 kg/m^2, age $\pm$ 5 years). Both participants with

MUO-PCOS and MHO-PCOS were recruited over a similar period of time.

Subjects to determine the prevalence of a clinical population with MHO-PCOS and MUO-PCOS. A cohort of 125 consecutive obese (BMI $\geq$ 30 kg/m^2) participants with PCOS aged 22–44 years were prospectively recruited at the Center for Androgen-Related Disorders at CSMC. All underwent a physical examination with blood sampling for hormone level measurements, as previously described (43–45). In addition to height, weight, and mF-G score, waist circumference was measured at the narrowest portion of the torso, approximately midway between the lower costal margin and the iliac crest, and hip circumference was measured over the widest portion of the gluteal and greater trochanteric regions, to calculate the waist-to-hip ratio (WHR). All also underwent a 2-hour 75-g oral glucose tolerance test (oGTT), with plasma insulin and glucose levels determined at 0 minute, 1 hour, and 2 hours.

Study exclusion criteria included pregnancy or lactation state, inability to assess menstruation or ovulation status (e.g., prior hysterectomy, bilateral oophorectomy, vaginal agenesis, postmenopausal or premenarcheal state), or use of any hormonal medication (including oral contraceptives, insulin-sensitizing agents, antidiabetic medications, antiandrogens, or glucocorticoids) within 3 months preceding the evaluation. All participants had normal thyroid-stimulating hormone, 17-hydroxyprogesterone, and prolactin levels, as previously described (43–45).

Subjects to determine dynamic whole-body insulin action and NEFA kinetics in MHO-PCOS vs. MUO-PCOS. From the above cohort, a subgroup of 16 non–diabetic-obese participants with PCOS were selected according to whether they were MHO-PCOS (n = 8) or MUO-PCOS (n = 8) as determined by their response to the modified frequently sampled intravenous glucose tolerance test (mFSIVGTT), as described previously (33, 34, 46). All subjects were not diabetic, and the groups were purposely matched for age, BMI, and race, as described previously (4, 5). It should be noted that this subgroup of 16 obese subjects with PCOS (out of the 125 obese subjects with PCOS) who additionally completed mFSIVGTT for both glucose and NEFA kinetics were part of the subjects used for our previous published study comparing NEFA kinetics in 29 subjects with PCOS and 29 healthy controls (33).

Metabolic assessment

After an overnight fast, blood samples were obtained on days 3 through 8 of a spontaneous or an oral micronized progesterone (Prometrium Solvay Pharmaceuticals, Marietta, GA)-induced withdrawal bleed (i.e., the follicular phase) for measurement of circulating total T, free T, and DHEAS levels, as well as insulin and glucose levels (47).

Oral glucose tolerance test. All 125 obese participants with PCOS underwent a standard 2-hour 75-g oGTT (48) and plasma insulin and glucose levels were determined at 0 minute, 1-hour, and 2 hours. In accordance with the American Diabetes Association guidelines, glucose tolerance was classified as follows: normal glucose tolerance, by a fasting glucose level of $<$100 mg/dL and/or a 2-hour glucose level of $<$140 mg/dL; prediabetes, by a fasting glucose level of 100–125 mg/dL or a 2-hour glucose level of 140–200 mg/dL; and T2DM, by a fasting glucose level of $\geq$126 mg/dL or a 2-hour glucose level of $\geq$200 mg/dL (48). An elevated 1-hour glucose level was defined as $\geq$155 mg/dL during the oGTT, a robust predictor of future risk for T2DM (49). Insulin data from the oGTT were used to calculate peak insulin, defined as the highest insulin levels reached during the oGTT (either at 1 hour or 2 hours) (50).

Modified frequently sampled intravenous glucose tolerance test. All 16 obese subjects with PCOS underwent an mFSIVGTT to assess dynamic whole-body insulin action and NEFA kinetics on days 3 through 8 of a spontaneous or induced withdrawal bleed, as described previously (29,33). In brief, after an overnight fast, one intravenous (IV) catheter was placed in each forearm (one for blood sampling and the other for glucose and insulin infusion) between 8:00 AM and 9:00 AM. Thereafter, IV glucose (0.3 g/kg) was injected at time 0 minutes, followed by an IV bolus of regular insulin (0.03 U/kg) at time 20 minutes. Blood samples (2.0 mL) were collected from −20 minutes (relative to the time of glucose administration) to +180 minutes. Plasma samples were drawn into prechilled tubes containing ethylenediaminetetraacetic acid (for insulin), sodium fluoride potassium oxalate (for glucose), or paraoxon (for NEFA) (29), and samples were frozen at −80°C until assayed. After assaying the plasma glucose, insulin, and total NEFA levels, the data were entered into the MINMOD computer program, and the data were analyzed using a minimal model of glucose kinetics to establish glucose-insulin interactions (33, 46) and a minimal model of NEFA to quantify the kinetics of NEFA metabolism (29, 33, 34). The levels at −20, −15, and 0 minutes were averaged to yield respective fasting values.

Determination of basal whole-body insulin and NEFA action and β-cell function. Basal whole-body state IR and β-cell function were assessed using the homeostasis model of assessment (HOMA) for IR (HOMA-IR) and HOMA-%β-cell function, respectively (51). Basal state IR in AT was estimated using the adipose tissue insulin resistance index (Adipo-IR = fasting plasma insulin × basal NEFA levels) (34).

Determination of dynamic whole-body insulin action and β-cell function. Whole-body glucose levels and insulin kinetics were based on the mFSIVGTT (4, 11, 33, 34, 46). Estimates of whole-body glucose levels and insulin kinetics included: acute insulin response to glucose (AIRg); insulin sensitivity index (Si); glucose effectiveness (Sg); and disposition index (Di = Si × AIRg).

Determination of dynamic NEFA kinetics. Nonesterified fatty acid kinetics were estimated as described previously (29, 33, 34) (Supplemental Table 1, available online). The degree of insulin-mediated suppression of plasma NEFA levels was assessed using the lowest plasma NEFA levels or the nadir in NEFA levels observed ($NEFA_{nadir}$), the time it took for NEFA levels to reach nadir ($TIME_{nadir}$), and the percent suppression in plasma NEFA levels from baseline to nadir ($\%NEFA_{supp}$). The peak rate of lipolysis was determined using peak S_{NEFA}, and peak NEFA uptake by K_{NEFA}, and the affinity constant

modulating lipolysis is depicted using φ. In addition, we determined the parameters of glucose utilization used to estimate NEFA kinetics, including mean baseline plasma glucose level, plasma NEFA fixed at time 0 before the start of the glucose infusion ($NEFA_0$), initial remote glucose level, rate of glucose entry into and removal from the remote compartment, the threshold plasma glucose (gs), which drives φ, and above which plasma glucose enters the remote compartment and NEFA suppression begins, after a delay of time (latency or the delay in time for NEFA levels to begin to drop).

Definition of MHO-PCOS and MUO-PCOS. Considering the entire cohort, in the basal state, MHO-PCOS was defined by a homeostasis model assessment for IR (HOMA-IR) index of ≥ 2.5 and as MUO-PCOS using a HOMA-IR of <2.5, as previously reported (20). Although HOMA-IR is easily determined, and the threshold cut-off value of HOMA-IR that defines IR is widely accepted as 2.5, the threshold cut-off level of Si (i.e., a measure of IR in a dynamic state) is not clearly defined. Consequently, for the 16 subjects with obesity assessed using mFSIVGTT, MHO-PCOS was defined using an Si in the uppermost quartile and MUO-PCOS using an Si in the lowest quartile of a previously studied cohort of 29 subjects with PCOS and 29 healthy controls (33). This analysis has been depicted in Supplemental Figure 1 (available online) because it is not part of the study. The Si in the upper and lower quartiles corresponded to Si values of ≥ 5.6 and ≤ 1.7 (mU/L per minute), respectively, as depicted in Supplemental Figure 1, similar to other studies (14, 52–54).

Biochemical analysis

Fasting blood samples for circulating total T, free T, DHEAS, NEFA, insulin, and glucose concentrations were obtained on days 3 through 8 of the menstrual cycle, as described previously (43–45, 55). Total T level was measured using high-turbulence liquid chromatography-tandem mass spectrometry and free T level using equilibrium dialysis (Quest Diagnostics, San Juan Capistrano, CA), as described previously (55). Serum DHEAS level was measured using a competitive immunoassay (Modular E170; Roche Diagnostics, Indianapolis, IN). Plasma insulin was assayed using chemiluminescence (ADVIA Centaur chemiluminescent immunoassay system; Siemens Healthcare, Deerfield, IN), and glucose levels using the hexokinase and glucose-6-phosphate dehydrogenase methods (Roche Applied Sciences, Indianapolis, IN). Samples, except for glucose, were batched at regular intervals for analysis to minimize the impact of interassay variability. The intraassay and interassay variations for total T, free T, and DHEAS levels have been reported previously and did not exceed 10% (43–45, 55).

In the subgroup of participants who underwent an mFSIVGTT, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured in fasting samples using standard methods. Plasma NEFA levels were determined using a colorimetric method (56) from Wako Diagnostics (Richmond, VA; catalog no. 991-34691) on the automated instrument, Elan ATAC8000 (Elan Diagnostics, Athlone, Ireland; interassay variation: 2.3%–4.8%; intraassay variation: 5.1%–8.6%) (56, 57). The method relies on the acylation of coenzyme A (CoA) using NEFA in the presence of added acyl-CoA synthetase. The resulting acyl-CoA is oxidized by added acyl-CoA oxidase, resulting in the generation of hydrogen peroxide. In the presence of peroxidase, hydrogen peroxide converts the substrate into a colored product, which can be read at 550 nm using the instrument.

Assessment of total, visceral, and subcutaneous fat mass

In addition to external tape measures, all obese subjects with PCOS who underwent an mFSIVGTT also completed an abdominal computerized axial tomography scan to assess abdominal adiposity. The techniques for determining abdominal computerized axial tomography scans for assessment of subcutaneous abdominal fat area, visceral abdominal fat area (VAT), and total abdominal fat area have been described previously (4, 58).

Statistical analysis

Shapiro-Wilks W-statistics was used to determine when nominal variables were normally distributed. All continuous variables but the mF-G score reasonably follow the parametric normal distribution on the original or log scale, with only two variables needing a log transformation (i.e., AIRg and $NEFA_{nadir}$). Intergroup differences were evaluated using the unpaired Student's *t*-test for normally distributed continuous variables or the Wilcoxon rank-sum test for mF-G score and %HOMA-β function to detect statistical differences between obese women with PCOS with IR (i.e., MUO-PCOS) and obese women with PCOS without IR (i.e., MHO-PCOS). Differences in mean plasma glucose and insulin levels, and mean VAT, HOMA-IR, HOMA-β%, Si, Adipo-IR, K_{NEFA}, $NEFA_{nadir}$, $TIME_{nadir}$, and $\%NEFA_{supp}$ values were further adjusted for BMI, using linear regression. Bivariate correlations between Si and indices and parameters of NEFA kinetics of interest in MUO-PCOS and MHO-PCOS were analyzed using the Pearson correlation coefficient.

To estimate power analysis, the sample size was assessed using HOMA-IR as the endpoint. On the basis of our previous studies of the effects of endogenous androgens on glucose uptake in PCOS vs. healthy control subjects matched for age, race, and BMI (4), a power analysis with a pooled standard deviation of 1.49, with an 80% power and an $\alpha = 0.05$, on the basis of unpaired *t* testing, indicated that a sample size of 28 participants per group was sufficient to detect a mean difference of 20% change in HOMA-IR between MUO-PCOS and control (MHO-PCOS).

The statistical level of significance was set at 0.05, and all hypothesis tests were two-sided. In determining whether or not to adjust α (*P*) values for multiple variables tested, we should note that we considered as primary endpoints to our analysis under the hypothesis explored in this study only one variable (HOMA-IR) when analyzing the cohort of 125 subjects with PCOS and only 4 variables denoting

TABLE 1

Characteristics of participants with MUO-PCOS and MHO-PCOS categorized using HOMA-IR.

Variables	MUO-PCOS[a] (n = 85)	MHO-PCOS[a] (n = 40)	*P* value between groups (unadjusted for BMI)	*P* value between groups (adjusted for BMI)[b]
Demographics				
Age (y)	30.1 ± 0.8	29.3 ± 1.0	.551	—
BMI (kg/m^2)	38.7 ± 0.7	35.8 ± 0.8	.012[c]	—
WHR	0.8 7 ± 0.01	0.82 ± 0.04	.077	—
Androgen level measures				
mF-G (hirsutism) score	7.6 ± 0.6	7.9 ± 0.9	.759	—
Free T level (pg/dL)	6.98 ± 0.92	5.52 ± 0.49	.278	—
Total T level (ng/dL)	45.08 ± 3.05	50.32 ± 3.86	.308	—
DHEAS level (μg/dL)	256.6 ± 14.5	259.1 ± 21.9	.923	—
Baseline insulin resistance and secretion				
HOMA-IR	7.5 ± 1.9	1.4 ± 0.1	.002[c]	.023[c]
HOMA-β%	132.6 ± 33.2	25.6 ± 2.6	.002[c]	.025[c]
Plasma glucose levels (mg/dL)				
Fasting glucose	91.9 ± 0.1.8	85.1 ± 1.5	.017[c]	.024[c]
1-h glucose	164.9 ± 5.1	136.4 ± 7.6	.002[c]	.008[c]
2-h glucose	135.5 ± 6.0	113.6 ± 7.3	.032[c]	.048[c]
Plasma insulin levels (μIU/mL)				
Fasting insulin	33.6 ± 8.4	6.6 ± 0.6	.002[c]	.025[c]
1-h insulin	180.2 ± 13.3	115.0 ± 25.3	.014[c]	.012[c]
2-h insulin	145.2 ± 10.5	94.7 ± 27.4	.029[c]	.030
Peak insulin	197.0 ± 12.1	125.9 ± 24.6	.006[c]	.005[c]
Glycemic abnormalities, n (%)				
Normal glucose tolerance	57 (67.1)	34 (85.0)	.035[c]	—
Prediabetes	19 (22.4)	3 (7.5)	.040[c]	—
Type 2 diabetes	9 (10.6)	3 (7.5)	.620	—
Elevate 1-h glucose[d]	38 (44.7)	8 (20.0)	.013[c]	—

Note: Variables are expressed as mean ± SEM, except the prevalence of glycemic abnormalities, which were expressed as numbers of subjects.
BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; HOMA-IR, homeostasis model of assessment for insulin resistance; mF-G = modified Ferriman-Gallwey; MHO-PCOS, metabolically healthy obese polycystic ovary syndrome; MUO-PCOS, metabolically unhealthy obese polycystic ovary syndrome; T = testosterone; WHR = waist-to-hip ratio.
[a] MHO-PCOS and MUO-PCOS were categorized on the basis of HOMA-IR < 2.5 and ≥ 2.5, respectively.
[b] HOMA-IR, HOMA-β%, and insulin and glucose values were adjusted for BMI.
[c] *P* values <0.05 are considered statistically significant.
[d] Denotes elevated 1-hour glucose level (i.e., ≥155 mg/dL) during oGTT.

Ezeh. NEFA in metabolic-health of obese PCOS. Fertil Steril 2024.

NEFA kinetics (Adipo-R, %NEFA$_{supp}$, K_{NEFA}, and S_{NEFA}) when studying our 16 subjects using the mFSIVGTT. All other comparisons were secondary, ancillary, or merely descriptive. Considering this, we chose not to adjust our results for multiple comparisons. All data are expressed as means ± SEM in the text.

RESULTS

Metabolic health in obese women with PCOS in the clinical setting

The baseline features of the entire study cohort of 125 consecutive obese women with PCOS classified as metabolically unhealthy (MUO-PCOS) or metabolically healthy (MHO-PCOS) according to baseline HOMA-IR are depicted in Table 1. Of the 125 obese women with consecutive PCOS studied, 85 (68%) were identified as MUO-PCOS (HOMA-IR ≥ 2.5) and 40 (32%) as MHO-PCOS (HOMA-IR < 2.5). Women in the MUO-PCOS and MHO-PCOS groups did not differ with respect to mean age, BMI, WHR, or degree of HA (i.e., mF-G score, free T level, total T level, and DHEAS level). Women with MUO-PCOS demonstrated higher fasting, 1-hour and 2-hour glucose levels, and fasting, 1-hour, and 2-hour insulin levels, and HOMA-β% values, than women with MHO-PCOS, both before and after adjustment for BMI. Although women with MUO-PCOS had a significantly higher prevalence of prediabetes and elevated 1-hour glucose levels than women with MHO-PCOS, the difference in the prevalence of T2DM did not reach the level of significance.

Dynamic whole-body insulin action and NEFA kinetics in women with MHO-PCOS vs. MUO-PCOS

By design, the women with MUO-PCOS and MHO-PCOS assessed using mFSIVGTT did not differ in age and BMI but differed in Si values (Table 2). Similar to the lack of statistical difference in mF-G score and circulating androgen levels observed among women with MUO-PCOS (n = 85) vs. MHO-PCOS (n = 40) above (Table 1), these measures of HA did not differ between the groups among the 16 subgroups of women with PCOS that underwent mFSIVGTT. Similarly, plasma lipoprotein levels also did not differ between the groups. Although the WHR did not differ between the groups, VAT was higher and the VAT-total abdominal fat area ratio trended higher in women with MUO-PCOS vs. MHO-PCOS, respectively (Table 2). The HOMA-IR, HOMA-β%, and fasting insulin levels were higher in women with MUO-PCOS than in MHO-PCOS (Table 2). As expected, Si was higher in women

TABLE 2

Characteristics of participants with MUO-PCOS and MHO-PCOS categorized using in vivo insulin sensitivity.

Variable	MUO-PCOS[a] (n = 8)	MHO-PCOS[a] (n = 8)	*P* value
Age (y)	30.9 ± 1.7	29.3 ± 2.3	.590
BMI (kg/m^2)	38.0 ± 1.8	36.5 ± 2.4	.619
WHR	0.89 ± 0.03	0.90 ± 0.04	.958
VAT (cm^2)	191.7 ± 31.2	111.2 ± 9.2	.021[b]
SAT (cm^2)	533.4 ± 71.3	507.5 ± 48.7	.764
TAT (cm^2)	725.1 ± 88.1	618.6 ± 44.7	.283
VAT/TAT ratio	0.26 ± 0.03	0.19 ± 0.03	.088
mFG score	7.5 ± 1.3	10.0 ± 2.4	.379
Free T (pg/mL)	5.2 ± 1.0	6.6 ± 1.3	.397
Total T (ng/dL)	46.8 ± 15.9	39.4 ± 4.6	.662
DHEAS (μg/dL)	256.6 ± 43.9	417.6 ± 63.8	.056
TC-cholesterol (mg/dL)	143.8 ± 10.9	117.3 ± 11.9	.138
HDL-cholesterol (mg/dL)	43.4 ± 4.2	40.3 ± 2.5	.522
LDL-cholesterol (mg/dL)	65.5 ± 8.2	62.7 ± 11.7	.858
Triglycerides (mg/dL)	133.6 ± 36.1	71.3 ± 5.7	.072
Measures of basal glucose metabolism			
Fasting plasma glucose (mg/dL)	95.8 ± 5.6	92.1 ± 3.8	.600
Fasting insulin (μIU/mL)	25.0 ± 3.9	11.9 ± 2.3	.012[b]
HOMA-IR	5.8 ± 0.9	2.7 ± 0.5	.006[b]
HOMA-β%	93.6 ± 16.9	44.0 ± 10.4	.026[b]
Measures of dynamic state glucose kinetics using mFSIGTT			
AIRg (mU/L/min)[c]	850.8 (65.72–1833.3)	563.9 (177.8–966.0)	.547
Di (AIRg × Si)	957.4 ± 201.6	1512.7 ± 217.0	.083
Si (mU/L/min)	1.24 ± 0.15	2.97 ± 0.37	<.001[b]
Sg (/min)	0.018 ± 0.003	0.013 ± 0.003	.228
Measures of basal state NEFA metabolism			
Fasting plasma NEFA (mmol/L)	0.625 ± 0.8	0.561 ± 0.8	.554
Adipo-IR (mmol/L/μIU/mL)	14.97 ± 2.73	6.56 ± 1.37	.016[b]
Measures of dynamic state NEFA kinetics using mFSIVGTT			
S_{NEFA} (μmol/L/min^1)	77.69 ± 9.92	102.43 ± 17.20	.233
K_{NEFA} (%/min)	0.058 ± 0.010	0.086 ± 0.007	.026[b]
$NEFA_0$ (mmol/L)	563.5 ± 81.1	483.1 ± 53.2	.421
φ (mmol/L)	0.05 ± 0.02	0.04 ± 0.01	.749
gs (mmol/L)	12.0 ± 1.3	10.6 ± 0.9	.416
k_C (%/min)	0.027 ± 0.008	0.038 ± 0.006	.264
τ (min)	11.36 ± 2.34	9.31 ± 2.14	.527
$NEFA_{nadir}$ (mmol/L)[d]	0.101 (0.051–0.276)	0.048 (0.024–0.068)	.018
$TIME_{nadir}$ (min)	80.0 ± 5.3	62.5 ± 4.1	.021
$\%NEFA_{supp}$	82.7 ± 3.0	90.8 ± 1.3	.027

Note: Values are expressed as means ± SEM and range, unless otherwise stated.
AIRg = acute insulin response to glucose; Adipo-IR = adipose insulin resistance; DHEAS = dehydroepiandrosterone sulfate; Di = disposition index; T = testosterone; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β% = homeostatic model assessment of beta-cell function; K_{NEFA} = peak rate of NEFA disposal from plasma pool; LDL = low-density lipoprotein cholesterol; mFG score = modified fatigue impact scale score; MHO-PCOS, metabolically healthy obese polycystic ovary syndrome; MUO-PCOS, metabolically unhealthy obese polycystic ovary syndrome; NEFA = nonesterified fatty acid; $NEFA_0$ = basal NEFA levels; $NEFA_{nadir}$ = the nadir in NEFA levels observed; SAT = subcutaneous adipose tissue; Si = insulin sensitivity index; S_{NEFA} = lipolysis rate; Sg = glucose effectiveness; TC = total cholesterol; TAT = total adipose tissue; $TIME_{nadir}$ = the time it took for NEFA levels to reach nadir; VAT = visceral adipose tissue; WHR = waist-to-hip ratio.
[a] MHO-PCOS and MUO-PCOS were categorized on the basis of Si ≥ 5.6 and ≤ 1.7 (min/μU per milliliter), respectively.
[b] *P* values < .05 are considered statistically significant.
[c] Geometric means, the antilog of the log scale mean, is reported for log-transformed data before analysis.

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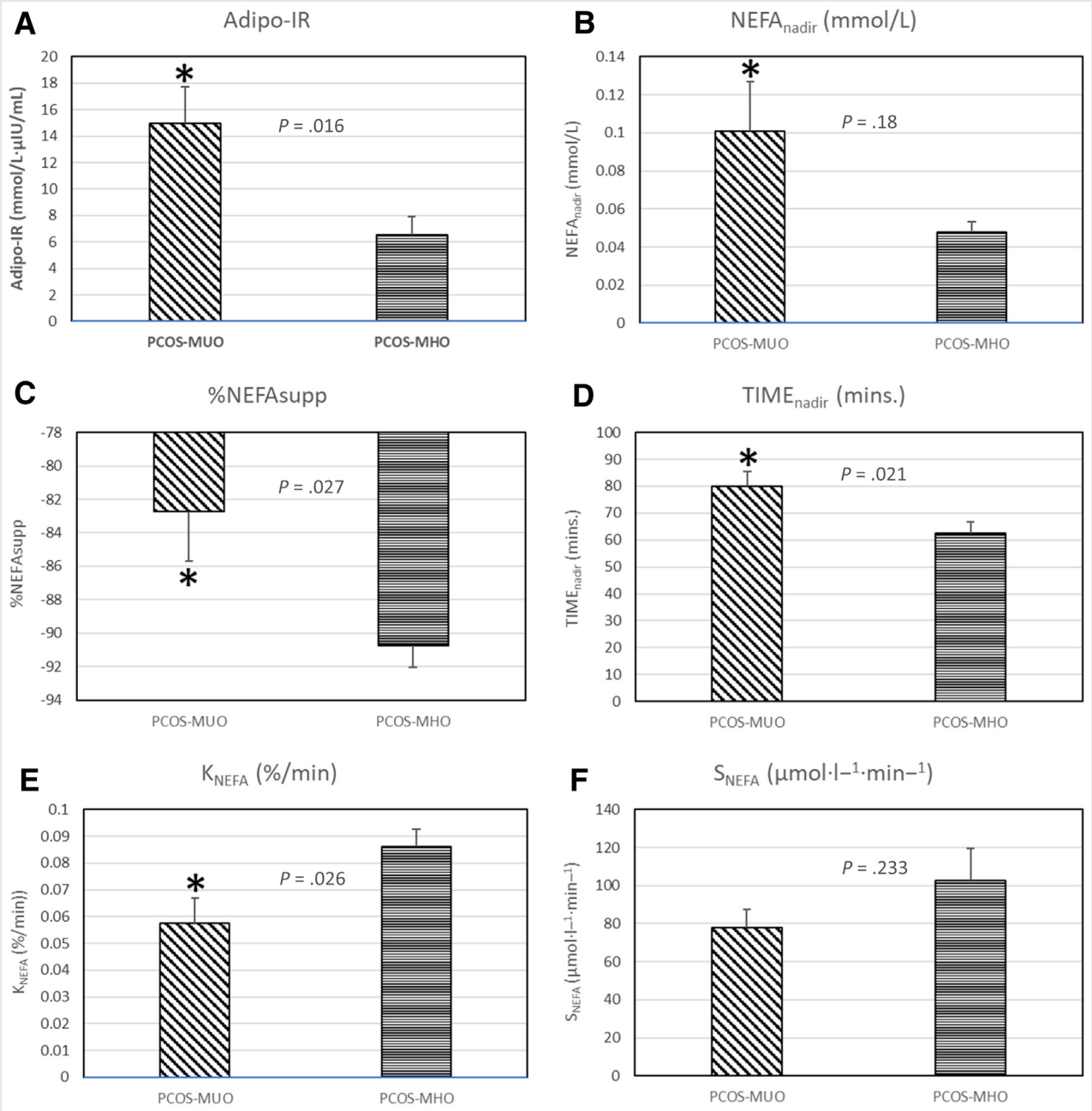
with MHO-PCOS than women with MUO-PCOS. The difference in Di did not reach significance between the two groups. The two groups had similar glucose effectiveness values (Sg). After adjustment for BMI, the differences in mean plasma insulin levels, VAT, HOMA-IR, HOMA-β%, Si, Adipo-IR, K_{NEFA}, $NEFA_{nadir}$, $TIME_{nadir}$, and $\%NEFA_{supp}$ remained statistically significant (data not shown).

Mean Adipo-IR, a measure of IR in AT in the basal state, was higher in women with MUO-PCOS than women with MHO-PCOS (Table 2 and Fig. 1A), mostly because of higher plasma fasting insulin levels in the former, because fasting total NEFA levels were similar between the two groups. Women with MUO-PCOS exhibited higher NEFA levels at nadir ($NEFA_{nadir}$) (Fig. 1B), less percent suppression of NEFA levels ($\%NEFA_{supp}$) (Fig. 1C), and a longer time to reach nadir of NEFA level ($TIME_{nadir}$) (Table 2 and Fig. 1D) than women with MHO-PCOS, consistent with diminished insulin-mediated NEFA suppression (i.e., increased dynamic state IR in AT) in the former group.

Women with MUO-PCOS had a lower peak rate of NEFA disposal from the plasma pool and β-oxidation (K_{NEFA}) than in women with MHO-PCOS (Fig. 1E). The peak rate of lipolysis (S_{NEFA}), the affinity constant modulating lipolysis (φ), and gs that drives φ did not differ between women with MUO-PCOS and MHO-PCOS (Table 2

FIGURE 1



Differences in measures of nonesterified fatty acid (NEFA) kinetics profile between women with metabolically healthy obese polycystic ovary syndrome (PCOS) (MHO-PCOS) and women with metabolically unhealthy obese PCOS (MUO-PCOS). On the basis of the degree of insulin sensitivity (Si), obese women with PCOS were subdivided into MUO-PCOS (Si $\leq$ 1.7 mU/L per minute) and MHO-PCOS (Si $\geq$ 5.6 [mU/L per minute]) groups. The groups were matched purposely for age and BMI. Mean $\pm$ SEM are depicted for Adipo-IR (**A**), NEFA$_{nadir}$ (**B**), %NEFA$_{supp}$ (**C**), TIME$_{nadir}$ (**D**), K$_{NEFA}$ (**E**), and S$_{NEFA}$ (**F**). Asterisks indicate *P* values of .027–.016 (see Table 2 for specific *P* values). Adipo-IR = adipose tissue insulin resistance index; BMI = body mass index; K$_{NEFA}$ = peak rate of NEFA disposal from plasma pool; NEFA$_{nadir}$ = the nadir in NEFA levels observed; %NEFA$_{supp}$ = the percent suppression in plasma NEFA levels from baseline to nadir; S$_{NEFA}$ = lipolysis rate; TIME$_{nadir}$ = the time it took for NEFA levels to reach nadir.

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and Fig. 1F). There was no difference in estimated baseline plasma NEFA levels (NEFA$_0$) between women with MUO-PCOS and MHO-PCOS. Similarly, other parameters of glucose utilization used to estimate NEFA kinetics, including removal from the remote compartment and after a delay of time, were similar between the two groups (Table 2), as were baseline plasma glucose level and initial remote glucose level (data not shown).

TABLE 3

Correlations of measures of insulin resistance in adipose tissue and nonesterified fatty acid release and uptake with measures of dynamic state whole-body insulin sensitivity in participants with MUO-PCOS and MHO-PCOS categorized using in vivo insulin sensitivity index.

	MUO-PCOS[a] (n = 8)		MHO-PCOS[a] (n = 8)	
Variable	**r**	***P* value**	**r**	***P* value**
Fasting NEFA levels	0.02	.962	−0.23	.587
Adipo-IR	−0.72	.045[b]	0.10	.810
S_{NEFA}	0.57	.141	0.20	.643
K_{NEFA}	0.75	.032[b]	−0.14	.737
$NEFA_{nadir}$[c]	−0.72	.043[b]	0.23	.587
$TIME_{nadir}$	−0.64	0.086	−0.32	.442
$\%NEFA_{supp}$	0.80	.016[b]	−0.41	.420

Note: Adipo-IR = adipose tissue insulin resistance index; BMI = body mass index; K_{NEFA} = peak rate of NEFA disposal from plasma pool; NEFA = nonesterified fatty acid; $NEFA_{nadir}$ = the nadir in NEFA levels observed; $\%NEFA_{supp}$ = the percent suppression in plasma NEFA levels from baseline to nadir; S_{NEFA} = lipolysis rate; $TIME_{nadir}$ = the time it took for NEFA levels to reach nadir.
[a] MHO-PCOS and MUO-PCOS were categorized on the basis of insulin sensitivity index ≥ 5.6 and ≤ 1.7 (min/μU per milliliter), respectively.
[b] *P* values <0.05 are considered statistically significant.
[c] Log-transformed data.

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Relation of NEFA kinetics with whole-body insulin action

In bivalent analysis, S_i correlated strongly and negatively with Adipo-IR and $NEFA_{nadir}$, and weakly and negatively with $\%TIME_{nadir}$ and positively with %NEFA and K_{NEFA} only in MUO-PCOS subjects (Table 3). No association between NEFA kinetic parameters and Si was observed in subjects with MHO-PCOS. Fasting plasma NEFA level showed no association with Si among either obese PCOS group. Similarly, gs and φ showed no association with Si in either the MUO-PCOS or MHO-PCOS groups (data not shown).

DISCUSSION

The prevalence of obesity in our referral population with PCOS was 64%, which is approximately twice that of our unselected population with PCOS in our previous study (10). Our current data indicate that even in the referral setting when a more severe phenotype is expected (10), approximately 30% of obese women with PCOS appear to be metabolically healthy, similar to the 30% reported in a clinical population on the basis of the insulin sensitivity index (14) and the 30% on the basis of epidemiological data generated from the National Health and Nutrition Examination Survey using HOMA-IR and other components of MetS as criteria (15). Our findings of higher degrees of hyperglycemia, hyperinsulinemia, and basal IR as well as greater visceral adiposity in metabolically unhealthy (i.e., MUO-PCOS) compared with metabolically healthy (i.e., MHO-PCOS) obese women with PCOS are consistent with previous reports (14–17, 21, 22, 26, 27).

Insulin normally suppresses the release of NEFAs from AT into the circulation (i.e. lipolysis) and modulates circulatory levels (i.e., adipose tissue insulin sensitivity), thereby limiting the availability of fatty acids as an energy source and, consequently, increasing systemic glucose utilization. There are limited studies on the role of NEFA kinetics in metabolic dysfunction in humans. Walker et al. (30) described an aberrant trajectory for total NEFA and individual free fatty acid subtypes in the total NEFA in response to glucose and insulin fluxes during mFSIVGTT in male and female adult subjects with MetS vs. healthy controls. We previously reported altered NEFA trafficking (33) and increased IR in AT among women with oligo-ovulatory PCOS compared with healthy controls (34), confirming aberrant NEFA metabolism in PCOS. In the present study, we questioned whether alterations in NEFA trafficking differed in women with MUO-PCOS vs. MHO-PCOS.

Because insulin depresses intracellular lipolysis, secretion of NEFA into circulation and circulatory NEFA levels, it is not surprising that our results indicate that women with MHO and MUO differ in NEFA tracking. Independent of age and BMI, women with MUO-PCOS have a reduced rate of NEFA uptake and alterations in measures of adipose tissue insulin sensitivity (i.e. basally [i.e., greater Adipo-IR] and dynamically [i.e., greater $NEFA_{nadir}$, longer $TIME_{nadir}$, and less $\%NEFA_{supp}$]) compared with women with MHO-PCOS. These data indicate that altered insulin-mediated NEFA suppression, rather than HA or rate of lipolysis, contributes to the variations in insulin sensitivity observed among obese women with PCOS.

The greater degree of impairment in insulin-mediated suppression of circulating NEFA levels (i.e., IR in AT) observed in women with MUO-PCOS in our study has important metabolic implications. Not only does IR in AT lead to ectopic fat triglyceride deposition in peripheral insulin-sensitive tissues accompanied by whole-body IR (31–37), but it also impairs insulin secretion because of altered glucose-stimulated pancreatic β-cell insulin secretion (59, 60) and leads to a higher risk of inefficient glucose oxidation because of substrate competition between the β-oxidation of NEFA and glucose in the mitochondria (i.e., Randle's glucose-fatty acid cycle) (61, 62) as a result of the associated increased availability of NEFA. Furthermore, NEFA metabolism is more sensitive to insulin action than glucose metabolism (63), with insulin inhibiting whole-body circulating NEFA levels to a greater extent than any other metabolites such as glucose (63–65). Consequently, IR in AT precedes the development of

peripheral IR (63–66), even before the observation of hyperglycemia in T2DM (64–66), partly because of the compensatory insulin response to IR, which maintains normal glucose homeostasis (46) until late in the disease course. Thus, the women with MUO-PCOS who had increased IR in AT in both basal (i.e., higher Adipo-IR) and dynamic states (i.e., a longer $TIME_{nadir}$, greater $NEFA_{nadir}$, and less % $NEFA_{supp}$) compared with women with MHO-PCOS potentially run a higher risk of the early development of T2DM.

Insulin also enhances NEFA uptake from the plasma pool, thereby increasing mitochondrial NEFA β-oxidation, especially during periods of high energy demand, such as in the basal state (i.e., fasting when the body is deprived of nutrients) and during strenuous exercise, when glucose levels are reduced (29–36). It should be noted that mitochondrial NEFA β-oxidation provides a greater number of calories than glucose per gram of the respective substrate (36, 67), and impaired NEFA uptake may be as critical as ectopic fat deposition in non-AT as a cause of IR (67). Because NEFA disposal from the plasma pool (K_{NEFA}) reflects NEFA mitochondrial β-oxidation rate, at least during fasting or during strong energy demand (29), the reduced K_{NEFA} value we observed in women with MUO-PCOS compared with women with MHO-PCOS reflects a potential reduction in the efficiency of these women's NEFA β-oxidation and reduced generation of calories. Our findings are consistent with other studies observing that the rate of plasma NEFA uptake and β-oxidation in skeletal muscles progressively decreases from healthy to obese insulin-resistant subjects and from MetS to T2DM compared with obese healthy controls matched for BMI (68, 69).

A number of reasons may explain the similar fasting plasma NEFA levels and adipocyte lipolysis rate between women MUO-PCOS and MHO-PCOS in our study. First, wide diurnal fluctuations in plasma NEFA levels in response to eating, exercise, or stress render fasting plasma NEFA levels, an imperfect estimate of NEFA metabolism (21, 29–31). Second, alterations in plasma NEFA levels are reflected more closely by the degree of insulin-mediated suppression of circulating NEFA rather than by adipocyte lipolysis rate, which is a saturable process kinetically (29, 65, 70–73). Third, the rate of adipocyte lipolysis is very sensitive to circulating insulin levels (63–65), with the result that the adipocyte lipolysis rate and fasting plasma NEFA are easily suppressed or normalized by compensatory hyperinsulinemia associated with IR (63–65, 73), a consistent finding in women with PCOS (4, 5, 11, 33, 34).

Controversy surrounds the definitions of MUO and MHO because of the lack of a universally standardized definition. Although some investigators based the definition on multiple variables, including the presence of MetS or some of its components, in the belief that these definitions relate to long-term CVD risk (15), and some have used the combination of these variables and HOMA-IR (20), some large-scale cohort studies, including a 30-year follow-up study, reported increased CVD risk and overall mortality in subjects with MHO despite the absence of MetS (74). Some investigators have attributed variations in definitions and prevalence of MHO or MUO to heterogeneity in the definition of MetS (75). In our study, only subjects who underwent mFSIVGTT consistently had lipid data, making it difficult to classify metabolic dysfunction on the basis of components of MetS for all the 125 subjects studied. The focus of our study was therefore not on the basis of MetS. Given these controversies, in the present study, we have defined MUO-PCOS and MHO-PCOS on the basis of insulin sensitivity estimated indirectly with HOMA-IR and directly with Si because the parameters used in other studies as mentioned above (including MetS) are causally linked to IR (76). The novel threshold Si level of ≤ 1.7 used for the definition of peripheral IR in our study is similar to 1.47 (52) and 2.1 (14) using mFSIVGTT reported in the general population, and the cutoff threshold level of Si of ≥ 5.6 for insulin sensitivity is similar to 6.54 using mFSIVGTT (52), and 6.1 and 6.3 using the euglycemic-hyperinsulinemic clamp (53, 54) in other studies.

Recent studies are increasingly using measures of adipocyte function for the definition of MHO or MUO and for exploring their underlying pathogenesis. Some investigators used metabolomics, including white AT immune cells and adipocytokines, oxidative phosphorylation, branched amino acid catabolism, and free fatty acid β oxidation, to achieve this classification (16), although others have used lipoprotein particle subclass profiles (17). Our pilot study has focused on NEFA dynamics because impaired insulin-mediated suppression of lipolysis and circulating NEFA levels and associated elevation in circulating NEFA are considered the most important determinants of IR and underlying metabolic risks, including MetS (29–36, 63–66) and even precede the development of IR in the skeletal muscle and liver (29–36, 63–66).

We expected to find differences in markers of hyperandrogenism between women with MHO and women with MUO, given that hyperinsulinemia drives hyperandrogenism, that androgens have been shown to modify adipocyte function (40, 41), and that there are some studies linking hyperandrogenemia to IR (38) and the origins of PCOS (39). The lack of significant differences in markers of hyperandrogenism between women with MUO and women with MHO in our pilot study reflects the complex interrelationship between adipocyte function, hyperandrogenemia, and IR (38–41). and other studies that show no relationship between hyperandrogenism and IR (25). Our power analysis indicates that we have an adequate sample size at least for the initial part of the study (MUO-PCOS, n = 85 vs. MHO-PCOS, n = 40), which found no significant difference in measures of HA between MUO and MHO. The lack of a significant difference in androgen levels between women with MUO-PCOS in the pilot part of the study ([n = 8] vs. women with MHO-PCOS [n = 8]) was not because of the small sample size.

The main strengths of our study are the comprehensive assessment of plasma NEFA kinetics on the basis of minimal models, which are less complex and expensive than techniques like isotope-labeled tracers (29), the use of well-phenotyped participants with PCOS, the matching of subjects with MUO-PCOS and MHO-PCOS when studying them using mFSIVGTT, and the prospective design. However, the study is limited by its cross-sectional nature and the small number of participants studied using the mFSIVGTT, which suggests that larger studies are needed to confirm our findings, and that the

findings should be interpreted with caution. Because there was no intent to originally do this study at the onset of collecting the cohort, obviously no power analysis could have been done prospectively in the original cohort. Furthermore, although we primarily compared four variables (Adipo-R, % $NEFA_{supp}$, K_{NEFA}, and S_{NEFA}) between the two groups (MUO-PCOS and MHO-PCOS), our study may be limited by comparing other multiple secondary variables, which could raise the risk of type one errors.

In conclusion, the novel findings of this study provide insight into the mechanisms underlying the disparity that exists between those women with PCOS who develop metabolic abnormalities and those who do not, in the face of similar degrees of adiposity. These data suggest that independent of age and BMI, metabolically unhealthy obese women with PCOS (MUO-PCOS) had reduced rates of NEFA uptake and altered insulin-mediated circulatory NEFA suppression but no difference in the degree of HA when compared with metabolically healthy obese women with PCOS (MHO-PCOS). Furthermore, our study confirmed that the determination of fasting NEFA levels alone is insufficient to detect alterations in NEFA metabolism in obese women with PCOS. These data suggest that altered insulin-mediated plasma NEFA suppression and rate of NEFA uptake, rather than HA or rate of lipolysis, contribute to the variations in insulin sensitivity and metabolic health observed in obese women with PCOS. Stratifying obese women with PCOS according to their metabolic or NEFA kinetic profile may offer new opportunities for a better understanding of the pathogenesis of MUO vs. MHO in PCOS. Further, our data suggest the feasibility of using Adipo-IR as a simpler screening tool to assess metabolic health in obese women with PCOS.

CRediT Authorship Contribution Statement

Uche Ezeh: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **YD Ida Chen:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation. **Marita Pall:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Conceptualization. **Richard P. Buyalos:** Writing – review & editing, Writing – original draft, Visualization, Resources, Conceptualization. **Jessica L. Chan:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Ricardo Azziz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Interests

U.E. serves as an investor in Concentric Analgesics, Inc. M.D.P. reports consulting fees from Ferring Pharmaceuticals; reports honorarium from Natera; and is on the Board of Directors of American Board of Obstetrics and Gynecology. R.A. reports funding from Foundation for Research and Education Excellence and National Institutes of Health for the submitted work; funding from Ferring Pharmaceuticals; reports royalties from Wolters Kluwer Health, Johns Hopkins University Press, Springer, and McGraw Hill; serves as a consultant for Spruce Bioscience, Core Access Surgical Technology, May Health, Rani Therapeutics, and Fortress Biotech; reports honoraria from Davidson-Mestman course; is an advisor for Arora Forge and investor in Martin Imaging; is on the data safety monitoring board for a multicenter randomized trial of personalized acupuncture, fixed acupuncture, letrozole and placebo on live birth for infertility in women with polycystic ovary syndrome and Supporting Understanding of PCOS Education and Research (SUPER) Study; is CEO of ASRM (1/20-6/22) outside the submitted work; serves as a consultant for Spruce Bioscience, Core Access Surgical Technology, May Health, Rani Therapeutics, and Fortress Biotech; and is advisor for Arora Forge and investor in Martin Imaging. Y.I.C. has nothing to disclose. M.P. has nothing to disclose. R.P.B. has nothing to disclose. J.L.C. has nothing to disclose.

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Alteraciones en el tráfico de ácidos grasos no esterificados, en lugar de hiperandrogenismo, contribuyen a la salud metabólica en pacientes obesas con síndrome de ovario poliquístico.

Objetivo: Determinar si alteraciones en la dinámica de los ácidos grasos no esterificados (NEFA) o el grado de hiperandrogenismo (HA) contribuyen a la diferencia en la sensibilidad a insulina entre mujeres obesas sanas metabólicamente con síndrome de ovario poliquístico (PCOS) (MHO-PCOS) y mujeres obesas metabólicamente insanas con PCOS (MUO-PCOS).

Diseño: Estudio prospectivo transversal.

Lugar: Centro académico de cuidados terciarios.

Pacientes(s): Ciento veinticinco pacientes obesas con PCOS.

Intervención(es): Mujeres obesas consecutivas (índice masa corporal [BMI] $\geq$ 30 kg/m^2) oligoovulatorias con PCOS fueron sometidas a prueba oral de tolerancia a la glucosa y un subgrupo de 16 participantes fue sometida a una prueba de tolerancia a la glucosa intravenosa modificada y de muestreo frecuente para determinar la dinámica glucosa-insulina y -NEFA.

Principal(es) medida(s) de resultado(s): Grado de resistencia a insulina (IR) en tejido adiposo (AT) basal (Adipo-IR) y dinámicamente (el nivel más bajo de NEFA observado [$NEFA_{nadir}$], el tiempo que requiere los niveles de NEFA para alcanzar el punto más bajo [$TIME_{nadir}$], el porcentaje de supresión de los niveles NEFA en plasma desde el basal al punto más bajo [%$NEFA_{supp}$]); ratio máximo de lipolisis [S_{NEFA}] y tasa máxima de eliminación de NEFA desde la reserva plasmatica (K_{NEFA}); interacción glucosa-insulina del cuerpo (respuesta aguda de insulina a glucosa [AIRg, índice de sensibilidad a insulina [Si], eficacia de la glucosa [Sg], e índice de disposición [Di]; y HA (índice hirsutismo, niveles de testosterona total y libre, y niveles de dehidroepiandrosterona sulfato).

Resultado(s): Un total de 85 mujeres (68%) eran NUO-PCOS y 40 (32%) eran MHO-PCOS utilizando el modelo de homeostasis de IR. Sujetos con MUO-PCOS y MHO-PCOS no eran diferentes para media de edad, BMI, ratio cintura-cadera, HA y niveles de lipoproteína. Mediante la prueba de tolerancia a la glucosa intravenosa modificada y de muestreo frecuente, ocho pacientes con MUO-PCOS tuvieron menor Si, K_{NEFA} y porcentaje de eliminación de los niveles NEFA en plasma desde el basal al punto más bajo (%$NEFA_{supp),}$ y mayor $TIME_{nadir}$, $NEFA_{nadir,}$ e índice basal de IR en tejido adiposo *(*Adipo-IR) que ocho sujetos con MHO-PCOS, aunque niveles similares de NEFA en ayunas y S_{NEFA}. Mujeres con MUO-PCOS tenían mayor índice de homeostasis -*ß%* y niveles de insulina en ayunas que mujeres con MHO-PCOS. En un análisis bivalente, Si correlacionó fuerte y negativamente con Adipo-IR y $NEFA_{nadir}$, débil y negativamente con $TIME_{nadir}$,y positivamente con K_{NEFA} y % $NEFA_{supp}$, solo en pacientes con MUO-PCOS.

Conclusión(es): Independientemente de edad y BMI, mujeres con MUO-PCOS tienen reducida absorción de NEFA y alteración en la eliminación de NEFA mediada por insulina, aunque no hay diferencia en HA en comparación con mujeres con MHO-PCOS. La alteración de la supresión de NEFA mediada por la insulina en lugar de HA o la tasa de lipolisis, contribuye a las variaciones en la sensibilidad a insulina entre mujeres obesas con PCOS.