Assessing Energy Requirements in Women With Polycystic Ovary Syndrome: A Comparison Against Doubly Labeled Water

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Context: Weight loss is prescribed to offset the deleterious consequences of polycystic ovary syndrome (PCOS), but a successful intervention requires an accurate assessment of energy requirements.

Objective: Describe energy requirements in women with PCOS and evaluate common prediction equations compared with doubly labeled water (DLW).

Design: Cross-sectional study.

Setting: Academic research center.

Participants: Twenty-eight weight-stable women with PCOS completed a 14-day DLW study along with measures of body composition and resting metabolic rate and assessment of physical activity by accelerometry.

Main Outcome: Total daily energy expenditure (TDEE) determined by DLW.

Results: TDEE was 2661 ± 373 kcal/d. TDEE estimated from four commonly used equations was within 4% to 6% of the TDEE measured by DLW. Hyperinsulinemia (fasting insulin and homeostatic model assessment of insulin resistance) was associated with TDEE estimates from all prediction equations (both $r = 0.45$; $P = 0.02$) but was not a significant covariate in a model that predicts TDEE. Similarly, hyperandrogenemia (total testosterone, free androgen index, and dehydroepiandrosterone sulfate) was not associated with TDEE. In weight-stable women with PCOS, the following equation derived from DLW can be used to determine energy requirements: TDEE (kcal/d) = 438 − [1.6 * Fat Mass (kg)] + [35.1 * Fat-Free Mass (kg)] + [16.2 * Age (y)]; $R^2 = 0.41$; $P = 0.005$.

Conclusions: Established equations using weight, height, and age performed well for predicting energy requirements in weight-stable women with PCOS, but more precise estimates require an accurate assessment of physical activity. Our equation derived from DLW data, which incorporates habitual physical activity, can also be used in women with PCOS; however, additional studies are needed for model validation. ***(J Clin Endocrinol Metab* 102: 1951–1959, 2017)**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women (1) affecting one in five women worldwide (2). Overweight and obesity augment the prevalence of PCOS, and increased adiposity is considered a dominant characteristic in 40% to 60% of cases (3, 4). Diagnostic criteria include irregular menses, androgen excess, and/or polycystic ovaries, with longer-term consequences being hyperinsulinemia and infertility (5, 6). Numerous pharmacological and lifestyle interventions to alleviate these

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Abbreviations: BMR, basal metabolic rate; CI, confidence interval; DLW, doubly labeled water; DRI, dietary reference intake; FAI, free androgen index; HOMA-IR, homeostatic model assessment of insulin resistance; PAF, physical activity factor; PAL, physical activity level; PCOS, polycystic ovary syndrome; RMR, resting metabolic rate; SHBG, sex hormone–binding globulin; TDEE, total daily energy expenditure; $TDEE^{DLW}$, TDEE measured by DLW; TOST, two one-sided *t* tests.

complications and enhance quality of life have been tested (7–9). Research studies suggest that metformin and combinations of oral contraceptive agents are commonly prescribed to alleviate reproductive complaints; however, for the overweight and obese patients seeking fertility, a weight loss of 5% to 10% through lifestyle modification is recommended as first-line treatment (10).

The dietary intake goal prescribed for weight loss is a proportion of the energy requirement and hence should result in a daily energy deficit conducive to weight loss. If the estimated energy requirement is inaccurate, it can lead to poor weight loss and reduced levels of adherence from patients (11).

The only direct method for estimating energy requirements involves caloric titration of food over several days or weeks to achieve energy balance (12, 13). Other objective yet indirect methods include doubly labeled water (DLW) and measurement of resting energy expenditure, with indirect calorimetry in combination with measures of physical activity. These methods rely on the assumption that if body weight is stable throughout the observation period, the energy expenditure must therefore be equivalent to the energy intake, giving rise to the estimated energy requirement for weight stability. Given the cost and inefficiencies of caloric titration in clinical settings, DLW is considered the gold standard approach because energy expenditure is assessed over several days while individuals continue their usual behaviors in free-living conditions. DLW studies also allow weight stability to be assessed simultaneously (14). However, DLW studies are not cost-effective or practical for use in clinical settings or large-scale trials; therefore, predictive equations that calculate energy requirements on the basis of variables such as age, sex, weight, height, body composition, and physical activity level are available and have been used in women with PCOS (5, 15, 16). In the past decade, the ability of prediction equations to estimate energy requirements has improved because several groups have developed equations from DLW data compiled across studies taking into account *all* types of energy expended throughout 7- to 14-day periods, including physical activities (6).

This study reports total daily energy requirements in women with PCOS from a DLW study. The aim was to (1) understand the determinants of energy requirements in women with PCOS, including the effects of the reproductive and metabolic hormonal milieu, and (2) compare the energy requirements by DLW analysis with estimates derived from commonly used equations to evaluate their use in women with PCOS.

Subjects and Methods

This report includes baseline data from subjects enrolled in the Effect of Weight and Insulin Resistance on Reproductive Function in PCOS, or PULSE, study (NCT01482286 in ClinicalTrials.gov), which was approved by the institutional review board at Pennington Biomedical Research Center. All subjects provided written informed consent prior to initiation of study procedures.

Subjects

Twenty-eight eligible overweight or obese women [body mass index (BMI) ≥ 25 kg/m^2] aged 20 to 40 years completed a 14-day DLW study. PCOS was defined according to the 1990 National Institutes of Health criteria, namely oligoovulation, androgen excess (clinical or biochemical), and exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism (17). Two screening visits were held approximately 7 days apart and included positive indication of irregular menses (*i.e.*, fewer than eight regular cycles in the past year), clinical and/or biochemical androgen excess [hirsutism rating >8 and/or free androgen index (FAI) > 3.85], and anovulation (*i.e.*, serum progesterone level <0.3 ng/mL). Participants were excluded for other potential causes of androgen excess, medication use, high physical activity level (PAL; > 2.6), and weight instability (± 2.5 kg) during the 14-day DLW study.

Clinic assessments

Study visits and clinic assessments occurred on days 1, 7, and 14 of the DLW study to coincide with dosing and subsequent urine collections and to measure weight, body composition, and resting metabolic rate (RMR). All outcomes were obtained while following standard operating procedures at Pennington Biomedical Research Center.

Anthropometry and body composition

Body weight was measured in the morning after an overnight fast while the patient was wearing only a preweighed hospital gown. Height was measured at screening using a wall-mounted stadiometer. Dual X-ray absorptiometry scans were performed using the Lunar iDXA whole-body scanner (General Electric, Milwaukee, WI).

Resting metabolic rate

RMR was measured over 35 minutes by indirect calorimetry (AEI Technologies, Naperville, IL) after a 30-minute rest. Inspired air values of O_2% and CO_2% in the final 25 minutes were used to calculate energy expenditure by the Weir equation.

Total daily energy expenditure

Total daily energy expenditure (TDEE) was measured over a 14-day period using DLW. Subjects were given an oral dose (1.0 g/kg body weight) of a mixture that contained 1 part deuterium (^{2}H 99.9% enriched) and 19 parts Oxygen-18 (^{18}O 10% enriched), followed by 100 mL of tap water used to rinse the dose container. The dose was given early in the morning after an overnight fast and collection of two baseline urine specimens. Two urine specimens were collected and discarded +1.5 hours and +3 hours postdose. Postdose urine specimens were collected at +4.5 hours and +6 hours on day 1 and days 7, 13, and 14. The ^{18}O isotope abundances were measured on a Finnigan MAT DeltaS Dual Inlet Gas Isotope Ratio Mass Spectrometer with a CO_2-water equilibration device (18). The ^{2}H abundances were measured on a Finnigan H/D device, which allows for high throughput and excellent precision (19). The rate of CO_2 production was calculated using the equations of Schoeller *et al.* (14, 19) and was converted to energy expenditure using the equation TDEE = rCO_2 (1.231 + 3.815 / RQ), where rCO_2 (L/d) is rate of carbon dioxide production and RQ is the respiratory quotient fixed at 0.86 for all women.

Physical activity

The PAL was calculated as the ratio of TDEE measured by DLW and RMR measured by the metabolic cart. Actual measured physical activity was also determined by a triaxial accelerometer (Sensewear Pro[3]; BodyMedia, Inc., Pittsburgh, PA) worn on the upper left arm during the first 7 days of the DLW study.

Clinical chemistry

Glucose and albumin were assayed using the DXC 600 Pro (Beckman Coulter Inc., Brea, CA). Immunoassays for sex hormone–binding globulin (SHBG), progesterone, and testosterone were assayed using the Immulite 2000 XPi (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) with chemiluminescent detection. The University of Virginia Ligand Core also completed assays for insulin on the Immulite 2000 XPi. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated to evaluate insulin resistance: HOMA-IR = (glucose × insulin)/405. The FAI was calculated by FAI = [total testosterone × 0.0347 × 100]/SHBG as well as an equation from Vermeulen *et al.* that includes albumin (20).

Prediction equations to estimate energy requirements

TDEE measured by DLW ($TDEE^{DLW}$) was compared with existing TDEE prediction equations, including

Eq. (1): Mifflin-St. Jeor equation for basal metabolic rate (BMR) using a standard PAL of 1.6 (group mean) for all subjects (21)

$$\begin{aligned} \mathrm{TDEE} = [&10*\mathrm{weight(kg)} + 6.25*\mathrm{height(cm)} \\ &- 5*\mathrm{age(y)} - 161]*\mathrm{standard\ PAL} \end{aligned}$$

which was derived from measurements of RMR by indirect calorimetry in 498 normal, overweight, and obese men and women aged 19 to 78 years. The equation for females (shown) uses mean weight (kg), height (cm), and age (y) as predictor variables to derive RMR. The predicted RMR is then multiplied by the standard PAL for all subjects, which coincides with sedentary behavior, an inclusion criterion for this study:

Eq. (2): Mifflin-St. Jeor equation with actual calculated PAL ($TDEE^{DLW}$/RMR).

Similar to Eq. (1) (21), the predicted RMR derived from weight, height, and age is multiplied by PAL, which was calculated for each subject by dividing her measured TDEE/RMR:

Eq. (3): Dietary reference intake (DRI 1) for TDEE in normal weight, overweight, and obese women (22)

$$\begin{aligned} \mathrm{TDEE} = 387 - [7.31*\mathrm{age(years)}] + \mathrm{PAF} \\ \times [10.9*\mathrm{weight(kg)}] + 660.7*\mathrm{height(m)} \end{aligned}$$

where physical activity factor (PAF) is 1.00 if PAL is $\geq$1.0 <1.4; 1.14 if PAL is $\geq$1.4 <1.6; 1.27 if PAL is $\geq$1.6 <1.9; and 1.45 if PAL is $\geq$1.9 <2.5.

This equation was derived from a DLW database of 238 women, aged 19 years and older, who had a BMI $\geq$18.5 kg/m^2. TDEE is predicted from age (y), height (m), weight (kg), and a PAF. The PAF was determined from the calculated PAL and is assumed to be within 1.0 to 2.5.

Eq. (4): Dietary reference intake (DRI 2) for TDEE in overweight and obese women (22)

$$\begin{aligned} \mathrm{TDEE} = 448 - [7.95*\mathrm{age(years)}] \\ + \mathrm{PAF}[11.4*\mathrm{weight(kg)} + 619*\mathrm{height(m)}] \end{aligned}$$

where PAF is 1.00 if PAL is $\geq$1.0 <1.4; 1.16 if PAL is $\geq$1.4 <1.6; 1.27 if PAL is $\geq$1.6 <1.9; and 1.44 if PAL is estimated to be $\geq$1.9 <2.5,was designed for TDEE predictions in adult women ($\geq$19 y) with a BMI $\geq$25 kg/m^2. Data were generated from a database of 195 overweight and obese women to predict TDEE from age, height, weight, and a PAF. The PAF was determined from the calculated PAL and is assumed to be within 1.0 to 2.5.

Power calculation and statistical analysis

Using archived data from previous studies completed at our institution in which DLW was used to measure TDEE, an estimate of variation in this method was calculated (standard deviation = 399 kcal) from 109 female subjects who matched the current cohort for age and BMI. This estimate was used to power the current study and to determine equivalence of estimates from DLW and several estimating equations. Power was assessed for testing the hypothesis of equivalence using the two one-sided *t* tests (TOST) methodology. At significance level α = 0.05, a total of 28 subjects were needed to achieve the desired 80% power to conclude that a given set of equation-based estimates is equivalent to DLW within a 10% margin of error, assuming that a correlation of at least 0.4 exists between the equation and DLW.

To test the relationship between TDEE and metabolic indicators, anthropometric data, and laboratory analyses, multivariate pairwise correlations were used. Insulin and subsequently HOMA-IR were not normally distributed and therefore were log-transformed. TOST methodology was used to assess equivalence of DLW-based estimates of energy expenditure with those from several estimating equations. Equivalence was investigated using the margin of error between DLW and equation estimates calculated as percent difference. The bounds used in the TOST procedure were selected as ±10% margin of error, and equivalence was concluded when the 90% confidence interval (CI) around the mean percent difference was contained within the bounds. To determine whether differences between each predicted energy expenditure equation and measured energy expenditure varied across the range of the mean of the estimated energy expenditure from each pair, Bland-Altman plots were created, and the proportional bias was assessed. Equivalency analyses were completed using SAS/STAT® software, Version 9.4, of the SAS System for Windows (Cary, NC). All other data analyses and statistical calculations were performed using JMP Pro 12 software.

Results

Subjects

Characteristics of study participants are listed in Table 1. The participants included 14 African American and 14 white women. Participants had a mean age of

Table 1. Baseline Characteristics of Women With Polycystic Ovary Syndrome

	Mean ± SD	Range
(N = 28)		
Race		
African American	14	
Caucasian	14	
Age, y	28.6 ± 5.0	20–39
Anthropometrics		
Weight, kg	104.1 ± 19.3	66.3–144.3
BMI, kg/m^2	39.9 ± 8.3	26.2–64.7
% Fat	48.7 ± 6.9	35.7–62.8
Fat mass, kg	51.6 ± 15.4	23.7–82.2
Fat-free mass, kg	52.5 ± 7.5	38.6–73.8
Metabolic indicators		
TDEE, kcal	2661 ± 373	2099–3399
RMR, kcal/d	1689 ± 230	1138–2283
PAL (TDEE/RMR)	1.6 ± 0.2	1.3–2.5
Laboratories		
Glucose, mg/dL	89.9 ± 6.9	77–105
Insulin, uU/mL	18.8 ± 10.6	5.7–53.2
HOMA-IR	4.3 ± 2.7	1.2–13.5
Progesterone, ng/mL[a]	0.7 ± 0.8	0.2–3.0
Albumin, g/dL	3.9 ± 0.3	3.3–4.5
SHBG, nmol/L[a]	27.2 ± 12.2	9.65–67.8
Total T, ng/dL[a]	63.9 ± 36.8	22.0–175.5
Free T, pg/mL[a]	13.3 ± 6.5	6.2–27.8
% Free T[a]	2.2 ± 0.5	1.1–3.1
FAI[a]	8.5 ± 3.8	3.1–16.1

Abbreviations: Free T, free testosterone; SD, standard deviation; Total T, total testosterone; % Free T, percentage of free testosterone.

[a]Averaged over two visits, approximately 1 week apart.

28.6 ± 5.0 years, with a mean BMI of 39.9 ± 8.3 kg/m^2 and 48.7 ± 6.9% body fat. The mean change in body weight during the 14-day DLW study was 0.5 ± 1.2 kg.

RMR and physical activity

Mean RMR was 1689 ± 230 kcal/d (range, 1138 to 2283 kcal/d) or 64% of TDEE^{DLW}. The mean PAL calculated from the ratio of TDEE^{DLW} to RMR was 1.6 ± 0.2, but it was variable among the cohort (range, 1.3 to 2.5); ~18% of subjects were classified as sedentary, 75% as low activity, and 7% as active.

Total daily energy expenditure

Energy requirements measured by DLW

The mean TDEE^{DLW} was 2661 ± 373 kcal/d, and it ranged between 2099 and 3399 kcal/d. All components of TDEE^{DLW} are shown in Fig. 1. TDEE^{DLW} was correlated with fat-free mass (R^2 = 0.36; P = 0.0007) but not with weight, height, or fat mass. TDEE^{DLW} was also positively associated with RMR (R^2 = 0.32; P = 0.002). TDEE^{DLW} was positively correlated with hyperinsulinemia; fasting insulin (R^2 = 0.20; P = 0.02), and HOMA-IR (R^2 = 0.20; P = 0.02) but was not associated with hyperandrogenemia assessed by total testosterone or FAI. Pairwise correlations with the prediction equations and insulin and HOMA-IR values show that hyperinsulinemia was positively correlated with both DRI equations (r = 0.45, P = 0.02; r = 0.44, P = 0.02 and r = 0.46, P = 0.02; r = 0.45, P = 0.02, respectively) and the Mifflin-St. Jeor equations (r = 0.41, P = 0.04; r = 0.44, P = 0.02 and r = 0.42, P = 0.03; r = 0.43, P = 0.03, respectively).

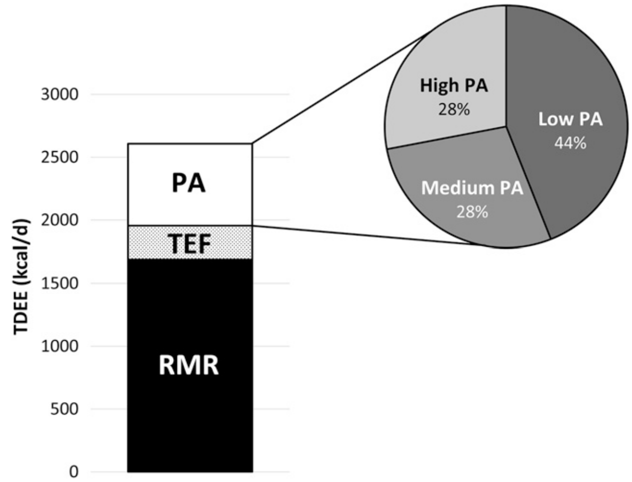

Figure 1. Components of TDEE in women with polycystic ovary syndrome (n = 28). Mean TDEE measured in kilocalories per day consists of RMR, thermic effect of food (TEF; calculated as 0.10 * TDEE), and physical activity (PA). PA was measured as active energy expenditure based on a Sensewear Pro[3] armband and is further broken down by level: Low PA was classified as <5000 steps per day, medium PA as 5001 to 7500 steps per day, and high PA as >7501 steps per day.

Energy requirements determined from prediction equations

Estimates of TDEE provided by each of the prediction equations are listed in Table 2, and all regressions between TDEE^{DLW} and each prediction equation are shown in Fig. 2. The TDEE predicted by Mifflin-St. Jeor (TDEE^{MSJStdPAL}) using a standard PAL of 1.6 was 2797 ± 341 kcal/d, which was not equivalent (6.4% higher; P = 0.12) to TDEE^{DLW}, and the mean difference was 135 ± 405 kcal/d (95% CI: 293, −22). The proportional bias was not significant across different amounts of TDEE (P = 0.62) [Fig. 3(a)]. TDEE estimated by Mifflin-St. Jeor [Eq. (1)] and a calculated PAL (TDEE^{MSJCalcPAL}) was 2757 ± 355 kcal/d, which was equivalent within 4% (P = 0.0002) to TDEE^{DLW}. The mean difference between the TDEE^{DLW} and TDEE^{MSJCalcPAL} was 95 ± 215 kcal/d (95% CI: 178, 12). The proportional bias was not significant across different amounts of TDEE (P = 0.65) [Fig. 3(b)].

The TDEE estimated from the DRI equation for normal, overweight, and obese females [TDEE^{DRI1}; Eq. (3)] was 2763 ± 291 kcal/d, which was also significantly equivalent within 5% (P = 0.0009) to TDEE^{DLW}, and the mean difference was 102 ± 222 kcal/d (95% CI: 187, 16).

Table 2. Comparison of Energy Requirement Equations in Women With Polycystic Ovary Syndrome

	Mean Difference – Bland-Altman			Linear Regression		Equivalency Testing		
Equation Comparison	**Mean**	**SD**	**95% CI**	R^2	***P* Value**	**Mean %**	**90% CI**	***P* Value**
1. Mifflin-St. Jeor equation with *standard* PAL	135.5	405	293, −22	0.12	0.06	6.4	1.4, 11.4	0.117
2. Mifflin-St. Jeor equation with *calculated* PAL	95.1	215	178, 12	0.68	**<0.0001**	4.0	1.4, 6.6	**0.0002**
3. Dietary reference intake equation 1	101.5	222	187, 16	0.65	**<0.0001**	4.6	1.9, 7.3	**0.0009**
4. Dietary reference intake equation 2	142.2	235	233, 51	0.60	**<0.0001**	6.2	3.3, 9.0	**0.016**

Mean difference from zero was obtained from Bland-Altman plots. Predicted versus actual values were used for the linear regression. Equivalence of calculated equations with TDEE by DLW using two one-sided *t* tests. The mean was determined by subtracting the TDEE from the DLW from the estimates calculated from the prediction equations and averaging the differences. Bold font indicates a significant *P* value ≤ 0.05.

The proportional bias was significant across different amounts of TDEE ($P = 0.04$) [Fig. 3(c)]. The DRI equation for overweight and obese females only ($TDEE^{DRI2}$) estimated $TDEE^{DRI2}$ to be 2804 ± 294 kcal/d and was statistically equivalent within 6.2% ($P = 0.02$) of $TDEE^{DLW}$, with a mean difference of 142 ± 235 kcal/d (95% CI: 233, 51). The proportional bias was not significant across different amounts of TDEE ($P = 0.06$) [Fig. 3(d)].

Prediction equation for TDEE

The best fit linear regression model for predicting TDEE in this cohort of women with PCOS was derived from fat mass (FM), fat-free mass (FFM), and age as predictors using stepwise regression with R^2 as the criterion:

$$\begin{aligned} \mathrm{TDEE}\left(\frac{\mathrm{kcal}}{\mathrm{d}}\right) &= 438 - [1.6 \times \mathrm{FM(kg)}] \\ &\quad + [35.1 \times \mathrm{FFM(kg)}] + [16.2 \times \mathrm{Age(yrs)}], \end{aligned}$$

$R^2 = 0.41$; $P = 0.005$.

Discussion

A key to successful weight loss programs is proper evaluation of energy requirements. This report of measured energy requirements in women with PCOS used DLW, a gold standard, to measure free-living energy expenditure. Leveraging these data, we evaluated the application of commonly used energy prediction equations in women with PCOS and also proposed a prediction equation for use in these women.

The first method of fertility treatment recommended to a woman with PCOS who is overweight/obese is a 5% to 10% weight loss through lifestyle modification (23, 24). Several groups have studied the impact of weight loss on fertility success in women with PCOS (25, 26). However, estimation of energy requirements to guide these interventions is limited (27, 28) and most likely contributes to the lack of effectiveness experienced in many patients as a negative energy balance must be achieved to lose weight.

Past weight loss interventions in women with PCOS have involved estimation of baseline energy needs using prediction equations (15, 16); however, the majority failed to mention if or how baseline energy requirements were calculated (27–29). This is concerning because a primary goal in many lifestyle interventions is to prescribe a tailored calorie deficit along with dietary counseling. Many studies in overweight and obese patients with PCOS still report using the Harris-Benedict equation to calculate energy requirements (27). Although the Harris-Benedict equation is one of the oldest and most well-known equations for assessing energy requirements (30), validation studies have demonstrated a substantial overestimation of energy requirements, from 10% to 43% in obese individuals (31, 32). In our cohort, Harris-Benedict was not statistically equivalent to $TDEE^{DLW}$ when using a standard PAL of 1.6 or when using a calculated individual PAL (10.8% equivalency, $P = 0.59$, and 8.3% equivalency, $P = 0.15$, respectively), with a mean difference of 244 ± 396 kcal/d for the standard PAL and 205 ± 230 kcal/d for the calculated individual PAL (data not shown). This is most likely due to some of the individuals in our cohort having a higher BMI.

The Mifflin-St. Jeor equation is now perhaps the most accepted equation for estimating basal energy requirements in otherwise healthy individuals. We calculated the energy requirement estimated by the Mifflin-St. Jeor equation using a standard PAL [$TDEE^{MSJStdPAL}$; Eq. (1)] and a calculated PAL [$TDEE^{MSJCalcPAL}$; Eq. (2)] and found the former differed significantly from the energy requirement measured by DLW. This discrepancy most likely points to the issue of applying a standardized level of physical activity to an individual, particularly as the intended use of the Mifflin-St. Jeor equation is for predicting BMR (a metabolic component separate from physical activity). In our subjects, BMR as calculated by the Mifflin-St. Jeor equation strongly correlated with RMR measured by indirect calorimetry ($R^2 = 0.68$; $P < 0.0001$;

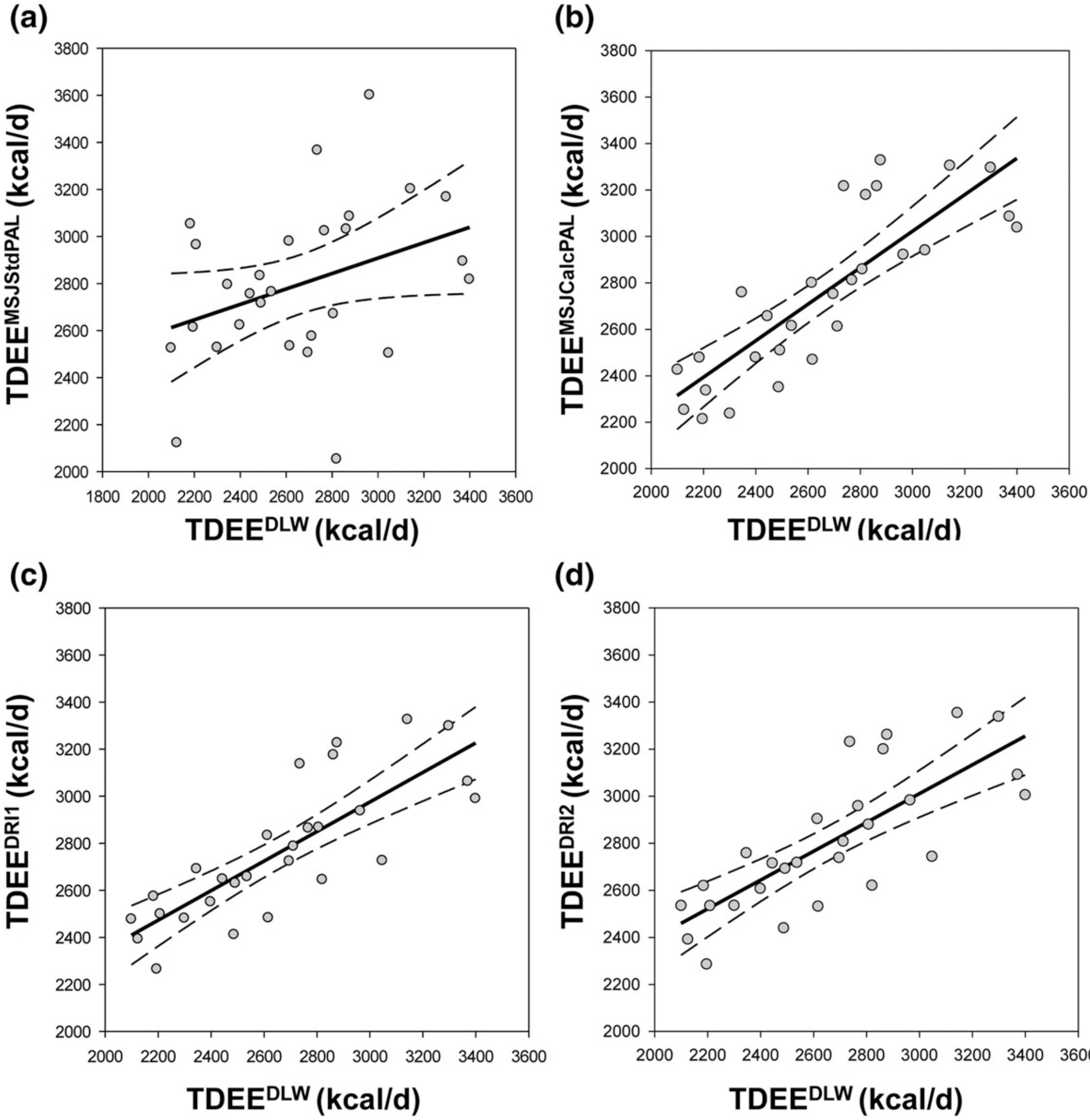

Figure 2. Regressions of total daily energy expenditure (TDEE) measured by DLW ($TDEE^{DLW}$) and four prediction equations for TDEE in women with polycystic ovary syndrome. (a) $TDEE^{MSJStdPAL}$ = the Mifflin-St. Jeor equation using a standard PAL of 1.6. (b) $TDEE^{MSJCalcPAL}$ = the Mifflin-St. Jeor equation using a calculated PAL for each subject. (c) $TDEE^{DRI1}$ = dietary reference intake equation 1 for normal weight, overweight, and obese women. (d) $TDEE^{DRI2}$ = dietary reference intake equation 2 for overweight and obese women. The solid black line indicates the line of best fit in the regression analysis, and the dashed lines indicate the 95% CIs. TDEE is measured in kilocalories per day.

data not shown). When we used an actual calculated PAL for each subject, the discrepancy between the estimated and actual TDEE improved from 6.4% to 4.0% [Eq. (1) and Eq. (2), respectively]. Although a calculated PAL from TDEE and RMR is not realistic outside a controlled research setting, the equivalence of the Mifflin-St. Jeor equations within 10% indicates that this approach can be applied in clinical and research settings with a reasonably high level of accuracy. An accelerometer device could be another option for obtaining a calculated PAL when DLW is not available.

Past studies evaluating free-living energy requirements in humans have shown that the metabolic size of the individual (*e.g.*, weight, height, fat-free mass, fat mass, and body surface area) as well as physical activity and RMR are key determinants of TDEE in weight-stable subjects (33–35). To our knowledge, no previous studies have examined if the unique metabolic and reproductive phenotype of PCOS patients affects TDEE. Daily energy requirements are affected by different physiological states, such as pregnancy and lactation; therefore, equations specific to these populations also exist. We hypothesized that PCOS may also represent a unique population indicative of slightly higher energy expenditures owing to the increased circulating androgen and insulin levels in these women. This hypothesis is supported by two key observations; per kilogram of body weight, men have higher energy requirements than women (36),

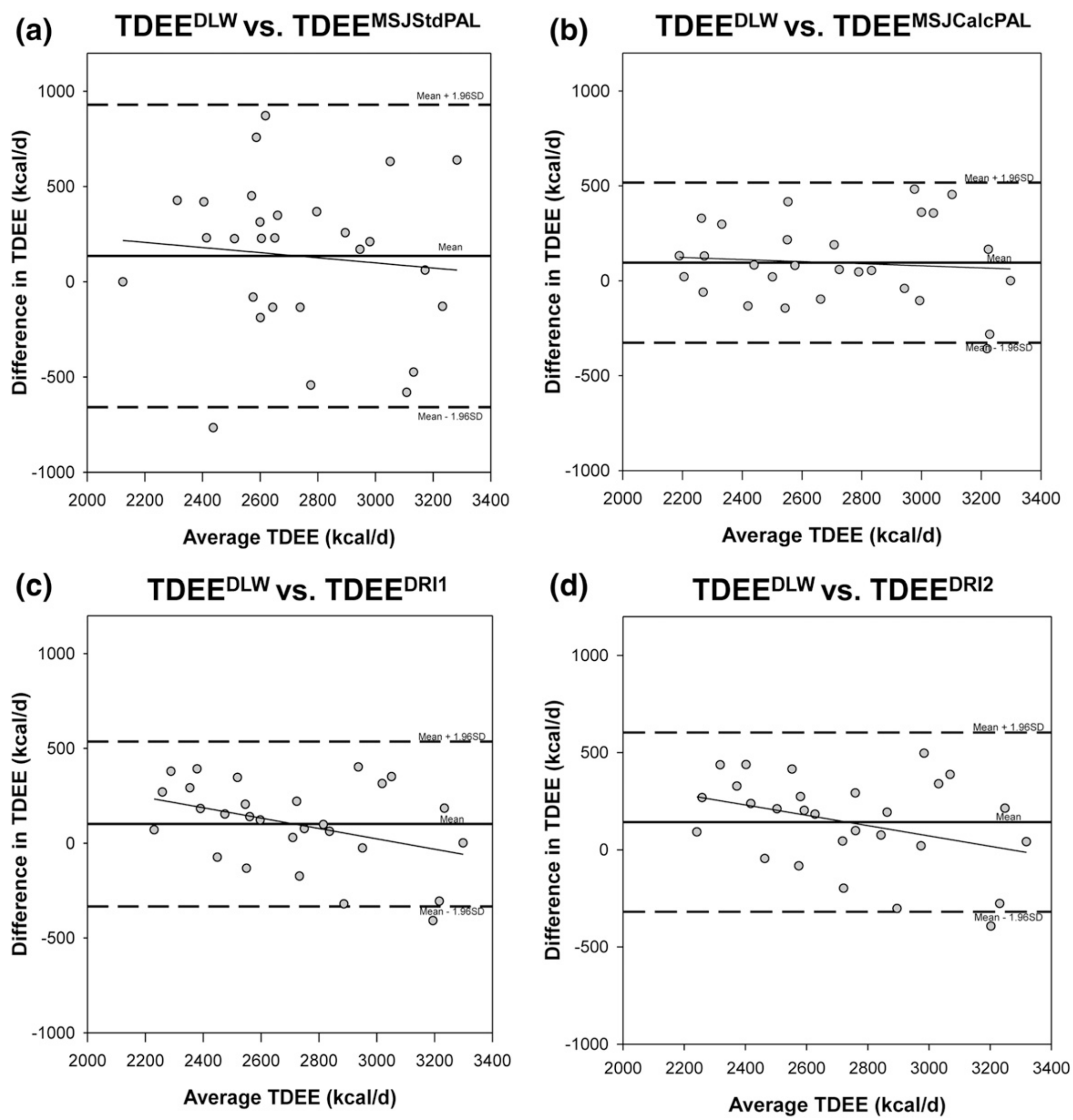

Figure 3. Bland-Altman plots of total daily energy expenditure (TDEE) measured by DLW compared with four prediction equations for TDEE in women with polycystic ovary syndrome. (a) $TDEE^{MSJStdPAL}$ = Mifflin-St. Jeor equation using a standard PAL of 1.6. (b) $TDEE^{MSJCalcPAL}$ = Mifflin-St. Jeor equation using a calculated PAL for each subject. (c) $TDEE^{DRI1}$ = dietary reference intake equation 1 for normal weight, overweight, and obese women. (d) $TDEE^{DRI2}$ = dietary reference intake equation 2 for overweight and obese women. The middle solid line indicates the mean difference, and the dashed lines indicate $\pm$1.96 standard deviation. TDEE is measured in kilocalories per day.

and energy requirements are higher in patients with type 2 diabetes mellitus than in individuals with normal glucose tolerance (37).

In addition to identifying the best existing energy requirement prediction equation for use in the PCOS population, we identified the predictors of TDEE in this population. We performed pairwise correlations with the prediction equations and insulin and HOMA-IR values. It is interesting to note that hyperinsulinemia was positively correlated with both DRI equations and with the Mifflin-St. Jeor equations. However, these indicators of hyperinsulinemia or measures of hyperandrogenemia did not explain the difference between the measured and predicted TDEE. Although our cohort was too small to both develop and validate a prediction equation unique to PCOS women, we report a prediction equation that is derived from DLW and relies on parameters of metabolic size as the determinants. Because the markers of hyperinsulinemia and hyperandrogenemia were not significant determinants of TDEE in our cohort, they are not included in the PCOS energy requirement model. It will be important for future DLW studies in women with PCOS to compile data, as has been done for other populations, to test the potential interaction with hyperinsulinemia and hyperandrogenemia (38, 39) and validate the model derived from this cohort.

In conclusion, the Mifflin-St. Jeor equations for BMR with measured physical activity [$TDEE^{MSJCalcPAL}$; Eq. (2)] and DRI equations for estimating TDEE in women [$TDEE^{DRI1}$; Eq. (3) and $TDEE^{DRI2}$; Eq. (4)] predicted energy requirements within 10% of TDEE measured by the gold standard technique of DLW in a cohort of weight-stable women with PCOS. Although hyperinsulinemia could partially explain some of the variance in TDEE in this cohort of women, it did not explain the variance between the two measurements and predictions. To better understand if the unique metabolic and reproductive phenotype of PCOS women contributes to differences in energy expenditures, studies in other cohorts are needed. This study proposes an energy requirement equation unique to PCOS women. Researchers attempting to achieve weight loss could use an equation such as this or other existing equations studied herein to estimate weight maintenance energy requirements and individualize dietary intake targets in weight loss interventions. As more studies in women with PCOS are completed, results should be compiled to develop and validate a unique equation for PCOS women that is reliable and robust and to properly evaluate the potential influence of hyperinsulinemia and hyperandrogenemia, which are unique to this condition.

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