Comparison of actual and predicted resting metabolic rate in women with lipedema

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Abstract

Background: An adequate dietary energy supply is particularly important in patients with lipedema as it promotes weight and fat loss. Accurate estimation of resting metabolic rate (RMR) allows implementing a proper calorie restriction diet in patients with lipedema. Therefore, an accurate assessment of energy demand in patients with lipedema is crucial in clinical practice. Our study aimed to compare actual resting metabolic rate (aRMR) with predicted resting metabolic rate (pRMR) in women with lipedema and to determine the association between individual anthropometric measurements and aRMR.

Methods: A total of 108 women diagnosed with lipedema were enrolled in the study. aRMR was measured by indirect calorimetry (IC) using FitMate WM metabolic system (Cosmed, Rome, Italy). pRMR was estimated with predictive equations and BIA. *All anthropometric measurements were based on BIA (bioelectric impedance analysis).*

Results: The mean aRMR in the study group was 1705.2 ± 320.7 kcal/day. Most methods of predicted RMR measurement used in our study significantly underpredicted aRMR in patients with lipedema. We reported statistically significant high correlations between all anthropometric measurements and aRMR/pRMR and a moderate correlation between visceral fat level (VFL) and aRMR.

Conclusions: aRMR in patients with lipedema calculated with predictive equations was significantly lower than aRMR measured with other methods. This study found the agreement of predictive equations compared to IC is low (<60%). Fat-free mass (FFM) is a stronger determinant of RMR in patients with lipedema than fat mass.

Introduction

Lipedema is a medical condition almost exclusively found in women which manifests as an excessive accumulation of subcutaneous adipose tissue [1]. It is characterized by pain and bilaterally symmetrical accumulation of adipose tissue, particularly in the lower part of the body [2]. Lipedema is estimated to affect approximately 11.0% of women worldwide [3]. Lipedema is often misdiagnosed as obesity, although patients with lipedema may be also obese [4, 5]. Obesity increases the risk of lipedema progression or developing obesity-related diseases, such as cardiovascular disease, type 2 diabetes, and osteoarthritis. Therefore, weight loss in patients with lipedema is a key element of lipedema management [4, 5]. Diets that contribute to weight loss can improve patients' mobility and decrease the risk of developing secondary lymphoedema [6].

One of the characteristic symptoms in patients with lipedema is regular increase in body weight and body fat which leads to an increased secretion of proinflammatory adipokines. Chronic positive energy balance and low physical activity are the main factors contributing to the systematic increase in body weight [7]. Therefore, an adequate dietary energy supply is particularly important in patients with lipedema as it promotes weight and fat loss.

According to the lipedema management guidelines, weight loss is particularly difficult for patients with lipedema because popular weight loss programs do not promote lipedemic fat loss [1, 4, 6, 8–10]. Furthermore, failed attempts to lose weight may result in compulsive eating, and consequently, lead to steady weight gain [6]. Since many patients with lipedema are overweight or obese, weight loss and reduction of overall adipose tissue can contribute to the treatment success [4, 10]. In patients with lipedema, obesity is treated with a calorie restriction diet [6, 8]. Therefore, accurate assessment of energy demand in patients with lipedema is crucial in clinical practice.

Correct estimation of resting metabolic rate (RMR) in patients with lipedema allows implementing a proper calorie restriction diet. RMR is one of the components of total energy expenditure (TEE), representing 60–75% of its value [11]. It is the value of energy expended by the body at rest during 24 h to maintain its function [12, 13]. RMR can be measured by indirect calorimetry (IC), BIA or with predictive equations [13]. The main benefit of performing IC is the prevention of overfeeding among patients thanks to the precise assessment and control of their energy needs. Measuring aRMR with IC is considered as the gold standard, particularly in patients with acute or chronic conditions [12]. However, performing IC in clinical routine requires specialist equipment, is expensive and not widely available.

If it is impossible to measure RMR by IC, using predictive equations is the most common method of RMR assessment [13]. However, although predictive equations are relatively reliable in healthy individuals, they may be inaccurate in case of chronic diseases [12, 13]. Predictive equations allow for a relatively quick and easy RMR estimation based on anthropometric data, such as height, weight and LBM. Due to the disproportionate content of body fat on the legs compared to the upper body, body weight may not be a very useful parameter to assess RMR in patients with lipedema [6]. Another method for RMR estimation is BIA that estimates the corporal compartments, including LBM [13]. This method is associated with lower costs than IC, and with relatively quick and easy implementation [13].

RMR depends on age, height, body weight, sex and body composition, including clean body mass (LBM) and body mass fat (BMF) [14, 15]. There is a strong relationship between weight and RMR [14]. Many studies have confirmed that RMR is mostly dependent on the amount of LBM [16, 17, 18] and, to some extent, on the amount of BMF [19]. LBM determines RMR in about 60–70%, whereas BMF only in 5–7% [20]. To date, no one has reported a relationship between anthropometric parameters, RMR and body composition in patients with lipedema.

Our study aimed to compare aRMR with pRMR in women with lipedema and to determine the association between individual anthropometric measurements and BMI with aRMR.

Materials And Methods

Characteristics of the study group

The study included 108 women with lipedema. The mean age of the study participants was 18-76 years (44.0 ± 13.5). Lipedema was diagnosed based on typical clinical symptoms [21]. Study exclusion criteria included: male sex, lymphoedema of the legs, and factors that excluded BIA measurement: pregnancy, metal implants, pacemakers, stents, or other devices emitting electronic signals. The study was conducted at Wroclaw Medical University, Poland. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Bioethical Commission of Wroclaw Medical University (No. KB - 456/2019). Written informed consent was obtained from all patients.

Resting metabolic rate assessment

aRMR was measured by IC with FitMate WM device (Cosmed, Rome, Italy). Before proceeding to the measurement, the study participants had been instructed to avoid food and drinks, except water, for 8 h and vigorous exercise for 48 h. The measurement was performed in the supine position, in a ventilated and darkened room, at a moderate temperature [11]. The study participants were examined in the morning after 7-9 h of sleep. Prior to the measurement, participants were given several minutes to rest in a seated position to optimize measurement conditions. Then, they were asked to put on a Fitmate WM face mask. The measurement took 10-20 min and was performed in isolation to separate participants from external noise. Fitmate WM device was calibrated before taking each measurement. Throughout the entire measurement process, its progress was monitored on the Fitmate WM screen [16]. The study participants were informed about the exact course of the procedure before the study commencement.

pRMR was calculated with the following predictive equations: Harris-Benedict [22], Mifflin et al. [23], Bernstein et al. [24], Owen et al. [25], FAO/WHO [26], Cunningham [27], Müller et al. [28], Korth et al. [29], Lazzer et al. [30], Huang et al. [31], Henry's [32], and the Institute of Medicine [33] (Table 1). All equations included age, height, weight, and lean body mass (LBM). pRMR was estimated with BIA, which is a measuring device estimating RMR based on LBM.

Table 1
Predictive equations used for RMR estimation

Equation	Description of the equation
Harris-Benedict [22]	$9.56 \times W + 1.85 \times H - 4.68 \times A + 655.09$
Mifflin et al. [23]	$9.99 \times W + 6.2 \times H - 4.92 \times A - 161$
Bernstein et al. [24]	$7.48 \times W - 0.42 \times H - 3 \times A + 844$
Owen et al. [25]	$7.18 \times W + 795$
FAO/WHO [26]	$13.3 \times W + 334 \times H \text{ (m)} + 35 \text{ (age 18 - 30)}$ $8.7 \times W - 25 \times H \text{ (m)} + 865 \text{ (age 31 - 60)}$ $9.2 \times W + 637 \times H \text{ (m)} - 302 \text{ (age >60)}.$
Cunningham [27]	$500 + (22 \times \text{LBM})$
Müller et al. [28]	$(0.047 \times W + 0.01452 \times A + 3.21) \times 239$
Korth et al. [29]	$(41.4 \times W + 35 \times H - 19.1 \times A - 1731.2) / 4,186$
Lazzer et al. [30]	$(0.042 \times W + 3.619 \times H \text{ (m)} - 2.678) \times 239$
Huang et al. [31]	$10.158 \times W + 3993 \times H - 1.44 \times A + 60.655$
Henry's [32]	$(0.0546 \times W + 2.33) \times 239 \text{ (age 18 - 30)}$ $(0.0407 \times W + 2.9) \times 239 \text{ (age 31 - 60)}$ $(0.0424 \times W + 2.38) \times 239 \text{ (age >60)}.$
IOM [33]	$247 - 2,637 \times A + 401 \times H \text{ (m)} + 8.6 \times W$

A - age [years]; H - height [cm]; W - weight [kg]; LBM - lean body mass [kg]; FAO -Food Agriculture Organization; WHO – the World Health Organization; IOM- the Institute of Medicine

Measurement of anthropometric parameters using BIA

Anthropometric measurements were performed with TANITA HR-001 analyzer (Tanita, Japan) and Jawon Medical X-Contact 353 8-electrode body composition analyzer (Jawon Medical co., Ltd., Republic of Korea). The following parameters were obtained: height [cm], weight [kg], percentage of body fat (PBF) [%], total body water (TBW) [%], body fat (BF) [kg], lean body mass (LBM) [kg], soft tissue mass [kg], muscle tissue mass [kg], and visceral fat level (VFL).

Before proceeding to the measurement, the study participants had been instructed to avoid food and drink for 4 h, vigorous exercise for 12 h, and taking diuretics for 6 h. Contraindications for BIA measurements included: pregnancy, pacemakers, or metal implants [13]. BMI was calculated as the ratio of body weight [kg] to the square of height [m²]. Waist and hip circumference were measured with a standard measuring tape with +/-1 cm accuracy. The mean value of the waist-hip ratio (WHR) was calculated as the ratio of waist to hip circumference.

Statistical analyses

The results were presented as mean values $\pm$ standard deviation, median, as well as minimum and maximum values. Normality of data distribution in the analyzed groups was tested with the Lilliefors test. Although the frequency distribution of some variables (based on the Shapiro-Wilk or Lilliefors tests) differed from the normal distribution (supplementary materials –Figure S1 and Figure S2), the analyses were performed with parametric methods. It was reasoned by high symmetry of frequency histograms and large sample size (N>100), which is usually considered large enough to use

parametric tests, even if the assumption of normal distribution is violated. Pearson correlation analysis was used to evaluate the relationship between aRMR and pRMR measured with BIA and between aRMR and anthropometric measurements. Interpretation of correlation coefficient was described as: poor ($r < 0.1$); weak ($r = 0.1-0.29$); moderate ($r = 0.3-0.49$); high ($r = 0.5-0.69$); very high ($r = 0.7-0.89$); almost complete ($r = 0.9-0.99$) [34]. Differences between aRMR and pRMR were assessed with Student's t-test. The consistency in individual measurements between aRMR and pRMR was assessed with the use of the Bland-Altman method. Correlations between aRMR and anthropometric measurements were analyzed with Pearson correlation analysis. The Pearson correlation coefficients r were compared with the use of a test based on the transformation of r to Fisher's z -value. Since many anthropometric variables are correlated, principal component analysis (PCA) was used to define a set of variables (Principal Components) among which each represents a group of strongly correlated variables (normalized Varimax rotation was applied). Results for all analyses were considered statistically significant at the level of $p < 0.05$. All statistical analyses were performed with STATISTICA v. 13 TIBCO Software Inc. 2017 (StatSoft Inc., USA).

Results

Characteristics of the study group

The age of the study participants ranged from 18 to 76 years old (mean age 44.0 ± 13.5). The mean body weight and height in the study group was 87.8 ± 22.6 kg and 165.9 ± 6.9 cm, equally. BMI results were interpreted on the basis of the classification of index values suggested by WHO [35]: <18.5 kg/m² - underweight; $18.5-24.9$ kg/m² - normal weight; $25.0-29.9$ kg/m² - overweight; $30.0-34.9$ kg/m² – obesity class I; $35.0-39.9$ kg/m²- obesity class II; >40.0 kg/m²- obesity class III. The mean value of BMI among the participants was 32.0 ± 8.7 kg/m². The 26.9% percentage of participants ($n = 29$) were of normal weight, 25.0% ($n = 27$) had obesity class I. An equal number of patients (17.6%; $n = 19$) were overweight or had obesity class III (17.6%; $n = 19$), and the lowest percentage of patients had obesity class II (13.0%; $n = 14$). The mean waist circumference in the study group was 96.1 ± 17.7 cm. The percentage of individuals whose waist circumference was greater than 80 cm but smaller than 88 cm was 13.9% ($n = 15$), while individuals whose waist circumference was greater than 88 cm represented the largest percentage of the subjects (64.8%; $n = 70$). Only 21.3% of the subjects ($n = 23$) had normal waist circumference. The mean value of WHR in the study group was 0.83 ± 0.1 . The WHR value was equal to or greater than 0.85 in 38.9% of all study participants ($n = 42$).

Actual and predicted resting metabolic rate (RMR)

The mean aRMR was 1705.2 ± 320.7 kcal/day. The mean pRMR ranged from 1281.1 ± 104.7 kcal/day (measured by BIA) to 1906.3 ± 276.3 kcal/day (estimated by Müller et al. predictive equation). Pearson correlation analysis showed that all predictive equations estimating RMR significantly correlated with aRMR. All correlation coefficients between RMR measured with predictive equations and aRMR were very high except for the correlation between aRMR and RMR calculated with BIA, which was statistically insignificant and weak.

The detailed results of characterization and the results of correlation between aRMR and pRMR are described are presented in **Table 2**.

Table 2

The characteristics of RMR estimated with different methods ($n=108$)

Method	RMR [kcal/day]				Pearson correlation coefficient
	Mean $\pm$ SD	Median	Min	Max	
aRMR (kcal/kg/day)	20.0 $\pm$ 3.7	19.7	10.2	30.1	-
aRMR (kcal/day)	1705.2 $\pm$ 320.7	1687.5	1032.0	2775.0	-
Harris-Benedict [22]	1596.0 $\pm$ 202.2	1565.1	1275.2	2204.7	0.753*
Mifflin et al. [23]	1528.5 $\pm$ 220.2	1495.2	1131.8	2132.3	0.734*
Bernstein et al. [24]	1299.2 $\pm$ 156.9	1269.4	1064.8	1794.3	0.759*
Owen et al. [25]	1425.5 $\pm$ 162.4	1406.0	1155.4	1920.8	0.739*
FAO/WHO [26]	1584.1 $\pm$ 199.5	1562.7	1223.7	2189.5	0.748*
Cunningham [27]	1574.4 $\pm$ 465.5	1468.5	908.6	3421.8	0.754*
Müller et al. [28]	1906.3 $\pm$ 276.3	1867.7	1414.4	2709.0	0.703*
Korth et al. [29]	1641.4 $\pm$ 224.1	1612.9	1219.4	2225.2	0.723*
Lazzer et al. [30]	1676.5 $\pm$ 237.2	1648.0	1213.2	2304.8	0.730*
Huang et al. [31]	1532.3 $\pm$ 220.3	1499.9	1162.1	2172.5	0.750*
Henry's [32]	1542.5 $\pm$ 214.8	1510.7	1211.9	2218.3	0.763*
IOM [33]	1551.5 $\pm$ 188.7	1518.5	1241.0	2093.9	0.749*

aRMR - actual resting metabolic rate; FAO - Food Agriculture Organization; WHO - the World Health Organization; IOM - the Institute of Medicine; BIA - bioelectrical impedance analysis; *p < 0.001.

We reported the smallest mean difference between pRMR and aRMR for Lazzer et al. equation (28.6 ± 219.3 kcal / day; p = 0.178), and the highest mean difference for BIA (424.0 ± 326.6 kcal / day; p < 0.001). Most of predictive equations and BIA significantly underpredicted aRMR, except for the Müller et al. equation [28], which significantly overpredicted RMR. The most overpredicted RMR was obtained with Bernstein et al. [24] and Owen et al. equations [25] (Table 3).

Table 3

Differences between aRMR and pRMR (n=108)

Method	Δ RMR kcal/day	SD	Δ RMR kcal/day % aRMR
Harris-Benedict [22]	109.1*	214.7	6.4
Mifflin et al. [23]	176.7*	218.3	10.4
Bernstein et al. [24]	406.0*	226.0	2.8
Owen et al. [25]	279.7*	228.7	16.4
FAO/WHO [26]	121.1*	216.6	7.1
Cunningham [27]	130.8*	307.5	7.7
Müller et al. [28]	-201.1*	233.8	-11.8
Korth et al. [29]	63.7*	221.7	3.7
Lazzer et al. [30]	28.6	219.3	1.7
Huang et al. [31]	172.9*	213.0	10.1
Henry's [32]	162.7*	209.4	9.5
IOM [33]	153.6*	218.7	9.0
BIA	424.0*	326.6	24.9

FAO – the Food Agriculture Organization; WHO – the World Health Organization; IOM - the Institute of Medicine; BIA- bioelectrical impedance analysis; Δ RMR – mean difference between aRMR and pRMR; *p<0.01; p<0.05 - statistically significant values; df = 107.

Korth et al. predictive equation was the most accurate in comparison to aRMR due to its lowest individual variability. Values of Korth et al. [29], Harris-Benedict [22] and Lazzer et al. [30] equations were within 10% of the measured aRMR in more than 50% of the study participants: (Figure 1).

Based on the Blind-Altman analysis results, we observed a significant dispersion of individual scores for most equations, which means that they were weakly correlated with aRMR. The only exception was for the Müller et al. equation [28], which significantly overestimated the value of aRMR, but to a similar extent in the entire set of predictive equations, regardless of the individual aRMR results (Figure 2). The Pearson's coefficients r for correlation between the averaged pRMR and aRMR values, and the difference between them are presented.

Anthropometric measurements vs aRMR and pRMR

The mean percentage of BF mass among our study participants was $37.5 \pm 7.4\%$. BF was higher than or equal to 30.0% in 88 patients (81.5%). Most study participants (47.2%; n = 51) were morbidly obese, with BF higher than 40.0%. VFL ranged from 3 to 20 (mean 13.4 ± 5.1). Over 70.0% (71.3%; n = 77) of study participants had a high VFL, including 43.5% with very high VFL. Characteristics of anthropometric measurements is shown in **Table 4**.

Table 4

Characteristics of anthropometric measurements (n=108)

Measurement	Mean $\pm$ SD	Median	Min	Max
Lean body mass - LBM [%]	53.4 $\pm$ 9.0	51.9	37.0	84.7
Lean body mass - LBM [kg]	48.8 $\pm$ 21.2	44.0	18.6	132.8
Soft lean mass - SLM [kg]	48.5 $\pm$ 7.8	46.8	34.1	76.0
Soft muscle mass - SMM [kg]	29.1 $\pm$ 4.7	28.0	20.4	45.6
Total body water - TBW [%]	38.5 $\pm$ 6.5	37.3	26.6	61.0
Mass body fat - MBF [kg]	34.4 $\pm$ 14.3	33.6	11.6	72.1
Percentage body fat - PBF [%]	37.5 $\pm$ 7.4	39.0	15.9	48.7
Visceral fat level - VFL	13.4 $\pm$ 5.1	14.0	3	20
Body Mass Index - BMI [kg/m ²]	32.0 $\pm$ 8.7	31.6	18.8	62.4

All anthropometric measurements positively correlated with aRMR and pRMR. We reported a moderate correlation between VFL and aRMR; a strong correlation between BMI and aRMR; and almost full correlation between BMI and the pRMR. **Table 5** presents detailed results of Pearson correlation analysis between anthropometric measurements and pRMR/aRMR.

Table 5

Results of Pearson correlation analysis between anthropometric measurements and pRMR/aRMR (n=108)

Method	Anthropometric measurements and BMI									
	LBM [%]	LBM [kg]	SLM [kg]	SMM [kg]	TBW [%]	MBF [kg]	PBF [%]	VFL	BMI [kg/m ²]	LBM [%]
Harris-Benedict [22]	.9613*	.9561*	.9560*	.9564*	.9612*	.8948*	.6948**	.6250**	.8373*	.9613*
Mifflin et al. [23]	.9569*	.9292*	.9557*	.9560*	.9568*	.8447*	.6295**	.5603**	.7680*	.9569*
Bernstein et al. [24]	.9613*	.9747*	.9522*	.9526*	.9612*	.9369*	.7553*	.6885**	.8946*	.9613*
Owen et al. [25]	.9552*	.9851*	.9417*	.9420*	.9551*	.9824*	.8362*	.7832*	.9515*	.9552*
FAO/WHO [26]	.9591*	.9699*	.9498*	.9500*	.9590*	.9403*	.7716*	.7055**	.8982*	.9591*
Cunningham [27]	.9776*	1.0000**	.9694*	.9696*	.9777*	.9447*	.7419*	.6816**	.9263*	.9776*
Müller et al. [28]	.9204*	.9624*	.9040*	.9043*	.9203*	.9851*	.8685*	.8262*	.9645*	.9204*
Korth et al. [29]	.9535*	.9165*	.9540*	.9542*	.9534*	.8242*	.6051**	.5373**	.7395*	.9535*
Lazzer et al. [30]	.9804*	.9666*	.9748*	.9750*	.9803*	.9164*	.7332*	.6782**	.8466*	.9804*
Huang et al. [31]	.9791*	.9758*	.9724*	.9727*	.9790*	.9272*	.7398*	.6778**	.8682*	.9791*
Henry's [32]	.9604*	.9767*	.9506*	.9509*	.9602*	.9454*	.7717*	.7049**	.9066*	.9604*
IOM [33]	.9766*	.9667*	.9714*	.9717*	.9765*	.9080*	.7123**	.6480**	.8441*	.9766*
RMR	.7340*	.7536*	.7273*	.7278*	.7328*	.7077**	.5421**	.4763**	.6854**	.7340*

FAO - Food Agriculture Organization; WHO - the World Health Organization; IOM - the Institute of Medicine; BIA - bioelectrical impedance analysis. p<0.05 - statistically significant values, *p < 0.01; **p < 0.001; p<0.05 - statistically significant values.

To further evaluate the correlation between anthropometric measurements and aRMR, we performed PCA. It enabled to define the two principal components, PC1 and PC2, which represent the sets of strongly intercorrelated variables (Table 6). They can be interpreted as fat free mass components and fat mass components with BMI, respectively. PC1 and PC2 groups significantly correlated with aRMR (r = 0.66 and r = 0.34, respectively; p < 0.001). However, PC1 group (fat-free mass components) more significantly correlated with aRMR than PC2 group (fat mass components with BMI). **Figure 3** presents the relationship between aRMR and PC1 (fat-free mass components) and PC2 (fat mass components with BMI).

Table 6

Results of PCA of the anthropometric measurements (n=108)

Anthropometric measurements	PC1	PC2
	Fat-free mass components	Fat mass components and BMI
LBM [%]	0.93	0.36
LBM [kg]	0.87	0.49
SLM [kg]	0.94	0.33
SMM [kg]	0.94	0.33
TBW [%]	0.93	0.36
MBF [kg]	0.67	0.74
PBF [%]	0.34	0.93
VFL	0.26	0.95
BMI [kg/m ²]	0.64	0.72
Part [%]	0.589	0.395

LBM - lean body mass; SLM - soft tissue mass; SMM - muscle tissue mass; TBW - total body water; MBF - mass body fat; PBF - percentage body fat; VFL - visceral fat level; BMI - body mass index

Discussion

Our study aimed to compare aRMR with pRMR in women with lipedema and to determine the association between individual anthropometric measurements and BMI with aRMR. To date, many studies have compared RMR estimated by IC and predictive equations in overweight and obese patients [36–40]. However, only one study assessed RMR in patients with lipedema. In 1949 Wold et al. found that aRMR in patients with lipedema was lower than RMR estimated with predictive equations. However, methodology of their study was not precisely defined [41]. The results of our study demonstrate a weak correlation between pRMR and aRMR in patients with lipedema. aRMR in patients with lipedema calculated with predictive equations was significantly lower than aRMR measured with other methods.

A proper calorie diet prevents weight gain and enables effective weight loss. Reduction of adipose tissue by losing weight may alleviate pain, improve mobility, and increase quality of life in patients with lipedema [3]. An effective diet can break the vicious cycle of dietary restrictions that lead to increased body weight [6]. Additionally, a low-calorie diet may have anti-inflammatory effects [42]. Correct RMR estimates in patients with lipedema allows calculating a proper calorie reduction diet to promote healthy weight loss. IC is considered to be an accurate method of measuring RMR in patients with excessive body weight due to its high level of concordance between the obtained results and actual energy expenditure [43]. Therefore, measuring RMR with IC allows for precisely estimation of actual energy expenditure in patients with lipedema. However, performing IC in clinical routine requires specialist equipment, is expensive and not widely available. Estimating RMR with predictive equations does not require any specialist equipment but is limited in patients with lipedema.

This study found the agreement of predictive equations compared to IC is low (< 60%). Most methods of RMR measurement used in our study significantly underpredicted aRMR in patients with lipedema. Based on individual differences between aRMR and pRMR, we found that methods for estimating RMR significantly and nonhomogeneously underestimated aRMR in the entire study group, depending on the individual baseline aRMR values. Therefore, the most applied equations remain useless in clinical practice due to large individual differences among the studied women. The results obtained by Müller et al. equation demonstrated the highest correlation with the individual aRMR values as this equation homogeneously overpredicted aRMR in the entire range, regardless of the baseline aRMR values. Therefore, Müller et al. equation can be considered the closest to aRMR in patients with lipedema when using the difference ($\Delta\text{RMR} - 201.1 \text{ kcal/day}$) in the individual estimation of RMR in clinical practice.

Other authors also reported a relatively low concordance between aRMR and pRMR in overweight patients, but found the Mifflin et al. [23] and Harris-Benedict equations [22] the most accurate [14, 36–40]. This was not the case in our study since we reported significant differences between aRMR measured with these two equations. Kruizenga et al. [37], who examined the validity of RMR predictive equations for underweight, normal weight, overweight, and obese inpatients and outpatients by comparison with IC, reported a low level of concordance between pRMR and aRMR measured with predictive equations, which is consistent with our study. The percentage of accurately predicted RMR did not exceed 49%. Authors emphasized IC as a preferred method for RMR assessment in obese patients. Our findings are also in line with the results obtained by Carrera-Gil et al. [38], who reported a low level of concordance between RMR measured by IC and estimated using Harris-Benedict and the Mifflin equations in patients with $\text{BMI} \geq 25 \text{ kg/m}^2$. Authors concluded that predictive equations did not include parameters with a significant impact on RMR and claimed their inaccuracy.

In this study more than 70.0% of our study participants were overweight (based on BMI), and more than 80.0% had BF over 30.0%. Due to the lower limbs disproportion, BMI and body weight were considered inaccurate obesity assessment tools in patients with lipedema [4, 6]. According to the Dutch guidelines for lipedema management, waist circumference is the most effective measure of obesity in adults [4]. Waist circumference was also measured as it is an effective tool in the assessment of adipose tissue distribution in the body. It can be used to monitor the results of obesity treatment which can be useful in clinical practice [6]. Waist circumference greater than 80 cm indicated an increased risk, and circumference greater than 88 cm indicated a significantly increased risk of metabolic complications [44]. 78.7% of the subjects had increased waist circumference (mean = $96.1 \pm 17.7 \text{ cm}$) which indicates high risk of metabolic complications. German guidelines recommend measuring WHR, which allows determining the distribution of BF and obesity type [9]. The interpretation of mean WHR and mean waist circumference values was based on the cut-off points proposed by WHO. The recommended WHR values should be lower than 0.85 as values that are greater or equal indicate abdominal obesity and a significantly increased metabolic risk [44]. In our study the mean WHR value was lower than 0.85. Consequently, due to the disproportionate content of body fat on the buttocks and thighs compared to the waist, WHR may not be very useful in patients with lipedema in clinical practice [6].

We found a stronger correlation between LBM, SLM, SMM, TBW and aRMR than between PBF, VFL, BMI and aRMR. Fat-free mass (FFM) is a stronger determinant of RMR in patients with lipedema than fat mass. Almajwal et al. [14], who evaluated the correlation between body composition and RMR in female patients, found that BF and LBM correlated with RMR in overweight patients and strongly correlated with RMR in obese patients. Contrary to our study, McMurray et al. [18] found that RMR decreased with increasing BMI, suggesting that RMR in obese women is lower than in women with normal weight. Authors suggested that this may be related to higher FM in obese patients, which shows a weaker correlation with RMR than LBM.

Limitations of this study was using a BIA method which can be an effective tool for assessing the prevalence and degree of obesity. However, in patients with a significant degree of obesity BIA tends to overpredict LBM and underpredict BF. Obese patients have expanded extracellular space in adipose tissue and higher percentage of LBM hydration than normal weight

patients. Therefore, their BF may be underpredicted because LBM and BF are estimated based on the total body water (TBW) measurement. The higher the BMI, the bigger the estimation error [45, 46].

Implementing a proper calorie reduction diet in patients with lipedema can significantly improve disease treatment and prevent its progression. In this study, we for the first time measured aRMR by IC in women with lipedema and correlated it with commonly available measurement methods used in clinical practice. We demonstrated that IC is the best tool to measure RMR in patients with lipedema. However, due to its low availability and high cost, Müller et al. equation with mean measurement difference is a potential option to determine RMR in clinical practice if IC is not available (e.g., in a dietitian's office, health clinic, or hospital).

Conclusions

The results of our study demonstrate the agreement of predictive equations compared to IC is low (< 60%) in patients with lipedema. RMR in patients with lipedema calculated with predictive equations was significantly lower than RMR measured with IC. We reported the strongest correlation between aRMR and pRMR for the Müller et al. equation. Therefore, we can conclude that this is the most useful equation in clinical practice if IC is not available (e.g., in a dietitian's office, health clinic, or hospital). Fat-free mass (FFM) is a stronger determinant of RMR in patients with lipedema than fat mass.

Abbreviations

aRMR – actual resting metabolic rate

BF - body fat

BIA - bioelectric impedance analysis

BMF - body mass fat

BMI – body mass index

FAO - Food Agriculture Organization

IC – indirect calorimetry

IOM - the Institute of Medicine

LBM - lean body mass

MBF - mass body fat

PBF - percentage of body fat

pRMR – predictive resting metabolic rate

PC1- group of fat-free mass components

PC2 - group of fat mass components with BMI

PCA - principal component analysis

RMR - resting metabolic rate

SLM - soft lean mass

SMM - soft muscle mass

TBW - total body water

VFL - visceral fat level

WHO – the World Health Organization

WHR - waist-hip ratio

Declarations

Ethics approval and consent to participate:

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Bioethical Commission of Wroclaw Medical University (No. KB - 456/2019).

Consent for publication:

Written informed consent was obtained from all patients.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

M.J. and B.R.-I. were responsible for the conception and design of this study. M.J. was responsible for the data collection and for writing the manuscript. K.K. was responsible for the statistical analysis. A.S. and B.R.-I. were responsible for revising the manuscript critically for essential content. All authors read and approved the final manuscript.

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Figures

Figure 1

Percent of aRMR with an individual bias [%] within $\pm 10\%$ of aRMR for each prediction equation

Figure 2

Bland-Altman plots of the consistency between various pRMRs and aRMR

Figure 3

Scatter plots presenting the relationship between aRMR and PC1 and PC2

Supplementary Files

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