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ORIGINAL ARTICLE

Does segmental body composition differ in women with Prader–Willi syndrome compared to women with essential obesity?

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Abstract
Background Subjects with Prader–Willi syndrome (PWS) have a higher fat mass and a lower fat-free mass compared to subjects with essential obesity. However, few data are presently available on the segmental body composition (BC) of PWS subjects.
Aim To evaluate whether women with PWS and women with essential obesity, matched for age and percent body fat, differ in segmental fat distribution and surrogate markers of cardiometabolic disease (CMD).
Subjects and methods 35 women with PWS and 50 women with essential obesity were matched for age and percent body fat using coarsened exact matching. BC was measured by dual-energy X-ray absorptiometry. Oral glucose tolerance testing and measurements of cholesterol, triglycerides, C-reactive protein, and blood pressure were performed. Comparisons between PWS and obese women were performed using generalized linear models.
Results Trunk fat was lower in PWS than in obese women on both absolute [−7.3 (95 % confidence interval −9.4 to −5.2) kg] and relative [−4.1 (−6.9 to −1.4) % of body fat] grounds. PWS and obese women had similar surrogate markers of CMD, with the exception of HDL-cholesterol, which was higher in PWS women.
Conclusion Trunk fat is lower in obese women with PWS than in those with essential obesity. Surrogate markers of CMD are, however, mostly similar in the two groups.

Keywords Prader–Willi syndrome · Essential obesity · Body composition · Body fat distribution · Dual-energy X-ray absorptiometry

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Introduction

Prader–Willi syndrome (PWS), the most common form of genetic obesity, is thought to arise from developmental abnormalities in the hypothalamus and is characterized by behavioral disturbances, short stature, hyperphagia, and childhood-onset obesity [1]. The body composition (BC) of PWS subjects is peculiar, as they not only have a higher fat mass (FM), but also have a lower fat-free mass (FFM) compared to those without PWS [2, 3]. While the average FM:FFM ratio is 0.75 in obese non-PWS subjects, it is close to 1.00 in obese PWS subjects [4]. Because excess body fat is associated with cardiometabolic disease (CMD) in the general population [5], the massively expanded FM of PWS subjects may contribute to their burden of CMD [6].

Although it has been convincingly shown that PWS is characterized by high FM and low FFM [4], much less is known on the segmental BC of PWS subjects. Cross-sectional studies using whole-body magnetic resonance imaging (MRI) have reported a lower visceral adipose tissue (VAT) in adult women with than in those without PWS [7, 8]. A cross-sectional study using computed tomography (CT) has confirmed that most of the abdominal fat of PWS adults is located subcutaneously [9]. However, cross-sectional studies using dual-energy X-ray absorptiometry (DXA) have reported similar values of trunk fat in children and adults with PWS [2, 3]. As excess visceral fat is associated with CMD [5], the lower VAT of PWS subjects may confer some protection against CMD [7]. Contrarily to MRI and CT, DXA cannot separate VAT from subcutaneous adipose tissue (SAT), but offers a more practical way to measure total and segmental BC. This is probably the reason why DXA has been employed in many studies of total BC in PWS patients [2, 3, 10–14].

Independently of the method used to measure body fat, the difference in percent body fat between PWS and non-PWS subjects should be taken into account when comparing their segmental BC and its functional correlates [14]. However, most of the available studies have matched PWS and non-PWS subjects on the basis of body mass index (BMI), which is not an accurate index of adiposity in PWS subjects [14]. Moreover, the segmental BC studies of PWS subjects that have been performed so far using DXA have focused on the fat content of the trunk, arms, and legs in relation to segmental mass [2, 3]. We believe that a better insight into the BC–CMD relationship can be gained by studying segmental fat not as a percentage of segmental mass, but as a percentage of total fat [15].

The aim of the present study was twofold: (a) to evaluate whether women with PWS and women with essential obesity matched for age and percent body fat have a different fat distribution and (b) to evaluate whether surrogate markers of CMD differ in the two groups.

Materials and methods

Subjects

35 women with PWS and 50 women with essential obesity were consecutively enrolled into the study at the Divisions of Auxology and Metabolic Diseases of the Istituto Auxologico Italiano (Piancavallo, Verbania, Italy). Inclusion criteria for all women were: (a) age $\geq$18 years, (b) BMI $\geq$30 kg/m^2 and (c) weight $\leq$140 kg (as the DXA scanner employed for the study could not accommodate heavier subjects). All measurements were performed within 24 h by the same trained operators as described below. Obese and PWS women were matched using coarsened exact matching as described in detail below [16].

Clinical and anthropometric evaluation

All women underwent a detailed clinical examination (clinical history and physical examination). PWS women underwent a Mini-Mental State Examination (MMSE), as per standard practice at our center. Physical activity was evaluated by interview. BMI was calculated as weight (kg)/height (m)^2. Diastolic and systolic blood pressures were measured in the supine position after 15 min of resting using a mercury sphygmomanometer with an appropriately sized cuff. Blood pressure was calculated as the mean of three repeated measurements.

Dual-energy X-ray absorptiometry

DXA was performed using a GE-Lunar Prodigy scanner (GE Medical Systems, Milwaukee, WI, USA). A head-to-toe scan was performed in the default mode with the subject lying supine on the scanner's bed. DXA scans were analyzed using GE Encore software version 8.80. The scanner was calibrated daily against the calibration block supplied by the manufacturer. The three-compartment DXA model separates body mass (BM) into FM, lean tissue mass (LTM) and bone mineral content (BMC), with the sum of LTM and BMC representing FFM. The regions of interest (ROI) for the identification of body segments (trunk, legs and arms) were automatically determined by the scanner. On the basis of two repeated measurements of ten adults with class 3 essential obesity, we calculated a within-day coefficient of variation (CV) $\leq$2.5 % for total FM, trunk FM, arm FM, and leg FM. Although these CVs are higher than those obtained in normal-weight adults with more recent versions of the GE-Lunar scanner [16], they do nonetheless indicate good reproducibility. Percent FFM and FM were calculated as (FFM/BM) $\times$ 100 and (FM/BM) $\times$ 100, respectively. Percent trunk fat, arm fat, and leg fat were calculated as (FM trunk/FM) $\times$ 100, (FM arm/FM) $\times$ 100, and (FM leg/FM) $\times$ 100, respectively.

Laboratory measurements

Glucose tolerance was evaluated by oral glucose tolerance testing (OGTT) using 1.75 g of glucose per kg of body weight (up to 75 g). Glucose and insulin were measured at 0, 30, 60, 90, and 120 min during OGTT. Glucose was measured using standard laboratory methods and insulin using a chemiluminescent immunoassay (Immulite 2000,

Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin resistance was estimated using the homeostasis model assessment method (HOMA-IR) [18]. The insulin sensitivity index (ISI) was calculated from OGTT and used as marker of insulin sensitivity [19]. The disposition index (DI), i.e., the product of ISI and the ratio between the incremental areas under the curve of insulin and glucose (dAUCr) during OGTT, was used as measure of beta-cell function [15, 20]. Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured using standard laboratory methods. CRP was measured using an immunoturbidimetric assay (CRP RX, Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

Coarsened exact matching (CEM) was used to match PWS and non-PWS women on age and percent body fat [16, 21]. Continuous measurements of PWS and non-PWS women were compared using a generalized linear model (GLM) with PWS status (0 = no; 1 = yes) as predictor, a Gaussian variance, and an identity link. Matching was taken into account using CEM-related weights and robust 95 % confidence intervals in all GLMs. Statistical analysis was performed using Stata 13.1 (Stata Corporation, College Station, TX, USA) together with the user-written cem command [16].

Table 1 Body composition and biochemical measurements of women with PWS and of those with essential obesity

	Women with PWS ($n = 35$)			Women with essential obesity ($n = 50$)		
	Mean	95LL	95UL	Mean	95LL	95UL
Age (years)[a]	30	27	32	29	27	31
Weight (kg)	85.6**	78.8	92.4	108.7	105.7	111.8
Height (m)	1.49**	1.47	1.52	1.62	1.60	1.64
BMI (kg/m^2)	38.6	35.3	41.9	41.4	40.6	42.2
FM (kg)	44.0**	39.6	48.4	54.0	51.7	56.3
FM/BM (%)[a]	53.8	52.0	55.6	53.3	50.8	55.7
LTM (kg)	35.1**	32.8	37.4	45.4	42.3	48.4
LTM/BM (%)	44.3	42.6	46.0	44.8	42.4	47.1
FM trunk (kg)	19.7*	18.0	21.3	26.9	25.6	28.2
FM trunk/FM (%)	45.8**	43.6	48.0	50.0	48.3	51.6
FM arm (kg)	6.9	5.6	8.2	7.8	7.0	8.6
FM arm/FM (%)	14.8	13.1	16.6	14.5	13.1	15.9
FM leg (kg)	17.4	15.4	19.5	19.3	18.0	20.6
FM leg/FM (%)	39.3**	37.6	41.1	35.6	34.1	37.0
Glucose (mg/dl)	84	80	88	82	80	85
Glucose at 120 min (mg/dl)	125	112	138	123	115	131
HOMA-IR	1.8	1.2	2.4	1.5	1.1	1.9
dAUCr	0.9	0.6	1.1	1.1	0.8	1.4
ISI	8.5	6.2	10.7	7.4	6.0	8.8
DI	6.8	4.2	9.4	7.1	5.4	8.7
Cholesterol (mg/dl)	187	177	197	182	165	199
HDL (mg/dl)	57**	52	61	46	44	49
LDL (mg/dl)	115	106	124	117	103	132
Triglycerides (mg/dl)	91	76	105	110	91	129
CRP (mg/dl)	1.1	0.8	1.5	0.8	0.6	1.1
Systolic blood pressure (mm Hg)	120	116	124	124	120	128
Diastolic blood pressure (mm Hg)	76	73	78	80	77	82

PWS Prader–Willi syndrome, *95LL* 95 % lower confidence limit of the mean, *95UL* 95 % upper confidence limit of the mean, *BMI* body mass index, *FM* fat mass, *BM* body mass, *LTM* lean tissue mass, *HOMA-IR* homeostasis model assessment-insulin resistance, *dAUCR* ratio between the incremental areas under the curve of insulin and glucose, *ISI* insulin sensitivity index, *DI* disposition index, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *CRP* C-reactive protein

* $p < 0.01$ and ** $p < 0.001$ vs. women with essential obesity

[a] Variables on which coarsened exact matching was performed (see text for details)

Results

The measurements of the women with PWS and those of women with essential obesity are reported in Table 1.

All PWS women showed the typical clinical phenotype [1]. 24 PWS women had interstitial deletion of the proximal long arm of chromosome 15; 10 had uniparental maternal disomy for chromosome 15; 1 had a positive methylation test, but the underlying genetic defect was not identified [1]. All PWS women had an MMSE score >24 and all women were engaged in ≤2 h per week of structured physical activity.

1 obese woman and 4 PWS women were being treated with oral hypoglycemic agents; 1 PWS woman with insulin; 1 PWS woman with a GLP-1 agonist; 3 obese and 4 PWS women with levothyroxine; 18 obese and 7 PWS women with antihypertensive drugs; 4 obese and 2 PWS women with hypocholesterolemic drugs; and 7 obese and 12 PWS women with neuroleptics. Nineteen PWS women were undergoing sex replacement therapy and 5 were being treated with GH from at least 1 year.

As a result of matching, PWS and obese women had a similar percent FM. However, PWS women had a lower FM than obese women because of their lower body weight. Trunk FM was lower in PWS than in obese women on both absolute [−7.3 (95 % CI −9.4 to −5.2) kg] and relative [−4.1 (−6.9 to −1.4) % of FM] grounds. Arm FM content was similar in the two groups, while leg FM content was higher in PWS women on relative grounds [+3.8 (+1.5 to +6.1) %]. The difference in trunk FM between PWS and obese women persisted [−3.8 (−6.1 to −1.5) % of FM] after age (continuous) and percent FM (continuous) were entered as regressors in the GLMs together with PWS status to control for residual confounding [16]. The percent body fat–height relationship was similar at the total and appendicular levels in obese and PWS women as detected by the testing of a PWS × height (discrete × continuous) interaction ($p > 0.05$ for all interactions, GLMs with family Gaussian, link identity, and CEM-related weights) [13].

PWS and obese women had similar surrogate markers of CMD, with the exception of HDL-cholesterol which was higher in PWS women [+10 (+5 to +15) mg/dl].

Discussion

In the present study, we compared the segmental distribution of body fat of women with PWS with that of women with essential obesity matched for age and percent body fat. We found that absolute and percent trunk fat was lower in PWS women. Surrogate markers of CMD were, however, mostly similar in PWS and obese women.

This study has some limitations that should be kept in mind. Firstly, we studied only adult women. This choice was done to avoid the confounding effects of growth and gender on segmental BC [22, 23], which cannot be properly evaluated with the sample size allowed by the study of a rare disease such as PWS. Further studies are needed to evaluate the effect of age and gender on the segmental (and total) BC of PWS subjects. Secondly, we used DXA to measure segmental BC. As DXA cannot separate VAT from SAT, we cannot speculate on the relative contribution of these compartments to CMD markers [7]. However, we were able to confirm that trunk fat was decreased on both absolute and relative grounds in women with PWS [7]. Thirdly, cohort studies and randomized controlled trials using lumbar CT have shown that treatment with growth hormone (GH) lowers VAT in PWS adults (although it is controversial how long such effect persists after GH suspension) [24–27]. Among the 35 women studied here, 9 had undergone and 5 were undergoing treatment with GH. These numbers are too low to assess the degree to which the difference in percent trunk fat between PWS and obese women can be attributed to previous or ongoing treatment with GH. Larger, most likely multi-center, studies are needed to test this hypothesis.

The findings of the present study agree with those of a study which employed whole-body MRI and found a lower VAT in PWS than in non-PWS women [7]. The findings of such study were confirmed by a more recent lumbar-CT study that showed that abdominal fat was distributed preferentially as SAT in PWS adults [9]. However, contrarily to the whole-body MRI study and the present study, the lumbar-CT study did not evaluate a group of women without PWS [9]. Very interestingly, the whole-body MRI study showed that surrogate markers of CMD were similar in PWS and obese women after the contribution of VAT was taken into account [7]. In the present study, we were able to replicate the findings of the whole-body MRI study on an external population of adult PWS women. We approached this comparison from a different perspective, using CEM to make PWS and obese women comparable for age and percent body fat. Coherently with the findings of the whole-body MRI study [7], we found that PWS and obese women had not only a lower trunk fat, but also similar CMD markers. HDL-cholesterol was however higher in PWS women, possibly contributing to a more favorable cardiovascular risk profile [5]. This finding might be explained by the lower VAT of PWS women as, at least in non-PWS subjects, an inverse relationship is known to exist between VAT and HDL [5].

The fact that PWS and obese women appear to have comparable traditional risk factors for CMD is very interesting, but should not be taken as evidence that PWS and obese subjects have a similar burden of CMD. Non-traditional risk factors

may in fact be responsible for the PWS–CMD association [12, 28, 29]. Establishing the true incidence of CMD in PWS is extremely challenging because of the rarity of the disease [6]. Few cases of coronary heart disease (CHD) have been reported in PWS subjects, but this may be simply explained by their early mortality as it takes more time for CHD to develop [30]. This implies that a thorough evaluation of the contribution of traditional and non-traditional risk factors to the burden of CMD in PWS subjects will require larger and most likely multi-center cohort studies. Such studies will also allow to better disentangle the BC–CMD relationship in PWS.

In conclusion, trunk fat is lower in obese women with PWS than in those with essential obesity. Surrogate markers of CMD are however mostly similar in the two groups.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All the procedures performed in this study were approved by the Ethical Committee of the Istituto Auxologico Italiano (Piancavallo, Verbania, Italy) and were in accordance with the 1964 Helsinki declaration and the Additional Protocol to the European Convention of Human Rights and Medicine, concerning Biomedical Research 2005.

Informed consent Written informed consent was obtained from the PWS patients and their parents or guardians. Written consent was also obtained from the women with essential obesity.

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