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Effects of a 6-month caloric restriction induced-weight loss program in obese postmenopausal women with and without the metabolic syndrome: a MONET study

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Abstract

Objective: To compare the effects of a caloric restriction (CR) on body composition, lipid profile, and glucose homeostasis in obese postmenopausal women with and without metabolic syndrome (MetS).

Methods: Secondary analyses were performed on 73 inactive obese postmenopausal women (age 57.7 ± 4.8 years; body mass index $32.4 \pm 4.6\,\text{kg/m}^2$) who participated in the 6-month CR arm of a study of the Montreal-Ottawa New Emerging Team. The harmonized MetS definition was used to categorize participants with MetS ($n = 20$, 27.39%) and without MetS ($n = 53$, 72.61%). Variables of interest were: body composition (dual-energy X-ray absorptiometry), body fat distribution (computed tomography scan), glucose homeostasis at fasting state and during a euglycemic/hyperinsulinemic clamp, fasting lipids, and resting blood pressure.

Results: By design, the MetS group had a worse cardiometabolic profile, whereas both groups were comparable for age. Fifty-five participants out of 73 displayed no change in MetS status after the intervention. Twelve participants out of 20 (or 60.0%) in the MetS group had no more MetS after weight loss ($P = \text{NS}$), whereas 6 participants out of 53 (or 11.3%) in the other group developed the MetS after the intervention ($P = \text{NS}$). Overall, indices of body composition and body fat distribution improved significantly and similarly in both groups (P between 0.03 and 0.0001). Furthermore, with the exception of triglyceride levels and triglycerides/high-density lipoprotein cholesterol ratio, which decrease significantly more in the MetS group ($P \leq 0.05$), no difference was observed between groups for the other variables of the cardiometabolic profile.

Conclusions: Despite no overall significant effects on MetS, heteregeneous results were obtained in response to weight loss in the present study, with some improving the MetS, whereas other displaying deteriorations. Further studies are needed to identify factors and phenotypes associated with positive and negative cardiometabolic responses to CR intervention.

Key Words: Caloric restriction – Menopause – Metabolic syndrome – Obesity – Physical inactivity – Weight loss.

To be considered as having metabolic syndrome (MetS), individuals must have at least three out of five of the following risk factors: high blood pressure, hyperglycemia, low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, and abdominal obesity.[1,2] A recent study by Aguilar et al reported an increased prevalence of MetS in the United States. From 2003 to 2012, data showed that the average prevalence of MetS was 33%, which was significantly higher in women compared with men (35.6% vs 30.3%).[3] The estimated prevalence of MetS in Canadian adults was 19.1% in 2009.[4] The prevalence of MetS increases with aging,[4] particularly among women during the transition from premenopause to postmenopause.[5] This is generally explained by ovarian failure or the metabolic consequences of central fat accumulation with estrogen deficiency.[5]

The MetS is considered a major public health issue since it has been associated with an increased risk for type 2 diabetes,[6] cardiovascular diseases, and mortality.[7] In this regard, a panel of experts has recently proposed that ''the ideal patient care model for MetS must accurately identify those at risk before MetS develops, and we must recognize subtypes and stages of MetS to more effectively direct prevention and therapies''.[2]

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Thus, several strategies have been proposed to prevent or treat the MetS.[2,8] Among them, caloric restriction (CR) is known to be effective in improving every component of MetS in men and women aged between 35 and 82 years[9]; and in reducing the number of components of MetS in obese older women.[10-13] However, some studies have shown negative responses after weight loss.[14-16] Karelis et al suggested that metabolically healthy but obese women may respond differently to a CR diet (between −500 and −800 kcal/d) compared with at-risk individuals who achieve a similar weight loss (6%-7%). Actually, they observed that insulin sensitivity significantly improved in at-risk participants, but significantly deteriorated in metabolically healthy but obese individuals in response to the 6-month diet.[15] Myette-Côté et al[16] also reported that there is an important interindividual variability regarding changes in glucose disposal after a 6-month CR-induced weight loss program in obese postmenopausal women. To our knowledge, only a few studies have investigated the impact of CR on the cardiometabolic profile in obese individuals with or without MetS.[14,17] Overall, these studies showed that 12 to 16 weeks of CR (between −500 and −800 kcal/d) were associated with improvements in body weight, body composition, and cardiometabolic profile, with greater effects in individuals displaying MetS.[14,17,18] However, it is important to note that these studies were done in young obese men and women,[17] or participants and African-American women aged between 30 and 50 years, and displaying a body mass index (BMI) above 25 kg/m^2.[14]

The present study was then conducted to compare the effects of a 6-month CR on weight, body composition, body fat distribution, lipid profile, and glucose homeostasis in inactive obese postmenopausal women with or without MetS, a subpopulation greatly affected by obesity, type 2 diabetes, and cardiovascular diseases.[19,20]

METHODS

Secondary analyses

For the present study, secondary analyses were done using data of overweight-obese postmenopausal women who participated in the CR arm of the MONET (‘‘Montreal-Ottawa New Emerging Team’’) intervention study. Details and objectives of the main study have been published elsewhere.[21] Women in the CR combined with resistance training arm of the original study were excluded to avoid the effect of exercise on the variables of interest.

Participants

Seventy-three postmenopausal women aged between 49 and 70 years (58.0 ± 4.9 years) were considered for data analyses. The following criteria were used for this study: BMI between 27 and 40 kg/m^2; cessation of menstruation for more than 1 year and follicle stimulating hormone levels at least 30 IU/L; less than 2 h/wk of structured exercise; nonsmoker; low to moderate alcohol consumption (less than two drinks a day); free of known inflammatory disease; and no use of hormone therapy. Participants with history or evidence of the following problems were excluded: coronary heart disease, peripheral vascular disease, or stroke; known renal or liver disease; diabetes; plasma cholesterol greater than 8.0 mmol/L; resting systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg; history of alcohol or drug abuse; asthma-requiring therapy; previous history of inflammatory disease or cancer; orthopedic limitations; body weight fluctuation of ±2.0 kg in the past 6 months; untreated thyroid or pituitary disease; and medications that could affect cardiovascular function and/or metabolism. The study was approved by the ‘‘Université de Montréal’’ Ethics Committee. After reading and signing the consent form, each participant was submitted to a series of tests and to the CR intervention.

Weight stabilization period

To reduce the confounding effect of acute weight loss on cardiometabolic variables, participants were submitted to a 4-week weight stabilization period (within 2.0 kg of body weight) before testing.[22,23] If the participants were unable to maintain their body weight, the stabilization period was prolonged until their weight was stable for 4 consecutive weeks.

Anthropometry

Participants’ height was measured using a standard stadiometer (Perspective Enterprises, Portage, MI). Body weight was obtained to the nearest 0.1 kg (Balance Industrielle Montreal, Montreal, Quebec, Canada). BMI was then calculated (BMI = weight [kg]/height [m^2]). Waist circumference was measured to the nearest 0.1 cm at the highest point of the iliac crest.

Fat mass (FM) and lean body mass (LBM) were measured using dual-energy X-ray absorptiometry (DEXA: software version 6.10.019, General Electric Lunar Prodigy, Madison, WI). Calibration was executed daily with a standard phantom before each test, and the intraclass coefficient correlation for test-retest for FM and LBM was 0.99 (n = 18).[24] FM index (FMI = FM [kg]/height [m^2]) and the LBM index (LBMI = LBM [kg]/height [m^2]) were also calculated without taking into account bone mass. The using of FMI and LBMI is appropriate to compare participants with different sizes and take into account the effect of aging on FM and LBM.[24-29]

Computed tomography

Abdominal visceral fat (VF) and the subcutaneous fat (SCF) area were measured using a GE Light Speed 16 computed tomography (CT) scanner (General Electric Medical Systems, Milwaukee, WI), as previously described.[16] Participants were examined in the supine position with both arms stretched above their head. Using a scout image of the body, the scan was positioned and established at the L4-L5 vertebral level.[30] The VF was quantified by delineating the intra-abdominal cavity at the internal most aspect of the abdominal and oblique muscle walls surrounding the cavity, and the posterior aspect of the vertebral body. The SCF area was quantified by highlighting fat located between the skin and the external-most aspect of the abdominal muscle wall. Deep SCF (DSCF) and superficial SCF (SSCF) areas were measured by delineating the subcutaneous fascia within the SCF and by computing areas of the layers of fat on each side of the fascia.[31] The cross-sectional areas of fat were highlighted and computed using an attenuation range of −190 to −30 Hounsfield Units (HU). With use of an attenuation range of 0 to 100 HU, the muscle attenuation quantified the surface area of the skeletal muscle. Test-retest measures of the different body fat distribution indexes on 10 CT scans yielded a mean absolute difference of ±1%.[30]

CR intervention

The main hypothesis of this study was to reduce body weight by 10% after a 6-month CR program. CR level was determined by subtracting 500 to 800 kcal/d from baseline resting metabolic rate, multiplied by a sedentary physical activity factor of 1.4.[32] For all participants, the diet was standardized accordingly to the recommendations of the American Heart Association[33] (55%, 30%, and 15% of energy intake from carbohydrates, total fat, and proteins). CR weight loss program has been previously described.[21]

Oral glucose tolerance test

To identify undiagnosed diabetic participants at baseline, which was an exclusion criterion, a 2-hour 75 g oral glucose tolerance test (OGTT) was performed in the morning after a 12-hour fast according to the guidelines of the American Diabetes Association.[34] Plasma glucose (COBAS INTEGRA 400+ [Roche Diagnostic, Montreal, Canada]) and insulin levels (using a human insulin-specific radioimmunoassay; RIA kit; Linco Research, St Charles, MO) were determined using blood samples collected at 0, 30, 60, 90, and 120 minutes. Details for procedures have been previously described.[21]

Insulin sensitivity

Participants underwent a 3-hour euglycemic/hyperinsulinemic clamp. After the standard procedure,[35] participants were required to come to the laboratory after an overnight fast of 12 hours. Testing began at 07:30 AM. An infusion of 20% dextrose and insulin was cannulated in an antecubital vein, whereas the other arm was cannulated for the sampling of blood. Over the span of 30 minutes, three basal samples of plasma glucose and insulin were taken. Subsequently, participants were given a primed-constant insulin infusion for 180 minutes, at the rate of 75 mU/m^2/min. Plasma glucose was measured every 10 minutes with a glucose analyzer (Beckman Instruments, Fullerton, CA) and maintained at fasting level using a variable infusion rate of 20% dextrose. During the last 30 minutes of the euglycemic/hyperinsulinemic clamp, blood was drawn every 10 minutes, to determine plasma glucose and insulin levels. The mean rate of glucose disposal (exogenous dextrose infusion), during the last 30 minutes of the clamp, was considered as the insulin sensitivity index, or ''M'' value.

Lipids profile

Total cholesterol (C), HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels were measured after 12 hours overnight fast. The COBAS INTEGRA 400 analyzer (Roche Diagnostics, Montreal, Canada) was used to analyze total cholesterol, HDL-C, and triglyceride levels, which were used in the Friedewald formula[36] to calculate LDL-C levels.

Resting blood pressure

After 10 minutes of rest, blood pressure was measured in a sitting position on the left arm (Dinamap, Welch Allyn, San Diego, CA). For each participant, we used an appropriate cuff size based on arm circumference.[37]

Characterization of participants with and without MetS

Participants were characterized as having the MetS based on the harmonized definition.[1] MetS required at least three of the following criteria: elevated waist circumference (>88 cm in women), hypertriglyceridemia (≥1.69 mmol/L), low HDL-C (<1.30 mmol/L in women), high blood pressure (≥130/85 mm Hg or pharmacological treatment for hypertension), and elevated fasting plasma glucose levels (≥5.6 mmol/L).

Statistical analyses

Data are presented as means ± SD. Unpaired *t* tests were performed to compare groups' means, whereas analysis of variance (ANOVA) for repeated measures were used to examine changes after the intervention within each group and between groups (time × group interaction). When a significant time × group interaction was found, a paired *t* test was performed to detect the time effect within each group. The McNemar's chi-square test was used for MetS paired change. All analyses were performed using SPSS 17.0 program for windows (SPSS, Chicago, IL), with statistical significance set at P less than 0.05.

RESULTS

Among our cohort (N = 73), 20 participants (27.4%) displayed MetS, whereas 53 (72.6%) did not have the condition at baseline (Table 1). The prevalence of the components of MetS was: none (4.1%), one (37%), two (31.5%), three (19.2%), and four (8.2%). Both groups were comparable for age. As anticipated, the MetS group displayed overall significantly worse values for body composition indices and the cardiometabolic profile compared with the group without MetS. Results showed that both groups significantly improve the majority of body composition and body fat distribution indices after the 6-month CR intervention (P between 0.02 and 0.0001), although no differences were observed between groups.

Measures of the cardiometabolic profile are presented in Table 2. Fasting glucose, total cholesterol, LDL-C, and resting systolic and diastolic blood pressure were similar between groups at baseline. However, participants with MetS had

TABLE 1. *Body composition of women with and without metabolic syndrome (MetS)*

	With MetS (n = 20)		Without MetS (n = 53)			
	Baseline	Post	Baseline	Post	Time effect, *P*	Time × groups effect, *P*
Age, y	56.9 ± 4.8	56.9 ± 4.8	58.7 ± 4.8	58.7 ± 4.8		
Body weight, kg	91.3 ± 14.3	84.4 ± 14.2[a]	81.7 ± 12.2[b]	76.6 ± 12.3	0.0001	NS
BMI, kg/m^2	34.5 ± 4.7	31.8 ± 4.4[a]	31.7 ± 4.3[b]	29.7 ± 4.2	0.0001	NS
Waist circumference, cm	101.4 ± 8.6	96.1 ± 8.5[a]	95.1 ± 8.5[b]	90.0 ± 9.1	0.0001	NS
DXA measures						
%FM	47.0 ± 4.7	43.9 ± 6.3	44.8 ± 4.5	42.3 ± 4.1	0.0001	NS
FMI, kg/m^2	16.3 ± 3.6	14.2 ± 3.3	14.4 ± 3.1	12.6 ± 3.2	0.0001	NS
Total FM, kg	43.1 ± 9.3	37.6 ± 10.1[a]	37.2 ± 8.3[b]	32.6 ± 8.3	0.0001	NS
Trunk FM, kg	21.3 ± 4.6	18.2 ± 5.6[a]	17.6 ± 3.8[b]	15.1 ± 4.3	0.0001	NS
Appendicular FM, kg	21.0 ± 4.8	18.5 ± 5.4	18.5 ± 4.5	16.4 ± 3.2	0.0001	NS
LBMI, kg/m^2	17.1 ± 1.8	16.6 ± 1.1[a]	16.3 ± 2.1[b]	16.1 ± 1.2	0.001	NS
Total LBM, kg	45.6 ± 7.3	44.1 ± 5.6[a]	42.0 ± 6.1[b]	41.5 ± 5.2	0.001	NS
Trunk LBM, kg	21.9 ± 4.2	21.1 ± 3.5[a]	19.2 ± 3.4[b]	19.0 ± 3.2	0.01	NS
Appendicular LBM, kg	20.2 ± 3.3	19.5 ± 2.3	19.4 ± 2.5	19.2 ± 2.1	0.01	NS
CT scan (L4-L5 level)						
Visceral fat (L4-L5, cm^2)	199 ± 49	169 ± 53	177 ± 55[b]	155 ± 57	0.000	NS
SCF (L4-L5, cm^2)	514 ± 114	451 ± 126	457 ± 112	409 ± 114	0.000	NS
SSCF (L4-L5, cm^2)	249 ± 53	218 ± 71	227 ± 68	194 ± 65	0.000	NS
DSCF (L4-L5, cm^2)	264 ± 74	233 ± 62	234 ± 61	214 ± 60	0.000	NS
Muscle attenuation (HU)	48.4 ± 4.6	47.9 ± 5.1	49.2 ± 3.0	49.3 ± 3.0	0.02	NS

Data are presented as means ± standard deviation.

Unpaired *t* tests were performed to compare groups' means, whereas ANOVA for repeated measures were used to examine changes after the caloric restriction (CR) intervention within each group and between groups (time × group).

%FM, per cent fat mass; ANOVA, analysis of variance; BMI, body mass index; CT, computed tomography; DSCF, deep subcutaneous fat; DXA, dual-energy X-ray absorptiometry; FM, fat mass; FMI, fat mass index; HU, hounsfield units; LBM, lean body mass; LBMI, lean body mass index; NS, not significant; SCF, subcutaneous fat; SSCF, superficial subcutaneous fat.

[a] Significant difference between groups after the CR intervention ($P < 0.05$).

[b] Significant difference between groups at baseline ($P < 0.05$).

worse values for fasting insulin, glucose disposal, triglycerides, HDL-C, total-C/HDL-C ratio, and triglycerides/HDL-C ratio. With the exception of triglycerides and triglycerides/HDL-C ratio, which were greatly reduced in participants with MetS ($P = 0.02$ and $P = 0.03$, respectively), both groups showed similar responses for the other cardiometabolic parameters after the intervention.

Finally, 55 patients displayed no change in MetS status after the intervention. Twelve out of 20 (60%) participants with MetS at baseline did not have the condition after the intervention ($P =$ NS; Table 3), with a mean number of MetS factors that decreased from 3.10 ± 0.32 to 2.17 ± 0.98 ($P \leq 0.001$; Fig. 1). For the participants without MetS at baseline, 6 out of 53 (11.3%) developed the condition after

TABLE 2. *Metabolic profile of women with and without metabolic syndrome (MetS)*

	With MetS (n = 20)		Without MetS (n = 53)			
	Baseline	Post	Baseline	Post	Time effect, *P*	Time × groups effect, *P*
Glucose homeostasis						
Fasting insulin, μU/mL	19.4 ± 8.8	15.8 ± 7.6	14.8 ± 4.7[a]	13.2 ± 5.1	0.0001	NS
Fasting glucose, mmol/L	5.37 ± 0.61	5.21 ± 0.59	5.08 ± 0.48	5.08 ± 0.53	NS	0.08
Glucose disposal, mg/kg/min	5.01 ± 1.20	5.95 ± 1.97[b]	6.33 ± 1.42[a]	6.80 ± 1.62	0.003	NS
Relative glucose disposal, mg/kg LBM/min	9.42 ± 2.35	10.45 ± 3.03	11.53 ± 2.43[a]	11.75 ± 2.54	NS	NS
Lipid profile						
Triglycerides, mmol/L	2.34 ± 0.72	1.95 ± 0.96[c]	1.46 ± 0.58[a]	1.38 ± 0.58	0.0001	0.02
Total cholesterol, mmol/L	5.14 ± 0.88	5.02 ± 0.91[b]	5.59 ± 0.95	5.53 ± 0.88	NS	NS
LDL-C, mmol/L	2.88 ± 0.79	2.97 ± 0.73[b]	3.38 ± 0.80	3.40 ± 0.78	NS	NS
HDL-C, mmol/L	1.18 ± 0.12	1.15 ± 0.15[b]	1.53 ± 0.31[a]	1.49 ± 0.27	NS	NS
Total cholesterol/HDL-C ratio	4.37 ± 0.81	4.42 ± 1.02[b]	3.72 ± 0.79[a]	3.82 ± 0.91	NS	NS
Triglyceride/HDL-C ratio	2.00 ± 0.63	1.76 ± 1.01[b,c]	1.01 ± 0.46[a]	0.99 ± 0.57	0.001	0.03
Resting blood pressure						
Systolic, mm Hg	122.4 ± 14.9	118.9 ± 17.6	121.8 ± 15.3	122.4 ± 16.9	NS	NS
Diastolic, mm Hg	77.5 ± 7.6	75.5 ± 6.4	75.7 ± 7.8	74.6 ± 8.3	0.08	NS

Data are presented as means ± SD.

Unpaired *t* tests were performed to compare groups' means, whereas ANOVA for repeated measures were used to examine changes after the caloric restriction (CR) intervention within each group and between groups (time × group interaction). When a significant time × group interaction was found, a paired *t* test was performed to quantify the time effect within each group.

ANOVA, analysis of variance; HDL-C, high-density lipoprotein cholesterol; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

[a] Significant difference between groups at baseline ($P < 0.05$)

[b] Significant difference between groups after CR intervention ($P < 0.05$).

[c] Significant change after the intervention ($P < 0.05$).

TABLE 3. *Paired change in MetS status after intervention*

MetS satus at baseline and MetS status after intervention			
	MetS status after-intervention		
MetS status at baseline	(−) MetS	(+) MetS	Total
(−) MetS	47	6 (11.3%)	53
(+) MetS	12 (60%)	8	20

McNemar's test for paired change in MetS status ($P = 0.238$).
MetS, metabolic syndrome; (−) MetS, without metabolic syndrome; (+) MetS, with metabolic syndrome.

the intervention ($P =$ NS; Table 3), with no significant change in the overall mean number of MetS factors (1.36 ± 0.76 to 1.30 ± 0.95, $P =$ NS; Fig. 1).

DISCUSSION

To our knowledge, only a few studies have compared the effect of weight loss on lipid profile and glucose homeostasis indices in individuals with or without MetS.[14,17,18] Except for plasma triglyceride levels and the triglyceride/HDL-C ratio, which decrease significantly more in participants with MetS, our results showed that both groups displayed similar improvements in lipid profile and glucose homeostasis indices. These results are not in agreement with those reported from other studies. For example, Case et al[17] showed significant improvements for total cholesterol, triglycerides, and fasting glucose levels in men and women (BMI $= 40.7 \pm 9.7\,\text{kg/m}^2$) aged between 35 and 55 years with MetS compared with those without MetS after a 16-week very low CR intervention. Also, Hong et al showed greater improvements for fasting glucose, total cholesterol, triglyceride, and LDL-C levels after a 12-week very low CR (energy intake between 500 and 800 kcal/d) combined with exercise and behavioral interventions in participants and African-American women ($40.8 \pm 10.1\,\text{kg/m}^2$) aged between 30 and 50 years with MetS or without MetS. Interestingly, these two latter studies also reported significant and greater improvements in body composition in participants with MetS compared with those without MetS, which was not the case in the present study.

Results of the present study are in agreement with those of Hong et al who reported that 38.3% (23/60) of their participants had their MetS resolved ($P = 0.024$), whereas 10.8% of them without MetS (10/92) presented with the condition after the CR intervention ($P = 0.024$). In comparison, 60% (12/20; $P =$ NS) of participants with MetS at baseline did not have the condition after the CR intervention. Overall, participants in this subgroup improved their triglyceride levels significantly, with a correlation of $r = 0.68$ ($P = 0.04$, data not shown) between changes in VF and changes in triglycerides. Interestingly, no association was observed between changes in triglyceride levels and changes in VF in participants who still had MetS after the intervention (data not shown). Also, no significant change for the other components of MetS was observed. Additionally, in the group of participants without MetS at baseline, 11.3% (6/53; $P =$ NS) of them presented with the condition after the CR intervention. We also performed power analysis to see if differences in P values between our study and the one by Hong et al were simply a question of number of participants. As a matter of fact, data indicated that 160 to 170 participants (with the same ratio per group) would have allowed us to detect significant changes in MetS status. Finally, and despite similar results, the study by Hong et al and ours present different characteristics related to study design and populations studied, as described in the previous paragraph, which reinforces the importance of our results.

Despite the importance of their results, Hong et al did not provide explanations or hypotheses to explain their observations. For that reason, exploratory analyses were performed to identify factors that could explain the variation in the responses to CR intervention for the cardiometabolic profile in the present study. For the group with MetS at baseline, we compared the 12 participants who did not have MetS after the CR intervention with those who still had MetS. Despite small differences, we observed that the subgroup without MetS after the CR intervention had significantly lower fat-free mass and VF at baseline (results not shown). Also, both groups decreased the majority of their anthropometrics indices significantly, with no significant difference between groups, after the CR intervention. Finally, no significant differences were found between both subgroups for changes in total energy intake, total daily energy expenditure, and physical activity energy expenditure (results not shown). Considering these observations, and the significant weight loss and VF reduction in both subgroups, it is difficult to explain why 12 out of 20 participants resolved their MetS, whereas others did not. Our observations suggest that other factors are involved. In this regard, data shown that the effect of dietary modifications on metabolic profile varies considerably between individuals.[35,38-41] In 1986, Katan et al[42] reported that some individuals categorized as ''lower responders'' appeared to be relatively insensitive to a dietary intervention with high cholesterol levels, whereas individuals categorized as ''higher responders'' display greater sensitivity to the intervention. Researchers proposed that ethnicity, hormonal status, obesity,

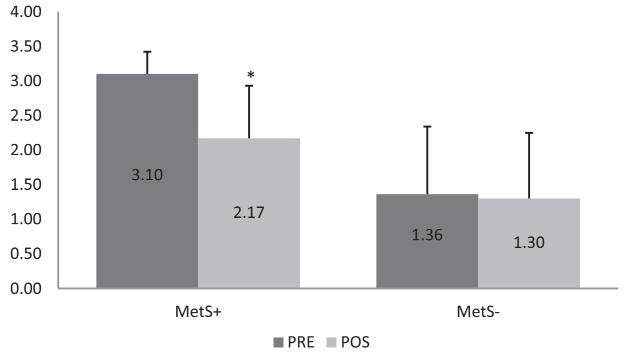

FIG. 1. Effect of caloric restriction intervention on the number of components of the metabolic syndrome (MetS) in participants with and without MetS. MetS+, with metabolic syndrome; MetS−, without metabolic syndrome. (*) $P < 0.001$ compared with baseline.

lipoprotein disorders, and genetic predisposition may partly explain the interindividual variation in response to diet interventions.[43-45] These observations were confirmed in more recent studies.[46-48] In their study, Herron et al investigated the effect of a rich dietary cholesterol supplementation (640 mg additional dietary cholesterol per day) in premenopausal participants and Hispanic women aged between 18 and 49 years. They reported that lower responders (<0.05 mmol/L increases in total plasma cholesterol for each additional 100 mg of dietary cholesterol consumed per day) had no impact on LDL-C or HDL-C levels during the intervention compared with higher responders (≥ 0.06 mmol/L increase in total blood cholesterol for each additional 100 mg of dietary cholesterol consumed per day), which increased both lipoproteins. Similar results were reported in men aged between 18 and 57 years.[48] Taken together, we may hypothesize that responders and nonresponders to CR intervention might be genetically predisposed to respond differently.

Another interesting finding of the present study is the metabolic deteriorations observed after the CR intervention in six participants in the group without MetS at baseline, considering the large amount of evidence concerning the beneficial effects of weight loss on metabolic profile.[49] It is important to note that both subgroups (without and with MetS development) had similar changes in body composition after the intervention. However, explanatory analyses revealed that at baseline, each participant in the group who developed MetS had cardiometabolic values near the proposed thresholds for each component of MetS (data not shown). On average, they also displayed negative responses for the majority of components of MetS after the CR intervention, but changes were not statistically significant ($P > 0.05$). In addition, we noted a significant reduction for total daily energy expenditure (-316 ± 296 kcal/d; $P = 0.04$) compared with those who were still free of MetS (-75 ± 61 kcal/d; $P = 0.15$) (data not shown). This reduction in total daily energy expenditure after CR-induced weight loss program is an untoward metabolic response that has been reported by other researchers.[50,51] All these observations could partly explain the development of MetS in this subgroup of participants after the CR intervention.

The negative cardiometabolic response observed after CR intervention in some individuals is clinically important as a hypocaloric diet is part of a standard of care in obese patients with MetS.[52,53] In this regard, other studies showed that the metabolic response after weight loss varies considerably between individuals. For example, Schaefer et al[54] reported variations between +13% and −39% for LDL-C in men, and between +13% and −39% in women following the ‘‘National Cholesterol Education Program’’ (NCEP) step 2 diets. In a meta-analysis published in 2005, examining the effects of very-low-carbohydrate diets on blood lipoproteins and cardiovascular disease risk factors, Volek et al[53] concluded that the response varies considerably between individuals; and CR was associated with increases in total cholesterol and LDL-C levels in some individuals. Similar results were reported in a meta-analysis of randomized controlled trials published by Nordmann et al[55] in 2006 after low-carbohydrate intervention. Genotype and environment could partly explain individual variations in response to dietary interventions.[56-58] Studies conducted in monozygotic and dizygotic twins have reported genetic-environment interaction effects regarding body composition,[59,60] whereas others showed that genetic components, independent of environmental factors, could be involved in the variability of cardiometabolic responses after weight loss interventions.[61-63]

It has been reported that persistent organic pollutants, preferentially stored in the fat compartment and released into the circulation during weight loss, may contribute to these negative responses and cardiometabolic deterioration after weight loss.[64] In this regard, Dirinck et al showed that, in obese women who lost body weight after 6 months, persistent organic pollutants in circulation increased by approximately 50%. The same study suggested that increases in persistent organic pollutant levels were more pronounced in participants losing more VF.[65] Also, the results of the studies suggest that high circulating levels of persistent organic pollutants are associated with higher prevalence of metabolically abnormal obese phenotype[66] and MetS,[67] and also with insulin resistance,[68] type 2 diabetes,[69,70] and cardiovascular diseases.[71] However, the association between persistent organic pollutants released from the adipose tissue and cardiometabolic disturbances remains unresolved.

Several limitations of our study should be noted. First, our cohort is composed of overweight and obese postmenopausal women, which limits the generalization of our results. Second, it is likely that the ‘‘relatively normal’’ cardiometabolic profile of participants at baseline may have limited our ability to observe improvements for some variables of interest. For example, Nicklas et al[72] reported that postmenopausal women with the most abnormal baseline cardiometabolic profile showed the greatest improvement after weight loss. Third, compared with Case et al, the modest decreases in body weight and visceral adipose tissue in both groups may also have limited our ability to detect significant cardiometabolic improvements. Fourth, our small sample size has limited our ability to detect significant changes in MetS status. However, as stated above, results from power analyses on our data indicated that 160 to 170 participants (with the same ratio per group) would have allowed us to detect significant changes in MetS status. Despite these limitations, the present study is strengthened by the well-characterized cohort using the best available techniques for the measurement of body composition, body fat distribution, and glucose disposal. Fifth, we used a 1-month weight stabilization period before testing to minimize the impact of body weight fluctuations on variables of interest.[22] Finally, despite the fact that the study population was composed only of overweight and obese postmenopausal women, we had a broad range of values for age, body composition, and body fat distribution. All in all, we believe that the methodology used strengthens our results.

CONCLUSIONS

In conclusion, participants with and without MetS experienced similar improvements for body composition, body fat distribution indices, and cardiometabolic profile after the CR restriction intervention. Despite no overall significant effects on MetS status in both groups, heterogeneous results were obtained in response to improvements in body composition in overweight/obese postmenopausal women, with some improving MetS, whereas others displaying deteriorations. These results seem to suggest that CR intervention may improve cardiometabolic profile in the majority of overweight or obese individuals, but some could see their metabolic status deteriorate such as developing MetS, especially if they reduce their total daily energy expenditure. Thus, we may need to reconsider the general concept that body weight loss translates to a better cardiometabolic profile in all individuals and that everyone can benefit equally from dietary intervention. More studies are, however, needed to better understand interindividual response to weight loss.

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