Effect of a low-calorie meal replacement diet and a usual low-calorie diet on resting metabolic rate and body composition in overweight and obese women

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Research Article

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Abstract

**Background:** Using meal replacement plans is one of the weight loss methods. A study on the effectiveness and efficiency of these methods seems necessary. In this study, we intend to determine and compare the effectiveness of Meal Replacement Therapy (MRT) and the Usual Low-Calorie diet (ULC) on Resting Metabolic Rate (RMR) and body composition in overweight and obese women.

**Methods:** This quasi-experimental clinical trial consisted of two groups of women aged 18 to 50 years with a BMI of 25 to 40. Participants were allowed to choose between MRT and ULC diets based on their preferences. Both groups received equal daily calories (1000-1200 kcal in the first four weeks and 1200-1400 kcal in the second four weeks), which BMI determined. Primary outcomes were BMI, weight, body composition, and RMR. Secondary outcomes were Fasting Plasma Glucose (FPG), insulin, lipid profile, and Physical symptoms.

**Results:** There were 35 participants in each group. There were no significant differences in the baseline anthropometric and metabolic measurements between the two groups (p>0.05). The only significant difference between the two groups was weight and BMI, lower in the MRT group (28.48kg/m² vs. 30.75kg/m²). RMR did not change in the MRT group but decreased significantly in the ULC group. Metabolic profile improved in both groups, but no significant difference was observed between the two groups (p>0.05).

**Conclusion:** The results of this study showed that meal replacement therapy is a more effective strategy for losing weight. Nevertheless, it is necessary to do further studies on meal replacements.

**Trial registration**

The study was approved on January 19, 2020, in the Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1398.744) as well as in the Iranian Registry of Clinical Trials (IRCT code: IRCT20200611047731N1. Registration date: 17-07-2020)

1 Background

Obesity is a complex and multifactorial condition that affects almost all body organs and predisposes them to many subsequent diseases (1). It is determined that one-third of the world's population is currently obese or overweight. According to the WHO, more than 1.9 billion adults, nearly 39% of the world's population, were overweight, and more than 650 million were obese in 2015 (2). Obesity is more common in women than men (3). Kelly et al. estimated that if the current trends continue that 57.8% of the world population in the year 2030 will be overweight or obese (4). A 5–10% weight reduction has been associated with a beneficial effect on health, but maintaining a weight loss is challenging (5). Poor adherence to diets is one of the main challenges of obesity clinics (6). Also, weight loss and negative energy balance cause a reduction in all the energy expenditure parts, i.e., resting energy expenditure, and
it can affect weight loss (7). Also, many factors (biological, behavioral, and environmental) affect weight loss resistance. Treatment of obesity needs continuous care and support (8).

Meal replacements are one of the weight loss methods. These replacements are ready-to-eat meals with specific amounts of calories and macronutrient distribution and are used as a complete meal. Meal replacements have advantages such as a more accurate calorie estimate, ease of use, and widespread access. In addition, meal replacements are rich in nutrients that prevent deficiencies in vitamins and minerals following a restricted diet (9)(10)(11). Given the emergence of this dietary approach, we aimed to determine and compare the effectiveness of Meal Replacement Therapy (MRT) and the usual low calorie (ULC) diet on resting metabolic rate and body composition in overweight and obese women.

2 Methods

2.1 Study design

This quasi-experimental clinical trial was conducted in 2021 in Imam Reza Teaching Hospital, affiliated with Mashhad University of Medical Sciences. All experiments were performed based on the ethical standards of the Mashhad University of Medical Sciences and the declaration of Helsinki. Volunteers were invited to study through an announcement at the nutrition clinic. The study design, advantages and disadvantages, and the diets were explained to the volunteers, and they obtained written consent. Participants were allowed to choose between the MRT and ULC diets based on their preferences to increase dietary adherence, so no randomization was performed. Thirty-five volunteers enrolled in each group. The study was approved on January 19, 2020, in the Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1398.744) as well as in the Iranian Registry of Clinical Trials (IRCT code: IRCT20200611047731N1 Registration date: 17-07-2020)

2.2 Study population

The study population was overweight and obese women who tended to lose weight and participate. Inclusion criteria included female gender, age 18 to 50 years, and BMI between 25 to 40(kg /m²). Exclusion criteria included pregnancy or lactation, drug and alcohol addiction, weight loss of more than 3kg in the last three months, diabetes type 1 and 2, hypertension, ischemic heart disease, thyroid disorders, and taking drugs with metabolic side effects.

Sample size was calculated based on the difference in means for RMR change reported by a previous study (12)using the following Eq. (13)considering type 1 and 2 errors of 5% and 20%, respectively.
The sample size was 32 subjects in each group. The sample size was increased to 35 subjects in each group considering dropout.

2.3 Intervention

2.3.1 Diets

The intervention duration was 8 weeks, consisting of two 4-week periods. The energy intake was calculated based on subjects' BMI (Table 1). In order to fit the diets into required energy intake of the subjects, subjects were grouped based on BMI. The energy intake in the second period (week 5 to 8) was determined by adding 200 kcals to the prescribed calories in the first period (Table 1). The energy intake and diet composition (50% of energy intake from carbohydrates, 30% from fat and 20% from protein) in both groups were similar.

\[
n = \left(\frac{z_{1-\alpha} + z_{1-\beta}}{2}\right)^2 \frac{\left(\frac{\sigma_1^2}{\mu_1} + \frac{\sigma_2^2}{\mu_2}\right)}{\left(\mu_1 - \mu_2\right)^2}
\]

The sample size was 32 subjects in each group. The sample size was increased to 35 subjects in each group considering dropout.

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Energy intake at first period (kcal/day)</th>
<th>Energy intake at second period (kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29.9 kg/m²</td>
<td>1000</td>
<td>1200</td>
</tr>
<tr>
<td>30-34.9 kg/m²</td>
<td>1100</td>
<td>1300</td>
</tr>
<tr>
<td>35-40 kg/m²</td>
<td>1200</td>
<td>1400</td>
</tr>
</tbody>
</table>

In the intervention group MRT (Nestle OPTIFAST) was provided for two meals in the first four weeks and one in the second four weeks. Subjects required to consume one sachet of OPTIFAST for each meal) one sachet instead of breakfast and one sachet instead of dinner in the first 4 weeks and one sachet instead of breakfast in the second four weeks). Each sachet provided 201 kcal and consisted of 20gr protein, 18.2gr carbohydrates, and 4.5gr fat. Therefore, 402 kcal in the first four weeks and 201 kcal in the second
four weeks of the intervention were provided from meal replacements. The composition of the other meals were adjusted based on the MRT.

The control group was asked to follow the dietary advice to receive the designated calories similar to the intervention group at each study period.

Both groups were asked not to take any dietary supplements and maintain their usual physical activity and sleep-wake pattern during the study period.

### 2.3.2 Participants follow-up and measurements

At the first visit, anthropometric measurements were assessed. These measurements were weight and determining body composition, including total body fat mass (TBFM), trunk fat mass (TFM), fat-free mass (FFM), and total body water (TBW) using the Tanita's Bioelectrical Impedance Analysis (BIA) device ((Tanita BC-418 MA, Tanita Corp. Tokyo, Japan) with an accuracy of 5% underwater weighing and DEXA. BMI was calculated using weight (kg)/height (m2). To reduce the measurement error at each visit, participants were asked to fast for at least 4 hours, but water consumption was allowed exercise, and consuming caffeinated substances was also limited to 4 to 6 hours before the measurements. Measurements were performed with an empty bladder.

The day after the first visit, the diet was determined, and indirect calorimetry (IC) and biochemical tests were performed for each participant. The resting metabolic rate was measured for 20 min using indirect calorimetry. Indirect calorimetry was performed using the Metalyzer 3B-R3 device (Cortex Biophysik, Germany) after fasting for 8–10 hours. To reduce the effect of the last meal on RMR, all participants were asked to eat a light and uniform dinner (bread, cheese, and cucumber). Consumption of caffeine, alcohol and energy drinks and strenuous exercise was limited from the day before the calorimetry. Before calorimetry, the participant was at rest in the supine position for 20 minutes. The ambient temperature was set at 20 to 25 degrees, and the calorimetric mask was well fitted. The present study was performed during the coronavirus epidemic; for this reason, when performing an IC test to prevent coronavirus, all necessary measures were taken according to a previously published preventive guideline in the same university where the study was undertaken (14).

A 5-ml venous blood sample was collected from the antecubital region of the arm after 12 hours of fasting. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured using Alpha-Classic AT Plus, and serum insulin was measured by quantitative luminescence assay after fasting for 10–12 hours. All the analyses were performed at the beginning of the study and were repeated eight weeks after the start of the study. The researcher contacted participants by telephone or social media channels during the study to reduce participant drop-out and increase dietary adherence. All diet-related questions were asked from the subjects through online or telephone contact.

### 2.4 Assessment of dietary intake, physical activity, and symptoms
A 24-hour dietary recall was completed every week to assess dietary intake during the study. Dietary intake data was analyzed using N4 software (First Databank Inc., San Bruno, CA, USA) for each day and the mean intake of the subjects was used for statistical analysis in the study (Table 2). To assess the level of physical activity to control its confounding effect, a pedometer (Omron HJ-303 Pocket Pedometer, England) was given to all participants to register their physical activity for a week, and their average weekly physical activity was calculated. Physical symptoms such as nausea, diarrhea, and hunger were recorded using a numerical scale of 1 to 10, with 10 being the most severe and 1 being the least severe.

### Table 2
Food intakes during the study

<table>
<thead>
<tr>
<th>Group</th>
<th>MRT</th>
<th>ULC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>1226 ± 97</td>
<td>1322 ± 110</td>
<td>0.840</td>
</tr>
<tr>
<td>Protein (gr)</td>
<td>77 ± 6.41</td>
<td>67 ± 7</td>
<td>0.552</td>
</tr>
<tr>
<td>Carbohydrate (gr)</td>
<td>132 ± 19</td>
<td>154 ± 20</td>
<td>0.518</td>
</tr>
<tr>
<td>Fat (gr)</td>
<td>43 ± 5</td>
<td>53 ± 6</td>
<td>0.245</td>
</tr>
<tr>
<td>Fiber (gr)</td>
<td>16 ± 2</td>
<td>18</td>
<td>0.660</td>
</tr>
<tr>
<td>Saturated Fat (gr)</td>
<td>13 ± 2</td>
<td>17 ± 2</td>
<td>0.013*</td>
</tr>
<tr>
<td>Sugar (gr)</td>
<td>62 ± 12</td>
<td>68 ± 16</td>
<td>0.480</td>
</tr>
</tbody>
</table>

P; The student’s T-test p-value

### 2.5 Outcomes and measurements

Primary outcomes were weight, BMI, TBFM, TFM, FFM, TBW, and RMR, and secondary outcomes were FPG, TG, total cholesterol, HDL, LDL, insulin level, and Physical symptoms.

### 2.6 Analysis

Statistical analysis was performed using SPSS version 20 (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test assessed the normality of the distribution. The student’s T-test and paired T-test were used to compare parametric variables and Mann Whitney U and Wilcoxon tests to compare nonparametric variables. The chi-square test was used to compare the distribution pattern of qualitative variables between groups. Analysis of covariance (ANCOVA) was used to control confounders’ effects, such as weight, calorie intake, baseline resting metabolic rate, physical activity, and age.
3 Results

There were 35 participants present in the each group, but in the MRT group, 31 women, and the ULC group, 30 women were present in the final analysis (Fig. 1). There was no significant difference in general characteristics, age, weight, and other baseline anthropometric measurements between the two groups (p > 0.05). Anthropometric results showed that weight, body fat and fat-free mass, and total body water significantly decreased in both groups (p < 0.05), but the only significant differences between the two groups were in weight and BMI. Final weight and BMI were significantly lower in the MRT group compared to ULC (74.67kg vs. 78.86kg and 28.48 kg/m$^2$ vs. 30.75 kg/m$^2$, respectively), but other anthropometric measurements did not differ between the two groups (p > 0.05) (Table 3).
Table 3
Baseline and final anthropometric and calorimetric findings

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>Final</th>
<th>P (PS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>80.41 ± 13.30</td>
<td>74.67 ± 12.17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>82.78 ± 12.23</td>
<td>78.86 ± 12.08</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.353</td>
<td>0.024*</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>30.64 ± 4.13</td>
<td>28.46 ± 3.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>32.29 ± 3.98</td>
<td>30.75 ± 3.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.902</td>
<td>0.045*</td>
<td></td>
</tr>
<tr>
<td>TBFM (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>35.30 ± 5.15</td>
<td>32.75 ± 5.58</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>36.09 ± 4.92</td>
<td>35.05 ± 5.50</td>
<td>0.002</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.396</td>
<td>0.512</td>
<td></td>
</tr>
<tr>
<td>TBFM (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>28.96 ± 8.79</td>
<td>25 ± 8.18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>30.24 ± 7.53</td>
<td>28.10 ± 7.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.107</td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td>FFM (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>51.44 ± 5.25</td>
<td>49.66 ± 4.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>52.55 ± 6.16</td>
<td>50.77 ± 5.80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.526</td>
<td>0.294</td>
<td></td>
</tr>
<tr>
<td>TFM (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>12.96 ± 4.67</td>
<td>11.21 ± 4.56</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>13.18 ± 3.87</td>
<td>12.31 ± 4.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.112</td>
<td>0.662</td>
<td></td>
</tr>
<tr>
<td>TBW (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>36.81 ± 3.79</td>
<td>35.58 ± 3.43</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ULC</td>
<td>37.65 ± 4.36</td>
<td>36.42 ± 4.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.552</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>RMR (KJ/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT</td>
<td>1372 ± 258</td>
<td>1343 ± 191</td>
<td>0.189</td>
</tr>
<tr>
<td>ULC</td>
<td>1628 ± 172</td>
<td>1483 ± 170</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.370</td>
<td>0.054</td>
<td></td>
</tr>
</tbody>
</table>

P, P-value; P (PS), paired-samples P-value; BMI, body mass index; TBFM, total body fat mass; FFM, fat-free mass; TFM, trunk fat mass; TBW, total body water; RMR, resting metabolic rate
There was no significant difference between the two groups in food intake, including calories, macronutrients, and fiber (p > 0.05), but the MRT group received less saturated fat (p < 0.05) (Table 2).

The resting metabolic rate (RMR) did not change significantly in the MRT group, but in the ULC group, it decreased significantly. However, the final difference between the two groups was just close to significant (p = 0.054) (Table 3).

The results of the metabolic profile showed that the plasma levels of total cholesterol, LDL, TG, FPG, and serum insulin were significantly reduced in both groups (p < 0.05), and there was no significant difference between the two groups (p > 0.05). However, HDL did not change significantly in the MRT group, but it decreased significantly in the ULC group (Table 4).
### Table 4
Baseline and final metabolic profile findings

<table>
<thead>
<tr>
<th>Time Point Variable</th>
<th>Baseline</th>
<th>Final</th>
<th>P (PS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>MRT</td>
<td>96.03 ± 8.24</td>
<td>91.10 ± 5.70</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>97.03 ± 7.83</td>
<td>93.22 ± 7.79</td>
</tr>
<tr>
<td></td>
<td>P (ANCOVA)</td>
<td>0.717</td>
<td>0.504</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>MRT</td>
<td>181.82 ± 40.87</td>
<td>165.68 ± 26.56</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>184 ± 48.79</td>
<td>168.48 ± 25.63</td>
</tr>
<tr>
<td></td>
<td>P (ANCOVA)</td>
<td>0.602</td>
<td>0.192</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>MRT</td>
<td>50.37 ± 9.36</td>
<td>48.93 ± 6.78</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>52.07 ± 9.04</td>
<td>44.96 ± 6.38</td>
</tr>
<tr>
<td></td>
<td>P (ANCOVA)</td>
<td>0.904</td>
<td>0.754</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>MRT</td>
<td>105.27 ± 28.03</td>
<td>86.51 ± 16.93</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>103.29 ± 34.32</td>
<td>86.55 ± 14.31</td>
</tr>
<tr>
<td></td>
<td>P (ANCOVA)</td>
<td>0.910</td>
<td>0.100</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>MRT</td>
<td>136.31 ± 94.69</td>
<td>107.51 ± 45.61</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>124.07 ± 50.77</td>
<td>110.29 ± 38.54</td>
</tr>
<tr>
<td></td>
<td>P (ANCOVA)</td>
<td>0.110</td>
<td>0.781</td>
</tr>
<tr>
<td>Serum insulin (mIU/dl)</td>
<td>MRT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ULC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time Point</td>
<td>Baseline</td>
<td>Final</td>
<td>P (PS)</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
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<td>--------</td>
</tr>
<tr>
<td>Variable</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P (ANCOVA)</td>
<td>0.261</td>
<td>0.274</td>
<td></td>
</tr>
</tbody>
</table>

P, P-value; P(PS), paired-samples P-value; BMI, body mass index; TBFM, total body fat mass; FFM, fat-free mass; TFM, trunk fat mass; TBW, total body water; RMR, resting metabolic rate

A pedometer assessed daily activity. The number of daily steps per week did not differ significantly between the two groups (3618 ± 2314 steps/day in the MRT group vs. 4188 ± 2552 steps/day in the ULC group). The severity of hunger feeling was higher in the ULC group, and the severity of nausea and diarrhea was higher in the MRT group, but there was no significant difference between the two groups in terms of other symptoms and overall satisfaction (Table 5).

Table 5
Evaluation of the severity of physical symptoms (Median and Interquartile)

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>MRT</th>
<th>ULC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hunger feeling</td>
<td>5(4–7)</td>
<td>6.5(5–8)</td>
<td>0.035*</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3(1–5)</td>
<td>2(1–1)</td>
<td>0.005*</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>4(3–6)</td>
<td>3(1.75–5.25)</td>
<td>0.260</td>
</tr>
<tr>
<td></td>
<td>constipation</td>
<td>4(2–5)</td>
<td>3(2–6)</td>
<td>0.907</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
<td>2(1–3)</td>
<td>1(1-1.25)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>dry mouth</td>
<td>2(1–3)</td>
<td>2(1–4)</td>
<td>0.219</td>
</tr>
<tr>
<td></td>
<td>headache</td>
<td>3(1–4)</td>
<td>3.5(1.75-6)</td>
<td>0.563</td>
</tr>
<tr>
<td></td>
<td>weakness</td>
<td>3(2–6)</td>
<td>4.5(2–8)</td>
<td>0.111</td>
</tr>
<tr>
<td></td>
<td>hair loss</td>
<td>4(2–6)</td>
<td>4(2–6)</td>
<td>0.884</td>
</tr>
<tr>
<td></td>
<td>Overall satisfaction</td>
<td>7(5–9)</td>
<td>7(5–8)</td>
<td>0.237</td>
</tr>
</tbody>
</table>

P; Mann Whitney U tests p-value

4 Discussion

The present study showed that both diets improve the metabolic profile and body composition, but the MRT causes more significant weight loss than the ULC diet.
In line with the present study results, in a study by Tsong-Ming Lu et al. (15), body weight and body fat levels were significantly reduced after eight weeks of a meal replacement diet. There was no control group in this study, and only pre-diet and post-diet evaluation was performed. Also, two meals were replaced with meal replacements, and calorie intake was limited so that women received less than 1,200 kcal per day and men less than 1,500 kcal per day. Also, in a 26-week study by Lewis et al. (16) and a 12-week study by Haywood et al. (17), consistent with our findings, MRT caused more significant weight loss. Although further weight loss occurred in the intervention group in the studies mentioned above, there was a difference in daily calorie intake and the distribution of macronutrients between the two study groups. For example, in the study by Haywood et al. (17), one group received only dietary recommendations; one group received a typical diet with a reduction of 500 kcal of the total daily requirement, which was 30% calories from protein, 30% calories from fat, and 40% total calories from carbohydrates, and the third group received a Very low calorie diets (VLCD) using meal replacement, which in this study, did not receive the same calories in the three groups.

Also, in a study by Lewis et al. (16), a group received a diet of 800 to 1200 kcal with 40% protein, 40% carbohydrates, and 20% fat in meal replacements based on BMI, while the control group received a diet with an emphasis on reducing fat intake to 25 to 30% of total calories and reducing 500 to 750 kcal of the total daily requirement. In this study, the caloric intake was different in the two groups. These differences in calories and macronutrient distribution between the two groups may have affected the results of these studies.

In a study by Chaiyasoot et al. (18), after 12 weeks of dieting, the MR group achieved more significant weight loss than the control group. In Metzne et al. (19) study, both groups received an energy-restricted diet of approximately 1200 kcal/d. The dietary intervention resulted in significant weight loss in both groups, without a significant difference between the two groups; however, the MR group's weight loss was higher than the Control group. In our study, similar to Metzne's study, the caloric intake between the two groups was the same, but the results of the two studies were different.

Differences in the results of studies may be due to differences in the duration of interventions and differences in the type and distribution of macronutrients in diets. For example, although meal replacements have been used in these studies, the type of replacements, calories, and distribution of macronutrients have varied.

In our study, hunger feeling was less common in the MRT group than in the ULC group. This may be one of the main reasons for more significant weight loss in this group, leading to greater adherence to the diet. Although no proper tools were used in this study to assess satiety or huger feeling, consuming more protein (10gr/day more in MR group(20)(21) and compounds in meal replacements in this group may increase satiety and thus increase adherence to the MRT diet.

In our study, the 24-hour dietary recalls were collected from participants, but these energy intake estimation tools are not quantitatively precise, although there was no significant difference in calorie intakes. In this nutritional assessment, the intake is often misreported, such as not remembering to
consume specific foods or incorrectly estimating portion sizes. So, the probability of misreporting food recalls may affect study results (22)(23). Another reason may be the meal replacement ingredients. For example, each meal replacement sachet contains 420mg of calcium, which can help regulate weight, reduce body fat, and increase energy expenditure (EE), according to previous studies (24). We compared the macronutrient intakes between the groups, and it is recommended to compare micronutrients in future studies.

Although non-significant compared to ULC, in our study, MRT caused a more significant reduction in TBFM. No significant difference was detected between the two groups in the study by Chaiyasoot et al. (18) in FM. However, in fat-free mass (FFM), there was a significant decrease in the MR group, but not in the control group, but in the study of Lewis et al. (16) MRT caused a more significant reduction in both TBFM and FFM, and in the study by Haywood et al. (17) MRT caused a higher decrease in fat mass and an increase in muscle mass. Differences in the results of studies may be due to differences in the duration of interventions and differences in the type and distribution of macronutrients in diets.

The present study's findings showed that after eight weeks of dieting, RMR decreased in both groups, but this decrease was not significant in the MRT group or comparison between the two groups. In the study by Smith-Ryan et al. (25), which used High-Fat Breakfast Meal Replacement, RMR also decreased, but the reduction was not significant. In Alex E. Mohr et al. study, In 2020 (26), consumption of an MR meal increases postprandial thermogenesis compared to a whole food meal.

Given that in our study, the reduction in FFM was equal in both groups, the lower decline in RMR in the MRT group could not be explained by maintaining FFM, but changes in sympathetic activity or other metabolic factors may affect the IC results. It should also be borne in mind that FFM is composed of different components, and that their changes may have been different between the two groups. For example, differences in organ changes with a high metabolism (e.g., skeletal muscle) or changes in total body water can affect FFM (27). Also, studies have shown that the weight of internal organs is sensitive to nutritional changes and can cause resting energy expenditure (REE) changes (28). In addition, meal replacement sachet contains vitamins and minerals required by the body, and differences in nutrient intake between the two groups may have affected the results and could explain the lower reduction in RMR in the MRT group. This explanation is based on the findings of previous studies. In a systematic review by Liu et al. (29) and a study by Carsten et al. (30), compounds such as vitamin D and vitamin A could alter the metabolism rate by acting on brown adipose tissue (BAT) thermogenesis. For example, vitamin A can increase the thermogenesis in BAT by increasing mitochondrial biogenesis and increasing the proliferation of the UCP1 gene, which may be one of the possible mechanisms for increasing RMR or preventing its decrease (29). Calcium can also be effective in weight regulation, which may be through thermogenesis and increasing energy consumption (31). Polyunsaturated fatty acids (PUFAs), such as linoleic acid, can produce more heat and higher EE than saturated fats by activating the transient receptor potential vanilloid1 (TRPV1) channel (29). In our study, saturated fat consumption was lower in the MRT group. Also, in this group, with each meal replacement sachet, 1.2 grams of linoleic acid was received, which can be one of the reasons for the difference in RMR changes between the two groups.
In the present study, after eight weeks of dieting, the lipid profile, fasting plasma glucose, and insulin decreased significantly in both groups, but there was no significant difference between the two groups. Consistent with our study, in a study by Lu et al. (15), the lipid profile improved after eight weeks of meal replacement, and serum insulin and HOMA-IR insulin resistance were significantly reduced. In the study of Metzner et al. (19), lipid profiles improved in both groups, and there was no significant difference between the two groups. In the study of Gómez et al. (32), one group replaced two meals a day, and the other group replaced one meal a day with meal replacements, no significant difference was observed in lipid profile changes between the two groups, and these results were consistent with our findings.

Contrary to our findings, in Chaiyasoot et al. (18) study, FPG was significantly reduced in the MR group after 12 weeks compared to baseline but not in the control group.

In our study, the level of satisfaction with the diet did not differ significantly between the two groups. However, gastrointestinal symptoms (nausea and diarrhea) were further reported in the intervention group. In the Davenport study (33), which was performed on two different meal replacements, The rate of bloating was higher in the group receiving Optifast. Also, in the Lewis study (16), 11 percent of those who found meal replacement experienced diarrhea, and 11.6 percent experienced nausea, while in the control group, this rate was 4 and 2 percent, respectively.

Our study evaluated several outcomes, including metabolic profile, RMR, dietary tolerability, physical symptoms, and weight changes. Furthermore, the study only included women, controlling one of the most important confounding factors. However, our study did not consider other variables affecting dieting success, such as sleep patterns and mental status. Due to the COVID-19 pandemic, there were many challenges in face-to-face and indirect calorimetry. In the last visit, indirect calorimetry was not performed on some people due to suspicious symptoms or unwillingness of the participant. We also did not calculate specific calorie requirements based on the individual needs, and although we used 24-hour dietary recall, reporting was poor. It would have been better to use a more valid method to assess the side effects of the diet. Finally, randomization and blinding were not possible due to the study design.

We suggest that in future studies:

- The intake of micronutrients, caffeine, and fatty acids be examined. (We propose that future research look into micronutrients, caffeine, and fatty acids.)
- Due to the possible effect of BMI on weight loss (34) and diet adherence, it is best to do further studies on people with a closer BMI range.
- To check food intake and adherence to the diet during the study, instead of a 24-hours recall, it is better to use a more reliable method) Web-based programs, mobile applications, and wearable devices)(35).
- If the study is performed during a coronavirus epidemic, consider more drop in outing rate.

5 Conclusion
In conclusion, the results of this study showed that both methods effectively improve metabolic factors and weight loss in the short term, but the use of meal replacements is a more effective strategy for weight loss. Meal replacements may also help maintain the resting metabolic rate. Nevertheless, it is necessary to do further studies on meal replacements. Gastrointestinal side effects such as nausea and diarrhea were present in some people who used meal replacement. So it is better to choose the appropriate diet, depending on the individual conditions.

**Abbreviations**

MRT
Meal Replacement Therapy
ULC
Usual Low-Calorie diet
RMR
Resting Metabolic Rate
BMI
Body Mass Index
FFM
fat-free mass
TBFM
total body fat mass
TFM
trunk fat mass
TBW
total body water
BIA
Bioelectrical Impedance Analysis
FPG
Fasting Plasma Glucose
REE
resting energy expenditure
TRPV1
transient receptor potential vanilloid1
PUFAs
Polyunsaturated fatty acids
BAT
brown adipose tissue
EE
energy expenditure
FPG
Fasting plasma glucose
TG
triglycerides
Tc
total cholesterol
HDL
high-density lipoprotein
LDL
low-density lipoprotein
IC
indirect calorimetry
VLCD
Very low calorie diets

Declarations

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Authors contributions

Study concept and design: MN, RR, and MK; acquisition of data: MK and NNA; analysis and interpretation of data: LJ; drafting of the manuscript: MK, NNA; critical revision of the manuscript: RR, MN and AJE. statistical analysis: LJ; obtained funding: MN; study supervision: MN. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets that support the findings of this study are available from Nutrition department of Mashhad University of Medical Sciences but restrictions apply to the availability of this data, and are not publicly available. Data are however available from the corresponding author on reasonable request and with permission of Nutrition department of Mashhad University of Medical Sciences.

Ethics approval and consent to participate
The study was approved on January 19, 2020, in the Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1398.744) as well as in the Iranian Registry of Clinical Trials (IRCT code: IRCT20200611047731N1 Registration date: 17-07-2020). Written informed consent (in Persian) was obtained from all participants.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare competing interests.

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**Figures**
Figure 1

flow diagram of participant enrolment and final analysis. After evaluating the information of 110 women, 73 women were eligible to enter the study, of whom 3 dropped out, and 70 were included in the study. 35 women entered the ULC group, and 35 women entered the MRT group, of whom 9 dropped out, and in the ULC group, 30 women and in the MRT group, 31 women were present in the final analysis. The rate of dropping out due to diet intolerance was higher in the control group.