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ARTICLE

A randomized controlled trial of a weight loss maintenance program in adults with obesity: the WLM3P study

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BACKGROUND/OBJECTIVES: The escalating obesity epidemic necessitates effective, sustainable weight loss (WL) and maintenance strategies. This study aimed to evaluate the effectiveness of the Weight Loss Maintenance 3 Phases Program (WLM3P) in achieving a clinically significant long-term weight loss (WL) (≥5% initial WL at 18 months) in adults with obesity compared to a standard low-carbohydrate diet (LCD).

SUBJECTS/METHODS: In this two-phase trial, 112 participants targeting initial WL (0–6 months) and subsequent maintenance (7–18 months) were randomly assigned to either WLM3P or LCD groups. Outcomes assessed included change in body weight (kg, %), improvements in body composition, and metabolic profile.

RESULTS: Of 112 randomized participants, 69% (n = 77) completed the study. At 18 months, WL in the WLM3P group (n = 40) was 15.5 ± 8.3% compared to 9.6 ± 8.5% in the LCD group (n = 37) ($p < 0.001$). The odds ratio of achieving WL ≥ 10% and ≥15% were significantly higher in the WLM3P group. Complete-case analysis revealed significantly greater improvements in BMI, body fat mass, visceral fat area, waist circumference, waist-to-hip ratio, HDL, and triglyceride/HDL ratio in WLM3P than in LCD. No serious adverse events were reported.

CONCLUSION: Both programs effectively promoted clinically relevant WL and its maintenance. However, the WLM3P program was more successful in helping participants achieve greater WL targets of ≥10% and ≥15%, along with other clinical benefits, after an 18-month intervention.

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INTRODUCTION

Obesity, an adiposity-based chronic disease, has escalated to epidemic levels worldwide [1], with Europe facing a particularly severe challenge as over half of its population is now overweight [2], and countries such as Portugal report distressingly high prevalence rates [3]. Given the serious implications of obesity, there is a pressing need for effective, accessible, and sustainable weight loss (WL) and maintenance strategies. Clinically meaningful WL, defined as a sustained reduction of at least 5% from baseline for a year or more, has been associated with improvements in metabolic health, psychological well-being, and decreased risk of chronic diseases [4–6]. However, traditional WL approaches often lead to rebound weight gain, underscoring the imperative for novel, evidence-based nutritional interventions [4–6].

The Weight Loss Maintenance 3 Phases Program (WLM3P) emerges as a pioneering, evidence-based intervention that adopts a highly structured and intensive lifestyle modification approach. This program was designed to improve adherence and comprehensively tackle obesity through seven core components: (1) dietary intervention structured into three distinct phases—two initial phases for WL, followed by a third phase focused on the maintenance of the achieved WL; (2) consistent, individualized one-to-one consultations to provide tailored support and guidance [4–6]; (3) behavioral strategies designed to promote sustainable lifestyle changes [4–6]; (4) time-restricted eating (TRE) protocols, a chrono-nutritional strategy, to align food intake with circadian rhythms [7, 8]; (5) dietary supplements to support nutritional needs and WL efforts [9, 10]; (6) high-protein foods to enhance satiety [11]; and (7) mobile/web application to facilitate participant engagement and adherence [12, 13].

The WLM3P's nutritional recommendations are predicated on a carbohydrate-restricted/high-protein diet, that has become a popular strategy for WL and to prevent weight regain [14–18]. According to Denning et al. [14], a low-carbohydrate diet (LCD) is defined as <26% of total energy intake from carbohydrate (%CTEI)

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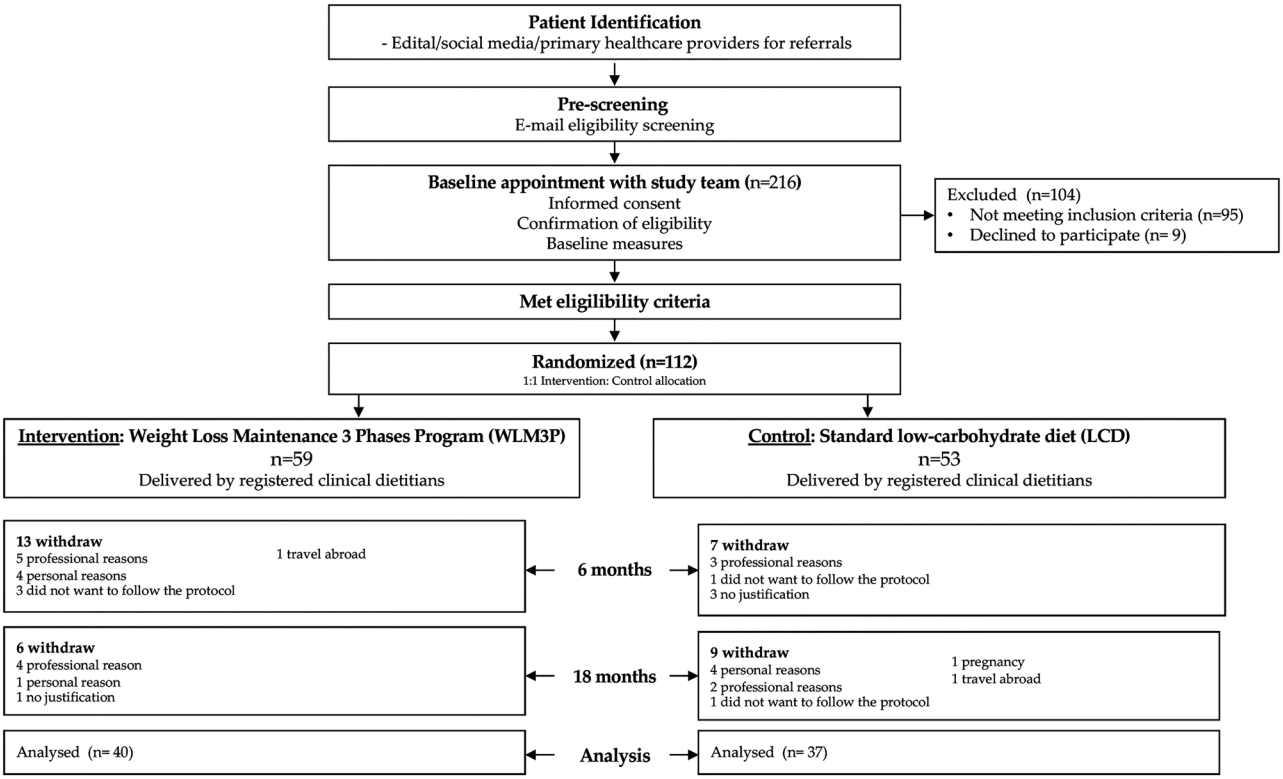

Fig. 1 Flow diagram of the study participants.

and moderate-carbohydrate diet 26–45% CTEI. High-protein diets contain >25% of total energy intake from protein (%PTEI) [18].

While these seven components show promise, ongoing research is essential to fully understand their long-term impacts. All components are delivered within a structured framework, aiming for achieving and maintaining clinically significant WL and emphasizing personalized care that considers cardiometabolic risk factors, dietary preferences, and long-term adherence [4–6]. The innovation of the WLM3P lies in its comprehensive and synergistic approach to weight management, which encompasses a multifaceted strategy beyond mere carbohydrate restriction, setting it apart from the conventional focus of standard LCD.

Therefore, this study aimed to evaluate the effectiveness of the WLM3P in supporting patients to achieve a clinically significant WL ≥ 5% at 6 months and maintain this benchmark at 18 months compared to a standard LCD in adults with obesity. We hypothesize that the WLM3P, with its comprehensive multicomponent methodology, will be more effective than a standard LCD in achieving and maintaining a clinically significant WL ≥ 5% in adults with obesity over an 18-month period.

MATERIALS AND METHODS

Trial design

The WLM3P study was a randomized controlled trial, comprising 18 months (6-month WL period followed by a 12-month weight maintenance period) study conducted at NOVA Medical School, NOVA University of Lisbon, between March 2020 and January 2023. Participants were randomly allocated (1:1) to either WLM3P (n = 59) (intervention group) or LCD (n = 53) (active control group) (Fig. 1).

Participants

A total of 112 participants (18–65 years) with obesity [body mass index (BMI) of 30.0–39.9 kg/m^2] of both genders were recruited. Briefly, the key exclusion criteria were planned or current pregnancy, diabetes, previous or planned bariatric surgery, current participation in a WL program, or use of other treatments for obesity (ex. medications), severe disease (advanced organ failure, dementia, or cancer), active abuse of drugs or alcohol or inability to perform Inbody® (e.g., limb amputation) (Supplementary Table S1). Participants were randomly assigned by clinical research coordinators to either the intervention or control group using an automated computer-generated randomization scheme (sequentially numbered). The randomization process was controlled by the Principal Investigator, who was not involved in recruitment or intervention delivery. Once recruited, participants were blinded to the treatment allocation and a study identification number was assigned. None of the randomized participants included in the study received any financial or in-kind support. The study was approved by the Ethics Committee of the NOVA Medical School (Lisbon, Portugal) (CEFCM Approval Number: 108/2018) and registered at www.clinicaltrials.gov (NCT04192357) before participants' recruitment. All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

Dietary interventions

In both groups, for WL period (months 0–6), dietary plans met 70% of participants' daily energy requirements (DER), and for weight maintenance period (months 6–18) 100% of participants' DER. Nutrition counseling (WL: 24 sessions in WLM3P, 6 sessions in LCD; weight maintenance: 12 sessions in both groups) provided clinical support, problem-solving, and maintenance efforts. In both interventions, participants were advised to eat more vegetables, avoid refined grains, sugar, trans fats, and focus on whole, nutrient-dense foods. Individual preferences were considered, and the meal preparation indications followed the Mediterranean diet principles. Physical activity counseling aimed for ≥150 min of moderate exercise per week (equivalent of ≥500 MET-min/week) [4] for both groups. Detailed descriptions of the dietary interventions, including macronutrient composition and session content, are provided in the Additional file 1: Appendix 1. Dietary Intervention details.

WLM3P (Intervention group). The WLM3P is a structured nutritional and behavioral program based on seven components: (1) dietary intervention with three phases [Phase 1 (1-month: low-carbohydrate (10–15% CTEI)/

high-protein diet (35–45% PTEI)); Phase 2 (5-month: low-carbohydrate (15–20% CTEI)/high-protein diet (30–40% PTEI)); Phase 3 (12-month: moderate-carbohydrate (35–45% CTEI)/high-protein (25–30% CTEI))] [14, 18]; (2) regular one-to-one personalized consultations [4–6] (WL phase: 24 presential sessions; maintenance phase: 12 presential sessions); (3) behavioral strategies (nutrition education and meal planning, motivational support and goal setting, chrono-nutrition, and physical activity) [4–6], (4) TRE (WL: 14:10 h | weight maintenance: 12:12 h) [7, 8]; (5) dietary supplements during WL phase [9, 10]; (6) high-protein specific food (high-protein pudding or drinks) [11]; and a (7) mobile/web app to track body composition progress, dietary plan prescriptions, and weekly goals definition [12, 13]. All dietary supplements and high-protein puddings/drinks were provided by the research team.

LCD (Active control group). Participants randomized to the control active group received a standard LCD divided into two periods [WL period (6-month: low-carbohydrate (≤26% CTEI)/high-protein diet (30–35% PTEI)), and weight maintenance period (12-month: moderate-carbohydrate (≤45% CTEI)/high-protein diet (25% PTEI))] [14, 18]. During the 6-month WL period, participants had 6 in-person sessions, followed by a monthly follow-up for 12 months (12 presential sessions).

Outcomes

Primary outcomes:

- The primary outcome was the change in body weight (kg, %) from baseline to the 6 and 18-month time points.

Secondary outcomes:

- Proportion of participants achieving weight reductions of at least 5, 10, or 15%.
- Changes in body composition, including body fat mass (BFM), skeletal muscle mass (SMM), visceral fat area (VFA), waist-to-hip ratio (WHR), and waist circumference (WC).
- Metabolic profile alterations, such as changes in glucose, insulin, Homeostasis Model for Assessment (HOMA), LDL-cholesterol, HDL-cholesterol, and triglycerides (TG).
- Blood pressure measurements, both systolic (SBP) and diastolic (DBP).
- Dropout rate.
- Changes in gut microbiota composition were also assessed in this trial; however, this will be reported later.

Additional information was collected: dietary intake, physical activity levels, habitual sleep time, fasting window, and adverse effects.

Assessments

At baseline, socio-demographic and medical history were collected through a self-report questionnaire. Potential changes in medication were assessed during each visit. Body composition was assessed monthly by bioelectrical impedance analysis (Inbody® model 770). Body mass index [weight (kg)/height (m^2)] and skeletal muscle mass-to-visceral fat area ratio (S/V ratio) were calculated. Waist circumference (WC) was measured according to the protocol defined by the Directorate-General of Health [19]. Comprehensive assessments were conducted at baseline, 6 months, and 18 months, encompassing: (1) fasting venous blood samples for biochemical analyses were determined by conducting standard laboratory assays; (2) blood pressure measurements obtained with the OMRON HEM-7361T, a validated automatic device, in accordance with the Directorate-General of Health's guidelines [20]; (3) dietary intake analysis based on a 3-day food diary, including two weekdays and one weekend day, using the Portuguese Food Composition Table [21]; (4) physical activity levels quantified in Metabolic Equivalent Task minutes per week (MET-min/week), according to the International Physical Activity Questionnaire (IPAQ) scoring protocol [22]; (5) habitual sleep duration estimated through a questionnaire, with a total weekly sleep score calculated by combining sleep minutes from weekdays and weekends [23]; (6) fasting window was determined by the interval between the first and last caloric intake of the day [7, 8]; and (7) adverse events were self-reported and assessed during each visit using a questionnaire, following the Good Clinical Practice and Health Research Authority guidelines [24].

Adherences measurements. Therapeutic adherence in the study was quantitatively assessed through the number of sessions attended [25] and dietary intake compliance using self-reported food diaries [26]. Within the WLM3P group, adherence to dietary supplements was assessed using a 5-point Likert scale, providing a range from complete non-adherence (0%) to full adherence (100%). Furthermore, compliance with the TRE protocol was determined by analyzing the fasting window duration [7, 8]. Physical activity adherence was quantified using the IPAQ [22].

Statistical analysis

The sample size calculation determined that 338 participants were needed to achieve an 80% power and a 5% error rate, assuming proportions of 50% and 35% in the intervention and control groups, respectively, achieving WL ≥ 5% at 18 months [6]. Considering a 32% attrition rate, recruitment aimed at 500 participants (250/group) but ended prematurely due to lower-than-expected recruitment rates [6]. Categorical variables are expressed as absolute (n) and relative (%) frequencies, while continuous variables are expressed as mean ± standard deviation or median and interquartile range [IQR: 25th, 75th percentile]. Data were tested for normality by performing the Kolmogorov–Smirnov test and analyzing the distribution using histograms. A comparison of variables in the same group (baseline vs. follow-up) was performed using parametric tests (paired Student's t test) and nonparametric tests (Wilcoxon test) as appropriate, considering normality assumptions. For between-group comparisons (WLM3P vs. LCD), parametric tests (Student's t test) and nonparametric tests (Mann–Whitney) were used as appropriate, considering normality assumptions. Hypotheses regarding categorical variables were tested using the chi-square test or Fisher's exact test, as appropriate. Logistic and linear regression models were carried out using each of the outcomes as dependent variables and as independent (explanatory) variables regarding the compared groups [intervention vs. control (reference)], adjusted for age, sex, baseline body mass index, and baseline glucose (used since differences were observed at baseline) at 6 and 18 months. Coefficient regression (beta) and 95% confidence intervals (95% CI) are presented. The significance level used was 0.05. Statistical analysis was performed using the Statistical Package for the Social Sciences version 29.

RESULTS

Participants characteristics

Among 216 adults with obesity screened for participation, a total of 112 individuals (mean age 45.0 ± 8.7 years) with a BMI of 34.0 ± 2.4 kg/m^2 and a body weight of 95.5 ± 11.6 kg was enrolled in the study. The majority of participants were Caucasian (98.2%), female (72.3%), married (43.8%), and college-educated (79.5%). Participants were randomly assigned to either WLM3P group (n = 59) or LCD group (n = 53). A total of 77 participants (69%) completed the study (Fig. 1). No significant differences in baseline characteristics were observed between the two groups, except for fasting glucose (Table 1).

Change in the primary outcome

In a complete-case analysis, the WLM3P group demonstrated a significant WL at 6 months, with an average percentage WL of 19.0 ± 5.2%, corresponding to a mean reduction of 18.1 ± 5.7 kg, compared to 11.9 ± 6.1% and a mean reduction of 11.5 ± 6.6 kg in the LCD group (n = 46 for each). At 18 months, the WLM3P group (n = 40) sustained a WL of 15.5 ± 8.3%, corresponding to a mean weight reduction of 14.8 ± 8.6 kg, while the LCD group (n = 37) maintained a WL of 9.6 ± 8.5%, with a mean weight reduction of 9.2 ± 8.3 kg (Table 2). Weight regain from the end of the WL phase to the end of the maintenance period (6–18 months) did not significantly differ between the groups (WLM3P: 4.3 ± 5.8%; LCD: 3.5 ± 4.8%; p = 0.357) (Table 3).

Secondary outcomes

The study demonstrated that most participants met or exceeded the 5% WL goal. At 6 months, 100% of the WLM3P group and 93.5% of the LCD group achieved this benchmark (p = 0.078), and at 18 months, the rates were 87.5% for WLM3P and 75.7% for LCD (p = 0.179). The WLM3P group had higher odds of achieving

Table 1. Baseline characteristics of study participants.

Characteristics	WLM3P group (n = 59)	LCD group (n = 53)	p value
Demographics			
Age (years)	44.0 ± 8.8	46.2 ± 8.4	0.176
Sex, n (%)			
Female	42 (71.2)	39 (73.6)	0.777
Male	17 (28.8)	14 (26.4)	
Body composition			
Body weight (kg)	95.5 ± 11.5	95.4 ± 11.9	0.940
BMI (kg/m^2)	33.9 ± 2.6	34.1 ± 2.2	0.852
BFM (kg)	41.0 ± 7.7	41.4 ± 6.4	0.737
BFM (%)	43.3 ± 6.7	43.6 ± 5.7	0.753
SMM (kg)	30.4 ± 6.1	30.1 ± 6.2	0.777
VFA (cm^2)	195.3 ± 36.3	197.6 ± 21.9	0.731
S/V ratio	0.2 ± 0.1	0.2 ± 0.1	0.523
WHR	1.0 ± 0.1	1.0 ± 0.1	0.656
WC (cm)	99.5 ± 9.8	102.2 ± 9.7	0.162
Blood pressure			
SBP (mm Hg)	123.5 ± 14.4	123.4 ± 10.9	0.948
DBP (mm Hg)	84.4 ± 9.4	84.7 ± 9.0	0.904
Metabolic profile			
Glucose (mg/dL)	83.0 ± 8.6	88.1 ± 10.3	0.008*
HOMA-IR	2.4 (1.9, 3.1)	2.8 (2.0, 3.7)	0.082
Insulin (mIU/L)	12.5 ± 5.1	14.5 ± 7.5	0.092
LDL (mg/dL)	112.5 ± 34.6	118.6 ± 28.7	0.318
HDL (mg/dL)	50.2 ± 12.6	53.8 ± 13.3	0.136
TG (mg/dL)	102.0 (77.0, 135.0)	115.0 (83.0, 143.0)	0.276
TG/HDL ratio	2.5 (1.6, 3.0)	2.2 (1.6, 3.1)	0.841

Data were presented as number of participants (%), mean ± standard deviation (±sd) for normally distributed variables or the median and interquartile (IQR: 25th, 75th percentile) for non-normal distribution variables. p values were computed with T test for independent samples; chi-square test and Mann–Whitney test as appropriate, considering the distribution of variables.
WLM3P Weight Loss Maintenance 3 Phases Program (Intervention group), *LCD* low-carbohydrate diet (Control group), *BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *BFM* body fat mass, *SMM* skeletal muscle mass, *S/V ratio* skeletal muscle mass-to-visceral fat area ratio, *VFA* visceral fat area, *WC* waist circumference, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* triglycerides, *TG/HDL ratio* triglyceride/high-density lipoprotein cholesterol.
Differences were statistically significant when *p < 0.05.

WL ≥ 10% and WL ≥ 15% at both 6 and 18 months (Supplementary Table S3). Between baseline and 18 months, the WLM3P group showed a greater reduction in BMI, BFM, VFA, WC, and WHR compared to the LCD group (Table 2). Both groups experienced a significant loss of SMM over the 6- and 18-month periods (p ≤ 0.001). Despite the SMM loss, the skeletal muscle mass-to-visceral fat area ratio (S/V ratio) improved, particularly at 6 months in the WLM3P group, indicating a favorable body composition change (Table 2).

The WLM3P group demonstrated metabolic improvements at 18 months, with a significant increase in HDL-cholesterol and a decrease in the atherogenic index, as evidenced by the TG/HDL ratio, compared in LCD group (Table 2). Additionally, the WLM3P group experienced a significant reduction of DBP at the 6-month mark. By the end of the study, there were no significant differences in DBP, including SBP, between the groups (Table 2). Among participants previously treated for hypertension (n = 19; 17%), n = 6 (7.8%) discontinued the antihypertensive medications [WLM3P group: 4 (10%); LCD group: 2 (5.4%)] and n = 4 (5.2%) reduced the dose and/or number of antihypertensive medications [WLM3P group: 1 (2.5%); LCD group: 3 (8.1%)] at 18 months.

Compliance and withdrawal

High adherence was observed in both the WLM3P and LCD groups, with attendance rates of 88.3% (32 out of 36 sessions) and 85.4% (15 out of 18 sessions), respectively.

The WLM3P group achieved a more substantial reduction in energy intake and carbohydrate consumption, with a corresponding increase in protein intake, compared to the LCD group at both 6 and 18 months. It is worth noting that both groups fell short of the recommended doses of 25 g/day of fiber (Supplementary Table S4). During the WL phase, 78.3% of WLM3P participants adhered to dietary supplements. By 6 months, physical activity levels increased in both groups, yet at 18 months, over half of the participants in each group did not reach the recommended activity levels (Supplementary Table S4). As anticipated, the WLM3P group exhibited longer median durations of overnight fasting compared to the LCD group (6-month: 13.5 h in WLM3P | 11.4 h in LCD; 18-month: 13.1 h in WLM3P; 11.3 h in LCD) (Supplementary Table S4). There were no changes in sleep duration from the beginning to the end of the study in either group (Supplementary Table S4).

The overall withdrawal rate from the study was 31% (n = 35), with no significant difference between the two groups [(32.2% (n = 19) in WLM3P and 30.2% (n = 16) in LCD; p = 0.818)]. The dropout pattern was analyzed by comparing the baseline characteristics of completers and non-completers, and our results showed no significant differences in body composition and biochemical parameters (Supplementary Table S5). Importantly, there were no withdrawals due to adverse events.

Adverse effects

In both groups, adverse effects occurred during the initial 6 months of the WL phase, with a higher prevalence observed in the WLM3P group (p = 0.020). These adverse effects were generally moderate and transient. The most reported was constipation (Supplementary Table S6). The WLM3P group, which included dietary supplements with diuretic characteristics during the WL phase, did not experience significant fluctuations in serum potassium and sodium levels (Supplementary Table S4).

DISCUSSION

Our 18-month randomized controlled trial provides evidence that the WLM3P is a more effective intervention than a standard LCD in achieving significant WL in adults with obesity. The WLM3P group not only maintained a mean WL of 15.5% at 18 months but also demonstrated a higher likelihood of achieving weight loss targets of ≥10% and ≥15%, which are associated with substantial clinical benefits and are often targeted for clinical objectives [4–6]. These results are particularly significant as they exceed typical outcomes from intensive lifestyle interventions at 12 months and are comparable to those achieved with obesity pharmacotherapy [27].

The WLM3P led to substantial reductions in BMI, BFM, VFA, WHR, and WC, surpassing the LCD group's results (Table 2 and Fig. 2). The S/V ratio significant improvement from baseline to 6 months in the WLM3P group may indicate a more effective preservation of a metabolically healthy state [28, 29].

Furthermore, the WLM3P group experienced greater increases in HDL-cholesterol and reductions in the TG/HDL (atherogenic index) compared to the LCD group at 18 months (Table 2 and Fig. 2),

Table 2. Changes in outcome measures among completing study participants – comparative analysis at 6, 18 months, and baseline by groups.

Variable	n	WLM3P group	n	LCD group	Estimated treatment difference (95% CI)	p value
Body composition						
Δ Body weight (Kg)						
6-month	46	−18.1 ± 5.7	46	−11.5 ± 6.6	−7.3 (− 9.7 to −4.9)	<0.001*
18-month	40	−14.8 ± 8.6	37	−9.2 ± 8.3	−5.6 (−9.7 to −1.7)	0.006*
Δ Body weight (%)						
6-month	46	−19.0 ± 5.2	46	−11.9 ± 6.1	−7.6 (−9.9 to −5.3)	<0.001*
18-month	40	−15.5 ± 8.3	37	−9.6 ± 8.5	−6.1 (−9.9 to −2.3)	0.002*
Δ BMI (kg/m^2)						
6-month	46	−6.5 ± 1.8	46	−4.0 ± 2.2	−2.6 (−3.5 to −1.8)	<0.001*
18-month	40	−5.3 ± 3.0	37	−3.2 ± 2.8	−2.1 (−3.5 to −0.8)	0.003*
Δ BFM (kg)						
6-month	46	−14.9 ± 5.4	46	−9.3 ± 5.8	−6.2 (−8.5 to −3.8)	<0.001*
18-month	40	−11.2 ± 7.4	37	−6.7 ± 7.2	−4.7 (−8.2 to −1.2)	0.009*
Δ BFM (%)						
6-month	46	−9.8 ± 5.4	46	−5.4 ± 4.1	−4.6 (−6.7 to −2.6)	<0.001*
18-month	40	−6.6 ± 6.2	37	−3.6 ± 5.0	−3.2 (−5.9 to 0.5)	0.023*
Δ SMM (kg)						
6-month	46	−2.0 ± 0.9	46	−1.4 ± 1.1	−0.7 (−1.1 to −0.2)	0.003*
18-month	40	−2.4 ± 1.4	37	−1.6 ± 1.4	−0.8 (−1.4 to −0.1)	0.028*
Δ VFA (cm^2)						
6-month	46	−72.7 ± 28.7	46	−42.7 ± 26.7	−31.2 (−42.9 to −19.5)	<0.001*
18-month	40	−53.1 ± 38.1	37	−29.8 ± 34.6	−23.3 (−40.7 to −5.8)	0.010*
Δ S/V ratio						
6-month	46	0.11 ± 0.13	46	0.06 ± 0.11	0.05 (0.01 to 0.09)	0.022*
18-month	40	0.07 ± 0.11	37	0.04 ± 0.09	0.03 (−0.02 to 0.07)	0.296
Δ WHR						
6-month	46	−0.09 ± 0.05	46	−0.04 ± 0.05	−0.04 (−0.06 to −0.02)	<0.001*
18-month	40	−0.07 ± 0.06	37	−0.03 ± 0.05	−0.04 (−0.12 to −0.06)	0.004*
Δ WC (cm)						
6-month	46	−14.6 ± 5.4	46	−9.6 ± 5.6	−5.7 (−8.1 to −3.4)	<0.001*
18-month	40	−12.2 ± 7.8	37	−8.8 ± 7.3	−3.8 (−7.3 to −0.1)	0.042*
Blood pressure						
Δ SBP (mm Hg)						
6-month	46	−9.5 (−19.5, −2.0)	46	−8.3 (−13.9, −0.5)	−2.3 (−6.7 to 2.1)	0.306
18-month	40	−8.4 (−17.4, −2.1)	37	−6.0 (−16.0, 2.0)	−1.6 (−6.3 to 3.2)	0.521
Δ DPB (mm Hg)						
6-month	46	−7.5 (−11.5, −4.0)	46	−6.0 (−9.0, −2.9)	−3.1 (−5.7 to −0.5)	0.021*
18-month	40	−4.0 (−10.4, 0.75)	37	−3.5 (−7.0, 3.3)	−2.8 (−6.3 to 0.7)	0.113
Metabolic profile						
Δ Glucose (mg/dL)						
6-month	46	−2.7 ± 7.9	45	−3.1 ± 8.9	−0.1 (−3.5 to 3.3)	0.143
18-month	39	−1.0 (−6.0, 6.0)	37	0.0 (−5.5, 4.5)	−0.4 (−4.0 to 3.1)	0.821
Δ Insulin (mIU/L)						
6-month	46	− 4.1 (−7.4, −1.5)	45	−4.2 (−6.5, −0.9)	−1.5 (−3.6 to 0.7)	0.174
18-month	39	−4.2 (−7.4, −1.8)	37	−2.5 (−6.4, 1.0)	−2.2 (−4.6 to 0.0)	0.050
Δ HOMA-IR						
6-month	46	−1.0 (−1.7, 0.2)	45	−1.0 (−1.6, 0.2)	−0.1 (−0.6 to 0.4)	0.694
18-month	39	−0.9 (−1.6, 0.2)	37	−0.7 (−1.2, 0.2)	−0.2 (−0.7 to 0.4)	0.554
Δ LDL (mg/dL)						
6-month	46	2.0 (−12.5, 13.0)	45	−4.0 (−16, 8.0)	5.8 (−3.5 to 15.1)	0.222
18-month	39	4.0 (−12.0, 14.0)	37	−10.0 (−21.0, 6.0)	3.8 (−6.3 to 13.8)	0.465

Table 2. continued

Variable	n	WLM3P group	n	LCD group	Estimated treatment difference (95% CI)	p value
Δ HDL (mg/dL)						
6-month	46	8.0 (3.0, 11.0)	45	5.0 (−0.5, 8.5)	3.9 (0.9 to 6.8)	0.010*
18-month	39	10.4 ± 11.4	37	5.3 ± 8.0	6.3 (1.7 to 10.9)	0.007*
Δ TG (mg/dL)						
6-month	46	−26.5 (−50.0, −9.8)	45	−25.0 (−64.5, 7.0)	−8.6 (−33.2 to 14.9)	0.473
18-month	39	−25.0 (−49.0, 7.0)	37	−6.0 (−36.0, 16.0)	−30.4 (−61.2 to 0.4)	0.053
Δ TG/HDL ratio						
6-month	46	−0.7 (−1.2, −0.4)	45	−0.7 (−1.5, −0.2)	−0.4 (−1.1 to 0.3)	0.242
18-month	39	−0.7 (−1.1, −0.3)	37	−0.3 (−1.1, 0.3)	−1.0 (−1.9 to −0.1)	0.036*

All data were presented as mean ± standard deviation (±sd) for normally distributed variables or the median and interquartile (IQR: 25th, 75th percentile) for non-normal distribution variables. Change scores from baseline were represented by "Δ" in the table. p values were computed with a linear regression model considering as confounders: age, sex, body mass index, and baseline glucose (used since differences were observed at baseline).
WLM3P Weight Loss Maintenance 3 Phases Program (Intervention group), *LCD* low-carbohydrate diet (Control group), *BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *BFM* body fat mass, *SMM* skeletal muscle mass, *S/V ratio* skeletal muscle mass-to-visceral fat area ratio, *VFA* visceral fat area, *WHR* waist-to-hip ratio, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* triglycerides, *TG/HDL ratio* triglyceride/high-density lipoprotein cholesterol.
Differences were statistically significant when *p < 0.05.

aligning with evidence that a carbohydrate-restricted/high-protein diet is efficacious in improving these lipid markers [30].

From a clinical perspective, the positive outcomes in both groups may be attributed to factors such as the extended duration of the intervention, which likely facilitated the establishment of new lifestyle habits [4, 5]; high emphasis on diet quality [31]; a reduction in total energy intake (Supplementary Table S4) [4, 5]; and a macronutrient composition that can favor body composition improvements and satiety [15, 17, 18]. A carbohydrate-restricted/high-protein diet may improve body composition by increasing secretion of satiety hormones, lipolysis, thermic effect of proteins, glucose homeostasis, and promoting preservation of SMM, which helps maintain resting energy expenditure despite WL [15, 18] and lower weight regain in the short term (3–12 months) [17]. High session attendance rates (superior to 60.5% reported by others WL intervention [32]), adequate sleep duration [33], and an increase in the proportion of participants achieving recommended physical activity levels also likely contributed to the groups' success [4, 5] (Supplementary Table S4).

Other components of the WLM3P program may also have positively influenced weight management. The WLM3P's high-intensity approach, including 24 sessions over 6 months, provided personalized guidance, support, goal setting, and nutritional education, which are crucial for long-term weight management success [4, 5]. The integration of TRE, prolonged nightly fasting (WL phase: median 13.5 h and weight maintenance phase: median 13.1 h; Supplementary Table S4), as a strategy could further enhance WL and health outcomes by promoting a metabolic switch and improving body composition [7, 8].

The WLM3P program also incorporates dietary supplements, including vitamins, minerals, and bioactive compounds (i.e., l-carnitine, caffeine, green tea, and chromium), which may synergistically or additively improve metabolic health outcomes through various mechanisms, including modulation of lipid and carbohydrate metabolism, appetite reduction, influence on intestinal microbiota activity, and increased energy expenditure [9, 10]. However, the efficacy and safety of WL programs that use supplements as adjuncts require further evaluation in randomized controlled trials to provide healthcare providers with evidence-based recommendations [9, 10]. Additionally, the WLM3P leverages a mobile/web platform to enhance adherence, track progress, and provide access to resources, aligning with contemporary digital integration trends in WL programs [12, 13].

Our study reported no serious adverse events, and the most common adverse event, constipation, occurred at a lower rate than in other WL programs [34], underscoring the tolerability of both groups. Electrolyte balance, an important consideration in programs including diuretic supplements [35], was not adversely affected by the WLM3P intervention (Supplementary Table S4). The withdrawal rate at 18 months in our study (31%) was slightly below the average for weight loss trials at 1 year (37%) [36]. One of the key strengths of our study is the extended period (18 months) of this randomized controlled trial, which allowed us to gather comprehensive and detailed information on weight changes across the study duration. However, it is important to acknowledge the limitations of this study. First, the small sample size might have limited the statistical power, primarily focusing on detecting differences in weight change between the two groups rather than secondary outcomes. Second, due to the study design, we are unable to distinguish between the individual components' effects of the WML3P, nor to analyze their interactions. Further research is warranted to dissect the contributions of each component and their synergistic or additive effects on weight management. Third, the control group in our study received active treatment with WL and weight maintenance-specific feedback. This might have influenced the outcomes, as a high percentage of participants in both groups achieved WL of ≥5%.

Fourth, we recognize the potential for bias and error in self-reported questionnaires and dietary records for assessing food intake [26], despite participants documenting and photographing their meals and our review process using a food quantification manual [37]. Future research with larger sample sizes is needed to obtain more robust and conclusive results.

In conclusion, our trial demonstrated that the WLM3P program was highly effective in helping adults with obesity achieve significant and sustained weight loss. The WLM3P resulted in a mean WL of 15.5%, with a large proportion of participants (87.5%) reaching the clinically significant milestone of 5% weight loss at the 18-month mark. Notably, the WLM3P program outperformed the LCD group in terms of achieving higher WL targets of 10 and 15%, as well as providing additional clinical benefits such as reducing BMI, body fat mass, visceral fat area, waist circumference, waist-to-hip ratio, and TG/HDL ratio, while increasing HDL-cholesterol levels. These improvements have important implications for the management of obesity-related metabolic disorders. Although our study did not specifically isolate the effects of individual program components, it provided valuable evidence of

Table 3. Change in body composition during the weight maintenance phase (6–18 months) among completing study participants, by groups.

Variable	WLM3P group (n = 39)	LCD group (n = 37)	Estimated treatment difference (95% CI)	p value
Δ Body weight (kg)	4.1 ± 6.1	3.5 ± 4.9	1.2 (−3.7 to 1.5)	0.381
Δ Body weight (%)	4.3 ± 5.8	3.5 ± 4.8	1.2 (−3.7 to 1.4)	0.357
Δ BFM (kg)	4.7 ± 5.3	3.8 ± 4.7	1.3 (−1.0 to 3.6)	0.254
Δ BFM (%)	3.9 ± 3.7	2.6 ± 3.4	1.4 (−0.2 to 3.1)	0.085
Δ SMM (kg)	−0.4 ± 1.3	−0.1 ± 0.9	−0.2 (−0.7 to 0.3)	0.384
Δ VFA (cm^2)	24.3 ± 25.1	18.0 ± 21.1	7.6 (−3.1 to 18.3)	0.165
Δ S/V ratio	−0.05 ± 0.09	−0.03 ± 0.08	−0.03 (−0.07 to 0.01)	0.141
Δ WHR	0.03 ± 0.04	0.02 ± 0.03	0.01 (−0.00 to 0.03)	0.080
Δ WC (cm)	3.1 ± 5.3	1.9 ± 4.3	1.6 (−0.7 to 3.8)	0.169

Change scores are represented by "Δ" in the table. All data were presented as mean ± standard deviation (±sd). p values were computed with a linear regression model considering as confounders: age, sex, body mass index, and baseline glucose (used since differences were observed at baseline).
WLM3P Weight Loss Maintenance 3 Phases Program (Intervention group), *LCD* low-carbohydrate diet (Control group), *BFM* body fat mass, *SMM* skeletal muscle mass, *VFA* visceral fat area, *S/V ratio* skeletal muscle mass-to-visceral fat area ratio, *WHR* waist-to-hip ratio, *WC* waist circumference.

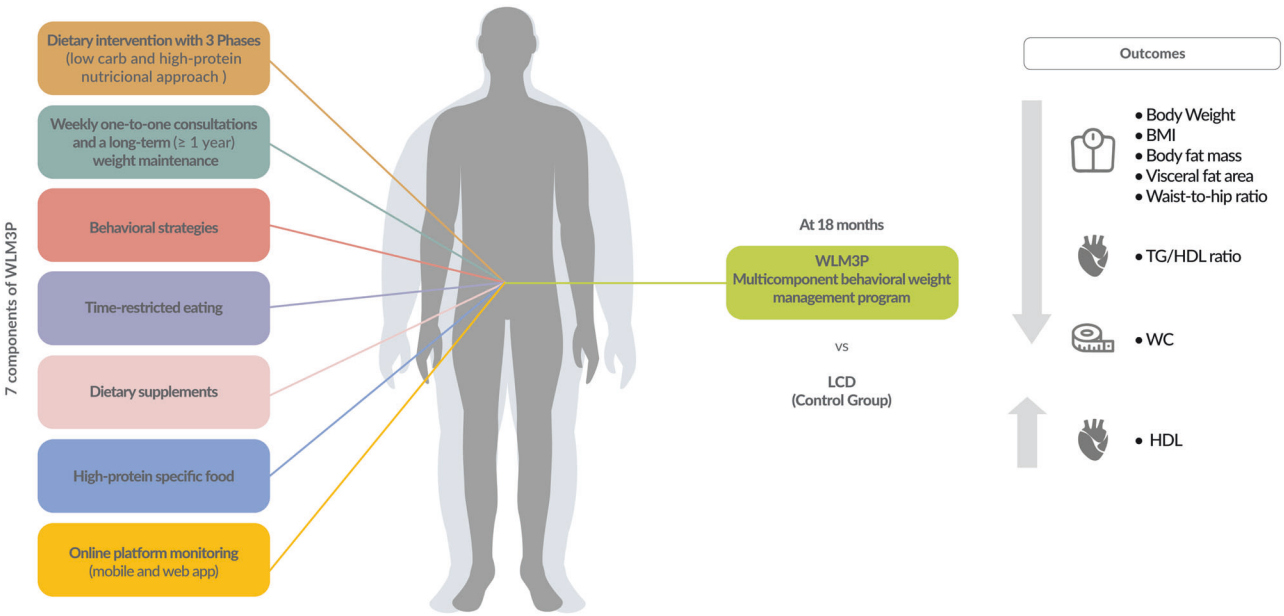

Fig. 2 WLM3P group results vs. LCD group at 18 months. WLM3P Weight Loss Maintenance 3 Phases Program (Intervention group), LCD low-carbohydrate diet (Control group), BMI body mass index (calculated as weight in kilograms divided by height in meters squared), TG/HDL ratio triglyceride/high-density lipoprotein cholesterol, WC waist circumference, HDLhigh-density lipoprotein cholesterol.

the overall efficacy of multicomponent behavioral weight management programs. These findings contribute to the existing knowledge base and emphasize the potential of multicomponent intensive behavioral weight management programs to address the growing obesity epidemic.

DATA AVAILABILITY

The full data sets generated during and/or analyzed during the current study are not publicly available because the ethics committee only allowed the use of the data in the context of the present research project; however, anonymized partial data sets or summaries of the data are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

André Moreira-Rosário, Conceição Calhau, Diana Teixeira, Filipa Cortez, Marta P. Silvestre, and Vanessa Pereira conceived the study design. André Moreira-Rosário and Marta P. Silvestre are the methodology and clinical nutrition leaders, respectively; in turn, Conceição Calhau is the principal investigator of this clinical trial. Vanessa Pereira was responsible for the protocol and procedures writing under the supervision of André Moreira-Rosário and Marta P. Silvestre. Vanessa Pereira drafted the manuscript. Cláudia Camila Dias was responsible for the statistical analysis plan and did not have any interference in the study design and implementation. Inês Barreiros-Mota, Conceição Calhau, Diana Teixeira, Filipa Cortez, Cláudia Camila Dias, André Moreira-Rosário, and Marta P. Silvestre reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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COMPETING INTERESTS

Vanessa Pereira and Filipa Cortez work at Farmodiética S.A., one of the study sponsors. The sponsor provided support in the form of salaries for the author (Vanessa Pereira) and research materials but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the paper. The other researchers do not have any relationship with this sponsor.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial was registered at clinical trials.gov under the identifier NCT04192357. The recruitment and data collection of this study have already been completed. The study was approved by the Ethics Committee of the NOVA Medical School (Lisbon, Portugal) (CEFCM Approval Number: 108/2018) and was registered at www.clinicaltrials.gov (NCT04192357) before participants' recruitment. All

participants provided written informed consent in accordance with the principles of the Declaration of Helsinki. Written informed consent has been obtained from the patients to publish this paper.

ADDITIONAL INFORMATION

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