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The Effectiveness of a Partial Meal Replacement Program in Extremely Obese Individuals: A Systematic Retrospective Chart Review of Medifast Weight Control Centers

Jessica R. Kiel[1,*], Christopher D. Coleman[1], Andrea H. Mitola[2], Janice S. Langford[1], Kevin N. Davis[1] and Linda M. Arterburn[1]

[1]Department of Scientific and Clinical Affairs, Medifast, USA

[2]Independent Consultant, Clifton Park, USA

*Corresponding author: Jessica R. Kiel, Department of Scientific and Clinical Affairs, Medifast, Inc. 11445 Cronhill Drive, Owings Mills, MD, 21117, USA, Tel: 410-504-8164; Fax: 443-471-3341; E-mail: JKiel@choosemedifast.com

Abstract

Background: Extreme obesity is associated with elevated risks of morbidities and mortality, and the prevalence of this condition has been rising. Lifestyle interventions are the cornerstone of all treatment options, yet relatively few studies have assessed the effectiveness of commercial programs for attaining clinically meaningful weight loss ($\geq 5\%$) in this population. The purpose of this study was to evaluate the effectiveness of the Medifast 5 & 2 & 2 Plan™ administered along with counseling in obese adults, a majority of whom were extremely obese.

Methods: We conducted a systematic retrospective chart review of 62 obese clients from 17 Medifast Weight Control Centers® (MWCCs). Weight, body composition and cardiometabolic risk factor data were abstracted through 24 weeks. Data were recorded electronically, and key data points were independently verified. The primary endpoint was change from baseline body weight at 12 weeks, assessed using Wilcoxon signed rank tests.

Results: The population consisted of 57% men, and 82% had a body mass index of ≥ 40 kg/m^2. Mean body weight among completers was reduced by 12.9 ± 7.1 kg (-8.6%, n=37) at the 12-week primary endpoint and by 19.3 ± 11.4 kg (-12.5%, n=17) at 24 weeks (p<0.0001). At 12 and 24 weeks, 76% and 88% of those remaining on the plan, respectively, had lost $\geq 5\%$ of their baseline body weight. Fat mass accounted for a majority (68-80%) of the weight lost, resulting in improvements in body composition. Significant improvements in blood pressure and central adiposity were also observed. Program adherence was >80%, and the meal plan was well-tolerated.

Conclusions: The 5 & 2 & 2 Plan used at MWCCs was effective for achieving clinically meaningful weight loss and improving cardiometabolic risk factors in a population of extremely obese individuals. This lifestyle program represents a viable first line approach for meeting treatment goals in extremely obese adults. #NCT02150837.

Abbreviations

BMI: Body Mass Index; CFR: Code of Federal Regulations; CI: Confidence Interval; ITT: Intention-To-Treat; LOCF: Last Observation Carried Forward; MWCC: Medifast Weight Control Center; PHI: Personal Health Information; TEE: Total Energy Expenditure

Introduction

More than one third of adults in the United States are obese, and while the prevalence of obesity appears to be plateauing, the prevalence of extreme obesity (body mass index (BMI) ≥ 40 kg/m^2) continues to rise [1-3]. The extremely obese now represent the fastest growing segment of the obese population, both in the United States and in several other developed countries [2-4]. The current rate of extreme obesity in US adults at 6.4% is expected to rise to approximately 9% by 2030 [5, 6]. This shift raises important public health concerns since the risk of obesity related co-morbidities and mortality increases with higher BMI [7, 8]. Extreme obesity is associated with a significantly elevated risk of total mortality, primarily due to heart disease, diabetes and cancer, as well as a reduction in mental well-being and quality of life [9, 10].

Pharmacotherapy used as an adjunct to lifestyle changes can assist with weight loss in individuals who are obese, but it is considered as a second line treatment when lifestyle intervention alone is not successful [11]. For the higher BMI categories, bariatric surgery is another treatment option that generally results in greater weight loss and improvements in co-morbid conditions compared to less invasive interventions [8]. However, this option is also only indicated for those who have not responded to lifestyle intervention alone. Additionally, not everyone is eligible for bariatric surgery, not everyone wants to have surgery, and the side effects associated with this option are generally higher than those of lifestyle interventions which can still result in a more modest weight loss of 5-10% that is clinically meaningful and has been shown to lower disease risk [12].

The disproportionate growth of the extremely obese population, combined with the increased health risks and the low number treated with surgical interventions, highlight the need for comprehensive

lifestyle interventions where the weight loss achieved is, at a minimum, clinically meaningful [9, 13]. In fact, current guidelines recommend participation in a comprehensive lifestyle program as the first step in the treatment of obesity, including extreme obesity, and lifestyle interventions serve as the basis for all treatments of obese individuals [8]. These same guidelines support the use of commercial programs that provide a comprehensive lifestyle intervention, provided they are backed by evidence of their safety and efficacy. However, few commercial programs have focused on the extremely obese population, and relatively few clinical studies have investigated the effectiveness of diet and lifestyle interventions in this population.

The Medifast 5 & 2 & 2 Plan™ is a commercial program often recommended for individuals with over 100 pounds (45.5 kg) of weight to lose or a BMI ≥40 kg/m^2. The 5 & 2 & 2 Plan is one of several programs that feature a combination of Medifast Meal Replacements, conventional food choices, and customizable levels of support for weight loss and weight maintenance. At Medifast Weight Control Centers® (MWCCs), the Medifast meal plans are combined with individualized one-on-one weekly counseling to create a comprehensive lifestyle program. Other Medifast plans (the 5 & 1 Plan® and the 4 & 2 & 1 Plan™) have been evaluated and shown to be effective for weight loss in overweight and obese populations [14-17]. In addition, previous studies have shown that portion-controlled meal replacements enhance dietary compliance and are helpful for achieving clinically meaningful, sustainable weight loss in overweight and obese populations [14, 15, 18-21], including those with extreme obesity [13, 22, 23]. The purpose of this study was to evaluate the effectiveness of the Medifast 5 & 2 & 2 Plan for weight loss over 24 weeks (12-week primary endpoint) by systematically reviewing charts from MWCC clients who followed this meal plan, the vast majority of whom were extremely obese. Secondary objectives included assessing effects on body composition and cardiometabolic risk factors in this population.

Methods

This study was a systematic retrospective chart review of MWCC clients who started the Medifast 5 & 2 & 2 Plan for weight loss on or after January 1, 2012 and completed the active weight loss phase of their program by March 31, 2014. Seventeen MWCCs were chosen for this study, based on (a) their close proximity to Medifast corporate headquarters (all MWCCs in Maryland) or (b) because they were among the centers with the largest base of clients following the 5 & 2 & 2 Plan - these were located in Texas, Florida and Pennsylvania. The MWCC point-of-sale system was used to identify charts of clients who purchased the 5 & 2 & 2 Plan. Once identified, charts were pre-screened at each MWCC for the presence of a signed personal health information (PHI) consent form (which included permission to use their data for research purposes), and then shipped to corporate headquarters for formal screening and data abstraction. Charts from clients who met the following study selection criteria were included: male or female overweight or obese adult (age ≥ 18 years, BMI ≥ 25 kg/m^2), signed a PHI form, started the 5 & 2 & 2 Plan after January 1, 2012, followed the 5 & 2 & 2 Plan for at least 2 weeks, was not in the active weight loss phase of their program at the time of screening, and was not concurrently using any other weight loss program or pharmacotherapy for weight loss. The study was approved by an independent institutional review board (Western Institutional Review Board, Puyallup, WA) which concluded that the study met the requirements for a waiver from the informed consent process per 45

CFR 66.116(d). This study adhered to current methodological standards for retrospective chart reviews [24] and was registered in the ClinicalTrials.gov database (#NCT02150837).

The weight management program offered at the MWCCs consists of weekly one-on-one in-person sessions with MWCC counselors who utilize motivational interviewing and a series of personalized behavior change strategies designed to develop behaviors that promote long-term weight management through a healthy lifestyle. MWCC counselors are trained using a combination of on-the-job and corporate-based training to ensure thorough knowledge of the Medifast products and programs and an understanding of the behavior change strategies used at MWCC. A client's weight loss goals are determined jointly by the counselor and client, which in turn determines the prescribed length of the client's active Weight Loss phase and overall weight management program. Programs generally include active Weight Loss, Transition, and Maintenance phases. The meal plan chosen for weight loss is also determined jointly based on a number of factors including the client's personal preferences, lifestyle, exercise habits and medical history.

The 5 & 2 & 2 Plan is a calorie- and portion-controlled meal plan designed to stimulate gradual, steady weight loss and provides 1,300-1,500 calories daily. It consists of 5 Medifast Meal Replacements (Medifast, Inc., Owings Mills, MD, USA), 2 self-prepared lean and green meals (each including 5-7 oz. of lean protein, 3 servings (∼1½ cups) of non-starchy vegetables, and up to 2 healthy fat servings), and 2 healthy snacks (fruit, dairy or whole grains). Medifast Meal Replacements, of which there are over 70 to choose from, each contain 90-110 calories, 11-15 g protein (primarily from soy and/or dairy), 8-15 g carbohydrates, and 0-3.5 g fat; they each share a similar nutritional profile and can be used interchangeably during the Weight Loss phase and with any of the Medifast weight loss meal plans. After completion of the Weight Loss phase, some MWCCs may include a Transition phase, during which total calories and conventional food choices are gradually increased. All individuals who have met their weight loss goal during the active Weight Loss phase or who have completed their prescribed weight loss weeks then have the option to enter the Maintenance phase. The Medifast Maintenance Plan is based on a client's Total Energy Expenditure (TEE) and generally includes 3 Medifast Meal Replacements and 3 self-prepared meals (consisting of conventional food choices with serving sizes based on the Exchange List for Weight Management; the number of servings is individualized based on TEE).

Data were recorded in client charts at MWCCs by counselors. Counselors were trained to use consistent procedures when obtaining weights and anthropometric measurements. Weight was measured to the nearest 0.1 pound using a high-quality digital scale. Body composition was assessed without shoes and in light indoor clothing by direct, segmental, multi-frequency bioelectrical impedance analysis using either an InBody 230® or InBody 370® body composition analyzer (InBody Co., Cerritos, CA, USA); measurements (fat mass, percent body fat and fat free mass) from the InBody analyzer are highly correlated (r ≥ 0.97) with those obtained using dual energy X-ray absorptiometry [25]. Blood pressure and pulse were measured using digital arm blood pressure monitors. Adherence was assessed based on clients' visit attendance and self-reported meal replacement consumption.

Weight, pulse, blood pressure, and adherence-related information were abstracted at baseline and weekly throughout the client's Weight Loss phase through 24 weeks plus at the Final Visit. The Final Visit

was defined as the client's last visit to the MWCC during active weight loss while following the 5 & 2 & 2 Plan; the time of the Final Visit varied by individual client. Anthropometrics and body composition information, which were measured approximately every 4 weeks at the MWCCs, were also collected. When available, body weight data and the corresponding dates were abstracted at the beginning and end of any other MWCC meal plans or program phases that followed a client's use of the 5 & 2 & 2 Plan.

Notations of adverse signs, symptoms or incidents that occurred while a client was on the 5 & 2 & 2 Plan were abstracted verbatim from the chart notes, regardless of whether or not the incident appeared to be related to the intervention. This information was reviewed and categorized by a registered nurse, and simple frequencies were tabulated.

Chart data were abstracted by trained study personnel directly into electronic case report forms developed using IBM SPSS Data Collection Author and Interviewer Version 7, according to conventions developed for this study. A two-user, independent (double-data) data entry procedure was used for verification of all key data points.

Power calculations and statistical analysis

The primary outcome in this study was change from baseline body weight at 12 weeks. Sample size was determined using a 10% standard deviation, 0.05 significance level and with the assumption that up to 50% of the charts would not have weight outcome data at the 12-week time point (e.g., clients completed their program, dropped out, switched to another meal plan before 12 weeks, or had missing data for this time point). From these assumptions, a minimum of 64 charts was required to attain 80% power in order to detect clinically meaningful weight loss of 5% from baseline using a paired t-test for a within-group comparison.

Data were analyzed according to a pre-defined statistical analysis plan. Wilcoxon signed rank tests (i.e., paired t-tests for repeated measures nonparametric data) were used to compare within group changes in weight at 12 weeks compared to baseline for the primary analysis and at other predetermined time points (1, 2, 4, 8, 16, 20 and 24 weeks). Due to the retrospective nature of the study, predefined windows that used data closest to the specified time point were established to optimize the sample without bias: data were included if available within ± 3 days for the 1 and 2 week time points, ± 7 days for the 4 week time point, and ± 10 days for the remaining time points. For the primary analysis, a completers analysis was used; this analysis included each chart that had data for the given outcome and time point, irrespective of whether the individual completed his/her entire program. Similar analyses were conducted on secondary outcomes. For comparison, an Intention-To-Treat (ITT) Last Observation Carried Forward (LOCF) analysis was pre-specified in the protocol, and performed for the primary outcome. If missing, imputed data were carried through from the last measured observation to each client's last prescribed week of weight loss. Additionally, in order to maximize the use of all data, including those with missing data, a pre-specified mixed model regression approach was used on the primary outcome, weight, with time as the independent variable and baseline weight as a covariate. The proportions of individuals achieving ≥ 5% and ≥ 10% weight loss from baseline were calculated. *Post hoc* subgroup analyses for each gender were performed for body weight. Significance was defined as p<0.05 with no adjustments for

multiplicity. Analyses were conducted using SPSS Version 14.0 and Stata Version 10.

Results

Chart selection and flow

Of the 87 charts received for screening, 62 met the study entry criteria and were included in the study; reasons for chart exclusions are shown in Figure 1. At 12 weeks, 37 individuals (60%) remained on the 5 & 2 & 2 Plan and were included in the completers analysis for the primary endpoint; at 24 weeks, 17 individuals (27%) remained on the plan. A major reason for discontinuing the 5 & 2 & 2 Plan was to switch to another Medifast meal plan (Figure 1). All 62 charts were included in the assessment for the Final Visit (Figure 1). The length of time to the Final Visit varied by individual (range 2-67 weeks). All 62 charts were included in the 12-week ITT analysis, and six charts were excluded from the 24-week ITT analysis because the individual's prescribed program length was less than 24 weeks (not shown).
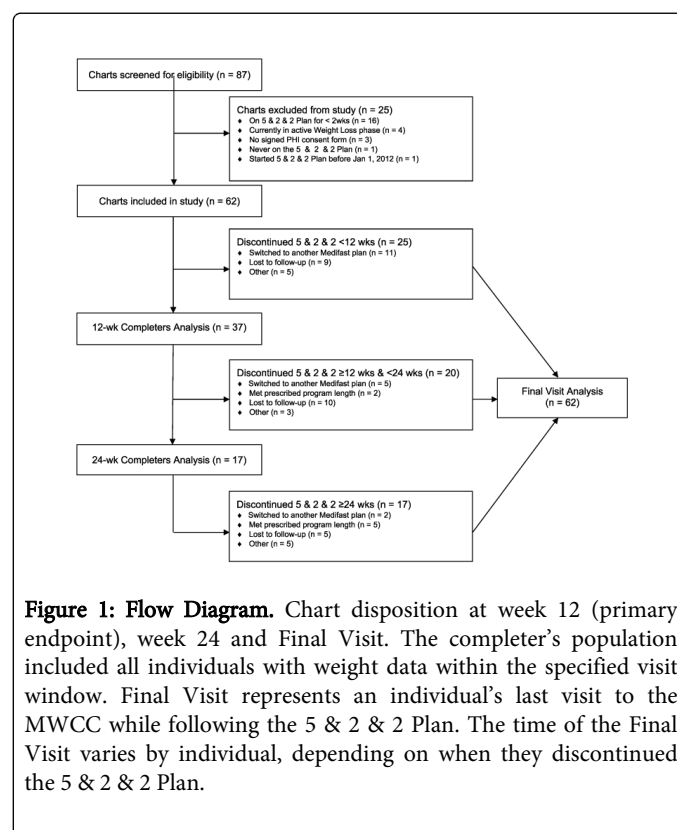
Figure 1: Flow Diagram. Chart disposition at week 12 (primary endpoint), week 24 and Final Visit. The completer's population included all individuals with weight data within the specified visit window. Final Visit represents an individual's last visit to the MWCC while following the 5 & 2 & 2 Plan. The time of the Final Visit varies by individual, depending on when they discontinued the 5 & 2 & 2 Plan.

Baseline characteristics

Baseline characteristics are summarized in Table 1. The mean age of the group was 46.8 ± 13.7 years, and there were more men (56.5%) than women in the group. The mean baseline body weight (148.7 ± 29.2 kg) and BMI (48.7 ± 9.9 kg/m^2) reflected the fact that most individuals (92%) were in the higher obesity classes (9.7% Class II (BMI ≥ 35 and < 40 kg/m^2) and 82.3% Class III (BMI ≥ 40 kg/m^2) obesity). Many reported having common obesity-related co-morbid conditions such as high blood pressure (41.9%), high blood sugar/diabetes (25.8%, predominantly Type 2 diabetes), sleep apnea (43.9%) and arthritis (24.1%).

| Demographic Characteristics	Mean ± SD or n (%)
N	62
Gender	
Female	27 (43.5%)
Male	35 (56.5%)
Age (yrs)	46.82 ± 13.74
Seniors (age ≥ 65 yrs)	7 (11.3%)
Weight (kg)	148.67 ± 29.2
BMI (kg/m^2)	48.73 ± 9.92
BMI Category	
Class I Obesity (BMI ≥ 30 and < 35 kg/m^2)	5 (8.1%)
Class II Obesity (BMI ≥ 35 and < 40 kg/m^2)	6 (9.7%)
Class III Obesity (BMI ≥ 40 kg/m^2)	51 (82.3%)
Current Smoker	5 (8.1%)
Co-Morbid Conditions	
Diabetes/High blood sugar	16 (25.81%)
High blood pressure	26 (41.94%)
Arthritis[a]	14 (24.1%)
Heart disease or past heart attack	2 (3.2%)
Liver disease	1 (1.6%)
Sleep apnea[b]	25 (43.9%)
High cholesterol[b]	18 (31.6%)
Thyroid disease	12 (19.4%)
[a]n=58, [b]n=57	

Table 1: Baseline characteristics.

Body weight and body mass index

For the primary endpoint at 12 weeks, weight among completers significantly decreased by a mean (± SD) of 12.9 ± 7.1 kg (-8.6%) from baseline (n=37, p < 0.0001, Figure 2), and all but one individual had lost weight. BMI decreased by 4.14 ± 2.29 kg/m^2 during this time interval (p < 0.0001). Overall, mean body weight decreased significantly compared to baseline throughout the entire 24 week study period (p < 0.0001, Figure 2). The most rapid reductions in baseline body weight occurred in the earlier time points, with decreases of 4.4 ± 2.3 kg or -3.0% (p < 0.0001, n=56) during the first 2 weeks and 6.5 ± 3.1 kg or -4.3% from baseline over the first 4 weeks on the plan (p < 0.0001, n=57). Among the 17 individuals who had weight data at 24 weeks, all had lost weight (mean -19.3 ± 11.4 kg, -12.5%), and BMI was reduced by 6.16 ± 3.54 kg/m^2 (p < 0.0001). In a random effects regression model, controlling for baseline weight, the average rates of weight loss (95% CI) over 2, 4, 12 and 24 weeks were -2.25 (-2.54, -1.95), -1.56 (-1.71, -1.42), -1.04 (-1.10, -0.98), and -0.79 (-0.85, -0.75) kg per week. Baseline weight and time were the only significant covariates in this model. Mean weight change at the Final Visit was -13.3 ± 12.6 kg

corresponding to an 8.8% reduction in baseline body weight (p<0.0001). Both males and females had significant reductions from baseline in body weight throughout the study period (p<0.05 for each gender at each time point (Figure 3)).
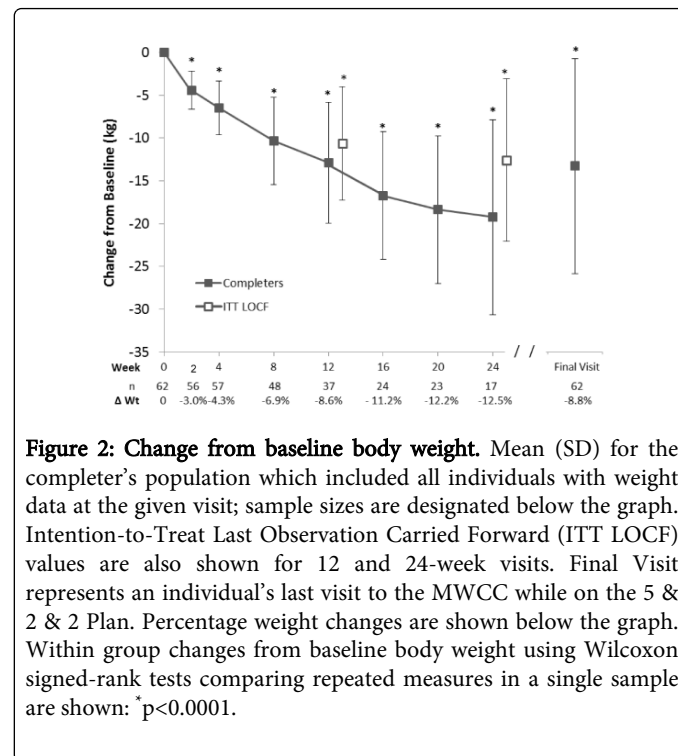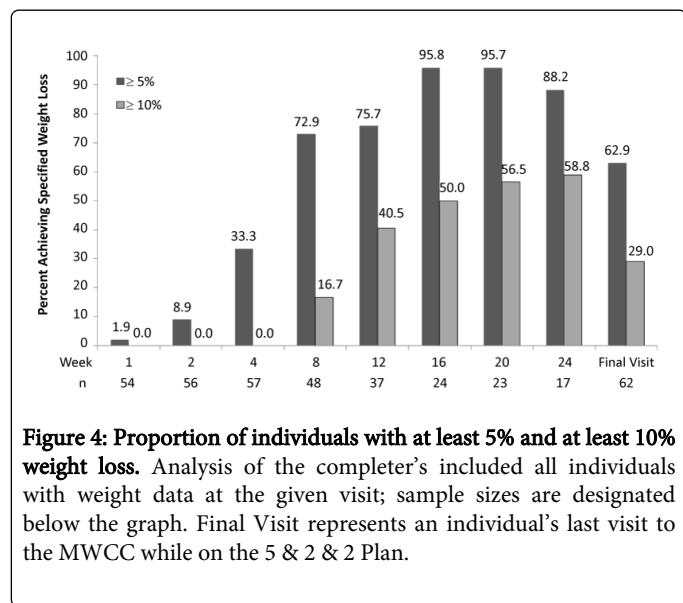

Figure 2: Change from baseline body weight. Mean (SD) for the completer's population which included all individuals with weight data at the given visit; sample sizes are designated below the graph. Intention-to-Treat Last Observation Carried Forward (ITT LOCF) values are also shown for 12 and 24-week visits. Final Visit represents an individual's last visit to the MWCC while on the 5 & 2 & 2 Plan. Percentage weight changes are shown below the graph. Within group changes from baseline body weight using Wilcoxon signed-rank tests comparing repeated measures in a single sample are shown: *p<0.0001.
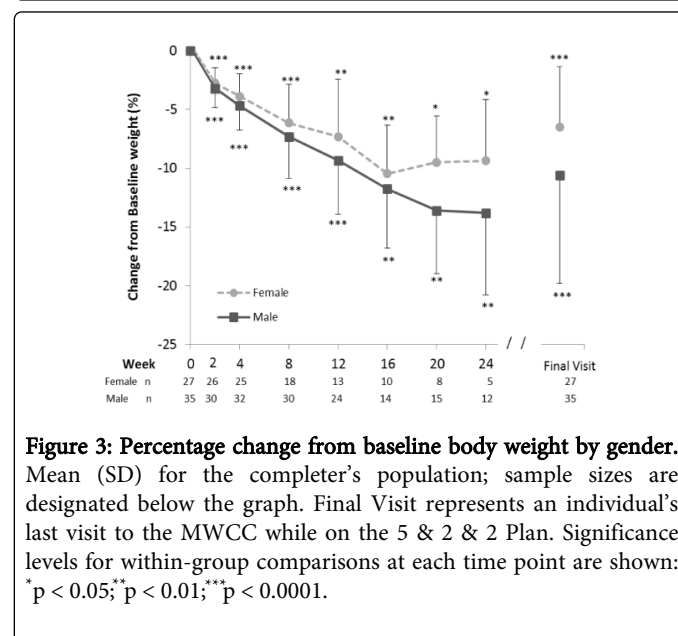
Figure 3: Percentage change from baseline body weight by gender. Mean (SD) for the completer's population; sample sizes are designated below the graph. Final Visit represents an individual's last visit to the MWCC while on the 5 & 2 & 2 Plan. Significance levels for within-group comparisons at each time point are shown: *p < 0.05; **p < 0.01; ***p < 0.0001.

The results of the ITT LOCF analyses also showed significant weight reductions throughout the 24 weeks (p<0.0001 at all time points; -10.6 ± 6.7 and -12.6 ± 9.5 kg at 12 and 24 weeks, respectively, see Figure 2). In the completers population (n=57) at week 4, 33% had lost at least 5% of their baseline body weight (Figure 4). Among individuals who followed the plan for at least 12 weeks (n=37), 76% had lost at least 5% and 41% had lost at least 10% of their baseline

body weight. At 24 weeks, 88% of those still on the program (n=17) lost at least 5% and 59% had lost at least 10% of their baseline body weight. At Final Visit (n=62), 62.9% had lost ≥ 5% of their baseline body weight. In the ITT analysis, 63% and 66% had lost ≥ 5% of their baseline weight by 12 (n=62) and 24 weeks (n=56), respectively (data not shown).


Figure 4: Proportion of individuals with at least 5% and at least 10% weight loss. Analysis of the completer's included all individuals with weight data at the given visit; sample sizes are designated below the graph. Final Visit represents an individual's last visit to the MWCC while on the 5 & 2 & 2 Plan.

Body composition

At baseline, lean body mass was 76.6 ± 14.3 kg and body fat mass was 69.3 ± 18.8 kg (n=45), with fat representing 47% of the body mass. Changes in absolute fat and lean mass in the completers are shown in Figure 5. Significant reductions (p < 0.05) in lean mass and fat mass were observed at all times through 20 weeks. Changes in lean mass were -2.5 ± 2.9 kg (-3.2% from baseline, p=0.023) and fat mass were -9.6 ± 3.7 kg (-16.7% from baseline, p=0.002) at 12 weeks. With the small sample size (n=4), reductions (-6.5 ± 4.2 kg lean mass and -25.9 ± 8.4 kg fat mass) at 24 weeks were not significant (p=0.068). As a percentage of total body mass, lean body mass increased from 53% at baseline to 61% at 12 weeks and to 66% at 24 weeks, while body fat mass decreased from 47% of body mass at baseline to 39% at 12 weeks and to 35% at 24 weeks. Lean mass represented between 20% and 33%, and fat mass accounted for 68% to 80% of the total body weight lost at the various times throughout the study period.

Cardiometabolic risk factors

The study group had a large proportion (42%) of individuals who self-reported high blood pressure at baseline. Measured mean systolic and diastolic blood pressures at baseline (n=31) were 139.8 ± 26.2 and 89.9 ± 12.4 mm Hg, respectively, and 26% were prehypertensive (systolic of > 120 and < 140 mm Hg and/or diastolic of > 80 and < 90 mm Hg) and 61% were hypertensive (systolic ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg) based on these measurements. Significant (p < 0.05) reductions in systolic and diastolic blood pressure were observed at all time points through 20 weeks (Figure 6). Systolic and diastolic blood pressure were reduced by 17.7 ± 17.6 (p=0.008) and 8.4 ± 8.0 mm Hg (p=0.003), respectively, at 12 weeks (n=13).
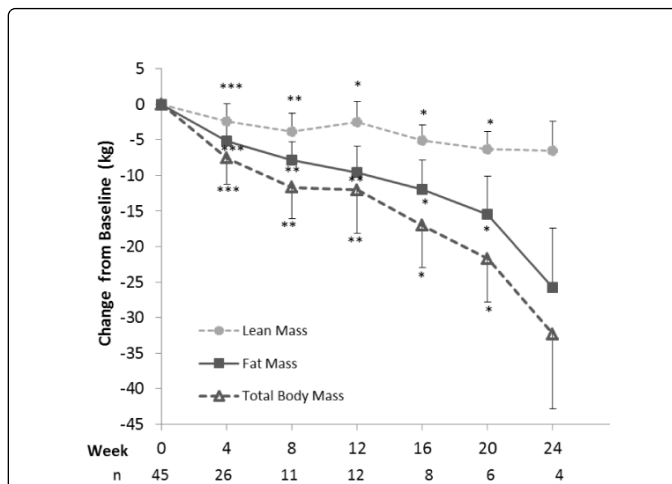
Figure 5: Changes in body weight, lean body mass and body fat mass. Mean (SD) for the completer's population; sample sizes are designated below the graph. Within group changes from baseline using Wilcoxon signed-rank tests comparing repeated measures in a single sample are shown: [*]p < 0.05; [**]p < 0.01; [***]p < 0.0001.
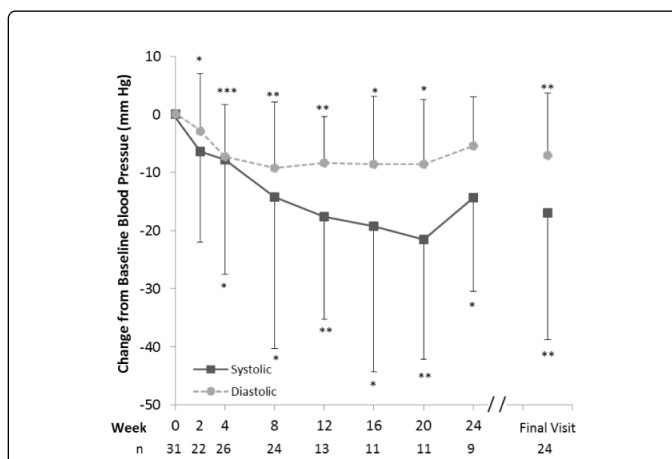
Figure 6: Change from baseline in systolic and diastolic blood pressure. Mean (SD) for the completers population; sample sizes are designated below the graph. Final Visit represents an individual's last visit to the MWCC while on the 5 & 2 & 2 Plan. Significance levels for within-group comparisons at each time point are shown: [*]p < 0.05; [**]p < 0.01; [***]p < 0.0001.

At 24 weeks (n=9), one person had an increase in systolic blood pressure, which in the context of the small sample size, led to a smaller average reduction in the systolic blood pressure (-14.3 ± 16.2 mm Hg, p=0.028) relative to previous weeks. There was a non-significant reduction in diastolic blood pressure (-5.4 ± 8.4 mm Hg, p=0.075) at 24 weeks. Overall, the improvements in blood pressure were reflected in favorable shifts in individual blood pressure categories (i.e. from hypertensive to prehypertensive or from prehypertensive to normal) in 26.9%, 53.8% and 44.4% of individuals at weeks 4, 12 and 24, respectively. Reductions in pulse rates were not significant at any time point (data not shown).

Baseline waist and hip circumferences of 136.2 ± 18.4 cm (n=52) and 150.4 ± 23.3 cm (n=49), respectively, decreased significantly through 20 weeks (p < 0.05), with non-significant reductions in both measures at 24 weeks. At 12 weeks, waist and hip circumferences decreased by 9.0 ± 4.7 cm and 10.6 ± 7.5 cm (n=10, p < 0.01), respectively, and at 24 weeks, by 10.0 ± 9.9 cm and 13.1 ± 8.5 cm (n=3, p=0.109), respectively. There were no changes in the waist-to-hip ratio.

Program information

Of the 5 meal replacements assigned per day, the average self-reported number consumed while individuals were on the 5 & 2 & 2 Plan ranged from 4.0 to 4.8 per day at the various times points, corresponding to 80% to 96% adherence throughout the 24-week study period. Adherence with weekly MWCC visits averaged 84% during the time individuals were on the 5 & 2 & 2 Plan.

Individuals on the 5 & 2 & 2 Plan were prescribed an average of 44.2 ± 19.5 weeks (range 14-100 weeks) of weight loss, and stayed on the 5 & 2 & 2 Plan for an average of 18.1 ± 15.8 weeks. Twenty nine percent (18/62) of the individuals who started the Weight Loss phase on the 5 & 2 & 2 Plan subsequently discontinued this plan in order to switch to one or more alternative Medifast weight loss plan(s) and spent an average of 28.6 additional weeks in active weight loss. During this time, they continued to lose an additional 8.8 ± 11.1 kg of body weight (p=0.002; -7.09% of their baseline body weight), for a total loss of approximately 19.6 ± 13.6 kg (-14.4% of their baseline body weight) over their entire Weight Loss phase (using the 5 & 2 & 2 Plan and other Medifast weight loss plans).

Eight percent (5/62) of individuals who originally started the 5 & 2 & 2 Plan entered the Transition phase. The average length of time spent in Transition was 4.2 weeks, during which time individuals regained 0.9 ± 3.1 kg (p=0.893). Eleven percent (7/62) entered the Maintenance phase after losing an average of 39.0 ± 20.7 kg (compared to baseline) during their entire prior Weight Loss and Transition phases, as applicable. While in the Maintenance phase, the group regained an average of 4.6 ± 8.1 kg (p=0.116) or 3.4% of their baseline body weight; the mean length of time spent in the Maintenance phase was 17 weeks. Despite this regain, those who entered the Maintenance phase experienced a total net weight loss (from baseline to the end of Maintenance) of 34.4 ± 19.2 kg (p=0.018) or 24% of their baseline weight.

Safety

Signs and symptoms occurring at frequencies of >5% included constipation (14.5%), hunger (19.4%), cravings (8.1%), stress/anxiety (8.1%), headache (9.7%) and generally feeling sick (21.0%) at some time during the period of study. This latter term was too general to categorize or assess further. Additionally, high blood pressure (not necessarily worsening) was noted in 16.1% of charts, half of which occurred in individuals who had self-reported pre-existing hypertension. There were two reports (3.2%) of serious medical incidents: a mini-stroke which did not appear to be related to the intervention since the individual had pre-existing atrial fibrillation and was on anti-coagulant medication, and a cholecystectomy which was attributed by the individual's physician to weight loss but not specifically to the meal plan *per se*. This latter event was the only report of a gall bladder-related incident.

Discussion

This systematic retrospective chart review evaluated the effectiveness of the Medifast 5 & 2 & 2 Plan as used by real-world customers at MWCCs for weight loss. The studied population was predominantly males (57%) and nearly all were in the higher obesity classes (92% Class II or III obesity), reflecting the demographics of clientele on this meal plan. In this population, the 5 & 2 & 2 Plan resulted in significant reductions in body weight over both 12- and 24-weeks. Initial weight loss was rapid (-1.56 kg/week over the first month) followed by a more moderate, yet steady and significant weight reduction over the entire study period (average of -1.04 and -0.79 kg/week over 12 and 24 weeks, respectively). Importantly, the 5 & 2 & 2 Plan was effective for achieving clinically meaningful weight loss of ≥ 5%, as outlined in recent obesity treatment guidelines [8]: among those remaining on the meal plan, one-third lost ≥ 5% of their baseline body weight by 4 weeks, 3 out of 4 achieved this goal by 12 weeks, and over 88% achieved at least 5% weight loss at all times thereafter. Assessing weight loss at the Final Visit, irrespective of how long an individual was on the 5 & 2 & 2 Plan, represents a stricter measure of effectiveness as it accounts for attrition that took place prior to 24 weeks; by this measure, nearly two-thirds achieved clinically meaningful weight loss of ≥ 5% by their Final Visit on the 5 & 2 & 2 Plan. Results from the ITT analyses at 12 and 24 weeks were similar to the Final Visit results, thus providing another robust assessment of effectiveness.

The 5 & 2 & 2 Plan generally compared favorably to other published lifestyle interventions in similar populations, although direct study comparisons are challenging given the heterogeneity in intervention types, study duration and study design. The pooled mean weight loss in a recent meta-analysis evaluating lifestyle interventions in short term studies (< 6 month duration) of individuals with class II and III obesity was 7.2 kg (95% CI: 8.9, 5.5) [23]. These lifestyle interventions included a nutrition component (education, recommendations, caloric restriction, etc.) together with a physical activity component. The mean weight loss in this study (-12.9 kg at 12 wks and -19.3 kg at 24 wks in the completers and -10.6 kg at 12 wks and -12.6 kg at 24 wks in the ITT analysis) was greater than the weight loss reported in most, but not all, studies included in that meta-analysis. Weight loss on the 5 & 2 & 2 Plan in both the completers and ITT populations at 6 months also exceeded that reported in two other studies evaluating the effect of physical activity along with behavioral intervention and caloric restriction in extremely obese adults [26, 27]. Not surprisingly, given that caloric intake associated with the 5 & 2 & 2 Plan is higher (1,300-1,500 kcal/day), weight loss on the 5 & 2 & 2 Plan was less than that observed in extremely obese individuals following a physician-supervised very-low or low energy diet using meal replacements (usually < 1,000 kcal/day) in conjunction with behavioral therapy [22].

In addition to measuring changes in total body weight, changes in body composition were also assessed. While there were significant reductions in both lean and fat mass, the majority (68-80%) of weight loss came from fat mass. Considering that lean mass accounted for an average of 20 to 33% of the weight reduction in this study, this program performed well compared to typical losses of 36% to 40% for men and 31% to 33% for women [28-31]. The retention of lean mass may be partially attributed to the extremely obese population studied, since large baseline fat mass appears to help spare lean mass loss during caloric deficit [29]. However, it may also be linked to the macronutrient composition of the meal plan which provides approximately 135-175 g of high quality protein per day. With the

group's mean baseline weight of 149 kg, this translates to an estimated 0.9 to 1.2 g protein per kg body weight, thus exceeding the average daily requirement of 0.8 g/kg and providing levels similar to those considered ideal for muscle retention during weight loss [32]. Likewise, preservation of lean mass has been observed in previous studies with mixed populations of overweight and obese individuals using other Medifast weight loss meal plans (the 5 & 1 Plan® and the 4 & 2 & 1 Plan™ which also provide > 100 g of protein/day), also suggesting that the combination of meal replacements and conventional foods recommended in these programs is beneficial for preserving lean mass during weight loss [14-17, 33]. While increases in activity and exercise are encouraged, none of the previously mentioned Medifast programs included a structured exercise regimen, further underscoring the likelihood that the macronutrient composition contributes to the observed preservation of lean muscle mass.

The achievement of clinically meaningful weight loss was reflected in the concomitant improvements in blood pressure. A substantial proportion of individuals (between 42% and 61% depending on whether assessed by self-report or measured) had high blood pressure at baseline, and the mean baseline systolic and diastolic blood pressures of the group (139.8 and 89.9 mm Hg, respectively) was nearly in the hypertensive range. However, at the 12-week primary endpoint, the mean systolic and diastolic blood pressures (116.9 and 79.5 mm Hg, respectively) fell into the normal range. The magnitude of the reduction in blood pressure (-17.7 mm Hg systolic and -8.4 mm Hg diastolic at 12 weeks) is clinically important and is large enough to have a significant impact on cardiovascular disease risk [34]. In fact, over 40% of individuals experienced an improvement in their blood pressure category at 12 and 24 weeks while on the 5 & 2 & 2 Plan. The apparent increase in the mean systolic blood pressure at 24 weeks appeared to have a basis in the small sample size rather than being representative of a true trend. Also of note with regard to cardiometabolic disease risk is the significant reduction (-9.0 cm) in waist circumference at 12 weeks. This measure is an indicator of visceral fat which is linked to diabetes and cardiovascular disease risk [35]. The reduction in waist circumference was directionally larger (-10.0 cm), but not significant at 24 weeks (p=0.109), a consequence of the small sample size.

Weight maintenance data in this study were limited by the small number of individuals (11%, n=7) who entered this phase. The available data indicate a non-significant trend toward partial weight regain (3.4% of baseline body weight), yet the overall mean weight change during the entire program (mean of 61 weeks over the Weight loss, Transition (as applicable) and Maintenance phases) was significant (-34 kg, or 24% below the group's baseline weight), suggesting the program was effective for weight loss and weight maintenance for the limited subset that entered the Maintenance phase.

All signs, symptoms and health-related incidents were collected and analyzed in a systematic fashion. When evaluated, these incidents were consistent with previously reported side effects [15], primarily constipation, and general complaints of hunger, cravings, and stress which are also often associated with intentional weight loss. Both obesity and weight loss are known to be significant risk factors for the development of gallstones [36, 37], and one person (1.6%) experienced gallbladder pain/stones, ultimately requiring surgery. Aside from this cholecystectomy, only one other serious (unrelated) incident was reported. The observed rate of serious events (3.2%) is similar to placebo rates seen in pharmacotherapy trials with obese populations [38-40]. Overall, the data suggest the 5 & 2 & 2 Plan was generally well-tolerated in this population of obese individuals.

One limitation of this study was the relatively small starting sample size (n=62) combined with attrition from the meal plan which, together, resulted in limited datasets, particularly at the later time points and for many of the secondary outcomes. Data at the primary endpoint, change in bodyweight at 12 weeks, was not available for approximately 40% of the starting study population. To address these concerns, tripartite analyses (completers, ITT and regression analyses) for body weight changes were conducted, the latter two of which accounted for missing data. All three analyses showed similar effectiveness, albeit with the greatest weight loss in the completer's analysis. As previously noted, many individuals switched to other Medifast weight loss plans over time, and a portion of the difference between the completers and ITT results can be attributed to the large proportion (29%) of individuals, who as their BMI dropped to below 40 kg/m^2, switched, per center procedure, to other Medifast weight loss plan(s), and continued to lose weight. These were among the most successful individuals on the 5 & 2 & 2 Plan, thus reducing the overall observed weight loss at the later time points in the ITT analysis. Retention on the 5 & 2 & 2 Plan at 12 weeks (60%) was in the range observed with some other commercial weight loss programs (approximately 45-70%), but was better if one considers the total proportion that continued on any of the Medifast weight loss plans at 12 weeks (n=48, 77%) [22, 41]. Another limitation was the retrospective nature of the study and absence of a control group. A larger, prospective, randomized, controlled trial could strengthen these results and address efficacy in a broader population. Nonetheless, the results are of interest since they are a true representation of the program's effectiveness in real clients in the weight loss centers.

In conclusion, the 5 & 2 & 2 Plan administered at MWCCs appeared to be well-tolerated and resulted in clinically meaningful weight loss in a majority of the study population, which consisted primarily of extremely obese individuals. Concomitant improvements in cardiometabolic risk factors were also observed. Based on these results, the 5 & 2 & 2 Plan represents a viable first line treatment option for individuals with extreme obesity and may have utility prior to advocating more intensive treatments, such as pharmacotherapy or bariatric surgery. Given the need for an accompanying lifestyle intervention, this program could also be an effective pairing for use with other treatment modalities.

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