REVIEW ARTICLE

Review of key findings from the OPTIWIN trial: Implications and future directions for medical weight management using total diet replacement

Authors
Shenelle A. Edwards-Hampton[1], Ruth Bernstein[1], Amy Rothberg[2], Laura Matarese[3], Sarah S. Cohen[4], Sally L. Coburn[5], Walter J. Pories[3], Judy Loper[6], Kristina H. Lewis[7], Jamy D. Ard[1*]

Affiliations
[1]Wake Forest Baptist Medical Center, Department of General Surgery, Weight Management Center, Winston Salem, NC, USA
[2]University of Michigan Health System, Department of Internal Medicine, Ann Arbor, MI, USA
[3]East Carolina University Brody School of Medicine, Department of Surgery, Greenville, NC, USA
[4]EpidStat Institute, Ann Arbor, MI, USA
[5]Alaska Premier Health, Anchorage, AK, USA
[6]The Central Ohio Nutrition Center, Inc., Gahanna, Ohio, USA
[1,7]Wake Forest School of Medicine, Department of Epidemiology and Prevention, Winston Salem, NC, USA

Correspondence
Shenelle A. Edwards-Hampton
4614 Country Club Rd.
Winston Salem, NC 27104
Wake Forest Baptist Medical Center
Email: saedward@wakehealth.edu

Abstract

Over the past century, obesity and obesity-related comorbidities have become one of the greatest public health threats, and rates of morbidity and mortality continue to grow at alarming rates across the globe. Even modest amounts of weight loss from baseline can lead to significant improvements in quality of life, physical functioning, and remission of co-morbid conditions. Interventions to reduce excess weight vary from nutrition and surgical interventions, to pharmacotherapy, to lifestyle behavioral therapy. Findings related to the efficacy of various lifestyle behavioral interventions for the treatment of obesity continue to be mixed. The purpose of this article is to review key findings from the OPTIWIN obesity treatment trial, which tested the long-term effectiveness of a total meal replacement dietary intervention compared to a gold standard food-based lifestyle behavioral treatment for obesity. Overall, participants in the total meal replacement group lost significantly more excess weight and total fat mass, and demonstrated greater reductions in waist circumference during the active weight loss phase (baseline to 26 weeks), compared to the food-based group. These differences were maintained during the maintenance phase (26-52 weeks). The food-based group also had a higher proportion of non-responders (e.g., failure to lose ≥ 3% of their initial body weight) than the meal replacement group at 26 and 52 weeks. Implications for findings and future directions for medical weight management using lifestyle interventions and meal replacement methods are also discussed.

1. Introduction

Rates of obesity across the globe have continued to rise over the years, despite a significant risk of increased morbidity and earlier mortality. Weight reduction can improve these co-morbidities and prevent the development of additional co-morbidities[1]. The reduction of excess weight is achieved through an energy deficit, via a reduction of food volume consumed, modified portions, reduced intake of certain macronutrients, or eliminating specific food groups[2]. This energy deficit can result in significant food preoccupation and reduced resting energy expenditure, in addition to a variety of other metabolic and psychological consequences[1]. Thus, obesity treatment requires a coordinated, multidisciplinary approach to achieve significant, long-term weight reduction.

Obesity treatment can be broadly categorized as surgical, pharmacological, or lifestyle behavioral therapy, and treatment within these categories can be used in conjunction with one another. Bariatric surgery results in the most robust and lasting effects of weight reduction[3]. Yet, bariatric surgery is not typically recommended as a first line of treatment for obesity for multiple reasons, including its invasive nature, long term side-effects, risk for complications, cost, and medical and psychological contraindications. Further, often for reasons similar to those just described, many individuals seeking obesity treatment do not qualify or wish to undergo surgical intervention[3, 4]. There has been an increased number of pharmacotherapy treatments developed for obesity over the last decade. However, the most frequently prescribed anti-obesity medications are not approved by the Food and Drug Administration for long-term use and discontinuation of these medications is correlated with weight regain[5]. Access to anti-obesity medications is often limited by poor insurance coverage and a paucity of medical providers actively prescribing these medications[1]. Further, anti-obesity medications are typically recommended in conjunction with a lifestyle behavioral program[6-8]. Accordingly, effective lifestyle behavioral obesity treatments continue to be a vital treatment option amidst the current obesity epidemic.

Lifestyle behavioral obesity treatments are targeted interventions that aim to alter eating behaviors and modify physical activity. There are a multitude of lifestyle behavioral therapies, ranging from self-help electronic applications (e.g., My Fitness Pal, Lose It applications), to proprietorial programs (e.g., WW, NutriSystem, Jenny Craig), to medically supervised weight loss treatments. Similarly, there is significant variation in the specific interventions that each of these treatments utilize, such as access to expert advice (counselors, dietitians, exercise physiologists, and/or medical providers), frequency of contact/visits, provision of meal replacements or pre-packaged foods, and use of pharmacotherapy. These comprehensive lifestyle interventions result in, on average, 7-10% initial weight loss in patients with obesity at one year[9, 10].

A great deal of variability also exists across the specific dietary recommendations made within lifestyle behavioral therapies. Dietary recommendations may include reduced caloric intake, or may utilize more directive dietary interventions, such as partial or total use of meal replacements. Total meal replacement (TMR) interventions are indicated within the context of medical weight loss programs that provide close medical monitoring and a coordinated, multi-disciplinary treatment approach. Historically, TMR was primarily studied in the context of short-term (i.e., less than 6 months) lifestyle behavioral obesity treatments. In those settings, TMR typically produced rapid short-term weight loss that surpassed food-based interventions but was generally followed by

rapid regain after the completion of the TMR intervention[2]. Thus, due to limited long-term data and lack of comparison trials, previous professional treatment guidelines only recommend limited, short-term use of TMR as a lifestyle behavioral intervention[2].

Despite the limitations of the previous research on use of TMR, there were several aspects of this approach that merited further consideration. TMR results in rapid initial weight loss, meeting the primary target of 5-10% initial weight reduction, which is associated with significant improvement in cardio-metabolic risk factors and longer term weight loss[7, 11]. Several studies have shown that low-calorie meal replacement interventions facilitate weight loss that is associated with reduced blood pressure, waist circumference, and an improved lipid profile[12, 13].

To provide a clearer assessment of the true impact of TMR as a part of a comprehensive lifestyle behavior intervention for obesity, there was a need for a well-designed comparative effectiveness trial. First, weight loss outcomes had to be assessed at 1 year to understand the durability of the intervention effects. Second, the comparator intervention had to be an effective evidence-based intervention. And third, the trial would need to assess the impact of the interventions on cardiometabolic risk and other complications of obesity. The current article reviews key findings from the OPTWIN study, which demonstrates the efficacy of the long-term use of a TMR lifestyle intervention compared to a food-based intervention that is commonly thought to be the "gold standard" lifestyle behavioral treatment for obesity.

2. Program Components

The OPTIWIN study, an open-label, randomized controlled trial at nine participating US centers, examined the effectiveness of the OPTIFAST® program (OP), a TMR program, compared to a food-based program (FB)[14]. All participants were 18-70 years old, nonsmokers, with BMI of 30-55 kg/m^2. Figure 1 displays the full inclusion/exclusion criteria and study assessment flow. Participants were randomized to OP or FB, with obesity treatment for 26 weeks, followed by a weight-maintenance phase through 52 weeks.

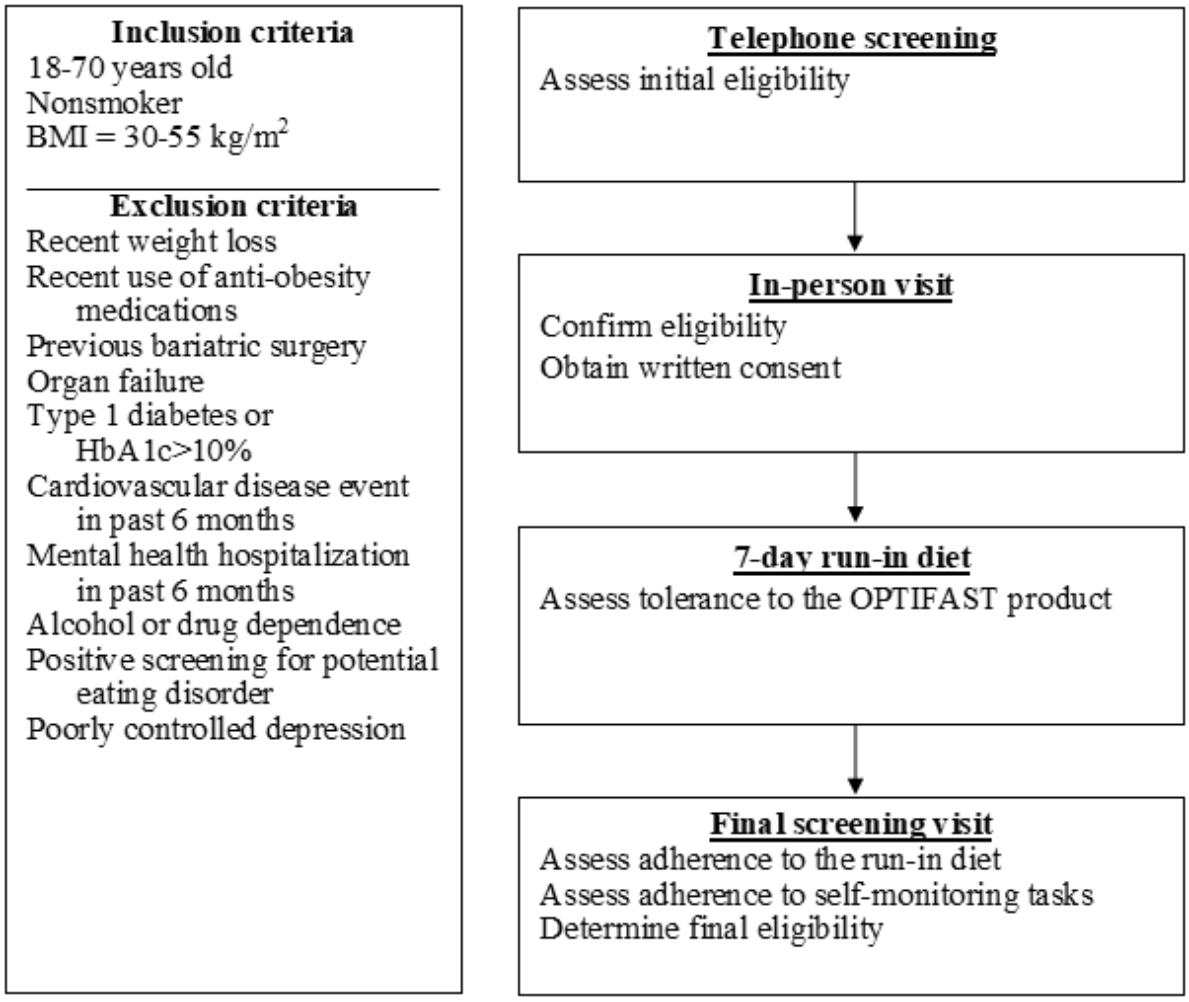

Figure 1. Study inclusion/exclusion criteria and study assessment flow

Participants in the OP were provided with meal replacements (MR; OPTIFAST; Nestle Health Science, Bridgewater, New Jersey) with the total caloric intake based on their baseline BMI (i.e., participants with BMI <45 received 5 MRs per day, totaling 800 kcals; participants with BMI 45-49.9 received 6 MRs per day, totaling 960 kcals; participants with BMI ≥ 50 received 6 MRs plus one meal of lean protein and one non-starchy vegetable per day, totaling 1,100-1,200 kcals). This prescription was continued for 12-16 weeks, per provider discretion and patient preference, followed by a gradual reintroduction of food through week 26. Patients continued to receive 1-2 MRs daily, following week 26, to achieve weight stability. The OP also included regular medical monitoring (i.e., 11 medical visits during weeks 1-26, 4 visits during weeks 27-52), labs (i.e., basic or comprehensive metabolic panel at weeks 2, 4, 6, 8, 10, 12, and 16), and individual counseling with trained interventionists (i.e., 16 individual counseling visits during weeks 1-26, 11 visits during weeks 27-52).

Comparatively, participants in the FB arm of the study were prescribed the Diabetes Prevention Program (DPP) intervention: a calorie restricted diet (i.e., a reduction of caloric intake by 500-750 kcals below estimated total calorie expenditure), which emphasized lower fat intake (25% - 30%)[15]. Participants received two medical monitoring and seven individual counseling visits during

weeks 1-26, and two medical monitoring and five individual counseling visits during weeks 27-52.

Participants in both programs received a comprehensive behavioral program, specific to each program, which included weekly 45- to 60-minute group behavioral sessions. Sessions were facilitated by a trained interventionist. Participants in both programs also received prescriptions for physical activity with a graduated target of 150-180 min/week of moderate to vigorous exercise. All participants were also instructed to record daily food and beverage intake, as well as physical activity, in written journals, which were reviewed weekly by the interventionist.

3. Effectiveness of the OPTIFAST® program versus food-based diet for weight loss and maintenance

The OPTIWIN study found that the OP program, compared to a FB diet and lifestyle interventions, resulted in significantly greater weight loss in adults with obesity[14]. Baseline BMI of the total study sample was 38.8 ± 5.9 kg/m^2. At the conclusion of the weight loss phase (26 weeks), OP percent change in body weight was 12.4% ± 0.6%, compared to 6.0% ± 0.6% in FB, representing a significant difference between the groups ($p < 0.001$). Both groups demonstrated changes in body composition. However, there were greater reductions in waist circumference and total fat mass amongst OP participants. Despite a higher percentage of total weight loss within OP participants, the proportion of weight loss from lean mass was similar across groups.

Table 1. Changes from baseline to 26 weeks and 52 weeks in BMI after a TMR (OP) program or food based (FB) program

Outcome	OP	FB	*p*
	Mean (SD)	*Mean (SD)*	
BMI			
Baseline	38.4 (5.5)	39.2 (6.2)	0.26
% Change at 26 weeks	-12.4 (0.6)	-6.0 (0.6)	<0.001
% Change at 52 weeks	-10.5 (0.6)	-5.5 (0.6)	<0.001
Waist Circumference (cm)			
Baseline	116.6 (14.0)	119.5 (15.2)	0.10
Change at 26 weeks	-12.0 (16.0)	-7.7 (8.3)	0.011
Change at 52 weeks	-11.9 (12.1)	-7.2 (9.3)	0.0011
Total Fat Mass (kg)			
Baseline	49.8 (11.8)	49.7 (11.7)	0.96
Change at 26 weeks	-11.3 (7.5)	-4.4 (5.9)	<0.0001
Change at 52 weeks	-9.7 (10.4)	-3.5 (6.6)	<0.0001
Non-responders			
Proportion at 26 weeks	15.6%	39.1%	
Proportion at 52 weeks	23.7%	43.5%	

Note: Baseline and change difference variables were compared using standard *t* tests. Change variables are defined as post-baseline value-baseline value.

Previous research has indicated that TMR programs may result in appropriate short-term weight loss, but that weight loss may not be maintained long-term and, thus, TMR programs may not be necessary or sufficient16. However, results from the OPTIWIN study found that weight loss was largely maintained within the OP group at 52 weeks, representing significant long-term weight loss. Specifically, weight change at 52 weeks was superior in OP at 10.5% ± 0.6%, compared to 5.5% ± 0.6% in FB, ($p < 0.001$). Higher proportions of OP participants achieved 5% (63.7%), 10% (43.7%), and 15% (30.0%) weight loss at 52 weeks, compared to FB participants who achieved 5% (42.0%), 10% (21.7%), and 15% (12.0%) weight loss (See Figure 2).

Importantly, there were no differences in adverse outcomes at 52 weeks between the FB and OP groups. These results indicate that the superior results in the OP group, compared to the FB group, are maintained long-term. These results * represent a significant contribution to the understanding of long-term maintenance within TMR programs for the reduction of excess weight.

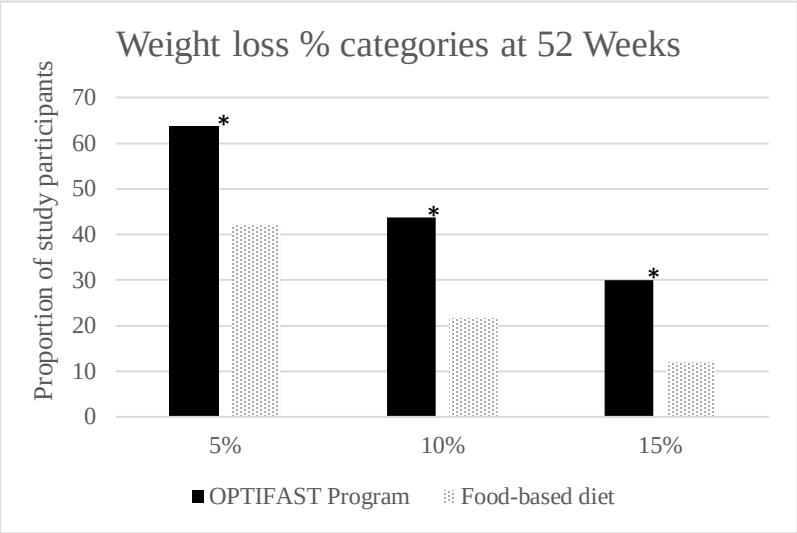

Figure 2. Proportion of participants who lost at least 5%, 10%, or 15% of initial body weight at week 52. *Significantly different from FB group at p<0.001.

4. Likelihood of treatment response and engagement in total meal replacement versus food-based diet

Lack of short-term, or more immediate weight loss, is also important to understand, particularly as it relates to treatment engagement. Analyses were conducted to further identify and understand differences in treatment responders vs non-responders between the OP and FB groups at 3, 6, and 12 months[17]. The proportion of non-responders (e.g., failure to lose ≥ 3% of their initial body weight) was significantly different between OP (15.6%) and FB (39.1%) at week 26[14].

Within the OP group, there was a 5.9% probability that treatment responders at 3 months would no longer be treatment responders at 6 months, and a 15.3% chance that treatment responders at 3 months would no longer be treatment responders at 12 months. Within the FB group, the same probabilities were 12.8% and 23.3%, respectively[17]. Within both groups, individuals who were classified as non-responders at 3 months had a high probability of remaining non-responders. At week 52, which represents the weight-maintenance phase, the proportion of non-responders in OP (23.7%) compared to FB (43.5%) continued to demonstrate the effectiveness of the OP program[14]. Thus, the OP group had fewer non-responders at treatment conclusion and fewer responders who became non-responders long-term.

When examining predictors of treatment non-response, previous obesity treatment attempts were significantly associated with non-responder status overall, such that increasing number of obesity treatment attempts were associated with increased odds of non-responder status (p = 0.0023). Within the FB group, non-responders reported significantly more previous obesity treatment attempts than FB treatment responders (+6.8, $p < 0.0001$), yet there was not a significant difference of previous obesity treatment attempts in OP non-responders and treatment responders (p = 0.54). Race and Type II Diabetes (T2D) status were also significantly associated with responder status. Specifically, African Americans had a predicted probability of non-response of 40%, while Caucasians had a predicted probability of non-response of 17% (p = 0.0075). Individuals with T2D had a higher predicted probability of non-response of 42%, compared to individuals without T2D, who had a predicted probability of non-response of 21% (p = 0.046). Increasing age was associated with decreased odds of being a non-responder; this association was trending toward significance (p = 0.071).

Differences in cardiometabolic risk factors in treatment responders vs non-responders were expected. Overall, treatment responders, compared to non-responders, demonstrated significant differences in all cardiometabolic risk factors at the 12-month time point (i.e., fasting blood glucose, HbA1c, insulin, blood pressure, waist circumference, HDL cholesterol, triglycerides; p range = < 0.0001 – 0.004), except total cholesterol and LDL cholesterol[17, 18]. OP responders demonstrated significantly greater improvements in waist circumference, HDL-cholesterol, and triglycerides, compared to FB responders (p range = <0.0001 – 0.02). Importantly, treatment responders demonstrated significantly lower prevalence of metabolic syndrome at 12 months, compared to non-responders. The prevalence of metabolic syndrome in both treatment groups decreased by approximately 50% ($p < 0.01$)[17].

Attendance to intervention visits (including all disciplines) was significantly related to success within the program. Specifically, those who attended at least 75% of both the group and clinic visits had -18.9% relative weight change in the OP group and -11.5% relative weight change in the FB group at 52 weeks[19]. Adherence to each program component was self-reported[17]. Overall, treatment responders reported higher adherence to their dietary and exercise plans, greater non-calorie fluid intake, greater minutes of physical activity, and fewer missed group behavioral sessions. When comparing by group, OP responders reported higher adherence to their meal plans and non-caloric fluid intake than FB responders. Within the FB group, responders and non-responders reported similar adherence to their diet plans.

5. Implications and future directions

Overall, results from the OPTIWIN trial indicate that a medically managed, TMR program with comprehensive behavioral support is an effective treatment for the reduction of excess weight and cardiometabolic risk factors. OP was associated with greater weight loss at 26 and 52 weeks compared to the FB intervention. OP was also associated with greater treatment response rates and fewer treatment non-responders compared to FB. Importantly, adherence to various aspects of the treatment was significantly related to better outcomes within both treatment groups, indicating that outcomes are tied to the individual's engagement with treatment. However, the OP treatment responders reported higher adherence to their assigned meal plan compared to FB responders, suggesting a higher level of engagement or ease of plan implementation for those in the OP arm.

To capitalize on these findings and continue to improve care, additional research is needed to understand potential mechanisms of success. Participants in the TMR arm of the OPTWIN trial had a higher frequency of contact with medical providers and a greater number of individual counseling visits than participants in the FB arm. There is a large body of evidence that demonstrates the importance of high-frequency, high-intensity counseling with a trained interventionist ($\geq$ 14 visits in first 6 months)[1] in successful lifestyle obesity treatment. Future research that explores the specific dose of provider and counseling visits that is key to successful outcomes in a TMR lifestyle program is indicated. Such findings will optimize efficiency and time/cost burdens for participants.

Additionally, as noted previously, a number of new anti-obesity medications have become available for use by medical providers over the past decade. While several anti-obesity medications provide traditional appetite suppression, others target unique mechanisms that drive energy consumption, such as hedonic and inhibitory neural pathways[20]. A recent study demonstrated greater weight loss outcomes, 1-year post-treatment, when liraglutide 3 mg was combined with intensive behavioral lifestyle therapy or intensive behavioral lifestyle therapy and partial meal replacement compared to intensive behavioral lifestyle therapy alone[21]. Combining liraglutide with the partial meal replacement treatment resulted in only marginally better weight loss at 24 weeks (-12.2% vs -10.1%) and no difference at 52 weeks. The effects of combining anti-obesity medication with partial meal replacement interventions may have sub-additive effects on weight loss outcomes; however, research that identifies the added benefit of anti-obesity medication within the context of a TMR lifestyle behavioral obesity treatment is needed. Investigation of use of TMR in patients who have experienced suboptimal weight loss or weight regain following bariatric surgery would also be of value. Finally, future studies should seek to identify characteristics that differentiate between treatment responders and non-responders to increase the likelihood of treatment response.

6. Conclusions

As noted earlier, there are multiple treatment options available for patients with obesity.

However, there are not clear indications for what treatments, or combinations of obesity treatments, should be utilized to optimize initial weight loss and long-term weight loss maintenance for a given patient. As clinicians look to recommend effective options for their patients, understanding the potential treatment response and effects on health outcomes is important for making an individualized treatment recommendation. Results from the OPTIWIN trial demonstrated that the

OPTIFAST® TMR program, is more effective than a traditional food-based obesity treatment program with regard to greater weight loss and maintenance, improvement in cardiometabolic risk factors, and adherence to the intervention. Findings lend support for broader use of TMR in lifestyle behavioral therapy weight loss programs.

References

1. 1. Heymsfield, S.B. and T.A. Wadden, Mechanisms, pathophysiology, and management of obesity. New England Journal of Medicine, 2017. **376**(3): p. 254-266.
2. 2. Members, E.P., et al., Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from the The Obesity Expert Panel, 2013. Obesity, 2014. **22**(S2): p. S5-S39.
3. 3. Courcoulas, A.P., et al., Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. The Journal of the American Medical Association, 2013. **310**(22): p. 2416-2425.
4. 4. Sadhasivam, S., et al., Refusals, denials, and patient choice: Reasons prospective patients do not undergo bariatric surgery. Surgery for Obesity and Related Diseases, 2007. **3**(5): p. 535-536.
5. 5. Kakkar, A.K. and N. Dahiya, Drug treatment of obesity: Current status and future prospects. European Journal of Internal Medicine, 2015. **26**(2): p. 89-94.
6. 6. Li, M. and B.M. Cheung, Pharmacotherapy for obesity. British Journal of Clinical Pharmacology, 2009. **68**(6): p. 804-810.
7. 7. Sweeting, A.N. and I.D. Caterson, Approaches to obesity management. Internal Medicine Journal, 2017. **47**(7): p. 734-739.
8. 8. Wadden, T.A., et al., Randomized trial of lifestyle modification and pharmacotherapy for obesity. New England Journal of Medicine, 2005. **353**(20): p. 2111-2120.
9. 9. Carvajal, R., et al., Managing obesity in primary care practice: A narrative review. Annals of the New York Academy of Sciences, 2013. **1281**: p. 191-206.
10. 10. Yanovski, S.Z. and J.A. Yanovski, Long-term drug treatment for obesity: A systematic and clinical review. The Journal of the American Medical Association, 2014. **311**(1): p. 74-86.
11. 11. Shiau, J.Y., D.Y. So, and R.R. Dent, Effects on diabetes medications, weight and glycated hemoglobin among adult patients with obesity and type 2 diabetes: 6-month observations from a full meal replacement, low-calorie diet weight management program. Canadian journal of diabetes, 2018. **42**(1): p. 56-60.
12. 12. Mulholland, Y., et al., Very-low-energy diets and morbidity: A systematic review of longer-term evidence. British Journal of Nutrition, 2012. **108**(5): p. 832-851.
13. 13. Rolland, C., M. Hession, and S. Murray, Randomized clinical trial of standard dietary treatment versus a low-carbohydrate/high-protein diet or the LighterLife Programme in the management of obesity. Journal of Diabetes, 2011. **3**(4): p. 356-356.
14. 14. Ard, J.D., et al., Effectiveness of a Total Meal Replacement Program (OPTIFAST Program) on weight loss:

results from the OPTIWIN Study. Obesity, 2019. **27**(1): p. 22-29.
15. 15. Group, D.P.P.R., The Diabetes Prevention Program (DPP): Description of lifestyle intervention. Diabetes Care, 2002. **25**: p. 2165-2171.
16. 16. Keogh, J.B. and P.M. Clifton, The role of meal replacements in obesity treatment. Obesity Reviews, 2005. **6**(3): p. 229-234.
17. 17. Ard, J.D., et al., Differences in treatment response to a total diet replacement intervention versus a food-based intervention: A secondary analysis of the OPTIWIN trial. Obesity Science & Practice, 2020: p. 1-10.
18. 18. Rothberg, A.E., et al. Effect of total meal replacement program compared with a reduced-energy food-based diet plan on glycemic status: Results from the OPTIWIN study. in American Diabetes Association 78th Scientific Session. 2018. Orlando, FL.
19. 19. Loper, J., et al., Level of engagement in participants completing meal replacement program is related to weight change, in Obesity Week. 2020: Atlanta, GA.
20. 20. LeBlanc, E.S., et al., Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. Jama, 2018. **320**(11): p. 1172-1191.
21. 21. Wadden, T.A., et al., Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: The Scale IBT randomized controlled trial. Obesity, 2020. **28**(3): p. 529-536.

