Received: 29 April 2024 | Revised: 24 June 2024 | Accepted: 2 July 2024
DOI: 10.1111/dom.15819

SPECIAL ISSUE ARTICLE

WILEY

The latest evidence and clinical guidelines for use of meal replacements in very-low-calorie diets or low-calorie diets for the treatment of obesity

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Abstract

Obesity is a complex chronic disease with increasing prevalence across the globe. Medical nutrition therapy (MNT) is an important component of obesity treatment, and low-calorie diets (LCDs) and very-low-calorie diets (VLCDs) are part of the MNT toolbox. This narrative review focuses on the latest evidence and clinical guidelines regarding the use and impact of meal replacements (MRs) as part of LCDs/VLCDs for the treatment of obesity and some associated complications. MRs can be used in conjunction with food as partial diet replacement (PDR) or can be used exclusively to serve as the sole source of dietary energy (total diet replacement [TDR]). Use of MR may be associated with better control of cravings and hunger typically observed during reduced calorie intake through effects of ketosis or stimuli narrowing, although the exact mechanisms for these effects remain unclear. Several clinical guidelines have endorsed the use of MRs as a part of MNT for obesity, primarily based on evidence that shows an average weight reduction of ∼10 kg or more with TDR over at least 12 months in large, randomized controlled trials. When compared to usual care controls, these effects are 6–8 kg greater, and when compared to food-based diets, the effects are nearly twice the effect of a food-based diet. MR-based diets have been found to be safe and associated with improvements in quality of life. These diets are also effective for improving key cardiometabolic health outcomes, including dysglycaemia, blood pressure, lipids, and metabolic associated fatty liver. The effectiveness, safety, and associated health improvement makes MRs use a valuable strategy for several higher risk clinical scenarios where weight reduction is indicated.

KEYWORDS
dietary intervention, effectiveness, obesity therapy, weight control

1 | INTRODUCTION

Obesity is a chronic, complex disease characterized by excess adiposity, and is associated with multiple complications that limit quality of life and shorten lifespan.[1] The global prevalence of obesity has grown at an alarming rate, more than doubling in adults since 1990.[2] There are significant economic costs associated with obesity, including increased healthcare costs, reduced workforce productivity, and significant disability.[3,4]

Because of the individual and collective burden of obesity, successful prevention and treatment is critical. There are several medical nutrition therapy (MNT) approaches for the treatment of obesity, including but not limited to caloric restriction, macronutrient modifications, intermittent fasting, and use of meal replacements (MRs). Findings from the literature indicate that the best MNT is the one that the individual can tolerate and maintain long term.[5–7] Thus, it is critical that healthcare providers know the various MNT treatment options and their associated benefits in order to recommend an individualized plan that is sustainable. The purpose of this article is to provide the reader with background on how MRs are used in MNT, and to review potential biobehavioral mechanisms of action, and the efficacy and safety of MRs as part of low-calorie diets (LCDs) and very-low-calorie diets (VLCDs). The authors also review recent clinical guidelines/position statements related to the use of MRs in LCDs and VLCDs and consider how MRs can be utilized as part of obesity treatment in the context of newer treatment options.

2 | MRs AND LCDs/VLCDs AS INTERVENTIONS FOR THE TREATMENT OF OBESITY

Meal replacements are commonly understood to be distinct, fixed-energy, portion-controlled food products or drinks (often fortified with essential vitamins and minerals) that are consumed in place of traditional foods to reduce energy intake.[8] MRs can be products specifically marketed for weight loss, such as protein shakes or bars, or can be portion-controlled conventional/frozen foods.[9] MR interventions are often a key component of an LCD/VLCD. The threshold for delineating VLCDs from LCDs has typically been 800 kcal/day, with VLCDs having a prescribed energy intake of less than 800 kcals/day. LCDs that use multiple servings of MRs, or partial diet replacement (PDRs), typically include a minimum of two MRs per day in conjunction with one balanced, energy-limited, nutritious meal with an overall prescribed energy intake of 1000–1200 kcal/day.[9–11] Total diet replacement (TDR) is a version of an LCD/VLCD that uses MRs to replace all food intake and serves as the sole source of dietary energy. While MRs can be used to replace a small portion of dietary intake or as a supplement to usual intake, this review will focus on the use of MRs as part of a weight-reducing LCD/VLCD, either as TDR or PDR.

There has been an extensive history of using MRs in MNT for obesity.[12,13] MRs are documented to have first been utilized early in the 20th century, as an alternative to the common practice of 'fasting' for weight loss. Fasting involved extreme caloric restriction via skipping meals or avoiding all food intake for an extended period. While this practice was effective in weight reduction, it resulted in significant lean mass losses and compromised health due to significant nutrient deficits.[14] Thus, high-quality, high-protein (such as milk derivatives containing essential amino acids or egg whites) drinks were formulated as a protein-sparing modified approach to VLCDs (400–600 kcal/day). This intervention proved successful, achieving rapid weight loss with minimal adverse side effects.[14,15] However, in the 1970s, low-quality, nutrient-deficient formulations comprising milk-based protein and hydrolysed collagen/gelatin began to be utilized in VLCDs. These products were associated with the deaths of 60 people in the United States due to cardiac complications associated with a prolonged starvation response.[16,17]

Since the early 1980s MRs have evolved and returned to high-quality, nutrient-fortified formulations that can adequately meet recommended vitamin and mineral intakes for many adults consuming reduced-calorie MRs.[18–20] However, particularly with use of TDR, nutritional needs may not be met in all cases and could require mineral and vitamin supplementation during use.[18] Overall, MR-based MNT with appropriately fortified formulations is an approach that can provide better nutrition than many self-selected, reduced-calorie diets.[18] Many popular dietary interventions, such as low-carbohydrate or low-fat diets, involve avoidance of key food groups (e.g., grains, fats/oils), increasing the risk of deficits in important nutrients/micronutrients (e.g., fibre).[21] Additionally, these diets require the consumer to select from any number of energy sources, placing increased burden on the consumer to understand and meet their nutritional needs while trying to limit energy intake. Variability in the food choices consumers make when trying to follow these diets could not only result in variable weight loss outcomes, but have important health consequences, such as increased risk for cardiovascular disease.[22]

3 | BIOBEHAVIOURAL MECHANISMS ASSOCIATED WITH USE OF MR IN LCD/VLCD INTERVENTIONS

Weight reduction initiated via caloric restriction is subject to a compensatory metabolic adaptation that works to limit the loss of mass, and if possible, restore the lost mass.[23] Difficulty achieving and maintaining weight loss has been shown to be associated with reports of increased hunger and reduced satiation during calorie-restricted interventions that are a result of the adaptive response.[24,25] These symptoms appear to be associated with elevations in hormone levels related to hunger (ghrelin) and satiety (peptide YY, leptin, amylin, and cholecystokinin) that frequently occur as a result of calorie-restricted weight loss interventions.[24–26]

Despite the expected increase in hunger with reduced calorie intake, several studies have shown that MR used as part of a VLCD has been associated with reduced cravings, symptoms of hunger, and improved satiety during treatment.[25,27,28] One short-term randomized controlled trial (RCT) of MR alone compared to MR plus phentermine showed that all participants had significant reductions in cravings for all foods groups, which was enhanced by the use of phentermine. Weight reduction was moderately correlated with the reduction for all food cravings and cravings for sweets.[29]

While the exact mechanisms responsible for reduced cravings, hunger, and improved satiety in the use MR as part of an LCD/VLCD are not known, it is possible that these findings are due to downregulation of reward and homeostatic regions of the brain that are known to drive food consumption.[30,31] A recent study using functional magnetic resonance imaging showed unique differences in neural activation in response to TDR when compared to food-based, calorie-restricted diets.[31] These differences appear to be tied to the avoidance of food-related stimuli that is inherent to the use of MR. More specifically, the cognitive restraint required by MR interventions that results in food avoidance appears to strengthen neural pathways associated with executive functioning, improving individuals' ability to practice dietary restraint in the future when compared to individuals who participated in food-based plans.[31–33] Further, reduced exposure to food-related stimuli appears to activate inhibitory signalling in pleasure and reward centres of the brain, reducing the positive valence of food.[31] Stimulus narrowing also likely reduces the gut/nutrient activation that occurs in response to food cues, reducing production of hunger hormones, such as ghrelin.[25] Depending on the formulation of the MR, the induction of ketosis may also impact appetite control. When using very-low-carbohydrate formulations, ketosis has been associated with improved appetite control and blunting of the expected rise in ghrelin hormone levels with energy deficit.[25]

4 | PRACTICAL IMPLICATIONS OF USE OF MR FOR THE TREATMENT OF OBESITY

Stimulus narrowing is an intervention intended to control the number of food-related stimuli in one's environment, typically by limiting one's exposure to choices.[34] MR can reduce the need for consumers to make choices between other high-energy-dense, nutrient-poor foods. Consistent, time-based intake of MR enables patients to be less reliant on recognition of hunger signals as a cue for energy intake, as such cues can be difficult to identify and easily confounded by psychosocial (e.g., emotional or environmental) and hedonic drives for energy consumption.[35]

Participants using MR in LCD/VLCD for weight loss find this dietary intervention easier to implement than many other MNT strategies.[36] In addition to the rewarding feedback of rapid, early weight loss, ease of adherence has also been tied to the convenience and accessibility of MR.[37–39] The stimulus narrowing and convenient nature of MR appears to play a role in individuals' ability to modify their food environment at home and in social situations, minimizing triggers for non-adherence.[39] Participants have also reported that MNT with MR facilitated increased awareness of their relationship with food, prompting implementation of helpful skills such as planning ahead, engaging in distracting activities, and requesting support from others.[37,39]

5 | CLINICAL GUIDELINES FOR THE TREATMENT OF OBESITY WITH USE OF MR

Several recent position statements and clinical practice guideline updates have reported evidence of the efficacy of use of MR in MNT. The 2013 guidelines on the identification and management of obesity in adults by the American Heart Association, American College of Cardiology, and the Obesity Society found strong evidence for the use of complete MR in a VLCD within the context of a comprehensive interdisciplinary setting.[40] An updated review of the literature and clinical practice guidelines for MNT was released by Obesity Canada and the Canadian Association of Bariatric Surgeons and Physicians in 2022. Evidence of reduced body weight, waist circumference, blood pressure, glycaemic control, and lower rates of attrition in treatments using MR when compared to traditional energy-restricted diets, was demonstrated at the 6- and 12-month time points. Strong evidence of longer-term benefits (3 years) of VLCDs with use of PDR in the context of intensive multidisciplinary treatment was also cited.[7,35,41] The European Association for the Study of Obesity released a position statement (2023) that expands on the Canadian Clinical Practice Guidelines for MNT, citing additional evidence for improved health outcomes, and possibly greater durability of outcomes, with use of PDR compared to usual care. Reviewed studies also show the efficacy of using a single MR, TDR, and the use of MRs for gestational weight gain. This evidence provides stronger justification for the use of MRs in the treatment of obesity than previously reported.[6]

6 | EFFICACY AND SAFETY OF TDR IN LCDs/VLCDs

The use of PDR has generally been accepted as low risk and is broadly accessible to any consumer, including through use of over-the-counter MR options.[8] However, TDR has been recommended primarily for use in settings with medical supervision and direction by a team of professionals with expertise in TDR to avoid adverse events.[40] Given this sense of increased risk, we have focused the review of efficacy and safety on TDR to provide a contemporary perspective from RCTs in a variety of settings.

Contemporary clinical trials of TDR of more than 6 months demonstrate consistent mean weight loss in a variety of clinical settings, disease states, and patient populations. In the Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET) trial investigators aimed to determine if referral by a primary care provider to a commercial TDR diet would be more effective for weight loss than usual care (i.e., 12-week nurse counselling programme).[42] Participants ($n = 278$) were 18 years or older and had a body mass index (BMI) ≥30 kg/m^2. TDR of 810 kcal/day was used for 8 weeks, followed by 4 weeks of food reintroduction. A maintenance intervention, where participants met monthly with the counsellor and used one MR daily, continued through 24 weeks. There were 22% and 31% of participants lost to follow-up for the TDR and control groups, respectively. The mean BMI ranged from 36.8 to 37.6 kg/m^2; 14%–16% of participants had type 2 diabetes mellitus (T2DM) at baseline. At 6 months, the TDR group lost 15.1 ± 8.7 kg, compared to 4.5 ± 6.2 kg for the controls. By 12 months, the TDR group maintained a weight loss of 10.7 ± 9.6 kg, which was 7.2 kg (95% confidence interval [CI] 4.9, 9.4) more than the control group. A total of 45.1% of the TDR participants lost ≥10% of their initial weight.

The Diabetes Remission Clinical Trial (DiRECT) was conducted in 49 primary care centres in England to compare a TDR diet to best practice care guidelines for achieving remission of T2DM.[43] Participants from the practices were recruited if they were aged 20–65 years, had a BMI 27–45 kg/m^2, were not on insulin, and had diabetes for 6 years or fewer. The TDR diet provided 825–853 kcal/day and was used for 3–5 months before food reintroduction, followed by a weight loss maintenance phase. Nurses or dietitians in the primary care office received training for the TDR treatment programme and were supervised by research dietitians. At 12 months, weight loss was statistically greater for the TDR diet group, achieving a mean weight loss of 10.0 kg, which was 8.8 kg (95% CI 10.3, 7.3) more than the control group. In all, 24% of the intervention group achieved at least 15-kg weight loss compared to 0% in the control group; similarly, 46% of the intervention group achieved diabetes remission, defined as a glycated haemoglobin 48 mmol/mol level <6.5% after at least 2 months without any antidiabetic medications, compared to 4% of the control group.

The OPTIWIN study compared TDR to a weight-reducing food-based diet patterned after the Diabetes Prevention Program.[44] In this RCT of 273 participants, the mean age was 47.1 ± 11.2 years and the average BMI was 38.8 kg/m^2. Participants implemented TDR for 12–16 weeks, with gradual food reintroduction up to Week 26; thereafter, the participants used 1–2 MRs daily for maintenance up to Week 52. The food-based diet prescribed a calorie reduction of 500–750 kcal/day below estimated total energy expenditure. Both groups had comprehensive behavioural counselling with weekly group sessions and prescriptions for physical activity of 150–180 min per week of moderate to vigorous exercise. Weight loss at 52 weeks was 10.5% ± 0.6% for the TDR group compared to 5.5% ± 0.6% for the food-based diet group. The proportion of participants who achieved ≥10% weight loss was 43.7% and 21.7% for TDR and the food-based diet, respectively.

The TEMPO study was an RCT that compared moderate energy restriction (25%–35% of estimated energy expenditure for 12 months) to TDR (65%–75% reduction in estimated energy expenditure for 4 months), followed by moderate energy restriction for 8 months in 101 postmenopausal women; both groups were prescribed protein intake of 1 g/kg of body weight.[45] Physical activity was prescribed with a target of achieving 8000–12 000 steps/day, including 30–60 min/day of moderate to vigorous intensity activity. Participants were postmenopausal females with an average BMI of 34.4 ± 2.5 kg/m^2. At 12 months, there was a −6.6 kg (95% confidence interval [CI] −8.2 to −5.1 kg) difference between the moderate (−8.4 kg) and severe (−15.3 kg) energy restriction groups. The proportion of participants who achieved at least 10% weight loss was 82.0% in the severe group compared to 27.5% in the moderate group.

While the previous trials had extended periods of TDR, the international, multicentre ALMASED-Concept-against-Overweight-and-Obesity-and-Related-Health-Risk (ACOORH) study was an RCT that only had a brief period of TDR. The study compared an MR-based lifestyle intervention to lifestyle intervention alone.[46] In this trial, 463 individuals with BMI of 27–35 kg/m^2 with at least one risk factor for metabolic syndrome were randomly assigned to lifestyle counselling on reduced calorie diets, increased physical activity, and provided with telemonitoring devices or the lifestyle counselling programme with the addition of a graduated MR diet (first week replacing all three main meals, Weeks 2–4 replacing breakfast and dinner, and Weeks 5–26 replacing dinner). After 12 weeks the difference between the MR-augmented diet and the lifestyle alone intervention was −3.2 kg (95% CI −4.0 to −2.5 kg). This difference narrowed to −1.8 kg (95% CI −2.8 to −0.8) by 52 weeks.

Adverse events in the trials of TDR generally include mild to moderate severity adverse events that include symptoms such as constipation, fatigue, headache and dizziness.[44] These type of symptoms are primarily attributed to the intervention, resulting from acute changes in nutrient intake (e.g., lower carbohydrate and sodium, increased percent of calories from protein), reduced energy consumption, diuresis and naturesis.[47,48] The symptoms typically present during the initiation of the VLCD.[49–51] The management of such symptoms is generally accomplished by altering the composition of the diet to include more fluid, increase electrolytes such as sodium, and adding fibre via supplementation.[49] The trials reviewed above did not have any evidence of increased risk of serious adverse effects, and such events were typically balanced across treatment groups.

Historically, concerns have been raised that abstinence or significant limits on food intake and associated psychological symptoms (i.e., negative affect associated with feelings of deprivation) could lead to disordered eating behaviours, such as binging, purging, or anorexic behaviour.[52] However, several studies have indicated no evidence of causality or increased risk for the development of disordered eating behaviours in individuals being treated for obesity via calorie-restricted methods.[41] Based on a systematic review, VLCD in medically supervised weight loss programmes did not activate disordered eating behaviours; on the contrary, VLCD interventions were associated with decreased binge eating behaviours.[53] In an RCT of women with obesity, a VLCD using MR was compared to a calorie-restricted food-based diet and a non-dieting approach that discouraged energy restriction. There was no evidence of disordered eating behaviours or binge eating disorder. Further, symptoms of depression decreased in calorie-restricted groups compared to the group that was not calorie-restricted.[54]

7 | IMPACT OF MR ON KEY HEALTH OUTCOMES

7.1 | Glycaemia

One of the most acute and direct impacts of MR on energy metabolism is on glycaemia. Blood glucose and insulin resistance can be changed in a matter of days when an energy deficit is established using a VLCD with MR.[55] With sustained weight loss, the longer-term effects on glycaemia are driven by reductions in fat deposition in the liver and pancreas, along with improvements in pancreatic beta-cell function.[56] As a result of the reduction in organ fat and improvements in insulin resistance, there are a cascade of improvements in several key health outcomes that will be discussed later, such as cardiovascular disease risk and metabolic dysfunction-associated fatty liver disease (MAFLD). Understanding the impact of MR-based VLCD on insulin resistance and glycaemia thus becomes central to understanding the pluripotent effect of this strategy for cardiometabolic health improvement.

Excess calories are converted to fat during positive energy balance, and deposition of that fat is primarily targeted to subcutaneous adipose depots. Once filled, the deposition of excess fat moves to ectopic fat depots that includes internal organs such as the liver.[57] As liver fat content increases, the liver becomes less sensitive to insulin signalling, leading to abnormal gluconeogenesis and a compensatory increase in insulin secretion to overcome insulin resistance. At the same time, very-low-density lipoprotein (VLDL) triglyceride production by the liver increases, promoting delivery to other tissues, including the pancreas. The uptake and accumulation of excess triglycerides by islet cells blunts the cells responsiveness to ingested glucose. This causes a reduction in first-phase insulin response and postprandial glucose elevation.[58] Ultimately, persistent elevations in serum glucose levels stimulate increased insulin secretion, driving lipogenesis, further liver fat deposition, and ongoing insulin resistance. This phenomenon of hepatic insulin resistance with resulting increased triglyceride production and pancreatic dysfunction caused by hepatic triglyceride excess, all driven by insulin resistance, is known as the twin cycle hypothesis and offers an explanation for the progression from obesity-associated hyperglycaemia to the eventual development of T2DM.[59]

The main benefit of MR on glycaemia is a result of sustained reduction in calorie intake with a large energy deficit created while providing sufficient protein to limit catabolism of skeletal muscle. The sustained energy deficit creates a significant improvement in insulin resistance that is a key feature of metabolic dysfunction driven by excess adiposity and intra-organ fat accumulation.[60] Hepatic fat content decreases quickly in the early phases of a VLCD.[55] As insulin resistance improves, glucose disposal in the periphery increases while abnormal gluconeogenesis at the liver decreases. There is also a decrease in VLDL triglyceride production and serum levels.[56] With ongoing weight reduction and the continued use of MR there is a gradual return of first-phase insulin responsiveness, but this typically lags behind the improvements in liver fat and insulin resistance.[55,56]

The effectiveness of MR on improving glycaemic outcomes and body weight in people with T2DM was recently assessed in a meta-analysis of 17 RCTs, which included 2112 participants with T2DM. The included trials compared MR interventions (replacing 1–3 meals per day) to conventional diabetic diets for at least 2 weeks' duration.[61] MR was associated with greater reductions in HbA1c, fasting blood glucose, and body weight. Five of the 17 studies used TDR, and when compared to PDR, subgroup analyses showed greater weight loss (−6.6 kg vs. −1.6 kg), HbA1c reduction (−0.72% vs. −0.32%) and decrease in fasting blood glucose (−1.45 mmol/L vs. −0.56 mmol/L).[61]

The effects of MR on glycaemic endpoints, such as incidence of achieving diabetes remission or normoglycaemia, have been primarily studied in the context of weight reduction interventions that use PDR or TDR. In the Look AHEAD trial, the use of MR was associated with greater weight loss, and greater weight loss was associated with higher probability of diabetes remission.[62,63] As noted above, DiRECT is the pivotal demonstration of the impact of TDR-induced weight loss on diabetes remission. Superior diabetes remission was achieved with a reduced number of prescribed antidiabetes medications decreased relative to the control group—by an average of 0.97 (95% CI 1.1, 0.8). TDR was associated with a lower mean HbA1c level (6.8% for intervention vs. 7.6% for control; $p < 0.0001$).[43] The Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) trial was the first RCT to test TDR in individuals from the Middle East and North Africa region.[64] A total of 158 participants were randomly assigned to usual care or intensive lifestyle intervention with a 12-week TDR phase (800–820 kcal/d) followed by 12 weeks of gradual food reintroduction and a maintenance strategy for the final 6 months. At 12 months, the intervention group had a weight loss of 11.98 kg (95% CI 9.72–14.23) compared with 3.98 kg (95% CI 2.78–5.18) in the control group (adjusted mean difference −6.08 kg [95% CI −8.37 to −3.79]; $p < 0.0001$). A higher proportion of intervention participants achieved 15% weight loss compared to control (21% vs. 1%), and diabetes remission was noted in 61% of intervention group participants compared to 12% remission in the control group. One-third of the intervention group achieved normoglycaemia compared to only 4% of the control group.[64]

7.2 | Cardiovascular disease risk

Weight reduction is a well-established means to reduce risk factors for cardiovascular disease beyond dysglycaemia, including blood pressure, lipids, and markers of inflammation.[65] Because many of these risk factors have a continuous relationship with body weight, greater reductions in body weight are typically associated with greater reductions in the risk marker.[66] Additionally, the dietary intake and nutrient composition can have direct effects on the risk marker, independent of the weight reduction effect.[67] In this regard, MR can be doubly effective because the use of MR as part of a weight reduction intervention leads to greater weight loss, and the nutritional composition of the MR diet can be effectively controlled to deliver high-quality nutrition in a way that optimizes CVD risk markers.

A post hoc analysis of the OPTIWIN trial is one example of the impact of TDR on atherosclerotic cardiovascular disease (ASCVD) risk.[68] Ten-year ASCVD risk was assessed based on the American College of Cardiology/American Heart Association pooled cohort equations including age, total cholesterol, high-density lipoprotein (HDL) cholesterol, treated/untreated systolic blood pressure, smoking status, and diabetes. At baseline, the ASCVD risk scores were generally low (<5%) for the majority of study participants, with an average of 2.6 ± 3.4% for the TDR group and 3.6 ± 5.1% for the food-based group. Blood pressure was 3.5/2.6 mmHg lower for the TDR group at Week

26; by Week 52, the difference had narrowed to 1.4/0.7 mmHg in favour of the TDR group but was no longer statistically significant. Lipids were significantly improved at Weeks 26 and 52 for the TDR group compared to the food-based diet. This included reductions of 0.14 mmol/L in low-density lipoprotein cholesterol and 0.28 mmol/L in triglycerides, along with an increase in HDL cholesterol of 0.11 mmol/L at 52 weeks. Even though the baseline ASCVD risk was low, there was a significant reduction in the ASCVD score for those on MR. Overall, the improvement in ASCVD risk score for the TDR group was significantly better at both 26 (−0.65%, 95% CI = −1.07, −0.23) and 52 weeks (−0.64%, 95% CI = −1.08, −0.20).[68]

The results of greater improvement in ASCVD risk and cardiovascular risk factors from the OPTIWIN trial could certainly be attributed to the larger amount of weight loss achieved with the TDR intervention, as analyses that matched for weight loss were not completed. However, other studies that have compared matched weight loss using MRs or food-based diets have demonstrated similar beneficial effects on cardiovascular risk factors and shown higher quality nutrient intake for MRs relative to a food-based diet.[18,69] Regardless, the impact of a larger amount of weight loss on CVD risk may be the ultimate driver of the risk-lowering effect; if this is the case, achieving weight loss of ≥10% may be key to demonstrating a reduction in CVD events with behavioural weight management.[68] Even though a reduction in CVD events was not achieved in the total Look AHEAD study population, a secondary ad hoc analysis showed that those who achieved at least 10% weight loss in the first year of the trial had a 21% lower risk of a major adverse cardiovascular event compared to those who did not lose weight.[70] As previously noted, higher average use of MR (servings/day) in the Look AHEAD trial was associated with greater weight loss.

7.3 | Metabolic-associated fatty liver disease

Historically, MAFLD has been treated with lifestyle interventions as the primary treatment strategy. Prior to the development of the highly effective glucagon-like peptide-1-based incretin mimetics that appear to have efficacy in the treatment of steatohepatitis and hepatic steatosis,[71] weight reduction of 7%–10% of body weight was considered the most effective non-pharmacological strategy to reduce liver fat content and prevent or regress fibrosis.[72] Despite the effectiveness of MR diets to achieve the target of 7%–10% weight reduction that has been associated with improvements in liver health, there are few prospective, randomized trials comparing MR to other treatments to assess effects on liver histology. One RCT of 60 patients preparing for bariatric surgery showed that 2-week VLCD use was effective for reducing liver fat content and improving liver histology. There were no differences in terms of fat content, histopathology, or other outcomes when comparing the VLCD as a food-based diet or as MR.[73] There are, however, a number of reports that describe reductions in liver volume and fat by imaging, improvements in fatty liver index, liver enzymes and stiffness, with the use of MR diets, with strong associations between the volume of weight loss and the changes in liver size and fat.[74–77]

7.4 | Body composition and physical function

As one of the benefits of using an MR-based MNT for obesity treatment is the larger volume of weight loss achieved, the resulting concern is that this degree of energy restriction leads to a significant proportion of the weight loss from lean compartments such as skeletal muscle and bone.[78] However, MR diets can be an efficient way to achieve protein and optimal micronutrient intakes that help to mitigate loss of lean mass despite reduced energy consumption. The TEMPO study compared severe energy restriction achieved with TDR to moderate energy restriction assessed changes in body composition.[45] Results showed that, despite a 6.6-kg greater weight loss at 12 months for the VLCD, the loss of lean mass was proportionally similar to total weight loss for each group. Of the total 15.3-kg weight loss for the VLCD group, 3.2 (95% CI −4.1 to −2.3) kg was lean mass compared to a weight change of −8.4 kg with 2.1 (95% CI −3.1 to −1.2) kg as lean mass for the moderated restriction group. The VLCD group had greater decreases in bone mineral density at the total hip site at 12 months after adjusting for total weight loss.

The other consideration related to change in body composition is the impact on physical function: Does a larger loss of lean mass lead to detrimental effects on physical function? There has been some evidence to suggest that, despite loss of lean mass, the quality of lean mass remaining is improved and there are no detrimental effects to physical function. The TEMPO study also provided an assessment of physical function using handgrip strength measurements. There were no significant differences between the treatment groups at the 12-month outcome assessment. The severe restriction group had no significant changes from baseline in handgrip strength.[45]

7.5 | Quality of life

Obesity has a significant impact on health-related quality of life (HRQOL), negatively affecting both physical and mental functioning.[79] Weight reduction via a number of methods has consistently been shown to improve quality of life in all domains. However, clinical concerns, such as adverse events and side effects, along with practical issues related to ease of implementation and burden of the intervention, can all influence the potential improvements of a weight reduction intervention on quality of life. An intervention that causes gastrointestinal distress or pain due to exercises that are overly strenuous or difficult to implement could decrease the perceived improvements in quality of life directly, or indirectly via early discontinuation or incomplete implementation of the intervention. An MR intervention could provide some potential advantages over food-based diets for improving HRQOL above and beyond the larger amount of weight loss achieved.

The ACOORH study provides a comparative assessment of HRQOL in an RCT comparing an MR-based lifestyle intervention for overweight and obesity to lifestyle intervention alone.[80] HRQOL was assessed at 1, 3 and 12 months using the 36-Item Short-Form Health Survey (SF-36)[81]; data were reported for 263 participants. There were early improvements in the physical component scores favouring the MR group (treatment difference = 2.7 [1.2; 4.2]; $p < 0.0001$) at 3 months that were sustained at 12 months (1.9 [0.3; 3.8]; $p = 0.021$]). While weight changes were associated with greater improvement in mental component scores, there were no statistically significant differences between the treatment groups. Another non-randomized controlled trial similarly compared the effects on HRQOL using the SF-36 for a lifestyle programme with or without MR.[82] There were 380 female participants (190/group) who were age- and weight-matched (means 51.4 ± 7.0 years, 35.5 ± 3.03 kg/m^2). HRQOL was assessed at baseline and 12 months. Weight reduction was similar in the two groups but favoured those who used MR (−6.6 ± 6.6 vs. −7.6 ± 7.9 kg; $p = 0.1$). Four of eight subcomponents of the SF-36 improved significantly in the lifestyle-only group, whereas seven of eight subcomponents improved significantly in the group using MR. The mental component summary score showed significantly greater improvement at 12 months in favour of the MR group (1.6 ± 5.68) versus the lifestyle-only group (0.5 ± 1.59).

8 | ROLE OF MR IN CURRENT TREATMENT LANDSCAPE

The role of MR in the current obesity treatment landscape includes some traditional indications and uses, along with new adjunctive roles as new treatment options have emerged. TDR continues to be an effective strategy for providing complete nutrition, structure, and stimulus control for individuals with obesity seeking an efficient lifestyle intervention as a part of their weight management treatment strategy. The emergence of third-generation antiobesity medications (AOMs) that are incretin-based, long-acting, and tend to achieve average weight losses of 15%[83,84] or more means that MR combined with these treatments can be used with a greater sense of self-efficacy and ease of implementation. Studies that have combined MR-based diets with the third-generation AOMs have not demonstrated greater weight loss than would be expected with use of the AOM alone, but properly designed clinical trials to test additivity have not been performed.[85] In this context, the use of MR may provide individuals on third-generation AOMs with more consistent nutrition and may support better quality weight loss by promoting greater retention of lean mass. More research is needed in this arena to determine how weight loss quality may be impacted with this combination of therapies.

Meal replacement has also been used with metabolic and bariatric surgery as a way to prepare patients for surgery as well as a way to support optimal nutrition postoperatively. There have been a variety of studies of preoperative weight loss using MR-based interventions that show benefits for reduced liver size, operative time, and total weight loss.[86] However, there have been a number of studies that have failed to demonstrate those same findings.[87] Ultimately, the use of MR in the pre- or post-bariatric surgery patients may depend more on taking a patient-centric approach to identifying the best dietary approach for the patient that optimizes nutritional intake.

Meal replacement may be also considered as part of a weight loss maintenance strategy for those who have to discontinue AOM therapy for any reason. While continued treatment with AOM is the general expectation given the chronicity of the disease, there are some individuals who might wish to try discontinuation or who lose access to the AOM. In these instances, use of MR could assist with maintaining an appropriate caloric intake for the weight-reduced state.

9 | SPECIFIC-USE CASES/CLINICAL SCENARIOS WHERE MR CAN BE HIGHLY EFFECTIVE

There are a number of clinical scenarios where MR may be highly effective, particularly for inducing weight reduction in a predictable and efficient manner while maintaining adequate nutrition in high-risk individuals. For example, MR has been used to address obesity in older adults at risk of sarcopenia. Effective delivery of higher protein intake in older adults who may have comorbidities that limit intake of food-based protein foods such as meat, can be accomplished with the use of MR. The higher protein intake in the setting of energy restriction is critical to limiting loss of lean mass and may be associated with improvements in physical function.[45,80,88] Pre-procedural weight loss is another area where use of MR can be highly effective, including for bariatric surgery and orthopaedic surgery. As previously noted, use of MR prior to bariatric surgery can result in reduced liver size and preoperative weight loss. For orthopaedic surgery, joint replacement is not routinely carried out for those with a BMI of 40 kg/m^2 or higher due to increased risk of complications and higher cost.[89] These patients are often at the additional disadvantage of having limited mobility with little ability to contribute to the energy deficit with physical activity or exercise. Given the volume of weight loss seen on average, MR can be effective for helping patients get to a BMI < 40 kg/m^2 to proceed with joint replacement. Research is still needed to demonstrate if indeed there is longer-term benefit for the patient for non-surgical weight loss after arthroplasty.[90] Another patient group that may experience significant benefit with the use of MR for weight loss is women with difficulty conceiving due to polycystic ovarian syndrome (PCOS). Due to contraindications for a number of weight loss strategies with pregnancy, the use of MR can be safe and effective for reducing metabolic syndrome-associated risks of PCOS.[91] Women with overweight or obesity may benefit from lifestyle interventions that include use of PDR during pregnancy to limit excess gestational weight gain.[92] Lastly, many of the same benefits for weight reduction and improvement in obesity-related complications seen in adults treated with MR are also observed in adolescents with obesity.[93]

10 | CONCLUSION

As global rates of obesity continue to rise, with costly consequences, there has been increased focus in the literature in understanding the complexity of obesity as a disease and pathways for successful treatment. There is strong evidence that MRs in VLCDs/LCDs are an effective, safe, and well-tolerated treatment for obesity. MRs can be effectively used as TDR, to induce weight loss, or as PDR to induce or sustain weight loss in a wide array of patients with obesity and associated complications. Use of MR is associated with improved glycaemic control, cardiovascular risk factors, MAFLD, mitigation of loss of lean muscle mass, physical functioning, and quality of life. As the options for obesity treatment continue to expand, additional research is needed to identify how to tailor available treatment options, including MR, in various settings and combinations to achieve the best outcomes most efficiently.

ACKNOWLEDGEMENT

This article was commissioned by the Editor has part of a Speciall themed issue made possible by funding from Nestle. Sponsor identity was not disclosed to authors prior to publication.

FUNDING INFORMATION

There was no external funding support for this work.

CONFLICT OF INTEREST STATEMENT

Dr Ard reports receiving personal fees and research support from Nestle Healthcare Nutrition, Eli Lilly, Novo Nordisk, WeightWatchers, Regeneron, Boehringer Ingelheim, and Intuitive; grants from Epitomee and United Health Group; and nonfinancial support from KVKTech outside the submitted work.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15819.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-e891. doi:10.1503/cmaj.191707
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;390(10113):2627-2642. doi:10.1016/S0140-6736(17)32129-3
3. Hammond RA, Levine R. The economic impact of obesity in the United States. *Diabetes Metab Syndr Obes*. 2010;30:285-295. doi:10.2147/dmsott.S7384
4. Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One*. 2021;16(3):e0247307. doi:10.1371/journal.pone.0247307
5. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA*. 2014;312(9):923-933. doi:10.1001/jama.2014.10397
6. Hassapidou M, Vlassopoulos A, Kalliostra M, et al. European Association for the study of obesity position statement on medical nutrition therapy for the management of overweight and obesity in adults developed in collaboration with the European federation of the associations of dietitians. *Obes Facts*. 2023;16(1):11-28. doi:10.1159/000528083
7. Garneau P, Glazer S, Jackson T, et al. Guidelines for Canadian bariatric surgical and medical centres: a statement from the Canadian Association of Bariatric Physicians and Surgeons. *Can J Surg*. 2022;65(2):E170-E177. doi:10.1503/cjs.020719
8. Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obes Rev*. 2019;20(4):569-587. doi:10.1111/obr.12816
9. Heymsfield SB, Mierlo CAJ, Knaap HCM, Heo M, Frier HI. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes (Lond)*. 2003;27(5):537-549. doi:10.1038/sj.ijo.0802258
10. Codex Alimentarius Commission. CODEX STAN 203 - standard for formula foods for use in very low energy diets for weight reduction. Food and Agriculture Organization of the United Nations. 2009.
11. Atkinson RL, Dietz WH, Foreyt JP, et al. Very low-calorie diets. *JAMA*. 1993;270(8):967-974. doi:10.1001/jama.1993.03510080071034
12. Cade J, O'Connell S. Management of weight problems and obesity: knowledge, attitudes and current practice of general practitioners. *Br J Gen Pract*. 1991;41(345):147-150.
13. Kristeller JL, Hoerr RA. Physician attitudes toward managing obesity: differences among six specialty groups. *Prev Med*. 1997;26(4):542-549. doi:10.1006/pmed.1997.0171
14. Howard AN. The historical development, efficacy and safety of very-low-calorie diets. *Int J Obes (Lond)*. 1981;5(3):195-208.
15. van Itallie TB. Liquid protein mayhem. *JAMA*. 1978;240(2):144-145. doi:10.1001/jama.1978.03290020066028
16. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring, Md)*. 2006;14(8):1283-1293. doi:10.1038/oby.2006.146
17. Sours HE, Frattali VP, Brand CD, et al. Sudden death associated with very low calorie weight reduction regimens. *Am J Clin Nutr*. 1981;34(4):453-461. doi:10.1093/ajcn/34.4.453
18. Ashley JM, Herzog H, Clodfelter S, Bovee V, Schrage J, Pritsos C. Nutrient adequacy during weight loss interventions: a randomized study in women comparing the dietary intake in a meal replacement group with a traditional food group. *Nutr J*. 2007;6(1):12. doi:10.1186/1475-2891-6-12
19. Raynor HA, Anderson AM, Miller GD, et al. Partial meal replacement plan and quality of the diet at 1 year: action for health in diabetes (Look AHEAD) trial. *J Acad Nutr Diet*. 2015;115(5):731-742. doi:10.1016/j.jand.2014.11.003
20. Röhling M, Stensitzky A, Oliveira CLP, et al. Effects of a protein-rich, low-glycaemic meal replacement on changes in dietary intake and body weight following a weight-management intervention-the ACOORH trial. *Nutrients*. 2021;13(2):376. doi:10.3390/nu13020376
21. Gardner CD, Kim S, Bersamin A, et al. Micronutrient quality of weight-loss diets that focus on macronutrients: results from the a TO Z study. *Am J Clin Nutr*. 2010;92(2):304-312. doi:10.3945/ajcn.2010.29468
22. Lagiou P, Sandin S, Lof M, Trichopoulos D, Adami HO, Weiderpass E. Low carbohydrate-high protein diet and incidence of cardiovascular

diseases in Swedish women: prospective cohort study. *BMJ*. 2012;344:e4026. doi:10.1136/bmj.e4026
23. Christoffersen BO, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E. Beyond appetite regulation: targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. *Obesity (Silver Spring)*. 2022;30(4):841-857. doi:10.1002/oby.23374
24. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604. doi:10.1056/NEJMoa1105816
25. Sumithran P, Prendergast LA, Delbridge E, et al. Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur J Clin Nutr*. 2013;67(7):759-764. doi:10.1038/ejcn.2013.90
26. Purcell KB, Sumithran PP, Prendergast LAP, Bouniu CJM, Delbridge EP, Proietto JP. The effect of rate of weight loss on long-term weight management: a randomised controlled trial. *Lancet Diabetes Endocrinol*. 2014;2(12):954-962. doi:10.1016/s2213-8587(14)70200-1
27. Gibson AA, Seimon RV, Lee CMY, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev*. 2015;16(1):64-76. doi:10.1111/obr.12230
28. Martin CK, O'Neil PM, Pawlow L. Changes in food cravings during low-calorie and very-low-calorie diets. *Obesity (Silver Spring, Md)*. 2006;14(1):115-121. doi:10.1038/oby.2006.14
29. Moldovan CP, Weldon AJ, Daher NS, et al. Effects of a meal replacement system alone or in combination with phentermine on weight loss and food cravings. *Obesity (Silver Spring)*. 2016;24(11):2344-2350. doi:10.1002/oby.21649
30. Alonso-Alonso M, Woods SC, Pelchat M, et al. Food reward system: current perspectives and future research needs. *Nutr Rev*. 2015;73(5):296-307. doi:10.1093/nutrit/nuv002
31. Kahathuduwa CN, Davis T, O'Boyle M, et al. Effects of 3-week total meal replacement vs. typical food-based diet on human brain functional magnetic resonance imaging food-cue reactivity and functional connectivity in people with obesity. *Appetite*. 2018;120:431-441. doi:10.1016/j.appet.2017.09.025
32. Kahathuduwa CN, Boyd LA, Davis T, O'Boyle M, Binks M. Brain regions involved in ingestive behavior and related psychological constructs in people undergoing calorie restriction. *Appetite*. 2016;107:348-361. doi:10.1016/j.appet.2016.08.112
33. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest*. 2008;118(7):2583-2591. doi:10.1172/jci35055
34. Weingarten HP. Stimulus control of eating: implications for a two-factor theory of hunger. *Appetite*. 1985;6(4):387-401. doi:10.1016/s0195-6663(85)80006-4
35. Brown A, Leeds AR. Very low-energy and low-energy formula diets: effects on weight loss, obesity co-morbidities and type 2 diabetes remission – an update on the evidence for their use in clinical practice. *Nutr Bull*. 2019;44(1):7-24. doi:10.1111/nbu.12372
36. Harper C, Maher J, Grunseit A, Seimon RV, Sainsbury A. Experiences of using very low energy diets for weight loss by people with overweight or obesity: a review of qualitative research. *Obes Rev*. 2018;19(10):1412-1423. doi:10.1111/obr.12715
37. Ostberg AL, Wikstrand I, Bengtsson Bostrom K. Group treatment of obesity in primary care practice: a qualitative study of patients' perspectives. *Scand J Public Health*. 2011;39(1):98-105. doi:10.1177/1403494810391524
38. Love JG, McKenzie JS, Nikokavoura EA, Broom J, Rolland C, Johnston KL. The experiences of women with polycystic ovary syndrome on a very low-calorie diet. *Int J Womens Health*. 2016;8:299-310. doi:10.2147/IJWH.S100385
39. Rehackova L, Araujo-Soares V, Adamson AJ, Steven S, Taylor R, Sniehotta FF. Acceptability of a very-low-energy diet in type 2 diabetes: patient experiences and behaviour regulation. *Diabet Med*. 2017;34(11):1554-1567. doi:10.1111/dme.13426
40. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline 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. *J Am Coll Cardiol*. 2014;63(25):2985-3023. doi:10.1016/j.jacc.2013.11.004
41. Brown JCC, Johnson Stoklossa C, Sievenpiper J. Canadian Adult Obesity Clinical Practice Guidelines: Medical Nutrition Therapy in Obesity Management. 2022 Accessed April, 2024. https://obesitycanadaguidelines.ca/guidelines/nutrition
42. Astbury NM, Aveyard P, Nickless A, et al. Doctor referral of overweight people to low energy total diet replacement treatment (DROPLET): pragmatic randomised controlled trial. *BMJ*. 2018;362:k3760. doi:10.1136/bmj.k3760
43. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1
44. Ard JD, Lewis KH, Rothberg A, et al. Effectiveness of a total meal replacement program (OPTIFAST program) on weight loss: results from the OPTIWIN study. *Obesity (Silver Spring)*. 2019;27(1):22-29. doi:10.1002/oby.22303
45. Seimon RV, Wild-Taylor AL, Keating SE, et al. Effect of weight loss via severe vs moderate energy restriction on lean mass and body composition among postmenopausal women with obesity: the TEMPO diet randomized clinical trial. *JAMA Netw Open*. 2019;2(10):e1913733. doi:10.1001/jamanetworkopen.2019.13733
46. Halle M, Röhling M, Banzer W, et al. Meal replacement by formula diet reduces weight more than a lifestyle intervention alone in patients with overweight or obesity and accompanied cardiovascular risk factors-the ACOORH trial. *Eur J Clin Nutr*. 2021;75(4):661-669. doi:10.1038/s41430-020-00783-4
47. Hartman AL, Vining EP. Clinical aspects of the ketogenic diet. *Epilepsia*. 2007;48(1):31-42. doi:10.1111/j.1528-1167.2007.00914.x
48. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia*. 2004;45(9):1116-1123. doi:10.1111/j.0013-9580.2004.10004.x
49. Westman EC, Yancy WS Jr. Using a low-carbohydrate diet to treat obesity and type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(5):255-260. doi:10.1097/MED.0000000000000565
50. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med*. 2004;140(10):769-777. doi:10.7326/0003-4819-140-10-200405180-00006
51. Harvey C, Schofield GM, Williden M. The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review. *PeerJ*. 2018;6:e4488. doi:10.7717/peerj.4488
52. Polivy J, Herman CP. Dieting and binging: a causal analysis. *Am Psychol*. 1985;40(2):193-201. doi:10.1037/0003-066x.40.2.193
53. Luz FQ, Hay P, Gibson AA, et al. Does severe dietary energy restriction increase binge eating in overweight or obese individuals? A systematic review. *Obes Rev*. 2015;16(8):652-665. doi:10.1111/obr.12295
54. Wadden TA, Foster GD, Sarwer DB, et al. Dieting and the development of eating disorders in obese women: results of a randomized controlled trial. *Am J Clin Nutr*. 2004;80(3):560-568. doi:10.1093/ajcn/80.3.560
55. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol.

Diabetologia. 2011;54(10):2506-2514. doi:10.1007/s00125-011-2204-7
56. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for beta cell recovery. *Cell Metab*. 2018;28(4):667. doi:10.1016/j.cmet.2018.08.010
57. Patel P, Abate N. Body fat distribution and insulin resistance. *Nutrients*. 2013;5(6):2019-2027. doi:10.3390/nu5062019
58. Tushuizen ME, Bunck MC, Pouwels PJ, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. *Diabetes Care*. 2007;30(11):2916-2921. doi:10.2337/dc07-0326
59. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. *J Intern Med*. 2021;289(6):754-770. doi:10.1111/joim.13214
60. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes*. 2005;54(3):603-608. doi:10.2337/diabetes.54.3.603
61. Ye W, Xu L, Ye Y, et al. Efficacy and safety of meal replacement in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2023;108(11):3041-3049. doi:10.1210/clinem/dgad273
62. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA*. 2012;308(23):2489-2496. doi:10.1001/jama.2012.67929
63. Wadden TA, West DS, Neiberg RH, et al. One-year weight losses in the Look AHEAD study: factors associated with success. *Obesity*. 2009;17(4):713-722. doi:10.1038/oby.2008.637
64. Taheri S, Zaghloul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2020;8(6):477-489. doi:10.1016/S2213-8587(20)30117-0
65. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline 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. *Circulation*. 2014;129(25 Suppl 2):S102-S138. doi:10.1161/01.cir.0000437739.71477.ee
66. Cefalu WT, Bray GA, Home PD, et al. Advances in the science, treatment, and prevention of the disease of obesity: reflections from a diabetes care editors' expert forum. *Diabetes Care*. 2015;38(8):1567-1582. doi:10.2337/dc15-1081
67. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. *Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture; 2020.
68. Ard JD, Neeland IJ, Rothberg AE, et al. The OPTIFAST total and partial meal replacement programme reduces cardiometabolic risk in adults with obesity: secondary and exploratory analysis of the OPTIWIN study. *Diabetes Obes Metab*. 2024;26(3):950-960. doi:10.1111/dom.15392
69. Armborst D, Metzner C, Bitterlich N, Lemperle M, Siener R. Effect of a weight-loss stabilization following a weight reduction with or without meal replacement on cardiometabolic risk in overweight women. A randomized controlled trial. *Int J Food Sci Nutr*. 2019;70(4):453-466. doi:10.1080/09637486.2018.1537363
70. Look ARG, Gregg EW, Jakicic JM, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4(11):913-921. doi:10.1016/S2213-8587(16)30162-0
71. Nevola R, Epifani R, Imbriani S, et al. GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. *Int J Mol Sci*. 2023;24(2):1703. doi:10.3390/ijms24021703
72. Koutoukidis DA, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179(9):1262-1271. doi:10.1001/jamainternmed.2019.2248
73. Baldry EL, Aithal GP, Kaye P, et al. Effects of short-term energy restriction on liver lipid content and inflammatory status in severely obese adults: results of a randomized controlled trial using 2 dietary approaches. *Diabetes Obes Metab*. 2017;19(8):1179-1183. doi:10.1111/dom.12918
74. Lange UG, Moulla Y, Schütz T, et al. Effectiveness and tolerability of a two-week hypocaloric protein-rich diet prior to obesity surgery with two different diet interventions: a prospective randomized trial. *Obes Surg*. 2022;32(9):2903-2913. doi:10.1007/s11695-022-06180-z
75. Lewis MC, Phillips ML, Slavotinek JP, Kow L, Thompson CH, Toouli J. Change in liver size and fat content after treatment with optifast very low calorie diet. *Obes Surg*. 2006;16(6):697-701. doi:10.1381/096089206777346682
76. Luis D, Primo D, Izaola O, Lopez JJ. Effects of a short-term meal replacement hypocaloric diet in subjects with obesity and high fatty liver index. *Nutrients*. 2022;14(24):5353. doi:10.3390/nu14245353
77. Scragg J, Avery L, Cassidy S, et al. Feasibility of a very low calorie diet to achieve a sustainable 10% weight loss in patients with nonalcoholic fatty liver disease. *Clin Transl Gastroenterol*. 2020;11(9):e00231. doi:10.14309/ctg.0000000000000231
78. Chaston TB, Dixon JB, O'Brien PE. Changes in fat-free mass during significant weight loss: a systematic review. *Int J Obes (Lond)*. 2007;31(5):743-750. doi:10.1038/sj.ijo.0803483
79. Doll HA, Petersen SE, Stewart-Brown SL. Obesity and physical and emotional well-being: associations between body mass index, chronic illness, and the physical and mental components of the SF-36 questionnaire. *Obes Res*. 2000;8(2):160-170. doi:10.1038/oby.2000.17
80. Kempf K, Röhling M, Banzer W, et al. High-protein, low-Glycaemic meal replacement improves physical health-related quality of life in high-risk persons for metabolic syndrome-a subanalysis of the randomised-controlled ACOORH trial. *Nutrients*. 2022;14(15):3161. doi:10.3390/nu14153161
81. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
82. Koohkan S, Schaffner D, Milliron BJ, et al. The impact of a weight reduction program with and without meal-replacement on health related quality of life in middle-aged obese females. *BMC Womens Health*. 2014;14(1):45. doi:10.1186/1472-6874-14-45
83. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
84. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
85. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831
86. McKechnie T, Lee Y, Dionne J, et al. Very low energy diets prior to bariatric surgery may reduce postoperative morbidity: a systematic review and meta-analysis of randomized controlled trials. *Front Nutr*. 2023;10:1211575. doi:10.3389/fnut.2023.1211575
87. Holderbaum M, Casagrande DS, Sussenbach S, Buss C. Effects of very low calorie diets on liver size and weight loss in the preoperative period of bariatric surgery: a systematic review. *Surg Obes Relat Dis*. 2018;14(2):237-244. doi:10.1016/j.soard.2017.09.531
88. Dainelli L, Luo DR, Cohen SS, et al. Health-related quality of life in weight loss interventions: results from the OPTIWIN trial. *Int J*

Environ Res Public Health. 2021;18(4):1785. doi:10.3390/ijerph18041785
89. D'Apuzzo MR, Novicoff WM, Browne JA. The John Insall award: morbid obesity independently impacts complications, mortality, and resource use after TKA. *Clin Orthop Relat Res*. 2015;473(1):57-63. doi:10.1007/s11999-014-3668-9
90. Godziuk K, Prado CM, Beaupre L, Jones CA, Werle JR, Forhan M. A critical review of weight loss recommendations before total knee arthroplasty. *Joint Bone Spine*. 2021;88(2):105114. doi:10.1016/j.jbspin.2020.105114
91. Legro RS, Dodson WC, Kris-Etherton PM, et al. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2015;100(11):4048-4058. doi:10.1210/jc.2015-2778
92. Mustad VA, Huynh DTT, López-Pedrosa JM, Campoy C, Rueda R. The role of dietary carbohydrates in gestational diabetes. *Nutrients*. 2020;12(2):385.
93. Andela S, Burrows TL, Baur LA, Coyle DH, Collins CE, Gow ML. Efficacy of very low-energy diet programs for weight loss: a systematic review with meta-analysis of intervention studies in children and adolescents with obesity. *Obes Rev*. 2019;20(6):871-882. doi:10.1111/obr.12830

How to cite this article: Edwards-Hampton SA, Ard J. The latest evidence and clinical guidelines for use of meal replacements in very-low-calorie diets or low-calorie diets for the treatment of obesity. *Diabetes Obes Metab*. 2024;26(Suppl. 4):28-38. doi:10.1111/dom.15819