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Precision Medicine in Weight Loss and Healthy Living

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Abstract

Obesity affects 600 million people globally and over one third of the American population. Along with associated comorbidities, including cardiovascular disease, stroke, diabetes, and cancer; the direct and indirect costs of managing obesity are 21% of the total medical costs. These factors shed light on why developing effective and pragmatic strategies to reduce body weight in obese individuals is a major public health concern. An estimated 60–70% of obese Americans attempt to lose weight each year, with only a small minority able to achieve and maintain long term weight loss. To address this issue a precision medicine approach for weight loss has been considered, which places an emphasis on sustainability and real-world application to individualized therapy. In this article we review weight loss interventions in the context of precision medicine and discuss the role of genetic and epigenetic factors, pharmacological interventions, lifestyle interventions, and bariatric surgery on weight loss.

Obesity affects more than 600 million people globally[1] and over 90 million Americans[2]. Obesity is associated with a multitude of chronic noncommunicable diseases, such as cardiovascular disease (CVD), stroke, diabetes, and cancer[3]. Obesity is also associated with high rates of disability[4] and all-cause mortality[5] . In the United States (US), the direct and indirect costs of managing obesity and its associated comorbidities are currently estimated at $149 billion per year[6], which is approximately 21% of total medical costs[6]. Additionally, the per-capita healthcare costs for obese individuals is 42% higher than those at normal weight[7] and 81% higher for those with morbid obesity [Body mass index (BMI) >40 kg/m^2] [8]. Due to these relationships, developing effective and pragmatic strategies to reduce body weight in obese individuals is a major public health concern[9].

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National guidelines for weight loss programs recommend a goal of at least a 10% reduction in body weight[10], yet health related benefits may be observed with body weight reductions as low as 5%[11] . An estimated 60–70% of obese Americans attempt to lose weight each year[12,13]. However, there is significant heterogeneity in the response to different weight loss programs and many clinical trials investigating weight loss lack generalizability to real-world practice[14]. Furthermore, many individuals who achieve weight loss goals following such programs fail to maintain body weight losses long term[15]. This may be due to the complex nature of obesity which involves genetic, epigenetic, and environmental factors[16–19]. To address this issue, a precision medicine approach for weight loss has been considered[20], since it acknowledges these multiple factors and places emphasis on sustainability and real-world application. The purpose of this paper is to review the evidence regarding different weight loss strategies from a precision medicine perspective which acknowledges the dynamic interaction between genetic, epigenetic and environmental factors.

Genetic and Epigenetic Factors

The framework for a genetic predisposition to obesity has been well established in the literature[18,21,22]. Previous studies have indicated that the contribution of genetic heritability to the development of obesity may be as high as 70%[18,21,22] and several genes have been identified as key contributors[23]. These genes may regulate food intake, nutrient preferences, energy expenditure, leptin sensitivity, and other biological aspects that might contribute to the risk of obesity[24]. The genome-wide association studies (GWAS) has led to the discovery of several genetic loci that carry polymorphisms or mutations that have been associated with obesity such as FTO (alpha-ketoglutarate dependent dioxygenase), MC4R (melanocortin 4 receptor), and POMC (proopiomelanocortin)[25]. Notably the *Ucp1* gene which is primarily expressed in brown adipose tissue, and aids in thermogenesis and regulation of energy expenditure, as well as protection against oxidative stress, has been a target of study[26]. In mouse models, the lack of *Ucp1* increases susceptibility to diet-induced obesity[27] while increased expression of *Ucp1* in white adipose tissue resulted in resistance to diet-induced obesity[28].

There are also several genetic syndromes related to obesity, including (1) Monogenic obesity, described as severe early-onset obesity that is primarily the result of mutations in genes of the hypothalamic/leptin/melanocortin axis resulting in changes to satiety development[29]; (2) Syndromic obesity, which is classified as severe obesity associated with additional phenotypes and other organ abnormalities such as Prader-Willi Synrdome (PWS)[29]; and (3) Oligogenic obesity, characterized by a variable degree of severity and is partly dependent on environmental factors and the absence of a specific phenotype; such as such as melanocortin 4 receptor (*MC4R*)-linked obesity[29]. However, these syndromes are rare compared to polygenic obesity, the most common form of obesity. Polygenic obesity, also known as common obesity, is a condition where several polymorphic genes related to obesity interact with each other and environmental factors that might amplify their contribution to obesity such as poor diet, physical inactivity, and excessive stress[29,30].

These genetic factors may partially explain the heterogeneity in success rates among individuals following a given weight loss intervention program. However, despite these findings there remains some uncertainty regarding the specific magnitude of the relationship between obesity and genetics[16–18]. Furthermore, the role of genetics in obesity can not entirely explain the steep increase in obesity prevalence in the past few decades. Accordingly, the role of environmental exposures and lifestyle risk factors and their interaction with genetics should be considered. Some studies have demonstrated significant variability in weight gain even in isogenic strains of mice while controlling environmental factors such as diet and activity. For example, a study by Koza et al investigated the effects of feeding genetically identical mice[17]. They found identical 8-week-old male B6 mice developed a highly variable rate of obesity after being fed a high fat diet while being under standard laboratory conditions[17]. Similar findings have been reported in human using twin studies which are considered to be the ideal model to distinguish genetic versus environmental contributions. In these studies, it has been shown that as the twins age, the more variable their body weight and BMI become, which is most likely attributable to the accumulation of different life exposures[31,32]..

One way by which environmental factors and life exposures control genes is via epigenetics; a meta-level of controlling genes. Recent work has demonstrated that there may be an epigenetic switch influences the risk of developing obesity[16]. A study by Whitelaw et al utilized a mouse model in which only one of two copies of the gene Trim28 were present in the genome of the same strain of mice[33]. Despite being genetically identical, these mice displayed large variations in their body weight indicating an underlying epigenetic mechanism[33]. Although most of the evidence for the epigenetic component comes from animal studies, some observational studies showed that children of women pregnant during the Dutch Famine or those who were exposed to obesogenic chemical products, developed obesity more than counterparts. These studies might suggest epigenetic modifications induced by environmental exposure as a contributor to the susceptibility to obesity[25,34,35]. In addition to the contribution of maternal and paternal nutrition and life exposure to the epigenetic tendency for obesity in the offspring[36,37], direct exposure of individuals to excess nutrition or obesogenic products induces epigenetic changes that predispose to obesity[38]. Several epigenome-wide methylation studies reported an association between BMI and altered methylation sites in genes such as CPT1A, ABCG1, PGC1A, HIF3A, and SREBF1; some of which have emerged as predictive biomarkers associated with lifestyle[39,40] or predictive of obesity and metabolic health[41–43].

Therapeutic Approaches for Weight Loss

There are many potential therapeutic interventions for weight loss. In obese individuals, the primary interventions for weight loss include lifestyle interventions, pharmacotherapy, and bariatric surgery[9,44]. However, there is some controversy regarding which interventions are the most successful for reducing weight and maintaining weight loss for each individual patient. Individual responses to weight loss interventions demonstrate heterogeneity, which is likely due to a multitude of factors. Individual patients may require different amounts of interaction or support from healthcare providers to attain a weight loss goal. The optimal setting and medium of provider interaction and education for weight loss may also vary

between individual patients. Certain patients may even be genetically predisposed to respond or not respond to different weight loss interventions. It is also important to acknowledge that the results of studies investigating weight loss may be influenced by the length of follow up and measures used to assess weight loss. There also tends to be an over-reliance on the use of body weight and BMI as weight loss outcomes instead of more robust measures such as body composition or at least waist circumference. The following sections will review the evidence regarding these weight loss interventions

Lifestyle Intervention Programs

Lifestyle intervention programs are a popular choice for weight loss for obese individuals. The core elements of such programs typically involve exercise training, dietary interventions, and patient education. The literature demonstrates that these programs can be successfully implemented using a variety of methods (supervised or limited supervision)[45–47], settings (hospital based, outpatient, community based, occupational or commercial) and with different providers (physicians, dieticians, physical therapists, exercise physiologists or nurses)[48,49]. The protocols and specific choice of interventions such as dietary intake, or the mode, intensity, and frequency of exercise training often vary across different programs. The basis for most of these programs are creating a caloric or energy deficit leading to weight loss[50]. While there appears to be some heterogeneity in participant response to these different weight loss programs[13,50–53], generally the outcomes are successful[50,51,53–55]. This provides clinicians a wide variety of options to implement in practice.

However, the volume and variety of published studies demonstrating successful weight loss outcomes may also make it difficult for health providers to determine which type of program will work best at the individual level. Additionally, the parameters of such studies investigating lifestyle interventions for weight loss may not be generalizable to clinical practice[49,56]. For example, most clinical trials usually are provided at no cost to participants, offer financial incentives, are closely monitored, and are staffed by highly trained individuals who might be employed specifically to implement the trial[51]. Such characteristics are not easily met outside research-focused programs.

While there have been many attempts to identify which specific factors predict successful weight loss and maintenance of weight loss using lifestyle intervention programs, the primary factor that predicts a successful response to weight loss programs is patient adherence[20,56]. This may be true even for surgical interventions for weight loss[57]. Therefore, perhaps the true precision medicine approach for weight loss does not involve structuring weight loss programs based on genetics but instead on factors which optimize patient adherence to facilitate a behavior change conducive to long term weight loss and management[56]. There are numerous options to choose and the optimal weight loss program for an individual patient is the one they can adhere to consistently[20]. In the following section we provide some factors which should be considered by healthcare providers when prescribing lifestyle interventions for weight loss to obese patients.

Patient Support and Contact

The amount of contact and support from providers has been shown to influence patient motivation to maintain lifestyle changes conducive to weight loss. A retrospective study by Lenoir investigated the effects of visit frequency on weight loss outcomes in 14,256 patients enrolled in a weight loss program[54]. The findings of this study demonstrated that patients who successfully maintained a ≥10% weight loss over 12 months received an average of 0.65 clinic visits/month, patients with an average of 0.48 visits/month failed to maintain a ≥10% weight loss, and those receiving an average of 0.39 visits/month failed to achieve a ≥10% weight loss[54]. In practice, this number of clinic visits may be difficult to achieve for many patients and healthcare providers. The use of telehealth and mobile devices may be an effective alternative to provide this necessary frequent patient support[58]. While the evidence on weight loss specifically is limited, recent studies indicate weekly video teleconferencing with patients may be an effective strategy to achieve significant weight loss in obese individuals[58]. However, some patients may prefer less provider contact for their weight loss program[45]. Therefore, when developing a weight loss program, clinicians should discuss and mutually determine the preferred minimal and maximal frequency of contact (including tele health and technology utilization) with each individual patient.

Financial Cost and Sustainability

The financial burden of lifestyle interventions may be a significant factor influencing adherence for many patients[53]. Travel to clinic visits, co-payments and deductibles, dietary programs, exercise equipment, and gym memberships can all present significant financial constraints for obese patients and are potentially unsustainable. This is important to acknowledge considering that higher rates of obesity are observed in patients of lower socioeconomic status[59]. Therefore, clinicians should discuss and mutually determine components of the lifestyle intervention programs that will fit within a reasonable and sustainable budget for each individual patient.

Patient Preferences and Enjoyment

The training mode implemented in most lifestyle intervention programs for weight loss is moderate intensity aerobic exercise training (AET)[46]. The evidence regarding this mode of training for weight loss is strong and the goal is generally to attain between 225–300 minutes per week[46]. However, AET for obese patients, especially those who are sedentary, may not be well tolerated or enjoyable which may present as psychosocial barriers to exercise adherence [60,61]. Recent studies have demonstrated that high intensity interval training (HIT) may be an effective alternative mode of exercise training for obese individuals[60,61]. HIT consists of short high-intensity intervals of exercise combined with lower-intensity intervals of recovery. When compared to moderate intensity AET, HIT has similar outcomes[60], shorter training durations, and higher levels of enjoyment in obese individuals[61]. Resistance training (RT) has also been found to be more enjoyable mode than moderate intensity AET in obese individuals[62]. However, while RT does result in improvements in body composition by increasing lean muscle mass, its effect on weight loss is limited.[63] Therefore, while moderate intensity AET is the mode of exercise most recommended by guidelines these other options should be considered by providers

especially during the initial stages of training. Providers should also discuss and determine the mode of exercise or physical activity that the patient enjoys and develop an exercise training program based on those preferences.

Similar findings are observed for the dietary aspect of lifestyle intervention programs for weight loss. Meal preparation and taste preferences are frequently reported as perceived barriers to healthy eating[64,65]. These preferences towards food may be influenced by the patient's family history and traditions. Early childhood food experiences influence preferences towards food choices and eating habits[66]. Understanding and acknowledging these factors may assist providers when recommending dietary interventions. Similar to exercise training recommendations for weight loss, providers should discuss and determine healthy food choices that the patient enjoys and develop dietary prescriptions based on those preferences.

Patient Cognitive Function and Education Level

An increasing body of evidence indicates that impairments in executive functions such as the ability to engage in goal-oriented behaviors, self-regulation, and working memory are common in obesity[67,68]. In fact, executive functions have been shown to predict mid-treatment weight loss outcomes in obese patients enrolled in lifestyle intervention programs[69]. Additionally, individuals with syndromic obesity may have intellectual disabilities[29]. These associations between executive functions and obesity indicate that providers should consider pre-treatment cognitive assessments when developing weight loss programs and individualize them according to each patient's cognitive abilities.

Setting Reasonable and Attainable Goals

Many patients have difficulty establishing realistically achievable weight loss goals. This inability to establish reasonably attainable goals may be influenced by misinformation from a variety of sources, such as friends, the media, and even healthcare professionals[70]. Many obese patients set goals of 20%–30% of initial body weight[71] instead of a more realistic goal such as 5%–15%. The use of realistic and attainable weight-loss goals is imperative for patient motivation and adherence. Healthcare providers should discuss and develop mutually determined weight-loss goals for each patient. These goals should also be quantifiable and consistently assessed for progress. The amount of weight lost at 8 weeks predicts the long term response[72], therefore weight loss goals or plans to modify a program should be based around this timeframe. It is also important to set other goals in addition to weight loss within a lifestyle intervention program. Patients may fail to meet their weight loss goals; however, they may still receive additional health related benefits from the program[73,74]. Meeting these other goals can be leveraged to facilitate patient long-term participation in lifestyle intervention programs.

Pharmacological Interventions for Weight Loss

Although lifestyle interventions have been shown to result in clinically significant weight loss in obese individuals, many populations face difficulties both achieving and maintaining long term weight loss[14,47,75]. Obese individuals participating in such programs may lose up

to 10% of body weight over a 4–6-month period before experiencing a plateau in weight loss[47,76]. This plateau in weight loss following such programs is often followed by weight regain within one year in many patients, and for some patients a full return to baseline body weight within 5 years[76]. The rate of failure to achieve and maintain weight loss goals tend to be even worse for less intensive programs such as those delivered by primary care providers[77]. For this reason, pharmacological therapies have been proposed as potential adjuncts to assist with weight management.

Historically, the success rate for developing both safe and effective weight loss medications has been limited[78]. Several of these medications have been withdrawn from the market due to safety concerns. However, newer weight loss medications tend to be more specific with their targets for weight control and are thus more effective and safer to administer[75,78,79]. Five weight loss medications have met Food and Drug Administration (FDA) regulations and are now available in the US: orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide[79]. A summary of these medications is provided in Table 1.

These approved medications, when prescribed with lifestyle interventions such as diet and exercise, have been shown to produce additional weight loss when compared to placebo[75,79]. The additional weight reduction ranges from approximately 3% of initial weight for both orlistat and lorcaserin and up to 9% for phentermine/topiramate-ER at 1 year[75]. However, the percentage of patients achieving clinically-meaningful weight loss (≥5%) with orlistat was 35–73%, 37–47% with lorcaserin, and 67–70% with phentermine/topiramate[75]. Therefore, like other weight loss interventions, there appears to be a heterogenous response to pharmacological approaches as well. Unfortunately, the evidence regarding predictors of response to these medications is limited[75]. Most studies investigating the response of these drugs demonstrate that the weight loss at 12 weeks predicts later weight loss at ≥1 year[80–82]. The FDA has set a minimum threshold of 3–5% of weight loss at 12 weeks for continuation based on the type of medication[75].

Bariatric Surgery

For obese patients with a BMI >40 kg/m^2 or a BMI >35 kg/m^2 with obesity related comorbidities who fail to lose weight from lifestyle interventions and pharmacological therapies[83], bariatric surgery (BS) is an increasingly popular treatment choice[84]. Bariatric surgery has consistently been shown to result in rapid weight loss and a reduction of obesity-related comorbidities such as hypertension, dyslipidemia, and diabetes[85]. The two most common procedures performed are the Roux-en-Y Gastric Bypass (RYGB) and Laparoscopic Sleeve Gastrectomy (LSG)[86]. Both procedures result in comparable reductions in excess weight body weight, typically >60% at 1 year[86]. Most patients demonstrate significant and stable weight reductions following BS even up to 12 years post-operatively[87]. Patients undergoing BS, specifically RGYB, have also reported changes in taste perception and food preference which may also contribute to long-term maintenance of weight loss[88].

However, weight loss tends to plateau 1 year post-operatively[86] and not all patients attain desired clinical outcomes for weight loss even with a successful surgery[89]. This matter becomes more pronounced beyond 2 years post-operatively[57] where patients may begin to

demonstrate weight regain (WR). Similar to other weight loss interventions, failure to achieve weight loss and WR following BS involves multiple factors and the exact mechanisms remains unclear. The evidence that does exist indicates that nutritional habits and psychological factors play a significant role in WR following BS[57,89]. Another key factor for WR may be a lack of physical activity and exercise. It is estimated that only 10–24% after BS meet minimal weekly physical activity recommendations[57]. However, there is limited data on how much physical activity is needed to prevent WR after bariatric surgery[57]. Individuals with greater preoperative weight and a higher initial BMI are at an increased risk for failing to achieve weight loss goals following BS[90]. However, the benefits of mandatory weight loss program preoperatively on the long term weight loss outcomes following BS is not supported by data reported in the literature[91].

Therefore, the recommended approach to optimize weight loss outcomes following BS involve patient education, diet and physical activity counseling, and long-term follow-up with a multidisciplinary team. Prior to BS patients should be evaluated for realistic goals, readiness for behavior change, and knowledge about both nutrition and exercise.

Conclusions

While the connotation of “Precision Medicine” is often clinical interventions that are optimized for a patient’s unique genetics, environmental and lifestyle factors are also included in the definition by the NIH. These other factors are as important as genetics, and potentially to greater degree in obese patients. Most obese patients demonstrate a polygenic manifestation with obesogenic genes which may be switched on or off by epigenetic regulators that are influenced by both lifestyle and environmental factors. While genetics may predispose individuals to obesity, clinically the interventions available for most providers target environmental and lifestyle factors of the patient.

There are a multitude different types of effective lifestyle intervention programs for weight loss. There is no singular mode or type of lifestyle intervention program for weight loss that works best for every individual patient. However, what does appear to work for every patient is the collaborative and iterative development of an individualized lifestyle intervention program which incorporates patient preferences and abilities to optimize patient adherence. Some obese patients may also require pharmacological interventions to help achieve weight loss goals. For obese patients who aren’t successful in losing weight following a lifestyle intervention program and pharmacological interventions, bariatric surgery is a well-supported option. However, even for those receiving bariatric surgery addressing environmental factors and optimizing adherence is still critical for successful weight loss outcomes. Future research should investigate the use of telehealth and wearable technologies to address lifestyle, environmental, and potentially genomic factors to optimize weight loss in obese patients.

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Alphabetical list of abbreviations:

AET	Aerobic exercise training
BS	Bariatric Surgery
BMI	Body mass index
CV	Cardiovascular
CVD	Cardiovascular disease
FDA	Food and Drug Administration
HIT	High intensity interval training
HLM	Healthy living medicine
MC4R	Melanocortin 4 receptor
NIH	National Institute of Health
RT	Resistance training
Ucp1	Uncoupling protein 1
US	United States
WR	Weight regain

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Table 1.

Summary of selected drugs with indication for obesity.

Medication	Mechanism of action	Efficacy
Orlistat	Gastrointestinal lipase inhibitor; prevents digestion of ~30% of ingested triacylglycerides.	60 mg, −2.5 kg (−1.5 to −3.5)[a], 120 mg, −3.4 kg (−3.2 to −3.6)[a, 75]
Lorcaserin	Selective serotonin 2C (5-HT2C) receptor antagonist to reduce appetite.[92]	10 mg, −3.6%[b, 93]
Phentermine/Topiramate	Noradrenergic and GABA receptor activator; AMPK/KA receptor antagonist causing suppressed appetite.	7.5 mg/46 mg, −6.6%[b, 94] 15 mg/92 mg, −8.6 to −9.3%[b, 95]
Bupriopion/Naltrexone	Dopamine and norepinephrine reuptake inhibitor; opioid receptor antagonist	360 mg/32 mg, −6.1%[b, 96]
Liraglutide	GLP-1 receptor agonist[97]	3 mg, −8%[b, 98]

[a]Values indicate 1–7 weight change relative to placebo, Mean (95% CI), kg

[b]Percentages indicate placebo-subtracted weight loss