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1 Overview

Summary and Quick Facts for Weight Management

- If overweight, shedding pounds is one of the most important things to do. The problem is that most diets don't address underlying factors that make it difficult to lose weight.
- This protocol will explain the many underlying factors to address, if looking to lose weight. Learn how to approach weight loss with an arsenal of complimentary diet and exercise habits, medication strategies and dietary supplements that target specific mechanisms to restore a healthy metabolism.
- This comprehensive approach to weight loss could help you slim down and improve many biomarkers of health.

Nutrients to Support Healthy Weight Loss

- **Lemon verbena and hibiscus**. Lemon verbena and hibiscus are botanicals with numerous medicinal properties. Multiple trials showed that a lemon verbena-hibiscus combination promoted weight loss and supported healthy cardiovascular biomarker levels in overweight and obese subjects.

- **Saffron.** In a study of 60 healthy mildly overweight women on an unrestricted diet, 176.5 mg saffron stigma extract daily for eight weeks produced an average weight loss of about 2 pounds. Much of this weight reduction was attributed to a reduction in snacking frequency.
- **DHEA and 7-keto DHEA.** Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone and a precursor to the sex steroids testosterone and estrogen. In a randomized controlled trial in 125 elderly men and women, 50 mg DHEA daily for two years lowered visceral fat mass, improved glucose tolerance, and decreased levels of inflammatory cytokines. 7-keto DHEA, a metabolite of DHEA, has been shown to increase resting energy expenditure.
- ***Sphaeranthus indicus* and *Garcinia mangostana*.** Mangosteen (*Garcinia mangostana*) is a tropical fruit native to Southeast Asia, where it has been used traditionally as a treatment for diabetes. Another medicinal plant, known as East Indian globe thistle (*Sphaeranthus indicus*), has demonstrated anti-inflammatory, blood glucose-lowering, and lipid-lowering activities in preclinical studies. Placebo-controlled trials have noted the efficacy of *S. indicus* plus mangosteen for increasing weight loss in subjects with overweight and obesity.
- ***Gynostemma pentaphyllum*.** Compounds extracted from gynostemma have been shown to activate adenosine monophosphate-activated protein kinase (AMPK), a critical enzyme that regulates cellular metabolism and other cell functions. In a randomized placebo-controlled trial that included 80 participants with obesity, 450 mg gynostemma extract per day for 12 weeks resulted in decreased body weight, total abdominal fat area, body fat mass, percent body fat, and BMI.

Further details on these and other nutrients that support healthy weight loss and weight management can be found in the **Nutrients** section of this protocol.

Why is it Important to Maintain a Healthy Body Weight?

Obesity is a multifaceted chronic disease characterized by excess body fat and increased body weight. Obesity impacts all aspects of physiology, and is associated with increased risk of most major chronic health conditions, including type 2 diabetes, cardiovascular disease, and some cancers. It is also associated with reduced life expectancy.

Alarmingly, the prevalence of obesity is increasing around the world, and the United States has one of the highest rates.

Why is it so Difficult to Lose Weight?

Many people mistakenly believe that weight gain and obesity can be easily resolved with simple adjustments to the energy equation: less energy in (as calories), more energy out (as exercise). While calorie reduction and regular exercise are key components of a healthy weight loss program, the complex nature of weight management and obesity makes successful weight loss extremely challenging.

Many factors influence bodyweight regulation:

- Intrinsic factors such as:
  - Genetics and epigenetics
  - The complex biology of adipose tissue
  - Adipokine signaling
  - Appetite regulation pathways
  - The microbiome
  - Insulin sensitivity
  - Circadian rhythms
  - Hormones

- Extrinsic factors such as:
  - Diet
  - Exercise
  - Lifestyle
  - Stress

Habits Associated with Sustained Weight Loss

Many people find long-term maintenance of weight loss is the most difficult aspect of successful weight management. With this in mind, researchers have collected observations regarding the habits and behaviors of individuals who are able to avoid weight regain. In general, successful and sustained weight loss has been correlated with the following:

- Eating a low-calorie diet that is
  - High in fiber
  - High in low-density foods such as fruits and vegetables
  - Moderate-to-high in protein
  - Low in fat
- Avoiding sweetened drinks
- Avoiding refined carbohydrates
- Eating breakfast
- Avoiding nighttime eating
- Having regular daily meals
- Avoiding snacks
- Engaging in regular exercise
- Getting adequate sleep (and maintaining a healthy circadian rhythm)
- Self-monitoring body weight
- Receiving support from those close to you
- Healthy **Stress Management**

Medical Approaches to Weight Loss

The mainstay of weight loss therapy is calorie reduction and exercise. Counseling, whether in individual or group sessions, increases the long-term efficacy of a lifestyle-based approach to weight loss by emphasizing strategies for maintaining adherence; however, for those with obesity or weight-related health problems, medical interventions may be a consideration. These include:

- Drug Therapies
  - Phentermine and other appetite suppressants
  - Phentermine-topiramate
  - Orlistat
  - Liraglutide
  - Naltrexone-bupropion
  - Metformin
  - Acarbose
- Emerging/Investigational Anti-Obesity Drugs
  - Sodium-glucose co-transport inhibitors
  - Beta-3 adrenergic receptor agonists
  - Monoamine reuptake inhibitors
- Bariatric Devices
  - Gastric balloons
  - Vagal nerve blockade
  - Gastric emptying systems
  - Gastric artery embolization
- Bariatric Surgeries
  - Sleeve gastrectomy
  - Roux-en-Y gastric bypass
  - Laparoscopic adjustable gastric band

2 Introduction

Obesity is a multifaceted chronic disease characterized by excess body fat and increased body weight. Metabolic dysfunction, due to unhealthy expansion of fat tissue, is the hallmark of obesity and its complications.[1,2] Abdominal obesity is the most commonly occurring component of metabolic syndrome—a group of interrelated risk factors for type 2 diabetes and cardiovascular disease (central obesity, high blood pressure, high cholesterol and triglyceride levels, and high blood glucose levels).[3]

There are multiple contributing causes of obesity and metabolic disturbance, encompassing such complex factors as human behavior and neuropsychological drivers, environmental conditions, genetics and epigenetics, hormonal and inflammatory signaling, and the microbiome.[4-6] As a metabolic disease, obesity impacts all aspects of physiology. Obesity is associated with increased risk of most major chronic health conditions, including type 2 diabetes, cardiovascular disease, and some cancers. It is also associated with reduced life expectancy.[4,5]

Alarmingly, the prevalence of obesity is increasing around the world, and the United States has one of the highest rates.[7] Based on the most current data collected through the ongoing National Health and Nutrition Examination Survey (NHANES), the Centers for Disease Control and Prevention reports obesity is more prevalent now than ever in the United States, affecting about 40% of adults and 18.5% of youth. The numbers are highest in those 40–59 years of age, and higher in women than men at every age.[8] Nearly half of US adults are projected to be obese by 2030.[9]

A comprehensive approach to healthy weight loss includes a healthy diet, regular physical activity, and social support. This strategy may be enhanced by integrative interventions that target various pathways which can support metabolic health.[10-12] In some cases, medications and surgery are considerations.

This protocol explores the most current scientific understanding of obesity. It also presents the scientific evidence for various dietary and lifestyle-oriented weight loss strategies, and evaluates the role of supplements in an integrative weight loss program. Well-supported nutritional supplements, including green tea, green coffee bean, chromium, whey protein, and probiotics, are further described.

3 Background

The Importance of Weight Loss

Excessive weight gain changes body composition by increasing fat tissue mass. This can lead to a cascade of disordered metabolic signaling that culminates in diseases such as diabetes and cardiovascular disease.[13] Overweight and obesity are associated with a host of health problems related to mechanical and metabolic stresses, including osteoarthritis, type 2 diabetes, stroke, coronary artery disease, and cancer. As a result, individuals with obesity are more likely to die prematurely than their normal weight counterparts.[14,15] On the other hand, weight loss is associated with many health improvements. Just 5–10% of body weight loss through dietary interventions can reduce fat mass, triggering positive changes in metabolism and lowering risks of metabolic disorders. The benefits are even greater with at least 15% of body weight loss.[14]

Many people mistakenly believe that weight gain and obesity can be easily resolved with simple adjustments to the energy equation: less energy in (as calories), more energy out (as exercise). While calorie reduction and regular exercise are key components of a healthy weight loss program, the complex nature of weight management and obesity makes successful weight loss extremely challenging.

Metabolism and Energy Balance

Metabolism, in simplest terms, is the entire process of transforming nutrients into energy. The macronutrients of food, namely protein, carbohydrate, and fat, are broken down and can be converted into energy. That energy is either consumed in the process of digesting food and moving nutrients, used to run the ordinary workings of the body's cells and tissues at rest, or used to fuel physical activity.[16,17] The total amount of energy a body uses over time to support all of these functions is sometimes called metabolic rate. The energy used by the body at rest is known as resting energy expenditure and is the largest contributor to metabolic rate, accounting for 60–75% of total energy expenditure.[16,18]

Resting Energy Expenditure

Resting energy expenditure (REE) is not static, but rather subject to the adaptive mechanisms in the body that

resist changes in weight and fat mass. For example, when calorie intake is reduced, the body compensates by decreasing REE. However, regular exercise increases REE, in part due to the higher metabolic activity of muscle compared with fat, so it is important to couple dieting with exercise.[18]

Energy Balance

When energy intake exceeds overall energy demand, signals from insulin and other metabolic regulators trigger nutrient uptake and storage. Tissues such as the liver and muscles have limited capacity to store glucose as glycogen, but fat tissue has virtually unlimited capacity to store excess energy as fat.[19] When energy intake is less than the body requires, fat stores are generally preserved until glucose stores are depleted.[20] Fat is the most efficient and abundant source of stored fuel, and our fat stores allow us to maintain long-term energy balance.[19,21] However, the balance between energy intake and overall energy expenditure is also malleable, and multiple factors, including composition of the diet, timing of eating, and timing and intensity of physical activity, influence how stored energy is used.[16,19,20]

Overcoming the body's adaptive mechanisms for preserving body weight and fat mass is essential for an effective healthy weight loss program. In fact, metabolic adaptation to weight loss is estimated to account for 50% of the discrepancy between expected and actual weight loss in individuals with obesity on weight loss programs.[22]

"Metabolically Healthy" Obesity

A large number of obese individuals have overt metabolic disease, such as type 2 diabetes or cardiovascular disease, or have multiple signs of metabolic dysfunction, such as high triglyceride levels, disordered cholesterol levels, high glucose levels, high blood pressure, and/or evidence of insulin resistance. But a substantial subset of obese individuals show no or few such signs, and are often referred to as the "metabolically healthy" obese.[23,24] Because this term has no official definition, estimates of the prevalence of metabolically healthy obesity vary. One report examined the findings from 40 studies and determined that, among obese individuals without overt metabolic disease, approximately 35% are metabolically healthy.[25]

Unfortunately, long-term studies indicate 30–50% of people with "metabolically healthy obesity" gradually progress to a metabolically unhealthy state.[23,25] Furthermore, although metabolically healthy obese individuals have lower rates of type 2 diabetes, cardiovascular disease, and death from any cause than their metabolically unhealthy counterparts, they still are at higher risk of developing metabolic abnormalities (eg, elevated blood pressure and abnormal blood lipid profile) compared with normal-weight people with good metabolic health.[23-25]

Researchers have found that, compared with obese individuals who are metabolically unhealthy, those who are metabolically healthy are more physically active and have better cardiorespiratory fitness.[26] There is also growing evidence that dietary factors such as low consumption of sugar and sugary beverages and high intake of whole fruit, whole grains, and vegetable protein are associated with better metabolic health in obese subjects.[23] Differences in gut microbiome and genetic factors affecting fat tissue function may also play important roles in determining metabolic health status in people with obesity.[27,28]

4 Intrinsic Factors Related to Body Weight Regulation

The Genetics and Epigenetics of Body Weight Regulation

Many people believe their body weight or inability to lose weight is "genetic." In fact, genetics does play a substantial role in some aspects of body weight regulation. For example, certain variations of genes related to leptin receptors have been found to be associated with increased susceptibility to obesity.[29]

In recent years, researchers have become increasingly interested in the role of epigenetics in body weight regulation. Epigenetic factors regulate the way genes are expressed without altering the underlying genetic code; essentially, epigenetics has to do with how genes are turned on and off. Unlike the genetic code, which is for the most part unchangeable, epigenetic modifications are influenced by environmental factors, including diet and lifestyle choices, as well as life experiences and exposures. Epigenetic changes occur during a lifetime and to

some extent can be passed on to offspring.[30]

Much of the epigenetic programming that affects us throughout life occurs before we are born. Some of the first evidence of this comes from observational studies in which children born to mothers who experienced famine during the Second World War were prone to obesity later in life. Even grandchildren of famine-exposed women have been found to have high rates of overweight and obesity demonstrating the heritability of epigenetics.[31] Maternal obesity, as well as metabolic disease in fathers, have also been found to cause epigenetic alterations favoring obesity and metabolic disturbances in children.[32] It is now known that epigenetics affect the levels and actions of key appetite regulators such as leptin.[33]

Evidence from animal and human studies suggest overeating, a Western-style high-fat/high-sugar diet, sedentary lifestyle, and exposure to environmental stimuli referred to as endocrine disrupters may contribute to epigenetic alterations related to obesity and metabolic disease risk.[29,30,34,35] On the other hand, calorie restriction without malnutrition, polyphenols from plant foods, and physical activity can trigger epigenetic modifications that support healthy body weight and metabolic regulation.[35-37]

The Complex Biology of Adipose Tissue

Adipose tissue and metabolism. Many problems associated with obesity begin in the adipose (fat) tissue. Adipose tissue is an organ, releasing hormones and other cell-signaling molecules that interact with the immune system and participate in regulating energy storage and use throughout the body.[1] Its main function is to store fatty acids and other lipids during times of energy excess (after eating) and release fatty acids to be used for energy production during times of energy deficit (fasting).[21,38] Adipose tissue also helps regulate body temperature and provides mechanical cushioning in some parts of the body.[21]

Adipose tissue expansion. Adipose tissue undergoes expansion and remodeling in response to calorie intake. In healthy conditions, excess calorie intake triggers an increase in the number of fat cells and their responsiveness to insulin. In unhealthy conditions, especially when excess calorie intake is chronic, fat cells increase in size as they accumulate more fatty acids, but their numbers diminish. The remaining enlarged fat cells become increasingly resistant to insulin and release inflammatory signals that initiate and perpetuate a cycle of tissue damage and chronic inflammation. This transformation of adipose tissue may lead to a condition known as lipotoxicity,[39] in which fat cells that are no longer able to respond to insulin release fatty acids and cholesterol that accumulate on the surfaces of organs such as the liver and heart, triggering more inflammatory signaling and further reducing insulin sensitivity. The result is a systemic metabolic disturbance that can lead to type 2 diabetes, cardiovascular disease, and many other chronic ailments.[1,21]

Visceral and subcutaneous adipose tissue. Whether or not adipose tissue becomes metabolically unbalanced depends in part on where it is located. Higher amounts of visceral adipose tissue, which is distributed around body organs, are more closely associated with inflammatory and metabolic disorders. Subcutaneous fat, which is present under the skin, is less likely to be associated with inflammatory and metabolic disruption; however, excess subcutaneous fat can still be problematic, particularly when it accumulates in the abdomen.[1,40]

White, brown, and beige adipose tissue. There are two main types of adipose tissue: white and brown. Brown adipose tissue is made up of fat cells that are rich in mitochondria and specialized for heat generation (thermogenesis), while white adipose tissue cells are more involved in metabolic activity.[21] A third type of adipose cell has recently been discovered within the white adipose tissue. Known as beige or brite (**br**own and wh**ite**) cells, these newly identified fat cells appear to have more flexibility in their function, and can be induced to increase their thermogenic activity through a process referred to as *browning*.[41] Conditions that activate the sympathetic or "fight or flight" aspect of the nervous system, such as exposure to cold temperature and extreme physical stress, increase the size and activity of brown adipose tissue and stimulate browning of white adipose tissue.[41,42] Hormones including thyroid hormone, insulin, leptin, and melatonin have all been shown to induce browning.[43] Other factors that may influence browning include diet, fasting, exercise, genetic and epigenetic factors, and the composition of the gut microbiome.[38,42]

Brown adipose tissue has been shown to be an important contributor to REE in animal models, but the contribution of brown adipose tissue to energy expenditure in humans is less well established. Higher amounts and activity of brown adipose tissue have been associated with healthier blood glucose control, insulin sensitivity,

fat distribution pattern, and body weight in human studies.[38,41] Strong inflammatory signaling associated with obesity, however, can impair brown and beige fat cells' ability to take up glucose and produce heat.[44]

Adipokines

Adipokines are cell-signaling molecules released by adipose tissue that affect both local and distant target tissues. Adipokines serve as a link between obesity and inflammation, and thus are critical in the development of obesity-related complications.[45] Levels of adipokines are related in part to the distribution and types of fat tissue in the body.[45] Adipokines not only impact inflammation and metabolic processes, but also help regulate appetite and body weight, and are often a target of weight loss strategies.[38,45]

Perhaps the best known adipokines are leptin and adiponectin, which are produced by all types of adipose cells. In healthy conditions, leptin's pro-inflammatory effects are balanced by adiponectin's anti-inflammatory effects.[46] High leptin and low adiponectin levels are associated with obesity and its complications, including type 2 diabetes, cardiovascular disease, and cancer.

Leptin. Despite its role in promoting inflammation, leptin has positive effects on metabolism such as enhancing insulin sensitivity, promoting white adipose browning and thermogenesis, increasing glucose uptake by cells, and reducing blood lipid levels.[40,43] Importantly, leptin also suppresses hunger. As part of an evolutionary defense against excessive weight loss, leptin release declines as fat mass diminishes; unfortunately, this adaptive mechanism interferes with healthy weight loss in people with overweight and obesity.[47] In addition, despite high leptin production in response to overeating, leptin responsiveness becomes blunted in those with obesity and insulin resistance, such that high circulating leptin levels lose their impact on appetite and metabolism, resulting in a state described as leptin resistance.[33,40,47]

Adiponectin. Adiponectin is important for healthy cellular metabolism and insulin sensitivity.[48] It also helps maintain healthy vascular function and inhibits formation of certain tissue-damaging free radicals. Adiponectin levels increase with fasting and exercise but decrease with overeating. In addition, dysfunctional obesity-related adipose tissue conditions such as hypoxia (low oxygen availability due to enlarged adipocyte size), increased inflammatory signaling, and high oxidative stress reduce adiponectin release.[40,48]

Irisin. Another adipokine, irisin, has recently attracted attention for its role in the browning of white fat. Irisin is a protein produced by white adipose tissue, as well as muscle tissue, and promotes thermogenesis.[45]

Appetite Regulation

Appetite and food intake are controlled by interplay between physiologic mechanisms and external factors.

Physiologic mechanisms. Appetite-suppressing signals, also known as satiety signals, are facilitated by the hormones leptin (secreted by adipose tissue) and insulin (secreted by the pancreas), as well as peptides produced in the brain; appetite-enhancing signals come from the brain peptides (known as neuropeptide Y and agouti-related peptide) to help maintain a balance between energy demands and availability.[49,50] The neurotransmitters GABA, serotonin, and oxytocin appear to influence behaviors related to eating.[50] In addition, the gut produces signaling molecules that alter appetite, such as cholecystokinin, which helps curb eating once the stomach is full, and ghrelin, which counterbalances the effects of leptin by stimulating appetite and eating.[49,50] This complex network of signals governs your desire to eat and motivation to modify behavior accordingly.[50]

The sensitivity of the neural pathways involved in appetite is greatly affected by genetic and epigenetic factors.[49] In obesity, signaling along these appetite-regulating pathways are generally diminished, which can make control over eating behaviors extremely difficult.[50]

Ghrelin. Ghrelin is a hormone produced mainly in the empty stomach with functions that overlap with those of adipokines. Ghrelin stimulates eating through complex effects in the brain, where it increases the drive to eat, enhances a sense of well-being from eating, modulates taste and smell, and upregulates food-seeking behavior.[51] It also contributes to regulating gut motility and digestive function, and has a range of metabolic effects, such as suppressing thermogenesis in brown adipose tissue; stimulating fat production and storage; and reducing insulin release and raising blood glucose levels.[52] Obesity has been linked to dysfunctional overproduction of ghrelin. Calorie reduction and weight loss further raise ghrelin levels, adding to the difficulty of achieving healthy weight loss.[53]

Insulin Resistance and Metabolic Syndrome

Insulin resistance and obesity are related conditions that often occur together. Insulin is a key metabolic hormone produced in the pancreas in response to high nutrient availability. In healthy conditions, insulin increases glucose uptake by cells, which store excess glucose as glycogen or fat, and prevents glucose generation while stimulating lipid production by the liver.[54] In unhealthy conditions, including those caused by a high-calorie, nutrient-poor diet, low-level inflammation causes fat cells to become increasingly resistant to the effects of insulin. As insulin resistance progresses, levels of both insulin and glucose rise, and adipose tissue releases free fatty acids into circulation.[54,55] These excess fatty acids then accumulate in organs that are not equipped to process and store extra fat. This abnormal deposition of fat is known as lipotoxicity, a condition that causes tissue and organ dysfunction and accelerates widespread inflammatory signaling, insulin resistance, and poor vascular function.[1,39,54]

Because insulin-resistant tissues generate high levels of tissue-damaging free radicals and instigate chronic low-level inflammation, insulin resistance has been suggested to be an important link between chronic metabolic and inflammatory disorders.[56] Long-term overeating and a high-fat, Western-type diet have been shown in many studies to raise the risk of insulin resistance and obesity (particularly in the abdomen), as well as high cholesterol and triglyceride levels and high blood pressure.[57] This cluster of related conditions, which often occur together and contribute to a higher risk of type 2 diabetes and cardiovascular disease, are called metabolic syndrome.[3,56] People with metabolic syndrome also have increased risks of neurological diseases, liver cirrhosis, autoimmune diseases, and some cancers, as well as death from all causes.[58,59]

The Role of the Microbiome

The community of microorganisms that inhabit the intestines, referred to as the gut microbiota, is increasingly being recognized as an important regulator of such fundamental body processes as digestion, immune function, metabolic function, behavior, mood, food preference, and appetite.[6,60] Gut microbes make many nutrients from our food more accessible, produce fermentation by-products, and send and receive signals from tissues and cells throughout the body, including the brain. The microbes and their surrounding environment are collectively called the microbiome. Through its communication networks, the microbiome is thought to modulate genetic expression, or epigenetics, and thus profoundly influence health.[61-63]

A Western-type diet can alter the microbiome in ways that may then lead to obesity by triggering changes in cognition, mood, and the drive to eat, as well as expression of proteins that control metabolism.[6,62] Factors such as changes in cycles of sleep, timing of eating, or time zone can alter the microbiome composition and disrupt circadian interactions between the microbiome and the body's innate systems, increasing the risk of metabolic disturbance and weight gain.[64] Imbalances of gut bacteria, or dysbiosis, might further contribute to weight gain, obesity, and other metabolic disorders by amplifying inflammatory immune activity, enhancing faulty adipose tissue expansion, and contributing to insulin resistance.[61,63,65]

Findings from the Human Microbiome Project show that people with obesity typically have microbiomes with less bacterial diversity overall, as well as more *Firmicutes* bacteria and less *Bacteroidetes* bacteria, compared with lean people. As *Firmicutes* possess more genes for enzymes involved in the metabolism of carbohydrates and fats than *Bacteroidetes*, generally speaking, *Firmicutes* bacteria are capable of facilitating more efficient extraction of energy from food, thus inducing more fat accumulation than *Bacteroidetes* bacteria.[66,67] Although not all studies have been able to observe this obesity-related microbiome pattern,[65] there is ample evidence that supporting a healthy microbiome is an important facet of a healthy weight loss program.

Circadian Rhythms and Metabolism

The human circadian clock (a complex network of feedback loops that modulates physiological systems in daily cycles) is an important regulator of virtually every biological system in the body and is recognized as a key factor affecting metabolism and body weight.[68,69] Central circadian control occurs in the brain and is primarily affected by light and dark cycles, but peripheral circadian system tissues respond to cues such as temperature, hormone and neurotransmitter levels, and certain nutrients, as well as sleeping, eating, and physical activity patterns.[70,71] These peripheral circadian networks can become misaligned with the central circadian clock in people affected by sleep disturbance, nighttime light exposure, shift work, jet lag, nighttime eating, and other nighttime activity.

Circadian desynchronization can then lead to fundamental disturbances of glucose and lipid metabolism and energy balance, and is associated with weight gain and metabolic disorders.[64,68,71]

Insulin sensitivity has been shown to have a circadian cycle, peaking in the morning and diminishing as the day progresses; therefore, the timing of food intake alters its glycemic effects.[69,71] Adipose tissue is responsive to circadian signals, releasing adipokines in a rhythmic pattern. For example, levels of leptin, an adipokine that quiets the appetite and increases thermogenesis, peak at night; however, conditions and behaviors that desynchronize the circadian system may disrupt leptin release and contribute to loss of normal energy balance.[70]

The gut microbiome is an important link in the human circadian system. Daily rhythms have been noted in microbiome composition and function, and these cycles affect metabolic activity in the body. Behaviors that contribute to weight gain, such as consuming a high-fat Western diet, overeating, and nighttime eating, may exert their unhealthy effects partly by disrupting the healthy rhythms of the microbiome.[64] In addition, conditions that alter the microbiome, such as use of some medications and diseases of the digestive tract, may contribute to poor sleep and metabolic problems by triggering circadian misalignment.[72]

Thyroid and Sex Hormones

Thyroid and sex hormones can also affect the body's propensity to preserve or lose weight.

Thyroid hormones. Hormones produced in the thyroid gland increase total energy expenditure by targeting cellular metabolism and energy production capacity, and contribute to weight control mechanisms through their actions on appetite, adipose tissue signaling, and the brain.[73-75] The main thyroid hormones are thyroxine (T4) and its active metabolite triiodothyronine (T3). Under stimulation by a hormone from the brain called thyroid stimulating hormone (TSH), the thyroid gland releases mainly T4, which is converted to T3 in other tissues.[76] The conversion rate of T4 to T3 has been found to be lower in those who have lost even a modest amount of weight, exemplifying the various innate mechanisms for preserving energy balance.[75] People with hypothyroidism are prone to weight gain and appear to have difficulty increasing their energy expenditure to support exercise.[77] It is important to test thyroid function in those struggling to lose weight, since treatment with thyroid hormone replacement therapy may be helpful in some cases[75]; however, thyroid hormone therapy is not safe for treatment of overweight and obesity in people with normal thyroid function.[74,76]

Estrogens and progesterone. Changes in female hormone levels throughout life contribute to well-known changes in metabolism. Higher estrogen levels in reproductive aged women favor subcutaneous fat accumulation, especially in the hips and thighs; conversely, after estrogen levels drop at menopause, women tend to accumulate central and visceral fat and lose muscle. The changes in body composition and fat distribution associated with estrogen loss are linked to metabolic disturbance and increased cardiovascular risk.[78] Estrogen also stimulates thermogenesis in brown adipose tissue, increasing total energy expenditure. A post-menopausal decrease in energy expenditure due to reduced estrogen-related thermogenesis may contribute to weight gain.[79]

Estrogens have been found to reduce sweet cravings and decrease appetite, possibly by increasing sensitivity to fullness signals from cholecystokinin. Progesterone, on the other hand, has little effect on metabolism but may increase eating, particularly during times of emotional stress. It is thought progesterone may enhance food-induced activation of reward pathways in the brain.[80] Studies have shown calorie intake decreases during the first half of the menstrual cycle to a minimum around ovulation and then rises to a maximum around menstruation, possibly due to fluctuations in estrogen and progesterone levels.[81] After menopause, estrogen replacement therapy may be beneficial for preserving healthy body composition and adipose tissue distribution, but these potential benefits must be weighed against possible increased risks of stroke and breast cancer.[78,82] For additional information, refer to Life Extension's **Female Hormone Restoration** protocol.

Androgens. Male hormones, or androgens, support muscle mass and normal insulin sensitivity, and low levels of testosterone, the main androgenic hormone, are associated with visceral obesity and metabolic syndrome in men.[83,84] Body composition and metabolic health have been noted to undergo negative changes as androgen levels decline with age. Testosterone replacement has been shown to have metabolic and other benefits in older men with testosterone deficiency.[84]

Dehydroepiandrosterone (DHEA) is an androgenic hormone produced in the adrenal gland. DHEA production drops gradually with age. A study in 13 female twin pairs, 10 of which had substantial differences in body weight

between co-twins, found having higher DHEA levels was associated with lower body weight and percent body fat.[85] Findings from animal research suggest lower DHEA levels may be associated with weight gain, muscle loss, and increased fat mass, as well as insulin resistance and other negative metabolic changes.[86,87]

5 Extrinsic Factors Related to Bodyweight Regulation

External conditions around eating, such as **caloric density and portion size**, and setting and social environment, can influence appetite and amount of food eaten.[50] For example, eating at home and family dinners have been associated with healthier food intake and lower risk of overweight and obesity, whereas watching television during meals is correlated with unhealthy eating and increased risk of obesity.[88,89] The ways these conditions influence appetite and weight loss varies greatly between individuals.[90]

Lifestyle can influence appetite control. Unfortunately for those trying to lose weight, calorie restriction and weight loss enhance appetite signaling, increasing the desire to eat. Combined with weight loss-associated changes in energy expenditure, the result is often inability to lose more weight or weight regain.[90] In those eating a high-calorie, high-fat diet, free saturated fatty acids can cross the blood-brain barrier and trigger inflammation in parts of the brain that, among other things, regulate appetite. These brain areas, like other parts of the body, then become resistant to signals from insulin and leptin.[49] On the other hand, short bouts of exercise can suppress appetite in the short term, and habitual exercise appears to improve sensitivity to the appetite-regulating system.[91]

Stress is one of the most important external factors affecting appetite and eating behaviors. Although the response to stress is highly individualized, in general, acute stress is associated with high levels of catecholamine neurotransmitters that reduce appetite, while chronic stress is usually associated with high levels of cortisol, a hormone that appears to promote a selective appetite for high-calorie palatable foods.[92] Often referred to as comfort foods, they are typically high in sugar and fat, and can stimulate reward pathways in the brain that reduce stress reactivity and may relieve negative emotions associated with stress. This may explain in part how stress can induce overeating of high-calorie foods,[92,93] and highlights the importance of stress management as part of a healthy approach to weight loss. For additional information, see Life Extension's **Stress Management** protocol.

6 Assessing Body Composition

The most commonly used measure for identifying overweight and obesity is body mass index, or BMI. BMI is calculated by dividing body weight in kilograms by height in meters squared. Because it does not distinguish between fat mass and lean muscle mass, nor take into account body fat distribution, BMI is limited in its usefulness[5,94]; nevertheless, it has been shown to be reasonably closely correlated with more definitive measures of visceral fat, such as computed tomography (CT) and magnetic resonance imaging (MRI), and with obesity-related complications.[5] Although these cutoff values may vary with ethnicity, according to the Centers for Disease Control and Prevention, an American or European adult with a BMI[95]:

- <18.5 kg/m^2 is considered underweight;
- between 18.5 and 24.9 kg/m^2 is considered normal weight;
- between 25 and 29.9 kg/m^2 is considered overweight;
- 30 kg/m^2 or higher is considered obese; and,
- >40 kg/m^2 is considered extremely or severely obese.

Abdominal fat is a stronger predictor of metabolic disease than body weight; therefore, assessment tools that take abdominal size into account better reflect health status with regard to overweight and obesity. Waist circumference and waist-to-height ratio (waist circumference divided by height) both correlate well with percent body fat and metabolic disease risk. With strong evidence for its usefulness and simplicity of measurement, waist circumference is now included among the diagnostic criteria for metabolic syndrome.[96] In general, a waist circumference of ≥40 inches (102 cm) in men or ≥35 inches (88 cm) in women is considered indicative of high metabolic risk. Waist-to-height ratio may be slightly more accurate than waist circumference and BMI, and has the added advantage of a single reference for people of all ages: a ratio of ≥0.5 is widely accepted as indicative of central obesity in children ≥6 years old as well as adults.[94,97,98]

A study that included 1,856 men and women between 46 and 73 years old used more than a dozen blood tests as

well as blood pressure and body measurements to assess metabolic health. Comparing metabolic health status to BMI and waist-to-height ratio, the study showed that a combined assessment of BMI and waist-to-height ratio provided the most accurate reflection of metabolic health.[99] Similarly, a study done in Singapore found participants with both a BMI ≥23 kg/m^2 and waist-to-height ratio ≥0.5 had the highest cardiovascular risk.[100]

7 Lab Tests That May Inform Your Weight Loss Plan

In addition to measures of body size and composition, certain blood tests can help identify underlying causes and evaluate metabolic health status in people who may be overweight or obese.

TEST	STANDARD REFERENCE RANGE (LabCorp Methodology)	OPTIMAL RANGE (LabCorp Methodology)
Total cholesterol	100–199 mg/dL	160–180 mg/dL
LDL-cholesterol	0–99 mg/dL	<80 mg/dL
HDL-cholesterol	>39 mg/dL	≥50 mg/dL
Triglycerides	<150 mg/dL	<80 mg/dL
Hemoglobin A1c (HbA1c)	<6.0%	5 - 5.4%
Fasting glucose	65–99 mg/dL	80–86 mg/dL
Fasting insulin	2.6–24.9 µIU/mL	<5 µIU/mL
C-reactive protein (CRP, high sensitivity)	Low risk: ≤1.0 mg/L	Men: <1.0 mg/L Women: <1.0 mg/L
Leptin	Established by lab and varies with body composition	
DHEA-sulfate	Men age 20–24 years: 164–530 µg/dL Women age 20–24: 110–432 µg/dL	Men: 350–500 µg/dL Women: 275–400 µg/dL
Total testosterone	Men: 264–916 ng/dL Women: 8–48 ng/dL	Men: 700–900 ng/dL Women: 35–45 ng/dL
Free testosterone	Men age 20 – 29: 9.3–26.5 pg/mL Women: 0.0–4.2 pg/mL	Men: 20–25 pg/mL Women: 2.1–4.2 pg/mL
Estradiol	Men: 7.6–42.6 pg/mL Women: Premenopausal: variable	Men: 20–30 pg/mL Women: Premenopausal: variable

	Postmenopausal: <6.0–54.7 pg/mL	Menopausal/ postmenopausal: 30–100 pg/mL
Progesterone	Women: Premenopausal: variable Postmenopausal: 0.1–0.1 ng/mL (without hormone replacement)	Women: Premenopausal: 15–23 ng/mL Menopausal/ postmenopausal: 2–6 ng/mL (with hormone replacement)
Thyroid stimulating hormone (TSH)	0.4–5.0 μIU/mL	May be age-dependent; Should be interpreted in the context of other thyroid parameters; 1–2 μIU/mL has been associated with higher metabolic rate than higher levels in some studies
Free thyroxine (T4)	0.82–1.77 ng/dL	1.46–1.77 ng/dL
Free triiodothyronine (T3)	2.0–4.4 pg/mL	3.4–4.2 pg/mL

8 Dietary and Lifestyle Approaches to Weight Loss

The most constant feature of all effective weight loss diets is they are low in calories.[101] Beyond that, popular weight loss diets vary considerably in terms of macronutrient composition, specific foods recommended, and timing of eating. These differences are purported to alter the fundamental mechanisms of weight control: energy balance, fat tissue signaling and widespread inflammation, insulin sensitivity and blood glucose control, appetite signaling, health of the microbiome, epigenetics of metabolism, and alignment with circadian rhythms. However, whether a diet will result in weight loss depends largely on individual characteristics that influence our response to dieting. Such characteristics are still poorly understood, but may be partly related to genetics. It is important to note that not all weight loss diets, even if they work, improve long-term health.

Altering Macronutrient Intake

Marketing campaigns associated with various weight-loss-oriented diet programs claim the diet in question can influence energy expenditure and appetite signaling, making weight loss easier and more effective, through manipulation of the proportions of macronutrients—carbohydrate, protein, and fat.[102] However, this is a contentious area of active debate and investigation among the nutrition research community. Below we present several common dietary approaches and discuss the evidence for their efficacy.

Low-fat diets. The low-fat diet, popularized by Dean Ornish, MD in the 1980s, was introduced as a cornerstone of a holistic approach to preventing and reversing heart disease. The Ornish diet, which is plant-based and derives ≤10% of calories from fat, emphasizes whole, unrefined foods and incorporates large amounts of low-calorie-density, high-nutrient foods like fruits and vegetables.[103] Research has shown that restricting saturated fat may be more important than total fat, and dietary fat reduction has metabolic benefits only if fat calories are not replaced with carbohydrates, particularly processed carbohydrates such as starches and sugars.[104,105]

Dietary Approaches to Stop Hypertension, or DASH, is a less restrictive low-fat diet in which no more than 30% of calories are from fat. It also limits intake of saturated fat, cholesterol, refined carbohydrates, sugars, and sodium.

DASH has been found to lower cardiovascular risk and blood pressure, promote weight loss, and reduce risk of type 2 diabetes. [106] A meta-analysis of 54 trials with a total of more than 30,000 overweight and obese participants found low-fat and low-saturated fat weight loss diets reduced premature mortality, resulting in six fewer deaths per 1,000 participants.[107]

In general, low-fat diets have similar weight loss effects as other diets with similar daily calorie intake.[101] Interestingly, their effects on markers of cardiovascular risk may be different than those of other weight loss diets. A meta-analysis that included 20 studies with a combined total of 2,106 overweight and obese participants found low-fat diets improved total and LDL-cholesterol levels more than high-fat diets, but high-fat diets improved HDL-cholesterol and triglyceride levels more than low-fat diets.[108] The possible implications of these differences for long-term health outcomes is still not clear.

Ketogenic or "keto" diets. Robert Atkins, MD, first proposed his ketogenic high-fat/low-carbohydrate weight loss diet in the 1970s. More recently, low-carbohydrate diets—referred to as "paleo" and "ketogenic" diets—have been popularized. Restricting carbohydrate intake reduces blood glucose and insulin levels and increases fat metabolism, resulting in increased levels of byproducts known as ketone bodies. By regulating glucose levels and stimulating ketosis, this diet may lead to better appetite signaling and glucose metabolism.[103,109] In general, low-carbohydrate diets high in fat and/or protein have been shown to induce more rapid weight loss than high-carbohydrate diets; however, to date, researchers have failed to find a significant advantage on long-term weight loss.[101,102] Furthermore, high-fat/low-carbohydrate diets have been found to have negative impacts on LDL-cholesterol levels and vascular health in some studies, even while having positive impacts on HDL-cholesterol and triglyceride levels.[108,110]

Very-low-carbohydrate diets such as the ketogenic diet include no more than 50 grams of carbohydrate per day. They are typically low in fruits, vegetables, and fiber, and rely on calories from animal fat and protein. This may lead to poorer long-term health outcomes.[103] In fact, a recent study that followed more than 15,000 adults for about 25 years noted very low carbohydrate intake (<40% of calories from carbohydrates), when accompanied by high intake of animal fat and protein, was associated with a 20% increase in death from any cause. The study also found very high carbohydrate intake (>70% of calories from carbohydrates) was associated with increased mortality, suggesting moderate carbohydrate intake may be optimal for long-term health.[111]

High-protein diets. Dietary protein reduces appetite, preserves muscle, supports insulin sensitivity, and promotes thermogenesis.[102,112] Comparison trials suggest high-protein diets have better short-term weight loss effects than high-carbohydrate diets, but findings from longer studies have been inconsistent.[101,102] One meta-analysis of studies found higher protein intake was associated with less weight regain after successful weight loss in overweight and obese subjects.[113] This may be due in part to protein's satiating effect.[112,114] It is important to note, however, that high intake of animal protein has been linked to increased risk of kidney stones as well as chronic health problems like heart disease, type 2 diabetes, and cancer. Plant proteins, on the other hand, are not associated with these health problems.[102]

Artificial Sweeteners and Weight Loss

Many people on weight loss diets use sugar substitutes to reduce their calorie intake while enjoying foods that taste sweet. Artificial sweeteners like aspartame, sucralose, and saccharin have been promoted to diabetics and dieters as healthy sugar alternatives for decades, but their role in metabolic disease now appears to be more complex than previously thought.[115] In fact, although the evidence is not conclusive, consumption of artificial sweeteners has been implicated as a possible contributor to the rising rates of obesity and diabetes, and may also be linked to the development of metabolic syndrome.[116-118]

Sweet-sensitive taste receptors are known to be present in the mouth, gut lining, pancreas, and brain.[119] By activating taste receptors throughout the body, artificial sweeteners can alter production of neurotransmitters and hormones that regulate appetite signaling and glucose metabolism, which has been found to trigger metabolic dysregulation in preclinical research.[115,119] In addition, animal studies suggest artificial sweeteners can cause inflammation in the digestive lining and alter the gut microbiome, potentially leading to leaky gut, systemic inflammation, and insulin resistance.[115,120]

Broader Dietary Patterns

Mediterranean diet. The Mediterranean diet is one of the best-supported dietary patterns for long-term metabolic health.[106] Although not inherently a weight loss diet, when implemented as a low-calorie diet and combined with exercise, the Mediterranean diet promotes weight loss similar to other diets with similar degrees of calorie restriction, while improving blood pressure, lipid levels, and other markers of cardiovascular risk.[121,122] With its emphasis on fruits, vegetables, whole grains, legumes, nuts, and olive oil, and inclusion of modest amounts of seafood, the Mediterranean diet provides abundant polyphenols, mono- and polyunsaturated fats, and fiber. These food components may support mechanisms for weight loss including stimulating thermogenesis, reducing inflammatory signaling, normalizing adipose tissue metabolism, triggering satiety signaling, and improving the health of the gut microbiome.[123,124]

Plant-based diet. Plant-based diets are associated with lower risks of metabolic disorders, including obesity, type 2 diabetes, and cardiovascular disease, whereas high meat intake is associated with weight gain, higher BMI, and poorer metabolic parameters.[125-127] Observational research indicates BMI increases as the amount of animal food in the diet increases, such that BMI is lowest in vegans (those who avoid all animal foods), higher in vegetarians who include dairy, eggs, and/or fish, and highest in non-vegetarians.[126] A meta-analysis that included 12 studies with 1,151 overweight and obese participants found vegetarian diets, and especially vegan diets, were associated with greater weight loss than calorie-matched non-vegetarian diets.[128] The positive health effects of plant-based diets may be due to the inherently high nutritional quality of most plant-based diets, which typically include more fruits, vegetables, and fiber than omnivorous diets.[127,129] Strict vegans should consider supplementing with vitamin B12 and possibly calcium.[129]

In a 16-week clinical trial, 75 participants with a BMI between 28 and 40 kg/m^2 were randomized to follow a low-fat vegan diet or maintain their current diet.[334] In the intervention group, insulin resistance decreased significantly, fat mass decreased an average of 9.5 pounds, and total weight decreased by 14.3 pounds, versus no significant changes in the control group.

In a second 16-week clinical trial, carried out by the same Principal Investigator, 244 participants with a BMI between 28 and 40 kg/m^2 were randomized to follow a low-fat vegan diet or continue their normal diet; this study assessed more variables than the first.[335] In the intervention group, there was a significant decrease in insulin resistance, fat mass, and visceral fat, and a total average weight loss of 13 pounds. Additionally, postprandial (after meal) energy expenditure increased 18.7% in the intervention group, indicating increased after-meal metabolism. Differences in intramyocellular lipids (fats stored in muscle cells) and hepatocellular lipids (fats stored in liver cells), both biomarkers associated with type 2 diabetes, were also measured. Results showed a mean decrease of 10.4% in intramyocellular cells and 34.4% in hepatocellular lipids in the intervention group. There were no significant changes in the control group for any outcomes or measurements.

Intermittent Fasting

Intermittent fasting has recently gained attention as a new strategy for re-establishing healthy metabolic function and losing weight. In addition to reducing total calorie intake, fasting for periods of 12 to 36 hours activates metabolic pathways that promote fat burning and may trigger weight loss without loss of muscle.[130]

Most intermittent fasting diet plans dictate either time-restricted eating daily or periodic fasts lasting up to 24 hours. One common example of time-restricted eating is fasting for 16 hours each day (usually including overnight) and eating according to appetite for the other eight hours. Prolonged overnight fasting not only reduces total calorie intake but also takes advantage of the body's circadian rhythms in ways that may further support healthy metabolism. Full-day fasts may be practiced on alternate days or one to two days per week, with very few (such as 25% of usual) or no calories taken on fasting days.[130] Despite the theoretical advantages of intermittent fasting, most research comparing it to general calorie restriction have found no differences in weight or body fat reduction.[131] Nevertheless, it is noteworthy that some studies have shown time-restricted eating with prolonged overnight fasting naturally results in reduced nighttime hunger, lower overall calorie intake, and weight loss that may be easier to sustain over time.[131] In addition, some evidence suggests intermittent fasting may induce less adaptive decline in energy expenditure, possibly leading to better long-term weight management.[130]

Habits Associated with Sustained Weight Loss

Many people find long-term maintenance of weight loss is the most difficult aspect of successful weight loss. With this in mind, researchers have collected observations regarding the habits and behaviors of individuals who are able to avoid weight regain. In general, successful and sustained weight loss has been correlated with the following[11,101,102,132,133]:

- Eating a low-calorie diet that is
  - High in fiber
  - High in low-density foods such as fruits and vegetables
  - Moderate-to-high in protein
  - Low in fat
- Avoiding sweetened drinks
- Avoiding refined carbohydrates
- Eating breakfast
- Avoiding nighttime eating
- Having regular daily meals
- Avoiding snacks
- Engaging in regular exercise
- Getting adequate sleep (and maintaining a healthy circadian rhythm)
- Self-monitoring body weight
- Receiving support from those close to you

Mobile Apps for Weight Loss: Using Technology to Make Weight Loss Easier

Food diaries have long been used to help track food intake. These tools may be simple, entailing a straightforward tabulation of calories or macronutrients (ie, carbohydrates, fats, and proteins). Other variations can be more detailed and require keeping track of not only the amounts but also types of carbohydrates and fats, for example. Regardless, most weight loss programs include some aspect of food tracking.

Modern mobile applications (also called mobile apps) have made it easier than ever to quickly track the calorie and nutrient content of the foods you eat. Apps intended to facilitate and assist dieting abound—some even integrate feedback systems to help keep you motivated to adhere to your weight loss plan.[340,341] But do these apps work? Multiple studies suggest they do.

A 2020 meta-analysis of 12 studies evaluated mobile apps designed to support weight loss, increase physical activity, and promote healthy eating. Compared with the control interventions, which typically consisted of weight loss advice and dietary suggestions but did not include a smartphone app, use of a cell phone app increased weight loss over six to nine months.[342]

In addition to the clinical trials, a “real world” study was performed, which included the use of a cell phone app with features to track weight loss, food and water intake, as well as physical activity.[343] The app also featured reminders (“push notifications”) to drink water and eat fruits and vegetables, educational information, and other challenge and reward features. App engagement features such as these have been shown to facilitate weight loss progress in other clinical trials.[344,345] Three-hundred forty-nine individuals with an average BMI of 27.52 kg/m^2 completed the 90-day study, about two-thirds of whom were female.[343] The supplement was provided at the same 500 mg/day dose in a yogurt-based drink. Additional recommendations included eating at least five servings of fruits/vegetables per day, drinking at least eight glasses of water daily, and engaging in regular physical activity with the goal of 300 minutes per week. Over 85% of individuals reported weight loss. Participants lost an average of 12.6 lbs. (4.1% of their body weight), with those in the age range of 51–60 years experiencing the greatest success, losing 5.3% of their body weight. Other benefits were observed as well including a 103% increase in fruit/vegetable consumption, 108% increase in water intake, and 33% increase in physical activity over baseline. Of the initial 349 users, 45 responded to a comprehensive survey about their experience with over 60% reporting the app to be useful. Similarly, 125 users responded to a briefer survey in which they shared their age. Among these respondents, participants aged 31 years and older found the app more helpful, with more than 70% of participants in this age group stating they would continue to use it.

Weight loss apps can increase adherence to healthy dietary and lifestyle changes, which may be their most important contribution to weight management. For instance, one study assessed the use of a cell phone weight loss app that included reminders to weigh in daily, record food intake, and engage in exercise. This reminder-based app was compared with a combination of monthly personal coaching calls, six initial weekly 2-hour group sessions with a dietitian, and a cell phone app that did *not* include reminders.[345] More frequent use of the app that included reminders was associated with greater weight loss. Not surprisingly, those with the app that included reminders used the app more and weighed themselves more often during the first six months.

Overall, evidence suggests achieving success with the help of a weight loss app may depend largely on finding an app that you will use regularly. Studies show that the more you are engaged with the app, the more likely you are to progress toward your goal.[344,345]

Exercise

Increasing physical activity during weight loss increases total energy expenditure and reduces the drop in REE triggered by calorie reduction and weight loss. When combined with reduced calorie intake, aerobic exercise has been shown to increase the likelihood of both short- and long-term weight loss.[134-136] Exercise has also been found to help preserve muscle mass, promote fat loss, and improve appetite regulation.[91] Furthermore, exercise is a critical part of a healthy lifestyle that supports metabolic and overall health; reduces risk of chronic diseases including obesity, type 2 diabetes, cardiovascular disease, and some cancers; and extends lifespan.[137] In fact, lack of physical activity has been estimated to be responsible for twice as many premature deaths as obesity.[138]

Of course, dietary and lifestyle changes work best when used together. In a randomized controlled trial of 147 overweight adults with type 2 diabetes, it was shown that an intensive lifestyle intervention (which included changes to diet and physical activity, and structured lifestyle support) was more effective than usual medical care at reducing body weight, improving glycemic control, and inducing remission of type 2 diabetes. The lifestyle intervention included low-calorie meal replacements in the first phase followed by a gradual reintroduction of food, plus exercise and lifestyle support. Participants in the intervention group lost over three times as much weight as those in the control group during the 12-month study. In addition, 61% of participants in the intervention group experienced remission of their diabetes, compared with only 12% in the control group. The intervention group also had better glucose control.[319] It is advisable for people who are overweight to consider implementing both dietary changes as well as a physical activity regimen with the help of their doctor.

Sticking to an exercise regime long-term is a major factor for sustained weight loss.[133,134] Therefore, it is important to choose a type of physical activity that is motivating and sustainable. The CDC recommends a minimum of 150 minutes of moderate-intensity aerobic activity spread throughout the week.[411] In order to contribute to sustained weight loss, exercise needs to be mainly aerobic, be of at least moderate intensity, and average four to five hours per week in duration. Time spent exercising is cumulative, and therefore is beneficial even when performed in multiple bouts lasting at least 10 minutes.[135,136]

Attention has focused in recent years on high-intensity interval training (HIIT) as a time-efficient way to achieve the benefits of exercise. Most HIIT protocols involve exercising at >90% of maximum heart rate for repeated short bouts of one to five minutes, with rest or low-intensity activity for several minutes between bouts. HIIT has been found to reduce total and visceral fat mass, even without weight loss.[139,140] This is important because fat mass, particularly visceral fat mass, is more closely associated with heart disease than BMI.[1,96] HIIT appears to be as beneficial for metabolic health as regular exercise, but has greater effects on fitness.[140] A meta-analysis of 18 studies comparing high-intensity exercise, including HIIT, to regular exercise programs involving moderate-intensity activity for longer time periods found high-intensity exercise had the same effects on BMI and waist circumference but resulted in greater reduction in percent body fat than regular exercise. In addition, HIIT led to more improvement in cardiopulmonary fitness than regular exercise.[141] For additional information about the benefits of physical activity, including HIIT, refer to Life Extension's **Exercise Enhancement** protocol.

Optimizing Fat Oxidation During Exercise

Fat oxidation during exercise is driven in part by the body's relative heart rate, which is defined as the percentage of maximum heart rate.[408] The relative heart rate varies by age group, with younger groups

benefitting from a higher relative heart rate during bouts of exercise compared with older groups who benefit from a lower relative heart rate.[409] Maintaining a relative heart rate within the suggested range helps maximize fat oxidation during exercise.[410]

A systematic review and meta-analysis of 64 studies suggests that the relative heart rate, instead of relative oxygen uptake, should be used to establish a maximal fat oxidation reference value in people with obesity.[410] The authors of this analysis recommend a relative heart rate of 61–66% for people with greater than 35% body fat and 57–64% for people with less than 35% body fat. They also found that training volume affects fat oxidation—more intense activity such as exercise on a treadmill requires a lower training volume than stationary cycling. Training volume must also be higher in adults than adolescents to achieve a similar level of fat oxidation. These proposed relative heart rates, determined by body fat percentage and age, are lower than what has been previously recommended to optimize cardiovascular fitness, suggesting that weight management does not require exercise as intense as once thought.[409] Table 1 provides guidelines for a suggested target relative heart rate to maximize fat oxidation.

Table 1. Suggested Relative Heart Rate (% of Maximum) During Moderate-intensity Aerobic Activity to Achieve Maximal Fat Oxidation as Determined by Age and Body Fat Percentage

Target Relative Heart Rate for Maximal Fat Oxidation (beats per minute)			
Age (years)	**Maximum Heart Rate***	**Body Fat < 35%**	**Body Fat > 35%**
20	200	114–128	122–132
30	190	108–122	116–125
40	180	103–115	110–119
50	170	97–109	104–112
60	160	91–102	98–106
70	150	86–96	92–99
80	140	80–90	85–92
90	130	74–83	79–86

*Maximum heart rate is calculated by subtracting an individual's age from 220.[409] A higher training volume is required for adults than adolescents to achieve a similar level fat oxidation.

In general, it is recommended to engage in at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity (or an equivalent combination of both) spread throughout the week, in addition to muscle-strengthening activities at least twice a week.[411] However, going beyond this amount can provide more health benefits. To contribute to sustained weight loss, exercise should be mainly aerobic, of moderate intensity, and an average of four to five hours total per week.[135,136]

Stress Management

One of the greatest challenges faced by people trying to lose weight is dealing with food cravings and the

emotional aspects of eating behavior. Stress, depression, and anxiety, as well as external food-related stimuli such as advertisements and ubiquitous food placement, conspire to create a virtually irresistible desire to eat.[142] Differences in neurocircuitry in people with overweight and obesity may further add to difficulties controlling food choices and eating behavior.[143,144] Stress management and cognitive behavioral techniques therefore have a potentially important role to play in successful and sustained weight loss.[145]

Mindfulness-based stress reduction (MBSR) is a validated eight-week stress management program based on cultivating awareness of the present moment. In uncontrolled research, MBSR reduced self-reported emotional eating, binge eating, and eating in response to external cues.[146,147] In a controlled trial, subjects who participated in a program teaching mindful eating and prolonged chewing lost more weight, engaged in less emotional- and cue-stimulated eating, and reported fewer cravings compared with matched counterparts placed on a waiting list.[148]

Cognitive behavioral therapy (CBT), a form of psychotherapy based on developing strategies for coping with unwanted or unhelpful thoughts and behaviors, is another option for managing the psychological aspects of weight loss and eating. CBT has been found to improve weight loss, increase restraint in eating, and reduce emotional eating and binge eating in clinical studies.[149,150] CBT may also help decrease the likelihood of weight regain after bariatric surgery.[151] For additional information on strategies for managing stress, refer to Life Extension's **Stress Management** protocol.

9 Medical and Surgical Approaches to Weight Loss

Reducing calorie intake and increasing physical activity are essential for weight loss. Getting into the right mindset is also important: behavioral counseling (in-person or virtual) can increase the chances of success when adopting new dietary and lifestyle changes for weight loss.[359]

If weight loss goals are not being met with comprehensive diet and lifestyle changes, medical or surgical interventions may be considered. Generally, drug therapy will only be considered for individuals with a BMI >30 kg/m^2 or for those whose BMI is slightly lower but who also have weight-related health problems.[360] Implantable bariatric devices or bariatric surgery may be appropriate is some cases.[361]

Drug Therapies

In 2022, a comprehensive review and meta-analysis published in *The Lancet* evaluated evidence from 143 randomized controlled trials in nearly 50,000 overweight and obese individuals. Each of the included trials lasted 12 weeks or longer. The authors concluded that two weight loss medications stood out for their effectiveness: **semaglutide (Wegovy)** and **phentermine-topiramate (Qsymia)**.

- Semaglutide is in a newer class of drugs called glucagon-like peptide-1 receptor agonists (GLP-1 RAs). It produced significantly greater weight loss than any of the other drugs evaluated in the 2022 analysis. The superiority of semaglutide may be partly attributable to its once-weekly dosing, which improves treatment compliance.[362]
- Qsymia is an extended-release combination of the stimulant phentermine and antiseizure drug topiramate.

Unfortunately, both semaglutide and phentermine-topiramate were often stopped because of side effects.

Contrave, a combination drug containing the opioid antagonist naltrexone and antidepressant bupropion, while effective for weight loss, had the highest rate of adverse effects of any of the medications evaluated in the meta-analysis.[362]

Several other drugs, such as metformin, orlistat (Xenical, Alli [OTC]), and sodium-glucose co-transport 2 (SGLT2) inhibitors, also have some potential to support weight loss efforts as adjuncts to diet and exercise. However, evidence for their effectiveness is less compelling.[362] Older drugs like metformin may be more practical to include in weight loss regimens, particularly as initial drug therapy, because they are far less expensive and more readily available than newer drugs like Wegovy.

Glucagon-like peptide-1 receptor agonists. Semaglutide and liraglutide (Saxenda), both given by injection, target the glucagon-like peptide-1 (GLP-1) receptor. The GLP-1 receptor is involved in regulating glucose metabolism, gastrointestinal motility, and hunger signaling. These drugs have demonstrated improvements in glycemic control, cardiovascular outcomes, all-cause mortality, and weight loss.[336,363,364]

Based on the 2022 comprehensive meta-analysis published in *The Lancet,* semaglutide can be considered best in class of all studied weight loss medications. It showed the highest degree of weight loss along with excellent compliance. From an evidence standpoint, it is the preferred first-line pharmacotherapy for weight loss.[361,362] However, it can be prohibitively expensive and difficult to obtain through insurance coverage. Despite receiving approval from the FDA for the treatment of obesity,[339,365] many insurance companies will not cover these drugs unless several other, cheaper, options have failed.

In a randomized controlled trial that included over 1,200 obese or overweight participants with type 2 diabetes, subcutaneous semaglutide (2.4 mg once weekly for 68 weeks) plus a lifestyle intervention led to a 9.6% reduction in mean body weight compared to 3.4% with placebo plus lifestyle intervention. More participants in the semaglutide group reached a 5% reduction in body weight (69%) than in the placebo group (29%) as well. Gastrointestinal side effects were seen more frequently in the semaglutide group (64% of participants) but were mostly mild to moderate.[337]

Multiple successful trials have also been completed in individuals without diabetes. One 68-week study, which included 1,961 adults with a BMI ≥30 (or ≥27 with concomitant weight-related health issues), found that once-weekly semaglutide injections led to an average weight loss of almost 15% versus 2.4% with placebo.[338] A separate randomized controlled trial that enrolled 902 participants examined the effect of semaglutide (2.4 mg once weekly) or placebo on weight loss. A total of 803 subjects completed a 20-week run-in phase on the medication, achieving an average of 10.6% weight loss. Subjects were then randomized to either semaglutide or placebo for a 48-week continuation of the trial. The semaglutide group experienced a 8% reduction in body weight from week 20 to 68 compared with a 7% *increase* in the placebo group.[366]

In the 2022 *Lancet* systematic review and meta-analysis, treatment with liraglutide resulted in a 4.7% loss of initial body weight, with nearly 5% of participants successfully losing 5% and 10% of body weight. However, it was also associated with high rates of adverse effects resulting in discontinuation of therapy.[362]

A clinical trial published in 2009 enrolled 564 obese individuals to compare the efficacy of subcutaneous liraglutide (1.2, 1.8, 2.4, or 3 mg once daily) or placebo to the older oral weight loss medication orlistat (120 mg three times daily) over 20 weeks. All study participants ate a reduced-calorie diet and increased physical activity throughout the trial. Liraglutide resulted in a dose-dependent increase in mean weight loss of 10.6, 12.1, 13.9, and 15.9 pounds, respectively, compared to 9 pounds with orlistat and 6.2 pounds with placebo. Furthermore, 76% of individuals lost more than 5% of their body weight with 3 mg liraglutide compared to 44% with orlistat and 30% with placebo.[367]

The efficacy of once-weekly semaglutide (2.4 mg) or once-daily liraglutide (3 mg) on weight loss was compared in a 68-week, open-label, placebo-controlled clinical trial enrolling 338 overweight or obese individuals without type 2 diabetes. Semaglutide administration resulted in an average weight loss of 15.8% compared to 6.4% with liraglutide. A higher proportion of participants also achieved weight loss milestones of 10%, 15%, and 20% or more weight loss with semaglutide than liraglutide. The proportion of participants with reported adverse gastrointestinal events were comparable with semaglutide (84%) and liraglutide (83%). However, discontinuation of treatment for any reason was only reported by 14% of semaglutide users compared with 28% of liraglutide users, confirming that semaglutide provides a superior treatment option for weight loss with higher patient compliance.[368]

Tirzepatide. Tirzepatide (Zepbound), an agonist of gastric inhibitory polypeptide (GIP) and GLP-1 receptors, was granted FDA approval in 2023 for chronic weight management in conjunction with a calorie-restricted diet and physical activity.

The SURMOUNT-1 clinical trial—the first phase III global clinical trial for tirzepatide—enrolled 2,539 non-diabetic overweight or obese adults to evaluate the efficacy and safety of tirzepatide (5 mg, 10 mg, or 15 mg) over 72 weeks. The mean baseline body weight of participants was 231 pounds. Significant reductions in body weight of 35 (16%), 49 (21.4%), and 52 (22.5%) pounds were observed in the 5 mg, 10 mg, and 15 mg tirzepatide groups, respectively. Subjects taking placebo lost only about 5 pounds. Body weight reductions of at least 20% were achieved in 50% (10 mg) and 57% (15 mg) of participants taking tirzepatide compared with only 3% of those taking placebo.[405]

The SURMOUNT-2 trial, a separate phase III trial conducted in seven countries, randomized 938 adults with type 2 diabetes and a BMI ≥ 27 kg/m^2 to receive tirzepatide (10 mg or 15 mg) or placebo once-weekly for 72 weeks. A significant reduction in bodyweight from baseline of 12.8% and 14.7% were observed in the 10 mg and 15 mg groups, respectively, compared with 3.2% in placebo.[406]

In the final clinical trial, the SURMOUNT-3 trial, the effect of tirzepatide on weight reduction after successful intensive lifestyle intervention was tested. The trial randomized 579 adults with BMI of ≥27 or ≥30 kg/m^2 who achieved ≥5% weight reduction after a 12-week lifestyle intervention to receive a maximum tolerated dose (10 or 15 mg) of tirzepatide or placebo for 72 weeks. At 72 weeks, those in the tirzepatide group had a significant reduction in body weight of 18.4% compared with a 2.5% increase with placebo.[407]

Multiple phase III studies have shown tirzepatide also assists in reducing body weight in people with type 2 diabetes.[383] In three separate trials, once weekly injections of tirzepatide (5 mg, 10 mg, or 15 mg) resulted in greater weight loss compared with placebo, semaglutide (1 mg once weekly), and insulin glargine controls. Among subjects with a mean BMI of just under 32 kg/m^2, tirzepatide induced a dose-dependent loss of body weight of up to 21 pounds.[384-386] The most common adverse events were mild and included nausea, diarrhea, and vomiting. There were no events of severe hypoglycemia. Importantly, this trial could not address the question of how tirzepatide compares with the standard weight-loss maintenance dosage (2.4 mg once weekly) of semaglutide.

In a separate trial examining tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg once weekly), more subjects reached weight loss targets (≥5% and ≥10%) following treatment with tirzepatide than placebo or dulaglutide (Trulicity) (1.5 mg once weekly).[387] The SURPASS-5 trial, a 40-week study that enrolled 475 individuals with type 2 diabetes, examined the addition of tirzepatide (5 mg, 10 mg, or 15 mg once weekly) to insulin compared with insulin alone in patients treated with or without metformin. Significant reductions in average body weight of 12, 17, and 19 pounds were observed in the 5 mg, 10 mg, and 15 mg tirzepatide dosage groups, respectively. Subjects receiving placebo gained about 4 pounds.[388]

Managing Side Effects of GLP-1 RA Drugs

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) drugs have been used in the United States since the approval of exenatide (Byetta) in 2005 for diabetes management. More recently, the use of GLP-1 RAs has expanded significantly for both weight loss and diabetes management. Drugs like semaglutide and tirzepatide, which also act as a glucose-dependent insulinotropic polypeptide (GIP) agonist, have shown remarkable efficacy in clinical trials for weight loss. These medications are now commonly known under brand names such as Ozempic, Wegovy, Rybelsus, Mounjaro, and Zepbound.

As GLP-1 RAs have become widely used for weight loss, there is growing interest in dietary and lifestyle changes to mitigate their side effects and maintain a healthy body composition during their use.[412]

Common Gastrointestinal Side Effects & Dietary Modifications

GLP-1 RA drugs slow the rate at which food moves through the digestive tract, leading to common gastrointestinal side effects like nausea, vomiting, and diarrhea.[413,414] Some dietary modifications that may alleviate these side effects include[412,415]:

- **Eating smaller portions**: Helps prevent overloading the digestive system.
- **Eating slowly**: Allows more time for digestive processes to work and may reduce nausea.
- **Stopping when full**: Prevents discomfort and potential vomiting.
- **Increasing fiber intake**: Can aid in digestion and help manage diarrhea and constipation.

Other helpful habits include maintaining a healthy diet, avoiding high-fat foods, increasing fluid intake, and not eating close to bedtime.

Optimizing Nutritional Intake

The significant reduction in caloric intake that arises with GLP-1 RA use may result in nutritional deficiencies or loss of lean mass.[416,417] Maintaining adequate protein intake can support fat loss while minimizing loss of lean mass that may result from reduced caloric intake.[418-420]

Certain nutritional factors may offer additional benefits for those taking GLP-1 RA drugs. However, further studies are needed to confirm their efficacy. For example:

- **Magnesium**: Has laxative effects that can help reduce constipation.[421]
- **Vitamin B12**: May help mitigate nausea and vomiting, potentially reducing the likelihood of treatment discontinuation.[422]
- **ß-hydroxy-ß-methylbutyrate (HMB)**: Supports muscle mass and strength, helping to maintain a healthy body composition during weight loss.[423]
- **Supplemental protein** (eg, whey, pea, etc.): Helps ensure adequate total protein intake.

People taking GLP-1 RA drugs should discuss supplemental nutrient options with a healthcare provider before making any changes to their medical regimen. Periodic assessment of blood levels of micronutrients, such as vitamins, minerals, and omega-3 fatty acids, may also be helpful since reduced food intake may affect nutritional status.[417]

Other Potential Side Effects

Although gastrointestinal-related side effects of GLP-1 RAs are likely to get the most attention, there are other potential adverse effects of which users should be aware. These include[424]:

- **Facial**: Potential skin sagging, amplified visibility of wrinkles due to depletion of facial fat, collagen, and elastin.
- **Oncological**: Increased risk of thyroid cancer and medullary thyroid cancer.
- **Renal/Kidney**: Possible correlation with acute kidney injury and other renal issues.
- **Glycemic Considerations**: Hypoglycemic events, especially when combined with certain other drugs.
- **Dermatological**: Rash, erythema, itching, potential for transient bumps, panniculitis with certain formulations.
- **Pancreas**: Elevated pancreatic enzymes, possible pancreatitis, and cholelithiasis with rapid weight loss.
- **Cardiovascular**: Increase in heart rate.
- **Allergenic and Immune Responses**: Antibody formation, possible hypersensitivity, rare severe anaphylactic responses.
- **Musculoskeletal**: Variable impacts on bone fracture risk among different GLP-1 RAs.

Dosage Adjustment & Working with Healthcare Providers

People experiencing side effects from GLP-1 RA drugs should work closely with their healthcare provider to adjust their dosage if necessary. This collaborative approach can help optimize treatment outcomes and minimize discomfort.

Sympathomimetic drugs (stimulants). Stimulant drugs have been used as appetite suppressants for decades. Although many have subsequently been pulled from the market, phentermine remains available by prescription.[369,370] It suppresses appetite primarily through stimulation of norepinephrine release from the hypothalamus (a brain region involved in hunger), though its stimulation of the sympathetic nervous system outside of the brain results in increased energy expenditure at rest and increased fat burning.[371,372] Phentermine is available as a standalone drug or combined with the antiseizure drug topiramate.

A 2022 systematic review and network meta-analysis published in *The Lancet* found that phentermine-topiramate treatment resulted in an average of nearly 8% weight loss—superior to most other medications studied or to lifestyle modifications alone. However, that study also found that phentermine-topiramate was among the medications most likely to be discontinued due to adverse effects, though its risk of gastrointestinal side effects was favorable compared with most other drugs.[362]

Stimulant weight loss drugs like phentermine should not be used by individuals with a history of cardiovascular disease or uncontrolled hypertension.[360] The most common side effects of phentermine-topiramate are dry mouth, constipation, and burning or prickling sensations, though rapid heart rate, cognitive and psychiatric disturbances, seizures, and glaucoma have also been reported. Phentermine is contraindicated in people with hyperthyroidism or current or recent use of MAO inhibitor.[373,374]

Orlistat. Orlistat interferes with fat digestion and absorption by inhibiting the action of lipase, a fat-degrading enzyme produced by the stomach and pancreas.[375] Although widely used for weight loss, a 2022 systematic review and meta-analysis published in *The Lancet* found that orlistat was not clearly superior to lifestyle modifications alone.[362]

Orlistat often causes digestive problems such as gas, oily stool and discharge, and diarrhea.[152,156] Because it reduces absorption of fat-soluble vitamins (A, D, E, and K), people taking orlistat should take a multivitamin supplement.[152]

Naltrexone-bupropion. Contrave, a combination drug containing the opioid receptor antagonist naltrexone and the antidepressant bupropion, acts as an appetite suppressant by targeting brain centers involved in hunger and appetite.[376,377] Naltrexone-bupropion is effective for weight loss, but often causes side effects severe enough to cause users to stop taking the drug.[362] Its most common side effects include nausea, constipation, headache, dizziness, insomnia, dry mouth, and diarrhea. Moreover, its unfavorable effects on blood pressure and heart rate mean that it is contraindicated in individuals with uncontrolled hypertension. [156]

Metformin. Metformin is a well-established blood glucose-lowering drug. Its long history of safe use and accessibility make it a first-line medication for treating **type 2 diabetes**. In the decades since its development and approval, metformin use has been associated with a range of metabolic benefits in diabetics, including improvements in lipid levels, non-alcoholic fatty liver disease, cognitive function, cardiovascular risk, cancer risk, and mortality.[158] Metformin's weight loss benefits may be related to metabolic effects including reduced liver gluconeogenesis and improved insulin sensitivity. However, emerging evidence suggests additional possible mechanisms include appetite regulation and modulating gut microbiome modulation.[159]

A 2022 *Lancet* systematic review and meta-analysis found that metformin was associated with only modest weight loss, perhaps no better than lifestyle changes alone. Metformin carried a low risk of side effects resulting in discontinuation, and a modest risk of gastrointestinal side effects. Nevertheless, overweight and obesity is a primary risk factor for type 2 diabetes and other metabolic disturbances, and metformin is one of the most commonly prescribed medications for diabetes. Additionally, metformin prevents progression to diabetes in those at risk of developing the condition.[378] In contrast, some widely used antidiabetic medications, including insulin and sulfonylureas, are associated with weight gain.[159,163] Digestive side effects of metformin can often be mitigated with extended-release formulations and/or dose titration guided by a clinician.

In the Diabetes Prevention Program, a randomized controlled trial that enrolled 3,234 overweight and obese individuals at risk of diabetes, a 5% or greater drop in body weight was achieved by 29% of those taking metformin, 63% using lifestyle interventions, and 13% receiving placebo after one year.[169,379] However, participants in the metformin group remained on the drug for up to 15 years, while long-term adherence to the lifestyle changes tapered off over time. During follow-up from year six to year 15, the average weight loss relative to baseline that was maintained in 6.2% of metformin users, 3.7% of lifestyle intervention participants, and 2.8% of placebo recipients.[171]

Emerging Anti-Obesity Drugs

Several drugs approved for other indications may hold promise as weight loss interventions. However, as of early 2022, none of the drugs or drug classes described in this section are approved specifically for weight loss in otherwise healthy people; this may change as more research is completed.

Sodium-glucose co-transporter 2 inhibitors. Sodium-glucose co-transporter 2 (SGLT2) inhibitors (eg, empagliflozin [Jardiance]) are a class of drugs used to treat type 2 diabetes. They work primarily by inhibiting reabsorption of glucose from the kidneys resulting in greater urinary glucose excretion.[182] SGLT2 inhibitors appear to be modestly effective weight loss agents with a favorable side effect profile.[362] They also carry a range of cardiovascular benefits.[380,381] In people with diabetes, SGLT2 inhibitors have been shown to reduce body weight by about 2 – 7 pounds, with weight stabilizing at around nine months of treatment.[382]

Peptide YY. Peptide YY (PYY) is a mediator of satiety that is released from certain cells in the gut after meals. Intravenous administration of a specific form of PYY, known as PYY_{3-36}, has been shown to reduce food intake in both rodents and humans. Clinical trials to examine the safety, tolerability, and pharmacokinetics of subcutaneously or sublingually administered PYY_{3-36} were in progress as of early 2022.[382,383]

Fibroblast growth factor 21. The metabolic benefits of fibroblast growth factor 21 (FGF21) in animal models suggest this growth factor may have promise as an anti-obesity medication. In animals, FGF21 causes weight loss and improved insulin sensitivity without hypoglycemia.[382,383] A clinical study including 50 participants examined the efficacy of an engineered FGF21 protein (5 mg, 25 mg, 100 mg, and 140 mg given intravenously twice weekly) over four weeks. The study found that the FGF21 protein led to significant reductions in weight for doses above 25 mg compared with placebo. A dose-response was not apparent.[382,389]

Neurotransmitter reuptake inhibitors. Tesofensine is an inhibitor of noradrenaline, dopamine, and serotonin reuptake originally developed for treatment of Parkinson and Alzheimer diseases. Although it did not meet the efficacy criteria for these indications, study participants lost weight. Tesofensine causes an increase in metabolic rate and appears to suppress appetite and reduce food intake; however, it also causes increased heart rate.[382,383] In a phase III trial of 372 obese subjects, oral tesofensine (0.25 mg and 0.5 mg once daily) resulted in reduced BMI and led to a 10% average weight loss at 24 weeks for both dosages compared with placebo.[382] In 2020, an application for approval of tesofensine as an anti-obesity drug was submitted to the Mexican government's food and drug administration (FDA).[390]

Because of tesofensine's cardiac risk, it has been made into a fixed-dose combination with the beta-blocker metaprolol, creating the drug Tesomet. Tesomet has received orphan drug designation from the United States FDA for the treatment of Prader-Willi syndrome, a genetic condition with prominent features of extreme hunger, overeating, and obesity.[391,392] Clinical investigation of Tesomet for treatment of Prader-Willi syndrome is ongoing.[393]

SIRT1 activators. Sirtuins are a family of signaling proteins involved in metabolic regulation. In preclinical research, activation of sirtuins has resulted in reduced lipid accumulation in response to excess energy intake.[382] Common drugs that activate SIRT1 include metformin and sildenafil (Viagra), while the branched chain amino acid leucine also has this effect. A clinical trial including 91 men and women examined a combination of leucine (1,100 mg), metformin (500 mg), and sildenafil (0.5 or 1 mg).[382,394] The combination with 1 mg sildenafil reduced weight by about 5 pounds after 16 weeks. the weight loss reached 11 pounds in subjects with elevated triglycerides.[394] Mild-to-moderate gastrointestinal adverse effects were likely attributable to metformin.

Leptin and MC4 receptor agonists. Leptin is a hormone released by fat cells that regulates satiety by acting on neurons in the hypothalamus, particularly through activation of a receptor known as melanocortin-4 (MC4).[383,395] In 2014, the FDA approved a synthetic analog of leptin known as metreleptin (Myalept) to help normalize metabolic disturbances in those with congenital leptin deficiency but not under conditions of common obesity. MC4 receptor agonists have been examined as an alternative but were largely abandoned as they are prone to cross-stimulation of MC1, MC3, and MC5 receptors that perturb various endocrine processes. MC4 receptor agonists also activate the sympathetic nervous system, increasing heart rate and blood pressure. However, setmelanotide (Imcivree), an MC4 receptor agonist, received FDA approval in 2020 for weight management related to certain genetic defects that can lead to severe obesity at a young age.[383] As of early 2022, setmelanotide is not approved for the treatment of obesity in individuals who do not have these genetic variants.

Cagrilintide. Amylin is a peptide that is co-secreted with insulin from the pancreas in response to food intake. It regulates satiety and food intake. A long-acting analogue of amylin known as cagrilintide, which requires only once-weekly subcutaneous injections, was under investigation for weight loss as of early 2022.[383] In a phase 2 trial in adults without diabetes and BMI over 30 kg/m^2, or 27 kg/m^2 plus comorbidities, cagrilintide was compared to liraglutide and placebo. Once-weekly cagrilintide (0.3, 0.6, 1.2, 2.4, or 4.5 mg) or once-daily liraglutide (3 mg) were each evaluated versus placebo. All doses of cagrilintide resulted in greater weight loss than placebo, while 4.5 mg cagrilintide outperformed liraglutide. In both comparisons, the 4.5 mg cagrilintide group averaged weight loss of 25 pounds in 26 weeks. Discontinuation due to adverse events was uncommon, occurring in only 4% of participants.[396] Another trial examined the safety of once-weekly cagrilintide (1.2 mg, 2.4 mg, and 4.5 mg) in combination with once-weekly semaglutide (2.4 mg), versus placebo, in adults 18–55 years old with BMIs of 27–39.9 kg/m^2. Cagrilintide at all doses, in combination with semaglutide, was superior for weight loss compared to placebo. The greatest weight loss compared to baseline occurred in the 2.4 mg cagrilintide group. Most adverse events were mild to moderate and occurred at a similar rate in all treatment groups.[383,397]

Bariatric Devices

Several medical devices are available to treat obesity in individuals who are struggling to control their weight despite significant lifestyle modifications, have poor treatment compliance, or do not qualify for bariatric surgery[184]:

- **Gastric balloons** partially fill the stomach and reduce its capacity for food. Balloons can be left in the stomach for up to six months.
- **Vagus nerve blockade therapy** decreases hunger signals from the stomach. A device is implanted at the junction of the esophagus and stomach and is connected to a pulse generator under the skin.
- **Gastric emptying system** allows the stomach to be emptied 20–30 minutes after eating via an external valve. A study published in 2019 found one such device, branded AspireAssist, to be effective and mostly safe for weight loss over a four-year period. Some adverse events were reported, including some requiring surgical resolution. This device is likely best suited for use in highly motivated patients who will adhere diligently to best usage practices.[183] (Note: the manufacturer of AspireAssist, Aspire Bariatrics, ceased operations in April 2022 resulting in the removal of the AspireAssist-branded device from the market. The device may return to the market under a new brand name in the future, but the likelihood of, or timeline for, such a return was unclear as of early 2022.)
- **Gastric artery embolization** is a new technique that involves inserting microparticles into the left gastric artery. By blocking blood supply to part of the stomach, the goal of the procedure is to reduce production of the hunger hormone ghrelin. Although early reports are promising, long-term data from larger groups of people are needed to evaluate the safety and efficacy of gastric artery embolization.[155,184]

Each of these devices can cause abdominal pain, nausea, and other digestive problems. Gastric emptying can also result in infection and dangerous electrolyte imbalance. In rare cases, gastric balloons can cause gastrointestinal obstruction or perforation.[152] In general, bariatric devices are only recommended after dietary, lifestyle, and pharmacologic interventions have been unsuccessful.[184]

Bariatric Surgeries

Bariatric surgeries, while often dramatically effective for weight loss and comorbid conditions including diabetes, are only indicated for people with a BMI ≥40 kg/m^2 or those with a BMI ≥35 kg/m^2 plus a weight-related comorbidity such as type 2 diabetes. All these surgical procedures cause changes in digestive function that can interfere with normal nutrient absorption and carry risks of various early and late complications.[152,361]

The most common surgery for weight loss is **sleeve gastrectomy**, in which a line of staples is placed vertically along the mid-stomach and the portion of stomach (about 80%) outside the staple line is removed.[398,399] Another common weight loss surgery is **Roux-en-Y gastric bypass**. In this surgery, a small pouch is created from the stomach and is connected to the mid-intestine (jejunum), bypassing most of the stomach and upper intestine (duodenum and part of the jejunum). Although gastric bypass is associated with the greatest long-term weight loss as well as frequent remission of type 2 diabetes, it is the most complex surgery with the greatest risk of surgical complications.[152]

The **laparoscopic adjustable gastric band** procedure is less commonly performed but is the least invasive option, and unlike other weight loss surgeries is reversible. It involves the placement of an adjustable band around the top of the stomach. Gastric bands are associated with the least long-term weight loss and greatest chance of weight regain compared with other bariatric surgeries.[152]

10 Nutrients

Modulating Appetite and Cravings

Lemon Verbena and hibiscus. Lemon verbena (*Lippia citriodora*, *Aloysia citriodora*) and hibiscus (*Hibiscus sabdariffa*) are botanicals with a history of medicinal use.[346,347] Both of these botanicals have numerous medicinal properties including general antioxidant, anti-inflammatory, and metabolic effects.[348]

Multiple randomized controlled clinical trials have evaluated combinations of lemon verbena and hibiscus extracts in overweight and obese subjects. These studies have yielded promising results for weight loss and

biomarker-based assessments of cardiovascular health. Moreover, the combination of these extracts was reported to be well tolerated with no treatment-related adverse events.

In overweight and obese women 30 to 75 years of age, supplementation with 500 mg of a lemon verbena-hibiscus combination daily for two months along with guidance to walk at least 30 minutes per day led to a significant decrease in body weight, BMI, percent body fat, and multiple other anthropometric parameters compared with placebo.[349] Weight loss averaged 7.7 lbs. in the supplement group versus 4.6 lbs. in the placebo group. As early as 30 days after beginning supplementation, subjective hunger scores were significantly lower and scores of fullness were higher in the intervention group than placebo group. Subjective scores of food craving for sweet, salty, savory, and fatty foods were also significantly decreased in the intervention group compared with placebo. Along with this, a significant increase in GLP-1 (associated with satiety) and a significant decrease in leptin and resistin were seen in the supplement group compared with placebo. Heart rate and systolic and diastolic blood pressure were also significantly lower in the intervention group at 30 days and study completion.

A subsequent randomized, double-blind, placebo-controlled trial considered the effects of the lemon verbena-hibiscus combination on overweight and obese women separately.[350] Guidance was provided to follow a balanced, isocaloric 2,200-calorie diet along with 30 minutes of walking daily. At the same 500 mg dose, taken daily before breakfast, significant improvements were seen compared with placebo in several anthropometric parameters of the overweight subjects. However, only body weight improved significantly in the obese group. Those in the overweight group lost an average of 8.2 lbs. versus an average loss of 10.3 lbs. in the obese group. A significant decrease in heart rate and systolic blood pressure was also seen in both groups compared with placebo.

Another trial in men and women with overweight and obesity with a BMI of 25–34.9 kg/m^2 included a 30-day washout and a crossover period.[351] The lemon verbena-hibiscus combination was taken daily for 60 days at a dose of 500 mg before breakfast, with no guidance on diet or exercise being given. After 60 days of supplementation, the primary parameters assessed were self-reported hunger, satiety, and fullness on a visual-analog scale (VAS); satiety hormones; and caloric consumption at an ad-libitum meal. These assessments were all done on day 60 of taking the product, with assessments of appetite at several timepoints before and after both supplementation and the ad-libitum test meal. Combination scores of overall appetite sensation and satiety quotient were developed from the measured parameters. When provided the ad-libitum meal, the subjects consumed significantly less calories after taking the supplement. Satiety was greater after taking the combination of extracts compared with placebo. GLP-1 and leptin were significantly altered with the intervention, pointing to their involvement in decreased calorie consumption and increased satiety.

A lower dosage of this extract combination, in the absence of diet and exercise, was found to improve body composition and cholesterol in participants with overweight. In a double-blind, randomized, controlled trial, 61 participants with a BMI of 25–29.9 kg/m^2 were instructed to take 300 mg of the lemon verbena-hibiscus combination before breakfast for 90 days.[1] After 60 days, supplementation resulted in an increase in feelings of satiety and satisfaction immediately after breakfast compared with placebo. However, it did not affect hunger in fasting conditions. A significant improvement in satiety immediately after breakfast was maintained after 90 days compared with placebo and baseline. Compared with baseline, participants taking the combination supplement also had an average reduction of 6.2 pounds (3.4%) of body weight, 5.7% of total body fat mass, and 8% of visceral fat. The changes were significant compared with placebo as well. Waist circumference, triceps skinfold, and total cholesterol also significantly decreased compared with baseline. Muscle mass remained unchanged.[425]

Preclinical research suggests specific mechanisms by which lemon verbena and hibiscus may impact metabolic health include inhibiting triglyceride accumulation in adipocytes, improving mitochondrial function, decreasing fatty acid synthesis, and increasing fatty acid oxidation.[352-354]

In mice with high-fat-diet-induced obesity, the combination of lemon verbena and hibiscus extracts was shown to decrease body and liver weight, white adipose tissue, and glucose levels. The combination also improved lipid profiles, glucose tolerance, and other metabolic parameters. Adiponectin increased while leptin decreased, suggesting that modulation of signaling by these adipokines (adipose tissue hormones) may have contributed to the improved metabolism, appetite regulation, and other positive outcomes observed in response to lemon

verbena and hibiscus supplementation. Moreover, lipid accumulation in adipocytes was decreased while genes that promote metabolism via thermogenesis (heat production) in white adipose tissue were upregulated. The altered gene expression correlated with increased AMPK activation and liver fatty acid oxidation, which both contribute to metabolic efficiency.[348] A study on cells in vitro also found the lemon verbena and hibiscus extracts increased AMPK activity and reduced adipocyte fat content.[350]

White kidney bean extract. White kidney bean (*Phaseolus vulgaris*) contains a compound that inhibits α-amylase, a digestive enzyme required for the conversion of starch to smaller sugars. By inhibiting α-amylase activity, white bean extract can reduce carbohydrate digestion and absorption, and has been reported to lower post-meal spike in blood glucose levels.[185,186] A meta-analysis that included 11 clinical trials (including some unpublished data from supplement manufacturers) with a combined total of 573 participants found white bean extract, at a dose of at least 1,200 mg per day for a minimum of four weeks, promoted weight loss in overweight and obese individuals. In addition, three trials examining the effect of white bean extract on fat loss reported significant reductions in fat mass in participants taking the extract.[187]

Saffron. Extracts of saffron (*Crocus sativus*) have been studied for a variety of applications, including pain relief, inflammation reduction, and memory and mood enhancement.[188] Saffron extract was shown to reduce symptoms of depression in a randomized controlled trial,[189] which may explain its potential for reducing the desire to eat. In a study of 60 healthy, mildly overweight women on an unrestricted diet, 176.5 mg saffron stigma extract daily for eight weeks produced an average weight loss of about 2 pounds. Much of this weight reduction was attributed to a reduction in snacking frequency; at the study's end, individuals on the saffron supplement reported having 5.8 snacks per week (compared with 8.9 snacks per week in the placebo group), a reduction in snacking frequency of 55% from pre-trial levels.[190]

Thylakoids. Thylakoids are components of plants that participate in plant metabolism. Studies have found that thylakoid ingestion by humans and some animal models helps reduce food cravings and may promote healthy weight loss. Thylakoid ingestion also appears to modulate glucose metabolism and inflammatory signaling.[191] Clinical trials have shown supplementation with thylakoid-rich plant preparations leads to greater weight loss than placebo treatment.[192] One trial that enrolled 38 overweight women found that thylakoid supplementation decreased subjects' urge to consume sweets and chocolate. In addition, subjects supplementing with thylakoids in this trial lost significantly more weight (about 3.3. pounds) than those taking placebo. Participants taking thylakoids also had reduced LDL and total cholesterol levels.[192,193]

Promoting Energy Expenditure

DHEA and 7-Keto DHEA. Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone and a precursor to the sex steroids testosterone and estrogen. Its production by the adrenal gland steadily declines with advancing age. Low DHEA levels have been correlated with higher body weight and percent body fat, and preclinical research suggests supplementation may improve body composition, adipose tissue distribution and function, and metabolism of lipids and carbohydrates.[85-87,194] Furthermore, an analysis of four clinical trials found DHEA supplementation increased preservation of bone and muscle mass in aging women.[195] One randomized controlled trial that included 61 postmenopausal women with obesity found treatment with 100 mg DHEA for three months resulted in greater weight loss and reductions in waist circumference, blood glucose levels, blood pressure, and other metabolic parameters.[196] In a randomized controlled trial in 125 elderly men and women, 50 mg DHEA daily for two years lowered visceral fat mass, improved glucose tolerance, and decreased levels of inflammatory cytokines.[197] Another trial found 50 mg DHEA per day for six months led to reduced abdominal fat and improved insulin sensitivity.[198]

7-Keto DHEA (3-acetyl-7-oxo-dehydroepiandrosterone), a metabolite of DHEA, has been suggested to be a thermogenic agent that could increase energy expenditure.[199] In overweight subjects maintained on a calorie-restricted diet, seven days of treatment with 7-Keto DHEA increased REE by 1.4%, whereas subjects taking placebo saw their REE decrease by 3.9%.[200] In another randomized controlled trial, overweight volunteers taking 100 mg 7-Keto DHEA twice daily lost significantly more weight and body fat than the placebo group (6.3 pounds vs. 2.2 pounds, respectively, and reductions in body fat of 1.8% vs. 0.57%).[201]

Inhibiting Absorption of Carbohydrates and Fats

Chromium. Chromium is well known for its ability to improve glucose and lipid metabolism.[202] Clinical evidence suggests it may also increase weight loss in overweight and obese individuals. Three meta-analyses of randomized controlled trials have noted small beneficial effects on weight loss when chromium was taken in doses of 200 or 400 mcg daily for a period of 12–16 weeks.[203-205] Chromium may be especially helpful for supporting weight loss in overweight and obese individuals with binge eating disorder. In one randomized controlled trial, chromium (as chromium picolinate) reduced binge eating frequency, improved mood, and resulted in more weight loss than placebo in overweight and obese subjects with binge eating disorder. A daily dose of 1,000 mcg was more effective than 600 mcg per day for increasing weight loss and reducing binge eating.[206]

Irvingia gabonensis. Extracts of the seeds of *Irvingia gabonensis*, a mango-like West African fruit, may reduce body fat and promote healthy blood lipid and fasting blood glucose levels. Irvingia extracts are thought to inhibit the growth of adipose tissue by down-regulating a protein involved in activating adipose cell growth and proliferation.[207] Three clinical trials in subjects with overweight and obesity have reported Irvingia seed extract decreased body fat, body weight, and waist circumference.[208-210] One of these trials reported particularly dramatic results. In the trial, Cameroon people who were overweight or obese took 150 mg Irvingia seed extract before meals for 10 weeks; subjects had greater reductions in body fat percentage (-6.3% vs. -1.9%), body weight (-28.2 pounds vs. -1.5 pounds), and waist circumference (-6.37 inches vs. -2.09 inches), as well as reductions in total- and LDL-cholesterol, C-reactive protein, and fasting blood glucose compared with placebo.[210,211] These impressive findings need to be confirmed through future research.

Fucoxanthin. Fucoxanthin is a carotenoid pigment from seaweed that has demonstrated several anti-obesity effects. Evidence shows fucoxanthin can inhibit the release and activity of fat-digesting enzymes known as lipases and, in this way, may reduce absorption of dietary fats. Like all carotenoids, fucoxanthin decreases inflammation and enhances free radical scavenging. In addition, fucoxanthin has been found to improve glucose and lipid metabolism, increase the use of fats for energy, and regulate adipose tissue function. Some of its effects appear to be related to modulating the expression of several genes.[212]

A randomized placebo-controlled trial examined the effects of a supplement with fucoxanthin in 151 premenopausal non-diabetic women with obesity. Women taking a supplement with 300 mg seaweed extract providing 2.4 mg of fucoxanthin, plus 200 mg pomegranate oil, daily for 16 weeks had greater reductions in body weight, body fat, liver fat, waist circumference, triglyceride levels, and levels of C-reactive protein (a marker of inflammation) compared with placebo.[213] In a pilot study with two participants, a seaweed plus pomegranate oil supplement providing 3 mg fucoxanthin daily increased brown adipose tissue after three months, suggesting it may increase thermogenesis and energy expenditure.[214]

Green tea. Green tea contains caffeine and is rich in polyphenolic compounds called catechins, including epigallocatechin gallate (EGCG), which is well known for its powerful antioxidant and anti-inflammatory effects.[215,216] It is a common ingredient in weight-loss products and findings from the majority of clinical trials generally support its use for this purpose. In fact, some research suggests green tea catechins and caffeine work synergistically to increase energy expenditure and fat burning.[215]

Meta-analyses and reviews of randomized controlled trials indicate green tea extract may have a small positive impact on body weight and fat mass in overweight and obese adults.[215,217-219] In general, the best results have been reported for those taking green tea extracts providing 100–460 mg EGCG per day for at least 12 weeks.[217]

Studies have shown that green tea extracts are able to inhibit the activities of several digestive enzymes, potentially reducing the breakdown and absorption of sugars and fats from the intestines.[220] Green tea and its polyphenols have also been shown to improve the gut microbiome and increase bacterial production of anti-inflammatory compounds, trigger positive epigenetic mechanisms, stimulate healthy adipose tissue metabolism, and possibly increase thermogenesis.[215,221,222] In addition, green tea has been shown to enhance the effects of exercise on fat burning.[223]

L-arabinose. Sucrose, or common table sugar, is composed of one molecule of glucose and one of fructose. In order to be utilized, it must be broken down by the digestive enzyme sucrase. L-arabinose is an indigestible plant sugar shown to inhibit sucrase, and animal research suggests it may reduce spikes in blood sugar and insulin levels, blood pressure, and fat synthesis that typically follow consumption of high-sugar food or drink.[224-226] Pilot

studies in healthy adults have shown L-arabinose reduces the impact of sugar consumption on blood glucose and insulin levels.[227,228]

Modulating Fat Tissue Physiology

Gynostemma. *Gynostemma pentaphyllum* is an Asian medicinal plant used to lower blood glucose and cholesterol levels, strengthen immunity, and stimulate weight loss. Compounds extracted from gynostemma have been shown to activate a critical enzyme that regulates cellular metabolism and other cell functions: adenosine monophosphate-activated protein kinase (AMPK).[237-239] In a randomized placebo-controlled trial that included 80 participants with obesity, 450 mg gynostemma extract per day for 12 weeks resulted in decreased body weight, total abdominal fat area, body fat mass, percent body fat, and BMI.[240] Animal research suggests treatment with gynostemma can induce gene expression changes that may result in decreased diet-related adipose tissue growth, weight gain, and metabolic disturbance.[241] In a study in mice fed a high-fat diet, treatment with gypenosides (active compounds from gynostemma) had positive effects on the gut microbiome, as well as gene expression, that may have contributed to its ability to increase thermogenesis and adipose tissue browning, reduce weight gain, and exert other metabolic benefits.[242]

Guarana. Guarana (*Paullinia cupana*) is an herbal source of caffeine commonly used for weight loss. In adults with BMI between 29 and 35 kg/m^2 participating in an eight-week randomized controlled trial, a combination of guarana and ma huang (*Ephedra sinica*), providing 240 mg caffeine and 72 mg of stimulating ephedrine alkaloids per day, led to greater weight loss, fat loss, and reductions in triglycerides compared with placebo; however, adverse side effects related to overstimulation were common and resulted in a high rate of withdrawal from the study.[259] In animal research, guarana seed powder reduced the negative effects of a high-fat Western-style diet, such as weight gain, lipid level disturbance, fat accumulation, insulin resistance, and adipose tissue dysregulation. It also appeared to increase brown adipose tissue expansion and activity, thereby increasing thermogenesis and energy expenditure.[260,261] Changes in gene expression through which guarana may exert benefits have also been identified.[261]

Garcinia mangostana and Sphaeranthus indicus. A combination of extracts from mangosteen fruit rind and *S. indicus* flowers has been shown to support weight loss. Promotion of fat cell breakdown (lipolysis) and inhibition of new fat cell formation (adipogenesis) are thought to contribute to these beneficial effects.[264,265]

Mangosteen (Garcinia mangostana) is a tropical fruit native to Southeast Asia where it has long been used as a traditional medicine. It promotes efficient blood sugar metabolism and mitigates inflammation and oxidative stress.[262] East Indian globe thistle (*Sphaeranthus indicus*) is another widely used medicinal plant. Preclinical cell and animal studies show extracts of *S. indicus* support healthy glucose and lipid metabolism as well as counteract inflammatory processes.[263]

A clinical trial randomized 57 overweight participants to 400 mg of a combination of *S. indicus* and mangosteen extracts or placebo. The extract combination comprised 300 mg of *S. indicus* and 100 mg of mangosteen in a 3:1 ratio (300 mg and 100 mg, respectively). Study participants took the placebo or the herbal combination twice daily for 16 weeks. subjects given the botanical combination lost an average of about 11 pounds and about 4 inches in both waist and hip circumference. On the other hand, those who took the placebo lost about 2 pounds and about 2 inches from their waist and hip circumferences. In addition, those who took the mangosteen and *S. indicus* extracts had greater reductions their levels of total cholesterol, LDL-cholesterol, and triglycerides than those who took the placebo.[264]

Other placebo-controlled trials have similarly demonstrated the efficacy of *S. indicus* plus mangosteen for weight loss in overweight and obese subjects.[265,266] In an eight-week randomized trial including 56 obese participants, those given the botanical combination lost about 11 pounds and nearly 5 inches in waist circumference. Those taking a placebo lost only about 3 pounds and 3 inches of waist circumference.[265] Another trial, involving 95 obese subjects, found supplementation with the botanical combination for eight weeks resulted in an average weight loss of almost 12 pounds. The placebo group lost only about 3 pounds. Those receiving the botanical compound also lost an average of nearly 5 inches in waist circumference and almost 3 inches in hip circumference, while those taking the placebo lost about 2 inches of waist circumference and just over 1 inch of hip circumference.[266] In all three of these trials, both the herbal combination and placebo groups were limited to

2,000 calories per day and walked 30 minutes five times per week.[264,265]

Conjugated linoleic acid. Conjugated linoleic acid (CLA) is the name given to a specific group of fatty acids derived from linoleic acid. Linoleic acid is an essential omega-6 fatty acid found in many plant foods, while CLA is produced through bacterial fermentation in the digestive tract of ruminant animals such as cows, goats, and sheep. Thus, some major food sources of CLA are beef and dairy products. CLA can also be synthetically produced from oils high in linoleic acid, such as soy, corn, safflower, and sunflower oils.[268,269]

CLA appears to promote fat breakdown, inhibit fatty acid production and storage, and reduce inflammatory signaling in fat tissue. It has also been shown to work at the epigenetic level, inducing fat browning by altering fat cells' production of enzymes involved in fat and glucose metabolism.[269,270] Although evidence from clinical trials is mixed, multiple randomized controlled trials have reported reductions in fat mass and body weight in overweight and obese subjects after taking 3–6 grams of CLA per day over time periods ranging from 12 weeks to two years.[268,269]

Additional Support

Lipoic acid. Alpha [α]-lipoic acid (ALA) is an organosulfur antioxidant produced by plants, animals, and humans. ALA is primarily found in the mitochondria of cells, where it facilitates various enzymatic reactions necessary for cell function. Two enantiomers (ie, mirror-image molecular structures) of ALA exist: "R" and "S." The R form of ALA is the primary natural form found in foods, such as meat and vegetables, and produced in humans. Therefore, the R-isomer of ALA is believed to be the form that exerts most of the biologic effects of ALA. In contrast, the S-isomer is not generally found in nature and is instead synthesized through chemical processes.[320] In some supplements, ALA may be provided in a mixture of R and S forms, called a racemic mixture. Other supplements provide 100% R-ALA, which could potentially maximize the weight loss benefits of ALA supplementation.[320,321]

ALA—and particularly R-ALA—has been shown to be effective for improving weight loss. In a 2020 randomized trial, 24 weeks of supplementation with R-ALA in 81 overweight adults with a BMI of 25 kg/m^2 or higher and elevated plasma triglyceride levels resulted in significantly more weight loss than placebo, with a relative reduction in BMI of 0.8 kg/m^2. The effect was more pronounced in obese participants with BMI of 35 kg/m^2 or higher. These participants had 4.8% more weight loss and 8.6% more body fat loss than those treated with placebo.[321] Racemic mixtures of R- and S-ALA have also shown benefit for weight loss; however, these changes may not be as large as those seen in the clinical trial evaluating R-ALA alone, with weight loss relative to placebo reported at 2.1% in one randomized controlled trial.[322-324] Meta-analyses of randomized controlled trials revealed that ALA supplementation results in weight loss of 0.69 to 1.27 kg (1.5 to 2.8 lb.) and BMI reductions of 0.38 to 0.43 kg/m^2.[325,326]

For people treated with medications that may cause weight gain, such as antipsychotics used to treat schizophrenia, ALA has been shown to have a protective effect. In a study of 22 overweight, clinically stable patients with schizophrenia, 600 to 1,800 mg ALA per day for 12 weeks resulted in significantly greater levels of weight loss and visceral fat levels relative to placebo.[327] In an open-label study, participants using antipsychotics who were treated with 1,200 mg ALA lost an average of 2.2 kg (4.8 lb.).[328]

Although the mechanism of action by which R-ALA exerts its weight loss effects is unclear, there is some evidence that these effects are linked to antioxidant effects and metabolic changes. In a randomized controlled trial, treatment with R-ALA increased the expression of the antioxidant gene *HMOX1* 22% more than placebo.[321] ALA has also been shown to substantially decrease levels of several inflammatory markers, including interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α).[329] Many of these inflammatory markers are produced by fat tissue and contribute to the chronic inflammatory state that has been associated with obesity.[329,330] ALA, alone and in combination with other ingredients, has also been shown to exert favorable metabolic changes, including reductions in glucose and insulin levels.[331-333] ALA may also affect cardiovascular risk factors, with one study showing that ALA treatment improved vascular tone in obese or overweight children and adolescents.[333]

Coffee. Both green and roasted coffee beans contain active constituents that may help promote healthy weight loss, including caffeine, a family of polyphenols called chlorogenic acids, and prebiotic compounds called mannooligosaccharides.[271,272] Coffee drinking has been linked to decreased risk of an array of chronic health

problems including heart disease, type 2 diabetes, and obesity, as well as lower risk of death from any cause, in multiple observational studies.[271] A review and meta-analysis of clinical trials examining the health effects of coffee determined three to four cups of coffee per day is associated with the greatest overall health benefit.[271] A recent study found coffee consumption was only correlated with lower body weight, BMI, and body fat in subjects with a particular variant of a gene involved in adipose tissue thermogenesis (heat generation).[273]

Green coffee beans, which are higher in chlorogenic acids than roasted beans, have been investigated for their ability to increase weight loss. A meta-analysis of 16 randomized controlled trials found supplementing with green coffee extract significantly reduced BMI, and had a greater weight-reducing effect in participants with a BMI indicating overweight or obesity (≥25 kg/m^2).[274] A randomized controlled trial in 52 normal-weight participants found drinking a beverage made from green and roasted coffee three times daily for eight weeks led to reductions in percent body fat, blood pressure, insulin resistance, blood glucose levels, and triglyceride levels, suggesting this combination may help prevent or treat metabolic syndrome.[275]

Whey protein. Whey protein supports the growth of muscle tissue, improves satiety signaling, and promotes thermogenesis.[276] Clinical trials indicate whey protein can help preserve lean body mass during body weight and fat mass reduction through diet and exercise in people with overweight and obesity.[277,278] A randomized controlled trial in women who regained weight after gastric bypass surgery found supplementing with whey protein (0.5 grams/kg of ideal body weight) for 16 weeks promoted greater body weight and fat mass reductions with no loss of lean body mass. [279] A meta-analysis of nine controlled trials determined whey protein not only enhanced weight and fat loss, it also decreased cardiovascular risk by improving lipid levels, blood glucose levels, and blood pressure.[280] Some studies indicate whey protein may attenuate the increase in appetite that usually accompanies calorie reduction and weight loss.[278]

Probiotics. Probiotics are microorganisms used to modulate the gut microbiome and promote health. Numerous clinical trials have investigated the potential of probiotic supplements to promote weight loss and prevent and treat metabolic disorders. Meta-analyses and reviews of randomized controlled trials show probiotic supplements containing various *Lactobacillus* and *Bifidobacterium* strains can help reduce body weight, BMI, waist circumference, fat mass, and percent body fat.[281-285] In addition, probiotic use is associated with improvements in cholesterol levels and markers of glucose metabolism.[281,284] One analysis determined the most robust effects have been associated with supplements containing two or more strains at modest doses (below 10 billion colony forming units [CFUs] per day).[281]

An abundance of the gut bacterium *Akkermansia muciniphila* has been correlated with metabolic health, and low amounts are found in people with obesity. A heat-killed form of *A. muciniphila* has shown promising effects in pilot trials in obese mice and humans, suggesting its potential as a therapeutic aid in weight loss.[286,287]

Fish oil. Omega-3 fatty acids from fish (mainly eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) have anti-inflammatory effects, and evidence suggests they may promote healthy metabolism by reducing insulin resistance and inflammatory signaling by adipose tissue.[288] Fish oil and omega-3 fatty acids may also increase satiety, improve regulation of leptin and adiponectin, and trigger epigenetic mechanisms associated with reduced growth of adipose tissue.[289,290] In a placebo controlled trial that included 65 overweight and obese participants with depression, taking 1,080 mg EPA and 720 mg DHA daily for 12 weeks decreased depression symptoms and enhanced weight loss.[291] A meta-analysis of randomized controlled trials determined omega-3 fatty acids from fish may induce reductions in waist circumference and triglyceride levels, indicating improved metabolic health, in individuals with overweight and obesity.[292]

Capsaicin. Capsaicin is an active compound and the primary capsaicinoid found in chili peppers (*Capsicum annuum*). It is responsible for their spicy taste. Capsaicin activates the sympathetic (fight-or-flight) part of the nervous system, reducing appetite while increasing thermogenesis, energy expenditure, and fat tissue breakdown (lipolysis).[293,294] Through these effects, capsaicin may counter the body's adaptive response to reduced calorie intake and enhance weight loss. Furthermore, it is thought to contribute to healthy metabolism by promoting normal sleep patterns through its analgesic action.[294]

A meta-analysis of eight randomized controlled trials with a combined total of 191 subjects found daily intake of at least 2 mg of capsaicin reduced appetite.[295] Another review noted capsaicin and related chili pepper

compounds can reduce appetite, calorie consumption, and abdominal adipose tissue mass.[296] In a placebo-controlled trial with 50 overweight women, those who received 50 mg capsaicin, along with 250 mg green tea and 100 mg ginger, twice daily for eight weeks lost significantly more weight than those who received placebo.[297] In a study investigating the short-term effects of capsaicin, a single 2 mg dose increased REE after a meal in obese young adults.[298]

A standardized extract of red chili peppers, known as Capsifen, has been shown to promote energy expenditure and weight loss. The capsaicinoids in Capsifen are encapsulated by a fenugreek-derived galactomannan fiber to provide sustained release, enhance bioavailability, and reduce gastrointestinal discomfort.[401,402] In a placebo-controlled trial with 24 overweight subjects, supplementation with 200 mg Capsifen once daily (providing 4 mg of capsaicinoids) decreased body weight by 2.1% and BMI by 2.2% compared with placebo. Participants in the Capsifen group also reported an improvement in uncontrolled eating and a reduction in appetite.[401,402,403]

Tryptophan and 5-HTP. Tryptophan is an essential amino acid and a precursor to serotonin, a neurotransmitter produced by gut microbes, intestinal cells, and brain cells.[299] Serotonin is involved in gastrointestinal function as well as mood, appetite, and energy balance regulation. In the brain, higher serotonin levels signal satiety and lower levels signal the desire to eat.[300] Calorie-restricted diets, while successful at reducing weight, have been shown to reduce circulating tryptophan levels by 15–21%. This may lead to reduced serotonin synthesis, worsening of mood, increased carbohydrate cravings, and an increased chance of weight regain.[301] In a study of 10 healthy, young, normal-weight men, 2- and 3-gram doses of tryptophan reduced energy intake compared with placebo when taken before a buffet-style meal.[302] In a study that included 10 obese subjects, 1, 2, or 3 grams of tryptophan, taken one hour before a meal, reduced calorie consumption. Its appetite-reducing effect increased as the dose of tryptophan increased. [303]

5-hydroxytryptophan (5-HTP) is a breakdown product made from tryptophan along the pathway that results in serotonin. Several clinical trials have reported beneficial effects of 5-HTP on weight loss.[304-306] In one randomized controlled trial that included 25 overweight patients with type 2 diabetes, 750 mg 5-HTP daily for two weeks reduced calorie consumption and body weight compared with placebo.[305]

Pine nut oil. Pine nut oil, which contains a constituent called pinolenic acid, has been shown to reduce food intake. When doses of pine nut oil ranging from 2 to 6 grams were given to overweight female subjects prior to a buffet-style meal, food consumption was reduced up to 9% compared with placebo. The researchers suggested this reduced food intake was attributable to pine nut oil's satiating effects, which may be mediated via modulation of cholecystokinin (CCK) and other appetite-suppressing compounds.[307] In a placebo-controlled crossover trial, 18 overweight women were given 3 grams of a pine nut oil extract or placebo before breakfast and were monitored for four hours. The treatment group reported lower appetite and had higher levels of hormones that suppress appetite during the four hours following pine nut oil compared with placebo.[308] Pine nut oil has been found to prevent diet-induced weight gain, fat mass gain, and abdominal fat accumulation in animals studies.[309,310] Some evidence suggests pine nut oil increases thermogenesis and improves metabolic activity in adipose tissue.[311]

L-carnitine. L-carnitine, a non-essential amino acid made in the body and obtained in the diet from meat and dairy foods, plays a key role in moving fatty acids across mitochondrial membranes and thereby facilitating fat metabolism.[312] A meta-analysis of 43 controlled trials with a combined total of 2,703 participants found supplementing with at least 2 grams per day of L-carnitine reduced body weight, body fat mass, and BMI in those with overweight and obesity.[313] Because L-carnitine reduces oxidative stress, supports healthy mitochondrial function, and exhibits cell-protective effects, it may also help prevent some of the many health problems associated with overweight and obesity.[312]

Coleus forskohlii. *Coleus forskohlii* is a medicinal plant from the Ayurvedic tradition. Its historical uses include treatment of high blood pressure, heart failure, eczema, digestive colic, respiratory ailments, painful urination, insomnia, and seizures.[314] Preclinical research shows forskolin, an active compound from Coleus, reduces inflammatory signaling by fat cells.[315]

In preliminary research, six overweight women treated with 250 mg *Coleus forskohlii* extract, standardized to contain 10% forskolin, twice daily for eight weeks lost an average of 10 pounds of body weight and 8% of body fat.[316] In a placebo-controlled trial in 23 overweight women, those receiving 250 mg *Coleus forskohlii* standardized

extract twice daily for 12 weeks lost 0.6 kg of body weight while those receiving placebo gained 1.3 kg; although the difference was not statistically significant, it did indicate a possible benefit of Coleus in slowing weight gain.[317] Another 12-week trial compared the effects of 250 mg *Coleus forskohlii* standardized extract twice daily to placebo in 30 adults with overweight or obesity eating a reduced-calorie diet. Coleus did not differ from placebo in its effect on body weight, but was associated with greater improvement in insulin levels and insulin resistance, suggesting it may have a role in improving metabolic health.[318]

Update History

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References