Obesity and Weight Loss

A startling **60 – 75%** of the adult population in the United States is overweight or obese (American Heart Assc. 2012). Around the world, the prevalence of obesity has nearly *doubled* from 1980 to 2008 (Stevens 2012).

Being overweight or obese significantly increases the risk of multiple **debilitating diseases** including cardiovascular disease, arthritis, high blood pressure, and malignancies such as breast, prostate, pancreatic and colon cancer (Aleksandrova 2013; Giles 2012; Allott 2012; Gribovskaja-Rupp 2011). Excess body weight also affects mobility, interferes with restful sleep, contributes to digestive disorders, and can contribute to an overall lower quality of life than that enjoyed by lean individuals (Schrager 2007; Sung 2011; Nguyen 2008; CDC 2011). Obesity results in shortening of the life span by an average of **eight to 10 years** compared with people at normal weight. For every **33 extra pounds**, risk of early death increases by around **30%** (OECD 2012).

For many aging obese individuals, the struggle to achieve a healthy body weight becomes a veritable battle against biology as a number of metabolic processes promote weight gain despite genuine efforts to decrease food consumption and increase energy expenditure (Cohen 2012; Müssig 2010; Biondi 2010).

Scientific investigations have shed light on the biology of weight loss in recent times. It turns out the battle against the bulge is much more complex than the overly simplistic “eat less food to lose weight” message often promoted by government health agencies.

In 2009, Life Extension described the ***Nine Pillars of Successful Weight Loss***. Each of the nine pillars represents a fundamental insight into sustainable weight. If any weight loss strategy is to be successful, it must evolve beyond the conventional cliché that weight loss only requires a reduction in food consumption. Instead, successful weight management requires a paradigm that acknowledges the multifactorial nature of obesity.

The ***Nine Pillars of Successful Weight Loss***that should not be overlooked if healthy weight management is to be achieved are:

- ***Restore insulin sensitivity***
- ***Restore youthful hormone balance***
- ***Control rate of carbohydrate absorption***
- ***Increase physical activity***
- ***Restore Brain Serotonin/ Suppress Hunger Signals***
- ***Restore resting energy expenditure rate***
- ***Restore healthy adipocyte (fat cell) signaling***
- ***Inhibit the lipase enzyme***
- ***Eat to live a long and healthy life***

This protocol will detail the biological underpinnings of obesity and weight gain. Consideration will be given to each **pillar of successful weight loss** in the context of obesity risk factors in order to highlight the inadequacies of typical weight loss strategies. Methods of utilizing novel natural compounds and strategically incorporating some pharmaceutical options to support critical metabolic factors for long-term weight management will be discussed.

Obesity and Weight Loss

Regulation of Body Weight

Our system of energy balance evolved to ensure that a healthy person maintained adequate reserves of body fat to sustain life through repeated times of food scarcity, including famine. Food energy abundance is a relatively recent phenomenon, quite dissimilar to the vast majority of time over the past 100000 years. In fact, body weight maintenance is achieved by the very complex and interrelated interaction of neurological and hormonal factors, with the goal of increasing appetite and preserving body fat when energy stores are low. Within the brain, a region called the *hypothalamus* monitors and integrates neurological signals and modulates appetite accordingly. Sensory cells located within the stomach walls that detect stretching of stomach tissue can directly signal satiety to the brain through nerve impulses. Indirectly, blood levels of glucose, fatty acids, and amino acids (components of proteins) stimulate the perception of satiety in brain centers and depress eating behavior. Additionally, a variety of hormones released at various levels of the gastrointestinal tract perform numerous functions in the balance of energy intake and

utilization. *Insulin* (released from the pancreas and critical for the uptake of glucose into cells) and *cholecystokinin (CCK)* (secreted by the upper part of the small intestine and important for triggering release of digestive enzymes and bile) are also potent satiety signals (Marieb 2010).

In addition, fat stores in the body are able to relay the overall state of energy storage to the brain through the secretion of the hormone ***leptin*** (Marieb 2010). Leptin is secreted into the blood by adipose (fat) cells in proportion to their levels of stored fats. It travels to the brain and acts upon the hypothalamus, stimulating the release of neurotransmitters that signal satiety, and suppressing those that signal hunger. Thus, leptin released by adipose tissue provides the brain with information on long-term energy economy, and allows it to adjust food intake accordingly (Begg 2012). However, this intricate system of appetite control can become perturbed in obesity, as excess fat stores contribute to chronically elevated leptin levels. This leads to down regulation of cellular sensitivity to the effects of leptin, a physiologic state known as ***leptin resistance***. Weight loss efforts put forth by obese individuals may be undermined by failure of the leptin system to suppress their appetite, resulting in excessive hunger (Myers 2010).

Another hormone derived from fat cells, called ***adiponectin***, is an *anti-obesity* signaling molecule; adiponectin signaling is disrupted in obesity-related diseases and states of insulin resistance (Shehzad 2012). Evidence suggests that leptin and adiponectin can work together to combat insulin resistance (Yamauchi 2001; Kadowaki 2011; Siasos 2012). ***Optimizing fat cell signaling*** thus represents an important aspect of any comprehensive weight-loss strategy.

Resting energy expenditure (REE) also influences weight gain and progression to obesity. REE is the rate at which metabolic activity burns calories during periods of rest or inactivity. Having a low REE may contribute to weight gain or make it difficult to lose weight. Studies show that REE is directly related to serum adiponectin levels, and that higher leptin levels (as occurs in leptin resistance; see below) are associated with decreased REE (Brusik 2012). Aging is also associated with decreased REE (Hunter 2001; Bosy-Westphal 2003). These findings suggest that boosting REE could be a valuable strategy to mitigate age-related weight gain.

Obesity and Weight Loss

Causes and Risk Factors for Obesity

Weight gain and progression to obesity can be caused by energy imbalances (Hill 2012).

Aging can negatively affect the balance of energy input and expenditure in several ways. The natural aging process is associated with hormonal changes, particularly *decreases in sex and thyroid hormones*, which contribute to a decrease in metabolism and energy expenditure. Advancing age is also associated with reduced insulin sensitivity, which may interfere with appetite control (Begg 2012; Paolisso 1999). With age also comes a decrease in physical activity, which further reduces energy expenditure. Only about a quarter of Americans aged 65 to 74 exercise daily; this drops to less than 1 in 10 at age 85 (AoA Statistics 2008). Obesity and decreased mobility in the aging individual may have reciprocal effects on one another; age-related increases in weight and reductions in muscle mass lead to decreased mobility and energy expenditure. In a review of 28 population studies of older obese individuals, all but one showed significant associations between obesity and reduced mobility (Vincent 2010).

SEX HORMONE AND THYROID HORMONE INSUFFICIENCIES/ IMBALANCES

Levels of sex hormones (such as testosterone and dehydroepiandrosterone [DHEA]) decline with age in both genders. This may lead to an increase in fat mass, reduction in lean body mass or central fat redistribution (Apostolopoulou 2012; Villareal 2004). Similarly, declining ***thyroid hormone levels*** are associated with reduced metabolic rate and thus obesity (Biondi 2010).

In men, free testosterone levels sharply declines between the ages of 40 and 80. Both free and total testosterone levels are significantly lower in overweight and obese men compared to those with weights in a normal range across all ages (Wu 2008). Men with low testosterone levels (hypogonadism) develop increased fat mass, and testosterone replacement therapy in hypogonadal men reduced fat mass by 6% in one study (Mårin 1995; Kaufman 2005).

Obesity and low testosterone have a complex relationship; low testosterone can be considered both a cause *and* consequence of obesity (Wu 2008). In men, increases in fat mass may also increase the ***conversion*** of testosterone to **estrogen** by the enzyme ***aromatase*** (Vermeulen 2002). While this conversion is a normal phenomenon, aromatization occurs more readily in fat tissue, and is increased by obesity, age, inflammation, insulin, leptin, and stress (Williams 2012). Thus, in older men with excessive abdominal fat, the ratios of testosterone to estrogen are lower than in younger men. Elevated estrogens, similar to low testosterone levels, are associated with increased abdominal fat (Vermeulen 2002). If a blood test reveals elevated estrogen (estradiol) levels in a man, a physician may prescribe an ***aromatase-inhibiting drug*** such as anastrozole (Arimidex®).

In women, estrogen levels decline suddenly with menopause. Hormone replacement has shown modest increases in lean body

mass and reductions in waist circumference and abdominal fat in some, but not all studies of post-menopausal women (Salpeter 2006; Mayes 2004; Norman 2000).

The thyroid is a central regulator of metabolism; it integrates signals from the brain and secretes thyroid hormone (thyroxine or T4) to influence metabolism in a variety of tissues (Biondi 2010). Thyroid dysfunction can affect body weight and composition, body temperature, and energy expenditure independent of physical activity. Depressed thyroid function (hypothyroidism) has been associated with decreased thermogenesis (conversion of stored energy into heat) and metabolic rate, and weight gain (Biondi 2010).

Clinical studies have shown that treatment of hypothyroidism with thyroxine may lead to weight loss, and population studies suggest that low T4 levels and high TSH levels are both associated with higher BMI (Asvold 2009). Depressed thyroid activity is also more common as people age; hypothyroidism in the general population is 3.7%, but is 5 times more common in individuals aged 80 or older when compared to 12 to 49 year-olds (Aoki 2007).

A significant number of patients with morbid obesity display elevated ***thyroid stimulating hormone*** (TSH) levels. TSH is produced in the brain by the pituitary gland, then travels to the thyroid and stimulates the production of thyroid hormone. Increased blood levels of TSH may indicate thyroid dysfunction and are associated with the progression of obesity (Rotondi 2011). For example, in one Norwegian study of over 27000 individuals older than 40, TSH correlated with BMI: for every unit that TSH increased, BMI increased by 0.41 in women and 0.48 in men (Asvold 2009).

INSULIN RESISTANCE AND/OR LEPTIN RESISTANCE

In addition to being a result of obesity, elevated levels of the hormones leptin and insulin in obese individuals may be indicative of a ***resistance*** to their activities. Insulin is a hormone that helps facilitate cellular uptake of glucose, primarily in the muscles, liver, and adipose tissue. When insulin resistance develops, glucose levels are no longer efficiently controlled by the action of insulin and blood levels become elevated, predisposing the insulin-resistant individual to several chronic diseases associated with aging (NDIC 2011). Moreover, while higher levels of both leptin and insulin normally suppress the desire to eat and stimulate energy expenditure, they are unable to perform this function in resistant individuals (Hagobian 2010).

- ***Insulin resistance*** is a consequence of sustained hyperinsulinemia (high insulin levels) and is complicated by chronic inflammation and obesity (Sung 2011; Ortega Martinez de Victoria 2009; Weisberg 2003). Strategies aimed at **improving insulin sensitivity** are an integral part of the *nine pillars of successful weight loss*. These strategies can include use of a low-cost prescription drug called ***metformin***, which is approved for the treatment of type 2 diabetes and can also help reduce body fat, and natural compounds that help promote healthy insulin signaling (see below) (Despres 2003; Berstein 2012).
- Similarly, ***leptin resistance*** results from sustained periods of high leptin secretion associated with high fat stores. In obese individuals, leptin may lose its ability to be transported into the brain (Jequier 2002). An interaction between leptin and the inflammatory biomarker **C-reactive protein (CRP)** in cell culture suggests a role of chronic inflammation in leptin resistance and the loss of appetite control. In an animal model of obesity, infusions of CRP countered the appetite-suppressing effects of leptin. The scientists who conducted these experiments postulated that CRP may bind to leptin and inhibit its physiologic functions (Chen 2006). Based upon these findings, interventions that ease inflammation, such as the plant compound ***curcumin*** and ***omega-3 fatty acids*** from fish oil, may help combat the detrimental effects of leptin resistance (Yu 2008; Shao 2012; Selenscig 2010; Tsitouras 2008). In addition, the mango-like fruit of ***Irvingia gabonensis***, a tree found in Africa, has also been shown to combat leptin resistance and lower CRP levels (Ngondi 2009; Oben 2008).

OVEREATING AND DINING OUT

Increases in daily average food consumption significantly contribute to weight gain in the United States (Swinburn 2009). Data from the National Health and Nutrition Examination Survey (NHANES) show a significant increase in average daily energy intake between 1971 and 2000, amounting to 168 calories per day for men, and 335 calories per day for women. Without increased expenditure, this represents potential theoretical weight gains of 18 pounds per year for men and 35 pounds per year for women (Hill 2012). A separate study estimates a 350 calorie per day increase for children (about one can of soda and a small order of French fries) and a 500 calorie per day increase for adults (about one large hamburger) over our daily calorie intake in the 1970s (Swinburn 2009).

Eating outside of the home can encourage overconsumption, especially of calorie-dense, nutrient-poor foods. Spending on food away from home has almost doubled in the last half century, rising to almost one-third of a person's calories in the United States (Cohen 2012). Half of Americans eat out 2 or more times per week, and 20% of males and 10% of females eat commercially prepared foods 6 or more times per week (Kant 2004).

People have a decreased ability to make healthy food choices away from home for several reasons. They tend to increase their consumption proportional to the amount of food they are served, and average portion sizes have been steadily increasing over the last 30 years (Rolls 2006; Nielsen 2003). Choices for foods consumed away from home are also influenced by marketing, and the relative abundance of high-calorie, low-nutrient choices compared to healthier ones. Fast food restaurants may also play into

inherent weaknesses in human cognitive capacity. Reasoned decisions are time-consuming; therefore, people often depend on automatic choices when they are hungry. When glucose levels are low, or a person is distracted or preoccupied, they tend to make less healthy food choices and are often unaware of the quality of food they have consumed. Although attempts have been made to provide point-of-sale nutritional labeling in many restaurants, there has been limited evidence of effect (Cohen 2012).

In an effort to avoid the caloric excess to which so many restaurant-goers succumb, suppression of *hunger signals* is likely to be of great benefit. To this end, several natural compounds, including ***saffron extract***, ***L-tryptophan***, and ***pine nut oil***, as well as the pharmaceutical drug *lorcaserin (Belviq®)* may be of benefit; each of these compounds is discussed in detail later in this protocol.

Another strategy to counter the excessive amount of calories encountered when dining out involves *"**preparing your body to eat**"* by taking measures to reduce the rate at which fats and carbohydrates are **absorbed**. Supplementing with ***green coffee extract*** before meals can slow carbohydrate absorption, helping to reduce after-meal spikes in glucose levels (Vinson 2012). These after-meal glucose spikes inflict damage to cells via multiple mechanisms and have been linked to cardiovascular disease, cancer, Alzheimer's disease, and kidney failure. Also, a pharmaceutical drug called ***orlistat***(Alli®, Xenical®) can help reduce the absorption of fats by inhibiting an enzyme called *lipase* (see below) (McClendon 2009; Smith 2012). Targeting after-meal spikes in blood levels of glucose (postprandial glycemia) and fatty acids (postprandial lipemia) is a critical step towards averting cardiovascular disease, for which obesity is a leading risk factor (Blaak 2012; Strojek 2007; Sahade 2012; Jackson 2012).

ALTERED SEROTONIN SIGNALING, CHRONIC STRESS, AND APPETITE

Low levels of the neurotransmitter serotonin, typically associated with depression, may be associated with weight gain. Serotonin interacts with receptors in the brain that regulate feeding behavior (Sargent 2009). When brain levels of serotonin are increased, the desire to eat is decreased; as serotonin levels drop, appetite is stimulated (Lam 2010). Mimicking the serotonin-receptor interaction has been the target of several anti-obesity drugs developed over the last 4 decades (Ioannides-Demos 2011). Moreover, studies have shown that obese individuals have low levels of *tryptophan*, a precursor to serotonin, in their blood (Breum 2003). These findings suggest that ***restoring serotonin signaling*** may be a way to combat hunger cravings that can preclude weight loss.

While stress is an important adaptation essential for survival, long-term stress can be damaging. ***Chronic stress*** can compromise the function of hormonal, gastrointestinal, and immune systems (De Vriendt 2009). Exposure to chronic stress has been associated with obesity and metabolic syndrome in human and animal studies (Müssig 2010). Stress increases production of the hormone *cortisol*, which when combined with access to abundant food, promotes the development of visceral obesity (Björntorp 1991).

Cortisol promotes weight gain in several ways. Visceral fat tissue contains a high number of cortisol receptors and responds to circulating cortisol by increasing fat cell growth and lipid storage (Fried 1993). Cortisol may also stimulate the neurotransmitters that signal hunger and decrease the activity of leptin, which signals satiety (Björntorp 2001). Activation of the stress response appears to stimulate the human appetite for highly palatable, energy-dense foods (Torres 2007), which may explain the association between emotional stress and increased food intake (Müssig 2010). A comprehensive overview of strategies to mitigate the negative effects of stress is available in the Stress Management protocol.

IMPORTANT OBESITY-RELATED TESTS

Knowledge of one's overall risk enables the selection of an appropriate weight loss strategy. For example, sufficient levels of thyroid hormone are necessary to minimize obesity risk; thyroid insufficiency can be treated with hormone replacement. Low levels of testosterone and estrogen are associated with weight gain in men and women, respectively, and sufficient DHEA is essential for sex hormone production. High cholesterol, high blood pressure, and chronic inflammation are all risk factors for one or more of the obesity-related diseases.

TEST	STANDARD REFERENCE RANGE	OPTIMAL LEVEL
Thyroid-stimulating hormone (TSH)	0.4 – 5.0 µIU/mL	1.0 – 2.0 µIU/mL
Free thyroxine (T4)	0.82 – 1.77 ng/dL	Upper third of reference range
Free triiodothyronine (T3)	2.0 – 4.4 pg/mL	3.4 – 4.2 pg/mL
Total cholesterol	100 – 199 mg/dL	160 – 180 mg/dL
LDL cholesterol	0 – 99 mg/dL	<100 mg/dL

HDL cholesterol	>39 mg/dL	>50 mg/dL
Triglycerides	0 – 149 mg/dL	<80 mg/dL
Sex hormone binding globulin (SHBG)	*Men* Age 20 – 49: 16.5 – 55.9 nmol/L Age >49: 19.3 – 76.4 nmol/L	30 – 40 nmol/L
	Women Age 20 – 49: 24.6 – 122 nmol/L Age >49: 17.3 – 125 nmol/L	60 – 80 nmol/L
Dehydroepiandrosterone sulfate (DHEA-S)	*Men* Age 20 – 24: 211 – 492 µg/dL	350 – 490 µg/dL
	Women Age 20 – 24: 148 – 407 µg/dL	275 – 400 µg/dL
Total testosterone	*Men* 348 – 1197 ng/dL	700 – 900 ng/dL
	Women *8 – 48 ng/dL*	35 – 45 ng/dL
Free testosterone	*Men* Age 20 – 29: 9.3 – 26.5 pg/mL	20 – 25 pg/mL
	Women 0.0 – 2.2 pg/mL	1 – 2.2 pg/mL
Estradiol	*Men* 7.6 – 42.6 pg/mL	20 – 30 pg/mL
	Women Premenopausal: varies Postmenopausal: <6.0 – 54.7 pg/mL	Premenopausal: varies Menopausal/ postmenopausal: 30 – 100 pg/mL
Progesterone	*Women* Premenopausal: varies Postmenopausal: 0.1 – 0.8 ng/mL	Premenopausal: varies Menopausal/ postmenopausal: 2 – 6 ng/mL
		Men

C-reactive protein (high sensitivity)	Low risk: ≤1.0 mg/L	<0.55 mg/L *Women* <1.5 mg/L
Insulin	2.6 – 24.9 µIU/mL	<5 µIU/mL
Glucose (fasting)	65 – 99 mg/dL	70 – 85 mg/dL
Blood Pressure (optimal)	≤120 / 80 mmHg	115 / 75 mmHg

*TSH=thyroid-stimulating hormone; LDL=low-density lipoprotein; HDL=high-density lipoprotein; DHEA-S=dehydroepiandrosterone sulfate; µIU/mL=microunits per milliliter; mg/dL=milligrams per deciliter; mg/L=milligrams per liter; µg/dL=micrograms per deciliter; ng/dL=nanograms per deciliter; ng/mL= nanograms per milliliter; pg/mL= picograms per milliliter; nmol/L=nanomole per liter; mmHg=millimeters of mercury.

Life Extension offers comprehensive blood test panels designed specifically to assess factors that may influence weight loss. Two versions are available; one for men (**Male Weight Loss Panel**) and one for women (**Female Weight Loss Panel**).

Obesity and Weight Loss

Consequences of Obesity

CHRONIC INFLAMMATION

Obese individuals have higher levels of inflammatory markers. Sustained, low-level inflammation has been implicated in the pathogenesis of several significant diseases, including heart disease, cancer, diabetes, and Alzheimer's disease (Hartaigh 2012; Touvier 2013; Cruz 2012; Holmes 2012). Fat tissue can act much like an endocrine (hormonal) gland, storing and secreting hormones and ***cytokines*** (signaling proteins involved in triggering the inflammatory response) into circulation and affecting metabolism throughout the body. Abdominal visceral fat cells may produce inflammatory molecules such as *tumor necrosis factor alpha (TNF-α)* and *interleukin-6* at levels sufficient to induce an inflammatory response (Trayhurn 2005; Schrager 2007). In overweight individuals, abdominal fat cells may be producing up to **35%** of the total interleukin-6 in the body (Mohamed-Ali 1997). Fat tissue can also be infiltrated by macrophages (cells of the immune system that mediate inflammation), which secrete pro-inflammatory cytokines. This accumulation of macrophages appears to be proportional to BMI, and may be a major cause of low-grade, systemic inflammation and insulin resistance in obese individuals (Ortega Martinez de Victoria 2009; Weisberg 2003).

CANCER

Obesity is a risk factor for several types of cancer. White adipose tissue (ie, "bad fat") can secrete a variety of hormones and growth factors that may stimulate cancer cell growth. Experimental cancer models in animals suggest that tumors may recruit healthy cells from elsewhere in the body (including white fat) to build the blood vessels critical for the progression of tumor growth (Zhang 2009).

Postmenopausal breast cancer risk increases with obesity, possibly through effects on systemic inflammation, or increases in circulating insulin and insulin-like growth factor 1 (IGF-1), both of which can promote tumor growth (Brown 2012). Obesity increases gastric and esophageal cancer risk; mechanisms for this also include increased insulin and IGF-1 signaling, as well as increased incidence of gastroesophageal reflux disease (GERD) (Li 2012). Population studies have implicated obesity as a risk factor for liver cancer (hepatocellular carcinoma). Along with obesity, nonalcoholic fatty liver disease (NAFLD), an increase in fat stores in the liver, is a hallmark of metabolic syndrome; the inflammation and liver fibrosis associated with fatty liver can progress into hepatocellular carcinoma (Shen 2012). Central obesity has been reported as a risk factor for colorectal cancer. Comprehensive reviews have estimated that colorectal cancer risk increases by 7% as BMI increases by 2 points, or 5% for each inch of waist circumference above normal (Sung 2011). Again, circulating growth factors and inflammatory cytokines are thought to contribute to the increase in abnormal cell proliferation. Some evidence suggests that the satiety hormone leptin may also play a role in colorectal cancer progression; cell culture studies have shown that leptin can increase the growth and proliferation of colon adenocarcinoma cells (Jaffe 2008).

Obesity may increase thyroid cancer risk; the rise in thyroid cancer incidence parallels that of obesity, although studies that explore the relationship between these two diseases have conflicting results (Fröhlich 2012). The effect of obesity on thyroid cancer may be due to increased insulin/IGF-1 expression; thyroid stimulating hormone levels are sensitive to insulin and IGF-1 levels, and all three hormones work together to stimulate thyroid activity. Increases in IGF-1 have been correlated with increased thyroid tumor diameter, and insulin resistance has been shown to be more frequent in thyroid cancer patients than in cancer-free controls (Mijovic

2011).

INSULIN RESISTANCE

Insensitivity of tissues to circulating insulin (ie, insulin resistance) is a hallmark of type 2 diabetes and metabolic syndrome and has obesity as a major risk factor. While moderate post-meal increases in insulin are normal and signal tissues to take up glucose and store it as glycogen and fat, overconsumption can lead to accelerated increases in fat mass and excessive insulin production (ie, hyperinsulinemia). Sustained hyperinsulinemia activates inflammatory pathways, which can lead to insulin resistance; although the mechanisms of this phenomenon are not clearly understood (Sung 2011; Bastard 2006). The appetite suppressing activity of insulin may be abolished in insulin-resistant obese individuals (Hagobian 2010), which may promote further weight gain by removing this important appetite control mechanism.

HIGH BLOOD PRESSURE

Increased blood pressure elevates the risk of several other diseases, including artherosclerosis, heart attack, heart failure, stroke, chronic kidney disease, and vision loss (Kones 2010; Emerging Risk Factors Collaboration 2010; Schnohr 2002). Excessive adipose tissue can increase blood pressure by several possible mechanisms: aside from its effect on inflammation, fat cells can be a source of the hypertensive proteins *renin* and *angiotensinogen*, and *angiotensin converting enzyme*, all of which work together to increase blood pressure by promoting water retention and causing constriction of blood vessels (Nguyen 2012b). Fat tissue also produces the satiety hormone leptin, which, in combination with the renin-angiotensin and sympathetic nervous systems, may influence blood pressure by causing the kidneys to retain sodium and water; high leptin levels are also related to insulin resistance, itself a risk factor for hypertension (Nguyen 2012b; Naumnik 2010). Compared to normal weight individuals, overweight individuals are 1.7 times as likely to have hypertension, while for obese individuals, the risk is 2.6-fold (Nguyen 2008). A BMI between 18.5 and 24.9 carries the lowest risk of hypertension. Reductions of systolic blood pressure by 5-20 mmHg per 22 pounds of weight loss have been observed in several studies (The Trials of Hypertension Prevention Collaborative Research Group 1997; He 2000).

ARTHRITIS

Excess weight puts additional mechanical stress on the joints. Obesity has been unequivocally associated with osteoarthritis risk, particularly in weight-bearing joints such as the knee and hip. In an analysis of 21 studies on obesity and knee osteoarthritis incidence, a 5 point increase in BMI was associated with a 35% increase in osteoarthritis risk; this effect was more significant in women than men (38% versus 22%, respectively) (Jiang 2012).

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms (heartburn) and/or complications (esophageal cancer) (Vakil 2006). Increased body mass and abdominal adiposity increases pressure on the stomach and lower esophagus. This can stress the lower esophageal valve, which is responsible for retaining acid in the stomach. When this valve is compromised, it loses its ability to maintain a seal against gastric reflux. Sustained abdominal pressure due to central obesity can also increase risk of hiatal hernia (the forcing of part of the stomach above the diaphragm into the chest cavity), another risk factor for gastric reflux (Festi 2009). Among 7 studies that examined the relationship between body mass and GERD complications, overweight individuals averaged a 43% increase, and obese individuals a 94% increase, in GERD symptoms over individuals with a normal body mass (Hampel 2005). Exposure to stomach acid also increases the rate of neoplastic alterations (abnormal cellular proliferation) within the esophagus, leading to the higher incidence of esophageal adenocarcinoma observed in overweight individuals in most of these studies.

SLEEP DISORDERS

Obesity is the strongest contributor to obstructive sleep apnea, a breathing disorder that occurs during sleep and causes symptoms ranging from restless sleep to low blood oxygen (hypoxemia). About 70% of people with obstructive sleep apnea are obese, and about 40% of obese individuals have sleep apnea. Among individuals with BMIs over 60, the prevalence of sleep apnea is 90%. Obese individuals are more likely to suffer from night eating syndrome or sleep-related eating disorder, disorders characterized by symptoms ranging from excessive nighttime hunger to unconscious nocturnal eating. The prevalence of these eating disorders among obese persons is 6–16%, as compared to 1.5% in the general population. Narcolepsy (excessive daytime sleepiness) is also more common in obese individuals (Akinnusi 2012).

Poor sleep quality is more than just a consequence of obesity. Rather, a ***vicious cycle*** in which obesity leads to impaired sleep leads to increased appetite leads to obesity may complicate weight loss efforts for many individuals. Studies show that sleep deprivation, as can occur when one's sleep is suboptimal due to obesity-related phenomena such as sleep apnea, is associated with increased appetite (Knutson 2007). In an insightful magnetic resonance imaging experiment, researchers showed that a brain region called the *anterior cingulate cortex* appears to be more responsive to anticipation of food following sleep deprivation as compared to a full-night of sleep. Increased neural activity in this brain region is associated with obesity, and its level of activation

correlated with appetite in this study (Benedict 2012). Thus, improving **sleep hygiene** and ensuring that restful, restorative sleep is attained is an integral aspect of successful weight loss. A number of strategies for improving sleep quality are discussed in the Insomnia protocol.

Obesity and Weight Loss

Diagnosis and Assessment of Obesity

DIAGNOSIS

Obesity is typically diagnosed and defined by analysis of body size, weight, and composition. **Body mass index (BMI)** is the most commonly accepted metric for defining obesity; it is a surrogate measurement of adiposity, calculated as body mass (in kilograms) divided by height squared (in meters). Alternatively, it can be calculated in Imperial units as [weight (in pounds) / height2 (in inches)] x 703 (Expert Treatment Panel 1998). The World Health Organization (WHO) definitions of overweight and obese are BMIs of ≥25 and ≥30 kg/m2, respectively (World Health Organization 1995).

WHO Classification of weight status by BMI: (World Health Organization 2000)

Status	BMI, kg/m2
Underweight	<18.5
Normal range	18.5-24.9
Overweight	25-29.9
Obese class I	30-34.9
Obese class II	35-39.9
Obese class III/Morbid obesity	≥40

Although BMI is strongly correlated with total body fat, it is not without limitations. For example, there are significant racial considerations that can influence its interpretation (eg, Asians typically carry more body fat, and Africans less, than Caucasians at any particular BMI). BMI overestimates body fat content for individuals with high muscle mass (such as athletes). Additionally, BMI cannot measure some changes in body composition; for example, the concurrent loss of lean muscle and increase in body fat in aging individuals might not result in a change in their BMI (Prentice 2001). Alternative measurements (eg, skin-fold thickness and waist-to-hip ratio) have been suggested as more accurate methods for body fat estimation, but in terms of predicting clinical outcomes, BMI has shown similar accuracy to these techniques and remains an acceptable measurement despite its shortcomings (Thomas 2011). BMI can be combined with waist circumference measurements, which can estimate an individual's abdominal fat content (abdominal or visceral fat is a greater risk factor for obesity-related diseases than total body fat). Waist circumference measurements of >102 cm (40 in.) for men, and >88 cm (35 in.) for women carry high risk of obesity-associated disease (eg, type 2 diabetes, cardiovascular disease, and hypertension) (Expert Treatment Panel 1998).

STUDY FUNDED BY LIFE EXTENSION FOUNDATION® REVEALS INADEQUACIES OF CONVENTIONAL BMI MEASUREMENTS

The most widely used tool to assess weight-related health status is the calculated ***body mass index (BMI)***, despite several shortcomings. Although a number of studies and analyses have established relatively consistent associations between various BMI ranges and risk of several diseases, the technique is unable to provide an accurate determination of body fat percentage (Owen 2009; Corley 2006). This leads to inevitable oversights as to obesity-related risks given the variation in adipose tissue distribution between individuals.

Scientists at the frontiers of obesity research recognize the inadequacy of relying on calculated BMI measurements and are vigorously investigating methods to circumvent its shortcomings.

A groundbreaking 2012 study supported by a grant from the non-profit Life Extension Foundation® meticulously examined the discrepancy between BMI-diagnosed obesity and obesity determined as a function of body fat content assessed by ***dual energy x-ray absorptiometry (DXA)***, a highly accurate, albeit expensive and cumbersome method of measuring body fat. This study evaluated 11 years of records pertaining to nearly 1400 patients for whom DXA-determined body fat and BMI measurements had been captured.

The results showed that BMI was a poor indicator of body fat content and may result in the underdiagnosis and undertreatment of individuals at risk for obesity-related diseases. Measurement of BMI alone was shown to be especially prone to underestimation of obesity in aging women: **48%** of women classified non-obese by BMI calculation were found to be obese when body fat percentage was determined by DXA.

The authors of this study simultaneously examined correlates between blood levels of ***leptin*** and DXA-determined body fat content; they found that leptin levels emulated the DXA findings in many cases.

Therefore, the researchers suggest blood levels of leptin can **complement** calculated BMI measurements to improve detection of obesity. For example, if a person has a "normal" BMI, but has very high leptin levels, they may still be at risk for obesity-related diseases and may benefit from anti-obesity intervention. Likewise, if a person with a BMI typically classified as "overweight" has low leptin levels, they may be at lower risk and not require aggressive anti-obesity intervention (Shah 2012).

While direct measurement of body fat by DXA remains a premium choice for determination of obesity-related disease, its high cost and limited availability make it an unreasonable option for many people. Emerging evidence suggests, however, that augmenting a calculated BMI measurement with leptin blood testing may help physicians determine patients' risks with improved clarity.

Obesity and Weight Loss

Conventional Obesity Management

A National Institutes of Health panel established recommendations for the treatment of obesity based on BMI, waist circumference, and overall disease risk (Expert Treatment Panel 1998). The Panel recommends low-calorie or very-low calorie diets as the cornerstone of any weight-loss strategy, such as to create a deficit of 500-1000 calories/day and a weight loss of 1-2 lb/week. Lifestyle modification and weight loss are the recommended methods for lowering blood pressure and blood lipids (LDL, total cholesterol, and triglycerides) in overweight/obese individuals, and for lowering blood glucose in overweight type 2 diabetes patients. The panel further recommends 30-45 minutes of moderate physical activity, 3-5 days per week, to promote weight loss and decrease abdominal fat.

Weight loss drugs may be incorporated into the weight loss plan for obese individuals (BMI ≥30) with no other risk factors or obesity-related diseases (eg, hypertension, heart disease, diabetes), or for overweight individuals with a BMI of ≥27 and obesity-related risk factors or diseases. Weight loss surgery is reserved for class III obese individuals (BMI ≥40), or class II individuals (BMI ≥35) at high risk of obesity-associated mortality and when non-invasive methods have failed (Expert Treatment Panel 1998; Mayo Clinic 2012).

PHARMACEUTICAL THERAPY

The drugs in this section are FDA-approved for the treatment of obesity.

Orlistat. While pharmaceutical approaches to obesity have traditionally addressed appetite suppression, orlistat (Alli®, Xenical®) works by *decreasing fat absorption* from the gut. It binds and inactivates pancreatic lipase, the enzyme responsible for breaking down dietary triglycerides into fatty acids so they can be absorbed through the intestinal wall (Xiao 2012).

Sixteen trials have observed orlistat's effects in over 10000 subjects, and have shown an average annual weight loss of 6.4 pounds when used over 12 months. It has been shown to reduce the incidence of diabetes, lower total & LDL cholesterol and blood pressure, and improve blood sugar control in patients with diabetes, while only slightly lowering HDL (good) cholesterol concentrations (Rucker 2007). The most common side effects of orlistat include diarrhea, flatulence, bloating, abdominal pain, and indigestion (Ioannides-Demos 2011). Although rare, serious liver damage has been reported from orlistat usage (Garber 2012). Life Extension suggests taking fat-soluble nutrients such as vitamin D, vitamin E, vitamin K, lutein, zeaxanthin, and fish oil at the time of the day furthest from the last orlistat dose, since it may impair their absorption.

Lorcaserin. Lorcaserin is a selective serotonin receptor agonist, specifically the 5-HT2C receptor, enhancing the satiating effects of serotonin in the central nervous system. Lorcaserin acts more selectively on serotonin receptors than the fenfluramine anti-obesity drugs that were introduced in the 1970s and withdrawn in 1997 due to increased risk of cardiac valvular disease. Lorcaserin acts on the 5-HT2C receptor, showing roughly 100-fold greater selectivity for the 5-HT2C receptor than the 5-HT2B receptor, and demonstrated no increase in the rate of valvular disease after 2 years of treatment (Ioannides-Demos 2011).

In 2 Phase III trials, lorcaserin treatment of 6380 non-diabetic patients aged 18-66 years with a BMI of 27–45 for 1 year resulted in a 5.8% weight loss, compared to 2.5% with placebo (Ioannides-Demos 2011). Lorcaserin was approved by the FDA in June 2012 under the brand name Belviq®, making it the first anti-obesity drug to be approved since orlistat in 1999 (Healy 2012). The most

frequent side effects for lorcaserin are headache, dizziness, and nausea. Also, there may be some potential for abuse due to the drug's hallucinogenic properties; the Drug Enforcement Administration (DEA) has thus proposed regulating lorcaserin as a schedule IV substance (Houck 2012).

Phentermine/topiramate. Topiramate is an approved anti-epileptic drug with appetite-suppressant activity; phentermine is an amphetamine that has been available in the United States as a short-term prescription weight-loss treatment. The combination has been investigated as an anti-obesity therapy; in a 28-week randomized trial, phentermine plus topiramate (92 mg/15 mg and 46 mg/7.5 mg doses) demonstrated a 9.2% weight loss compared to a 6.4% weight loss with topiramate alone, 6.1% for phentermine alone, and 1.7% for placebo (Ioannides-Demos 2011).

Phentermine/topiramate was approved by the FDA under the brand name Qsymia® in July 2012 (Gann 2012). The combination is also in clinical development for sleep apnea syndrome and type 2 diabetes (Cameron 2012). Potential side effects include depression and cognitive complaints, potential cardiovascular risk, and an increase in heart rate (Hiatt 2012).

BARIATRIC SURGERY

Bariatric surgical procedures modify the size or course of the gastrointestinal tract to attenuate the appetite. Five bariatric procedures have been developed, although the 2 most common (Roux-en-Y gastric bypass and Laproscopic gastric band) represented about 49% and 42% of procedures in the United States in 2008, respectively. Gastric bypass reduces the stomach to a small pouch and bypasses part of the small intestine. The laproscopic gastric band fits around the upper part of the stomach, also creating a smaller stomach pouch that limits food consumption. A newer procedure, sleeve gastrectomy, is increasing in popularity; it only removes part of the stomach, but leaves its connection to the intestines intact (Dixon 2012).

Bariatric procedures reduce hunger and caloric intake, and have resulted in average weight losses of 20-35%, depending on surgical technique. They have also been shown to affect food preferences by a yet unknown mechanism; gastric banding usually limits consumption of breads and pasta, and gastric bypass reduces intake of sweet and fatty foods and possibly increases vegetable consumption. Several studies of bariatric surgery in diabetic patients have demonstrated a reduction in high blood sugar levels and insulin resistance, and reduced the need for blood sugar-lowering medications. Most of these procedures are permanent, require lifelong follow-up, and are not without surgical risk. Because they dramatically alter gastrointestinal anatomy and physiology, they can also lead to malabsorption and deficiency of certain nutrients (particularly vitamin B12, iron, folate, calcium, vitamin D, zinc, and copper) (Dixon 2012).

Obesity and Weight Loss

Novel and Emerging Therapies for Obesity

Temporary surgical procedures/ endosleeves. The duodenojejunal bypass sleeve (DJBS) is a flexible, nutrient-impermeable plastic sleeve that is surgically inserted into the upper part of the small intestine (duodenum). The sleeve serves as a barrier to nutrient absorption, simulating the effect of a Roux-en-Y gastric bypass, but is a reversible procedure (Gersin 2007). By preventing absorption in the part of the small intestine closest to the stomach, the sleeve may also delay gastric emptying and stimulate satiety (Nguyen 2012a). DJBSs are temporary devices for weight loss; in human trials they were left in place for 3 months and successfully removed, resulting in the loss of 22-24% of excess weight. Complications include esophageal tears, bloating, upper gastrointestinal bleeding, and movement of the sleeve (Nguyen 2012a).

Metformin. Metformin, a first-line anti-diabetic drug with a long history of safety and efficacy, has shown promising results as an anti-obesity therapy. While not currently approved for weight loss, studies have shown average weight losses between 4.4 and 6.6 pounds, reaching up to 19.8 pounds in some studies. Metformin also has the added benefit of being known to prevent progression to diabetes in pre-diabetic patients (Garber 2012). Metformin may also reduce the activity of inflammatory cytokines; low-grade inflammation is associated with the incidence of metabolic disorders (eg, obesity and diabetes) (Molavi 2007; Buler 2012). Finally, metformin can produce many of the gene expression changes associated with long-term caloric restriction in animal models, possibly due to its influence on insulin or IGF-1 signaling (Dhahbi 2005).

Acarbose. Acarbose (Precose®) is an oral anti-diabetic agent that delays glucose release from complex carbohydrates by inhibiting the activity of the enzyme alpha-glucosidase, and can lead to a reduction of post-meal blood glucose levels (Hanefeld 2004). Two comprehensive reviews of more than 30 randomized, double-blind, placebo-controlled trials with a minimum acarbose treatment course of 12-weeks have shown its ability to significantly improve glycemic control and lower glycated hemoglobin (HbA1c) in type 2 diabetic patients (Van de Laar 2005). The first of the 2 analyses (7 acarbose studies) (Hanefeld 2004) demonstrated lower triglyceride levels and systolic blood pressure in the acarbose treatment group, and a significant effect on reducing the risk of heart attack and other cardiovascular events. Across these studies, there was a slight average reduction in body weight of 2.4 pounds among type 2 diabetic patients on acarbose therapy, compared to 1.8 pounds for the placebo group; BMI data also showed a similar modest reduction with acarbose treatment. In the second review (Van de Laar 2005), the weight-lowering effects of acarbose were not clinically significant.

Obesity and Weight Loss

Nine Pillars of Successful Weight Loss

Rebalancing energy intake and expenditure to lose weight, by reducing caloric intake and increasing physical activity, is requisite for any weight loss regimen. However, alterations in metabolism, including age-related hormonal changes, can complicate successful weight loss by necessitating dramatic reductions in caloric intake that are difficult to sustain (Apostolopoulou 2012; Begg 2012; Aoki 2007; Björntorp 2001). Therefore, it is important to consider a multimodal approach to weight loss, in which low-calorie diet and exercise are augmented by steps to restore optimal levels of steroid and thyroid hormones, promote insulin sensitivity, and modulate macronutrient absorption. By this approach, one might not only increase their chance of successful weight and body fat loss, but also potentially reduce many of the other risks associated with obesity such as cardiovascular disease and cancer.

EAT FOR A LONG AND HEALTHY LIFE

Caloric restriction. Caloric restriction is the dramatic reduction of dietary calories to a level short of malnutrition (Lane 1998). Restriction of energy intake slows down the body's growth processes, and causes it to instead focus on protective repair mechanisms; the overall effect is an improvement in several measures of wellbeing. Even in lean, healthy individuals, moderate caloric restriction (22-30% decreases in caloric intake from normal levels) improves heart function, reduces markers of inflammation (eg, C-reactive protein and tumor necrosis factor alpha [TNF-a]), reduces risk factors for cardiovascular disease (eg, LDL-C, triglycerides, and blood pressure), and reduces diabetes risk factors (eg, fasting blood glucose and insulin levels) (Walford 2002; Fontana 2004, 2006; Meyer 2006). The multicenter CALERIE trial on the effects of calorie-restricted diets in otherwise healthy, overweight volunteers has shown that moderate caloric restriction can reduce several cardiovascular risk factors (LDL-C, triglycerides, blood pressure, and C-reactive protein), in addition to promoting weight loss (Lefevre 2009).

It is important to remember that as more calories are eliminated from the diet, dietary levels of essential nutrients drop and may need to be replaced; in studies of 4 popular diet plans that limited calories to 1100-1700 per day (including the NIH and American Heart Association-recommended "DASH diet"), all were found to be on average only 43.5% sufficient in Recommended Daily Intakes (RDIs) for 27 essential micronutrients values, and deficient in 15 of them (Calton 2010). Eating for a long and healthy life likely involves calorie restriction and nutrient supplementation. Refer to the Life Extension protocol on Caloric Restriction for additional information on energy-restricted diets and a comprehensive list of nutrients that may simulate caloric restriction.

INCREASE PHYSICAL ACTIVITY

Increased physical activity promotes weight loss by addressing both sides of the energy balance equation. It increases energy expenditure leading to reduced body weight and fat mass, and exercise reduces appetite at least in the short term by delaying gastric emptying, or possibly increasing the body's sensitivity to hormones that control appetite such as cholecystokinin (King 2012). It may also protect against the insulin resistance associated with obesity (Maarbjerg 2011). Several intervention studies in both young (Hebden 2012) and older adults have shown small-to-moderate decreases in body weight, fat mass, and/or waist circumference with regular, moderate exercise (30-45 minutes of moderate exercise, 3-5 times per week), especially when combined with reduced calorie diets. Exercise may also offset some of the lean muscle loss associated with weight loss in older individuals; loss of lean body mass is associated with decreased independence among this group (Stehr 2012).

RESTORE RESTING ENERGY EXPENDITURE

Black coffee consumption. Black coffee consumption has been associated with reductions in body weight; it adds fluid to the diet without adding additional calories, and contains compounds (eg, chlorogenic acid and caffeine) that may promote weight reduction (Dennis 2009; Onakpoya 2011). In a large population study of almost 60000 healthy men and women over a 12-year period, coffee consumption was associated with less weight gain in women (Lopez-Garcia 2006). While some of this may have been attributable to caffeine content, the same study also revealed modest associations between greater decaffeinated coffee consumption and less weight gain, suggesting other components of coffee may also protect against weight gain. Intervention studies have reported similarly positive results. In one study, 33 healthy volunteers saw slight reductions of body weight and body fat following 4 weeks of consumption of 750 mL brewed coffee per day that contained both green and roasted coffee constituents (Bakuradze 2011). In a second study, 15 overweight and obese volunteers consumed 11 grams per day of instant coffee enriched with 1000 mg chlorogenic acid (approximately 5 cups coffee per day) for 12 weeks and saw reductions in body weight of almost 12 pounds, compared to a loss of 3.7 pounds among volunteers who drank regular instant coffee (Thom 2007).

Green tea polyphenols. Green tea has exhibited anti-inflammatory activity in dozens of laboratory and animal studies (Singh 2010), as well as cholesterol-lowering effects in human trials (averaging about 9 mg/dL of LDL cholesterol decrease across 4 studies) (Hooper 2008). The effect of green tea on body composition has been the subject of at least 21 unique trials. Two analyses of these trials suggest a modest effect of green tea on body weight (Johnson 2012; Hursel 2009; Phung 2010). In an analysis of 11

randomized, controlled trials of green tea consumption for 12–13 weeks duration, green tea decreased body weight by about 3 pounds compared to control in Asian participants (Hursel 2009). A second analysis of 15 randomized trials demonstrated that consumption of green tea catechins with caffeine produced a greater decrease in BMI and body weight compared to control (Phung 2010).

Fucoxanthin. Fucoxanthin is a carotenoid from brown seaweed that has been shown to reduce white fat levels in animal models, by increasing energy expenditure through the activation of the thermogenic factor mitochondrial *uncoupling protein 1 (UCP1)* (Maeda 2005, D'Orazio 2012). In a 16 week trial of 151 obese, pre-menopausal women with and without non-alcoholic fatty liver disease (NAFLD), consumption of a combination of 2.4 mg fucoxanthin and 300 mg *pomegranate seed oil*, along with a reduced calorie diet (1800 calories/day), resulted in a significant reduction of body weight compared to placebo (an average of 12.1 pounds lost in NAFLD patients and 10.8 pounds lost in non-NAFLD patients) (Abidov 2010). Serum triglycerides and C-reactive protein levels also dropped in both groups taking fucoxanthin/pomegranate seed oil compared to control.

Fish oil. Fish oil, a rich source of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can only be synthesized to a limited extent by humans but are nonetheless essential for several metabolic processes. Omega-3 fatty acids have been well studied for the prevention of cardiovascular disease and their ability to lower inflammation and reduce hypertension; these processes are all associated with the progression of obesity and metabolic syndrome (Marik 2009; Geleijnse 2002). Some evidence suggests EPA and DHA may promote thermogenesis (Li 2008). Omega-3 fatty acids from fish oil may have protective effects against weight gain independent of their blood-pressure-lowering and anti-inflammatory roles. When combined with regular aerobic exercise, 6 grams per day of fish oil for 12 weeks demonstrated significantly lowered triglycerides, increased HDL cholesterol, improved endothelium-dependent arterial vasodilation, and improved arterial compliance in a study of 75 overweight volunteers (Hill 2007). Additionally, both fish oil and exercise independently reduced body fat, albeit modestly. Incorporating lean or oily fish, or fish oil into energy-restricted diets (1600 calories per day) resulted in about 2.2 pounds more loss of weight over 4 weeks than diets without fish in a group of 138 overweight and obese men (Thorsdottir 2007).

Capsaicin/ Cayenne. Capsaicin is a major “spicy” constituent of chili peppers (eg, cayenne). Regular intake of chili peppers delays oxidation of serum lipids, which contributes to reducing the risk of cardiovascular disease (Ahuja 2006). Because of the sensation of heat and increased energy expenditure when they are eaten, chili peppers are thought of as potential interventions for obesity management (Luo 2011). Capsaicin has been studied as a potential thermogenic compound in 10 long- and short-term studies, mostly in Asian populations where it is more commonly consumed. Results of capsaicin studies are mixed; it appears to significantly increase energy expenditure (up to 30% in some studies) and decrease appetite and energy intake, but these results are more robust in Asian participants than Caucasians (Hursel 2010).

Another compound that may increase resting energy expenditure is 3-acetyl-7-oxo-dehydroepiandrosterone ***(7-Keto® DHEA)***. For more information, see the discussion on restoring youthful hormone balance later in this protocol.

RESTORE HEALTHY ADIPOCYTE (FAT CELL) SIGNALING

Irvingia gabonensis. *Irvingia gabonensis* is a mango-like West African fruit; extracts of its seeds have been shown to reduce fat stores, and promote healthy blood lipid and fasting blood glucose levels (Egras 2011). *Irvingia gabonensis* extracts are thought to work by inhibiting adipogenesis (ie, the development of fat cells) by down-regulating a protein involved in activating fat cell growth and proliferation. Three randomized controlled trials have investigated Irvingia extracts in healthy volunteers; all have demonstrated its ability to significantly decrease body fat stores, weight, and waist circumference (Ngondi 2005, 2009; Oben 2008). When compared to placebo, healthy overweight and/or obese volunteers taking 150 mg of *Irvingia gabonensis* seed extract before meals for 10 weeks exhibited a significantly greater decrease in body fat percentage (6.3% versus 1.9%), body weight (28.2 pounds versus 1.5 pounds), and waist circumference (-6.37 inches versus -2.09 inches), as well as significant drops in total- and LDL-cholesterol, C-reactive protein, and fasting blood glucose (Ngondi 2009). These kinds of results are seldom duplicated outside the clinical study setting, however.

Sphaeranthus indicus and Mangosteen (Garcinia mangostana). Mangosteen has long been used as a diabetic treatment in Southeast Asia; modern investigations suggest antioxidant and anti-inflammatory activities, especially in white adipose tissue (Devalaraja 2011). *Sphaeranthus indicus* (*S. indicus*) has been widely used in Ayurvedic medicine for a variety of ailments, and has been studied for its anti-inflammatory, blood sugar-lowering, and lipid-lowering activities in animal and cell culture models (Galani 2010). In a trial of 60 obese volunteers, 30 were randomized to receive 800 mg per day of the *S. indicus* and mangosteen combination for 8 weeks, while maintaining a restricted 2000 calorie per day diet and exercising (walking) for 30 minutes, 5 times a week. After 8 weeks, the group receiving the dual plant extract exhibited significant reductions in body weight (11 pounds versus 3.3 pounds for placebo), BMI (2.05 versus 0.5 for placebo), waist circumference (4.05 inches versus 2.02 for placebo), as well statistically significant reductions in total cholesterol, serum triglycerides, and serum glucose (Lau 2011).

RESTORE BRAIN SEROTONIN/ SUPPRESS HUNGER SIGNALS

Tryptophan. Tryptophan is an essential amino acid and a precursor to serotonin, a neurotransmitter involved in gastrointestinal

function as well as mood and feeding behavior. Increases in brain levels of serotonin signal satiety, while decreases signal the desire to eat (Lam 2010). Multiple studies have shown that calorie-restricted diets, while successful at reducing weight, also reduce circulating tryptophan levels by 14-23%. This may lead to reduced serotonin synthesis, increased hunger, and a reduction in the probability of maintaining weight loss (Wolfe 1997). In a study of 10 healthy, young, normal-weight men, 2- and 3-gram doses of tryptophan reduced energy intake compared to placebo when taken before a buffet-style meal (Hrboticky 1985). In 10 obese subjects, 1, 2, or 3 grams of tryptophan taken one hour before a plated meal reduced calorie consumption in a dose-dependent manner (Cavaliere 1997).

Saffron. Extracts of saffron stigma (*Crocus sativus*) have been studied for a variety of applications, including pain relief, anti-inflammation, and memory enhancement. In animal models, high doses of saffron have been shown to possess an antidepressent-like activity, 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 of saffron stigma extract per day for 8 weeks produced an average weight loss of about 2 pounds. Much of this weight reduction is attributed to a reduction in snacking frequency; at the study's end, individuals on the saffron supplement reported having 5.5 snacks per week (compared to 8.9 snacks per week in the placebo group), a reduction in snacking frequency of 55% from pre-trial levels (Gout 2010).

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 to placebo. The researchers suggested that this reduction of 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 (Hughes 2008).

CONTROL RATE OF CARBOHYDRATE ABSORPTION

Green coffee extract. Green coffee extract, an *antioxidant-rich* mixture from unroasted coffee beans, has been shown to temper deadly after-meal spikes in glucose and to combat insulin resistance in animals (Yamaguchi 2008; Ho 2012; Vinson 2012; Nagendran 2011). Higher intakes have been associated with weight loss benefits (Onakpoya 2011).

To determine conclusively whether green coffee bean extract has an *anti-obesity* benefit, scientists set up a randomized, double-blind, placebo-controlled, linear dose, crossover study on humans (Vinson 2012). In a crossover study, participants are cycled through different phases of treatment and placebo. In this case, subjects took a high dose of *green coffee bean extract* for 6 weeks, a lower dose of *green coffee bean extract* for 6 weeks, and a placebo for 6 weeks in a randomized, double-blind manner. Between phases, there was a 2-week "washout" period, making the entire study 22 weeks long. Crossover studies are considered sound, because each person in the test group serves as his or her own control. This improves the chances of getting an accurate result, because it eliminates the possibility of the outcome reflecting a difference between the active and control groups. To ensure the findings were more representative, the investigation enlisted both men and women.

Participants were restricted to those who were classified as obese or pre-obese, because people who have these conditions are subject to obesity's *metabolic effects* and find weight loss difficult to achieve. To further ensure that any effect on weight, body fat or BMI could be solely attributed to the extract, there were **no significant changes in dietary calories** or in the dietary percentages of carbohydrates, fat, and proteins at any time during the study. There were also no significant changes in exercise. Daily 350 mg capsules of **green coffee bean extract** were the only intervention, although in a non- study situation, people seeking weight reduction would ideally combine **green coffee bean extract** with lower calorie consumption and greater physical activity to promote maximum weight loss (Vinson 2012).

During the high-dose phase, subjects took 350 mg of extract, three times daily. The lower dose phase included 350 mg of extract, taken twice daily (Vinson 2012). The placebo phase involved a 350 mg dose three times daily of an inert capsule containing an inactive substance. The striking results were published in January 2012 (Vinson 2012). Over the 22-week trial, investigators found that all subjects experienced a reduction in body weight, BMI, and body fat during both the high-dose and low-dose phases of the study, but not in the placebo phase! After 12 weeks of administering 350 mg green coffee bean extract three times a day the scientists found that:

- Weight decreased by over 17.6 pounds on average— with some subjects losing more than 22.7 pounds
- BMI decreased by an average of 2.92
- Body fat percentage decreased by an average of 4.44%, with some subjects dropping their body fat percentage by 6.44%
- Heart rate decreased by a significant average of 2.56 beats per minute

The substantial anti-obesity impact was clearly reflected in the finding that a remarkable 37% of participants who were assessed as having pre-obesity (25-30 BMI) at the start of the study had their condition reversed to the normal weight range.

A study follow-up showed that, contrasting with food-restriction diets, a surprising **87.5%** of the test subjects were able to maintain

their weight loss after completing the study. No side effects were observed. This and other studies demonstrate the importance of **"*preparing your body to eat*"** by taking **green coffee bean extract** before each meal. The dual effects of reducing ***after-meal* glucose** and inducing meaningful **weight loss** make it a supplement that virtually every aging person should take before eating.

In 2011, a detailed review of 3 studies of green coffee extract (180-200 mg per day) for 4-12 weeks in a total of 142 overweight volunteers demonstrated an average reduction in body weight of 5.4 pounds compared to placebo (Onakpoya 2011).

A compound called ***chlorogenic acid*** may be largely responsible for the weight loss benefits associated with green coffee extract. Chlorogenic acid is not found in great quantities in most conventional coffee beverages, since the roasting process dramatically reduces its content (although methods of retaining or re-infusing chlorogenic acid into roasted coffee have been developed). Chlorogenic acid has been shown to reduce glucose absorption in healthy volunteers (Thom 2007), which may be one way green coffee extract combats weight gain (Shimoda 2006). Moreover, chlorogenic acid may control glucose via inhibition of an enzyme called *glucose-6-phosphatase*, which is involved in the generation of glucose by the liver through a process known as **gluconeogenesis** (Arion 1997; Henry-Vitrac 2010). Inhibition of gluconeogenesis may help normalize fasting glucose levels.

One compelling study showed that people not taking green coffee extract had glucose levels of 130 mg/dL one hour after sugar ingestion. In study subjects taking 400 mg of green coffee extract, glucose levels dropped to 93 mg/dL after sugar ingestion (Nagendran 2011). The difference between having a postload glucose reading of 93 mg/dL compared to 130 mg/dL is about a 70% reduction in heart attack risk (Gerstein 1999).

Seaweed extracts. Extracts from kelp (*Ascophyllum nodosum*) and bladderwrack (*Fucus vesiculosus*) have been demonstrated to inhibit the activity of the digestive enzymes alpha-amylase (α-amylase) and alpha-glucosidase (α-glucosidase) (Paradis 2011); inhibition of these enzymes interferes with the digestion of dietary starches, and may reduce or slow the absorption of high glycemic carbohydrates (Preuss 2009). A proprietary composition of demineralized polyphenols from brown seaweed was examined in 23 volunteers for its ability to reduce post-meal blood glucose and insulin secretion following consumption of a carbohydrate-containing meal. When taken just prior to the consumption of a meal containing 50 grams of carbohydrates (from bread), 500 mg of the seaweed extract was associated with a 12.1% reduction in insulin excretion and a 7.9% increase in insulin sensitivity when compared to placebo (Paradis 2011).

White kidney bean extract (Phaseolus vulgaris). White kidney bean contains an inhibitor of *α-amylase* (ie, a pancreatic digestive enzyme required for the conversion of starches to simpler sugars in animals) (Barrett 2011). By inhibiting α-amylase, absorption of starch from the diet is attenuated; individuals can still include a reasonable carbohydrate proportion in their diet but lessen or slow the absorption of high glycemic carbohydrates (Preuss 2009). Ten clinical trials have investigated the carbohydrate-blocking activity of *Phaseolus vulgaris* extracts. In 3 randomized, controlled studies, overweight and obese volunteers taking Phaseolus extracts (at doses ranging from 445 mg for 4 weeks to 3000 mg for 8–12 weeks) exhibited reduced body weights compared to controls (ranging from 1.9 to 6.9 pounds lost). A fourth study showed a loss in body weight only among participants who consumed the greatest amount of carbohydrates. Additional trials demonstrated significant weight loss over time, as well as reductions in plasma triglycerides and post-meal blood glucose (Barrett 2011).

L-arabinose. Sucrose (common sugar) is composed of 2 simple sugar molecules, glucose and fructose. It is poorly absorbed in the intestine in this form. In order to be utilized, it must first be broken down by the digestive enzyme ***sucrase***. Blocking the enzymatic action of sucrase therefore reduces uptake of sucrose.

Researchers have identified a potent sucrase inhibitor called ***L-arabinose***. L-arabinose, an indigestible plant compound, cannot be absorbed into the blood. Instead, it remains in the digestive tract and is eventually excreted (Seri 1996; Osaki 2001). By blocking metabolism of sucrose, L-arabinose inhibits the spike in blood sugar and fat synthesis that would otherwise follow a sugar-rich meal (Osaki 2001). In animal models, L-arabinose virtually eliminated the rise in blood sugar following administration of sucrose, with blood glucose levels rising only 2% higher than in control animals that did not receive sucrose. L-arabinose did not exert any effect on serum glucose levels in control animals that did not receive sucrose (Preuss 2007a).

L-arabinose has been shown to be safe in both short- and long-term studies, and may contribute to lowered levels of glycosylated hemoglobin (hemoglobin A1C), a measure of chronic exposure to sugar in the blood. A study concluded that combining L-arabinose and white kidney bean extract not only smoothed out postprandial glucose spikes and reduced insulin levels, it lowered systolic blood pressure as well (Preuss 2007b).

Glucomannan. Glucomannan is a soluble fiber derived from *Amorphophallus konjac.* It is thought to prolong gastric emptying time, which has several anti-obesity outcomes. It may increase satiety, reduce body weight, reduce the post-meal rise in plasma glucose, suppress liver cholesterol synthesis, and increase the elimination of cholesterol-containing bile acids (Doi 1995). An analysis of 14 randomized, controlled studies of glucomannan usage by 531 hyperlipidemic, diabetic, or obese adults and children demonstrated its ability to affect modest reductions in body weight (an average reduction of 1.8 pounds across all studies), when supplied at dosages between 3 and 15 grams per day (Sood 2008). Additionally, glucomannan demonstrated significant average reductions in total cholesterol (-19.28 mg/dL), LDL cholesterol (-15.99 mg/dL), triglycerides (-11.08 mg/dL), and fasting blood

glucose (-7.44 mg/dL). ***Propolmannan*** is the name of a well-studied glucomannan soluble fiber.

Propolmannan and the Role of Bile Acids in Dietary Fat Absorption

Bile acids are excreted from the liver into the small intestine where they facilitate the *absorption* of dietary **fats** into the bloodstream. Dietary fat absorption is dependent on bile acids and the *lipase enzyme*. An intact soluble fiber binds to bile acids in the small intestine, thus helping to impede absorption of dietary fats (while simultaneously reducing serum LDL and total cholesterol).

Specially processed, ***propolmannan*** is a plant-derived polysaccharide fiber. Propolmannan is patented in 33 countries as a purified fiber that does not break down in the digestive tract.

Published research reveals propolmannan's ability to not only increase the amount of bile acids in feces, but also reduce the rate of carbohydrate absorption and the subsequent glucose/insulin spike in the blood. When propolmannan is taken before meals, consistent and significant reductions in blood triglyceride, LDL, and total cholesterol are observed (Doi 1990).

RESTORE YOUTHFUL HORMONE BALANCE

Hormone replacement therapy, using natural compounds like *dehydroepiandrosterone (DHEA)* and *Armour® thyroid*, may help aging individuals overcome some of the barriers that insufficient or imbalanced hormone levels pose against successful weight loss. Comprehensive blood testing to assess hormone levels should be undertaken before beginning a hormone restoration regimen under the care of an experienced physician. The Male Weight Loss Panel or Female Weight Loss Panel are designed specifically to assess blood parameters that may influence weight loss. More information is available in the chapters on Male and Female hormone restoration, as well as the Thyroid Regulation chapter.

DHEA and 7-Keto® DHEA. Low levels of sex hormones are associated with obesity (Apostolopoulou 2012), as well as systemic increases in inflammatory markers (Singh 2011). Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone, a precursor to the sex steroids testosterone and estrogen. DHEA is abundant in youth, but steadily declines with advancing age and may be partially responsible for age-related decreases in sex steroids (Heffner 2011). DHEA supplementation (50 mg per day for 2 years) in elderly volunteers significantly lowered visceral fat mass and improved glucose tolerance, as well as decreased levels of inflammatory cytokines in a small study (Weiss 2011). High-dose DHEA induced thermogenesis, decreased body fat without decreasing food intake, and decreased glucose levels in animal models; ***7-Keto® DHEA*** (3-acetyl-7-oxo-dehydroepiandrosterone) was shown to be 4-fold more thermogenic than DHEA (Ihler 2003). It may work by increasing the shuttling of energy substrates into the mitochondria for conversion into heat/energy, and may act upon the same enzyme systems as the thyroid hormone T3 (Bobyleva 1997; Ihler 2003). In human studies, overweight volunteers taking 100 mg of 7-Keto® DHEA twice daily lost significantly more weight and body fat than did the placebo group (6.3 pounds versus 2.2 pounds, respectively, and reductions in body fat of 1.8% versus 0.57%) (Kalman 2000). This weight reduction may be related to 7-Keto® DHEA's effect on increasing resting energy expenditure (REE). In overweight subjects maintained on a calorie-restricted diet, 7 days of treatment with 7-Keto® DHEA increased REE by 1.4% (equivalent to an extra 115 calories burned per day), whereas subjects taking placebo saw their REE decrease by 3.9% (Zenk 2007). Studies in healthy volunteers demonstrated that 7-Keto® DHEA does not activate the androgen receptor and is not converted to other androgens or estrogens in the body (Davidson 2000).

RESTORE INSULIN SENSITIVITY

Restoring the function of insulin at the cellular level is paramount to combatting diseases related to chronically elevated glucose levels. Several medical strategies can help accomplish this. ***Metformin*** is a blood-sugar-regulating drug used to treat diabetes (Barbero-Becerra 2012); doses ranging from 250 – 850 mg 3 times daily with meals may help facilitate weight loss and promote insulin sensitivity. A physician should be consulted before a metformin regimen is initiated. Restoring youthful levels of ***testosterone*** may help men improve their insulin sensitivity as well (De Maddalena 2012). In addition, a number of natural strategies may help improve insulin sensitivity.

Chromium. Chromium is an essential trace mineral and cofactor to insulin. Chromium enhances insulin activity and has been the subject of a number of studies assessing its effects on carbohydrate, protein, and lipid metabolism.

Magnesium. Magnesium is an essential trace mineral with several potential protective activities against obesity-associated diseases. Population studies suggest a relationship between low magnesium and increased risk of metabolic syndrome and diabetes (Champagne 2008), and a controlled trial has demonstrated its ability to decrease fasting insulin concentrations by 2.2 µIU/mL in otherwise healthy overweight volunteers (Chacko 2011). Additionally, magnesium may enhance satiety (Liu 2006).

INHIBIT THE LIPASE ENZYME

The lipase enzyme is responsible for facilitating the absorption of dietary fats. Taking steps to reduce the activity of the lipase

enzyme may reduce the total amount of dietary fat absorbed. The pharmaceutical drug ***orlistat*** (Alli®, Xenical®), a lipase inhibitor, is sometimes prescribed by physicians as part of a weight management plan. In addition, the following natural intervention may help control fat absorption.

Green tea. Green tea is rich in powerful antioxidants called catechins. Studies have shown that green tea extracts are able to inhibit the activity of the lipase enzyme and reduce absorption of fats from the intestine (Juhel 2000; Koo 2007). In an animal model of obesity induced by a high-fat diet, supplementation with the green tea catechin ***epigallocatechin gallate (EGCG)*** attenuated insulin resistance and reduced cholesterol levels. Moreover, 16-weeks of treatment with EGCG mitigated increases in body weight, body fat, and visceral fat compared to no treatment. The researchers postulated that these anti-obesity effects may have been conferred in part by a reduction in fat absorption, which was obviated by increased fecal lipid content in animals that received the extract (Bose 2008). Another experiment showed that EGCG reduced the incorporation of lipids into fat cells, suggesting that green tea not only combats fat absorption from the gut, but also acts at the cellular level to combat fat storage (Lee 2009). A similarly designed trial in animals showed that 17 weeks of supplementation with EGCG offset some of the metabolic effects of a high-fat, Western-style diet including body weight gain and symptoms of metabolic syndrome; it also reduced markers of inflammation. Again, these results were partly attributed to reduced fat absorption (Chen 2011). In a human trial among moderately obese subjects, 3 months of supplementation with a green tea extract standardized to catechins reduced body weight by 4.6% and waist circumference by 4.4%; these study investigators also cited the ability of green tea constituents to reduce the activity of the lipase enzyme as a mechanism behind the observed metabolic benefits (Chantre 2002).

Life Extension Suggestions

EAT TO LIVE A LONG AND HEALTHY LIFE

Life Extension encourages anyone striving to lose weight to consider adopting a calorie-restricted, but nutrition-dense diet. A detailed explanation of this type of dietary pattern is presented in the Caloric Restriction protocol.

INCREASE PHYSICAL ACTIVITY

Increasing physical activity is one of the most effective means of attaining a negative energy balance, which facilitates weight loss. Physical exercise should be undertaken regularly in accordance with one's overall health and mobility. Anyone with a physical impairment, such as extreme obesity or severe osteoarthritis, should consult a healthcare provider prior to embarking on an exercise regimen.

RESTORE RESTING ENERGY EXPENDITURE

- **Green tea extract**: 725 – 1450 mg daily with meals
- **Fucoxanthin**: 200 mg three times daily
- **Fish oil** (with olive polyphenols): providing 1400 mg EPA and 1000 mg DHA daily
- **Cayenne**: 600 mg once or twice daily with meals

RESTORE HEALTHY ADIPOCYTE (FAT CELL) SIGNALING

- ***Irvingia gabonensis***: 150 mg twice daily
- **Sphaeranthus indicus and Mangosteen** (*Garcinia mangostana*): 800 mg daily

RESTORE BRAIN SEROTONIN / SUPPRESS HUNGER SIGNALS

- **L-tryptophan**: 500 – 1500 mg daily
- **Saffron extract**: 88 – 176 mg daily
- **Pine nut oil**: 3000 – 6000 mg daily

CONTROL RATE OF CARBOHYDRATE ABSORPTION AND GLUCOSE SYNTHESIS

- **Green Coffee Extract** as GCATM (std. to 50% chlorogenic acid): 350 mg three times daily (before meals)
- **Seaweed extracts** (from *Ascophyllum nodosum* and *Fucus vesiculosus*): 250 mg daily
- **White kidney bean extract**: 445 mg before carbohydrate containing meals
- **L-arabinose**: 550 mg before carbohydrate containing meals
- **Propolmannan**: 1000 – 2000 mg before meals

***Pharmaceutical support*:**

- **Acarbose:** 25 – 100 mg before meals

RESTORE YOUTHFUL HORMONE BALANCE

- **Dehydroepiandrosterone** (DHEA): 15 – 25 mg daily for women; 25 – 75 mg daily for men (depending on blood test results)
- **7-Keto® DHEA**: 100 mg twice daily

***Pharmaceutical support*:**

- **Natural** (bioidentical) **hormone replacement therapy** (if needed): as directed by an experienced physician
- **Thyroid hormone replacement therapy (if needed)**: as directed
- **Aromatase inhibitor** (if needed; men only): 0.5 mg twice weekly until estradiol levels are between 20 – 30 pg/mL of blood

RESTORE INSULIN SENSITIVITY

- **Chromium**: 500 – 1000 mcg daily
- **Magnesium**: 160 – 800 mg daily

***Pharmaceutical support*:**

- **Metformin**: 250 – 850 mg before meals (no more than three times a day)

INHIBIT THE LIPASE ENZYME

- **Green tea extract** (std. to 98% polyphenols): 725 – 1450 mg daily

***Pharmaceutical support*:**

- **Orlistat** (Alli®, Xenical®): 60 – 120 mg before meals (no more than three times daily)

In addition, the following **blood testing** resource may be helpful:

Male Weight Loss Panel or **Female Weight Loss Panel**

Safety Caveats

Fish Oil

- If you are taking anti-coagulant or anti-platelet medications, or have a bleeding disorder, consult your healthcare provider before taking this product.

Irvingia gabonensis

- Because this product may lower blood glucose, consult your healthcare provider before taking this product if you are taking blood glucose lowering medication.

L-tryptophan

- If you are pregnant, may become pregnant, breastfeeding, or are taking medications such as SSRIs or MAOIs, consult your healthcare provider before using this product.

Saffron extract

- Do not exceed recommended dose. Consult your healthcare practitioner before using this product if you are taking anti-

coagulant or anti-platelet medications or if you have a bleeding disorder or kidney disease. Avoid using during pregnancy.

Propolmannan

- Take at least two hours apart from medications. Because this product may lower blood glucose, consult your healthcare provider before taking this product if you are taking blood glucose lowering medication. Taking fiber products without adequate liquid may increase the risk of choking. Consult your healthcare provider before taking this product if you have difficulty swallowing or esophageal narrowing.

DHEA

- Do not use DHEA if you are at risk for or have been diagnosed as having any type of hormonal cancer, such as prostate or breast cancer.

Chromium

- Because this product may lower blood glucose, consult your healthcare provider before taking this product if you are taking blood lowering medication.

Magnesium

- If taken in high doses, magnesium may have a laxative effect. If this occurs, divide dosing, reduce intake, or discontinue product.

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.