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## Aims and Scope

*Heart and Metabolism* is a quarterly journal focusing on the management of myocardial ischemia. Its aim is to inform cardiologists and other specialists about the newest findings of the role of metabolism in cardiac disease and to create awareness of its potential clinical implications. The management of patients with angina, as well as those with heart failure and hypertrophic or dilated cardiomyopathy, will also be discussed. Moreover, the effects of metabolic diseases such as diabetes mellitus on the heart will be highlighted. Each issue will include an editorial, followed by articles on a key topic. Experts in the field will explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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*The figures on the cover show variability in body composition in a lean person (top) and an obese person. Reproduced with permission from: Kaiser T, Schunkert H. Kardiovaskuläre Veränderungen bei Adipositas. Herz 2001;26:194–201.*

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# Obesity — a modifiable risk factor

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“No!! I am not obese, I am only well developed!” With these words the corpulent hero Obelix of the popular French cartoon series angrily refuses to be described as obese. It is a common experience in daily medical practice that in many obese patients it is difficult to address this particular risk factor. However, the growing evidence indicating a causal relationship between obesity and cardiovascular disease means we can no longer ignore the issue of excess weight. In 1997 a World Health Organization (WHO) press release concluded that “Obesity’s impact is so diverse and extreme that it should now be regarded as one of the greatest neglected public health problems of our time with an impact on health which may well prove to be as great as that of smoking” [1].

Who is obese? From a sociocultural point of view, the answer differs from country to country and from century to century. For example, the change in the perception of “corpulence” over the past centuries is quite apparent from the sensual paintings by the baroque artist Peter Paul Rubens (1577–1640). From a medical point of view, obesity has been defined by the WHO as a body mass index (BMI) above 30 kg/m<sup>2</sup>, whereby BMI is the body weight in kilograms divided by the square of the height in meters. However, cardiovascular risk starts to increase well below the threshold of obesity. In a recently published prospective cohort study including adults of both sexes, cardiovascular risk began to increase at approximately 25 kg/m<sup>2</sup> [2]. Consequently, the WHO defines a BMI of 25 to 29.9 kg/m<sup>2</sup> not as normal but as “overweight”. Overweight individuals have roughly double the risk of fatal or nonfatal heart disease [3]. Beyond the threshold value

of obesity, risk increases steeply [3]. In the Nurses Health Study each kilogram of weight gain from the age of 18 years was associated with a 3.1% higher relative risk of cardiovascular disease [4]. The increase of risk in obesity is in part explained by the frequent association of overweight with other risk factors, including hypertension, dyslipidemia, type 2 diabetes, and enhanced thrombotic risk. However, multivariate analysis clearly indicates that after correction for confounding factors, overweight remains an independent risk factor.

Obesity is a major challenge to modern cardiovascular medicine, not only because of the enhanced individual risk but also because of its epidemiological importance. In industrialized countries 15% to 25% of the adult population are obese. According to estimates by the WHO in the year 2000, there are more than 300 million obese individuals worldwide. This number is considerably higher than the 1995 estimate, indicating that we currently face an explosion of this health problem. Since genetic predisposition does not change rapidly, environmental factors including eating behavior and reduced physical activity are likely to play a major role in the increased prevalence of obesity.

The high incidence of overweight and obesity, the associated cardiovascular risk, and the metabolic origin of the condition are reason enough to focus this issue of *Heart and Metabolism* on obesity. In metabolic terms, obesity is an imbalance between nutritional energy supply and energy expenditure. Until recently, little was known of the feedback loops which ensure whole-body energy homeostasis and avoid excess proliferation of adipose tissue. During recent years exciting new

observations on the crosstalk between adipose tissue and the brain have been reported, which are summarized in two articles in this issue. Randy Seeley and Stephen Woods provide a concise review of current knowledge on how the brain perceives adipose tissue mass and translates this information into adaptation of energy homeostasis. Gema Frühbeck presents the regulatory mechanisms of energy storage in peripheral tissues. In his clinical review, Martin Alpert explains how obesity may contribute to increased cardiovascular morbidity and mortality by a number of mechanisms which include the development of hypertrophy, leading in some cases to obesity cardiomyopathy and an enhanced risk of coronary events. Echocardiography has proven useful to noninvasively monitor the impact of obesity on cardiac structure and function, as described by Heribert Schunkert.

Obesity is a modifiable risk factor. Thus far, no controlled clinical studies have proven the effect of intentional weight loss on longevity in unselected obese populations. Nevertheless, a reduction in mortality has been observed in obese patients with diabetes [5]. Furthermore, the benefits of weight reduction on hypertension, dyslipidemia, and diabetes are well documented and provide a strong incentive to treat obesity.

Decreasing caloric intake and increasing physical activity remain the fundamentals of obesity treatment. Unfortunately, the success rate of weight reduction and maintenance of normal weight is often unsatisfactory. Taking care of obese patients is a major challenge that requires a multidisciplinary approach. In selected patients new therapeutic strategies must be considered, as discussed by Maria Collazo-Clavell in her article. ■

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# The brain and regulation of body weight

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## Abstract

Over the last decade, increasing evidence supports an important role of the brain in the control of energy balance and disorders of energy balance such as obesity. Total body adipose tissue is carefully regulated by negative feedback from hormonal signals that reflect the status of peripheral fat stores. Adiposity signals, such as leptin and insulin, then act directly upon hypothalamic circuits. These hypothalamic neuropeptide systems can be divided into two categories. Anabolic systems are activated by low levels of adiposity signals and work to increase food intake, decrease energy expenditure, and increase body fat stores. Catabolic systems are activated by high levels of adiposity signals and work to decrease food intake, increase energy expenditure, and decrease body fat stores. Traditional means for losing weight are plagued by very low success rates likely due to these redundant and overlapping neuroendocrine responses that serve to maintain energy balance. The substantial progress in this area has led to the possibility of understanding obesity as a disorder related to these neuroendocrine systems and that effective treatment options can result from targeting the brain rather than just the adipocyte.

■ *Heart Metab.* 2002;17:4–7.

**Keywords:** Obesity, neuropeptide Y, pro-opiomelanocortin, melanocortin, leptin, insulin,  $\alpha$ -melanocyte stimulating hormone, food intake, energy expenditure

## Adiposity signals

The last 10 years has seen a revolution in the scientific understanding of how body weight is regulated. The timing of this revolution is none too soon since the need for therapeutic interventions for disorders of body weight regulation such as obesity is becoming paramount. In the USA, obesity now afflicts 19.8% of the population, with an additional 35.1% classed as overweight; individuals in each of these categories are at increased risk for heart disease, diabetes mellitus, and some cancers [1]. It is currently estimated that 300 000 people die each year in the USA as a result of obesity, ranking it among the most severe public health crises we face [2]. The urgent clinical need to treat obesity has accelerated

the pace of research on how energy balance is normally maintained by matching energy intake to energy expenditure over long periods of time.

Under most circumstances, changes of body fat simply reflect the difference between energy intake and energy expenditure. A half-century ago, Kennedy [3] proposed that energy balance is maintained by the monitoring of total body fat stores by the brain, and the brain in turn adjusting caloric intake and/or caloric expenditure to keep body fat stores within a narrow range. A critical issue was determining how the brain monitors the total amount of adipose (fat) tissue, since it is scattered and distributed throughout the body. The answer is that the brain is sensitive to the levels of endocrine signals (hormones), which

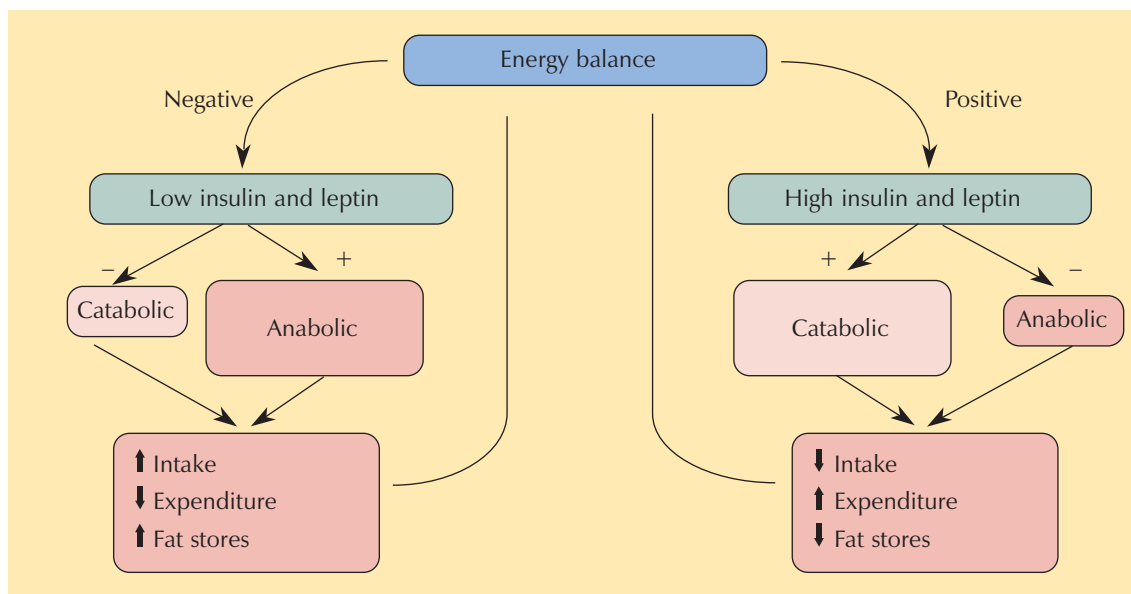


Figure 1. Model of the regulation of energy balance via neuroendocrine responses to alterations of energy balance.

are proportional to the amount of stored fat. Several hormones meet the criteria for being “adiposity signals” that provide negative feedback to the brain in this process and help maintain relatively constant adipose stores [4]. The two best known are the adipocyte hormone leptin and the pancreatic hormone insulin. Both hormones circulate in direct proportion to the total amount of adipose tissue, both cross the blood–brain barrier by receptor-mediated uptake systems, and both have specific receptors located in regions of the brain associated with the control of body weight [5–9]. Administration of either leptin or insulin directly into the CNS results in a dose-dependent reduction in food intake and body weight loss that is not attributable to incapacitation or illness [10–12]. Importantly, genetic manipulations that result in reduced leptin or insulin signaling in the CNS result in increased food intake and obesity [13, 14].

### Brain effectors to regulate energy

Since the discovery of leptin in 1994, considerable attention has been focused on the brain systems that are the target for the

actions of adiposity signals to regulate energy balance. These systems can be divided into two broad categories. The first includes “anabolic” effectors: neural circuits that produce an increase in caloric intake, a decrease in caloric expenditure, and a net gain in body energy stores when they are activated. These anabolic systems are activated during times of negative energy balance when levels of adiposity signals are low. The second category comprises “catabolic” effectors: neural circuits that produce a reduction in food intake, an increase in energy expenditure, and a net loss in body energy stores when activated. Catabolic systems are activated during times of positive energy balance when levels of adiposity signals are high (Figure 1).

Modern molecular biology has identified a number of brain neuropeptides that can be categorized as having either a net anabolic or a net catabolic action. For simplicity, we focus on those systems that are directly regulated by leptin. Neurons containing the signaling form of the leptin receptor (LepRb), as well as the insulin receptor, are localized in the arcuate nucleus of the hypothalamus [15, 16]. Within the arcuate, there are two identified populations of neurons. One population comprises

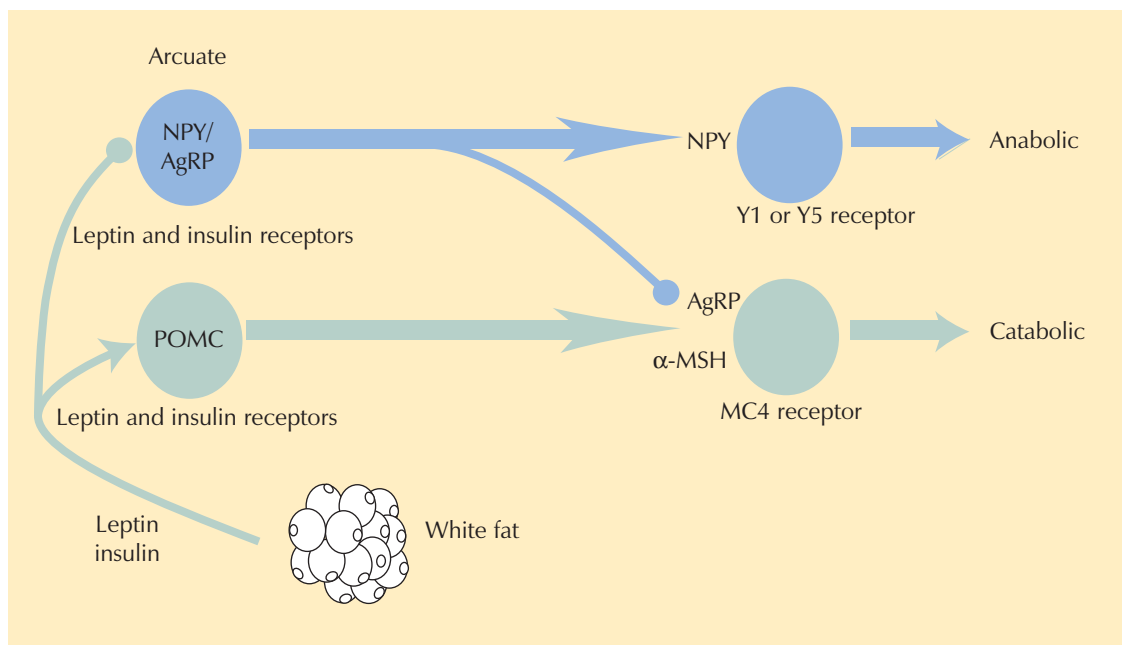


Figure 2. Relationship of arcuate nucleus neuropeptide systems that influence food intake and energy expenditure

neurons that synthesize pro-opiomelanocortin (POMC), a precursor molecule for several important neuropeptides including  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH). In the periphery  $\alpha$ -MSH regulates skin and hair color, but in the brain  $\alpha$ -MSH potently inhibits food intake and increases energy expenditure via its interaction with melanocortin (MC) receptors 3 and 4 [17]. Importantly, POMC neurons express leptin and insulin receptors, and POMC gene expression is inhibited during negative energy balance when insulin and leptin levels are low, and stimulated during positive energy balance [18–20]. A state of positive energy balance can be mimicked by administering either leptin or insulin directly into the CNS, and the response is a reduction of food intake and body weight. Thus POMC/ $\alpha$ -MSH and its associated receptor have all the hallmarks of a catabolic effector system.

The second population of neurons in the arcuate synthesize neuropeptide Y (NPY). Although NPY is synthesized in numerous regions of the brain, only the NPY neurons in the arcuate express leptin receptors, and the expression of NPY is increased during negative

energy balance and inhibited by both leptin and insulin [5, 7]. Moreover, administration of NPY directly into the brain elicits a robust increase of food intake and concomitant decrease of energy expenditure. Thus, the NPY system has all the hallmarks of an anabolic effector system. NPY neurons in the arcuate nucleus synthesize a second neuropeptide termed *agouti*-related peptide (AgRP). AgRP is unique in that it is a potent endogenous antagonist of MC3 and MC4 receptors and therefore works to counter the effects of  $\alpha$ -MSH [21]. AgRP expression is elevated during negative energy balance and inhibited by adiposity signals. Like NPY, AgRP potently stimulates food intake when administered into the CNS [22].

### The difficulty of maintaining weight loss

The picture that emerges is a powerful set of neuroendocrine responses during negative energy balance that make maintaining sustained weight loss exceedingly difficult. When inadequate food is consumed, energy stored

in adipose tissue is used as fuel, and levels of insulin and leptin fall. As a result of the reduced signaling of these hormones in the arcuate,  $\alpha$ -MSH activity falls while NPY activity rises. Additionally,  $\alpha$ -MSH activity is further diminished by increased release of AgRP that antagonizes  $\alpha$ -MSH action at MC3/4 receptors (Figure 2). Most weight loss strategies are likely to fall prey to these neuroendocrine responses that encourage the maintenance of energy stores in mammalian species. Successful treatment of obesity will likely require a more complete understanding of the highly interconnected and redundant CNS systems that normally maintain energy balance. Only when we are able to harness these CNS responses that normally work against the obese patient are we likely to provide effective treatment strategies for obesity.

Needless to say, the advances in understanding the critical role of the brain to regulate body weight opens up the possibility that at least some of the underlying etiologies of obesity are the result of either environmental or genetic influences that either increase anabolic signaling or decrease catabolic signaling within the brain. Exploring these hypotheses in humans is extraordinarily difficult, but some data do provide evidence for substantial genetic links between decreased melanocortin system activity and obesity [23]. However, progress is being made to describe CNS changes in a number of animal models that become obese when exposed to specific dietary regimens [24, 25]. This is an exciting time because no longer are we limited to thinking of obesity as a disease specifically of fat cells. Rather, it is a disease of a body weight regulatory system of which the brain is an essential component. This opens up both new opportunities for understanding why some individuals become obese and how we might treat them. ■

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# Obesity and cardiovascular disease

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## Abstract

Obesity affects the heart in two major ways. It produces hemodynamic and cardiac structural changes that may alter left ventricular function. These alterations are most pronounced in severely obese persons and may predispose to congestive heart failure in such individuals. Obesity also affects the heart through its association with coronary heart disease. This report describes the alterations in cardiac performance and morphology associated with obesity, discusses their clinical sequelae, and reviews the evidence linking obesity to coronary heart disease.

■ *Heart Metab.* 2002;17:8–10.

**Keywords:** Obesity cardiomyopathy, congestive heart failure, eccentric left ventricular hypertrophy, cardiovascular risk factors, coronary artery disease

## Effects of obesity on cardiac performance and morphology

Obesity, particularly severe obesity, produces a variety of alterations in cardiac function and morphology [1–27]. When obesity is severe and chronic, these abnormalities may cause congestive heart failure [1–22].

### *Cardiac hemodynamics, cardiac morphology, and left ventricular function with obesity*

Due to the intense vascularity of fat and to a decrease in systemic vascular resistance, there is a linear increase in total blood volume and cardiac output with increasing adipose accumulation. Since there is no change in heart rate, the augmentation of cardiac output is attributable to an increase in stroke volume [3–6]. Cardiac work rises in excess of that predicted for ideal body weight due to an

increase in stroke work [6]. Oxygen consumption increases and the arteriovenous oxygen difference widens due to the avid metabolic activity of fat [5, 6]. There is a leftward shift in the Frank-Starling curve due to incremental increases in left ventricular pressure and volume [7]. Left ventricular end-diastolic pressure is elevated in many, but not all, severely obese individuals [6–9]. Right heart pressures are also commonly elevated, presumably due to similar hemodynamic alterations or left heart failure [6–9].

Hypertension occurs in 60% of obese persons [4]. Cardiac hemodynamic alterations in such individuals are as previously described except for disproportionately elevated left ventricular stroke work [4, 10]. Systemic vascular resistance is higher than in normotensive obese persons but is lower than that expected in hypertensive lean individuals [4, 10]. The coexistence of systemic hypertension and obesity imparts a double burden on the heart due to a simultaneous increase in afterload and preload [4, 10].

Exercise is able to produce an increase in oxygen intake and cardiac output at mild to moderate workloads but falls toward normal with higher workloads [4, 11]. With exercise, left ventricular end-diastolic pressure often exceeds 20 mm Hg in obese individuals, thus predisposing to pulmonary congestion [4, 11].

The aforementioned hemodynamic alterations may produce changes in cardiac morphology and left ventricular function, particularly in those who are more severely and chronically (usually  $\geq 15$  years) obese [12–18]. The increase in total blood volume and cardiac output leads to left ventricular dilatation [4, 12]. Such hypercirculation may also contribute to enlargement of the left atrium, right ventricle, and right atrium [12]. Dilatation of the left ventricle produces an increase in left ventricular wall stress in accordance with the law of Laplace [4, 12]. This leads to secondary or “eccentric” hypertrophy which is characterized by a high left ventricular radius/thickness or volume/mass ratio and is an attempt to normalize left ventricular wall stress [4, 12]. If wall stress normalizes (adequate hypertrophy), diastolic dysfunction may occur, but systolic function remains normal [14, 18]. If wall stress remains chronically high (inadequate hypertrophy), left ventricular systolic dysfunction may ensue [4, 16, 17]. In hypertensive obese individuals, left ventricular volume is lower and left ventricular wall thickness is greater than in normotensive obese persons, suggesting a hybrid form of hypertrophy [12]. Myocardial fat infiltration, when present, does not typically predispose to left ventricular dysfunction [12].

*Most of the hemodynamic and cardiac structural alterations associated with obesity are reversible with substantial weight loss*

Most, but not all, of the aforementioned hemodynamic and cardiac structural alterations associated with obesity are reversible with substantial weight loss [4, 12, 16, 18–22]. Total blood volume, oxygen con-

sumption, cardiac output, stroke volume, and systemic blood pressure all decrease with weight reduction [4]. In contrast, systemic vascular resistance changes little (if at all), left ventricular end-diastolic pressure commonly remains elevated, and myocardial wall compliance tends to remain abnormal [4]. Weight loss may also fail to fully normalize elevated right heart pressures [4]. There is convincing evidence that substantial weight reduction in severely obese individuals produces regression of left ventricular hypertrophy, improvement of cardiac Doppler-derived indices of left ventricular diastolic dysfunction, and improvement of left ventricular systolic dysfunction in those with impaired systolic function prior to weight loss [12, 16, 18, 20–22].

It is important to emphasize that most of the information concerning cardiac function and morphology in obesity has been derived from studies of severely obese patients. Data derived from studies of mildly to moderately obese subjects are less consistent.

### ***Obesity cardiomyopathy***

Obesity cardiomyopathy is the clinical syndrome of congestive heart failure that evolves from the cardiac functional and structural alterations described in the previous section [23]. The syndrome of obesity cardiomyopathy is seen exclusively in severely obese individuals [23]. Left heart failure predominates [23]; right heart failure occurs as a result of hypercirculation and left heart failure [23]. In some cases, pulmonary hypertension associated with hypoxia due to sleep apnea with or without alveolar hypoventilation may contribute to right heart failure [23]. Sleep apnea occurs in more than 50%, and clinically important alveolar hypoventilation in 5% to 10% of severely obese individuals [23].

Early on, weight gain precedes and then accompanies progressive dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, lower-extremity edema, and, in some cases, increased abdominal girth [23–26]. These episodes may wax and wane with changes in body weight. Initially, these symptoms occur

in the presence of impaired left ventricular diastolic function and normal left ventricular systolic function [23–26]. When symptoms of pulmonary and systemic congestion become persistent, left ventricular systolic dysfunction becomes more prevalent [23]. In those with obesity hypoventilation syndrome (sometimes referred to as “Pickwickian” syndrome), there is an accentuation of symptoms of right heart failure which in the advanced stages may be accompanied by somnolence, confusion, disorientation, or coma [23–26]. Physical findings in obesity cardiomyopathy include gallop rhythm (atrial and ventricular), pulmonary crackles, jugular venous distension, hepatogastric reflux, lower extremity edema, and ascites. In those with obesity hypoventilation syndrome, the aforementioned signs may be accompanied by cyanosis, Cheyne-Stokes respiration, conjunctival suffusion, retinal venous congestion, and papilledema [23–26].

Acute episodes of congestive heart failure are treated with dietary salt restriction, low-flow inspired oxygen, and diuretics [23]. Angiotensin-converting enzyme inhibitors should be employed when left ventricular systolic function is depressed and may be used for systemic hypertension [23]. Digitalis may be useful in patients with atrial fibrillation (for rate control) or in those with left ventricular systolic dysfunction [23]. The role of such drugs as angiotensin receptor blockers, hydralazine, nitrates, spironolactone, and  $\beta$ -blockers in obesity cardiomyopathy has not been established.

Although there is clearcut evidence that substantial weight loss produces regression of left ventricular hypertrophy and improvement of both left ventricular diastolic filling and left ventricular systolic function when such abnormalities are present, information is sparse concerning the effect of weight loss on congestive heart failure in patients with obesity cardiomyopathy [16, 18]. Several case reports and two small series suggest that the clinical manifestations of obesity hypoventilation syndrome can be reversed with substantial weight loss [23–27]. Another small study documented improvement in NYHA functional class following substantial weight loss in most patients

with severe obesity and congestive heart failure but without hypoventilation [26].

## Obesity and coronary heart disease

Obesity has long been cited as a cardiovascular risk factor [28–45]. While its relation to multiple traditional and nontraditional cardiovascular risk factors is unquestioned, the role of obesity as an independent risk factor is less certain. Methods used to determine the relation between obesity and coronary heart disease include: (1) epidemiologic studies relating morbidity or mortality to some measure of total body fat or fat distribution (including those designed to determine if obesity is an independent risk factor); (2) cross-sectional studies assessing the relation of body fat to coronary anatomy; and (3) studies determining the relation of obesity to cardiovascular risk factors [28].

### Epidemiologic studies

There is an impressive body of epidemiologic evidence relating obesity to coronary heart disease and cardiovascular mortality. Obesity was a powerful predictor of coronary heart disease in studies of 1000 to 2000 middle-aged men followed for 10 to 18 years whose relative weight was above 140% or whose body mass index (BMI) was above 30 kg/m<sup>2</sup> [28]. The Honolulu Heart Program and Paris Prospective Study showed that for any given BMI, the risk of coronary heart disease increased twofold with successively higher quintiles and deciles of the Trunk Fat Index [30, 31]. The Normative Aging Study showed an inverse correlation between age at onset of obesity and the probability of developing coronary heart disease [28]. The Framingham Heart Study and the Manitoba Study identified obesity as an independent risk predictor for coronary heart disease after 26 years of follow-up, particularly in women [32, 33]. The Study of Men Born in 1913 and several smaller studies have identified central obesity as an independent risk factor for coronary heart disease [34].

In contrast, the Pooling Project showed no clear aged-adjusted or age-specific association between obesity and coronary heart disease mortality [28]. In the Twin Cities Prospective Study, 284 healthy middle-aged men were followed for up to 35 years [28]. No obesity index discriminated those who lived from those who died. In the Charleston Heart Study, neither BMI nor fat patterning predicted coronary heart disease mortality during 25 years of follow-up [28].

Criticisms of epidemiologic studies, which may help to explain these conflicting results, include: (1) failure to control for cardiovascular risk factors; (2) failure to include some cardiovascular risk factors in the analysis; (3) misclassification bias; (4) small cohort size and short-term follow-up; and (5) dilution of the influence of high-risk groups by inclusion of all obese subjects [28].

### **Anatomic studies**

Anatomic studies attempting to relate obesity to coronary heart disease have similarly produced conflicting results [28]. A large autopsy study of male accident victims aged 25 to 64 years showed a weak correlation between abdominal panniculus size and the presence of raised coronary lesions in Caucasian but not African-American men [28]. In another postmortem study, coronary heart disease severity was greater and catastrophic coronary heart disease events were more frequent in obese men but not in obese women [28]. In an autopsy study of Japanese-Americans there was a positive correlation between coronary heart disease and relative weight greater than 116% [28]. An autopsy study of 1260 patients showed that advanced coronary heart disease was twice as common in those with an abdominal panniculus greater than 3 cm than in those with poor or average nutritional status [28]. In another study, the severity of coronary atherosclerosis correlated positively with the size of adipocytes but not with the number of fat cells, suggesting that environmental factors may be more important than genetic influences in the development of coronary

heart disease in obese individuals [28].

In contrast, several postmortem studies have reported no difference in the frequency of coronary heart disease death or morbidity in men and women based on obesity indexes [28]. Moreover, 12 studies using coronary angiography as a diagnostic probe have failed to demonstrate a consistent relation between obesity and coronary heart disease [28].

### **Obesity and cardiovascular risk factors**

Obesity is renowned for the bad company it keeps. A variety of traditional and novel cardiovascular risk factors occur with greater prevalence in obese than in lean persons and are particularly likely to cluster in those with central obesity [27–43]. As previously noted, systemic hypertension occurs more commonly in obese persons than in lean individuals. Diabetes mellitus occurs with significantly higher frequency in obese than in lean persons.

*Obesity is renowned for  
the bad company it keeps*

The presence of excessive visceral fat predisposes to increased lipolysis and free fatty acid production. This is thought to decrease glucose utilization and increase glucose production, leading to glucose intolerance [28]. Hyperinsulinemia results and contributes to insulin resistance, which in turn increases free fatty acid production, decreases high-density lipoprotein production, and decreases low-density lipoprotein particle size [28, 37, 38]. Triglyceride elevation frequently accompanies these metabolic alterations. Central obesity in association with systemic hypertension, insulin resistance (with or without glucose intolerance), and atherogenic dyslipidemia comprises the metabolic syndrome, itself a powerful risk factor for coronary artery disease [28, 37–40]. A variety of thrombogenic factors have been associated with central obesity including elevated plasma fibrinogen levels, impaired fibrinolysis, increased factor VII and

VIIc activity, and increased plasminogen activator inhibitor levels [41–43]. Plasma homocysteine concentrations are higher in centrally obese than in lean patients [28]. Lipoprotein(a) may also be elevated in obesity [28]. Plasma leptin, which correlates positively with fat mass, was recently identified as an independent cardiovascular risk factor [44]. Obesity has been associated with endothelial dysfunction, an early stage of coronary atherosclerosis.

## Effect of weight reduction

Although weight reduction may favorably modify such cardiovascular risk factors as systemic hypertension, diabetes mellitus, and dyslipidemia, there is currently no evidence showing that weight loss, in the absence of risk factor modification, alters coronary heart disease risk [45, 46].

## Summary

Obesity produces a variety of alterations in cardiac function and morphology. In the severely obese, these changes, in association with altered pulmonary function, may predispose to congestive heart failure (obesity cardiomyopathy). Many of these abnormalities are reversible with substantial weight loss. The preponderance of evidence suggests that there is an association between coronary heart disease and obesity, particularly central obesity. This association is due in large part to the association of obesity with a variety of traditional and novel cardiovascular risk factors. There is substantial evidence that obesity also serves as an independent risk factor for coronary atherosclerosis. ■

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# Echocardiographic and hemodynamic data in obese patients

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### Abstract

Obesity entails a wide variety of adaptations in the cardiovascular system. Specifically, high body mass index results in an increase in heart rate and blood volume, as well as in systolic and diastolic hypertension. Not surprisingly, these changes affect cardiac geometry and mass. In addition to anthropometric factors, neurohormonal and inflammatory systems may be activated, resulting in further cardiac and vascular remodeling. In synergy, these maladaptive changes in the obese organism increase the risk of coronary heart disease and congestive heart failure. This review focuses on the hemodynamic mechanisms involved in these processes.

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**Keywords:** Obesity, left ventricular hypertrophy, cardiac remodeling, fat mass, hypertension

### Hemodynamic adaptations to obesity

Cardiac alterations in patients with obesity reflect an integrated response to multiple hemodynamic, metabolic, and inflammatory derangements. Most notably, the risk of arterial hypertension increases dramatically with obesity. For example, in the Augsburg MONICA survey, the prevalence of arterial hypertension in middle-aged lean subjects was 19%. This number increased to 55% in those with a body mass index (BMI) above 30 kg/m<sup>2</sup> irrespective of age and gender. Regarding the incidence of hypertension the Framingham Heart Study documented that a weight gain of 5% increases the risk of hypertension by 30% within a 4-year period [1]. Not surprisingly, average systolic and diastolic blood pressures display marked differences according to categories of BMI (Figure 1).

In addition to blood pressure, the viscosity of the blood determines cardiac afterload. In this respect, obese individuals present with elevated hematocrit as well as elevated fibrinogen levels (Figure 2) [2]. In concert, these changes alter the rheological properties,

adding further to the pressure load on the hearts of obese individuals [2]. In addition to pressure overload, volume load of the heart is elevated in obese individuals. In fact, cardiac output increases in parallel with body weight, suggesting an adaptive response of the heart to serve the increased circulatory demands [3]. Cardiac output in the MONICA population showed a highly significant increase with increasing categories of BMI (Figure 3). Finally, individuals with obesity present with higher heart rates, a finding that probably reflects increased sympathetic drive (Figure 3) [4].

Taken together, the heart of an obese person is faced by a series of maladaptive mechanisms that synergistically increase pressure and volume load as well as heart rate. Structural changes to the cardiac muscle are an inevitable consequence.

### Changes in cardiac mass and geometry

In light of the hemodynamic changes, it is no surprise that obesity alters left ventricular (LV)

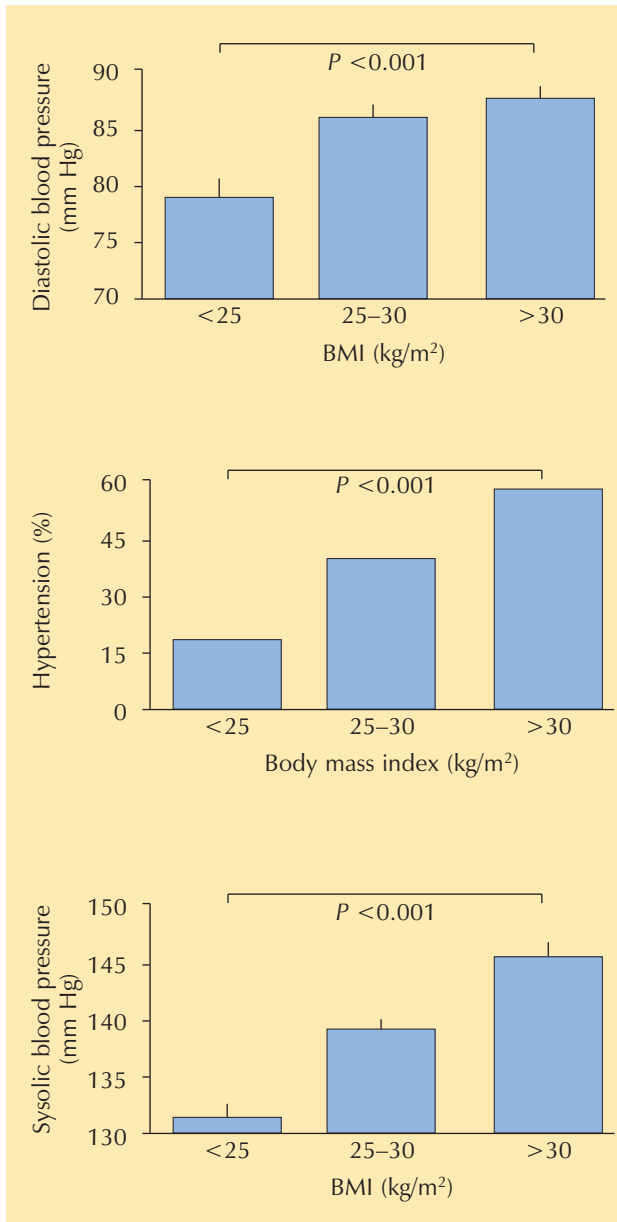


Figure 1. Systolic and diastolic blood pressures and the prevalence of hypertension in 1670 individuals in the Augsburg MONICA surveys. Data are adjusted for age and gender. With increasing BMI, a substantial increase was observed for each parameter, documenting the profound effects of obesity on cardiac afterload.

mass and geometry. Most significantly, obesity results in an increased risk of left ventricular hypertrophy (LVH) [5]. Even after adjustment for age, gender, and blood pressure, the Fram-

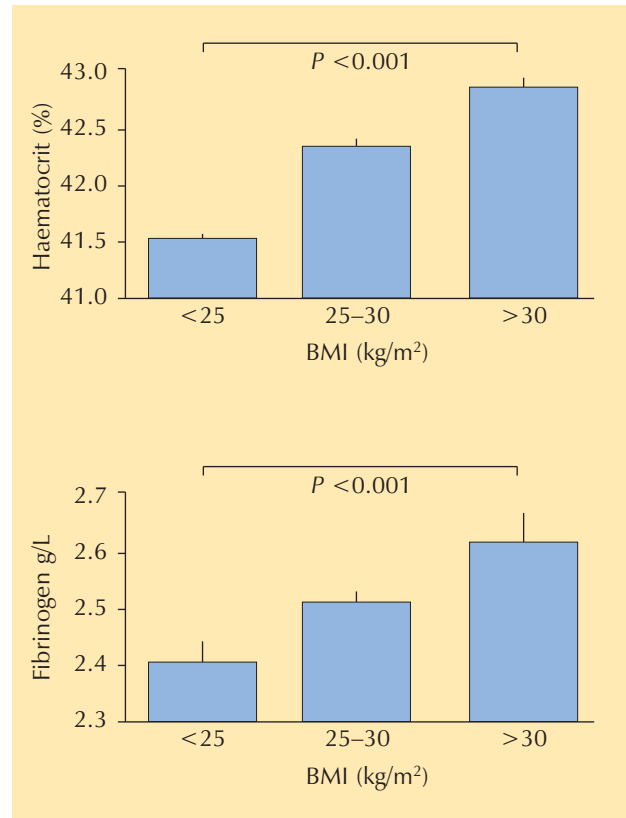


Figure 2. Hematocrit and fibrinogen levels in 1670 individuals in the Augsburg MONICA surveys. Both key determinants of blood viscosity increase with obesity, adding to the pressure load of the heart.

ingham Heart Study demonstrated highly significant relations between BMI and LV dimensions and wall thicknesses [6, 7]. The probability of LVH rises from 5.5% in lean subjects to 29.9% in obese subjects (Figure 4). Indeed, obesity may confer a higher risk for LVH than arterial hypertension [8].

Echocardiographic analyses have provided further evidence of the adaptive changes in cardiac geometry in obese individuals. Particularly, echocardiography allows the investigator to establish whether the pathological increase in LV mass is due to dilatation of the heart (eccentric LVH) or due to thickening of its walls (concentric LVH). In obesity, LVH is caused to a variable extent by increases in LV volume and LV wall thickness [8–10]. Indeed, obesity in the absence of hypertension was found to predominantly increase volume load. Subsequently,

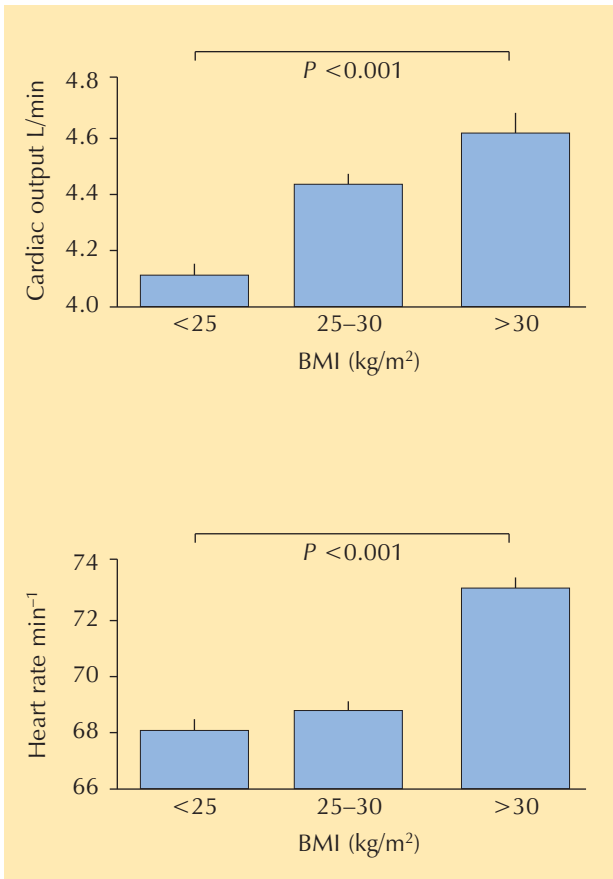


Figure 3. Cardiac output and heart rate in 1134 individuals in the Augsburg MONICA surveys. The data document that the volume and chronotropic demands on the heart increase in parallel with BMI.

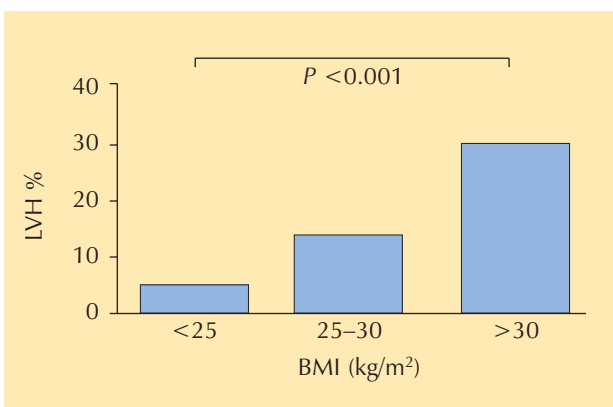


Figure 4. Prevalence of LVH in 1670 individuals in the Augsburg MONICA surveys. With increasing BMI, a substantial increase in LVH was observed, documenting the profound risk related to obesity with respect to cardiac hypertrophy.

LV dimensions increase and so thus the risk of eccentric LVH. By contrast, obesity in conjunction with hypertension resulted predominantly in increased LV wall thickness [11].

### Coexistence of obesity and hypertension

Obesity is considered to be the most frequently occurring secondary form of arterial hypertension. Thus, both conditions may often be found in combination. With respect to cardiac geometry, Kuch and coworkers analyzed the combined effects of obesity and hypertension [10]. Most notably, the coexistence of hypertension and obesity produced a concentric pattern of LVH. Accordingly, in obese, hypertensive individuals the predominant cardiac effects were seen in the form of increased posterior and septal thicknesses. The additive effects of obesity and hypertension with respect to the most important hemodynamic and cardiac structural parameters are summarized in Figure 5 [11].

### Differentiation between fat and fat-free mass

In order to elucidate the mechanisms that form the link between obesity and cardiac structural changes it may be of interest to take a closer look at body composition. Roughly, body composition may be divided into fat and fat-free mass. With respect to the heart, this distinction is of particular interest since fat mass is poorly perfused whereas fat-free mass determines the circulatory demands. Obesity not only results in an increase in fat mass but also an increase in fat-free mass in an average ratio of 8:2 [12]. However, there may be substantial interindividual variability with respect to body composition in obese subjects. Therefore, the Strong Heart and Augsburg MONICA studies used body impedance measurements in order to distinguish between poorly perfused fat mass and metabolically active fat-free mass [9, 13]. LV dimensions were found to be strongly associated with fat-free mass,

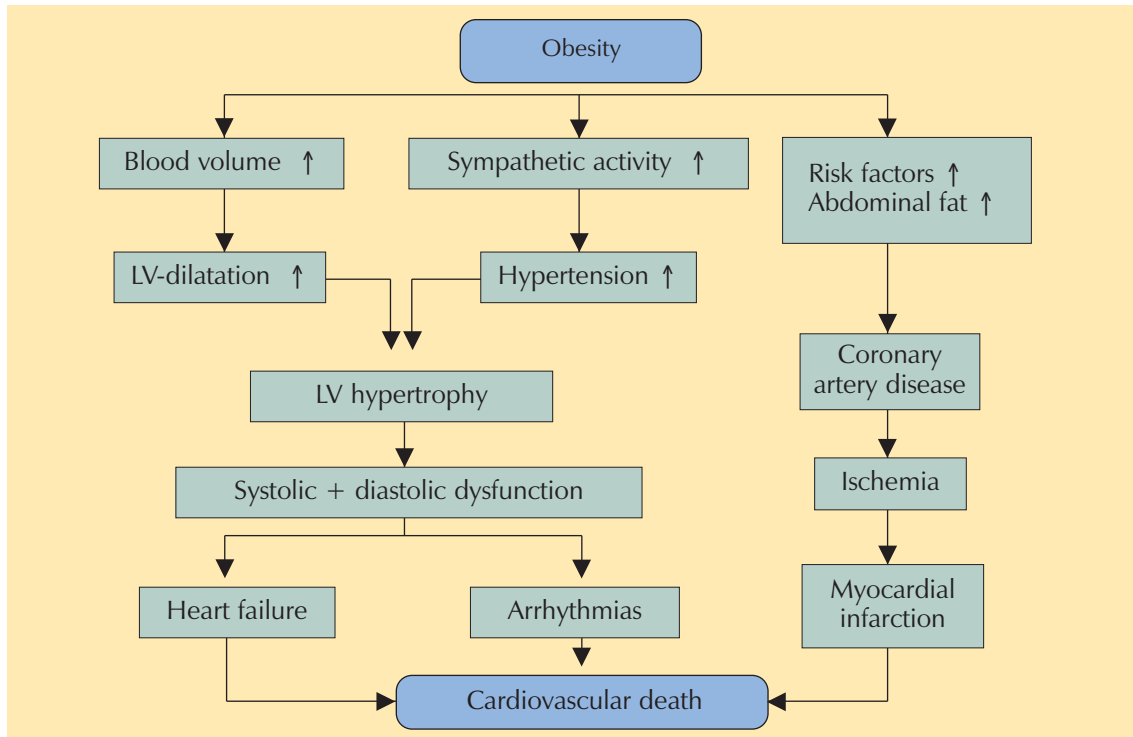


Figure 5. Flow chart showing the hemodynamic, structural, and functional alterations of the heart observed in obese patients (adapted from [8]).

whereas septal and posterior wall thicknesses correlated with fat mass. These data suggest that differential mechanisms may contribute to the increase in LV dimension and wall thickness in obese individuals.

The disproportional increase in LV wall thickness, as observed with elevated fat mass, mimics the effects of arterial hypertension. By contrast, an increase in fat-free body mass (visceral organs, musculature) increases the circulatory demands and may result in a balanced increase in cardiac size. Thus, with respect to the heart, the pathological component of obesity is largely the increase in fat mass that results in pressure overload and, subsequently, concentric remodeling of the myocardium.

### Cardiac function and obesity

LVH has been identified as one of the strongest predictors of heart failure [14]. Thus,

the changes in cardiac morphology and geometry of obese individuals are only intermediate steps towards a profound alteration in cardiac function (Figure 5). Most prominently, the chronic elevation of cardiac pressure load and secondary concentric LVH result in a progressive impairment of LV filling, leading to a high risk of diastolic heart failure. Accordingly, obesity has been identified as an independent predictor of LV diastolic dysfunction in the general population [15].

With excessive obesity, alterations in systolic function may also become evident. In particular, longstanding obesity may result in a decrease in mid-wall fiber shortening and ejection fraction [16]. In conjunction, diastolic and systolic malfunction of the heart, along with obesity itself, contributes to the symptomatology of obese individuals, most notably dyspnea and reduced exercise capacity.

In addition to changes in cardiac function, cardiac arrhythmias are frequently found in obese subjects [17]. Particularly if there is a

concentric pattern of LVH, the prevalence of ventricular ectopic beats is substantially raised. Moreover, obesity is a significant risk factor for atrial fibrillation [18]. In this respect the hyperdynamic circulation in conjunction with diastolic dysfunction, as observed in obesity, may constitute important pathophysiological mechanisms that cause atrial enlargement and, subsequently, fibrillation. In addition to the respective symptoms, these arrhythmias may also contribute to the elevated cardiovascular risk observed in obese individuals (Figure 5).

## Regression of hypertension and LVH by weight reduction

Numerous interventional studies have documented that weight reduction reduces the risk of arterial hypertension and LVH in obese individuals. In fact, in some studies, weight reduction was more successful than pharmacological therapy with respect to LVH regression and blood pressure lowering [19]. Undoubtedly, weight reduction helps to limit hypotensive pharmacotherapy in obese individuals. Moreover, sympathetic drive and heart rate variability may be substantially improved by weight loss [20]. It is unclear at present whether weight reduction also has beneficial effects on long-term disturbances of systolic and diastolic cardiac function in obesity. However, there is no doubt that the clinical symptoms of heart failure such as dyspnea and reduced exercise capacity respond well to weight reduction. In addition, preliminary evidence suggests that pharmacologically assisted weight reduction has beneficial effects on cardiac geometry and function [21].

## Conclusion

The heart of an obese individual is subjected to a multitude of hemodynamic, neuroendocrine, and metabolic factors that, in conjunction, lead to volume and pressure load on the heart. Depending on the admixture of contributing factors, either eccentric or con-

centric LVH develops as an intermediate step. Ultimately, symptoms of heart failure or cardiac arrhythmias develop, increasing the risk of cardiac death. Emphasis should therefore be focused on weight reduction and prevention of cardiac alterations secondary to obesity. ■

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# Diets, medications, and surgery

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### Abstract

The rising prevalence of obesity, defined as a body mass index  $>30$  kg/m<sup>2</sup>, has prompted the need for effective interventions. Unfortunately, weight loss programs are associated with high rates of recidivism. This paper reviews the current literature with regard to the use of diets, medications, and surgery in the management of obesity. Clinical application of these interventions is dependent on a good understanding of their efficacy and potential complications.

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**Keywords:** Obesity, weight loss, bariatric surgery

### Introduction

Obesity is defined as a body mass index (BMI)  $>30$  kg/m<sup>2</sup> and is becoming more prevalent worldwide. It is associated with multiple medical complications including type 2 diabetes mellitus, hypertension, and dyslipidemia. Modest weight loss (5% to 10%) has been shown to reduce the risks for many associated complications [1]. However, weight loss remains a challenging endeavor. A successful weight loss program encompasses long-term dietary modification with caloric restriction, an increased level of physical activity, and changing behaviors that are counterproductive to weight management. Novel medical therapies and current surgical procedures offer important therapeutic alternatives in the management of obesity.

defined as a daily caloric intake ranging from 1000 to 1500 kcal/day. Caloric restriction can be achieved in various ways, commonly by limiting the intake of fat or by decreasing the portion size of various nutrients. Most studies have reported an average weight loss of 8% from initial weight in clinical trials ranging from 3 to 12 months' duration [1]. A VLCD is a more restrictive regimen ( $<800$  kcal/day) completed under medical supervision. It is associated with a greater initial weight loss (15% to 20%) when compared with LCD. However, VLCD have a higher rate of weight regain and have not been shown to be more effective than LCD after 1 year of therapy [2, 3]. Improved outcomes of VLCD have been reported when combined with behavioral therapy and, most recently, sibutramine [4]. It is unknown if these interventions will improve the clinical utility of VLCD.

### Diets

A diet prescription remains the cornerstone of weight loss therapy. Two dietary treatments frequently studied are low calorie diets (LCD) and very low calorie diets (VLCD). An LCD is

### Medications

Two medications are currently available for the prolonged management of obesity: sibutramine and orlistat. Pharmacotherapy can be

# New therapeutic approaches

Diets, medications, and surgery

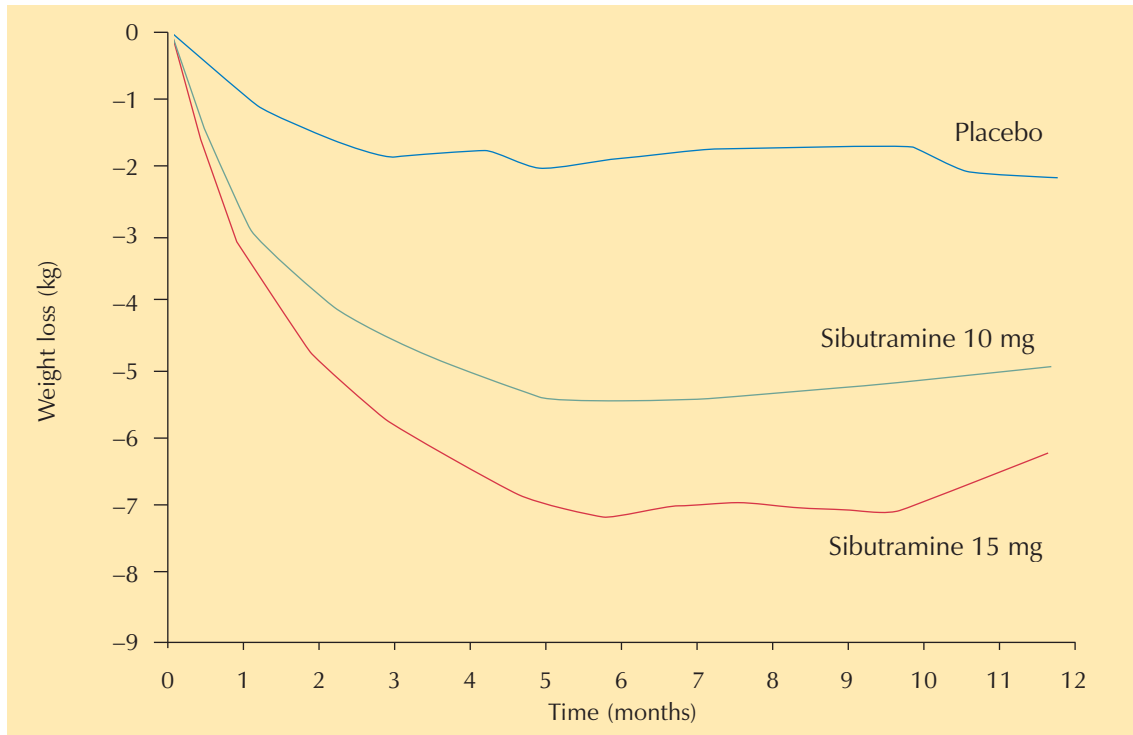


Figure 1. Weight changes observed during a 12-month trial of sibutramine 10 mg ( $n = 81$ ) or 15 mg ( $n = 94$ ), and placebo ( $n = 80$ ) [5].

considered in individuals with a BMI  $>30$   $\text{kg}/\text{m}^2$  or  $>27$   $\text{kg}/\text{m}^2$  in the presence of medical complications that would benefit from weight loss [1]. Drug selection is guided by

potential side effects, contraindications to their use, and their impact on an individual patient. The initiation of medical therapy should not be an isolated intervention. It

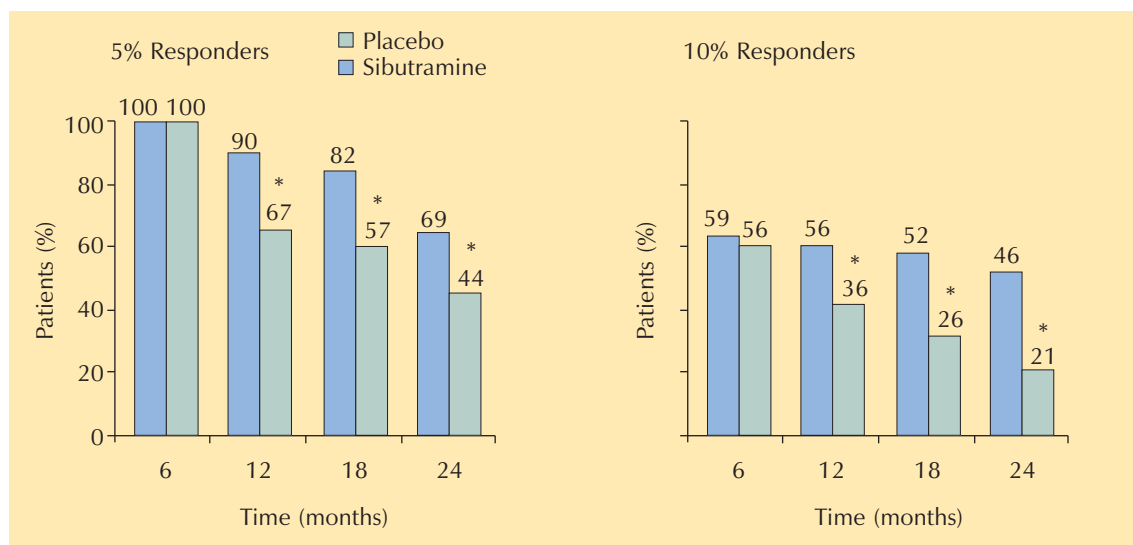


Figure 2. Percentage of patients maintaining a greater than 5% weight loss with sibutramine ( $n = 350$ ) vs placebo ( $n = 114$ ) over a 24-month period ( $*P < 0.001$ ) [6].

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should be combined with guidance regarding dietary modification, physical activity, and behavioral therapy to help change behaviors counterproductive to weight loss. Regular visits should monitor progress and potential side effects of medication. A multidisciplinary team involving physicians, dietitians, psychologist, and, when deemed necessary, exercise physiologists best accomplishes this.

Sibutramine is a serotonin and adrenaline reuptake inhibitor shown to promote satiety. Dosages of 10 mg and 15 mg daily led to a statistically significant weight loss when compared with placebo after 12 months (Figure 1) [5]. Sibutramine is also superior to placebo at promoting weight maintenance at doses up to 20 mg/day (Figure 2) [6]. Clinical efficacy can be determined early in a therapeutic trial. “Nonresponders” who failed to achieve a 1% weight loss at 4 weeks did not experience additional weight loss despite continued therapy. Common side effects included dryness of

the mouth, constipation, and insomnia. A significant rise in blood pressure was observed in some subjects and this should be routinely monitored [5]. Sibutramine should be used with caution with other preparations that influence serotonin metabolism due to the potential risk for “serotonin syndrome,” a condition caused by central and peripheral serotonergic hyperstimulation.

Orlistat is a gastric and pancreatic lipase inhibitor that inhibits the breakdown and absorption of dietary fat [7]. At current recommended doses of 120 mg three times per day it is associated with malabsorption of 30% of ingested fat, which can provide a caloric deficit of about 200 kcal/day. Double-blind placebo-controlled trials have shown orlistat to be superior to placebo at promoting weight loss for up to 1 year (Figure 3). Orlistat was also statistically superior to placebo in promoting weight maintenance (Figure 4) [8–10]. In a study by Sjöström et al [8], the cohort

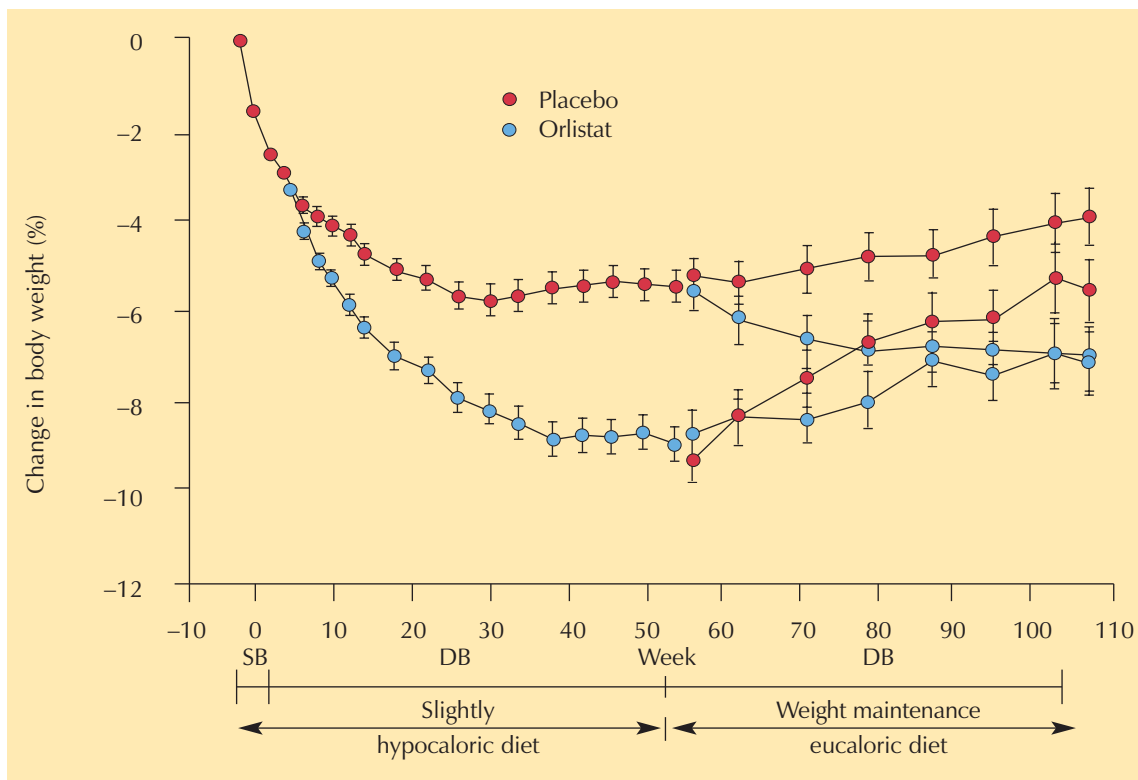


Figure 3. Mean percentage change in weight with orlistat during an initial 12-month weight loss period followed by a 12-month weight maintenance phase [8]. SB, Single-blind; DB, double-blind.

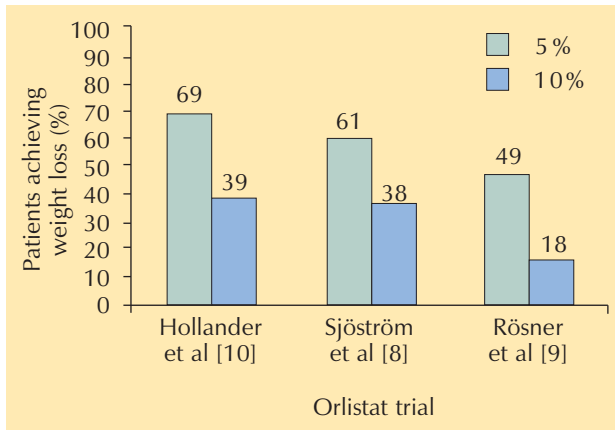


Figure 4. Percentage of patients losing 5% or greater of their initial body weight during three orlistat trials [8–10].

initially treated with placebo and later randomized to orlistat experienced the best outcome. Their weights continued to decrease to a final weight not statistically different to that of the subjects who remained on orlistat for the full 2-year study. This strongly suggests that this medication is most effective in individuals who have already established lifestyle changes in enhancing continued weight loss.

The most common side effects were gastrointestinal and were influenced by the amount of dietary fat.

Decreased vitamin levels were observed during clinical studies. No vitamin deficiencies were reported and the changes initially observed were corrected with administration of a daily multivitamin.

## Surgery

Bariatric surgery has been available for decades, although the procedures performed have varied over the years. Initial aggressive surgeries such as the jejunoileal bypass were associated with significant weight loss, however the metabolic complications limited its continued clinical application [11]. The surgical procedures available today follow two basic principles to promote weight loss: gastric restriction limiting food intake with or without intestinal bypass promoting either a “dumping physiology” or less vigorous malabsorption.

Table I. Recommended criteria for patient selection when considering bariatric surgery.

Weight
45.5 kg or 100% above desirable weight for over 5 years
BMI >40 kg/m <sup>2</sup>
BMI >35 kg/m <sup>2</sup> with medical complications
Failure of nonsurgical attempts at weight reduction
Psychological stability
Absence of uncontrolled psychiatric disorder
Absence of substance abuse
Understanding of risk and benefits of procedure
Commitment to lifestyle changes and scheduled follow-up visits

Patient selection is a rigorous process. It serves to assure an individual patient fulfills accepted criteria (Table I), provides informed consent regarding risk and benefits of intervention, and hopes to prepare patients, medically and psychologically, to improve long-term outcome and minimize risks. The most common bariatric procedures performed today include the vertical banded gastroplasty (Figure 5), Roux-en-Y gastric bypass (Figure 6), and the biliopancreatic bypass (Figure 7).

All three procedures lead to significant weight loss, often with improvement of pre-existing metabolic complications (Table II)

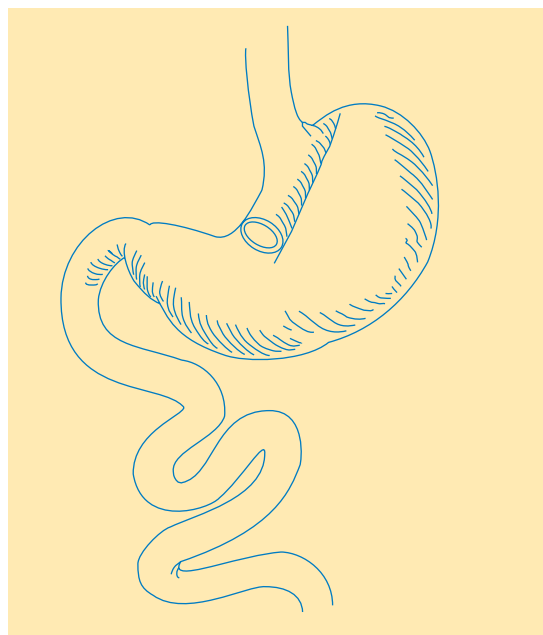


Figure 5. Vertical banded gastroplasty.

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Table II. Weight loss reported by various bariatric surgical procedures [13–15].

	Excess weight lost		
	1 to 2 Years	5 to 6 Years	8 to 10 Years
Vertical banded gastroplasty	50%	25%	
Roux-en-Y gastric bypass	65% to 80%	58%	55%
Biliopancreatic diversion	78%	78%	77%

[12–15]. Gastric restrictive surgeries are associated with less weight loss and higher rates of recidivism, and as a result are less commonly performed [13].

Surgeries leading to nutrient malabsorption lead to greater weight loss but at the risk of nutritional deficiencies. Deficiencies in iron, folate, vitamin B<sub>12</sub>, and fat-soluble vitamins have been reported after Roux-en-Y gastric bypass and biliopancreatic diversion [12, 15].

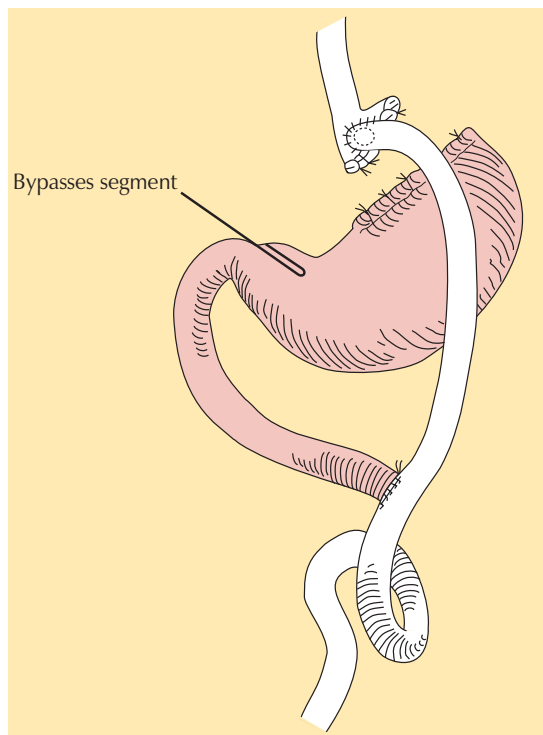


Figure 6. Roux-en-Y gastric bypass surgery procedure.

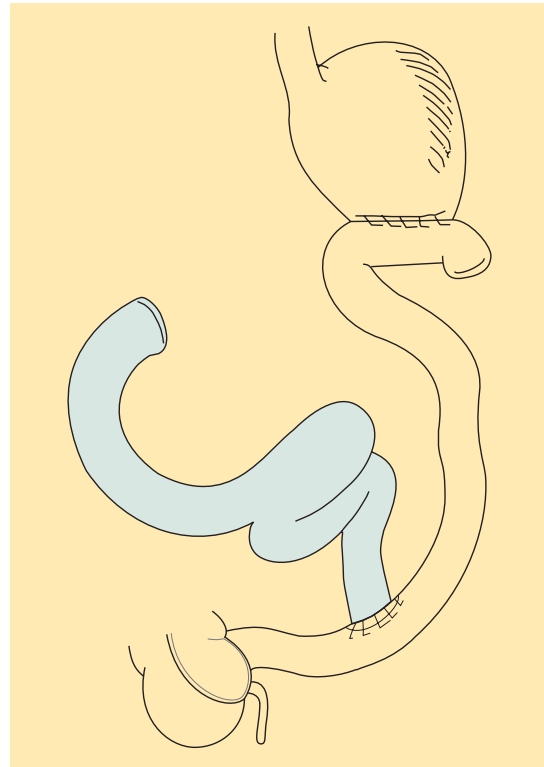


Figure 7. Biliopancreatic diversion.

Routine vitamin supplementation and careful monitoring for potential deficiencies is recommended. Protein deficiency is a common finding after biliopancreatic diversion. Hypoalbuminemia is reported in 20% of patients 6 months after surgery. Despite dietary counseling to optimize the intake of protein calories, the yearly revision rate because of hypoalbuminemia is 0.1% [12].

Bariatric surgery has a perioperative mortality of less than 1% and the incidence of perioperative complications is <2%. Later complications such as incisional hernias and gallbladder disease range between 10% and 30% [12–16].

These procedures are now offered laparoscopically with decreased perioperative morbidity and decreased length of hospital stay. However, reoperation rates for device-related complications are higher [17].

Despite the risks, bariatric surgery is currently the most effective therapy for medically complicated obesity.

## Summary

The prevalence of obesity and its associated morbidity has prompted the need for effective weight loss therapy. Sustained lifestyle changes such as dietary modification are imperative for long-term success but have been plagued by high rates of recidivism. To date, the best dietary prescription is one leading to modest caloric restriction since more aggressive VLCD have not been proven to be more efficacious in the long term. Sibutramine and orlistat offer effective therapeutic alternatives to facilitate weight loss when the basic components of a weight loss program are in place. Several bariatric procedures currently performed are effective treatments for the carefully selected patient with medically complicated obesity. ■

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# Rationale for a metabolic intervention in obese patients with coronary heart disease

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## Abstract

Obesity and diabetes are common associated risk factors that contribute to increased cardiovascular mortality. Their prevalence is increased in patients with coronary artery disease; coexisting changes in cardiac metabolism worsen the consequences of myocardial ischemia. Pharmacologic manipulation of cardiac metabolism has proved to be a rational approach to patients with coronary heart disease and diabetes, and/or obesity. This is evidenced by the clinical benefits that can be derived from the use of trimetazidine, the first 3-ketoacyl-CoA-thiolase inhibitor, a metabolic anti-ischemic agent that optimizes cardiac metabolism secondary to a reduction in fatty acid oxidation. ■ *Heart Metab.* 2002;17:26–30.

**Keywords:** Obesity, coronary artery disease, trimetazidine, cardiac metabolism

## Introduction

Obesity is a complex, multifactorial, chronic disease characterized by excess body fat resulting from an imbalance between energy expenditure and caloric intake. The causes of this imbalance appear to be physiological, metabolic, and genetic, as well as environmental, cultural, and social.

Overweight and obesity are recognized as a major cause of the increase in serious and life-threatening diseases, in particular excessive cardiovascular mortality [1]. The relationship between body mass index and mortality is curvilinear [2, 3].

The primary comorbidities of obesity are type 2 diabetes, cardiovascular diseases, hypertension, reproductive disorders, certain cancers, and respiratory diseases.

Patients with intra-abdominal fat accumulation (android obesity) tend to have a cluster of metabolic abnormalities known as the metabolic syndrome, or syndrome X [4]. A combination of insulin resistance, hyperinsulinemia, dyslipidemia, and essential hypertension is the hallmark of the metabolic syndrome [5, 6]. All

are major risk factors for most coronary diseases, and a correlation has been shown between android obesity, elevated risk for coronary artery disease, and mortality [5, 7, 8].

## Obesity, insulin resistance, dyslipidemia, and coronary heart disease: a fatal combination?

Although genetic factors clearly play a role in the development of insulin resistance or type 2 diabetes, obesity is the most potent environmental risk factor for type 2 diabetes [9]. Both obesity and diabetes are increasing at an alarming rate among the general population; the prevalence of diabetes is 3.8 times higher in overweight than in normal subjects 20 to 45 years of age [10].

Type 2 diabetes and obesity are associated with a cluster of atherogenic risk factors: weight gain and visceral adiposity give rise to an increased insulin requirement which may lead to hyperinsulinemia and, ultimately, diabetes [5, 11–13]. Several factors may contribute to the development of insulin resis-

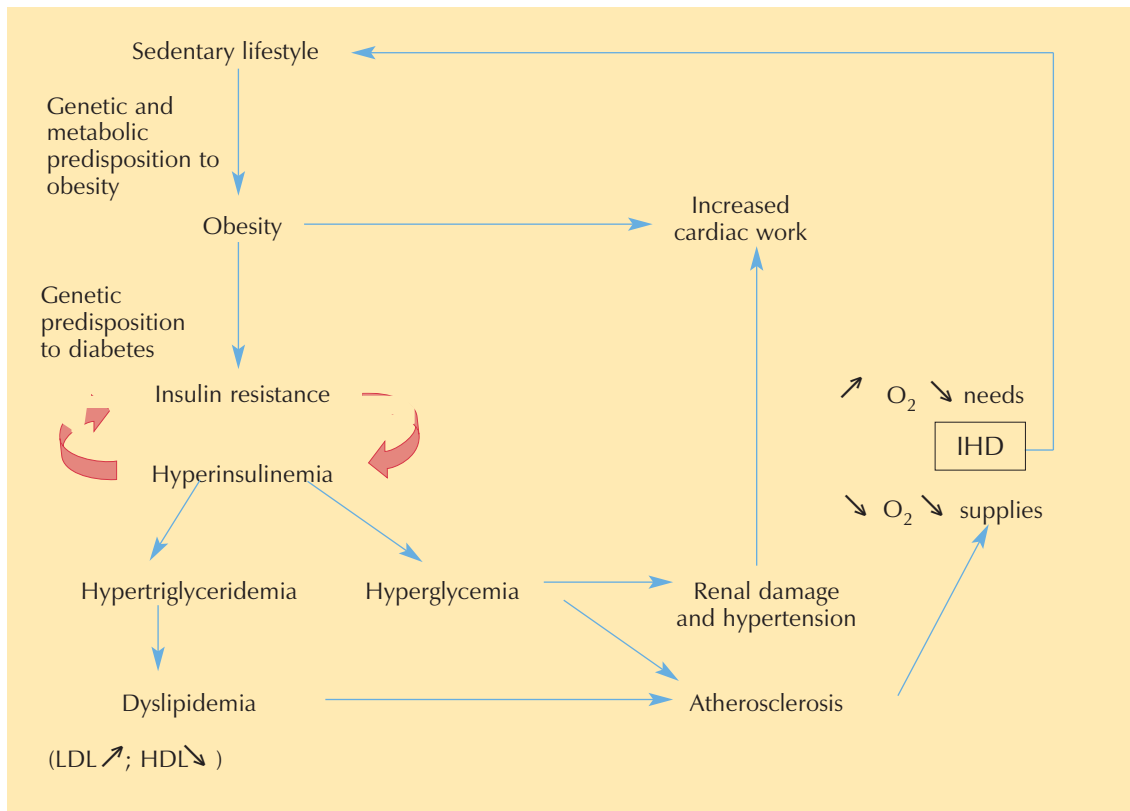


Figure 1. Interrelations between obesity, cardiovascular risk factors, and IHD. IHD, Ischemic heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

tance in the obese patient, including abnormalities in free fatty acids, hormone signaling, and genetic polymorphisms [14, 15]. The increased levels of plasma free fatty acids and steroid hormone abnormalities observed in obese patients may modify insulin sensitivity in the peripheral tissues [16].

Hypertriglyceridemia in association with hypercholesterolemia is common in obesity and type 2 diabetes, exacerbating a genetic predisposition to coronary artery disease [8]. The underlying metabolic abnormalities behind dyslipidemia are insulin resistance and hyperinsulinemia. Hypertriglyceridemia further leads to an increase in low-density lipoprotein cholesterol; a decrease in high-density lipoprotein cholesterol is also commonly observed [17].

Primary cardiovascular risk factors such as lack of physical exercise, insulin resistance (and associated hyperinsulinemia), dyslipi-

demia, and type 2 diabetes are present in the obese patient [18]. All those risk factors, together with the increased demand that obesity imposes on the heart to supply blood to the peripheral organs, explain the raised prevalence of cardiovascular disease including coronary artery disease and heart attacks in obese patients (Figure 1) [11].

## Trimetazidine: a rational choice in coronary patients at increased cardiovascular risk

Changes in cardiac metabolism during ischemia represent an inevitable step in the ischemic cascade, which is exacerbated in obese patients (Figure 2). Concomitant diabetes present in obese patients has a negative impact on myocardial metabolism: diabetes impairs glycolysis, pyruvate oxidation, and lac-

## Focus on trimetazidine (Vastarel)

Trimetazidine in obese patients with CHD

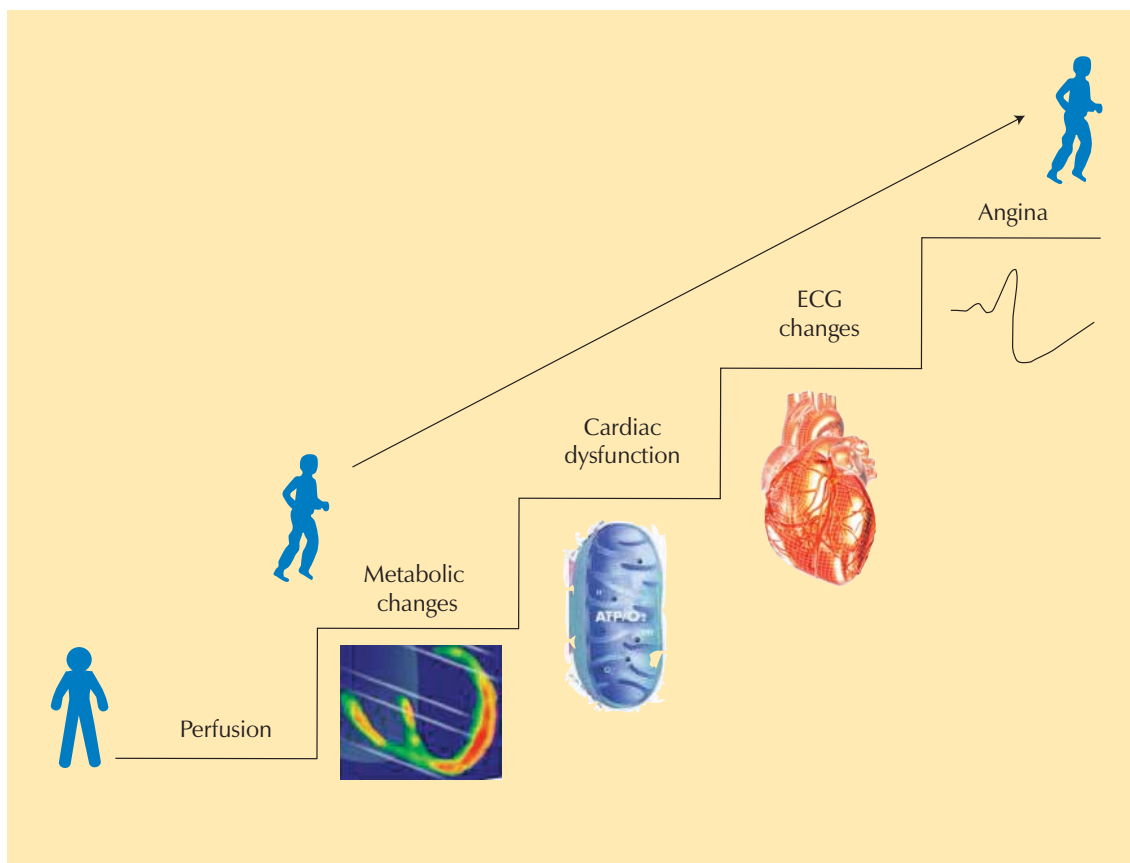


Figure 2. The ischemic cascade: from myocardial ischemia to angina.

tate uptake, and creates a greater dependency on fatty acids (which are in excess in the obese patient) as a source of acetyl-CoA. It contributes to the increase in ischemic symptoms since more oxygen is required to produce each molecule of ATP than via the carbohydrate pathway. Shifting cardiac metabolism away from fatty acid oxidation to glucose oxidation can significantly improve cardiac efficiency (cardiac work/oxygen consumed) [19]. In this context, manipulation of cardiac metabolism that results in a switch to optimal substrate utilization is particularly appropriate.

Thus, trimetazidine, with its specific metabolic mechanism of action, is a treatment of choice for obese diabetic patients with coronary heart disease. Trimetazidine is a metabolic anti-ischemic agent known to optimize cardiac energy metabolism without causing any adverse hemodynamic effects. It acts by

inhibiting long-chain 3-ketoacyl-CoA-thiolase, which results in partial inhibition of fatty acid oxidation and stimulation of glucose oxidation [20]. This shift in substrate preference leads to a 12% improvement in ATP production, limits cell acidosis, and preserves the contractile function of the heart [21].

The anti-ischemic and cardioprotective effect of trimetazidine translates into clinical benefits. The first-line antianginal efficacy of trimetazidine has been confirmed in monotherapy versus placebo [22] and in comparison with reference drugs [23, 24]. Trimetazidine has also proven additive value in combination with conventional agents in patients resistant to  $\beta$ -blockers [25, 26] and calcium antagonists [27, 28].

Trimetazidine has been shown to be particularly suitable for diabetic patients since the diabetic heart has an increased sensitivity to

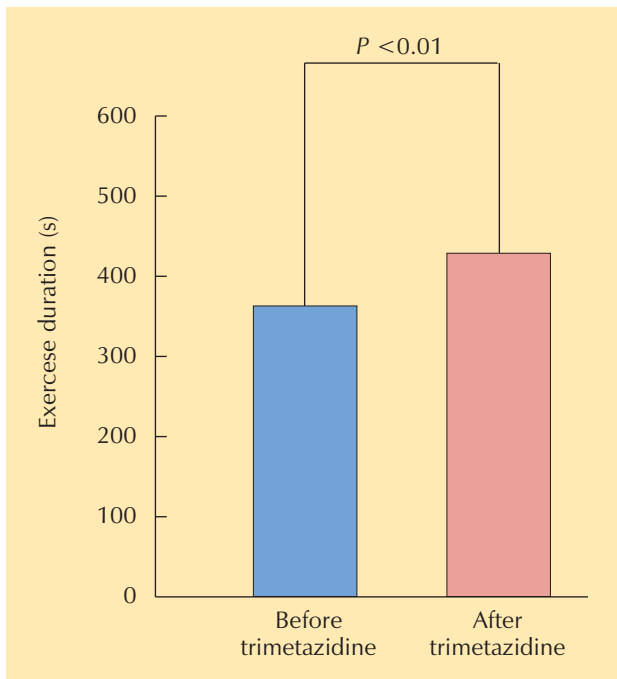


Figure 3. Effect of trimetazidine on exercise duration in diabetic patients with angina.

ischemia due to a greater reliance on fatty acid oxidation. This was evidenced in a sub-analysis of anti-ischemic efficacy and tolerability from a multicenter study. Trimetazidine 20 mg tid improved cardiac markers in 50 diabetic coronary patients after 1 month of therapy [29]. Ergometric parameters, such as exercise duration (Figure 3), were significantly enhanced. Another trial assessed the short- and long-term efficacy of trimetazidine in coronary patients with diabetes and ischemic dilated cardiomyopathy in addition to standard therapy. Results demonstrated a significant improvement in symptoms, left ventricular function, glucose metabolism, and endothelial function in comparison with placebo [30].

Taken together, these data strongly suggest that pharmacological manipulation of cardiac metabolism with a metabolic anti-ischemic agent such as trimetazidine is a sound choice in coronary patients with concomitant risk factors such as diabetes and obesity. ■

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# Helping your patients confront their cardiovascular risk

## How to motivate your patient

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### Abstract

We propose the use of a simple chart to identify, together with the patient, his or her cardiovascular risk factors. This procedure is particularly helpful for the development of psycho-pedagogical strategies aimed at motivating patients to modify their life style behavior. We also use model showing the chain of events which lead a person to make a successful change.

In the precontemplation stage, the negative aspects of exercising or dieting overcome the potential advantages. We must, for the time being, limit ourselves to provide information. At the contemplation stage, the negative and positive aspects are still not balanced. We can help by encouraging the thought that change is possible by promoting its advantages. The preparation stage is the appropriate time to make realistic plans and to negotiate "baby step" objectives. Once patients have embarked upon the action stage, it is important to encourage success whilst providing help to overcome the remaining obstacles. Finally, we reach the maintenance stage where patients discover more advantages than disadvantages. It is important to strengthen their commitment and to reinforce success while maintaining strategies to prevent relapse.

In conclusion, physicians are frequently in a rush to go straight to the action stage and propose strategies that do not respect patients' own pace. We must prepare our patients and wait for them in order to improve their motivation. ■ *Heart Metab.* 2002;17:31–34.

**Keywords:** cardiovascular risk, life style, motivation, behavior, physical exercise, maintenance, relapse

We probably do not need to convince health care providers of the importance of making patients aware of their cardiovascular risk. Several large longitudinal studies have proven its efficacy. Nevertheless, we, as health care providers, have to tackle the issue of patient motivation to modify existing behaviors. We propose the use of a simple chart to identify, together with the patient, his or her cardiovascular risk factors (*Figure 1*). Let us take one example.

A 55-year-old businessman in good general health comes for a routine medical check-up. He has no symptoms of angina pectoris or peripheral vascular disease. He reports sailing during the summertime and skiing for 1 week during the winter. His father died at the age of 55 from acute myocardial infarction and his mother is currently being treated for hypertension. A physical examination reveals: good general health status, weight 80 kg, height 1.75 m,



# Case report

## Patient recognition of cardiovascular risk

patient's risk is calculated prior to the development of strategies.

If we follow the chart for the example above, our patient scores 4 points for his glucose intolerance, 6 points for his hypertension (160/95), and 27 points for his total cholesterol based on his age of 55, which gives him a total score of 37 points. In this setting, HDL cholesterol concentration acts as a correction factor for total cholesterol. For this particular patient, the correction will be 1 (×1). This makes a total score of 37. The right-hand column shows that his chances of having an ischemic event in the next 6 years approach 15.5%.

### How to motivate your patient

This patient should be advised to control his food intake, lose weight, and exercise in order to reduce his cholesterol, glycemia, and blood pressure. But how can we promote a lifestyle change on a long-term basis? Motivation is the result of the interaction between personal goals (life project), an emotional stimulation (to feel like doing something) and self-efficacy. The patient's life project is based on his targets, beliefs, and values. It is a mixture of his life history, his successes, and his feelings. The life project may not always be entirely clear to the patient himself; nevertheless, it is the root for his motivation.

The need for change becomes clear once the patient perceives a contradiction between his life project and current reality. This imbalance may prompt the appearance of negative emotions such as anger and fear, but these will likely encourage him to seek a new situation that is more in accordance with his personal life project [1, 2].

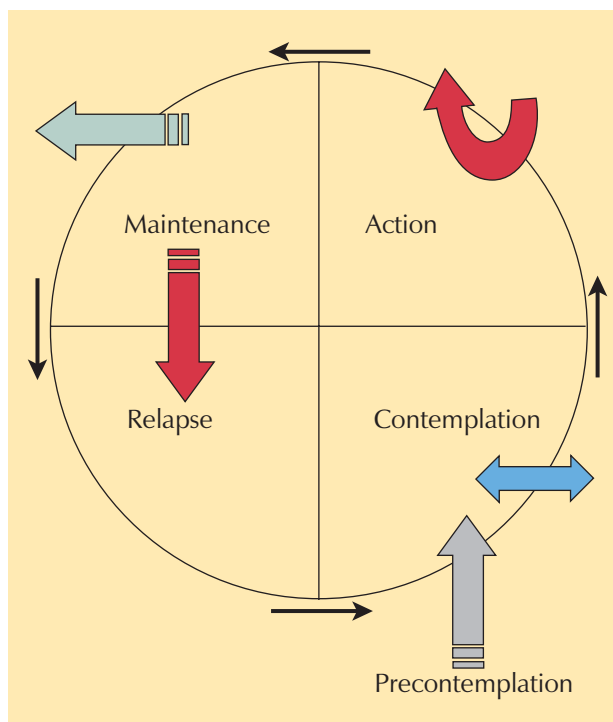


Figure 2: The transtheoretical model. After Di Clemente, Prochaska [6].

This course is not easily accomplished since the patient is confronted with the dilemma of change [3]: either continue with his current behavior and obtain immediate gratification but run the risk of further negative consequences, or change his current behavior, undergo the immediate negative consequences (eg frustration) but gain some potential benefits.

Depending on the patient's capacity to solve this dilemma, he will choose either to change or not to change. At this point it is important to allow the patient to make a free choice that is not influenced by his immediate environment or the protective attitude of the health care

Table 1. Early stages of behavioral change with regard to exercise.

Precontemplation stage	I hate exercise I don't feel like exercising	Give information, Raise awareness Discuss representations, beliefs
Contemplation stage	Maybe I <i>could</i> exercise	Encourage thought that change is possible Help patients overcome their ambivalence

## Case report

Alain Golay, Francesca Amati, Annick Riecker-Agranier, J. Ybarra

Table II. Later stages of behavioral change with regard to exercise.

Preparation	I intend to take a walk if it is sunny	Have a realistic plan Negotiate objectives
Action	I do exercise	Encouragement Success reinforcement Prevent relapse
Maintenance	I do not feel good without exercising I have regained 1 kg and I quit!	Strengthen commitment Identify strategies to prevent relapse

provider. Any attempted influence could have the opposite effect and reinforce the patient's defensive attitudes, manifesting in denial and/or resistance to the proposed remedy [4, 5].

Prochaska and Di Clemente [6] have formulated a model called the transtheoretical model, showing the chain of events which lead a person to make a successful change. Using it helps us to adapt our strategies according to the patient's particular situation. Interestingly, it also requires some behavior modification on the part of the health care provider (Figure 2).

### How to help the patient accept physical exercise

Approximately 85% of patients find themselves in the precontemplation or contemplation stage (Table I), in that they do not feel like exercising. Unfortunately, we frequently tend to propose action strategies: "you just need to walk more," "you must go to the fitness club, swim," while patients just do not feel like moving at all. In the precontemplation stage, the negative aspects of exercising overcome the potential advantages. At this stage, patients often cannot bear the thought of exercising. Hence, we must, for the time being, limit ourselves to providing information.

Later on, at the contemplation stage, the negative and positive aspects are still not yet in equilibrium and the patient feels ambivalent towards exercise. At this stage we can help by encouraging the thought that change is possible and by promoting its advantages.

Around 15% of our patients are in later stages. At the preparation stage, the patient catches a glimpse of undertaking physical activity under certain conditions: he will try to have a walk *if it is sunny*. This is the appropriate time to make plans to negotiate realistic objectives and identify the potential advantages of exercising. This stage is crucial before attempting to progress to the action stage.

Once patients have embarked upon the action stage — exercising — they still have to make a considerable effort. It is important to reinforce and encourage success whilst providing help to overcome the remaining obstacles. The chances of quitting physical activity remain high within the following 6 months if the goals are unrealistic.

Finally, we reach the maintenance stage where patients discover more advantages than disadvantages, and sometimes even do not feel good unless they exercise. It is important to strengthen their commitment and continue to reinforce and encourage success while maintaining and identifying strategies to prevent relapse.

We, as health care providers, are frequently in a rush to go straight to the action stage and propose strategies that do not respect patients' own pace. We must prepare our patients and wait for them. The patient's inner change must take place before his external change. Finally, we must remember that the more accurate and reachable our goals, the greater our successes will be. ■

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## Case report

### *Patient recognition of cardiovascular risk*

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# Physiology and pathophysiology of energy storage

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## Abstract

Studies of adipose tissue metabolism and body weight regulation are increasing our understanding of the intricate balance of energy homeostasis. Fat cells actively secrete a large number of growth factors, hormones, and cytokines, which influence fuel storage, mobilization, and utilization in both central and peripheral systems. Adipocytes display a wide repertoire of metabolic processes to guarantee continuous availability of energy despite a highly variable supply. This article reviews the sophisticated integrated mechanisms that operate in an orchestrated manner in adipose tissue on several physiological levels, enabling the organism to adapt to a wide range of metabolic challenges. ■ *Heart Metab.* 2002;17:35–39.

**Keywords:** Obesity, adipokines, leptin, tumor necrosis factor- $\alpha$ , interleukins, resistin

## Introduction

The ability to ensure continuous availability of energy despite a highly variable supply is a major determinant of the survival of all species. In this sense, the primary role of adipocytes was thought to be fat storage. Unlike protein or glycogen, which require water, the hydrophobic nature of fat results in the advantage of highly efficient storage. In addition, oxidation of fat yields twice as much energy as that of carbohydrate or protein. Adipose tissue, considered to lack any specific metabolic activity, therefore received little attention.

Until the 1990s adipose tissue had been largely considered to be an inert storage depot with access to stored triacylglycerols being regulated mainly by adrenergic stimulation [1, 2]. This view remained prevalent until research focused attention on the relevant role of adipose tissue as a source of metabolic fuel [3]. In recent years, interest in the biology of adipose tissue has emerged in relation to the discovery

of a host of adipocyte-derived factors that contribute to energy homeostasis [4–6]. It is now well established that several growth factors and cytokines secreted by adipose tissue play a key role in cell differentiation, energy metabolism, and insulin resistance. The physiological relevance of this endocrine organ is evident from the fact that the absence of adipose tissue, as observed in lipodystrophy, is as detrimental as an excess of body fat [7].

In order to store triacylglycerol during periods of caloric excess and to mobilize this reserve when expenditure exceeds energy intake, adipocytes dispose of a whole range of enzymes for both lipolysis and de novo lipogenesis reactions [8]. In fat cells, the regulation of these processes is exquisitely responsive to hormones, cytokines, and other factors that are involved in energy metabolism [3, 5]. Preadipocytes first appear late in embryonic life, although major expansion of the white adipocyte population is delayed until shortly after birth [9].

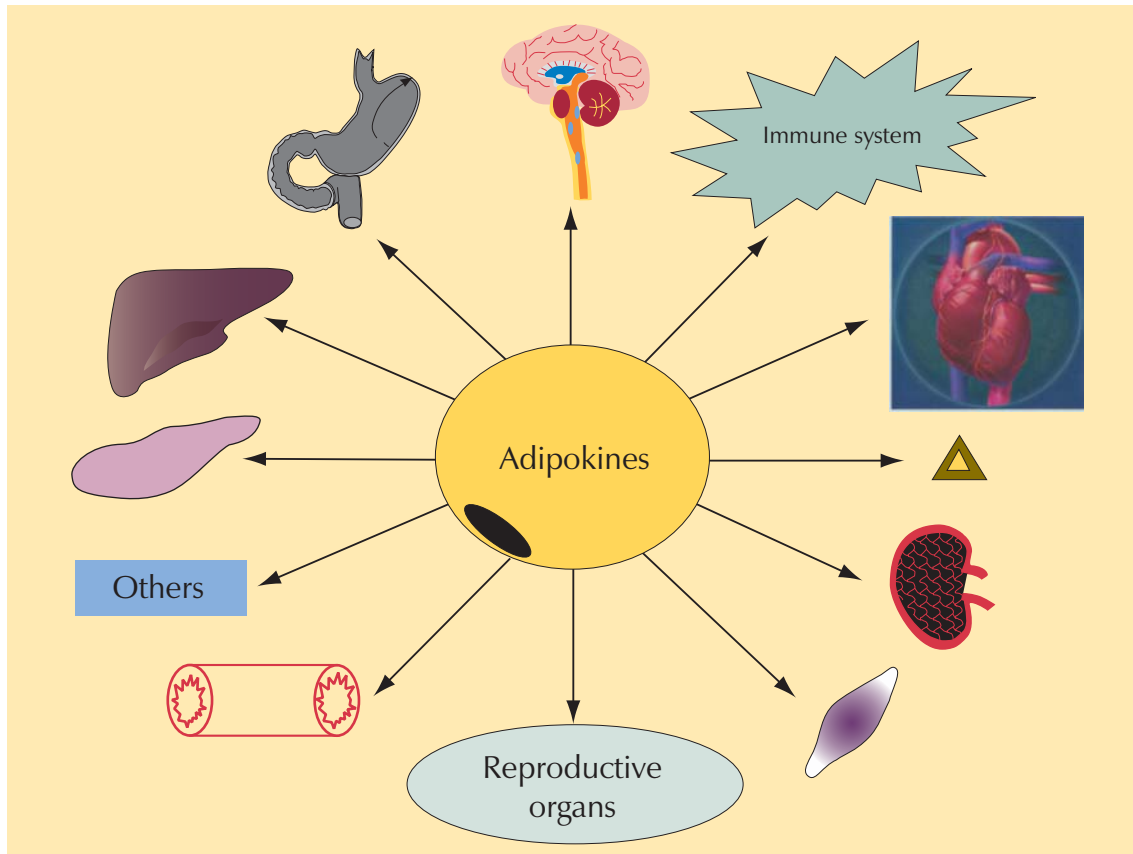


Figure 1. Production of adipocyte-derived factors exerts a role on both the central nervous system and the periphery.

### Adipocyte-derived factors

In a dynamic view of the adipocyte a wide range of signals emanates from white adipose tissue to impinge on the function of several organs (Figure 1). White adipose tissue is actively involved in cell function regulation through a complex network of endocrine, paracrine, and autocrine signals, which influence the response of many tissues, including the hypothalamus, as well as mainly metabolic organs such as pancreas, liver, skeletal muscle, kidneys, adrenal glands, or the cardiovascular system. Adipocytes act as endocrine secretory cells [10, 11]; numerous hormones, growth factors, and cytokines are expressed in white adipose tissue, such as leptin, tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-6 (IL-6), and their respective soluble receptors [3, 5]. White adipose tissue also secretes important regulators

of lipoprotein metabolism such as lipoprotein lipase, apolipoprotein E, and cholesteryl ester transfer protein. The increasing number of products secreted by adipocytes also includes angiotensinogen, plasminogen activator inhibitor-1, tissue factor, transforming growth factor- $\beta$ , and inducible nitric oxide synthase (iNOS). The role of insulin-like growth factor-1, glucocorticoids, and sex steroids in adipose tissue proliferation, heterogeneity, and distribution is beginning to be better understood. However, the influence of acylation stimulating protein, adipophilin, adipoQ, adipisin, monobutyryl, *agouti* protein, and factors related to proinflammatory and immune processes remains to be fully elucidated [5]. These relationships show that white adipose tissue can no longer be considered to be a passive bystander in whole body pathophysiology, since it lies at the heart of a network of signals

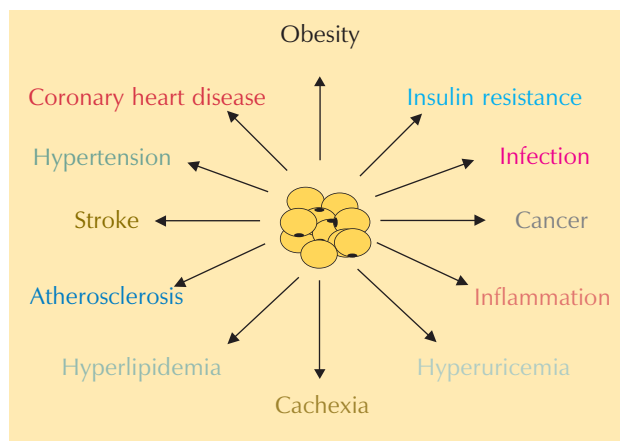


Figure 2. Pathophysiological complications associated with adipose tissue dysfunction.

leading to important health complications in case of faulty functioning (Figure 2).

More recently, identification of a series of new molecules implicated in obesity and adipose tissue development has been published. The gene *Lpin1* has been shown to encode a novel nuclear protein, which has been named lipin [12]. The discovery of lipin has revealed a new factor required for normal adipose tissue development and metabolism. Elucidation of the molecular function of lipin will likely lead to new insights into these processes [13]. This novel family of nuclear proteins contains at least three members in mammalian species. The human ortholog *LPIN1* is a potential candidate gene for lipodystrophy.

The discovery of a novel hormone, which researchers named resistin (for resistance to insulin), was reported in 2001 [14, 15]. The knocking out of the glucose transporter gene *GLUT4* in mice resulted in normal growth and adipose tissue mass despite markedly impaired insulin-stimulated glucose uptake in adipocytes [16]. Although *GLUT4* expression was preserved in muscle, these rodents developed insulin resistance in muscle and liver, as shown by decreased biological responses and impaired activation of phosphoinositide-3-OH kinase. Therefore, adipose-selective depletion of *GLUT4* in mice led to impaired glucose tolerance and insulin resistance with preserved adipose mass. Consequently, insulin resistance occurred secondarily in muscle and liver, as

evidenced by defective proximal signaling and reduced physiological responses. Moreover, the insulin resistance could not be accounted for by changes in circulating free fatty acids, triglycerides, or leptin, or by changes in  $TNF\alpha$  expression in adipose tissue. Thus, selective downregulation of *GLUT4* and glucose transport in adipose tissue can cause insulin resistance and, thereby, increase the risk of developing diabetes.

Acetyl-coenzyme A carboxylase 2 has been shown to be a key metabolite in the regulation of energy homeostasis [17]. The absence of this enzyme resulted in higher fatty acid oxidation rates in heart and skeletal muscle followed by a marked decrease in fat storage despite increased food intake.

### Energy metabolism

Throughout the 2.5-million-year history of human development the principal threat to survival has been recurrent famine. The evolution of adipocytes provided a means for coping with the cycles of undernutrition by enabling the preloading of calories for subsequent use. During the 20th century, however, an unprecedented change in the pattern of caloric availability took place in many developed countries. Recurrent undernutrition was replaced by unending overnutrition, the consequences of which were greatly amplified by the permanent state of physical inactivity imposed by sedentary occupations and immobilizing technologies of modern life [18]. Obesity results from an energy imbalance, where energy intake exceeds energy expenditure over a sustained period of time [19]. Body weight increases when more energy is taken in than is burnt off. Maintenance of energy balance is a complex phenomenon affected by nutritional, endocrine, nervous, physical, and psychosocial factors, as depicted in Figure 3. Genetic as well as environmental factors affect appetite, food choices, metabolism, activity, and how the body fine-tunes the balance between energy intake and expenditure, affecting everything from food intake to how fat is stored in the body.

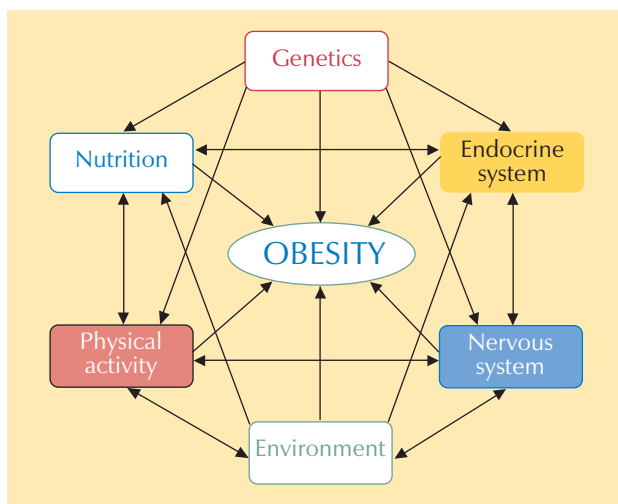


Figure 3. Schematic representation of the multifactorial factors influencing the development of obesity.

### Insulin resistance

Although it is well known that the increased storage of triglycerides in adipocytes promotes insulin resistance, how this exerts a detrimental impact in muscle, liver, and elsewhere in the body has not been completely elucidated. A variety of adipocyte-derived molecules have been proposed as potential mediators of the resistance to insulin associated with obesity. Among the numerous peptides secreted by fat cells that may lead to insulin resistance  $\text{TNF}\alpha$  and leptin stand out [5, 20]. Both are overexpressed in adipocytes from obese individuals and can cause insulin resistance through their effects on insulin-mediated cellular signaling pathways. Hotamisligil's group [21] was the first to report a close relationship between increased adipose  $\text{TNF}\alpha$  expression and features of insulin resistance in rodent models of obesity and type 2 diabetes mellitus. Furthermore, it has been reported that  $\text{TNF}\alpha$  induces phosphorylation of the insulin receptor substrate (IRS)-1 at serine residues and that serine-phosphorylated IRS-1 operates as an inhibitor of insulin receptor activity [22]. Leptin is not only a central regulator of body fat mass, by decreasing food intake and increasing energy expenditure, but could also be involved in the induction of insulin resistance,

possibly via peripheral mechanisms of action [6]. Recent reports suggest complex interactions between the leptin and insulin signaling pathways. In fact, leptin can act through some components of the insulin signaling cascade, such as IRS-1 and IRS-2, phosphatidylinositol 3-kinase, and mitogen-activated protein kinase, and can modify insulin-induced changes in gene expression in vitro and in vivo [20, 23, 24]. A divergence of leptin effects on insulin-stimulated IRS-1- and IRS-2-mediated signaling and downstream kinases suggests a complex and multidimensional interaction between these two hormonal signaling systems. Leptin rapidly activates signaling pathways directly at the level of insulin-sensitive tissues through the functional leptin receptor, and these pathways overlap with, but are distinct from, those engaged by insulin. Thus, evidence suggests that other factors are also required for the development of insulin resistance.

Resistin may be an important link between increased fat mass and insulin resistance since its concentrations are decreased in a mouse model of insulin-deficiency diabetes, and insulin administration rapidly normalizes resistin levels in adipose tissue [25, 26]. Therefore, insulin apparently modulates its own activity through the regulation of resistin.

Recently, compelling evidence has been reported that a mitochondrial anion carrier called uncoupling protein-2 is a critical modulator of insulin secretion and that an increase in this protein may cause  $\beta$ -cell dysfunction [27–29]. Another knockout model, the targeted disruption of the gene encoding iNOS, provides evidence for the involvement of iNOS in the development of muscle insulin resistance in diet-induced obesity [30]. Moreover, rodents lacking IL-6 developed obesity, displayed decreased glucose tolerance and increased triglyceride concentrations. Furthermore, endogenous IL-6 has been shown to exert a tonic suppression of fat mass at the central nervous system in mice, probably due to stimulation of energy expenditure in addition to inhibition of feeding [31].

## Summary

The above scientific evidence has transformed our thinking about the adipocyte. It can no longer be regarded as a passive depot tissue for storing excess energy in the form of triglyceride but has to be considered as an extremely active cell that regulates the pathways responsible for energy homeostasis and whose activity is exquisitely regulated by a complex network of autocrine, paracrine, and neuroendocrine signals. ■

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# Featured research

## Abstracts and commentaries

### Alterations of the circadian clock in the heart by streptozotocin-induced diabetes

Young ME, Wilson CR, Razeghi P, Guthrie PH, Taegtmeier H. *J Mol Cell Cardiol.* 2002;34:223–231.

The heart possesses a fully functional internal clock [1]. This clock provides the selective advantage of anticipation, enabling the organ to prepare for a given stimulus, thereby optimizing the appropriate response. As many of the potential timekeepers (zeitgebers) are altered in diabetes, and given that the morphology, gene expression, metabolism, and contractile performance of the heart are also altered in diabetes, the authors investigated whether the clock of the heart is also affected within this environment.

The circadian patterns of gene expression of several components of the mammalian clock were compared in hearts isolated from control and insulin-dependent diabetic (induced by streptozotocin  $\beta$ -cell destruction) rats. All components of the clock investigated, possessed circadian rhythms of gene expression. In the hearts isolated from diabetic rats, the phases of these circadian rhythms were altered (approximately 3 hours early) in comparison with those of control rats. The clock in the heart has therefore lost normal synchronization with its environment during diabetes.

### Commentary

It is likely that insulin, or an additional humoral factor which is influenced by insulin (either directly or indirectly), acts as a zeitgeber in the heart. These results are consistent with a recently published study showing that restriction of caloric intake causes phase shifting of peripheral clocks, including the clock of

the heart [2]. Streptozotocin is commonly used for the induction of diabetes in rodent models. Despite this, it is possible that the streptozotocin-induced alterations of the circadian clock in the heart are independent of diabetes development. Additional models of diabetes might provide useful information to clarify this issue. It is also possible that during prolonged periods of uncontrolled diabetes, alterations of the circadian clock in the heart are amplified. Long-term studies are therefore required to investigate this possibility. If diabetes is impairing the normal rhythms of neurohumoral zeitgebers, it is likely that the central clock is relatively unaltered. Future studies will be required to answer these important questions, as well to identify the major zeitgebers affecting the circadian clock of the heart.

Alterations of the clock in the heart could result in a loss of the synchronization between the stimulus and responsiveness of the system, eg, responsiveness to increased sympathetic activity in the early hours of the morning for humans, or increased fatty acid availability (due to lipolysis) during an overnight fast. Whether such loss of synchronization plays a role in the development of contractile dysfunction associated with the heart during diabetes requires elucidation.

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*Danielle Feuvray*

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**Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease**

Zoccali C, Mallamaci F, Tripepi G, et al.  
*J Am Soc Nephrol.* 2002;13:14–41.

Adiponectin, which is a secretory protein of adipose tissue, attenuates endothelial inflammatory responses in vitro. In human subjects, plasma adiponectin concentrations are reduced among patients with atherosclerotic complications but are substantially increased among patients with advanced renal failure. The clinical and biochemical correlates of plasma adiponectin levels were investigated and the predictive power of adiponectin levels with respect to survival rates and cardiovascular events was prospectively tested in a cohort of 227 hemodialysis patients, who were monitored for  $31 \pm 13$  months. Plasma adiponectin levels were 2.5 times higher ( $P < 0.0001$ ) among dialysis patients ( $15.0 \pm 7.7 \mu\text{g/mL}$ ) than among healthy subjects ( $6.3 \pm 2.0 \mu\text{g/mL}$ ), were independent of age, and were higher ( $P = 0.03$ ) among women ( $15.2 \pm 7.9 \mu\text{g/mL}$ ) than among men ( $14.0 \pm 7.4 \mu\text{g/mL}$ ). For both genders, plasma adiponectin levels were inversely related to body mass index, plasma leptin, insulin, and serum triglyceride levels, and homeostatic model assessment index values.

Furthermore, plasma adiponectin levels were directly related to high-density lipoprotein cholesterol and inversely related to von Willebrand factor levels. Plasma adiponectin levels were lower ( $P < 0.05$ ) among patients who experienced new cardiovascular events ( $13.7 \pm 7.3 \mu\text{g/mL}$ ) than among event-free patients ( $15.8 \pm 7.8 \mu\text{g/mL}$ ).

There was a 3% risk reduction for each 1  $\mu\text{g/mL}$  increase in plasma adiponectin levels, and the relative risk of adverse cardiovascular events was 1.56 times (95% CI, 1.12–1.99 times) higher among patients in the first adiponectin tertile, compared with those in the third tertile. Plasma adiponectin levels are an inverse predictor of cardiovascular outcomes among patients with endstage renal disease.

Furthermore, adiponectin is related to several metabolic risk factors in a manner consistent with the hypothesis that this protein acts as a protective factor for the cardiovascular system.

**Predictive value of the adipocyte-derived plasma protein adiponectin for restenosis after elective coronary stenting**

Shimada K, Miyauchi K, Mokuno H, et al.  
*Jpn Heart J.* 2002;43:85–91.

The purpose of this study was to test the hypothesis that plasma levels of adiponectin can predict angiographic in-stent restenosis after coronary stenting. We prospectively examined adiponectin levels in 127 consecutive patients undergoing elective coronary stenting. Restenosis was defined as more than 50% stenosis at follow-up study by quantitative coronary angiography. There were no significant differences in clinical characteristics or angiographic findings between the groups with restenosis and no restenosis. The levels of adiponectin did not differ between the restenosis group and the no-restenosis group ( $5.7 \pm 2.8$  vs  $5.9 \pm 3.6 \mu\text{g/mL}$ ,  $P = 0.72$ ). The plasma levels of adiponectin were not related to the late loss index after coronary stenting ( $r = 0.01$ ,  $P = 0.89$ ). The levels of adiponectin were significantly lower in men than in women ( $5.5 \pm 3.2$  vs  $8.8 \pm 3.7 \mu\text{g/mL}$ ,  $P < 0.001$ ), and were negatively correlated with body mass index ( $r = -0.21$ ,  $P = 0.01$ ). We analyzed adiponectin levels in male, female, obese, nonobese, diabetic, and nondiabetic patients; however, there were no significant differences between the restenosis group and the no-restenosis group. This study demonstrated that the measurement of adiponectin could not predict angiographic restenosis after elective coronary stenting, whereas the plasma levels of adiponectin were associated with some coronary risk factors in patients with coronary artery disease.

### Commentary

Adiponectin is a novel, adipocyte-derived hormone that has recently generated considerable interest in the research community. Adiponectin has an important role in the regulation of energy homeostasis and insulin sensitivity, and also appears to have antiatherogenic properties due to an attenuation of endothelial inflammation. Levels of circulating adiponectin are decreased in type 1 diabetic patients, insulin-resistant patients, as well as in obese individuals. Weight reduction in diabetes subjects also results in a significant increase in adiponectin levels. Emerging evidence suggests that adiponectin plays a protective role against insulin resistance and atherosclerosis. Because of the beneficial actions of adiponectin on energy homeostasis, a number of clinical studies have suggested that plasma adiponectin levels negatively correlate with the severity of insulin resistance and obesity. These recent articles also suggest that low plasma adiponectin levels are predictive for restenosis after elective coronary stenting, as well as adverse cardiovascular outcomes among patients with endstage renal disease. Due to the potential adverse metabolic implications of decreasing plasma adiponectin levels, a large research effort is presently underway to understand the molecular basis of the beneficial actions of adiponectin. The exciting developments in adiponectin research in the last few years suggest that increasing adiponectin levels may be a therapeutic approach to treating obesity, insulin resistance, and atherosclerosis.

Gary D. Lopaschuk

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### Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin

Knowler WC, Barrett-Connor E, Fowler SE, et al, for the Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393–403.

Type 2 diabetes affects approximately 8% of adults in the United States. Some risk factors — elevated plasma glucose concentrations in the fasting state and after an oral glucose load, overweight, and a sedentary lifestyle — are potentially reversible. We hypothesized that modifying these factors with a lifestyle intervention program or the administration of metformin would prevent or delay the development of diabetes. We randomly assigned 3234 nondiabetic persons with elevated fasting and postload plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle modification program with the goals of at least a 7% weight loss and at least 150 min of physical activity per week. The mean age of the participants was 51 years, and the mean body mass index was 34.0 kg/m<sup>2</sup>; 68% were women and 45% were members of minority groups. The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. Lifestyle intervention reduced the incidence by 58% (95% CI, 48%–66%) and metformin by 31% (95% CI, 17%–43%), compared with placebo; lifestyle intervention was significantly more effective than metformin. To prevent one case of diabetes during a period of 3 years, 6.9 persons would have to participate in the lifestyle intervention program, and 13.9 would have to receive metformin. Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. Lifestyle intervention was more effective than metformin.

### Commentary

Lifestyles. Individuals in the study with a body mass index >24 kg/m<sup>2</sup>, a plasma glucose of

5.3 to 6.9 mM/L in the fasting state and 7.8 to 11 mM/L after a 2-hour post-75-g oral glucose load were randomized to three interventions. The lifestyle intervention was systematic, intensive, and individualized. Its purpose was to achieve and maintain a weight reduction of 7% of initial body weight through a low-calorie, low-fat diet and moderate exercise of at least 150 min/week. This was attempted through a curriculum of 16 lessons, taught on a one-to-one basis during the first 24 weeks after randomization. The study participants were recruited from within the USA and over 40% were from minority ethnic groups, predominantly African American and Hispanic. The delivery of the lifestyle curriculum was sensitive to cultural issues. In addition to the 16 sessions, monthly individual and group sessions were held to reinforce the lifestyle advice.

The average weight of individuals in the lifestyle group was 94 kg. Six months after randomization this group had lost an average of 7 kg, with some weight gain over the ensuing years; however, even after 4 years, the cohort was 4 kg lighter than at randomization.

Lifestyle intervention and metformin similarly reduced fasting glucose levels but lifestyle intervention had a greater effect on glycosylated hemoglobin and postload glucose.

The authors estimate that 10 million individuals in the USA meet the entry criteria for this study. It is reassuring to know that there is hope for this huge and growing population. All it needs is time and motivation.

*Michael Marber*

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# Glossary

Gary D. Lopaschuk

### **Acetyl-coenzyme A carboxylase (ACC) 2**

Acetyl-coenzyme A carboxylase (ACC) is a key enzyme involved in both the synthesis and metabolism of fatty acids. ACC produces malonyl coenzyme A, which is both a substrate for fatty acid biosynthesis and a potent inhibitor of mitochondrial fatty acid uptake. Heart and muscle primarily express ACC2, which is the isoform of ACC that is thought to be primarily involved in the regulation of fatty acid oxidation.

### **Acylation stimulating protein (ASP)**

Acylation stimulating protein (ASP) is an adipocyte-derived protein that upregulates triacylglycerol synthesis in adipocytes. ASP has recently been suggested to play an important role in the regulation of lipoprotein metabolism and triacylglycerol storage. ASP also appears to have role in the regulation of energy balance.

### **Adipophilin**

Adipophilin is a protein that is involved in lipid transport or storage. Adipophilin, which was initially described in adipocytes, is associated with lipid accumulation in cells. It is found in many cells and may be a new marker for the identification of specialized differentiated cells containing lipid droplets and for diseases associated with fat-accumulating cells.

### **Adipsin**

Adipsin is one of a number of physiologically important proteins excreted by adipocytes. Adipsin has a role in the regulation of energy intake and storage, and works with acylation stimulating protein to regulate lipoprotein metabolism and triacylglycerol storage. In the gut, adipsin facilitates removal of lipid from chylomicrons.

### **Agouti protein**

*Agouti* protein is an endogenous antagonist of melanocortin receptors that have been implicated as part of the hypothalamic mechanism that mediates leptin-induced hypophagia. The *agouti* protein has a role in controlling energy homeostasis and possibly human pigmentation.

### **Angiotensinogen**

The renin-angiotensin system is widely known for its importance in controlling blood pressure, electrolyte homeostasis, and volume regulation. Angiotensinogen is an early intermediate of this pathway, and polymorphisms in this gene contribute to the pathogenesis of both hypertension and cardiovascular disease.

### **Apolipoprotein (apo) E**

Apolipoprotein (apo) E is one of the proteins associated with circulating lipoproteins. Polymorphisms in the apo E gene result in the development of atherosclerosis and increase the risk for heart disease, stroke, and Alzheimer's disease.

### **Cholesterol ester transfer protein (CETP)**

Cholesterol ester transfer protein (CETP) facilitates reverse cholesterol transport from high-density lipoprotein (HDL) to triacylglycerol-rich lipoproteins. High plasma levels of CETP are correlated with low HDL cholesterol levels, a strong risk factor for coronary artery disease.

### **Cytokines**

Cytokines refer to a group of compounds that are produced under a variety of conditions, including during immune response and inflammatory reactions. Tumor necrosis factor- $\alpha$  and interleukin-1 are examples of two cytokines.

## **Glucocorticoids**

Glucocorticoids are steroids produced by the adrenal gland that have diverse actions on the body, including control of glucose metabolism, and control gene expression. Glucocorticoids regulate the transcription of a large number of genes, including a number of gluconeogenic genes in the liver.

## **Inducible nitric oxide synthase (iNOS)**

Nitric oxide synthase (NOS) is the enzyme responsible for synthesizing nitric oxide (NO). NO has received considerable research attention, since it is not only a vasodilator but is also important in numerous other processes, including apoptosis. Inducible NOS (iNOS) is an isoform of NOS that can be dramatically induced under a variety of conditions. One example of this is the dramatic expression of iNOS in muscle following sepsis.

## **Insulin receptor substrate (IRS)-1**

Insulin receptor substrate (IRS)-1 is a key protein in the insulin-signaling pathway. Binding of insulin to the receptor results in activation of IRS-1. IRS-1 then alters the activity of a number of downstream signaling pathways to mediate the diverse effects of insulin.

## **Interleukin-6 (IL-6)**

Interleukin-6 (IL-6) is a proinflammatory cytokine involved in many immune responses, including physiological stress reactions. IL-6 is also involved in several diseases, including lymphoid malignancies. This cytokine binds to soluble IL-6 receptor circulating in blood, leading to signal transduction. A significant correlation between circulating IL-6 level and insulin sensitivity has recently been found in humans.

## **Leptin**

Leptin is secreted from adipocytes and is thought to enter the brain to regulate and coordinate metabolism, feeding behavior, energy balance, and reproduction. There are many additional sites of leptin production (including human placenta, ovary, stomach, skeletal muscle, mammary gland, pituitary gland, and brain), as well as sites of peripheral leptin action, including muscle and heart.

## **Lipin**

Lipin is the product of the gene that is mutated in fatty liver dystrophy. Mice with this mutation exhibit several phenotypic abnormalities, including hyperlipidemia, defects in adipocyte differentiation, impaired glucose tolerance, and slow growth.

## **Lipogenesis**

Lipogenesis is a term describing the synthesis of lipids. It occurs primarily in the liver and adipocytes.

## **Lipoprotein lipase (LPL)**

Lipoprotein lipase (LPL) is an enzyme that cleaves fatty acids from triacylglycerol contained within lipoproteins, with the subsequent release of fatty acids. LPL associated with the endothelium is a major source of fatty acids for both heart and skeletal muscle.

## **Mitogen-activated protein kinase (MAPK)**

Mitogen-activated protein kinase (MAPK) is one of the kinases in the MAPK superfamily. This kinase pathway is engaged by phosphorylation in response to environmental stress signals and has many cellular actions, including a role in cell proliferation.

## **Monobutyryl**

Monobutyryl is a novel angiogenic compound that is synthesized and secreted during the differentiation of adipocytes. It has a major role as a differentiation-dependent angiogenic molecule.

## **Phosphatidylinositol 3-kinase**

Phosphatidylinositol 3-kinase is an intracellular kinase activated by lipids that phosphorylates the cellular phospholipid, phosphatidylinositol. The product of this reaction is involved in many intracellular signaling pathways, including the control of energy metabolism.

## **Plasminogen activator inhibitor (PAI)-1**

Plasminogen activator inhibitor (PAI)-1 is a protein that inhibits fibrinolysis and proteolysis. Increases in PAI-1 levels have been associated with increased risk of myocardial infarction and decreased risk of cerebrovascular events.

**Resistin**

Resistin is an adipose tissue-specific factor which is reported to induce insulin resistance, linking diabetes to obesity.

**Triacylglycerol**

Triacylglycerol is the major storage form of fatty acids in the body and consists of three fatty acids attached to a glycerol backbone. Fatty acid storage in adipocytes primarily occurs in the form of triacylglycerol. The heart also contains sizable triacylglycerol stores as a source of fatty acids for energy production.

**Tumor necrosis factor- $\alpha$  (TNF $\alpha$ )**

Tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) is a cytokine that has diverse actions in the body. TNF $\alpha$  binds to cardiac receptors and mediates a number of cellular processes, including the promotion of apoptosis (programmed cell death), and activation of inducible nitric oxide synthase.