CHAPTER 24.

Obesity

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Summary

The adverse effects of obesity support the use of biomarkers to help elucidate disease mechanism, therapeutic interventions, and preventive strategies. Emerging biomarkers for obesity-associated cardiovascular disease (CVD), type 2 diabetes and cancer play diverse roles in biological pathways including immune modulation and fat metabolism. Animal and *in vitro* data support the association of these biomarkers with obesity-associated diseases, but evidence in humans is still lacking. In humans, plasma levels of biomarkers are widely used to determine risk, but many studies are limited by ethnicity/race, gender or sample size. In this chapter, the use of biomarkers in obesity research and in the context of CVD, type 2 diabetes and cancer will be discussed. Markers of exposure (adipokines), effect (resulting metabolic abnormalities), and susceptibility (genetic determinants for obesity and related disorders) are covered for each of the three diseases.

Introduction

Obesity epidemiology has typically relied upon long-established markers, such as blood cholesterol, triglycerides and blood pressure. It is now recognized that novel, non-traditional biomarkers have the potential to augment the utility of traditional markers. Emerging as a more formative tool in obesity epidemiology, the majority of non-traditional biomarkers act in relation to fat cells, or adipocytes. Acting as endocrine organs, adipocytes produce a variety of peptides and metabolites that result in a cascade of events leading to inflammation and oxidative stress. These products are being explored as biomarkers for the prevention, diagnosis, risk stratification and control of obesity co-morbidities, such as cardiovascular disease (CVD) (1,2), type 2 diabetes (3,4) and certain cancers (5,6). Despite the dangerous health effects of obesity, little is known regarding the clinical utility of adipokines in modifying disease risk, especially cancer.

This chapter focuses on the use of non-traditional biomarkers in obesity research and more specifically, in

the context of CVD, type 2 diabetes and cancer. Adipokines will be referred to as markers of exposure and the resulting metabolic abnormalities as markers of effect. Genetic determinants for obesity and related disorders are referred to as markers of susceptibility. Markers of exposure, effect and susceptibility are discussed for each of the three co-morbidities.

Obesity is multifactorial

Generally defined, obesity is a state of excess weight gain and increased body fat that is disproportionate to the individual's height. Obesity is a prevalent disorder adversely impacting quality of life (7,8) and life expectancy (9). In the USA it is estimated that 32% of adults and 17% of children and adolescents aged 2–19 years were obese in 2003–2004, a dramatic increase from the previous two decades (10), justifying the need for prevention of obesity and related disorders. Caused by a combination of genetic, metabolic and environmental factors, obesity is characterized by an imbalance between energy intake and energy expenditure. This imbalance is closely regulated by signals emanating from and controlled by the central nervous system.

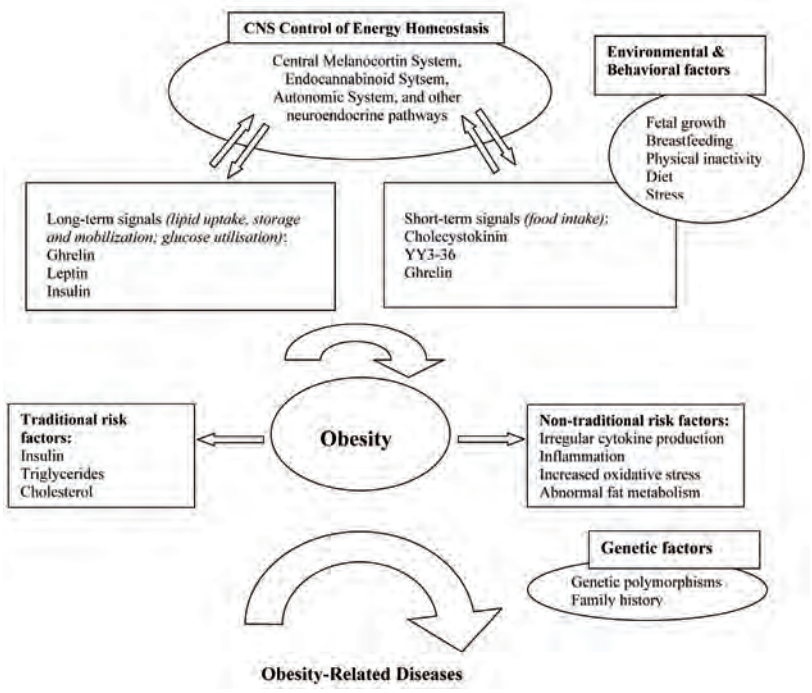
The central melanocortin system is integral in regulating food intake and peripheral lipid metabolism (11). Peripheral signalling molecules, such as ghrelin (12) and cholecystokinin (13), communicate with this system to control energy metabolism (11). Other signalling networks, such as the endocannabinoids (14), are believed to be involved in the development of obesity. In addition to the central nervous system, the adipose tissue is integral in the development of obesity because its expansion signifies the obese state (Figure 24.1).

Adipose tissue is an active organ innervated by the sympathetic nervous system (15), communicating with the hypothalamo-pituitary axis and the adrenal glands (16) to influence food intake, hunger, energy expenditure and adipose tissue mass. Adipose tissue secretes a variety of signals that influence energy balance, including leptin and adiponectin (17). Leptin reduces food intake, and resistance to its activities is often found in obesity. Adiponectin promotes insulin sensitivity and exhibits anti-inflammatory actions (17). In addition to the influence of adipose tissue, obesity can be caused by inherited defects.

Rare, monogenic forms of obesity are caused by single genetic mutations in genes, such as leptin, leptin receptor and pro-opiomelanocortin, as well as chromosomal rearrangements (18). These defects are among the few direct causes of obesity and are not the focus of this chapter.

Non-genetic causes of obesity are commonly implicated in the current rise in obesity prevalence in the USA and worldwide. Modifiable behavioural risk factors, including energy intake and a sedentary lifestyle, are principal components in the development of obesity (19,20). As a result, improving dietary habits by increasing the intake of fruits and vegetables and decreasing fat-laden foods, together with an active lifestyle, are vital techniques for the prevention of obesity and have been

Figure 24.1. The central melanocortin system, endocannabinoid system, and autonomic system are among the most important central nervous system (CNS) control areas regulating energy intake and expenditure. Short-term signals control food intake, while long-term signals chronically regulate lipid storage and metabolism, as well as glucose homeostasis. The signals simultaneously exert their peripheral effects to control energy metabolism via multiple tissues including adipose tissues. Fat deposition modifies adipose tissue function, leading to abnormal production of various molecules. The resulting potential biomarkers occur at various stages in the course of obesity and may interact with environmental, behavioural, and genetic factors and possibly with traditional risk factors, leading to disease manifestations.



the focus of large obesity prevention trials (21).

Just as obesity is a complex disorder, molecular biomarkers that occur in obesity and that help identify individuals most at risk for subsequent cardiovascular disease, diabetes or cancer are complex. There is a significant degree of functional overlap among the biomarkers, and in some cases it is hard to discern the order in which they first appear in the body. For simplicity, however, the biomarkers have been broadly classified into exposure, effect or susceptibility (Table 24.1).

Overview of inflammation and oxidative stress

Abnormal adipokine production with consequent inflammation and oxidative stress may play an instrumental role in obesity-related disorders. Increased accumulation of adipose tissue, particularly visceral obesity, causes abnormal cytokine release and macrophage recruitment, all of which induce systemic inflammation (22).

Accumulation of adipose tissue also leads to increased oxidative stress partly via the oxidant effects of free fatty acids (23). Leukocytes derived from obese individuals and healthy individuals infused with free fatty acids generate reactive oxygen species (24,25). Consequently, reactive oxygen species induce a pro-inflammatory state and promote adverse metabolic complications, such as insulin resistance (23). Despite the association of oxidative stress with CVD independent of traditional risk factors (26), prospective clinical trials of antioxidant supplementation for reducing CVD risk provide conflicting evidence (27,28), possibly due to lack of a strong effect of oxidative stress on atherosclerosis, choice of antioxidant therapy, confounding by other dietary and non-dietary factors, or unsuitable choice of the biomarker. Nevertheless, oxidative stress is increasingly recognized as a potential mechanism for obesity-related disorders, hence it is included in this chapter.

Owing to the clear link between fat accumulation, inflammation and oxidative stress, the following three sections focus on these mechanisms in the context of CVD, diabetes and cancer. The sections are not intended to be all-inclusive, but aim to introduce the reader to major biomarkers of potential benefit in disease prevention and early detection. A brief introduction to the major epidemiologic study designs used to evaluate the biomarkers and common methodological issues then follows.

Biomarkers of obesity and subsequent cardiovascular disease

For the purposes of this section, cardiovascular disease (CVD) outcomes comprise cerebrovascular disease (cerebral embolism, thrombosis and haemorrhage), peripheral arterial disease, coronary heart disease, and atherosclerosis. Different mechanisms are implicated in the link between obesity and CVD. For example, the fetal origin of metabolic risk (29), epigenetic gene regulation (30), and the “pup in a cup” model (31) are potential causes of increased CVD risk in obesity. In addition, cardiovascular injury is promoted by adipokines, cytokines and other molecules that affect multiple pathways, such as lipid metabolism and immune modulation, eventually leading to inflammation or oxidative stress (32).

Inflammatory biomarkers that are elevated in obesity include leptin, plasminogen activator inhibitor 1, and adiponectin. Beyond regulation of energy expenditure, leptin induces a myriad of inflammatory mediators (33) and alters myocardial structure (34). Leptin has extensive regulatory functions and has been

Table 24.1. Classification of molecular biomarkers for obesity and subsequent cardiovascular disease, diabetes or cancer

Class	Molecular biomarkers	Examples of studies
Exposure	Adipokines: surrogates for adipose tissue deposition	Characterise adipose tissue type and activity; association with disease outcome; assess change with weight loss
Effect	Markers of inflammation and oxidative stress: mechanisms by which obesity may exert its toxic effects	Monitor disease progression; association with disease outcome; disease prognosis; disease intervention
Genetic susceptibility	Gene polymorphisms: account for variation in susceptibility to obesity-related disorders	Gene-phenotype relations; heritable variations in the quantity of systemic biomarkers; risk stratification

implicated in multiple adverse CVD endpoints independent of traditional risk factors. The National Health and Nutrition Examination Survey (NHANES) III was used to conduct a retrospective analysis of leptin concentrations and history of myocardial infarction and stroke (35). Plasminogen activator inhibitor 1 is an indirect correlate of abdominal obesity (36), though the molecular mechanism is still uncertain (37). Increased plasminogen activator inhibitor 1 contributes to CVD by impairing fibrinolysis and promoting cardiovascular tissue remodeling and the formation of blood clots. Its involvement in CVD is still controversial, as shown, for example, in a case–control study and meta-analysis on stroke (38,39); nevertheless, data suggest a role in patients with a prior history of CVD. In these patients, genetic variants in plasminogen activator inhibitor 1 have been implicated in disease recurrence such as recurrent myocardial infarction (40,41). Plasminogen activator inhibitor 1 is also associated with traditional risk factors, as well as other CVD risk indicators including low adiponectin (42). Adiponectin is a protective molecule inversely related to obesity and the associated metabolic abnormalities (43), and some studies, including prospective evaluations, strongly suggest that low plasma concentrations are implicated in increased CVD risk (43–45). Adiponectin's protective effects arise from its versatile immune functions and its ability to protect the vascular endothelium by antagonising inflammation and oxidative stress (43).

A hallmark of oxidative stress, reactive oxygen species mount their effects by reacting with diverse biological molecules including lipids and lipid derivatives. For example, oxidized low density lipoproteins are readily taken up by macrophages, thus promoting atherosclerosis (46). F_2-isoprostanes are prostaglandin-like compounds formed from the oxidation of cell membrane-derived fatty acids and have been implicated in atherosclerosis (47). The Framingham Heart Study was accessed to examine the utility of using F_2-isoprostane as a biomarker of oxidative stress. After adjustment for age and sex, it was found that the biomarker was increased in obese individuals (48).

In addition to oxidation products, enzymatic manipulation of reactive oxygen species further determines the effects of oxidative stress. One of the most studied oxidative stress-related enzymes in the field of cardiovascular medicine is glutathione peroxidase 1, an antioxidant that has been shown to drop in obese individuals in both prospective (49) and cross-sectional (50) studies. It is also expressed in the endothelium and protects blood vessels against oxidative stress, not just by counteracting reactive oxygen species, but by inhibiting oxidative enzymes that contribute to atherosclerosis (51).

Other potential markers of CVD risk in obese individuals include monocyte chemoattractant protein 1 (52). In addition to macrophages and endothelial cells in the vascular wall, monocyte chemoattractant protein 1 is synthesized by adipose tissues. Microarray gene expression profiles of subcutaneous adipose tissues demonstrate increased expression in obese compared to non-obese individuals (53). By recruiting macrophages to blood vessel walls, this chemokine contributes to atherosclerosis, but its link to CVD risk is still under investigation (54), as some studies do not find an association with subsequent cardiovascular events. Other studies provide evidence, however, for a role in long-term CVD prognosis. For example, prospective evaluation of patients with acute coronary syndromes indicates that monocyte chemoattractant protein 1 is independently associated with long-term mortality and cardiovascular events (55). Another biomarker that is associated with obesity and cardiovascular events is the angiotensin converting enzyme (56,57). In addition to blood pressure regulation, this enzyme exerts local pro-inflammatory effects in several tissues, including cardiac myocytes, and has long been employed for the management of heart failure. A recent meta-analysis maintains that angiotensin converting enzyme inhibitors reduce the risk of cardiovascular mortality, as well as specific endpoints, such as myocardial infarction and stroke, but the mechanism is yet to be explained (58). Table 24.2 summarizes the effects of the above biomarkers, as well as other molecules that can potentially be used for disease prevention or intervention. Also, see Chapter 20 for additional discussion of biomarkers associated with CVD.

Biomarkers of obesity and type 2 diabetes

Insulin resistance is a precursor of type 2 diabetes, an inflammatory condition (59,60) characterized by glucose intolerance (61). Due to the central role of glucose metabolism in the pathogenesis of type 2 diabetes, molecular biomarkers that function in this pathway may prove instrumental in targeting individuals with the highest risk for disease, designing tailored interventions, and improving risk stratification. One gene involved in glucose synthesis is PCK1, encoding the enzyme phosphoenolpyruvate carboxykinase. PCK1 is expressed in adipocytes, intestinal epithelia,

Table 24.2. Biomarkers associated with obesity and cardiovascular disease outcomes

Class	Biomarker	Disease/risk factor (Reference)
Exposure	Interleukin 18	Coronary heart disease (113)
	Leptin	Haemorrhagic stroke (114) Acute myocardial infarction (115)
	Plasminogen activator inhibitor 1	Recurrent myocardial infarction (116)
	Low adiponectin	Coronary artery disease (43-45)
Effect	Oxidized low density lipoproteins	Ischemic damage in cortical lesions (115) Coronary heart disease (117)
	Glutathione peroxidase	Reduced risk of death from cardiovascular events or non-fatal myocardial infarction (118)
	F_2-Isoprostanes	Coronary artery calcification (119) Coronary artery stenosis (120)
	Monocyte chemoattractant protein 1	Long-term mortality and cardiovascular events (55)
Genetic susceptibility	Angiotensin-converting enzyme	Coronary heart disease (121,122)
	Plasminogen activator inhibitor 1	Recurrent myocardial infarction (40,41)

and hepatocytes. Hepatic overexpression is associated with a diabetic phenotype in mice and overexpression in adipose tissues causes obesity. Among the few human studies performed to date, some show a link between PCK1 variants with type 2 diabetes (62). Another gene, ectonucleotide pyrophosphatase/phosphodiesterase 1, has shown conflicting associations with type 2 diabetes and obesity, but its role as an inhibitor of insulin signalling warrants further examination as a potential candidate gene for obesity-associated type 2 diabetes. In some populations, polymorphisms in this gene are associated with childhood and adult obesity, as well as type 2 diabetes in obese individuals (63–65) (see Chapter 7). Further population-based studies are needed to validate its use as a predictive biomarker. Glucose homeostasis is also regulated by several obesity-associated adipokines that control multiple immune pathways. Low adiponectin concentrations (66,67) and high tumour necrosis factor-α levels (68–70) have often been associated with insulin resistance. Despite conflicting evidence, promoter polymorphisms in the tumour necrosis factor-α gene have been implicated in increased insulin resistance, particularly in obese adults with type 2 diabetes (71–73). Further, one large (n = 809) population-based cross-sectional study of unrelated Caucasians showed that this gene interacts with adiponectin resulting in lower adiponectin levels and higher glucose and insulin concentrations two hours after glucose administration (74).

In addition to glucose, perturbed fatty acid metabolism, uptake and transport has been implicated in insulin resistance and diabetes. Uptake of fatty acids is partly controlled by fatty acid translocase (CD36), which regulates long chain fatty acid transport in skeletal muscles and adipose tissue (75). Subcutaneous adipose tissue expression of this binding protein was increased in obese individuals and further increased in those with type 2 diabetes (75). A promoter polymorphism in CD36 was also linked with insulin resistance and type 2 diabetes (76). Interestingly, CD36 is linked to oxidative stress, because it is a scavenger receptor for oxidized lipoproteins on the surface of macrophages, rendering them insulin-resistant (77).

Other genetic candidates include stearoyl-coenzyme A desaturase type 1 (SCD1) and 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), a glucocorticoid-amplifying enzyme. Genetic variants in the fatty acid metabolizing enzyme SCD1 have been linked with decreased waist circumference and improved insulin sensitivity in adults (78). The glucocorticoid-amplifying enzyme 11HSD1 is an intriguing molecule with varying roles ranging from regulation of adipocyte differentiation to possible amplification of macrophage-driven adipose tissue inflammation in obesity (79). It stimulates lipid synthesis in the intra-abdominal fat depots of diet-induced obese mice (80). Several studies find

dysregulated adipose tissue activity in obesity (81) and type 2 diabetes (82), including one prospective study (83). Lipid storage and adipocyte differentiation is partially regulated by peroxisome proliferator-activated receptor gamma (PPAR-γ). This nuclear receptor is highly expressed in adipose tissues and favourably controls the release of several adipokines, such as adiponectin, leptin, resistin, interleukin 6 and monocyte chemoattractant protein 1, mounting anti-inflammatory and anticoagulant actions that intensely counteract the adipose tissue dysfunction plaguing obesity (84,85). Notably, PPAR-γ improves glucose uptake and insulin sensitivity, as evidenced by the actions of receptor agonists for treatment of type 2 diabetes. According to multiple investigations, a Pro12Ala polymorphism that decreases receptor activity, protects against hyperinsulinemia, type 2 diabetes (86), and high free fatty acid concentrations (87). The Ala12 carriers show up to a 19% risk reduction, and the protective effect is greatest at a lower body mass index (BMI) (88). It is important to note that, as in the case with any gene, the effects of this variant can be modified by other genetic influences, such as variants within the same or other genes, and by environmental factors, such as diet, BMI or physical activity. Indeed, physical activity was found to modify its effect in one follow-up study (89). LDL receptor-related protein 1 is another vital regulator of systemic lipid transport and absorption in liver, muscle, heart and adipocytes. This receptor plays a role in the uptake and hydrolysis of triglyceride-rich lipoproteins. Adipose-specific knockout mice are protected from diet-induced obesity and exhibit increased metabolic rate and glucose tolerance (90). By understanding the potential role of LDL receptor-related protein 1 in humans, this receptor can potentially serve as a valuable marker for conferring susceptibility to obesity and type 2 diabetes in individuals at risk. In addition to the above biomarkers, other candidates for obesity-associated insulin resistance and type 2 diabetes are highlighted in Table 24.3.

Biomarkers of obesity and cancer

Cancer is a condition of uncontrolled cell growth triggered by a variety of factors. It is estimated that one third of all cancer deaths in 2006 were related to physical inactivity, nutrition and obesity (91). Compared to other known genetic or environmental risk factors for cancer, obesity may play a minor role. Nevertheless, its effect can be magnified in susceptible individuals, such as those with a family history of cancer or who belong to a particular race or gender.

Table 24.3. Biomarkers associated with obesity and type 2 diabetes risk

Class	Biomarker	Disease/Risk Factor (Reference)
Exposure	Lipocalin 2	Insulin sensitivity (123)
	Cideb	Insulin sensitivity (124)
	Monocyte chemoattractant protein 1	Insulin resistance (125)
	Interleukin 8	Insulin resistance (126)
	Low adiponectin	Insulin resistance (66,67)
Genetic Susceptibility	SCD1	Insulin sensitivity (78)
	PCK1	Blood glucose and triglyceride synthesis (62)
	11HSD1	Fasting glucose and insulin resistance (82,83) Increased lipid synthesis and adipose tissue mass in mice (80)
	CD36	Insulin resistance and type 2 diabetes (75,76)
	Peroxisome proliferator-activated receptor gamma	Type 2 diabetes (86)
	Ectonucleotide pyrophosphatase/ phosphodiesterase 1	Type 2 diabetes (64,65)
	Tumour necrosis factor-α	Increased postprandial free fatty acid concentrations and insulin resistance (71,72) associated with lower adiponectin concentrations (74)

Defined using BMI or a high upper body (central) fat distribution, obesity modified risk for the development and progression of cancers affecting multiple target organs, including the gastrointestinal system (92–94), ovaries (95), breasts (96) and prostate (97). For example, women with a high BMI exhibited cytological abnormalities in the breast that may predispose to cancer (98). A few of the many possible mechanisms implicated in these findings is detection bias, hormonal imbalance (e.g. sex hormones or insulin) or genetic predisposition. Notably, abnormal adipokine regulation is another potential mechanism for this predisposition.

In the obese environment, insulin stimulates leptin activity in breast cancer cells (99), and an imbalance in leptin and adiponectin secretion is highly implicated as one mechanism for breast cancer development (100). Leptin exerts mitogentic and antiangiogenic effects that appear to be counteracted by adiponectin, which is decreased in obesity and protects against breast cancer (101). High leptin or low adiponectin levels are also implicated in other malignancies, such as non-Hodgkin lymphoma (102) and endometrial cancer (103).

In addition to adipokines, genetic variants in lipid metabolizing genes are associated with breast cancer, such as the leptin receptor and the paraoxonase gene (*PON1*), which prevents low density lipoprotein oxidation. Polymorphisms in these genes are protective against breast cancer development in postmenopausal Caucasian women with benign breast disease (104) (these findings should be interpreted with caution due to the small number of cases (61 cases out of a total of 994)). The aforementioned molecules and other molecules putatively implicated in obesity-linked cancer are summarized in Table 24.4.

Common epidemiological study designs and methodological issues

Multiple epidemiologic study designs have been used to examine putative biomarkers in human populations (see Chapter 14). Case–control and cross-sectional studies are among the most common designs. Relatively cheap and rapid, the designs are a sound stepping stone for collecting background information on the desired criteria for any biomarker, including average plasma concentrations, inter-individual and intra-individual variability, effect size in cases compared to controls, stability, half-life, circadian variation and ethnic/racial differences, as well as age and gender effects. Several biomarkers illustrated in this chapter have been preliminarily identified and repeatedly investigated using these designs to justify further study in more demanding prospective evaluations. More difficult to conduct, population-based prospective, longitudinal studies and randomized controlled trials greatly help strengthen the predictive role of the biomarker and support its predictive and clinical utility.

Conclusions and future directions

The adverse effects of obesity propagate through many human generations, begging the use of biomarkers that help elucidate disease mechanism, therapeutic interventions and preventive strategies. Emerging biomarkers

Table 24.4. Biomarkers associated with obesity and cancer risk

Class	Biomarker	Disease/Risk factor (Reference)
Exposure	Leptin	Cellular proliferation, anti-apoptosis (126) Differentiation of breast cancer (99)
	Adiponectin	Antiangiogenic (127) Low levels implicated in breast cancer (128) and prostate cancer (129)
	Interleukin 6	Prostate cancer (129) Breast cancer (130)
Effect	Vascular endothelial growth factor	Regulates angiogenesis and cell migration, implicated in prostate cancer (129)
Genetic susceptibility	Leptin receptor	Polymorphism associated with lower risk of breast cancer in benign breast disease (104)
	PON1	Polymorphism associated with lower risk of breast cancer in benign breast disease (104)

for obesity-associated CVD, type 2 diabetes or cancer play diverse roles in biological pathways including immune modulation and fat metabolism. Support for the association of these biomarkers with obesity-associated diseases stems from animal and *in vitro* data, but evidence in humans is still lacking. In humans, plasma levels of biomarkers or genetic polymorphisms are widely used to determine risk, but many studies are limited by ethnicity/race, gender or sample size. These deficits are perhaps the most challenging to overcome in future studies, but it is the only way by which a biomarker can be validated for reliable use in human populations. Along these lines, there has recently been a series of large-scale genome-wide association studies of BMI that are uncovering a substantial number of new loci associated with obesity (105–111).

In the field of chronic inflammatory disorders exist acute indicators, such as C-reactive protein, an acute phase protein that rises in any inflammatory condition, and chronic prognostic indicators, such as monocyte chemoattractant protein 1 in the case of CVD. Management of obesity-associated disorders may benefit from the use of acute indicators augmented with chronic markers to better predict disease progression. In fact, multiple biomarkers may be required to complement standard traditional risk factors to enhance risk stratification and to develop measurable therapeutic targets.

Additional measures of obesity aside from the typical BMI are required to better characterize obesity in the context of other chronic disorders. Other non-invasive measures (e.g. waist circumference, waist-to-height ratio and the conicity index) are surrogates of abdominal (central) obesity. Central obesity is often found to predict disease outcome better than BMI (112). One major cause of central obesity is a large visceral adipose tissue distribution. Visceral adipose tissue actively expresses and secretes a myriad of adipokines and other agents that act locally and systemically to promote obesity-associated disorders. Therefore, central obesity should be fully investigated in the context of relevant biomarkers, for it may add to their predictive utility and clinical validity.

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