Reducing the risk of macrovascular complications of diabetes: focus on visceral fat

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Practice Points

- Patients with Type 2 diabetes and their clinicians should be aware of the very elevated risk of cardiovascular disease associated with this condition and the importance that abdominal/visceral fat plays in development of cardiovascular complications.
- Identification of abnormally obese patients that are at the highest risk for cardiovascular disease is essential in clinical practice.
- Waist circumference and lipid profile, especially triglyceride levels, are an easy method to identify those at highest risk.
- Patients with Type 2 diabetes should receive extensive education regarding the risk associated with excess abdominal obesity/visceral fat and how a slight reduction in this fat depot is associated with significant clinical improvements.
- Modest weight loss associated with modest reduction in waist circumference should be extensively discussed with every patient. It should be emphasized that this degree of weight loss is realistic and could be achieved in most patients.
- Methods to reduce abdominal fat should include both dietary intervention as well as an increase in activity level.

SUMMARY   Macrovascular complications of Type 2 diabetes account for the majority of mortality in this condition and are related to insulin resistance. Abdominal obesity, and especially visceral fat, has proven to be particularly important in these associations. Indeed the risk for Type 2 diabetes and its complications is more closely related to visceral fat than overall obesity. Whether visceral fat by itself is pathogenic or a marker for ectopic accumulation of fat or a combination of both remains unresolved. Inflammation has now been established as a major pathway linking insulin resistance to obesity. Adipose tissue macrophage infiltration has been implicated in the activation of inflammatory pathways and development of insulin resistance. However, the mechanisms leading to these events are not clearly identified and remain active areas of investigation.

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Macrovascular complications in Type 2 diabetes

Macrovascular complications are common in patients with Type 2 diabetes (DM2) and remain the major cause of mortality in these patients [1]. In some studies, the risk for myocardial infarction among patients with DM2 and no history of cardiovascular disease is the same as the risk for myocardial infarction in patients with prior cardiac disease who do not have diabetes [2]. Furthermore, in patients with DM2 and history of myocardial infarction, the risk for subsequent myocardial infarction is more than double compared to those without diabetes [2]. A recent meta-analysis of 102 prospective studies that included approximately 700,000 subjects without cardiovascular disease at baseline revealed a twofold excess risk for developing vascular disease in subjects with DM2 [3]. This increase in risk was independent of other conventional risk factors such as LDL cholesterol [3]. Glycemic control has much less impact on macrovascular compared to microvascular complications of DM2 [1,4–6]. The macrovascular complications of DM2 are most closely related to the presence of insulin resistance and the resultant metabolic syndrome [7–9]. Obesity, especially the abdominal type, is strongly associated with presence of insulin resistance, DM2 and cardiovascular disease [10–13]. In this article we focus on the role of adipose tissue, especially intra-abdominal fat (visceral fat), on development of macrovascular complications in patients with DM2.

Metabolically benign obesity in humans

Not all obese individuals are at increased risk for metabolic disorders. The existence of benign obesity or overweight and obese individuals who are metabolically healthy is well recognized. A number of studies have demonstrated that up to 30% of obese individuals are metabolically healthy [14,15]. For example among the National Health and Nutrition Examination Survey (NHANES) cohort, 51% of the overweight adults and 32% of the obese adults were metabolically healthy [14]. These individuals did not have any history of metabolic or cardiovascular disease and were free of any cardiometabolic abnormalities that included elevated blood pressure, triglycerides, fasting plasma glucose, C-reactive protein, and the homeostasis model assessment of insulin resistance, as well as low HDL cholesterol level [14]. In this study, there were no sex differences in the prevalence of this phenotype [14], although sex hormones are known to impact body composition [16] and hence metabolic risk [17]. Similar data has been reported in smaller cohorts [15]. In one study that included careful evaluation of fat depots by MRI, insulin-sensitive obese subjects had less intrahepatic fat, an indicator of ectopic fat deposition, compared to equally obese but insulin resistant subjects [15]. In a more recent study, morbidly obese insulin resistant subjects had higher amounts of visceral fat, higher levels of systemic inflammatory markers and higher infiltration of macrophages in visceral fat compared with morbidly obese insulin-sensitive subjects [18]. As will be discussed later, adipose tissue macrophage (ATM) infiltration is considered a major mechanism for the development of insulin resistance. Regional variations in body fat have been able to account for some of the differences in risk of metabolic and cardiovascular disorders associated with obesity. For example, large-scale prospective epidemiologic studies have revealed that an increase in waist circumference, rather than overall adiposity, was associated with increased risk of cardiovascular disease [19]. Furthermore, greater accumulation of fat in the lower half of the body, as demonstrated by greater hip circumference, was associated with fewer cardiovascular events [20]. Additionally, for a given BMI, individuals with variation in waist circumference have been shown to have a different metabolic profile [19–21].

The concept that fat deposited in different locations may have different metabolic risk has been recognized for some time. In a publication in the 1950s, French physician Jean Vague described two different types of obesity: android and gynoid that had different metabolic profiles [22]. In his observations, he noted the presence of metabolic abnormalities most commonly in individuals with android body habitus or abdominal obesity [22]. Since this original description, our understanding of regional variation in body fat and metabolic and cardiovascular risk has expanded enormously. Recent imaging studies that allow for characterization of abdominal fat have further shed light on these associations. The following sections will discuss the mechanisms involved in these associations.

Abdominal obesity & insulin resistance

Insulin resistance is the common trait linking DM2 and the metabolic syndrome. Insulin resistance has been shown to correlate strongly
with abdominal obesity and especially visceral fat. Studies that have measured insulin sensitivity using the euglycemic hyperinsulinemic clamp technique and quantified visceral fat by imaging techniques have clearly shown that glucose disposal is inversely related to visceral and not subcutaneous or total adipose tissue in both men and women [23]. These findings are also true for patients with DM2 in whom both peripheral and hepatic insulin sensitivity, as determined by euglycemic hyperinsulinemic clamp and isotopic administration, have been shown to correlate only with visceral fat and not subcutaneous abdominal fat [24]. In patients with DM2 excess visceral fat, but not subcutaneous abdominal fat, is strongly associated with increased endogenous glucose production, which is an early and prominent abnormality in this condition and the source for fasting hyperglycemia [25]. Waist circumference and visceral fat but not subcutaneous abdominal fat have also been shown to be strong predictors of development of DM2 in a large cohort of obese subjects with prediabetes who participated in the diabetes prevention program [26].

The metabolic syndrome, the constellation of insulin resistance, hypertension, dyslipidemia and abdominal adiposity, is now recognized as a major risk factor for cardiovascular disease [8,27]. It is important to note that abdominal obesity and not BMI is a major feature of the metabolic syndrome, again underscoring the importance of central fat rather than overall adiposity in the pathogenesis of metabolic disorders. A number of studies have also shown that the metabolic syndrome is a very good predictor for development of DM2 [28] with comparable sensitivity to that of impaired glucose tolerance [29]. The risk for cardiovascular disease and diabetes with the metabolic syndrome is greater than that for simple obesity. Again, insulin resistance is an essential factor associated with the metabolic syndrome [30], although there is considerable controversy regarding the underlying pathophysiological process leading to the metabolic syndrome and some have actually questioned the existence of a discrete syndrome [31].

Waist circumference is traditionally used as a surrogate for abdominal fat. However, relation of waist circumference to abdominal adiposity is complicated as this measurement correlates well with the amount of total abdominal fat but cannot distinguish between subcutaneous and visceral depots. As will be discussed later, these two fat depots are not the same in terms of metabolic and cardiovascular risk. Individuals with the same waist circumference may have a significantly different quantity of visceral and subcutaneous abdominal fat. Quantification of abdominal fat depots requires abdominal imaging by computed tomography or MRI. Using these techniques, one can identify the impact of the two abdominal fat depots, subcutaneous and visceral, respectively, on metabolic and cardiovascular risk.

**Role of visceral fat**

Numerous epidemiologic as well as physiologic studies have suggested that visceral fat is more strongly associated with metabolic risk factors and cardiovascular disease than subcutaneous abdominal fat [32,33]. For instance, individuals matched for subcutaneous abdominal fat but with different degrees of visceral fat have been shown to have markedly different levels of insulin resistance and glucose tolerance [34]. However, individuals with differing amount of subcutaneous fat but similar visceral fat content did not differ in insulin sensitivity [12]. Surgical removal of abdominal subcutaneous fat in obese subjects did not result in metabolic improvements or beneficial changes in cardiovascular risk factors [35]. Conversely, removal of visceral fat has led to metabolic improvements [36], although this has not been a universal finding [37]. In the diabetes prevention program, visceral fat, but not subcutaneous abdominal fat, predicted development of DM2 [26]. As mentioned in the previous section, insulin resistance is also more closely related to visceral compared with subcutaneous abdominal fat in both diabetic and nondiabetic populations [23,24]. Additionally, visceral fat is a major determinant of the metabolic syndrome [38].

There is also some evidence that the associations between visceral fat and metabolic abnormalities may even be stronger in subjects with DM2 compared with populations without diabetes. In the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) cohort that consists only of subjects with DM2, we demonstrated that the atherogenic lipoprotein profile commonly observed in insulin-resistant states was only associated with visceral fat, independent of overall adiposity and waist circumference [39]. We did not find any associations between subcutaneous abdominal fat or BMI and the atherogenic lipoprotein profile [39]. Similarly in our cohort, visceral fat was strongly
correlated with inflammatory markers and these associations were independent of BMI [40]. Subcutaneous abdominal fat was not related to any of the inflammatory markers [40]. Findings from the Framingham cohort, which consists predominantly of subjects with normal glucose tolerance, demonstrated associations between both visceral and subcutaneous abdominal fat depots and the metabolic risk factors and inflammatory markers, but the associations remained stronger for visceral fat [41–43]. The relationship between central fat depots and metabolic risk could be modified in diabetes either by the more severe degree of insulin resistance in DM2 compared to obese nondiabetic subjects, or by the failure of insulin secretion to compensate for the metabolic derangements produced by insulin resistance [24,44]. Furthermore, as will be discussed in detail later, increasing evidence indicates that adipose tissue, especially visceral fat, is the source of a number of hormones [45], cytokines and inflammatory factors [46] that can impact substrate flux and lipid metabolism in distant tissues. It is possible that this secretory pattern is altered by the presence of DM2 [47].

Visceral fat may also be a surrogate for ectopic fat deposition. It is well established that accumulation of fat in ectopic locations such as liver, skeletal muscle, pancreas and heart is associated with a number of metabolic abnormalities among which are insulin resistance and β-cell dysfunction, the two abnormalities associated with development of DM2 [33,48,49]. Observations from lipodystrophic states have revealed that the absence of subcutaneous fat is associated with severe hypertriglyceridaemia and ectopic deposition of fat and resultant severe insulin resistance and metabolic disorders [50]. These observations suggest that subcutaneous adipose tissue may act as a ‘metabolic sink’ that protects individuals from developing metabolic disorders in response to positive energy balance as a result of sedentary lifestyles and poor dietary habits [51]. Based on this hypothesis, excess visceral fat may only be a marker for dysfunctional subcutaneous fat that is unable to expand in response to positive energy balance, thereby leading to ectopic fat deposition. Support for this hypothesis is provided by studies that have matched obese subjects for visceral fat content and have demonstrated an association between the metabolic abnormalities and excess fat in other ectopic locations such as intrahepatic fat [48]. There are additional reports that implicate accumulation of fat in ectopic locations such as liver and skeletal muscle in the development of insulin resistance in human subjects independently of visceral fat [15,51]. It has been demonstrated that in lean insulin-resistant human subjects, there is impairment in carbohydrate utilization by skeletal muscle and carbohydrates are, therefore, redirected to the liver with a resultant increase in hepatic fat content and hepatic de novo lipogenesis [51]. This occurs independently from any changes in visceral fat depot [51]. The underlying mechanisms for the development of insulin resistance in response to ectopic accumulation of fat in skeletal muscle and liver are still under investigation, but it appears that intracellular accumulation of fat in these organs is associated with impairment in insulin signaling pathways through activation of protein kinases and generation of reactive oxygen species that adversely impact glucose transport [52]. Reactive oxygen species have been implicated as a common trigger of insulin resistance and can be activated by multiple mechanisms including inflammatory cytokines as well as the accumulation of lipid intermediaries related to increased intramyocellular fat or defects in mitochondrial metabolism [53].

The portal hypothesis is another mechanism that has been formulated to explain the impact of visceral fat on insulin sensitivity and metabolism [54]. According to this hypothesis, increased delivery of free fatty acids released from visceral fat and transported directly to the liver via the portal vein leads to the development of hepatic insulin resistance, hepatic fat accumulation, and promotion of an atherogenic lipid profile [55–57]. Compared to adipose tissue from other sites, visceral fat is more lipolytically active [58] and is more resistant to insulin-mediated suppression of lipolysis leading to a greater free fatty acid turnover [56,59]. Thus, accumulation of visceral fat and a higher rate of lipolysis in visceral depots may lead to increased fatty acid flux into the liver and promote gluconeogenesis [60] and hepatic lipogenesis [61]. In addition to free fatty acids, portal delivery of inflammatory cytokines has also been implicated in the pathogenesis of hepatic insulin resistance. As will be discussed later, inflammation is a major pathway that links obesity (especially abdominal obesity) to insulin resistance. A recent study in mice, indicates that only direct delivery of inflammatory cytokines released from visceral fat to the liver by the portal vein, as opposed to release of the same cytokines in the systemic circulation, will lead to
development of glucose intolerance and insulin resistance [62]. Even though the portal hypothesis is based on strong physiological basis and there is considerable support in its favor, it is not free of controversy. Some have argued that increased lipolysis in the visceral fat depot without evidence for higher rate of fat deposition in this depot should lead to its eventual disappearance, which is not the case [63].

**Role of subcutaneous abdominal fat**

The impact of subcutaneous abdominal fat on metabolic and cardiovascular risk remains controversial. Subcutaneous abdominal fat is the largest fat depot and has been shown to be the primary source of free fatty acids in the systemic circulation [64]. There are some studies that have demonstrated a strong correlation between subcutaneous abdominal fat and metabolic risk [65,66], but in general these studies are fewer in number than those that demonstrate adverse associations with visceral fat. Furthermore, the associations between visceral fat and metabolic abnormalities are always much stronger than those reported between subcutaneous abdominal fat and metabolic abnormalities in the same cohort of subjects [41,42]. However, there are important ethnic differences in abdominal fat distribution as well as in the association of specific abdominal fat depots to insulin sensitivity and metabolic risk. For example, African–Americans have been shown to have a lower quantity of visceral fat compared with other racial and ethnic groups, but a similar degree of metabolic risk, in general [26,67–69]. Subcutaneous abdominal fat has been shown to have stronger correlation with metabolic risk, especially in African–American women [70]. The underlying mechanisms of these racial and gender differences have not been well established.

**Inflammation link between obesity & metabolic disorders**

In the past 15 years, inflammation has emerged as a new concept linking obesity to insulin resistance, DM2 and other metabolic disorders and cardiovascular disease. The association between inflammation and metabolic disease was strongly suggested by numerous epidemiological studies that demonstrated increased levels of markers of inflammation and coagulation and acute phase reactants such as C-reactive protein in obesity, and in particular, abdominal obesity [71,72], DM2 [73–75], the metabolic syndrome [76] and cardiovascular disease [77–83]. Further support for this concept was provided by experimental models that clearly established a role for inflammatory cytokines in the pathogenesis of insulin resistance. A report by Hotamisligil et al. in 1993 demonstrated that the level of the inflammatory cytokine, TNF-α, was increased in the adipose tissue of obese rodents and that neutralizing TNF-α led to improvements in insulin sensitivity [84]. Another report from the same year, demonstrated that TNF-α impaired early events in insulin transduction pathways by reducing tyrosine phosphorylation of the insulin receptor and insulin receptor substrates [85]. Although species differences with regards to these inflammatory pathways exist, these experimental models provided a clear mechanism by which inflammation can lead to the development of insulin resistance.

Around the same time, it became increasingly evident that obesity is a state of low grade chronic inflammation [45]. Inflammatory markers are elevated in the obese, and in particular the viscerally obese [72]. Weight loss is associated with a reduction in the level of the inflammatory markers [86]. Adipose tissue is now recognized as a complex endocrine organ capable of producing a number of hormones and cytokines, including TNF-α, IL-6 and monocyte chemoattractant protein-1 [45] and adipokines such as leptin and adiponectin that are implicated in the pathogenesis of insulin resistance as demonstrated in Figure 1. While adipokines such as leptin and adiponectin are exclusively produced by adipocytes, inflammatory cytokines can be produced by both adipocytes and ATM [45]. Animal and human studies have revealed that the expansion of adipose tissue is accompanied by increased infiltration of macrophages that are the main source for production and release of inflammatory cytokines such as TNF-α and IL-6 [87,89]. Diet and exercise have been shown to reduce ATM infiltration in severely obese subjects and this phenomenon is associated with a reduction in inflammation [90]. In morbidly obese humans, weight loss by bariatric surgery is associated with a reduction in ATM infiltration [88].

In addition to increased ATM infiltration, obesity is associated with changes in macrophage activation that has been best described in rodents [91]. Macrophage activation has been defined by two separate polarization states, M1 and M2 in rodent models [91]. M1 refers to ‘classically activated’ macrophages that have enhanced
proinflammatory cytokine production (TNF-α, IL-6). M2 or ‘alternatively activated’ macrophages have low pro-inflammatory cytokine expression and generate high levels of anti-inflammatory cytokines such as IL-10 [91]. Diet-induced obesity in rodents shifts the ATM polarization from M2 to M1 with increases in the expression of genes coding for TNF-α and inducible nitric oxide synthase and decreases in expression of anti-inflammatory genes such as IL-10 (M2 state) [91]. In humans the state of macrophage activation in adipose tissue with obesity is more controversial. Some groups have shown an increase infiltration of M1 (classically activated) macrophages in obese humans to be similar to rodents [92], while some have shown an increase infiltration in M2 (alternatively activated) macrophages leading to increased fibrosis and insulin resistance [93]. Still other investigators have demonstrated distinct subsets of macrophages that have features of both M1- and M2-activated macrophages [94].

Inflammation & visceral fat
Visceral fat has been shown to secrete higher quantities of inflammatory cytokines [72,95]. The portal vein contains much higher concentrations of IL-6 compared with the peripheral circulation in morbidly obese subjects undergoing bariatric surgery [96]. It has also been demonstrated that visceral fat cells from obese subjects release more IL-6 compared with subcutaneous abdominal fat cells [97]. Increased delivery of IL-6 by the portal circulation to the liver can lead to increased synthesis of acute phase reactants, such as
C-reactive protein, an independent risk factor for metabolic and cardiovascular disease [77,79–83]. Expression of a number of inflammatory markers such as IL-6 [97], monocyte chemoattractant protein-1 [98] and plasminogen activator inhibitor-1 [99] are increased in visceral compared with subcutaneous abdominal fat as demonstrated in Figure 1. Expression of the anti-inflammatory adipokine, adiponectin, has also been found to be lower in visceral compared with subcutaneous abdominal fat [100]. Furthermore, imaging studies have demonstrated that increasing amounts of visceral fat are associated with increasing circulating levels of inflammatory cytokines [101]. These associations seem even stronger in subjects with DM2 in whom we have only demonstrated an association between visceral fat depot and inflammatory markers independent of BMI and subcutaneous abdominal fat [40].

A few recent studies demonstrate that ATM infiltration is increased in visceral compared with subcutaneous abdominal fat, especially in abdominally obese humans [102,103]. Furthermore, the number of visceral macrophages, but not subcutaneous macrophages, correlated with waist circumference and with the number of metabolic syndrome parameters [102]. Preferential macrophase infiltration in visceral fat was only observed in the obese that had abnormalities in glucose tolerance, again indicating that increased inflammation in visceral fat maybe an important mechanism leading to development of metabolic abnormalities [102].

Reducing cardiovascular disease in DM2 by targeting visceral adiposity

Since visceral fat has the strongest associations with metabolic and cardiovascular disease especially in patients with DM2, even slight alteration in the size of this fat depot can have significant impact on insulin sensitivity, lipid profile and cardiovascular risk. A systematic review of 61 studies in humans indicates that visceral fat mass is lost preferentially with modest weight loss [104]. In clinical practice, this could translate into minimal weight loss, resulting in significant metabolic improvements [90]. This concept has been proven by studies such as the Diabetes Prevention Program in which modest weight loss of approximately 6 kg by lifestyle intervention resulted in a greater than 50% reduction in risk for development of DM2 over a 4-year period [105]. In this study lifestyle intervention was more successful than metformin therapy in prevention of DM2 [105]. Slight decreases in waist circumference of approximately 5–6 cm by lifestyle intervention has also been reported to lead to significant reductions in visceral fat and subsequent metabolic risk [33]. In humans, diet and exercise with resultant modest weight loss are associated with a reduction in ATM infiltration in adipose tissue [90]. The reduction in ATM infiltration is associated with a parallel decrease in levels of C-reactive protein, IL-6 and monocyte chemoattractant protein-1, and an increase in adiponectin levels [90].

Another challenge in clinical practice is identification of obese subjects who are visceroally obese and hence at the highest risk for metabolic and cardiovascular disorders. Visceral fat can only be quantified by abdominal CT or MRI imaging, which are expensive procedures and are not practical in routine clinical care of patients We have recently shown that in patients with DM2, those with the greatest amount of visceral fat can be identified by applying the criterion for ‘hypertriglyceridemic waist’ [106,107]. This criterion was originally identified by Despres and colleagues [106] and utilizes a combination of waist circumference (>90 cm in men or >85 cm in women) and a fasting triglyceride level (≥217 mg/dl), which is easily obtainable in clinical practice. Applying this criterion to clinical practice may prove very helpful in identifying the individuals at highest risk for metabolic and cardiovascular disease who will most benefit from lifestyle interventions.

Conclusion & future perspective

Over the past few decades it has become increasingly clear that cardiovascular disease and risk is highly related to abdominal fat and visceral adiposity, especially in patients with DM2. ATM infiltration is the mechanism that most likely accounts for these strong associations through increased production and secretion of inflammatory cytokines.

At this point, there are many areas of uncertainty that require further investigation. The inciting events leading to ATM infiltration with obesity remain to be better identified. Unlike rodents, the macrophage activation states in humans are not clearly identified and are subject of intense study. Identification of these mechanistic pathways are essential not only in enhancing our understanding of the disease process but also in developing effective therapies that can target the early events in the development of insulin resistance.
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Review


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