Some 250 years ago, Joannes Baptista Morgagni clearly described increased intraabdominal and mediastinal fat accumulation in android obesity. Remarkably, he also recognized the association between visceral obesity, hypertension, hyperuricemia, atherosclerosis, and obstructive sleep apnea syndrome, long before the modern recognition of this syndrome.

Two hundred years later, the French physician Jean Vague “rediscovered” the importance of the “android” obesity phenotype and its association with diabetes, atherosclerosis, gout, and uric-acid calculous disease. Since then, countless epidemiological and physiological studies have documented the importance of “upper body” or “abdominal” obesity as a determinant of insulin resistance. Type 2 diabetes, hypertension, dyslipidemia, and cardiovascular morbidity and mortality. Together, these studies have culminated in the current concept of the “hypertriglyceridemic waistline” and have seen the introduction of waist circumference as a defining feature of the metabolic syndrome.

In this issue of Hypertension, Sironi et al. essentially confirm the early observations of Morgagni on the relationship between intraabdominal and intrathoracic fat accumulation and hypertension using state-of-the-art MRI. Not only did newly diagnosed untreated hypertensive men have 60% more visceral and mediastinal fat than normotensive individuals, but the size of both fat depots was also positively correlated to blood pressure and inversely correlated to insulin sensitivity.

Whereas much has been written on the importance of android obesity and the role of visceral adipose tissue in the metabolic syndrome, little is known about the nature and role of mediastinal fat. Anecdotal reports have described increased mediastinal fat mass in patients with simple obesity, type 2 diabetes, hypertension, dyslipidemia, and cardiovascular morbidity and mortality. Together, these studies have culminated in the current concept of the “hypertriglyceridemic waistline” and have seen the introduction of waist circumference as a defining feature of the metabolic syndrome.

Despite remarkable recent progress in our understanding of the complex biology of fat tissue and its relationship to health and disease, the comparative study of different adipose tissue depots remains in its infancy. Nevertheless, it is now apparent that adipose tissue is a complex and diverse organ with functions that go beyond the simple storage of excess calories. Indeed, comparative studies of adipose tissue across species have provided fascinating insights into the wide range of morphologies and functions of what is certainly one of the most versatile of tissues.

Although in a clinical setting abdominal adiposity is generally assessed by measuring waist circumference, it is important to note that abdominal adipose tissue is in fact distributed across different depots of varying significance and function. Thus, subcutaneous abdominal fat can be divided into superficial and deep layers, the latter of which has been reported to have a greater influence on insulin resistance, hypertension, and other features of the metabolic syndrome than superficial abdominal fat. Subcutaneous fat is in turn quite different from intraabdominal fat, which consists of both retroperitoneal and intraperitoneal or visceral depots, the latter of which are again divided into mesenteric and omental fat.

Numerous studies have documented important morphological and functional differences between visceral and subcutaneous adipose tissue. Visceral adipocytes are generally smaller and more lipolytically active than subcutaneous adipocytes, thereby exposing the liver to a higher concentration of free fatty acids. Visceral adipose tissue has also been reported to generate greater quantities of angiotensinogen, plasminogen activator inhibitor-1, tumor necrosis factor-α, and resistin, whereas production of leptin and adiponectin was reported to be lower. Visceral adipocytes are also more sensitive to glucocorticoids and may express higher levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), the enzyme that regenerates active cortisol from inactive 11-keto forms. Interestingly, aP2-HSD1 mice with relative transgenic overexpression of this enzyme in fat cells not only develop visceral obesity with insulin resistance and dyslipidemia, but also salt-sensitive hypertension.

The question, however, remains whether or not visceral adiposity is merely a marker of the metabolic syndrome or whether it directly contributes to the development of this syndrome. In fact a number of recent studies have tried to delineate the potential role of visceral adiposity versus the deposition of excess lipids in other organs in the development of insulin resistance and the metabolic syndrome. Thus, an increasing number of studies have now addressed the “lipotoxicity” hypothesis that suggests that intramyocellular and hepatic lipid deposition rather than visceral fat may play a key role in the development of insulin resistance. In 1 study of women who had a history of gestational diabetes, who
were carefully matched for both total and visceral fat, women with higher hepatic fat content were more insulin resistant and had higher blood pressure. Nevertheless, causal involvement of visceral obesity in the metabolic syndrome is suggested by the intriguing observation that surgical removal of visceral fat results in marked improvement in the metabolic syndrome both in animals and humans. This is also in line with the present observation by Sironi et al that a 1-kg increase in visceral fat predicts a 10 mm Hg increase in blood pressure.

In their study, Sironi et al also demonstrate that the dynamics of β-cell function, in contrast to insulin sensitivity, are apparently not primarily related to the presence of visceral or mediastinal fat. Rather, this finding suggests that other factors than just the presence of excess abdominal fat must contribute to the development of β-cell failure and the manifestation of type 2 diabetes.

Overall this article raises a number of interesting research issues: What are the biological determinants of visceral and mediastinal fat accumulation? What is the functional significance of increased mediastinal fat, and how similar is mediastinal to visceral fat? Does weight loss equally reverse both fat depots? Clearly, the study of adipose tissue biology and its fascinating relationship to health and disease will remain a focus of interest for the legions of researchers who are now increasingly turning their attention to the study of obesity and its complications.

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References


