Is intra-abdominal obesity a unique risk factor for metabolic syndrome in non-diabetics?

Excess body fat imparts risk for metabolic syndrome, diabetes and cardiovascular disease. A question that has engendered interest is whether the risk imparted by obesity results from excess visceral or subcutaneous adiposity. Regardless of the controversy, excess abdominal fat is viewed as a risk factor for diabetes and cardiovascular disease. In fact, waist girth is now part of the assessment tools for metabolic syndrome as recommended by the Adult Treatment Panel (ATP) III guidelines. In recent years the definition has been revised for non-Europeans because body mass index (BMI) and waist girth definitions of overweight and obesity for persons of European ancestry do not always apply to non-Europeans. Of late, guidelines for South Asians at risk for metabolic syndrome also have been introduced in India. An underlying assumption in all of these guidelines is that a clustering of metabolic risk factors predisposing to diabetes mellitus and/or cardiovascular disease is associated with central obesity. Whether the central obesity paradigm holds in the future depends on new developments in the research on adipose tissue function. In recent years, the study of the impact of obesity on health in various populations has proven very instructive as well.

One population of interest is South Asians who have the highest risk for type 2 diabetes mellitus and/or cardiovascular disease. In rural areas, the prevalence of diabetes is ~2 per cent while in urban India it is ~11 per cent and for South Asians living in South Africa, United Kingdom or the United States it is as high as 15 per cent. Coronary artery disease is also prevalent in urban Indian areas and much higher in migrant South Asians compared to those of European ancestry. Of interest, the high prevalence of type 2 diabetes mellitus in South Asians has not been entirely attributed to obesity. South Asians also have a high prevalence of insulin resistance beyond that expected for a given BMI. It has been suggested that insulin resistance per se is the underlying cause of metabolic risk leading to type 2 diabetes and/or cardiovascular disease.

South Asians with metabolic risk for cardiovascular disease have a BMI that seemingly fits the phenotype of “metabolic obesity”, a term introduced by Ruderman et al some years ago. Briefly, the phenotype includes individuals who do not meet BMI criteria for overweight or obesity but who have metabolic alterations typically seen in those who meet the obese (overweight) BMI criteria. The phenotype includes hyperinsulinism and increased fat cell size as seen in some patients with type 2 diabetes mellitus, in about 20 per cent of subjects with MODY, and in some patients with endogenous hypertriglyceridemia. The phenotype is also present in the offspring of subjects with hypertriglyceridemia who have only hyperinsulinism and normotriglyceridemia. “Metabolic obesity” also appears to be prevalent in middle-aged men and women. It has also been reported that hyperinsulinism in middle-aged normal-weight men is associated with an increased fat cell size. Some possible mechanism underlying hyperinsulinism in individuals with “metabolic obesity”, includes beta-cell hyperplasia, physical inactivity, and/or a manifestation of gene-environment interactions that remain uncharacterized. Another question of interest is whether “metabolic obesity” is associated with central obesity.

The study published in this issue of the journal focuses on the association of abdominal fat mass to metabolic syndrome risk in South Asians. This study goes beyond BMI and waist girth characterization of metabolic syndrome in South Asians. Forty nine men and 71 women participated in this cross-sectional study. They had a BMI of 23 kg/m² and 24 kg/m², respectively. Twenty-three per cent of the study volunteers had metabolic syndrome by South Asian Modified ATP
III criteria. For the study group as a whole, average levels of plasma triglyceride and LDL cholesterol were not elevated and women had low HDL cholesterol by NHANES III criteria. Average blood pressure for the group was not elevated. The question addressed in the study was whether the metabolic syndrome risk was associated with visceral or subcutaneous abdominal fat as assessed by computed tomography of the abdomen at the L4-L5 vertebral level. Visceral fat correlated with metabolic variables but subcutaneous fat did not. Similarly, visceral fat showed significant association with metabolic syndrome. Thus the authors conclude that in non-diabetic South Asians, it is the visceral fat and not the subcutaneous fat that seemingly imparts risk for metabolic syndrome. This is an interesting observation that warrants mechanistic studies.

Visceral fat has been reported to associate with plasma triglycerides in a number of epidemiological studies. It is suggested that this fat depot, perfused by the portal circulation, delivers substrates to the liver that in excess, can result in hepatic insulin resistance. This in turn can lead to hyperglycemia and/or hypertriglyceridemia. Other equally plausible explanation that has been offered by a number of investigators including Sandeep et al., is that visceral adipokines and cytokines can contribute to insulin resistance and the metabolic syndrome features. Until mechanistic studies are conducted, however, it is difficult to equate visceral fat correlations to metabolic syndrome causation.

The findings of Sandeep et al. are partially supported by those of Chandalia et al. who examined the relation of body composition to insulin resistance. These investigators also asked a similar question of whether greater insulin resistance in South Asians could be explained by increased visceral (intraperitoneal) fat or abdominal subcutaneous fat. Their study included 29 South Asian and 18 European-American men of similar age. BMIs and girths were comparable between the study groups and as expected, South Asians had a greater per cent body fat per BMI than their European counterparts. Visceral fat assessed by magnetic resonance spectroscopy, was similar in both groups but the subcutaneous abdominal fat was greater in the South Asian group. That is, the ratio of visceral-to-subcutaneous fat was significantly lower in the South Asian group. This group also had lower levels of plasma adiponectin and higher leptin and non-esterified fatty acid levels. The Spearman correlation of glucose disposal to visceral fat was higher than the correlation with abdominal subcutaneous fat mass in both groups. However, these investigators extended their analysis to examine subcutaneous abdominal adipocytes and noted that the cells are larger than in the European group who were more insulin sensitive. The adipocyte size correlated inversely with glucose disposal rates and adiponectin levels in both groups. Chandalia and co-investigators concluded that insulin resistance in young South Asian men can be observed in the absence of increased intraperitoneal (visceral) fat mass and that insulin resistance is related to large subcutaneous abdominal adipocyte size. These observations raise the question of the role of hyperplasia versus hypertrophy in subcutaneous abdominal fat in relation to insulin resistance. This question has been of great interest in the field of obesity and is currently revisited by a number of laboratories. Of equal importance is the cellular characterization of the visceral fat. There are emerging reports that macrophage infiltration occurs in these fat depots and that cytokines derived from this fat depot may contribute to the pathogenesis of insulin resistance.

Emerging results on adipose tissue cellularity seem to challenge the interpretation of association studies on the role of visceral versus subcutaneous fat mass in insulin resistance and metabolic risk for cardiovascular disease. More work is needed to reconcile these apparent contradictions. However, the emerging data are insufficient to replace measures of central obesity in clinical assessment of metabolic syndrome. In this regard, the work of Sandeep et al. is supportive of the central obesity paradigm for metabolic syndrome.

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