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Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis

Allan D Sniderman,[1]* Raj Bhopal,[2] Dorairaj Prabhakaran,[3] Nizal Sarrafzadegan[4] and Andre Tchernof[5]

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The rates of coronary disease have accelerated dramatically amongst South Asians, driven to an important extent by the atherogenic dyslipidemia and type 2 diabetes that have become so common amongst them. These precursors of vascular disease appear at lower absolute amounts of adipose tissue in South Asians than in whites. In this paper, we set out a new hypothesis—the adipose tissue overflow hypothesis—to account for these findings. The adipose tissue mass within our bodies can be divided into three different compartments: superficial subcutaneous adipose tissue, deep subcutaneous adipose tissue and visceral adipose tissue. The superficial subcutaneous adipose tissue compartment is the primary compartment, is present throughout the body, and constitutes the vast majority of the adipose tissue in the lower limb. With energy excess, the secondary adipose tissue compartments—the deep subcutaneous (mainly upper body) and the visceral adipose tissue compartments—become more prominent. Superficial subcutaneous adipose tissue is relatively inert metabolically, whereas the other two compartments are characterized by higher transmembrane fatty acid flux rates and thus are more closely linked to dyslipidemia and dysglycemia. We hypothesize that the superficial subcutaneous adipose tissue compartment is larger in whites than in South Asians. If so, as obesity develops, South Asians exhaust the storage capacity of their superficial subcutaneous adipose tissue compartment before whites do and that is why they develop the metabolic complications of upper body obesity at lower absolute masses of adipose tissue than white people.

Keywords Abdominal obesity, WHR ratio, apoB, coronary disease risk, adipose tissue

As the wealth of the peoples of the developing world mounts, albeit too slowly and too unequally, so does the frequency of vascular disease. Indeed, the rate at which vascular disease is increasing in the developing countries is so startling, it appears they may not be merely recapitulating the history of vascular disease within the developed countries, they may be overshooting it, as indeed, appears to have happened to South Asians in the UK. In this regard, there is strong evidence that the metabolic consequences of obesity—dyslipidemia [hypertriglyceridemia, low HDL (high-density lipoproteins) and increased numbers of small dense LDL (low-density lipoproteins) particles] and dysglycemia (insulin resistance and type 2 diabetes)—are manifest at lower absolute amounts of total body fat in South Asians than in whites [for review see Ref. (1)]. Indeed, these differences are so large that the BMI-based definition of obesity is now much lower in South Asians than in whites.[2] But why would South Asians be more susceptible to the atherogenic consequences of obesity and why would abdominal obesity develop earlier in South Asians than in whites? In this paper, we suggest that differences in the development of superficial adipose tissue compartment may be a responsible factor.

[1] Division of Cardiology, McGill University Health Science Centre, Montreal, QC, Canada.

[2] Division of Community Health Sciences, University of Edinburgh, Edinburgh, Scotland, UK.

[3] All India Institutes of Medical Sciences, New Delhi, India.

[4] Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

[5] Molecular Endocrinology and Oncology Research Centre, Laval University Medical Research Centre, Laval, QC, Canada.

Corresponding author. Mike Rosenbloom Laboratory for Cardiovascular Research, Room H7.22, McGill University Health Centre, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1. E-mail: allan.sniderman@muhc.mcgill.ca

Types of adipose tissue

There are three major zones of adipose tissue: superficial subcutaneous adipose tissue, deep subcutaneous adipose tissue,

and visceral or intra-abdominal adipose tissue.[3–6] We believe the superficial subcutaneous layer is the primary compartment, the others secondary compartments. Each has characteristic morphological and functional features (Table 1).

The superficial and deep subcutaneous adipose tissue compartments are separated by a fascial plane, which can be recognized on CT or MRI (Figure 1). Fat within the superficial subcutaneous layer is organized into tightly packed lobules, whereas fat in the deeper subcutaneous layer is found in lobules that are larger, more irregular, and less well organized. Intra-abdominal fat differs yet again in that it is even more vascular and the lobules are less well defined. There is, therefore, a definite gradient towards less organization and more vascularization of the adipose tissue depots moving from outside to inside. Visceral adipose tissue is the smallest of the three adipose tissue compartments, but the one most often linked to metabolic complications. Less well appreciated is that studies have also shown similar relations for deep subcutaneous adipose tissue, particularly with regard to the risk of dysglycemia.[7–10]

Superficial subcutaneous adipose tissue is found everywhere under the skin with the largest amounts in the lower limbs. Deep subcutaneous adipose tissue is located principally in the trunk of the upper body, and visceral adipose tissue, by definition, is present only in the abdomen. In the lower body, superficial subcutaneous adipose tissue makes up the vast majority with the rest divided between deep subcutaneous adipose tissue and the inter-muscular and intra-muscular adipose tissue depots.

Expansion of these different adipose tissue compartments produces different risks for disease. Upper body obesity—in particular expansion of the deep subcutaneous compartment and of the visceral adipose tissue depots—has been repeatedly linked to an increased risk of dyslipidemia, dysglycemia and vascular disease.[11,12] By contrast, greater lower body adipose

Table 1 Adipose tissue compartments

	SSAT	DSAT	VAT
Development sequence	Primary	Secondary	Secondary
Demarcation of lobules[3]	Best demarcated	Intermediate	Least demarcated
Vascularity of lobules[41,42]	Least vascular	Intermediate?	Most vascular
Stability of triglyceride stores[17,41,43,44]	Most stable	Intermediate?	Least stable
Atherogenic dyslipidemia[5,8,9,11,13,15,17,45]	Moderate association	(Very) strong association	Very strong association
Dysglycemia[7,8,12–15,17,46,47]	Moderate association	Very strong association	Very strong association
Cytokine secretion[20,21,48]	Least adverse	Unknown	Most adverse

SSAT = superficial subcutaneous adipose tissue; DSAT = deep subcutaneous adipose tissue; VAT = visceral adipose tissue.

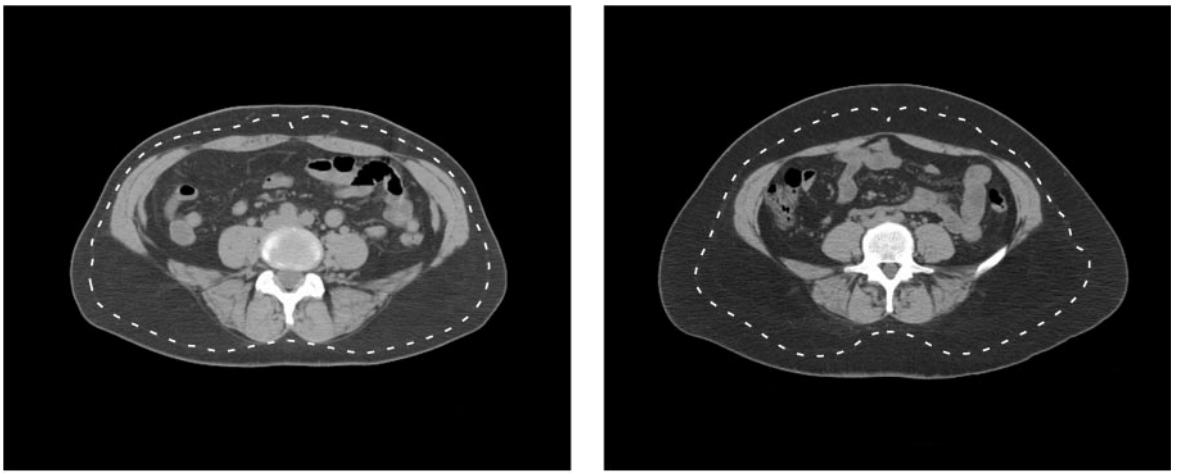

Figure 1 Cross-sectional computed tomography scans of two women. The woman on the left has high proportion of superficial subcutaneous fat compared to the woman on the right. The subcutaneous fascial plane (dashed line) was delineated using the computer interface of the scanner and the area of each compartment was quantitated separately. The age and anthropometric characteristics of the two women are indicated at the bottom of each scan

tissue mass has been associated with better metabolic outcomes.[13–15]

Relation of adipocyte size and distribution to adipocyte function and dyslipidemia

Visceral adipocytes tend to be smaller than abdominal subcutaneous adipocytes but, nonetheless, have greater transmembrane fluxes of fatty acids.[16] Lower body adipocytes, which are almost all superficial subcutaneous adipocytes, have the lowest transmembrane fatty acid fluxes of all and thus represent the most stable stores of triglyceride.[17]

The cellular bases for these differences are not well explicated, but limited evidence suggests they may be related to differing sensitivities to both positive and negative lipolytic stimuli including catecholamines, insulin, and acylation stimulating protein.[17] The relationship between the morphology, the degree of organization and the vascularity on the one hand, and the metabolic activity of the different adipose tissue compartments on the other, seems unlikely to be coincidental.

The dyslipidemia associated with upper body obesity—by which we mean expansion of the secondary adipose tissue stores, the deep subcutaneous and visceral adipose tissue depots, which are restricted to the upper body—is probably a consequence of the increased adipocyte transmembrane flux of fatty acids. Only adipocytes can release free fatty acids into the circulation and so the efflux of fatty acids from adipocytes determines systemic and portal fatty acid flux. As transmembrane adipocyte fatty acid flux increases, the influx of fatty acids into the adipocyte increases during the postprandial period, whereas the efflux of fatty acids from the adipocyte into the systemic circulation increases during the interprandial period. Increased efflux of fatty acids from adipocytes produces increased flux of fatty acids to the liver, which results, in turn, in greater hepatic triglyceride and cholesterol synthesis and increased secretion of apoB particles by the liver.[18]

The increased secretion of very-low-density lipoprotein (VLDL) particles by the liver produces higher plasma triglyceride levels and higher plasma apoB because most of the VLDL particles are quickly converted to LDL particles. Cholesterol ester transfer protein mediated exchange of core lipids amongst the plasma lipoproteins including HDL results in triglyceride enrichment of many of the LDL and HDL particles. Hydrolysis of this triglyceride produces the cholesterol-depleted, small, dense LDL so characteristic of this atherogenic dyslipidemia. LDL cholesterol levels may be normal or increased.[19]

In either case, LDL cholesterol will necessarily underestimate the atherogenic risk due to LDL when small dense LDL are present because these smaller, denser LDL particles contain less cholesterol than the larger LDL particles that usually predominate. HDL cholesterol and apoA-I levels are also lower in these subjects because the smaller triglyceride-rich HDL particles tend to be cleared more rapidly than the larger ones. Thus all the major features of this atherogenic dyslipoproteinemia—increased triglycerides, normal or only moderately increased LDL cholesterol, elevated apoB and decreased apoA-I or HDL C—can be traced to adipocyte transmembrane fatty acid flux, which in turn is dependent on adipocyte size, number, and location.[17]

Cytokine secretion has also been related to adipocyte site and size.[17] Similarly to transmembrane adipocyte flux, adverse cytokine secretion profiles, such as higher plasma levels of TNF-α and IL-6 with lower plasma levels of adiponectin, have been more closely associated with visceral adipocytes compared to other adipocytes.[20,21]

With this background, we can now present our hypothesis in more detail.

Why might South Asians be more susceptible to the metabolic complications of obesity than white people?

Our hypothesis is that the primary adipose tissue compartment is less developed in South Asians than in white people. A reduced capacity to store fatty acids in the primary adipose tissue compartment, which results in earlier utilization of the secondary compartments, would explain why at similar BMI, the waist to hip ratio of South Asians is greater than whites. It would also explain why, at the same BMI, the atherogenic lipoprotein profile we have described is more pronounced in South Asians than in whites. Our hypothesis might also help explain why white people appear to be relatively protected from the metabolic syndrome and diabetes in comparison to many non-white populations, including Africans, middle east, south east Asia, South Asia, native populations from the Americas, and Australasian aborigines.[1]

Adipose tissue mass increases both by increases in the size of pre-existing adipocytes and by the development of new cells through adipogenesis.[22] Energy excess thus initiates the sequence first of enlargement of adipocytes and then their proliferation.[23] Our model posits that superficial adipose tissue is the first adipose tissue compartment to develop and mature. Any limitation in the capacity of the primary adipose tissue compartment to store all the excess energy as triglyceride would lead to the development and expansion of the two secondary adipose tissue depots. It is their temporal appearance that is ordered: superficial subcutaneous adipose tissue first, then deep subcutaneous and visceral. That does not mean, however, that all increase in superficial subcutaneous adipose tissue ceases as soon as the secondary stores start to be developed. Rather, we suggest that it is the rate of expansion that differs. Initially, there is virtually only the primary depot and in the normal non-obese individual, superficial subcutaneous adipose remains the dominant compartment through normal maturation and puberty. Only with sustained excess energy intake do the secondary compartments develop substantially. Once the primary compartment cannot keep up, excess energy intake necessarily results in more rapid and prominent development of the secondary adipose tissue stores compared with the primary depot. Continued energy excess results, eventually, in ectopic deposition of fat within tissues such as skeletal muscle. This model is consistent with the observations that most of the fat gained or lost in adults undergoing weight gain or loss is located in the upper body secondary adipose tissue compartments.[24]

Evidence supporting the hypothesis

Most of the available data on fat distribution deals with Asian Indians, although in many cases similar results have been reported for other South Asians. Compelling evidence from studies in migrants and in natives indicates that adult Indians have more adipose tissue mass for a given BMI than white Caucasians and African Americans [for review see Ref. (1)]. Moreover, the distribution of adipose tissue varies such that more of the adipose tissue is in the upper body rather than the lower body, with Indians having greater visceral fat mass than white Caucasians or African Americans at comparable BMI.[1] Visceral adiposity in Indians is associated with greater truncal subcutaneous adipose tissue mass.[25] Forouhi *et al.*[1] provide abdominal CT scan measurements in a comparative study of men and women of European origin and South Asians in London. In South Asian men, both BMI and waist were marginally lower, but the visceral fat compartment was larger than in Europeans. In South Asian women, BMI and waist were slightly higher but visceral fat was much greater than in European women. Subcutaneous fat around the abdomen was also greater in South Asians, but there were no measures of superficial and deep subcutaneous fat compartments. Taken together, these data are consistent with the hypothesis we have put forward—smaller storage capacity of the primary superficial adipose tissue zone with the necessity for earlier overflow to secondary, metabolically more active, zones.

Major differences are present at birth: South Asian babies, on average, are significantly smaller by every measure than Caucasian babies.[26,27] This includes skinfold thickness, an index of the mass of superficial subcutaneous adipose tissue. It has been argued that because these differences are less pronounced than those of weight and height, for example, Indian babies are relatively obese at birth.[28] Nonetheless, in absolute terms, primary superficial adipose tissue mass is significantly less in Indian babies who, compared with white babies in London, have substantially less peripheral fat as indicated by triceps skinfold thickness, with little difference in the central fat as indicated by subscapular skinfold thickness.[26]

An MRI-based study demonstrated that growth restricted newborn infants born at or near term had significantly reduced total percentage adipose tissue and subcutaneous adipose tissue, particularly in the lower limbs. Intra-abdominal tissue was not reduced but made up only a very small portion of the total.[29]

Of particular importance are the observations that differences in birth weight persist in babies born to women of South Asian descent who were born and brought up in the UK. These observations argue strongly against differences in nutrition as an explanation for these findings.[30,31]

Peters and Ulijaszek examined subscapular and triceps skinfold thickness and arm circumference in 2224 Indo-Pakistani children in East Midlands, England. They concluded that the Indo-Pakistani children deposited more fat on the trunk and less on the upper limb relative to the British standards.[32] Similar observations had been made in a number of studies on children, adolescents and adults, and the findings seem generalizable internationally. Gulliford *et al.*[33] found the same pattern in children of Indian and African descent in Trinidad and Tobago. Whincup *et al.*[34] showed high susceptibility to insulin resistance in South Asian schoolchildren compared with white ones, despite similar indicators of obesity. Misra proposed that body fat patterning is critical in explaining cardiovascular disease and diabetes in Asian Indians and his recent review places emphasis on the potential importance of excess central fat, compared to a deficit of peripheral fat, as indicated by skinfold measurements.[35]

In addition, hypertriglyceridemia and increased apoB, as opposed to simple elevations of total or LDL cholesterol, distinguish the lipid profiles of migrant versus rural South Asians.[36] As we have noted, this atherogenic lipoprotein profile is the consequence of adipose-derived increased fatty acid flux.[17] The overall relations between low birth weight and subsequent risks of dyslipidemia and dysglycemia are not unique to South Asians. On the contrary, they have been noted in many different groups.[37] This suggests that distribution of primary adipose tissue is the key to understanding dyslipidemia amongst the peoples of South Asia compared with white populations.

Other theories

Neel put forward the thrifty gene hypothesis in 1962.[38] This hypothesis states that conditions of scarcity favour those with a parsimonious metabolism but such people are disadvantaged when food supply is abundant. However, most of South Asia is warm and fertile, supporting a huge population, both historically and currently, and this does not provide immediate face validity for this argument. Barker and other investigators[39] noted a relation between low birth weight and increased adult health risk with an increased prevalence of dyslipidemia, diabetes, hypertension and vascular disease. They attributed the low birth weight to fetal undernutrition, which they believe to be the critical causal event. Others have felt the most important determinant was not low birthweight *per se* but rather the exaggerated catch-up growth that occurred subsequently.[40] Neither hypothesis, however, would explain systematic differences amongst the peoples of the world. Moreover, birth weight is low in areas in India in which the people are poor but not malnourished and remains low in offspring of South Asians born in the UK.[31] Fetal undernutrition is considered the cause of the low birth weight in the Barker hypothesis whereas we speculate that the reduced development of adipose tissue—that is, a smaller primary adipose tissue compartment—relates to a more primordial cause. We are considering whether this difference between Caucasians and South Asians could relate to environmental differences such as climate but we lack sufficient data to respond to reasonable challenges to this concept.

Testing the adipose tissue compartment overflow hypothesis

The adipose tissue compartment overflow hypothesis states that substantial differences in the primary adipose tissue compartment exist between South Asians and white people. In the face of excess energy intake, the more limited the reservoir capacity of the primary compartment, the earlier and the more substantial must be the expansion of the secondary adipose

tissue compartments. These compartments are characterized by higher transmembrane fatty acid fluxes and the net result is that the incidence of dysglycemia, atherogenic dyslipidemia and their product—accelerated vascular disease—is more common in South Asians than in white people at the same absolute adipose tissue body mass.

It will require effort to test this hypothesis. The first initiatives will be descriptive. Using either CT or MRI, the masses of the three compartments can be quantified, examined in cross-sectional studies, and tracked longitudinally in cohorts. Our hypothesis predicts that the primary adipose tissue compartment will be smaller in lean South Asian people than lean white people; that as total adipose tissue mass expands, the superficial adipose tissue compartment is the first to increase in size, followed by the other two; that this crossover will happen earlier in South Asians than in whites; and finally that the ratio of the secondary to the primary compartments will parallel the apoB/apoA-I ratio and indices of dysglycemia. But these studies will only demonstrate consistency with the hypothesis, not causality and they will certainly not reveal the mechanisms responsible.

Our hypothesis posits that South Asians have a lower fat storage capacity in their primary adipose tissue compartment than whites. But is this due to an inherently lower number of adipocytes or to a limitation of those present to take up triglyceride? Unfortunately, reliable methods to measure adipocyte number accurately have not yet been developed. Moreover, a detailed understanding of the cellular and molecular events regulating fat partitioning into a given compartment is still lacking. Exploring this hypothesis, testing this hypothesis, perhaps even extending this hypothesis will require a partnership of enquiry between those engaged in epidemiology, evolutionary and molecular biology, medical imaging, and physiology.

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