Editorial

Energy Partitioning in Gluteal-Femoral Fat: Does the Metabolic Fate of Triglycerides Affect Coronary Heart Disease Risk?

Isabelle Lemieux

Jean Vague from the University of Marseille was the first to foresee the importance of regional adipose tissue distribution when he suggested that a "male" pattern of body fat distribution, which he referred to as android obesity, was the form of obesity more likely to be accompanied by diabetes, hypertension, and heart disease, as opposed to the typical, rather benign, "female" pattern of body fatness, which he described as gynoid obesity.[1] In the early 80's, the late Per Björntörp from the University of Gothenburg in Sweden had come across Vague's literature, and he took advantage of the availability of anthropometric variables such as waist and hip circumferences to develop a simple index of body fat distribution, the waist to hip ratio (WHR).[2–5] Having access to two prospective studies of middle-aged men and women, the Swedish team found that the proportion of abdominal fat (as crudely appreciated by the WHR) was an independent risk factor for the development of cardiovascular disease and diabetes over a follow-up period of more than a decade.[2,3] Simultaneously, in the United States, Ahmed Kissebah and his group[6] also generated results emphasizing the importance of regional adipose tissue distribution as an important correlate of metabolic complications that had been, in the past, associated with excess weight per se. These results published in the early 80's have generated great interest from the scientific and medical community, and over the last 20 years a flourishing and abundant literature has been published on the topic. As for many groups around the world, the publication of Björntörp's early results raised our interest, and we initially focused our investigations on the study of the contribution of adipose tissue distribution to the variation of plasma lipid and lipoprotein levels. Using simple skinfold measurements as indices of subcutaneous fat accumulation, we first reported in 1985 that abdominal fat accumulation was a correlate of the reduced high-density lipoprotein (HDL)-cholesterol levels found in obesity, whereas leg fat accumulation was not associated with any evidence of metabolic prejudice whatsoever.[7] With the development of imaging techniques such as MRI or computed tomography, it has been possible to measure with greater accuracy regional adipose tissue accumulation and, particularly, to distinguish subcutaneous abdominal fat from the fat located in the abdominal cavity which we described as intra-abdominal or visceral adipose tissue. In an issue of this journal published 14 years ago,[8] we reviewed the evidence that we had published at that time which had clearly indicated that a selective deposition of visceral adipose tissue was associated with a whole cluster of metabolic abnormalities which were later defined as the features of the metabolic syndrome. Thus, in 1990, we had already described the relationship between abdominal fat mass, visceral adipose tissue accumulation, and the features of the atherogenic dyslipidemia of the metabolic syndrome, which include hypertriglyceridemia, elevated apolipoprotein B concentration, an increased proportion of small low-density lipoprotein (LDL) particles, and reduced HDL-cholesterol levels, particularly in the cardioprotective HDL_2 subfraction.[8]

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Okura et al[9] report further evidence that body fat distribution, as assessed by either dual-energy X-ray absorptiometry (DXA) or computed tomography, is an important correlate of metabolic risk variables modulating coronary heart disease risk in women. However, they found no relationship between abdominal subcutaneous adipose tissue and metabolic parameters. Not only did they find evidence that abdominal fat accumulation causes prejudice to the metabolic risk profile, but they also observed that peripheral subcutaneous fat accumulation (fat tissue in legs) might be cardioprotective. The authors also reported similar findings after a 14-week weight reduction program with diet and exercise. These results are interesting and add to the already published evidence for such cardioprotective "effect" of peripheral fat accumulation. For instance, Terry et al[10] have shown that for any given waist circumference, individuals with a preferential thigh fat accumulation had a more favorable plasma lipoprotein-lipid profile. In 1991, our group also published evidence that mid-thigh fat accumulation was positively correlated with HDL_2-cholesterol levels and with the HDL_2-cholesterol/HDL_3-cholesterol ratio, and this relationship could be explained by the elevated mid-thigh adipose tissue lipoprotein lipase activity, contributing to raise HDL_2-cholesterol levels.[11] Finally, also using DXA methodology, Tanko et al[12] recently reported that the localization of body fat in elderly women was apparently more important than total fatness per se as a predictor of the comorbidities of obesity. They also found in that study that among women

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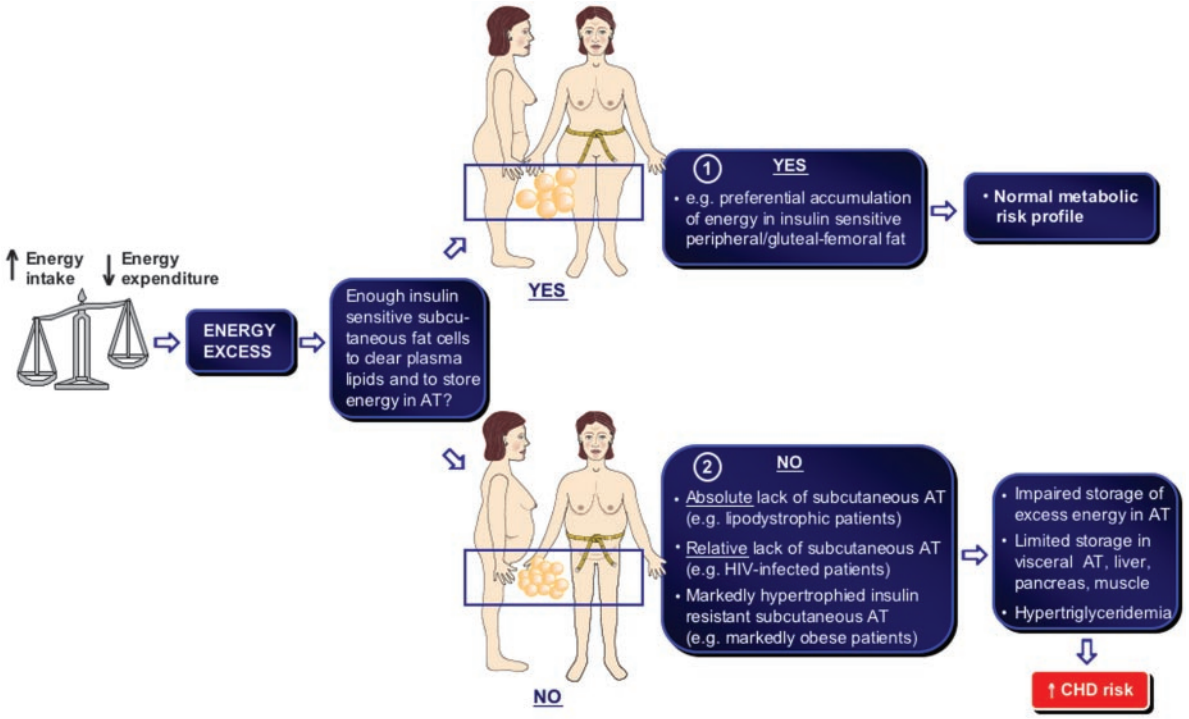

Model showing the potential contribution of subcutaneous gluteal-femoral adipose tissue (AT) as a possible cardioprotective "metabolic sink". Two obesity phenotypes at both ends of the spectrum are shown: 1, The energy surplus is preferentially accumulated in gluteal-femoral fat, having little impact on the metabolic risk profile. 2, The energy surplus accumulates in the atherogenic visceral depot (which could be crudely assessed by an increased waist circumference) as well as in liver, pancreas, and muscle mass due to a lack (absolute or relative) of subcutaneous AT or in the presence of insulin resistant markedly hypertrophied adipose cells leading to a cluster of metabolic abnormalities referred to as the metabolic syndrome. CHD indicates coronary heart disease.

with a history of myocardial infarction, the percentage of central fat was significantly higher compared with women with no manifest coronary disease, with no differences in the percentage of peripheral fat being noted. The authors also concluded that whereas a central fat mass pattern was associated with an atherogenic profile, a peripheral fat mass pattern rather appeared to be predictive of a favorable metabolic profile.

Why Would Gluteal-Femoral Fat Be Cardioprotective?

It is possible that when exposed to an energy surplus, subcutaneous peripheral fat might represent an insulin sensitive "metabolic sink" which may, through an elevated adipose tissue lipoprotein lipase activity, favor the catabolism of triglyceride-rich lipoproteins, the clearance of triglycerides of dietary origin, and their storage in adipose cells (Figure). Such preferential partitioning of extra energy into gluteal-femoral fat in women might eventually lead to a more favorable lipid profile (lower triglyceride and increased HDL-cholesterol levels) leading to some cardioprotection. In this context, the paper by Okura and colleagues[9] provides further evidence that adipose tissue is not a homogeneous organ and that it has a much more important role to play than simply the storage and mobilization of fat (Figure). In both men and women, there is probably a minimal amount of insulin-sensitive adipose tissue, which is required for the proper clearance of dietary triglycerides. A clinical example of the consequence of a lack of adipose tissue is found in the lipodystrophic patients who are characterized by a severe insulin resistant state and by ectopic triglyceride accumulation causing serious metabolic prejudice as fat accumulates in the liver, pancreas, and in muscles (Figure).[13,14] Clearly, the optimal approach to limit fat accumulation in ectopic depots and in the atherogenic visceral adipose tissue is to remain in energy balance with proper nutritional habits and an adequate level of physical activity. However, a better understanding of the complex interrelationships between visceral adipose tissue accumulation and metabolic processes governing regional adipose tissue accumulation may lead to the development of new pharmacological approaches to limit ectopic fat accumulation and related health hazards. In this regard, the development of glitazones which have been shown to promote the channelling of energy in "good" subcutaneous adipose tissue has provided further evidence that regional adipose tissue distribution plays an important role, and that glitazones may create a healthy "metabolic sink" by reshaping adipose tissue distribution in previously insulin resistant individuals.[15,16]

In summary, results of the intervention study by Okura and colleagues[9] demonstrate that localization of fat mass is clearly more important than obesity per se in the evaluation of the atherogenic metabolic risk profile in women. Thus, information on regional body composition changes during weight reduction is also essential to properly evaluate the impact on coronary heart disease risk factors.

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