Although cross-sectional studies during the past 40 years have indicated that abdominal obesity is closely associated with hypertension, noninsulin-dependent diabetes mellitus (NIDDM), and other metabolic aberrations, it was not until recently that prospective epidemiological studies have demonstrated the predictive power of this factor for NIDDM, cardiovascular disease (CVD), and premature death in both men and women. Furthermore, such population studies have shown the close statistical correlation between the abdominal distribution of adipose tissue and the previously established risk factors for NIDDM and CVD (elevated concentrations of very low density lipoproteins [VLDL], low density lipoproteins [LDL], apoprotein [apo] B-100, insulin, hypertension, and smoking). 

The relationship between abdominal obesity and these disease end points and their risk factors might be explained in principle either by a direct causal relationship or by an unknown factor causing abdominal distribution of body fat as a parallel phenomenon to the diseases. Recent evidence is now appearing which, combined with previously available information, actually suggests a causal connection between abdominally localized adipose tissue and most of the previously established risk factors for CVD and NIDDM. This will be briefly summarized in the following. (For more comprehensive reviews of this field in general, see references 1 to 5).

The Metabolic Characteristics of "Portal" Adipose Tissue

Abdominal distribution of body fat is usually measured in epidemiological studies as the ratio of the circumferences of the waist and hip, the waist/hip ratio (WHR). Several recent studies have now shown that although the WHR is a convenient method to evaluate the abdominal distribution of body fat in epidemiological studies, it is the mass of intra-abdominal fat that is most closely associated statistically to the established CVD and NIDDM risk factors mentioned above (for reviews and detailed references, see references 1 to 5).

Intra-abdominal adipose tissue has some metabolic characteristics that are unique in comparison with other adipose tissues, and, interestingly, this seems to be most pronounced for the regions that are drained by the portal circulation (omental and mesenteric adipose tissues). These portal adipose tissues have an exceedingly sensitive system for the mobilization of free fatty acids (FFA) due to a preponderance of β-adrenergic receptors and little α-adrenergic inhibition. This is seen in normal men and in abdominally obese women, but not in normal women or obese women with a gluteal-femoral adipose tissue distribution.6,7 Men, normal or obese, have at least twice the proportion of total fat localized to the intra-abdominal depots compared to women.8 Other observations suggest that the insulin inhibition of FFA release from omental fat is blunted due to a low density of insulin receptors.8 Taken together, these observations indicate that the lipid mobilization capacity of portal adipose tissues is indeed pronounced in men and in abdominally obese women. These people have a portal adipose tissue, which is specifically sensitive to lipolytic stimuli, and the mass of this tissue is also enlarged.

This situation would be expected to result in high portal FFA concentrations in situations where FFA mobilization is triggered, such as stress, anger, frustration, and smoking. In contrast, normal nonobese women and women with a gluteal-femoral fat accumulation have insignificant amounts of portal fat and consequently little risk of increased portal FFA concentrations. In fact, gluteal-femoral adipose tissue seems to be difficult to mobilize in women except during lactation, suggesting that the function of this adipose tissue is to be a reserve for energy needed during lactation.10 Women who are obese by enlargement of these depots can thus be considered to be in a condition of an exaggeration of normal physiology and should thus not be expected to be exposed to a derangement of metabolism or other risks, which indeed also seems to be the case.1

Portal Free Fatty Acids and Hepatic Production of Lipoproteins

Exposure of the liver to elevated concentrations of portal FFA might be the key to several important consequences. First, it has long been known that this is followed by an increased secretion of VLDL by the liver.11 Recent studies seem to have clarified the mechanism involved. Apo B-100, the protein backbone of VLDL and LDL, is apparently synthesized in excess in the liver. This is at least partly due to an unusually long half-life of the mRNA for apo B-100, securing translation of apo B-100 for prolonged periods of time. Secretion of VLDL seems to be mainly regulated by the synthesis of triglyceride for transport, in turn dependent on the availability of fatty acids.12 Thus portal FFA probably regulate the synthesis and secretion of VLDL and apo B-100. Retention of LDL in the circulation is dependent on both the rate of production and the rate of removal. An increased synthesis would then be a factor tending to increase the concentration of circulating VLDL, LDL, and apo B-100.

Portal Free Fatty Acids and Hepatic Gluconeogenesis

It has long been known that fatty acids stimulate hepatic gluconeogenesis via regulatory key enzymes and
that the reduction-oxidation status in the cell is of crucial importance. In isolated hepatocytes, fatty acids also stimulate gluconeogenesis from pyruvate, lactate, and alanine. This is, however, abolished by prevention of the oxidation of these fatty acids. Recent studies have demonstrated the powerful effects of this mechanism in the intact animal. In rats with diabetes induced by streptozotocin, the administration of nicotinic acid, a powerful inhibitor of fatty acid mobilization from adipose tissue, or Etomoxir prevented FFA oxidation in liver mitochondria and actually normalized the blood glucose levels. This was presumably due to a release of the gluconeogenic effects of fatty acid oxidation in the liver. Analogous studies in humans have shown that the elevation of circulating FFA is followed by a marked increase in splanchnic production of glucose, a phenomenon characteristic of abdominal obesity.

Taken together, there is considerable evidence that fatty acids stimulate hepatic gluconeogenesis and that fatty acid oxidation is necessary to obtain this effect.

**Portal Free Fatty Acids and Hepatic Insulin Clearance**

Recent studies have shown that FFA also interfere with hepatic clearance of insulin. In isolated hepatocytes, different fatty acids in physiological concentrations known to occur in portal circulation inhibit insulin binding. This is due to a decreased number of insulin receptors apparently caused by receptor internalization and is followed by a parallel decrease in insulin degradation. Furthermore, the action of insulin is also inhibited (Kissebah, personal communication). Interestingly, preventing fatty acid oxidation by treating the donor animals with Etomoxir abolishes the fatty acid effects (Svedberg, personal communication).

Fatty acids at the same concentrations shown to inhibit insulin binding and effects in isolated hepatocytes have previously been shown to inhibit insulin clearance in the in situ perfused rat liver. This effect is dependent on the age and nutritional status of the animal and is specific for fatty acids, because glucose or lactate do not have such effects (unpublished observations). Furthermore, the overfeeding of rats, resulting in increased portal FFA concentrations, was followed by a decreased hepatic clearance of insulin, inversely parallel to hepatic triglyceride contents, which, in turn, was regulated by the concentrations of portal FFA concentrations.

Obesity in humans seems to be followed by a decreased hepatic clearance of insulin. Peiris et al. have in recent elegant studies shown that this is a characteristic of abdominally obese subjects. This is exaggerating the peripheral hyperinsulinemia, which is also caused by an increased insulin secretion, known to follow obesity in general.

Recently, hyperinsulinemia and early essential hypertension have been linked statistically. Furthermore, mechanisms by which hyperinsulinemia causes elevated blood pressure have been suggested.

**Summary of Effects of Portal Free Fatty Acids on Hepatic Metabolism**

Taken together, these observations show the profound effects of fatty acids on the hepatic regulation of energy metabolism. The parallel nature of the stimulation of gluconeogenesis and the inhibition of hepatic uptake of insulin, both dependent on fatty acid oxidation, is striking. In the postaJimentary state, when portal FFA provide the main energy to the liver, insulin is not needed for hepatic metabolism and may, in fact, inhibit gluconeogenesis. It is, therefore, logical that fatty acids exert this duplicate effect of stimulating gluconeogenesis and preventing cellular insulin availability. It is also meaningful that excess portal FFA are in this situation transported to the periphery as VLDL for energy purposes.

With this background, it is easy to imagine the consequences of an enlargement of the lipolytically active portal adipose tissues, such as in abdominal obesity. Excess FFA concentrations in the portal vein would be a first logical consequence. This, in turn, would presumably be followed by increased concentrations of circulating VLDL and, when increased, by a risk that LDL and apo B-100 might be retained in the circulation. Hepatic glucose production might be elevated as a consequence of the stimulatory effects of FFA combined with the diminished checking of hepatic gluconeogenesis by insulin. Furthermore, it would be expected that hyperinsulinemia would be caused by increased secretion due to obesity itself and exaggerated by a decreased hepatic clearance of insulin. In addition, there is now considerable evidence linking hyperinsulinemia and hypertension causally. Consequently, the end result of this would be elevated circulating concentrations of VLDL, LDL, apo B-100, glucose, and insulin, as well as hypertension. These are all established risk factors for CVD and NIDDM, which thus can be created by elevated portal FFA concentrations, due in turn to enlarged, lipolytic, sensitive portal adipose tissue in abdominal obesity. This is summarized schematically in Figure 1.

Porto adipose tissue may, consequently, act as a generator for several of the most powerful risk factors for CVD, stroke, and NIDDM. This might then explain the statistical associations found between abdominal obesity and the development of the diseases mentioned. In analogy, obesity localized to other adipose tissue regions would not be associated with these risk factors and endpoints. This is in excellent agreement with prospective epidemiological studies.

In addition to providing a way to understand the causal links between abdominal obesity and morbidity, this hypothesis seems to have the potential of also explaining why CVD, stroke, NIDDM, and their risk factors are so often seen as a cluster of associated phenomena with variations in the expression of the clinical consequences. Abdominal obesity is a major component of this syndrome. In fact, enlarged portal adipose tissues might be a crucial factor expressing this cluster of conditions triggered by the mentioned effects of high concentrations of portal FFA.
Why Does Excess Depot Fat Accumulate In Visceral Depots?

There are endocrine aberrations associated with an abdominal preponderance of depot fat accumulation in both men and women. These phenomena can be summarized as a preponderance of corticosteroid effects, while sex steroid hormone secretion is inhibited. This is, for example, a known neuroendocrine consequence of certain types of stress, alcohol, and smoking, all found in subjects with exaggerated visceral accumulation of adipose tissue fat. The explanation for a redistribution of depot fat caused by this endocrine perturbation is most likely regional differences in steroid hormone receptor density combined with a genetic predisposition. For example, glucocorticoid receptor density seems to be higher in intra-abdominal than in other adipose tissues. The full expression of these mechanisms are seen dramatically in Cushing’s syndrome.

Primary and Secondary Risk Factors for Cardiovascular Disease, Stroke, and Noninsulin-dependent Diabetes

The risk factor pattern for CVD, stroke, and NIDDM is complex and the information is not fully consistent, although the main risk factors for these diseases are found consistently and seem to be conclusively established. These risk factors can be thought of as early disease symptoms (for example slight hyperglycemia in relation to NIDDM and ischemic ECG in relation to CVD), while others can be considered as disease triggers (for example hypertension in relation to stroke and hypercholesterolemia in relation to CVD). These established risk factors are all close to the disease processes, which make them easy to discover consistently in epidemiological, prospective studies.

There are, however, also a number of other, less well-established risk factors for the diseases in question. The inconsistent findings here might be due to a longer distance between these various phenomena and the disease mechanism, allowing interference with confounding factors. One example is saturated fat in the diet, which is not always found as a risk factor for CVD in spite of the fact that its relationship to elevated LDL now must be considered established. Elevated LDL is, however, consistently found to be a powerful risk factor for CVD. The longer distance between saturated fat and the disease process of CVD than between LDL and CVD might be weakening the statistical associations because of interference by confounding factors.

There is a group of other phenomena that have been reported as associated with the risk of developing CVD, stroke, and NIDDM, but the information is also inconsistent. These include, among others, socio-economic factors, stress, and alcohol. These factors might generate established risk factors via an accumulation of intra-abdominal fat, in turn caused by the neuroendocrine imbalance mentioned above, common for these conditions. Such “primary” risk factors might then generate the immediate triggers, the established risk indicators, which might be considered as “secondary” risk factors. This is summarized schematically in Figure 2.

Future Developments

Although this field is a recent re-opening of old thoughts emanating originally from anthropometric observations and research, it is apparent that further explorations along these lines should be fruitful. Some of the major unclear points will be mentioned here starting from the primary end of the postulated chain of events. Studies on a putative role of such factors as stress, socio-economic factors, and alcohol in relation to CVD and NIDDM based on reliable biologic markers are needed. The pathogenesis of the endocrine aberrations associated with the abdominal localization of adipose tissue is of primary importance. In a next step, the
mechanisms whereby this is followed by a redistribution of adipose tissue is another area that is incompletely known. Furthermore, we do not know why portal adipose tissue is highly lipolytically active in obesity in men and in abdominally obese women. Essential details linking portal adipose tissue metabolism to hepatic generation of secondary risk factors are also missing. The fatty acid effects on hepatic insulin clearance need better documentation in abdominal obesity in humans, and we need actual measurements of portal concentrations of FFA in this condition. The topography of the portal vein unfortunately makes these studies difficult. Inference from information from animal models would be useful, and an adequate animal model is therefore badly needed. In general, studies including experimental manipulations of crucial factors, such as portal FFA concentrations and steroid hormone action, seem to have a potential to yield valuable information. It seems clear that these new developments hold great promise for a better understanding of the precursors of several prevalent diseases.

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