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REVIEW

Adipose tissue and metabolic syndrome: too much, too little or neither

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ABSTRACT

Obesity is strongly associated with metabolic syndrome. Recent research suggests that excess adipose tissue plays an important role in development of the syndrome. On the other hand, persons with a deficiency of adipose tissue (e.g. lipodystrophy) also manifest the metabolic syndrome. In some animal models, expansion of adipose tissue pools mitigates adverse metabolic components (e.g. insulin resistance, hyperglycaemia and dyslipidemia). Hence, there are conflicting data as to whether adipose tissue worsens the metabolic syndrome or protects against it. This conflict may relate partly to locations of adipose tissue pools. For instance, lower body adipose tissue may be protective whereas upper body adipose tissue may promote the syndrome. One view holds that in either case, the accumulation of ectopic fat in muscle and liver is the driving factor underlying the syndrome. If so, there may be some link between adipose tissue fat and ectopic fat. But the mechanisms underlying this connection are not clear. A stronger association appears to exist between excessive caloric intake and ectopic fat accumulation. Adipose tissue may act as a buffer to reduce the impact of excess energy consumption by fat storage; but once a constant weight has been achieved, it is unclear whether adipose tissue influences levels of ectopic fat. Another mechanism whereby adipose tissue could worsen the metabolic syndrome is through release of adipokines. This is an intriguing mechanism, but the impact of adipokines on metabolic syndrome risk factors is uncertain. Thus, many potential connections between adipose tissue and metabolic syndrome remain to unravelled.

Keywords Adipose tissue, ectopic fat, insulin resistance, metabolic syndrome, obesity, overnutrition.

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The metabolic syndrome occurs in 20–40% of the worldwide adult population [1]. This syndrome predisposes to cardiovascular disease (CVD) [2]. Its features are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG], elevated apolipoprotein B [apo B] and reduced high-density lipoprotein [HDL-C]), elevated blood pressure, elevated glucose levels, and pro-inflammatory and pro-thrombotic states. Those features other than abdominal obesity are commonly called *metabolic risk factors*. Persons with the metabolic syndrome carry an approximate twofold increase in risk for CVD [3]. Atherogenic dyslipidemia, hypertension and hyperglycaemia (diabetes) are well-established *major risk factors* for CVD; they are known to directly cause vascular disease. Pro-thrombotic state and pro-inflammatory states are called *emerging risk factors* [4,5]; they associate with CVD and are plausibly in the chain of causation, but their quantitative contributions to CVD remain uncertain.

In 1988, Reaven [6] postulated that insulin resistance underlies the metabolic syndrome. Many investigators accept this mechanism. But others see excessive nutrient energy and concomitant obesity as primary. Support for the latter view comes from the fact that most people with metabolic syndrome are overweight or obese. For example, Park *et al.* [7] found that among US adults the metabolic syndrome occurs in 4·6%, 22·4% and 59·6% of normal weight, overweight and obese men, respectively. Distribution was similar for US women [7]. We must therefore ask whether adipose tissue itself plays a pivotal role in causation of metabolic syndrome. This paper will examine this possibility.

Adipose tissue deficiency and metabolic syndrome

Adipose tissue is a fat storage organ. Most people believe that excess adipose tissue is detrimental. But an opposing argument is that adipose tissue defends against metabolic consequences of overnutrition. For example, patients having deficiency of adipose tissue (lipodystrophy) redistribute fat to skeletal muscle and liver [8–10]. This *ectopic fat* seemingly underlies severe insulin resistance, fatty liver, diabetes and hypertriglyceridemia. The metabolic syndrome phenotype accompanies

lipodystrophy in both humans and animal models [11–13]. Conversely, some genetically obese animals manifest similar metabolic abnormalities; but when their adipose tissue is expanded more through genetic manipulation, metabolic risk factors disappear [14]. This suggests that adding more adipose tissue to existing obesity mitigates the metabolic syndrome. In animal models, adipose tissue apparently acts as a buffer against metabolic risk factors; and by the same token, buffering is impaired in the presence of adipose tissue deficiency [14].

If adipose tissue protects against the metabolic syndrome, this protection might reside in fat storage capacity. Excess fat is stored either by increasing the size or number of adipocytes. Accordingly, earlier investigators identified two types of obesity in experimental animals: hyperplastic and hypertrophic [15]. In most obese humans, both number and sizes of adipocytes are increased [16,17]. Nevertheless, Salans *et al.* [18] and Sjöström and Björntorp [19] reported that one or the other pattern usually dominates among obese individuals. The hypercellular form occurred in those with severe obesity of early onset. The hypertropic form, in contrast, began later in life and occurred with less severe obesity. Theoretically, hyperplastic obesity should protect against metabolic risk factors better than hypertropic obesity, because of greater potential for fat storage. Some investigators indeed favour the view that hypertrophic obesity results from deficient adipocyte replication and an insufficient lipid storage capacity [20–22].

Some insulin-resistant individuals in fact show an excess of small 'immature' adipocytes compared to larger cells [23,24]. Very possibly, smaller cells fail to mature into larger cells. If this failure occurs, fat storage capacity should be limited and excess fat could be redistributed to ectopic sites. Young adult men of South Asian ethnicity likewise have a high proportion of small adipocytes relative to larger adipocytes [25]; it is well known that South Asians are prone to insulin resistance, metabolic syndrome and type 2 diabetes [26–28]. In yet another report, an apparent defect in adipogenesis was noted in obese adolescents with insulin resistance [29]. All of these studies are consistent with the concept of metabolic syndrome being related to insufficient fat storage capacity.

Obesity and metabolic syndrome: the fatty acid theory

Beyond adipocyte size and number, adipocytes occur in different body fat pools, which may vary in metabolic characteristics. For simplicity, there are three adipose tissue locations: lower body subcutaneous, upper body subcutaneous and intraperitoneal (visceral) [30,31]. The latter two together are commonly called *upper body fat*. The term *upper body obesity* signifies accumulation of excessive adipose tissue predominately in the upper body. Excess fat in intraperitoneal adipose tissue can be called *visceral obesity*. In men with upper body obesity, excessive fat usually occurs in both subcutaneous and visceral pools [32]. In most women with upper body obesity, reserve fat is stored largely in subcutaneous adipose tissue; visceral adipose tissue usually is minimally expanded [32]. Upper body obesity accompanies metabolic syndrome more commonly than does lower body obesity [33–35]. There is some dispute as to which pool of upper body fat is more untoward. Some investigators postulate that excess visceral fat directly causes adverse metabolic consequences [36–41]. Others put more blame on an excess of upper body subcutaneous fat [42–46].

A widely held view is that obesity predisposes to ectopic fat and hence metabolic risk factors. The *fatty acid theory* identifies elevation of plasma nonesterified fatty acids (NEFA) as the mediating factor [47–54]. According to this theory, the size of adipose tissue fat stores determines plasma NEFA levels, and the latter in turn determine amounts of ectopic fat. But this premise must to be modified to some extent by body fat distribution. For example, women with upper body obesity generally have high plasma NEFA levels, whereas those with lower body obesity have near normal plasma NEFA [55]. This finding and others like it make upper body obesity the core of the fatty acid theory. Jensen [35] recently reviewed the role of three major pools of adipose tissue on NEFA metabolism. Adipose tissue compartments in lower body, upper body subcutaneous and visceral regions apparently differ in their actions on fatty acid metabolism and on their associations with metabolic risk factors. Jensen and colleagues [56–58] showed that upper body subcutaneous fat accounts for most NEFA in the systemic circulation; but when visceral adipose tissue is also expanded, portal NEFA are derived about equally from subcutaneous and visceral compartments. Higher concentrations of portal NEFA accompanying greater stores of upper body fat could explain increased liver-fat content [59,60], higher plasma levels of very low-density lipoprotein triglyceride (VLDL-TG) [31] and other components of atherogenic dyslipidemia [61,62]. At the same time, elevated systemic NEFA coming from subcutaneous adipose tissue in the upper body should contribute to insulin resistance in skeletal muscle [42,55].

In contrast to the findings with upper body obesity, persons with predominant lower body obesity are less susceptible to metabolic risk factors [31,63–69]. One idea is that lower body adipose tissue sequesters fat in 'safe' pools, which do not feed excess NEFA into the circulation. According to this notion, lower body adipose tissue protects against metabolic syndrome. If true, a deficiency of lower body adipose tissue could shift fat to upper body pools where NEFA release is more labile. Thus, at present it is uncertain whether ectopic fat accumulates as a consequence of too little fat storage in the

lower body or too much adipose tissue in the upper body [70]. Karpe and Pinnick [63] recently summarized the association of different adipose tissue pools with metabolic syndrome. They suggest that profound functional differences exist between the upper body and lower body tissues and these differences are determined by site-specific sets of developmental genes.

It may be useful to inquire about the sources of adipose tissue TG that supply plasma NEFA. In the steady state, efflux of NEFA from adipose tissue must equal this tissue's synthesis of TG. Adipose tissue TG comes from three sources: lipolysis of TG in lipoproteins (chylomicrons and VLDL), limited *de novo* lipogenesis in adipose tissue [71] and reuptake of small amounts of newly released NEFA [72]. Lipolysis of lipoprotein TG undoubtedly dominates. With this said, why is it that persons with upper body obesity have higher plasma NEFA than do those with lower body obesity? Obviously those with upper body obesity have a greater cycling of fatty acids through adipose tissue pools. The most likely reason is that people with upper body obesity consume more nutrient energy than those with lower body obesity because the former have more total body fat [31,73]. One important and unresolved question is whether visceral adipose tissue preferentially steals fatty acids from circulating lipoprotein TG and shunts them directly into the liver [74]. If so, this mechanism could enhance ectopic fat in the liver and induce its metabolic consequences [75].

Of note, release of excess NEFA from adipose tissue as the major cause metabolic syndrome seemingly does not apply to obese Pima Indians. In this intensely studied population, obese Pima men, in contrast to Caucasians, do not have elevated fasting NEFA despite having predominant upper body obesity [76]. Moreover, they have lower plasma TG and lower hepatic secretion of VLDL-TG than do comparable obese Caucasian men [76]. Obese Pima men have hepatic secretion rates for VLDL-TG and plasma TG levels similar to those of nonobese Caucasians [76,77]. In contrast, hepatic outputs of VLDL-TG and plasma TG levels are much higher in obese Caucasians compared to nonobese counterparts [75]. This apparent paradox for Pima men is unexplained. Although lower NEFA levels may protect Pima men against dyslipidemia, they do not prevent insulin resistance or type 2 diabetes. In Pima Indians, total body fat predicts insulin resistance and incidence of type 2 diabetes [78,79]; this prediction is independent of body fat distribution. A relatively low NEFA flux in obese Pima Indians casts some doubt on the fatty acid theory of insulin resistance, as noted by Lillioja and Bogardus [78]. Karpe *et al.* [73] likewise call for a revaluation of the fatty acid theory of insulin resistance and metabolic syndrome.

But before dismissing the fatty acid theory altogether, however, we might ask whether other sources of fatty acids, independent of NEFA released by adipose tissue, can cause ectopic fat accumulation. When dietary fat is absorbed, chylomicron-TG enters the circulation and undergoes lipolysis by lipoprotein lipase. Most of the fatty acids released by lipoprotein lipase are taken up immediately by adipose tissue and incorporated into TG. But normally during lipolysis, about one-quarter to one-third of newly hydrolysed fatty acids are not taken up into adipose tissue and *spill over* into the circulation as NEFA. The latter theoretically could enhance ectopic-lipid accumulation [74,80–82]. The percentage spillover is reduced by obesity [83], especially by lower body obesity [82]. Excess adipose tissue seemingly mitigates spillover of fatty acids through increased adipose tissue uptake. But even so, sequestration of more postprandial fatty acids in adipose tissue as TG must be only temporary. To avoid progressive accumulation of fat in adipose tissue, fatty acids must be returned to the circulation during fasting.

Dietary carbohydrate is another source of plasma NEFA, but through an indirect route. A high intake of carbohydrates will induce hepatic lipogenesis, raise hepatic TG content [80,84] and increase plasma VLDL-TG levels [85,86]. Lipolysis of plasma VLDL-TG derived from *de novo* lipogenesis thus will contribute to adipose tissue TG. The latter in turn will feed more NEFA to muscle, where it can raise insulin resistance. Thus, for fatty acid metabolism, it makes little difference whether nutrient energy is consumed as fat or carbohydrate. Carbohydrates become fat through *de novo* lipogenesis. Ratios fat-to-carbohydrate in the diet have little effect on amounts of fat stored in adipose tissue; and neither does the degree of insulin resistance in obese persons depend on relative proportions of dietary fat and carbohydrate [87]. Whether high-carbohydrate diets affect insulin sensitivity in ways other than through increased lipogenesis is uncertain.

In spite of several cavets, the fatty acid theory of metabolic syndrome still lives. There are a variety of pathways whereby muscle and liver may be overloaded with lipid so as to engender metabolic risk factors, particularly insulin resistance and dyslipidemia. Adipose tissue is only one of these pathways through which fatty acids can flux. At present, we cannot assume that there is a one-to-one relationship between adipose tissue stores and ectopic fat. But high levels of ectopic fat could still be a final common pathway to the metabolic syndrome.

Emerging risk factors of adipocyte origin

In recent years, another theory has been advanced to explain why obesity might foster the metabolic syndrome. Adipose tissue is known to release a variety of products including leptin, adiponectin, inflammatory cytokines, resistin, visfatin, plasminogen activator inhibitor-1 (PAI-1) and angiotensinogen. These products, often called *adipokines*, can be looked upon as emerging metabolic risk factors. Some of these can be considered negative risk factors in that they potentially protect against

diabetes and CVD; others are positive risk factors because they may predispose to metabolic disease or CVD. In fact, a very large number of potentially bioactive molecules have been found to be released by adipose tissue [88]. There has been extensive research and discussion of how various adipokines may modify systemic metabolism [89]. To the extent to which adipokine release is modified in obese persons, the potential exists for a direct link between adipose tissue and metabolic risk factors.

Leptin, one factor released by adipose tissue, is known to dampen energy intake [90]. In this regards, it can be considered a protective factor. Humans who are genetically deficient in leptin have voracious appetites and develop severe obesity [91,92]. In otherwise normal individuals, when adipose tissue expands, leptin release is enhanced [93]). Obese persons have high leptin levels, which theoretically could curtail further food intake through suppression of the appetite [94]. Conversely, generalized lipodystrophy is accompanied by leptin deficiency, which leads to excessive food intake. Humans with generalized lipodystrophy usually exhibit severe hypertriglyceridemia and glucose intolerance. These abnormalities might be attributed to a lack of fat storage capacity in adipose tissue; but in fact, they appear to be due largely to excessive food intake. In lipodystrophic patients, leptin replacement diminishes appetite and curtails metabolic risk factors [95]. One large epidemiologic study suggested that caloric consumption in obese individuals is inversely related to leptin levels [96]. But this finding is not definitive. Whether the rise in leptin with obesity acts as a governor on food intake is uncertain. On the other hand, many reports suggest that leptin suppresses the metabolic syndrome independent of its effects on appetite [90,97]. Perhaps in this way leptin acts as a protective factor.

Another leading candidate for a protective adipokine is adiponectin. Many studies show that adiponectin levels are inversely associated with metabolic risk factors [98]. Adiponectin release is reduced in obese persons, which opens the door to adverse consequences. But to definitively prove a systemic role for adiponectin, studies are needed in individuals with genetic deficiencies of this protein. So far however, few families with genetically reduced adiponectin have been identified. An exception is one family where a gene mutation impairs assembly of high-molecular-weight adiponectin; here, an adiponectin deficiency associated with early onset obesity and metabolic syndrome [99]. Other studies have examined effects of polymorphisms in the adiponectin gene in the general population. In these studies, no consistent relation has been found between variation in the adiponectin gene and insulin resistance [100,101]. The strength of the action of adiponectin to suppress metabolic risk factors thus remains uncertain.

One emerging metabolic risk factor is a pro-inflammatory state [102]. Excess adipose tissue may contribute to this putative risk factor. For example, obesity is accompanied by macrophage accumulation in adipose tissue [103]. Presumably death of lipid-engorged adipocytes stimulates an influx of macrophages. Cytokines released in this process apparently spill into the circulation and possibly cause systemic inflammation and/or insulin resistance [104]. The best evidence for a systemic response to localized inflammation in adipose tissue is an increase in plasma C-reactive protein (CRP) [105–107]. The association of a high CRP with both diabetes and CVD is consistent with a role of inflammation induced by adipose tissue in systemic metabolic disease [108–110]. Of course, this association does not necessarily signify causation. A more direct test of the pro-inflammatory hypothesis is an ongoing clinical trial to determine whether a low-dose of methotrexate, an anti-inflammatory drug, will reduce risk for CVD and diabetes [111].

Another emerging metabolic risk factor is a pro-thrombotic state [102]. Although a variety of pro-thrombotic factors have been noted in patients with metabolic syndrome, the most consistent finding is an increase in plasma PAI-I. Upper body adipose tissue appears to be a source of circulating PAI-I [112,113]. Prospective studies indicate that higher levels of PAI-I frequently accompany acute cardiovascular syndromes [114,115]. The action of PAI-1 to block plasminogen activation could initiate or worsen thrombotic events, although direct causation is difficult to prove.

Hypertension is major risk factor accompanying the metabolic syndrome. A large body of evidence implicates obesity in the causation of hypertension [116,117]. Several mechanisms have been proposed: enhanced renal reabsorption of sodium, expansion of intravascular volume, activations of the renin–angiotensin–aldosterone system and sympathetic nervous system, release of angiotensinogen from adipose tissue, and insulin resistance [118–120]. Whether hypertension is mediated through adipokines remains to be confirmed, but several have been implicated, that is, increased leptin [121], reduced adiponectin [122], inflammatory cytokines [123] and angiotensinogen.

In spite of a growing body of literature implicating adipokines in the pathogenesis of the diabetes and CVD, a solid connection is by no means definitive. Most of the evidence falls under the category of association, hence the term *emerging risk factor*. The adipokine theory of metabolic syndrome derives largely from animal studies and epidemiology. The findings are provocative; but genetic studies in families with adipokine deficiency or therapeutic trials with adipokine blockers or enhancers will be required to nail down causative connections.

Overnutrition vs. adiposity

The severe metabolic syndrome observed in persons with lipodystrophy provides insight into causation of the syndrome.

In lipodystrophic individuals, leptin deficiency induces overnutrition. Their excessive caloric intake obviously overwhelms metabolic defences and leads to severe ectopic fat accumulation and its consequences. These are largely reversed by leptin therapy. The extent to which a lack of fat storage capacity with lipodystrophy independently produces metabolic risk factors is uncertain.

What are the defences against overnutrition? Storage of excess energy in adipose tissue during weight gain is the first defence. When weight stabilizes, adipose no longer serves this role. Storage capacity appears to be variable. For example, fat storage capacity in persons with predominant hyperplastic obesity appears to be greater than in those with hypertrophic obesity. Once weight is stabilized, however, obese people still consume more energy than do nonobese individuals [124,125]. It is doubtful that white adipose tissue alone can oxidize all the excess energy consumed by obese persons. As a matter of fact, weight gain is accompanied by an increase in lean body mass [126]. As obesity develops, there is an almost 1 : 1 increase in fat and lean mass [78]. A significant portion of the increase in weight occurs in the form of skeletal muscle [127,128]. Consequently, disposal of excess energy by more lean body mass could help to buffer the caloric overload in obese individuals. But when excess calories are not completely buffered by increases in adipose tissue and muscle, ectopic fat will accumulate in skeletal muscle, liver and perhaps other tissues. As discussed before, this ectopic fat may well be a driver of the metabolic syndrome [129]. In the final analysis, the metabolic syndrome is the consequence of dietary nutrient overload that cannot be adequately buffered by various metabolic defences.

The best evidence for the critical role of nutrient intake as the primary factor responsible for the metabolic syndrome comes from studies in patients undergoing bariatric surgery [130,131]. In these studies, caloric intake is reduced by surgery, but in most patients, significant obesity remains. Meta-analysis of these studies shows dramatic reductions and often total reversal of metabolic abnormalities even in the presence of substantial residual obesity [130]. Another trial, the Diabetes Prevention Program [132], illustrates the potential of energy restriction to modify metabolic risk. In this large study of individuals with prediabetes, caloric restriction reduced total body weight by only 5–10%, but conversion to diabetes was dramatically decreased; at the same time, the incidence of new-onset metabolic syndrome was curtailed and metabolic risk factors were strikingly reduced [133,134]. These benefits occurred in the face of substantial remaining obesity. Studies on the pathways whereby nutrient overload enhances metabolic risk are of great interest. The role of adipose tissue both in protection and causation is particularly germane. But at this time, it is unclear whether amounts or characteristics of adipose tissue present at constant body weight play a major role buffering excess energy or whether an excess of adipose tissue independent of caloric intake is a direct cause of metabolic syndrome.

Nonobese metabolic syndrome

Some people exhibit the metabolic syndrome even in the absence of obesity [135]. Examples include lean adults with primary insulin resistance of muscle [136,137], offspring of parents with diabetes [138], lean South Asians [28,139] and some genetic forms of hypertriglyceridemia [140]. These examples appear to represent genetic susceptibility to metabolic syndrome. On the other hand, many people are resistant to this syndrome even in the presence of obesity [141]. They presumably are genetically resistant. The mechanisms responsible for differences in expression of the metabolic syndrome at each end of the genetic spectrum are ripe for research.

Therapeutic implications

These considerations suggest that for prevention or treatment of metabolic syndrome priority should be given to energy balance – either decreasing nutrient energy or enhancing its expenditure. For the population as a whole, this will require behavioural modification of lifestyle habits. But for individuals who fail to reverse the metabolic syndrome through behaviour modification, pharmacological approaches to suppressing the appetite would be welcome. For some, bariatric surgery may be the best option; the improvement of the syndrome following surgery has been impressive [130]. If caloric restriction fails to reverse the syndrome, it will be necessary to treat each risk factor individually. To reduce all metabolic risk factors, multiple drugs may be required. The disadvantages to polypharmacy for management of multiple metabolic risk factors however are well known [142].

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