

Overnutrition, ectopic lipid and the metabolic syndrome

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ABSTRACT

The metabolic syndrome is a constellation of metabolic risk factors including atherogenic dyslipidemia (elevated serum triglycerides, reduced high-density lipoprotein (HDL) cholesterol), elevated blood pressure, dysglycemia (insulin resistance and elevated serum glucose), a pro-inflammatory state, and a prothrombotic state. Most persons with metabolic syndrome are obese, and usually have abdominal obesity. Generally, obesity is a reflection of overnutrition. A current view is that when adipose tissue fails to store all excess nutrients as triglyceride, lipid begins to accumulate in various tissues (eg, muscle, liver, pancreas, and heart). This accumulation is called ectopic lipid. Various mechanisms have been proposed whereby ectopic lipid is detrimental in different tissues; these derangements induce metabolic risk factors. The foundation of the metabolic syndrome thus appears to be overnutrition, that is, more nutrient intake than can be safely disposed by lipid oxidation. Excess dietary carbohydrate also induces ectopic lipid. Of interest, less than half of obese individuals develop metabolic syndrome. Through various mechanisms they adapt to overnutrition so as to minimize lipid overload in tissues, and consequently, prevent the syndrome.

The metabolic syndrome is a constellation of metabolic risk factors including atherogenic dyslipidemia (elevated serum triglycerides, reduced high-density lipoprotein (HDL) cholesterol), elevated blood pressure, dysglycemia (insulin resistance and elevated serum glucose), a pro-inflammatory state and a prothrombotic state.^{1–2} When present in combination, these factors essentially double the risk for atherosclerotic cardiovascular disease (ASCVD);^{3–5} they also increase risk for type 2 diabetes about fivefold.² Most persons with metabolic syndrome are obese. This implies that overnutrition contributes to the syndrome.⁶ Still, less than half of obese individuals manifest multiple metabolic risk factors.⁷ Many persons seemingly are able to adapt to overnutrition so as to prevent the syndrome. The following discussion examines potential mechanisms underlying the metabolic syndrome and considers how the body defends against overload of nutrient energy.

The most plausible, unifying hypothesis for the pathogenesis of metabolic syndrome is that overnutrition drives accumulation of excess lipid in organs or tissues; this in turn deranges

metabolic processes and predisposes to metabolic risk factors.⁶ Excess lipid in adipose tissue is called obesity; in other tissues, it is called ectopic lipid. In this document, overnutrition will be defined as the any excess of nutrient energy that causes ectopic lipid accumulation outside adipose tissue. The essential pathways whereby overnutrition drives development of ectopic lipid are shown in [figure 1](#). Excess nutrients come from either dietary triglyceride or carbohydrate. Dietary triglyceride enters the circulation with chylomicrons. Triglycerides are hydrolyzed to fatty acids by lipoprotein lipase (LPL); and most of released fatty acids enter adipose tissue, where they are re-esterified to triglyceride. A portion of fatty acids released by LPL bypasses adipose tissue and enters a variety of tissues. Adipose tissue releases non-esterified fatty acids (NEFA), which pass into the circulation and likewise reach many tissues. Glucose derived from dietary carbohydrate goes directly into the same tissues. When excess glucose is consumed, it can be converted to fatty acids through a process known as lipogenesis. All carbohydrates and lipids are ultimately disposed by oxidation. At constant body weight, oxidation rates of triglyceride and carbohydrate equal their intakes, and lipid content of adipose tissue remains unchanged. An imbalance between intake and oxidation occurs only during periods of weight gain or loss. These facts are well known, but often are forgotten when the mechanisms for ectopic lipid and metabolic syndrome are discussed.

Whereas tissue overload by lipid predisposes to metabolic syndrome, and may be necessary for its development, it seemingly is not sufficient. Other factors, acting in local tissues, appear necessary for the clinical syndrome to present. The following briefly discusses the origins of ectopic lipid, and considers additional factors that bring out the syndrome.

ADIPOSE TISSUE

One emerging view holds that adipose tissue protects against accumulation of ectopic lipid and hence prevents metabolic syndrome through fat storage.^{8–11} If excess dietary nutrients could be stored fully in adipose tissue, ectopic lipid should not occur. Thus the metabolic syndrome may reflect insufficient adipose tissue to store the load of fat imposed upon it by a high-calorie diet. The best example of this mechanism is the rare condition called



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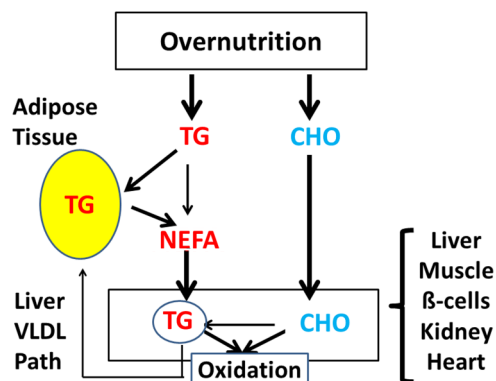


Figure 1 Major pathways for triglyceride (TG) and carbohydrate (CHO), in the form of glucose, derived from the diet. These pathways are described in detail in the text. NEFA, non-esterified fatty acids.

lipodystrophy.^{12 13} This is a condition of severe deficiency in adipose tissue; hence, consumed lipids cannot be adequately stored in adipose tissue and other tissues become overloaded. This precipitates the metabolic syndrome. Theoretically, even in the absence of lipodystrophy, the syndrome could occur if adipose tissue storage capacity is exceeded, even in the presence of clinical obesity.

Adipose tissue is the major site of uptake for lipid released during lipolysis of triglyceride-rich lipoproteins (TGRLP). These lipoproteins consist of chylomicrons, derived from dietary fat, and of very low-density lipoproteins (VLDL), produced by the liver. Fatty acids freed during lipolysis of TGRLP are taken up by adipose tissue and are re-esterified as triglycerides. In turn, adipose-tissue triglyceride undergoes lipolysis and releases NEFA into the circulation. During weight gain, fat storage is positive; at constant weight, no net storage of triglyceride occurs. NEFA release occurs mainly, but not exclusively, in the fasting state. Its release is regulated mainly by insulin. During fasting, when insulin levels are low, NEFA release is high; conversely, in the postprandial state, when insulin levels are high, NEFA release is suppressed. Thus, when excess calories are consumed, increased quantities of fatty acids cycle through adipose tissue.

Increased release of NEFA from adipose tissue in obese persons is commonly believed to be a cause of metabolic syndrome. Of course, high NEFA levels are the result of increased uptake of fatty acids by adipose tissue in response to overnutrition; elevated plasma NEFA therefore cannot be blamed on abnormalities in adipose tissue. For example, with caloric restriction, plasma NEFA levels rapidly decline despite persistent obesity.¹⁴ Indeed, fasting NEFA concentrations correlate relatively poorly with body-fat content.¹⁵ This finding likely reflects variability in caloric intake among individuals.

There are three adipose-tissue compartments that have been linked in various ways to metabolic syndrome. These are upper-body subcutaneous adipose tissue (UBSQ-AT), lower-body subcutaneous adipose tissue (LBSQ-AT) (gluteofemoral fat), and visceral adipose tissue (VAT).^{16 17} Upper-body fat, sometimes referred to as abdominal fat, actually includes all truncal fat, and represents the combination of UBSQ-AT and VAT compartments. Each

adipose-tissue compartment can be discussed briefly relative to metabolic syndrome. **Figure 2** shows apparent magnitudes of flow of fatty acids through these compartments.

Truncal adipose tissue correlates better with metabolic syndrome than does lower body adipose tissue.^{18–20} UBSQ-AT is the largest component of truncal adipose tissue.^{21–23} It predominates in release of NEFA into the systemic and splanchnic circulations;^{21–23} thus UBSQ-AT could be a major source of ectopic lipid. Compared to LBSQ-AT, UBSQ-AT appears to be more insulin resistant;^{24–26} this means that UBSQ-AT more readily releases its fatty acids into the circulation, that is, it has higher turnover rates of fatty acids.²⁷ Although UBSQ obesity is often implicated in causation of ectopic lipid, more likely, it just acts as a conduit for transfer of excess nutrient fatty acids to the circulation, as suggested in **figure 1**.

A high VAT likewise has been strongly associated with metabolic syndrome.^{28–34} It is particularly correlated with hepatic ectopic lipid.³⁵ Fatty acids entering the splanchnic circulation are destined for the liver. These can come from UBSQ-AT or directly from splanchnic lipolysis of TGRLP.³⁶ Presumably, visceral obesity is a response to a greater flux of NEFA through the splanchnic bed.

Compared to upper body compartments, LBSQ-AT seems to possess a lower rate of turnover of fatty acids. Individuals with predominant lower body obesity have relatively normal plasma levels and turnover rates for NEFA.²⁷ Lower body obesity has been postulated to be protective against the metabolic syndrome.³⁷ More likely, it is relatively neutral, rather than being protective, because of its relatively low turnover rate for fatty acids.²⁷

When obesity is present, adipose tissue becomes inflamed. This inflammation results from invasion by macrophages secondary to adipose-tissue dysfunction.³⁸ Consequently, the adipose-tissue bed releases inflammatory cytokines and prothrombotic factors into the systemic circulation. Release of excess cytokines may induce a generalized proinflammatory state, which could contribute to both ASCVD³⁹ and diabetes.⁴⁰ Release of prothrombotic factors may likewise predispose to acute ASCVD events. A host of other ‘adipokines’ has been identified.⁴¹ Whether these

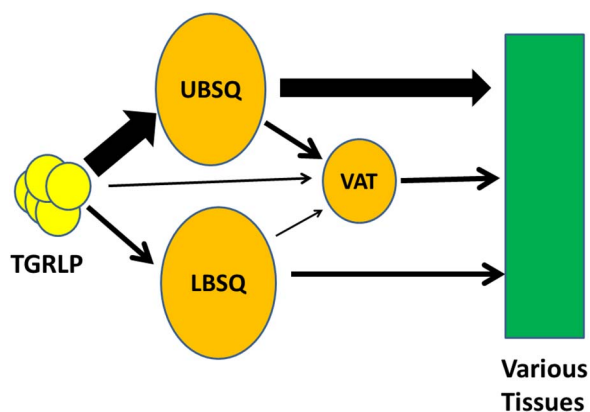


Figure 2 Pathways for fatty acids released by hydrolysis of triglyceride in triglyceride-rich lipoproteins (TGRLP). See text for details. Three major adipose tissue compartments are shown: upper body subcutaneous (UBSQ), lower body subcutaneous (LBSQ), and visceral (VAT). The size of the arrows reflects the magnitude of the flux through each pathway.

participate in the relationship between obesity and metabolic syndrome remains to be determined.

MUSCLE

Overnutrition increases lean body mass as well as adipose-tissue triglyceride.⁴² A greater lean body mass occurs in many tissues, but especially muscle. This results in greater energy expenditure, which should buffer against ectopic-lipid accumulation. When overnutrition induces high NEFA levels, muscle uptake of NEFA is enhanced. A greater muscle mass (and mitochondrial number), secondary to greater energy intake, defends against ectopic lipid. But imbalance between NEFA uptake and oxidation by muscle results in ectopic lipid and contributes to insulin resistance.⁴³ The latter, of course, predisposes to hyperglycemia, an important metabolic risk factor.

LIVER

A high caloric intake increases the nutrient load on the liver. Like in muscle, high levels of fasting NEFA derived from adipose tissue raise hepatic uptake of fatty acids. As well, the liver has other sources of fatty acids. Among these are fatty acids released by lipolysis of TGRLP in the splanchnic circulation⁴⁴ and hepatic uptake of chylomicron remnants. Further, when muscle is insulin resistant, more glucose is routed to the liver, which stimulates de novo synthesis of fatty acids.⁴⁵ Thus, hepatic ectopic lipid in one way or another represents a product of overnutrition.

Ectopic lipid in the liver is synonymous with non-alcoholic fatty liver (NAFL). The latter in turn predisposes to non-alcoholic steatohepatitis, which can sometimes produce cirrhosis or liver cancer. NAFL occurs almost exclusively in obese persons;⁴⁶ hence overnutrition is an underlying cause. But many obese individuals are able to avoid NAFL,⁴⁶ presumably by incorporating excess lipid into VLDL or by enhancing fatty acid oxidation. Conversely, in some individuals, these two pathways are sluggish and trap fat in the liver.⁴⁷

An increased load of fatty acids on the liver typically causes overproduction of VLDL particles.⁴⁸ Overproduction raises plasma triglycerides, provided they are not rapidly removed by enhanced lipolysis.⁴⁸ An elevation in VLDL triglyceride is one important metabolic risk factor. Increased production of VLDL particles can further raise the plasma apolipoprotein B—another lipoprotein risk factor. Finally, hepatic lipid overload stimulates the synthesis of hepatic lipase,⁴⁹ an enzyme that degrades HDL particles and lowers HDL-cholesterol concentrations. Thus, an increased lipid load in the liver, which results from overnutrition, is the underlying cause of atherogenic dyslipidemia.

KIDNEY

Elevated blood pressure commonly occurs with the metabolic syndrome. Hyperinsulinemia is one factor implicated in causation of hypertension.⁵⁰ Another contributor may be accumulation of ectopic lipid in the renal sinus and perinephric region.⁵¹ Renal sinus fat may compress venules and lymphatics in the kidney and thus impair blood pressure regulation. Moreover, excess lipid in the perinephric region may compress the kidneys, induce ischemia and cause hypertension.⁵²

PANCREAS

Fatty acids as well as glucose stimulates insulin secretion.^{53–56} With overnutrition, excess fatty acids entering pancreatic β -cells likely are one cause of increased insulin secretion and hyperinsulinemia found in obese individuals. In accord, ectopic lipid has been observed in β -cells of obese, prediabetic animal models.⁵⁷ Over time, ectopic lipid may destroy β -cells through overstimulation of insulin secretion and lipotoxicity.⁵⁸ The latter effect could account for the apparent ‘insulin exhaustion’ commonly observed in patients with type 2 diabetes. Of interest, MR spectroscopy shows that the pancreas contains ectopic lipid when diabetes is present, whereas it generally is absent when diabetes is not present.⁵⁹

HEART

In many obese persons, ectopic lipid accumulation is found to occur in and around the heart.⁶⁰ Several investigations suggest that lipid accumulation is detrimental to cardiac function (for a detailed review see reference).⁶¹

CARBOHYDRATE OVERNUTRITION

Most evidence supports the concept that fatty acids represent the final common pathway to tissue nutrient overload. Less attention has been given to the possible untoward effects of excessive intake of carbohydrate. For example, high-carbohydrate intakes enhance postprandial glycemia, which itself may be detrimental over the long run. Postprandial hyperglycemia may cause oxidative stress or otherwise be glucotoxic in a variety of tissues.^{62–63} Chronic overstimulation of insulin secretion induced by dietary carbohydrate could have at least two untoward effects. First, β -cell function may be impaired by chronic glucotoxicity;^{63–65} and second, carbohydrate-induced hyperinsulinemia may suppress muscle insulin sensitivity.^{66–68} Hyperinsulinemia associated with excess dietary carbohydrate may be secondary to fatty acids produced by lipogenesis in β -cells. Moreover, high-carbohydrate intakes can induce lipogenesis in the liver;^{69–70} fatty acids produced in this way can feed into the final common pathway of ectopic lipid accumulation (figure 1). Thus the role of carbohydrate overnutrition in the development of metabolic syndrome should not be overlooked. It is worthy of more investigation.

OVERFEEDING STUDIES

One approach to understanding the effects of overnutrition on the metabolic profile is through overfeeding studies. Many such studies have been carried out.^{71–76} They indicate that overnutrition produces a deterioration of metabolic status, although there is considerable individual variability in response. Such investigations are potentially useful for identifying those who are particularly susceptible to the development of metabolic risk factors.

GENETIC FACTORS

The host of genetic factors likely act at tissue levels to influence the response to nutrient excess. Several genome-wide association studies have been carried out to search for genes contributing to the metabolic syndrome.^{77–80} These studies suggest that multiple different genes act simultaneously to modify metabolic risk factors. But occasionally,

monogenic or oligogenic factors can predominate. In some cases, genetic abnormalities appear to predispose to ectopic lipid accumulation; in others, defects may elicit metabolic risk factors in those who already have ectopic lipid.

THERAPEUTIC IMPLICATIONS

Energy intake

In obese individuals, caloric restriction is followed by loss of adipose-tissue triglyceride and diminished proinflammatory cytokines, prothrombotic factors and plasma NEFA.^{14 81 82} With reduced caloric intake, muscle insulin resistance declines; hepatic steatosis diminishes; dyslipidemia frequently disappears; and blood pressure falls. As shown with bariatric surgery, all of these favorable changes occur long before substantial weight reduction takes place.^{83 84} These findings confirm that metabolic syndrome is driven largely by a high intake of nutrient energy. In the future, management of the metabolic syndrome should put priority on curbing caloric intake.

In the pharmacological arena, more emphasis needs to be placed on developing new agents that will safely reduce energy intake. This is because decreasing energy intake will treat all the metabolic risk factors at once. Research on the role of the hypothalamus in regulating energy appetite may uncover new avenues of therapy.⁸⁵ But equally important is the need for public health measures to dampen overconsumption of nutrient energy. This can be better achieved through public education combined with edification of individuals at risk.

Energy expenditure

Ectopic fat results from an imbalance between energy intake and expenditure. A high caloric intake expands lean body mass and promotes energy expenditure; the latter helps to buffer ectopic lipid deposition. Nonetheless, in many people, expansion of lean body mass is insufficient to prevent ectopic lipid. The most obvious way to enhance energy expenditure is through greater physical activity. The ability of physical fitness and physical activity to reduce metabolic risk factors is well established.⁸⁶ Some investigators speculate that tissue utilization of energy could be increased through pharmacological agents. To date this possibility has not been realized, but remains on the list of potential therapies for metabolic syndrome. Agents that could enhance nutrient oxidation should be particularly attractive.

Management of individual metabolic risk factors

Multiple cardiovascular risk factors can be treated individually with various drugs.⁸⁷ Among these are drugs that favorably modify lipid levels, control blood pressure and reduce hyperglycemia. Antiplatelet drugs should decrease a prothrombotic state; aspirin for example is known to reduce cardiovascular events. Currently, anti-inflammatory drugs are being tested for efficacy to prevent atherosclerotic events. At present, in patients with metabolic syndrome, we must depend on polypharmacy for treatment of individual metabolic risk factors.⁸⁷ Hopefully, the future will bring more effective interventions to modify caloric imbalance, which is the major driver of the syndrome.

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