

The liver is the key organ for the development of metabolic syndrome

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The metabolic syndrome affects more than a third of the US and Mexican populations, predisposing to the development of some metabolic disorders.^{1,2}

In fact, it is well recognized that subjects with generalized obesity suffer from a high risk of insulin resistance and its metabolic complications, such as type 2 diabetes mellitus, hypertriglyceridemia, low levels of high density lipoprotein cholesterol, hypertension, hepatic steatosis, hyperuricemia, and atherosclerotic vascular disease.³

Insulin resistance has long been considered to have a central role in the development of a range of metabolic disorders. Some of the links between components of the metabolic syndrome relate to insulin resistance, although about 30% of patients with the metabolic syndrome have normal insulin sensitivity.⁴ Insulin resistance is characterized by high plasma insulin concentration that fails to suppress plasma glucose normally.

Under normal conditions, insulin regulates uptake, oxidation, and storage of fuel within insulin-sensitive tissues—liver, skeletal muscle, and adipose tissue. Insulin affects energy regulation via intracellular signalling cascades that originate at the insulin receptor. Binding of insulin to its receptor stimulates autophosphorylation of tyrosine residues that act as docking sites for ‘downstream’ signaling molecules; the latter include the janus-activated kinases (JAK) and insulin receptor substrates (IRS)-1 and IRS-2. Several disease processes alter the operation of these signalling pathways.⁵

What is not clear is the time course of the development of insulin resistance. It appears that hepatic

insulin resistance may be the primary defect. Recent reports point to that effect.

1. It has been shown in the dog that metabolic syndrome can be induced with modest increases in dietary fat intake that result in subcutaneous and visceral fat depots with very little change in body weight.⁶ Under these circumstances insulin’s ability to suppress endogenous glucose production by the liver was markedly impaired while peripheral insulin resistance was modest.
2. It is tempting to speculate that the early inability of liver to respond to insulin might occur in response to the early secretion of proinflammatory cytokines by local adipocytes and hepatic inflammatory cells, and that continuous production of TNF by these inflammatory cells might induce JNK activation in fatty livers.⁷ Another source of JNK activation is cellular oxidative stress.⁷
3. Wasada, *et al.*⁸ believe that hepatic steatosis is independently associated with insulin resistance regardless of extrahepatic adiposity and might be the earliest event in the pathogenesis of the metabolic syndrome.
4. In addition, Seppälä-Lindroos, *et al.*⁹ have reported that fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. They have gone on to compare the association of fat in the liver rather than muscle with features of the metabolic syndrome.¹⁰
5. Using a rat model, Samuel, *et al.*¹¹ have shown a positive linear correlation between liver triglyceride (TG) content and the inability of insulin to suppress endogenous glucose production, which could be attributed to impaired insulin stimulated phosphorylation of IRS-1 and IRS-2 tyrosines secondary to activation of PKC- ϵ and Jun-NH2-terminal kinase 1 (JNK1) by accumulation of intracellular fatty acid metabolites.

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6. From studies in transgenic mice,¹² it has also been suggested that hepatic overexpression of 11beta-hydroxysteroid dehydrogenase type 1 may relate to the pathogenesis in humans of specific fatty liver, insulin-resistant, and hypersensitive syndromes without obesity (the metabolically obese, normal-weight individual).

It has been suggested that insulin resistance is a related characteristic that may be an essential link between central fat and metabolic abnormalities. It is believed that the hyperinsulinemia that accompanies insulin resistance in non-diabetic but at-risk individuals may magnify, or even mediate, some of the detrimental effects of visceral adiposity.¹³

7. In a recent study Fabbrini, *et al.*¹⁴ hypothesized that high intrahepatic TG (IHTG) content, not increased visceral adipose tissue (VAT) volume, is the primary marker of metabolic abnormalities associated with obesity and high IHTG content which is associated with alterations in adipose tissue and skeletal muscle CD36 gene expression and protein content, which is consistent with redirecting plasma fatty acids away from fat. The authors compared two groups of obese patients which were matched for age, sex, BMI, and percentage of body fat, but differed in either IHTG content or VAT volume. They assessed hepatic, skeletal muscle, and adipose tissue insulin sensitivities, as well as VLDL-TG secretion rate. They concluded that IHTG content, rather than VAT, is the main determinant of insulin resistance at the whole-body level.¹⁴

8. Just recently Fabbrini, *et al.*¹⁵ have further shown that by decreasing VAT by omentectomy, alone or in combination with RYGB surgery, does not improve metabolic function in obese patients.

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