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Hepatic steatosis: the common denominator for insulin resistance in obese and lipoatrophic subjects

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Insulin normally inhibits the production of both glucose and triglycerides (VLDL) from the liver. If the liver is fatty, these inhibitory actions of insulin are impaired. This results in mild hyperglycaemia (leading to hyperinsulinaemia) and hypertriglyceridaemia. The amount of fat in the liver, rather than the amount of subcutaneous fat, seems to determine the degree of insulin resistance, as both individuals with too little fat (lipoatrophy) and too much subcutaneous fat (obesity) have an increased amount of fat in the liver and are insulin resistant. Hyperinsulinaemia is a consequence rather than cause of fat accumulation in the liver, since chronic hyperinsulinaemia induced by insulin therapy decreases liver fat content.

An increase in liver fat content has been shown to predict, independent of other cardiovascular risk factors, type 2 diabetes and cardiovascular disease. This is easily explained by the fact that the liver, once fatty, overproduces most of the known cardiovascular risk factors. These include in addition to VLDL and glucose, CRP, PAI-1, fibrinogen and coagulation factors. Liver fat content can be non-invasively accurately quantified by proton magnetic resonance spectroscopy. The exact causes of variation in liver fat content are poorly understood. The amount of visceral fat is correlated with liver fat but does not, even in patients with markedly increased visceral fat, explain more than a minor fraction of variation in liver fat content.

Despite marked differences in adipose tissue mass between obese and lipoatrophic individuals, these two groups are characterized by in part similar alterations in adipose tissue metabolism. In both groups, the number of macrophages is increased. TNF α expression and production from macrophages are increased. TNF α induces insulin

resistance in adipose cells. One mechanism via which this occurs is downregulation of adiponectin expression. Serum levels of adiponectin are low in both insulin-resistant obese and lipotrophic subjects. Genetic causes in variation in liver fat content have been sparsely studied. Liver fat content can be decreased by weight loss and by a low as compared to a high fat diet. In addition, treatment of both lipodystrophic and type 2 diabetic patients with PPAR γ agonists but not metformin decreases liver fat content and increases serum adiponectin levels. The fatty liver may help to explain why some, but not all, obese individuals are insulin resistant and why even lean individuals lacking subcutaneous fat are insulin resistant, and thereby at risk of developing type 2 diabetes and cardiovascular disease.



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