Pathophysiology of obesity-induced insulin resistance and type 2 diabetes mellitus

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Introduction

Obesity is clinically defined as a body mass index (BMI) of ≥ 30 kg/m² (a BMI of 30 represents an overweight of approximately 30 lb (14 kg) for any given height). It is a disease that is highly prevalent at all ages and is quickly reaching pandemic proportions. Obesity is associated with significant comorbidity and increased mortality. The exact etiology of this disease in the majority of humans is not known. It is, however, widely accepted that obesity results from a chronic imbalance between energy intake and energy expenditure. Obesity is heritable; it is likely that genes (as yet, mostly unidentified) controlling eating behavior and daily physical activity interact with the environment to increase the susceptibility to weight gain in certain groups of individuals.

Clinicians have observed for centuries that fatter people are more likely to have type 2 diabetes mellitus (T2DM) and overwhelming evidence has accumulated to prove this clinical impression accurate. The association of obesity with T2DM has been observed in comparisons of different populations and within populations. Prospective studies of pre-diabetic subjects have shown conclusively that obesity and its duration are major risk factors for T2DM. Nonetheless, the remarkable consistency of the association between the two diseases, obesity is neither sufficient nor necessary for the development of T2DM. For example, many U.S. Caucasians are overweight or obese, but less than 10% of the population has T2DM.

Glucotoxicity

Physiologically, glycemia is maintained within a very narrow range by the pancreatic insulin secretory response to fluxes of macronutrients produced by daily meals. Despite these fluctuations, fasting glycemia is homeostatically controlled, i.e., glucose always returns to the initial level after each meal. We have recently coined the expression “glucose allostasis” to better describe the changes that take place when insulin resistance ensues. In response to insulin resistance, a small increase in fasting glycemia (even in the normal glucose range) becomes...
one of the signals for the compensatory increase in insulin secretion (rather than resulting from a lack of it)\(^30\). As long as insulin resistance and the resulting mild hyperglycemia persist, the pancreas is forced to constantly over-secrete insulin, a condition termed ‘allostatic load’. Prospective analysis shows that normal glucose tolerant individuals with a high pancreatic allostatic load have an increased risk of developing type 2 diabetes compared to individuals with a low pancreatic allostatic load\(^30\). Thus, obesity-induced insulin resistance may cause T2DM by increasing the allostatic load of the pancreas.

One of the possible ways that an increased allostatic load can eventually lead to failure of the endocrine pancreas is through the direct detrimental affect of hyperglycemia on the beta cell, which is commonly referred to as glucotoxicity\(^31\). Mechanisms include decrease in expression of relevant genes (insulin receptor, GLUT2, glucokinase, inward rectifier potassium channel), beta cell de-differentiation and increased apoptosis\(^32,33\). Also, it has been suggested that chronic hyperglycemia per se can worsen insulin resistance\(^34\).

### Lipotoxicity

How does obesity cause insulin resistance in the first place? Many studies indicate that over a wide range of insulin action, from the greatest insulin resistance to the greatest insulin sensitivity, glucose storage, not glucose oxidation, makes a progressively greater contribution to glucose uptake\(^35,36\). Thus, the effect of obesity on insulin action is likely to be mediated by a progressive decline in muscle glycogen synthase activity and glycogenesis\(^37,38\).

There is strong evidence that acute and chronic increases in fatty acid supply to peripheral tissues may play an important role in impairing glucose uptake and storage in the muscle\(^39-42\). A theory has been set forth proposing that the adipose tissue plays a crucial role in buffering the flux of FFA in the postprandial period and that this buffering action becomes progressively impaired as obesity develops, which would in turn expose extra adipose tissues to excessive lipid fluxes\(^43\). This theory is partially supported by the following observations. Obesity-induced insulin resistance is associated with increased lipid concentrations in insulin-responsive tissues\(^44-47\). Normal glucose tolerant people with enlarged subcutaneous abdominal adipocytes\(^48\) and elevated levels of FFA\(^49\) (possible markers of reduced adipose tissue buffering action\(^50\)) are at increased risk of developing T2DM. People with lipodystrophy (very little or no adipose tissue available to buffer daily lipid fluxes) are also insulin resistant and prone to T2DM\(^51\).

Nonetheless, direct experimental evidence that the adipose tissue progressively loses its normal ability to buffer excessive lipid fluxes as obesity develops is still lacking and it has been difficult to directly demonstrate an increase in FFA flux to the muscle of obese subject (and in fact the reverse has been reported\(^52\)).

Finally, we are still missing an unequivocal biochemical explanation for a role for FFA in regulating glycogen synthesis. Some possible mechanisms have been proposed, including the effect of long chain fatty acids on glycogen synthase\(^53,54\), cellular membrane fluidity\(^55\), translocation of GLUT4 containing vesicles\(^56\) and activation of the hexosamine pathway\(^57\).

The toxic effect of lipids may extend to the beta cell. FFA serve as an important source of energy for most body tissues, but they have a broader function as signals in a variety of cellular processes. One such role is to enhance the responsiveness of the pancreas to a variety of insulin secretagogues\(^60\). However, numerous studies indicate that chronic exposure of the pancreas to elevated FFA concentrations has deleterious effect on the beta cells\(^59,60\). Possible mechanisms underlying the lipotoxic effect of FFA on the beta cell include overproduction of NO\(^61\), interleukin-1B\(^62\), and ceramide\(^63\), the latter likely responsible for the accelerated apoptosis observed in fat-laden beta cells.

### Adipokines

The adipose tissue is increasingly recognized as an endocrine organ\(^64\) (Figure 1). Others and we have observed that many of the hormones that are secreted by the adipose tissue (TNF-\(\alpha\), IL-6, complement C3, MIF, adiponectin) are associated with insulin
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**Figure 1.** The adipocyte is an endocrine cell capable of secreting proteins that act as endocrine, paracrine and metabolic signals to proximal and distant tissues and organs. These signals may be the pathophysiological link between obesity and many associated comorbid conditions, including type 2 diabetes, hypertension, dyslipidemias and atherosclerosis.

**Figure 2.** A schematic representation of the hypothetical link between adipokines, the NFκB/IκB pro-inflammatory pathway and insulin action. The figure shows the mechanism by which salicylates, which are thought to block IKKβ73, may be able to improve insulin resistance by mechanisms that remain to be elucidated. IR, insulin receptor. IRS, insulin receptor substrates.
resistance, often independently of the degree of adiposity. More important, several prospective studies have shown a relationship between adipokines (IL-6 and adiponectin) and the risk of developing T2DM. The exact biological mechanism underlying this association remains obscure, but in vitro studies suggest that the effect of adipokines on insulin action may be related to their ability to activate NF-κB, a transcription factor that plays a key role in inflammatory and immune responses. A dipokines stimulate the pro-inflammatory effects of NF-κB by modulating the action of IKK (IKK). IKK phosphorylates (inactivates) IKKs, proteins that maintain NF-κB in an inactive state in the cytoplasm. Some experiments suggest that one of the catalytic subunits of IKK released in the process (IKKβ) can impair insulin action (Figure 2).

While the role of the NF-κB/IKK pathway in modulating insulin action remains an area of intense investigation, there is mounting evidence that a chronic low-grade activation of the immune system may play an etiologic role in the development of T2DM. Numerous prospective studies have now shown that high levels of inflammatory markers such as sialic acid, oromucoid acid, CRP, serum immunoglobulins and WBC predict T2DM. Therefore, it is possible that an adipokine-induced activation of the immune system may mediate the effect of over-nutrition on insulin resistance and later development of T2DM. The effect of adipokines on insulin secretory function is unclear at this point.

**Conclusion**

Obesity is a major cause of type 2 diabetes (T2DM) in all affected populations. Nonetheless, obesity is neither sufficient nor necessary to develop T2DM. In some predisposed individuals and populations, obesity increases the risk of T2DM by causing insulin resistance and directly or indirectly affecting the ability of the pancreas to secrete adequate amounts of insulin.

No simple metabolic defect is likely to explain the cause of obesity-induced T2DM in large numbers of people and the precise link(s) between obesity and T2DM have yet to be unequivocally identified. A complete understanding of the causes of T2DM will require a better knowledge of the environmental and molecular genetic determinants of both insulin action and insulin secretory function, and, equally important, a better knowledge of how they interact pathophysiologically.

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