Role of Lipids in Insulin Resistance and Type 2 Diabetes Mellitus Development

Type 2 diabetes mellitus is a worldwide disease with high prevalence. Moreover, although large differences can be observed in various countries, it displays a rapid, constant increase associated with increase in lifespan. Together with obesity it constitutes one of the most relevant medical and social problems of our time because of associated disabilities and the high cost of treating complications. It has been calculated that the cost of diabetes in the US has risen four-fold, from $20.4 billion in 1987 to $91.8 billion in 1992.1,2

In spite of this, the pathogenesis of type 2 diabetes remains elusive, and interpretation of the complexity of factors contributing to its development is very puzzling. Recently, the role of lipids in the pathogenesis of insulin resistance—a condition very often associated with type 2 diabetes mellitus, particularly if overweight or frank obesity is also present—has been regarded as one of the major pathogenetic determinants. Therefore, the interplay of lipids, insulin resistance, and even type 2 diabetes mellitus is of great interest.

Insulin resistance is the phenomenon for which supranormal insulin concentrations are required to obtain a normal glucose uptake by insulin-dependent tissues, such as skeletal muscle. Whether increased insulin concentrations lead to insulin resistance or vice versa remains, however, controversial. This is due also to the lack of a durable experimental hyperinsulimemic model that would allow determination of whether or not insulin resistance arises in response to abnormally elevated plasma insulin levels. An elegant study performed in cafeteria-fed rats3—a good model of diet-induced human obesity—showed that the animals developed early obesity, hepatic insulin resistance, and hyperinsulinemia at the same time, but only in response to glucose challenge.
This study seems, therefore, to support the contention that hyperinsulinemia does not play a causative role in the development of insulin resistance. In humans, however, available data are largely discordant.

Insulin resistance arises and develops in adipose, liver, and muscle tissue. The muscle fibers principally involved in the insulin-resistance syndrome are those of type IIb, which are responsible for long-term dynamic exercise. Type IIb muscle fibers are adapted primarily to glucose combustion, mostly in an anaerobic process. In obese, insulin-resistant subjects hyperinsulinemia decreases the activity of muscle lipoprotein lipase, which further raises plasma lipid levels. This, in turn, brings about an increase of type IIb muscle fibers, thus boosting insulin resistance.

It is well-known that insulin is an antilipolytic hormone that inhibits lipoprotein lipase (LPL) activity. Insulin controls triacylglycerol synthesis, facilitating the rapid reduction of triacylglycerol levels mainly via free fatty acid (FFA) flux inhibition as it happens in type 1 diabetes mellitus at the onset of insulin treatment. In this perspective, a recent study on a large cohort of healthy middle-aged males showed that hyperinsulinemia in response to intravenous glucose load may have a permissive effect on triacylglycerol synthesis or release independent of the FFA response.

Recently, it has also been demonstrated that insulin secretion may be directly down-regulated by lipids. Chronic hyperlipidemia results in inhibition of insulin secretion rates, likely through an increase of fat oxidation in β-cells, which can at least partially explain the “well-known” exhaustion of β-cells in obese subjects. Pancreatic islets contain high levels of triacylglycerol comparable to those found in the liver and fatty acids appear to be a major source of energy. The most relevant effect of glucose stimulation on islets is, probably, the relative shift from fatty acids to glucose as oxidative fuel, in this way regulating insulin secretion.

Other studies failed to demonstrate an inhibitory effect of FFA on insulin-mediated glucose uptake in healthy volunteers, obese subjects, and patients with type 2 diabetes mellitus. However, it must be pointed out that fat-induced inhibition of glucose uptake takes place after more than 3 h of fat infusion. In fact, in type 2 diabetic patients long-term fat infusion inhibits total glucose uptake during both isoglycemic and euglycemic clamping, the major effect being exerted on non-oxidative glucose metabolism, which mostly reflects glycogen synthesis, whereas the impairment of glucose oxidation accounts for only one third of the observed effect. Moreover, the impairment of glycogen synthesis is dependent on the FFA concentration: ~0.75 mmol/L concentration of FFA is effective in inhibiting non-oxidative glucose disposal, whereas FFA lower than ~0.5 mmol/L are not.

Proposed mechanisms of fat-induced insulin resistance include two possible explanations: the classical Randle hypothesis, in which FFA exert their effect through initial competitive inhibition of pyruvate dehydrogenase, and the second one, proposed by Roden et al., wherein a sophisticated method employing simultaneous 13C and 14P nuclear magnetic resonance spectroscopy takes place. According to these authors, elevation in plasma FFA concentration causes insulin resistance by inhibition of glucose transport, phosphorylation, or both. Further supporting this mechanism is the observation that GLUT4 receptor expression is suppressed in skeletal muscle of high-fat-fed rats.

Along the same lines, it has been recently shown that morbidly obese diabetic patients who have undergone a lipid malabsorption bariatric procedure (biliopancreatic diversion, BPD), attained a normalization of insulin sensitivity and glucose tolerance. This significant improvement in metabolism was noticeable before the operation had major effects on body weight. A complete reversion of the insulin-resistant diabetes mellitus was also observed in one normal-weight girl with chylomiconemia secondary to familial LPL deficiency who underwent BPD in order to obtained, through lipid malabsorption, a decrease of very high plasma triacylglycerol levels.

The decrease in FFA is associated with the improvement of glucose oxidation, whereas the lowering of triacylglycerols is associated with the increase of glucose storage. This indirectly suggests a reversibility of both glucose oxidase and glycogen synthase inhibition as well as an increased pyruvate dehydrogenase complex activity, which is known to be reduced in obese individuals. It has been hypothesized that in diabetes there is a shift in substrate utilization from carbohydrates to lipids, large proportion of the increase in lipid oxidation, characteristic of obesity and obese type 2 diabetics, can be explained by an increase in intramuscular triacylglycerol mobilization.

In conclusion, if hyperlipidemia really represented a major risk factor for the development of insulin resistance syndrome or even type 2 diabetes mellitus, then a primary prevention program would be of real value. However, further investigations need to be performed in order to better pinpoint the possible central role of lipids in the physiopathology of insulin resistance and type 2 diabetes mellitus.

REFERENCES

Central venous catheters (CVCs) have become an integral part of both medical and surgical practice and are used for cardiovascular monitoring and as a means of delivering certain drugs and parenteral nutrition. Complications associated with CVCs include those related to their insertion, such as pneumothorax, arterial puncture, and nerve injury, and problems occurring as a consequence of their use, in particular thrombosis and infection. CVC infection remains the most common and potentially most serious complication associated with central venous catheterization and can occur in about 10% of patients (range 3–30%, dependent on patient group). There is no universally recognized definition of CVC infection and thus assessment and comparison of different studies is often extremely difficult and misleading. The use of clinical symptoms and signs and differing methods of catheter and peripheral blood culture techniques have resulted in a multitude of definitions relating to catheter colonization. Catheter-related sepsis (CRS) is the most clinically relevant part of the spectrum of catheter colonization. The most widely recognized definition of CRS includes a significantly colonized CVC associated with a peripheral bacteremia caused by the same microorganism. This issue is complicated by the often unreserved acceptance of the roll plate method of catheter analysis as the gold standard by which all other methods have been judged. The technique requires a culture result of as few as 15 microorganisms to be considered a positive, but is prone to contamination from heavy skin colonization (accentuated by occlusive dressings) upon catheter removal, and potential heavy contamination from leakage of endoluminal fluid during specimen transit. These factors make it a sensitive but very non-specific test for CRS; a positive result can represent endoluminal colonization as well as extraluminal contamination/colonization. Despite being simple and cheap, a major drawback of the technique is that it requires catheter sacrifice to enable a diagnosis. Up to 80% of CVCs implicated as a source of sepsis are, in fact, sterile, and thus the technique, as with others, results in the needless removal of the vast majority of CVCs.

What is therefore required is a method of CVC analysis that is both sensitive and specific for the diagnosis of CRS and does not require CVC sacrifice. Endoluminal brushing has been demonstrated in consecutive studies of over 400 CVCs to be both sensitive (90 and 95%) and specific (84%) for the diagnosis of CRS. A further more detailed study, as yet unpublished, consisting of more than 60 proven cases of CRS has shown the technique to be 95% sensitive and 96% specific for the diagnosis of CRS. Other endoluminal methods of analysis, including tip flush, paired quantitative blood cultures, and scanning electron microscopy, have revealed that in almost all our CRS cases the catheter lumen is lined with a profusely colonized biofilm, most often extending from the catheter hub to tip in its entirety; bacterial counts from this endoluminal material exceeding the extraluminal counts by up to 100-fold. These results strongly suggest that endoluminal colonization is paramount in the development of CRS. The reported success of endoluminal lock techniques and frequent failure of systemic antibiotics in treating CRS, the high sensitivity and specificity of differential quantitative blood cultures in the diagnosis of CRS, the well-recognized clinical signs associated with flushing or infusing through infected CVCs, and, finally, the failure of silver and chlorhexidine catheters to reduce the incidence of CRS in several recent studies seem to support the hypothesis that endoluminal catheter colonization is pivotal in the development of CRS.

The administration of parenteral nutrition via a CVC has been widely quoted as one of the significant risk factors associated with the development of CRS. In our studies, in all cases of proven CRS occurring in triple lumen catheters the lumen used to administer total parenteral nutrition was found to be significantly colonized, confirming that the infusion of lipid, carbohydrate, and other nutritional substrates seems to favor the growth of endoluminal microorganisms.