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COMMENTARY

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Mitochondrial dysfunction in adipocytes: the culprit in type 2 diabetes?

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Abbreviations mtDNA: mitochondrial DNA · TZD: thiazolidinedione

The current epidemic of type 2 diabetes is largely the result of excessive food intake and a concomitant reduction in physical exercise associated with decreased combustion of food components in the mitochondria. The excess of ingested food is largely converted into triglycerides that are predominantly stored in adipocytes and, to a minor extent, in other locations such as in muscle and liver. Epidemiological data show a particularly strong association between hepatic accumulation of fat and the development of whole-body insulin resistance, which predisposes to the subsequent development of glucose intolerance [1].

The mechanisms linking obesity with whole-body insulin resistance are not fully understood, and various mechanisms have been suggested, such as a direct effect of fatty acids on insulin receptor signalling leading to an insulin-resistant state in the target tissues for insulin action. Metabolic dysregulation in adipocytes may also contribute to a state of whole-body insulin resistance by altering the pattern of adipokine/cytokine expression in response to obesity. The subsequent development of glucose intolerance may involve fatty acid-induced failure (lipotoxicity) of pancreatic beta cells to secrete sufficient amounts of insulin to meet the increased demand for insulin in the insulin-resistant state [2]. Despite our lack of detailed knowledge on the relative contributions of these various players, the data are mostly compatible with the concept that we become insulin resistant and more prone to type 2 diabetes as something changes in the metabolism and storage of fat. This concept is supported by the observation that diabetes develops at an early age in monogenetic forms of congenital lipodystrophy, in which triglyceride cannot be synthesised or properly stored in adipocytes, and which are characterised by hepatic steatosis [3]. Partial lipodystrophy, induced by the combined use of protease inhibitors and nucleoside analogues that interfere with mitochondrial DNA (mtDNA) replication during antiretroviral therapy, also enhances the risk of type 2 diabetes [4].

Mitochondria are key players in oxidative disposal of excess fatty acids, and also modulate the distribution of body fat. Patients with mutations in mtDNA often have intracellular triglyceride droplets, compatible with reduced beta-oxidation [5], and redistribution of body fat leading to lipomas may also occur [6]. Many pathogenic mutations in mtDNA have been identified, and these give rise to a wide variety of syndromes, many of which are associated with diabetes. The presence of diabetes is frequently overshadowed by more pronounced clinical hallmarks of such mitochondrial syndromes, and in the past was frequently overlooked. However, there are a few mtDNA mutations, most prominently the 3243A>G mutation, that are associated with a syndrome in which diabetes is the main clinical phenotype. Taken together, these data show that normal mitochondrial function is needed for proper lipid metabolism and maintenance of glucose homeostasis.

The most prominent abnormality in patients with deletions and point mutations in mtDNA is insulinopenia due to attenuated glucose-induced insulin secretion. In patients with maternally inherited diabetes and deafness due to a 3243A>G mutation in mtDNA, it takes on average 38 years before beta cell dysfunction becomes manifest [7]. This indicates that insulinopenia may be a secondary consequence of long-term mitochondrial dysfunction rather than the direct result of resetting the glucose sensor in pancreatic beta cells. This sensor depends on mitochondrial function in addition to a number of other intermediates of the glucose-sensing pathway. Mutations in the

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other genes of this pathway (including those for glucokinase [*GCK*], KIR6.2 [*KCNJ11*] and SUR1 [*ABCC8*]) present with dysregulated insulin secretion in neonatal life [8, 9].

In this issue of *Diabetologia*, Choo et al. [10] highlight mitochondrial function in adipocytes as a potential pathogenic factor in the development of diabetes. They studied two obese models of mice (*ob/ob* with normoglycaemia and *db/db* with hyperglycaemia), and observed that, in the *db/db* mice, levels of key proteins of the respiratory chain were strongly reduced in adipocytes but not in other tissues. A similar finding was noted in another animal model of diabetes, the Otsuka Long–Evans Tokushima fatty rat. When the morphology of the mitochondria was examined by electron microscopy in *db/db* and *ob/ob* mice, none of the mitochondria in adipocytes of *db/db* mice appeared normal, in contrast to those in adipocytes from *ob/ob* mice, although some abnormalities were also observed in these cells. The abnormal mitochondrial morphology in the *db/db* adipocytes was associated with a reduced rate of beta-oxidation of palmitic acid. When the *db/db* mice were treated with the thiazolidinedione (TZD)-derivative rosiglitazone, mitochondrial morphology and levels of respiratory chain proteins were restored in adipocytes, fatty acid oxidation was improved, and hyperglycaemia was reduced. These data are in line with recent studies by Bogacka et al. and Wilson-Fritch et al., which showed that TZDs induce mitochondrial biogenesis, both in human and mouse adipocytes, with concomitant upregulation of genes involved in fatty acid beta-oxidation [11, 12].

Since an excess of fatty acids is quite toxic to mitochondria, these observations support a pathogenic model for type 2 diabetes in which the overloading of adipocytes with NEFAs induces mitochondrial damage, leading to a reduced capacity for beta-oxidation of fatty acids, which makes matters worse. As a result, triglycerides accumulate in other tissues, such as liver and pancreatic beta cells. This, in turn, results in metabolic dysregulation of the liver and pancreatic beta cells, leading to insulin resistance and insufficient secretion of insulin. TZDs improve mitochondrial function and enhance beta-oxidation of fatty acids in adipocytes, thereby protecting other tissues against fatty acid overload. This pathophysiological model also explains the beneficial effect of physical exercise, which creates an additional sink for fatty acids in muscle.

Although these studies suggest a direct role for mitochondria [10–12], they do not exclude the alternative possibility that TZD-induced improvements in mitochondrial function in adipocytes are an indirect consequence of improved glycaemic control, which was also a feature of these studies. Hyperglycaemia may itself switch cellular metabolism to a glycolytic state, leading to the reduced expression of mitochondrial genes, as observed, for example, in the study of insulin-regulated vs diabetes-regulated gene expression in MIRKO mice [13]. Lower glucose concentrations may have contributed to the increase in mitochondrial function seen in these studies, and future investigations will need to clarify the effect of treating hyperglycaemia upon mitochondrial function and beta-oxidation of fatty acids.

Adipocytes are important and exciting cells that have long been neglected by researchers; indeed, some individuals have them removed by liposuction. The recent discovery of adipokines has placed adipocytes back in the centre of the metabolic stage. The recent publications by Choo et al., Bogacka et al. and Wilson-Fritsch et al. [10–12] have introduced another exciting possibility into adipocyte research: that mitochondria in adipocytes may shield against the development of type 2 diabetes.

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