Mechanisms contributing to the development of type 2 diabetes

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Abstract

We are in the midst of an explosion in the prevalence of type 2 diabetes with a key concern that this will translate into a major future burden of diabetes-related complications. To develop rational and effective means of preventing type 2 diabetes and its complications, we need to understand the mechanisms that predispose to the development of diabetes in at-risk individuals. In this brief review, we provide an overview of the principal metabolic changes that have been identified in at-risk individuals and how they contribute to the progression from normal glucose tolerance (NGT) through to type 2 diabetes. Specifically, both impaired insulin action and defective insulin secretion are key predictors of type 2 diabetes, and both are evident in at-risk individuals well before the development of frank diabetes. These changes are associated with an increased prevalence of adverse cardiovascular risk factors. It is clear, therefore, that the identification of at-risk individuals provides the opportunity to introduce measures to try to prevent the development of type 2 diabetes and the associated cardiovascular disease.

Introduction

The global epidemic of diabetes is increasing at an alarming rate and it is predicted that by 2025, 333 million people will be suffering from the burden of the disease world-wide. More than 95% of this group will comprise type 2 diabetes. It is well known that type 2 diabetes is preceded by a long asymptomatic period where subjects deteriorate from NGT to IGT and are later diagnosed with type 2 diabetes. This period approximates between 6–10 years depending upon individual subject variation. It has been estimated that there are currently about 314 million subjects with IGT and by 2025 a staggering 472 million will have IGT. It is known from epidemiological studies that IGT and IFG are metabolic states with increased risk of future type 2 diabetes, of which at least 30% go on to develop diabetes. There is now good evidence that lifestyle or pharmacological interventions at this stage are beneficial in preventing or delaying the onset of diabetes and thereby preventing early development of complications. In this review we discuss the mechanisms responsible for the change from NGT to type 2 diabetes.

Inherited risk of type 2 diabetes

Type 2 diabetes is known to have a strong familial basis and at least 40% of siblings of subjects with type 2 diabetes can expect to develop the disease based on the assumption that survival will be to the age of 80 years. The risk of developing diabetes was estimated as 2.3 to 3.9 times greater in offspring with one or two affected parents, respectively, when compared with offspring with two non-diabetic parents in the Pima Indian population. Further evidence for the genetic nature of the disease comes from a number of twin studies. In one particular study, when monozygotic twins who share identical genetic information were analysed, the concordance rate for type 2 diabetes was increased at 58% compared with the expected prevalence of 10%.

The prevalence of type 2 diabetes varies greatly between ethnic populations and in different parts of the world. It remains to be clarified whether this increased risk in certain populations is
due to common environmental or genetic determinants. The genetic influence is supported by the fact that type 2 diabetes has a higher prevalence in certain populations like American Indians, Pacific islanders and Asian Indians. The prevalence is even higher when there is limited foreign genetic mixture as shown in Pima Indians (figure 1).11

Pathogenesis of type 2 diabetes
Type 2 diabetes is a chronic disorder of carbohydrate and lipid metabolism and is known for its heterogeneity. It is caused by impaired insulin action in muscle and adipose tissue, defective insulin secretion and inadequate suppression of hepatic glucose output (figure 2). During a meal the normal response is to suppress HGO and to enhance glucose uptake in the liver and muscle. This needs an appropriate insulin secretory response and adequate hepatic and muscle insulin sensitivity for glucose uptake. It is important to note that pre-diabetes forms a part of continuum between NGT and diabetes. Many of the abnormalities that characterise the diabetic state, such as insulin resistance and defects in beta-cell function, are evident in at-risk but non-diabetic subjects such as first degree relatives of subjects with type 2 diabetes. It is therefore evident, that these changes evolve long before the development of frank diabetes.

Defects in subjects at risk of type 2 diabetes
Beta-cell function
One of the most striking observations from the United Kingdom Prospective Diabetes Study (UKPDS) was the significant decrease in beta-cell function of up to 50% of normal, in subjects with a recent diagnosis of type 2 diabetes.12 Extrapolating the data from the same study suggests that this decline starts approximately 10–12 years before the diagnosis of diabetes (figure 3). It is now universally accepted that beta-cell dysfunction is a hallmark of diabetes and is also related to hyperglycaemia. This dysfunction is manifest through different ways which includes reduced insulin release in response to glucose and other non-glucose secretagogues, changes in pulsatile and oscillatory insulin secretion and an abnormality in the effective conversion of proinsulin to insulin.13 There is enough evidence to infer that these changes start well before the diagnosis of the disease and most abnormalities have been noted in pre-diabetic individuals. These defects have been identified in high-risk individuals for type 2 diabetes such as subjects with first degree relatives with diabetes and women with a history of gestational diabetes or polycystic ovarian syndrome.13 Insulin release from the pancreas is biphasic, with the initial brief spike which lasts for 10 minutes called the first phase insulin release. This is followed by a prolonged second phase which plateau by 2–3 hours. When subjects with IGT were studied by Gerich et al. using the hyperglycaemic clamp technique,14 they noted significant reductions in both first and second phase insulin secretion. Notably, when NGT subjects with and without a positive family history of diabetes were examined, NGT subjects with a positive family history had significant defects in both phases of insulin secretion.14 The importance of beta-cell dysfunction in the pathogenesis of pre-diabetes is also emphasised by the defects in the oscillatory insulin release in NGT first degree relatives with type 2 diabetes.15 Furthermore, increased non-stationarity and disorderliness of rapid pulsatile insulin secre-
tion in NGT subjects with a family history of diabetes suggests beta-cell dysfunction is an early and fundamental defect in the development of type 2 diabetes.18

Muscle
Skeletal muscle is responsible for 80% of glucose disposal in peripheral tissues and hence plays an important part in regulating carbohydrate metabolism. In type 2 diabetes the ability of insulin to stimulate glucose uptake, glycogen synthesis and glucose oxidation in skeletal muscle is impaired.17 These defects have also been identified in pre-diabetic individuals with IGT and glucose tolerant first degree relatives of subjects with type 2 diabetes.19,20 Rothman et al. studied non-diabetic first degree relatives using magnetic resonance spectroscopy and found evidence of decreased insulin stimulated glucose uptake and glycogen synthesis.20 The same workers have recently extended their studies by using magnetic resonance spectroscopy to investigate skeletal muscle energy metabolism.21 They found that mitochondrial oxidation was decreased in insulin resistant first degree relatives, and this in turn was associated with an increase in intramyocellular lipid content. They proposed that the defect of mitochondrial function may represent the primary defect in skeletal muscle and that the decreased oxidative function leads to the accumulation of intramyocellular lipid and secondary insulin resistance.

In individuals with IGT as in type 2 diabetic individuals the most proximal defect in the signalling pathway has been identified as the inability of insulin to stimulate tyrosine phosphorylation of its receptor. New defects in the activation of IRS-1 and reduced ability to associate with the p85 subunit of PI-3 kinase have been identified recently.22-24 Other studies have noted the inability of PI-3 kinase to induce GLUT4 translocation and to activate GLUT4 transporter is impaired.23,25 The retention of this defect of insulin action in cultured muscle cells suggest that there may be an inherited basis.

Liver
Type 2 diabetes is characterised by a raised fasting blood glucose that is associated with raised HGO. In normal individuals HGO is suppressed markedly with even small increments of insulin. In individuals with diabetes this sensitivity appears to be diminished in spite of hyperinsulinaemia. Results from studies on pre-diabetic individuals have been variable and inconclusive. In individuals with IGT, post-absorptive HGO remains in the normal range, possibly because post-absorptive hyperinsulinaemia overcomes hepatic insulin resistance. However, immediately following a meal, plasma insulin concentrations may be inadequate to suppress HGO.27 Roberston et al. and Lillioja et al. identified reduced hepatic insulin sensitivity as a cause of raised HGO but in these studies no attempts were made to exclude confounding factors such as differing portal insulin levels.28,29 Berri et al. co-infused insulin, glucagon and somatostatin (which suppresses endoge-
and smoking, the two-hour plasma glucose value was a better predictor than fasting glucose concentration.\(^\text{27,28}\) However, a population-based cross-sectional study.\(^\text{29}\) Heldgaard et al. recently demonstrated a similar cardiovascular risk factor profile in Danish subjects with IFG and IGT. Clearly, more studies are needed in this area to predict and target appropriate individuals with higher risk.

**Cardiovascular risk in subjects at increased risk of type 2 diabetes**

The review so far has tended to focus on aspects of carbohydrate metabolism in subjects at risk of type 2 diabetes. However, it is well documented that at-risk subjects such as the non-diabetic relatives of type 2 diabetic families have an increased prevalence of other adverse metabolic and anthropometric characteristics. We and others\(^\text{40,41}\) have shown that such relatives tend to be more obese compared to subjects with no family history of type 2 diabetes and have associated abnormalities of lipid metabolism.\(^\text{42}\) It is likely that both shared lifestyle and genetic factors contribute to the increased prevalence of obesity that in turn will contribute to the insulin resistance. In addition, obesity is a feature of the metabolic syndrome that includes other adverse cardiovascular risk factors such as abnormal glucose tolerance, raised triglyceride and low HDL-c levels, high blood pressure and insulin resistance.\(^\text{39}\) The prevalence of these and other adverse cardiovascular risk factors is increased in the non-diabetic, but at-risk, relatives of type 2 diabetic families.\(^\text{44,46}\) This highlights that these subjects are predisposed not only to type 2 diabetes, but also to cardiovascular disease.

**Summary**

It is evident that many of the metabolic defects that characterise type 2 diabetes are present in non-diabetic but at-risk subjects, such as first-degree relatives of type 2 diabetic patients, well before the development of the diabetic state. Defining these defects is important for the future development of rational and targeted measures for the prevention of both type 2 diabetes and the associated cardiovascular disease.

**References**

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