METABOLIC CHANGES IN DIABETES

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SUMMARY

Diabetes is not a single disease but a group of diseases characterised by hyperglycaemia. The most important regulator of glucose uptake from the blood is the hormone insulin, which is produced by islet beta cells and acts on insulin receptors to promote nutrient uptake and processing. A decrease in either insulin secretion or sensitivity can cause diabetes. Exposure to prolonged hyperglycaemia causes reversible and then irreversible changes to tissue metabolism and structure. These changes may be responsible for the potentially devastating complications of diabetes.

Industrialisation in the last century has altered the balance of major diseases. One hundred years ago, epidemics of infectious diseases were the main cause of mortality. Today, non-communicable diseases including cancer, arterial disease and diabetes are the major causes of death in the Western world. There is a very real prospect that industrialisation of Asia and Africa will herald an epidemic of these non-communicable diseases.

Diabetes is characterised by a persistently increased blood glucose level. There are many causes of diabetes, just as there are many causes of anaemia, including endocrine diseases, liver diseases or drugs. The commonest causes of diabetes are insulin-dependent or type 1 diabetes (IDDM) and non-insulin-dependent or type 2 diabetes (NIDDM).

Diabetes is a major international health problem affecting possibly some 60 million people world-wide. In the industrialised Western world, diabetes is the commonest cause of blindness during working life, the second commonest cause of renal failure, and a major risk factor for leg amputations. On average diabetes reduces life expectancy by a decade, an effect largely attributable to macrovascular disease. Thus, diabetes causes both microvascular and macrovascular disease.

NORMAL GLUCOSE METABOLISM

Glucose is produced by the liver by gluconeogenesis and glycogenolysis. The main substrates for gluconeogenesis are alanine and glutamine, glycerol, lactate and pyruvate. Glycogenolysis is controlled by the synthesis or degradation of glycogen; the hormone glucagon stimulates glycogenolysis while the hormone insulin inhibits it. Glucose is taken up from the circulation by the splanchnic bed, adipose tissue, skeletal muscle and brain. Glucose utilisation in skeletal muscle is by oxidative and non-oxidative processes.[1] The non-oxidative pathway determines, in the main, the rate of glucose uptake and glucose incorporation into glycogen. The most important regulator of glucose uptake is the hormone insulin.[2]

Insulin is coded by a gene on chromosome 11, initially processed as a prohormone (preproinsulin) and secreted by beta cells in the islets of Langerhans of the pancreas.[3] Conversion of proinsulin to insulin involves the removal of a connecting peptide, C-peptide, in the Golgi apparatus by enzymes with trypsin- and carboxypeptidase-like activity. Insulin then co-precipitates with zinc ions as microcrystals in the secretory granules. Insulin secretion follows stimulation of the islet beta cell by glucose or other secretagogues. Glucose metabolism is required for insulin release to be stimulated and this triggers a sequence of events including generation of ATP, closure of K^+ channels in the beta cell membrane and increased Ca^{2+} entry into the cell.

Insulin acts on target cells via *insulin receptors*. These receptors, coded by genes on chromosome 19, mediate the intracellular action of insulin to stimulate nutrient uptake and processing.[4] Insulin receptors lie on the target cell surface and straddle it. The receptor is composed of two alpha subunits linked covalently to two beta subunits. Insulin binds to the alpha subunits initiating a series of steps involving phosphorylation and autophosphorylation of tyrosine residues. The receptor–hormone complex is internalised, insulin is degraded and the receptor is recycled to the cell surface.

A decrease in either the secretion of insulin or the sensitivity to insulin causes a rise in blood glucose through reduced glucose utilisation. The diagnosis of diabetes mellitus is established by a raised blood glucose level: the

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venous whole blood glucose must be over 10 mmol/l in samples taken at random or 2 hours after a 75 g oral glucose load. In IDDM hyperglycaemia results from decreased insulin secretion due to beta cell destruction. In NIDDM a decrease in both insulin secretion and insulin sensitivity may operate to cause hyperglycaemia and the relative contribution of each defect can vary from individual to individual.

NON-INSULIN-DEPENDENT DIABETES

Non-insulin-dependent diabetes affects at least 2% of the population and no race is immune from the disease; among the Pima Indians of Arizona and Nauruans from Polynesia, half the adult population is diabetic. The prevalence of NIDDM increases with increasing age: in the elderly the prevalence can be striking, reaching 45% in men aged 75–79 years in east Finland. In part this increase may be due to an age-related deterioration in glucose tolerance. Thus, while fasting blood glucose levels remain fairly constant with age the glucose level 2 hours after oral glucose rises steadily. In the absence of prospective studies this age-related effect is ignored for the purposes of defining the disease.

Pathogenesis

The islets of Langerhans in patients with NIDDM appear normal except for amyloid deposits and a reduction in the beta cell mass to about 60% of normal. In general, the secreted insulin has a normal structure though there is a tendency to secrete a relative excess of proinsulin. The disease is characterised by a decreased beta cell secretory capacity, insulin resistance and hepatic glucose overproduction.[4-6] The onset of the diabetes is insidious, probably occurring several years before the clinical diagnosis. Since hyperglycaemia itself can induce beta cell dysfunction and insulin insensitivity it has proved impossible to distinguish primary changes leading to diabetes from those which are secondary to the disease.

To address this problem, studies have been performed on non-diabetic children of diabetic patients. These children show fasting hyperglycaemia, impaired glucose tolerance, decreased glucose clearance, fasting hyperinsulinaemia, either decreased or increased insulin responses to glucose, and impaired insulin-mediated glucose disposal due to reduced non-oxidative glucose metabolism. It remains to be determined whether these changes presage diabetes. The one study which followed patients prospectively found that offspring who developed diabetes, as compared with those who did not, were initially more obese and had decreased glucose tolerance and glucose clearance, fasting hyperinsulinaemia and increased second phase insulin responses.[7] The development of NIDDM was both preceded and predicted by defects in insulin-dependent and insulin-independent glucose uptake, changes which could precede the onset of hyperglycaemia and diabetes by more than a decade.[8] These observations are consistent with the finding that the initial lesion in NIDDM is due to peripheral insulin resistance not beta cell dysfunction. However, it is widely believed that neither abnormal insulin secretion nor abnormal sensitivity to insulin alone can explain the glucose intolerance of NIDDM.

Aetiology

The most powerful evidence that NIDDM is predominantly inherited comes from the study of identical twins: more identical than non-identical twins of diabetic patients are concordant for NIDDM (see Table I).[9,10] Recent evidence suggests that some individuals with maturity onset diabetes in the young (MODY) have a defect (both missense and nonsense mutations have been reported) in their glucokinase gene promoter region which might account for up to 40% of these cases. Rare genetic defects in the insulin gene and in the insulin receptor have also been described which may cause diabetes.[11,12]

The estimated heritability of NIDDM is about 82% (Table I). In assessing the role of the environment in causing NIDDM it is important to understand that heritability is not an invariant index of a genetic influence. It describes the genetic effect under particular environmental conditions. Different estimates of heritability might be obtained if twins were studied in different environments. A number of non-genetic factors have been implicated in the aetiology of this disease, including nutrition, obesity, ageing and reduced exercise.

Nutrition. The incidence of NIDDM decreases during food shortage. However, high carbohydrate diets improve insulin sensitivity in both normal and NIDDM subjects through physiological adaptation to an altered fuel supply and not reversal of a pathological process. The change from hunter-gatherer to a modern diet may be responsible, in part, for the virtual epidemic of diabetes in migrant populations and previously isolated communities. At present, however, there is no direct evidence that dietary factors cause NIDDM although they may influence rate of progression to clinical symptoms. Recent studies do indicate a relationship between low birth weight and impaired glucose tolerance in later life;[13] if confirmed, this association could be due to poor nutrition *in utero* limiting pancreatic development.

Obesity. Obesity is not a major factor but can potentiate NIDDM in genetically susceptible individuals. Offspring of NIDDM patients who subsequently develop NIDDM themselves are more likely to be obese when young. In one study, those subjects with low birth weight who became obese were particularly prone to diabetes.[13] Individuals with upper body obesity are also at particularly high risk

Table I. Proband concordance of non-insulin-dependent diabetes mellitus after first and second oral glucose tolerance tests

	First test[a] (%)	Second test[b] (%)
Identical twins	29	58
Non-identical twins	14	17

[a] First test: subjects aged 42–55 years.
[b] Second test: subjects aged 52–65 years.

of NIDDM. Nevertheless, there are no differences in the relative contributions of decreased insulin secretion and decreased insulin sensitivity between obese and lean NIDDM subjects.

Ageing and Exercise. Ageing is not associated with decreased insulin secretion nor with decreased insulin sensitivity in physically active subjects. However, lack of exercise in the elderly may hasten the appearance of hyperglycaemia. Recent prospective studies of populations at risk of diabetes suggest that physical activity protects against the development of NIDDM.

INSULIN-DEPENDENT DIABETES

There is worldwide variability in the average annual incidence of IDDM under the age of 15 years ranging from 1.7 per 100 000 person-years in Japan to 29.5 per 100 000 person-years in Finland. Incidence rates in Western industrialised countries establish IDDM as the second commonest chronic childhood illness after asthma.

Pathogenesis

Insulin-dependent diabetes is due to destruction of the beta cells in the islets of Langerhans. The disease is caused by environmental factors operating in a genetically susceptible host in early childhood to initiate the destruction of the insulin secreting cells, probably by an immune process.[9] In some genetically susceptible individuals this immune process can persist in association with chronic progressive beta cell destruction over many months, even years, and lead to IDDM, but in others it may remit spontaneously without diabetes developing.[9]

At diagnosis about 80% of islets contain no beta cells and the islets may be heavily infiltrated with lymphocytes. There is no evidence that the exocrine pancreatic cells or the other islet cells are involved in this destructive process. The limited secretion of insulin by patients with IDDM results in them being prone to increased ketoneogenesis. In the absence of insulin treatment such patients will die in diabetic ketoacidosis.

METABOLIC CONSEQUENCIES OF HYPERGLYCAEMIA

A common health aim is to reduce the morbidity and mortality associated with diabetes. Risk factors for macrovascular disease are well established in the non-diabetic population and include hypercholesterolaemia, increased plasma fibrinogen, smoking, obesity and hypertension. The evidence is that in the diabetic population the same risk factors operate but, if anything, diabetes has an additive effect with them. In addition, in NIDDM there is a tendency for some of these risk factors to aggregate; these patients are particularly at risk of obesity, dyslipidaemia and hypertension. A common feature of these changes is their association with insensitivity to insulin, an observation which has led to the proposal that insulin resistance is the single unifying factor causing an excess risk of macrovascular disease in Western society.[3] The association of major risk factors for macrovascular disease has been called the New World Syndrome, the Matabolic Syndrome or Syndrome X.

The cause of microvascular disease is not clearly defined but the belief is that hyperglycaemia is a major factor and, probably the major factor. Microvascular complications are not simply genetically determined since the non-diabetic identical twins of diabetic patients do not get them. For complications to develop hyperglycaemia must be present. The cause of the hyperglycaemia, i.e. the cause of the diabetes, is irrelevant since microvascular complications are a feature of all types of diabetes. As diabetes is defined by hyperglycaemia it reasonable to anticipate that these microvascular complications should result from this hyperglycaemia. It is clear that the risk of diabetic complications is related to the duration of the disease.[14] A number of studies have demonstrated a relationship between the level of blood glucose and the risk of developing complications. Thus, in one study an average blood glucose more than 50% above the normal range was associated with a 40% risk of developing severe retinopathy at 14 years: in contrast, this risk was only 5% in those patients with blood glucose levels close to the normal range.[14]

Pregnancy

It is known that hyperglycaemia can influence fetal development.[15] The incidence of major and minor congenital anomalies in children of patients with diabetes is between 6% and 9%, that is up to 3 times greater than in the general population. The most prevalent congenital anomalies in children of diabetic patients include caudal regression syndrome, neural tube defects and cardiac anomalies. The excess in malformations is confined to patients whose diabetes antedates their pregnancy. In addition, the malformations arise from developmental changes likely to have occurred before the seventh week of gestation. It was proposed that the excess congenital anomalies in children of patients with diabetes was due to hyperglycaemia in early fetal life. This hypothesis was tested by measuring glycated haemoglobin, an index of blood glucose levels, over the previous 2 months. Children of patients with high glycated haemoglobin levels had a striking excess of congenital anomalies which reached 22% if the glycated haemoglobin was greater than 10%. The risk of major malformations can be reduced to non-diabetic levels if the diabetic mother is treated to obtain normal glycated haemoglobin levels before conception.[15] The mechanism of this embryopathy is not clear. Pre-pregnancy counselling is now routine in diabetic clinics and patients are advised to obtain near-normal blood glucose levels before conception.

Mechanisms

Exposure to hyperglycaemia can cause acute reversible metabolic changes and, if prolonged, cumulative irreversible changes. Three broad mechanisms have been described for glucose-induced damage.[16] First, glucose and other sugars can bond with any exposed lysine residues or (in the case of haemoglobin) valine, or any protein.

This process of glycation can alter the structure and function of the protein. Further changes can lead to glycation products with extensive cross-linkage called advanced glycation end products – an irreversible change. These molecules may lead to the production of free oxygen radicals which could themselves cause tissue damage. The second mechanism is the production of excess sorbitol though a normally redundant pathway involving the enzyme aldose reductase. Sorbitol cannot readily leave a cell and accumulation of the alcohol sugar could lead to osmotically driven overhydration of the tissue and damage. The third mechanism involves the direct competition between glucose and myoinositol. Myoinositol is an important substrate in cellular energy production, and its structure is very similar to that of glucose. Excess glucose can therefore compete for myoinositol uptake by a cell, leading to myoinositol depletion.

CONCLUSION

These observations suggest that hyperglycaemia, but also the level of other major risk factors, plays an important role in producing the complications of diabetes. The days of regarding diabetes as simply a sugar problem are gone. In the absence of a successful primary prevention policy for diabetes we seek to reverse the level of these risk factors towards normal.

Key words: Diabetes, Glucose, Glycation, Insulin.

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