Clinical review

Science, medicine, and the future

Non-insulin dependent diabetes mellitus: the gathering storm

Stephen O'Rahilly

Summary

A massive increase in the global prevalence of non-insulin dependent diabetes is likely to occur as "Westernisation" of dietary habits and patterns of physical activity becomes more widespread. Advances in molecular and cellular science may provide some useful insights and therapeutic tools to assist in the fight against the severe consequences of this epidemic. These will include the better identification of specific aetiological subtypes of the disease; the identification of new drugs through the better understanding of the biology of insulin secretion and action; and the targeting of therapies to specific subtypes of the disease. In addition, knowledge of the precise mode of action and antidiabetes drugs may facilitate the design of more effective non-pharmacological manipulations; the genetic identification of "high risk" asymptomatic people may allow us to target screening and preventive strategies more effectively; and investigations into the mechanisms that underlie the link between low birth weight and later diabetes should provide new routes towards treatment and prevention. Barriers to the implementation of the global measures required to stem the predicted flood of non-insulin dependent diabetes may prove insuperable, but if we are to have any success, then close collaboration between clinicians, epidemiologists, public health physicians, and laboratory scientists will be essential.

Non-insulin dependent diabetes mellitus affects about 2% of the British population. It is often referred to as "mild" diabetes, but it results in a huge burden of human misery. It is among the commonest causes of blindness in middle aged and elderly people and an important cause of renal failure resulting in the need for dialysis or kidney transplantation. It is the most common condition leading to (non-trauma related) lower limb amputation. In addition, people with non-insulin dependent diabetes have a greatly increased risk of myocardial infarction or stroke, and when these events happen the resulting functional disability is usually greater than that which occurs in non-diabetic people. As if that were not enough, some people with diabetes are made to believe that the development of the disease and their failure to avoid the often devastating consequences are, in some way, their own fault. Not surprisingly, low self esteem and even clinical depression often occur.

The beginnings of a worldwide epidemic of non-insulin dependent diabetes are readily discernible. The prevalence of diabetes in South Asian immigrants to Britain, for example, is 20-30% in the 40 to 75 year age group.[1] Similar figures are now appearing from studies of migrants from rural to urban areas within less developed countries. By 2020 there will be an estimated 250 million people with non-insulin dependent diabetes in the world.[2] Apart from the human suffering, this epidemic will undoubtedly limit the funds available for the treatment and prevention of other diseases in poorer countries.

Does scientific research hold out any hope for the effective treatment and, preferably, prevention of this rampant disease? I'm not sure, but in this article I shall examine the possible routes whereby scientific knowledge might be translated into practical benefits. In ascending order of importance these might include increased understanding of the causes of non-insulin dependent diabetes, improved treatments which have beneficial effects on outcome and do not make excessive demands on the patient, and prevention of the disease.

Understanding the causes

Identification of specific aetiological subtypes

Molecular geneticists are beginning to identify specific and definable subtypes of non-insulin dependent diabetes. These advances have come from two basic approaches. The first is to work out the molecules involved in the normal processes of insulin secretion and action and then examine whether patients with inherited forms of diabetes have any genetic defects in these molecules. This is more elegantly done when physiological investigation has established whether the form of diabetes to be studied is more closely related to defective insulin secretion or to defective insulin action (commonly termed insulin resistance).

The second approach is to find families with clearly inherited forms of diabetes and use the detailed map of the human genome to identify relatively small areas of the genome which track with the disease in families.

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Table 1 Single gene disorders that result in subtypes of non-insulin dependent diabetes

Gene	Mode of inheritance	Molecular basis for hyperglycaemia	Special features
Insulin	Dominant	Production of ineffective forms of insulin	Very rare. Most patients with mutant insulins do not have diabetes
Insulin receptor[3]	Dominant or recessive	Impaired insulin signalling	Most patients initially present with other clinical features of severe insulin resistance
Glucokinase[4 5]	Dominant	Impaired insulin secretion	Mild and relatively stable form of early onset disease (MODY 2)
HNF1α (hepatocyte nuclear factor 1α)[6]	Dominant	Progressive impairment of insulin secretion (? due to gradual loss of β cells)	Progressive form of early onset disease (MODY 3)
HNF4α (hepatocyte nuclear factor 4α)[7]	Dominant	Progressive impairment of insulin secretion (? due to gradual loss of β cells)	Very rare, progressive form of early onset disease (MODY 1)
Mitochondrial genome[8]	Maternal	Impaired insulin secretion (predominantly)	One mutation (in the tRNA for leucine) may account for up to 1% of cases of non-insulin dependent diabetes. Often associated with other abnormalities, eg deafness

Scientists can then home in on the defective gene using a technique called positional cloning.

Together, these methods have defined several specific genetic subtypes of non-insulin dependent diabetes (table 1). Although finding single gene mutations that cause subtypes of diabetes is exciting, the mutations detected to date are likely to contribute to less than 5% (some would say less than 1%) of cases of non-insulin dependent diabetes and the range and power of available treatments is, as yet, very limited.

Multifactorial non-insulin dependent diabetes

Although genetic factors are highly likely to have a role in this disease, single gene disorders are unlikely to account for all, or even most, cases of non-insulin dependent diabetes. It is also important to remember that non-insulin dependent diabetes can be the presenting feature of a wide variety of disorders—for example, haemochromatosis, chronic pancreatitis, Cushing's disease, and acromegaly. In addition, many patients with apparent non-insulin dependent diabetes have a more slowly progressive form of the autoimmune β cell destruction more typically associated with insulin dependent diabetes and tend ultimately to need insulin treatment.

Not all scientific advances contributing to our current understanding of non-insulin dependent diabetes have come from molecular biology. Over 30 years of clinical, pathophysiological, and epidemiological studies have led to a model of the time dependent decline in β cell function and insulin sensitivity that ultimately results in the development of non-insulin dependent diabetes in middle age (fig 1). This provides a conceptual framework for examining the way that genetic variation and environmental factors can affect the lifelong control of glucose metabolism.

Genes contributing to multifactorial non-insulin dependent diabetes

The identification of sequence variants in genes that do not directly cause but predispose to or protect from development of non-insulin dependent diabetes has been more difficult than for many other diseases for three main reasons. Firstly, non-insulin dependent diabetes represents a somewhat arbitrarily defined point on a continuum of glucose tolerance. Secondly, it tends to present quite late in life so gathering large numbers of multigenerational families affected by the condition has been difficult, and, thirdly, there are lots of different ways that someone can end up having the disease. But large scale genetic studies of multifactorial diabetes are beginning to bear fruit, and it will be intriguing to see how these insights can be generalised to the understanding of the disease.

Environmental factors

Genetic variation alone clearly cannot explain the explosive increase in the incidence of non-insulin dependent diabetes that occurs when underdeveloped populations adopt a Western lifestyle. An important area of research will be to discover which aspects of Westernisation (such as total energy intake, nutrient balance, micronutrient consumption, exercise patterns, and environmental toxins) might trigger the disease, although it is clear that lack of exercise and development of central obesity have important effects.

The discovery by Barker and colleagues of a link between birth weight and development of several degenerative diseases in adulthood has opened up an entirely new area of medical research.[9] The idea that prenatal nutrition (or other aspects of maternal health during gestation and lactation) might affect the predisposition to diabetes[10] may hold out hope for the development of practical early preventive strategies.

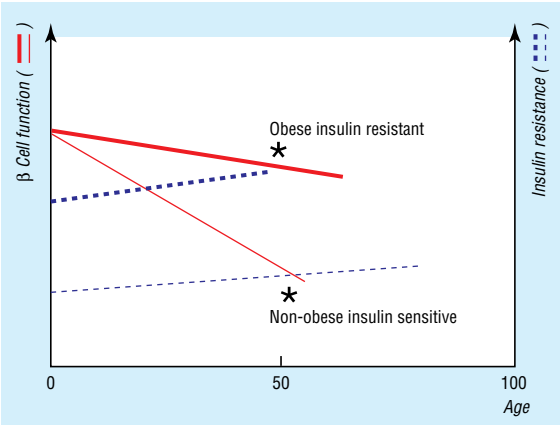

Fig 1 Declining β cell function combines with increasing insulin resistance to produce non-insulin dependent diabetes. When insulin resistance is severe only a small fall in β cell function is required to produce diabetes (thick lines). Conversely, in insulin sensitive subjects (such as native Japanese) a more severe fall in β cell function is required (thin lines)

Table 2 Single gene disorders leading to severe obesity in mice

Syndrome	Mutant gene product	Function of normal gene product	Possible mechanisms leading to obesity
ob/ob (recessive)	Leptin	Hormone secreted by fat cells which affects the control of energy balance	Lack of feedback signal from fat depots
db/db (recessive)	Leptin receptor	Hypothalamic receptor for leptin	Failure to sense circulating leptin levels
fat/fat (recessive)	Carboxypeptidase E	Processing of some pro-neuropeptides and pro-hormones	? Incorrect processing of regulatory pro-peptides in hypothalamus
Agouti (dominant)	Agouti protein	Control of hair colour	Ectopic expression in brain may lead to inhibition of signalling through melanocortin-like receptors involved in energy balance
Tubby/tubby (recessive)	Novel intracellular protein	Unknown function.Expressed in hypothalamus	? Role in intracellular signalling in hypothalamus

Role of obesity in non-insulin dependent diabetes

The most common factor resulting in insulin resistance (one of the two main pathophysiological features of non-insulin dependent diabetes) is an excessive fat mass, particularly when the excess body fat is located in visceral rather than peripheral, subcutaneous depots. Many exciting conceptual advances in metabolism have recently come from the investigation of the reasons behind the severe obesity found in several different single gene disorders in mice (table 2). The most important of these relates to the discovery that fat cells produce a hormone called leptin, which acts as a feedback signal to centres in the hypothalamus controlling food intake, energy expenditure, and the hormonal axes controlling adrenal and gonadal function (fig 2).[11] This hormone is present in humans and is likely to serve the same functions. Most obese people have a normal leptin gene sequence and, in general, fat people have higher plasma leptin levels than thin people. However, we do not yet know whether the relation between fat mass and plasma leptin concentration is more subtly disturbed in those destined to become obese.

Very obese people have an extremely high chance of developing non-insulin dependent diabetes, but overcoming obesity is difficult and weight loss is rarely sustained. I predict that even if leptin does not prove clinically useful in treating obesity, insights resulting from its discovery will lead to useful drug treatment. However, the control and distribution of such drugs will raise ethical and financial dilemmas much greater than those currently faced in, for example, growth hormone replacement.

Designing better treatments

In many people with non-insulin dependent diabetes insulin is less effective at lowering blood glucose than it is in non-diabetic subjects. This contributes directly to hyperglycaemia, may exhaust β cells as they try to overcome the insensitivity of muscle, liver, and fat to insulin, and might contribute to some of the macrovascular complications of non-insulin dependent diabetes through the ill defined toxic effects of chronically high insulin concentrations.

Restricting energy intake, reducing saturated fat intake, and increasing physical exercise all improve insulin sensitivity and, consequently, glycaemic control and other vascular risk factors in diabetic people. Sadly, however, these measures usually fail because of the difficulties people have in changing the habits of a lifetime and the inexorable progression of the disease. Thus, drugs are usually required. The only widely available drug which directly improves insulin sensitivity in non-insulin dependent diabetes is metformin. It is modestly effective, causes nausea or diarrhoea, or both, in many patients, and we don't really know how it works.

It is hard to make logical, scientifically based, therapeutic advances on the basis of a compound whose mechanism of action is so obscure. That is partly why a new class of insulin sensitising agents, the thiazolidinediones, has caused so much interest. Of these drugs, troglitazone is now marketed in some countries. They were discovered by happy accident. However, recently

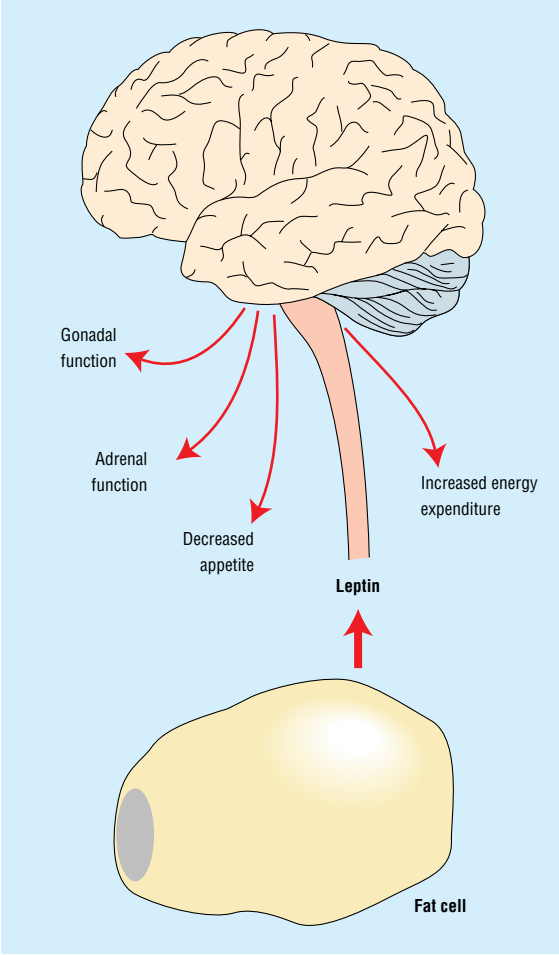

Fig 2 Role of leptin in controlling energy balance and hypothalamic function

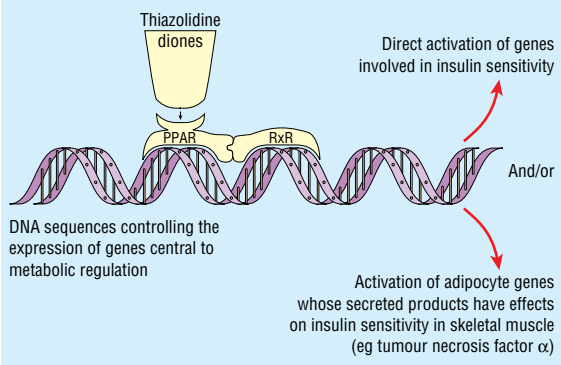

Fig 3 Peroxisome proliferator activated receptor (PPARγ) binds DNA together with a partner, the retinoic acid X receptor (RXR) in fat and musculoskeletal cells. Thiazolidinediones, which lower insulin resistance in non-insulin dependent diabetic patients, bind to PPARγ and activate it

they have been found to bind with high affinity and activate a nuclear hormone receptor called peroxisome proliferator activated receptor (PPAR) γ. This family of receptors gained its unwieldy name because one of its members seems to mediate the effects of certain drugs to stimulate the proliferation of peroxisomes in liver cells. The ligand which binds naturally to PPARγ has not been identified. Scientists originally identified the receptor as potentially important in promoting the differentiation of fat cells.[12] One of the factors controlling fat cell differentiation is the switching on of genes mediating insulin action. Accordingly, stimulation of PPARγ has been shown to turn on the expression of several genes involved in glucose and lipid metabolism.

Although fat cells dispose of some glucose, the most important site of disposal is skeletal muscle. One of the big remaining questions is whether thiazolidinediones improve insulin sensitivity by acting only on fat cells (where PPARγ is most highly expressed) or whether they can directly improve insulin action in skeletal muscle, where the receptor is expressed at a much lower level (fig 3). Wherever they act, thiazolidinediones do improve insulin action in insulin resistant people.[13] Because we think that we know how these drugs might work, we may be able rapidly to design better drugs, or more effective targeted dietary manipulations, to improve treatment.

Improving β cell function

Basic and clinical science has discovered a lot about how the insulin secreting β cell of the pancreas works. We also know exactly what is wrong with it in one uncommon form of non-insulin dependent diabetes and have some clues regarding how it might go wrong in multifactorial forms of the disease. β cells secrete insulin in response to glucose, not through a cell surface receptor for glucose but through the metabolism of glucose, which generates intracellular ATP. Intracellular ATP concentrations directly affect the behaviour of ion channels in the β cell membrane such that at high intracellular ATP concentrations a potassium channel is blocked, leading to the opening of a voltage sensitive calcium channel. The rapid influx of calcium causes the disgorgement of granules containing insulin from the β cell (fig 4). This process needs to be tightly regulated because secreting far too much insulin would rapidly result in death through depriving the brain of glucose.

The increasing knowledge of the molecules involved in β cell function provides an array of new potential targets for drug development. Additionally, the increasing knowledge of the precise molecular nature of the β cell defect in some forms of non-insulin dependent diabetes may allow more rational use of such drugs. For example, if, as in one form of maturity onset diabetes of the young, a genetic defect exists which impairs the β cells' ability to generate intracellular ATP, then drugs such as sulphonylureas, which act directly on the ATP sensitive potassium channel in the β cells, should be able to bypass this defect. Although these drugs were discovered many decades ago by serendipity, we can expect the development of designer drugs specifically targeted to compensate for or bypass inherent genetic abnormalities within molecules of the β cell.

The reason for the inexorable fall in β cells in multifactorial non-insulin dependent diabetes is difficult to understand and treat. It might relate to the progressive accumulation of islet amyloid, much like the amyloid material found in the brains of people with Alzheimer's disease but made from islet amyloid polypeptide or amylin.[14,15] What this molecule is doing in the normal β cell and why it forms deposits in islets of diabetic patients is still a mystery.

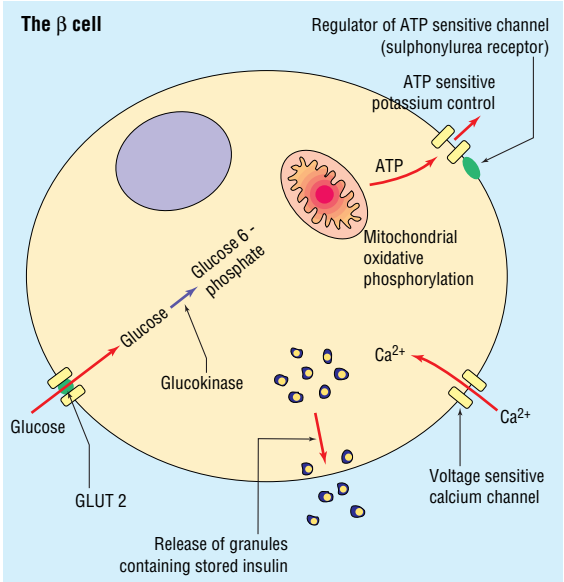

Fig 4 Regulation of insulin release by β cells in response to glucose. Glucose enters β cells through a transporter (GLUT 2) where it is phosphorylated to glucose 6-phosphate by glucokinase which enters the pathways of glycolysis and oxidative phosphorylation to generate ATP. Potassium channels in the β cell are blocked by raised intracellular ATP concentrations causing the cell to depolarise and voltage sensitive calcium channels to open. Rapid entry of calcium into the cell triggers the release of stored granules containing insulin

Making best use of current knowledge

One of the (only partly valid) criticisms of endocrinologists is that they spend their time diagnosing and treating rare and interesting diseases but have no interest in the public health in general. Non-insulin dependent diabetes is the disease with which endocrinologists, armed with results of ongoing non-molecular clinical research, will soon be able to dispel these notions for good. When the United Kingdom prospective diabetes study[16] reports its findings we will know which is the best of the currently available therapeutic strategies for lowering plasma glucose concentration. Similarly, this and other prospective, randomised multicentre studies will allow us to use the best possible combinations of antihypertensive and hypolipidaemic treatments to reduce the burden of heart attacks and strokes in patients with non-insulin dependent diabetes.

Early detection of non-insulin dependent diabetes by screening seems promising in terms of reduced morbidity and cost effectiveness.[17] However, we will need to prove this unequivocally by large (and expensive) studies which are unlikely to be funded by the pharmaceutical industry.

The ultimate goal must be, of course, prevention. Several clinical trials of both behavioural and drug treatment are currently ongoing and are largely being conducted in high risk subjects. Preventive strategies aimed at the entire population will require greater knowledge of the precise environmental factors, both before and after birth, that predispose to the disease.

Conclusions

A global epidemic of non-insulin dependent diabetes is on the horizon. The rapidly accumulating knowledge of the biology of normal insulin secretion and action will inevitably lead to the development of new, logically based, interventions. However, advances in molecular and cellular sciences alone are unlikely to be able to provide panaceas for diabetes. New treatments will need to be combined with the results of research into the reason for the explosion in non-insulin dependent diabetes concurrent with the spread of Western lifestyles. Non-pharmacological methods of treatment and primary prevention such as nutritional, behavioural, social, and environmental manipulation will be important in controlling non-insulin dependent diabetes. The problems of this disease show the necessity for clinicians, nutritionists, molecular geneticists, physiologists, biochemists, psychologists, epidemiologists, and others to collaborate intelligently so that their research can be translated into real benefits for humankind.

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Future of non-insulin dependent diabetes

- The global prevalence of non-insulin dependent diabetes will increase greatly as Westernisation of dietary habits and patterns of physical activity become more widespread
- Better identification of specific aetiological subtypes of non-insulin dependent diabetes will lead to better information on prognosis and targeting of treatment
- New drugs will be developed through better understanding of the biology of insulin secretion and action
- Knowledge of the mode of action of antidiabetic drugs may allow us to design more effective nutritional manipulations
- Genetic identification of people at high risk may allow screening and preventive strategies to be better targeted.
- Study of leptin secretion and action will lead to the development of drugs for treating obesity.

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