

# Tackling, treating and preventing the impending diabetes tidal wave

This report is from a symposium that took place on 18 November 2006 at the Primary Care Diabetes Society conference in Birmingham. The event was sponsored by GlaxoSmithKline.

**‘A cultural evolution has left the world facing the prospect of a diabetes tidal wave.’**

**Dr Cleland**

## Introduction

The world faces a rapid increase in the prevalence of type 2 diabetes. This change is explained by the plentiful supply of food and the more sedentary lifestyles that people now lead. In his presentation, Steve Cleland outlined the number of people diagnosed with type 2 diabetes, explained the biochemical basis for the symptoms and how treatment options work.

**‘W**e must intervene early in people with type 2 diabetes, before  $\beta$ -cell failure becomes irreversible,’ said Steve Cleland, Consultant Diabetologist, Glasgow. A cultural evolution has left the world facing the prospect of a ‘diabetes tidal wave’. Dr Cleland explained the cultural evolution as the move from primitive man who went out to hunt for food, to modern man who has more food than he requires and lives a very sedentary lifestyle.

### More obesity

In the past 15 years in the US, for example, obesity has increased dramatically. In most states the prevalence of type 2 diabetes is over 20% and in 10 states is in excess of 25%. This problem is not restricted to the US, as the annual rate of increase of obesity in the UK was 0.75% per annum between 1980 and 1998. Increases in other western countries, such as Italy and France, have been

much more modest, which may be another endorsement of the Mediterranean diet. ‘In the UK we are leading the way in terms of people getting fat fastest’, commented Dr Cleland. Between 2000 and 2010 the prevalence of the disease is predicted to increase by 23% in North America, 24% in Europe, 50% in Africa and 57% in Asia (Wild et al, 2004). This demonstrates that obesity is not just a problem of the western world. As a result, by 2010, it is predicted that 350 million people worldwide will have type 2 diabetes.

### Serious disease

We also should not regard diabetes as a mild disease, said Dr Cleland. Diabetic retinopathy (the leading cause of blindness in the world), diabetic nephropathy, stroke, cardiovascular disease and diabetic neuropathy all occur in people with diabetes – in fact eight out of ten people with diabetes die from a cardiovascular event. Currently

10% of the NHS budget is accounted for by treating diabetes (Reckless, 2004), but that figure is heading towards 15% in the next few years. Dialysis units are struggling to cope with the number of people with type 2 diabetes.

### Raised BMI

Dr Cleland reminded participants that the risk of diabetes increases dramatically in a person who is overweight or obese (Chan et al, 1994). This link between obesity and diabetes was described as ‘Diabesity’. Even a person with a BMI of 29 kg/m<sup>2</sup> has a four- to five-fold increase in the risk of diabetes compared with someone who is very lean. If the BMI is greater than 35 kg/m<sup>2</sup>, there is about a 40–50 fold increase in the risk of diabetes (Chan et al, 1994). ‘Obesity is the main factor driving type 2 diabetes,’ he said.

### Increased CVD risk

A study published in *The Lancet* earlier this year looked at the relationship between age and cardiovascular disease in women with diabetes. We already know that cardiovascular events are occurring about 15 years earlier in men with diabetes than those without. This new data showed that in women the difference is even greater, with a 50-year-old woman with diabetes having the same risk of cardiovascular events as a 75-year-old woman without diabetes (Booth et al, 2006).

### Central obesity

Central fat stores that become dysfunctional are a very

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common characteristic of type 2 diabetes. Waist circumference is becoming particularly useful for monitoring people with type 2 diabetes. When a person has central obesity, fatty acids and adipocytokines are released from that store and the first organ they hit via the portal circulation is the liver. Blood goes from there around the body, affecting skeletal muscles, the pancreas, cardiovascular system, etc.

Fatty acids and adipocytokines leaking out of cells cause the phenomenon of fatty liver, which Dr Cleland suggested is seen more often now, with mild derangement of liver function tests (particularly alanine aminotransferase). People with central obesity also get ectopic fat accumulation in the muscle cells, with accumulation of globules of triglycerides and this has quite profound effects on the insulin handling of glucose in muscle cells. Fatty acids in the bloodstream significantly impair endothelial function. Fatty acids are also toxic to pancreatic  $\beta$ -cells, and are the main drivers of  $\beta$ -cell failure.

### **Mitochondrial dysfunction**

Explaining the biochemical basis of type 2 diabetes, Dr Cleland said that mitochondria take the fuels in our body and convert them into the energy which keeps us alive. Mitochondria can take in either glucose or fatty acids when producing energy. If a person becomes obese and has excess fatty acids and also becomes sedentary, they do not need much energy. This results in fatty acids in their cells which are required in lower quantities and therefore do not get oxidised in the mitochondria.

There is a feedback mechanism which reduces the amount of glucose coming into the cell and this is where we understand insulin resistance to occur in some cells. Too many fatty acids increase oxidative stress

and poison and damage the mitochondria and the cell. This results in accelerated ageing of the cell.

In the liver, hepatic insulin resistance occurs, causing basal hyperglycaemia through gluconeogenesis. This is seen in the classic symptom of high fasting blood glucose levels. Fatty liver occurs and the handling of lipids is altered with high triglyceride and low HDL cholesterol levels. Fatty acid oxidation results in insulin resistance in the muscle and post-prandial hyperglycaemia.

In the vasculature, oxidative stress reduces the levels of nitric oxide, a key molecule for protecting the endothelium and preventing future plaques and atherosclerosis. The risk of hypertension, endothelial permeability, inflammation, thrombosis and coagulation all increase, resulting in a greater risk of a myocardial infarction or stroke. In the pancreas there is a double whammy, because the  $\beta$ -cells are at particular risk of oxidative stress from fatty acids.

### **Strategies for treatment**

There are four different strategies for improving mitochondrial fatty acid oxidation and therefore treating type 2 diabetes, said Dr Cleland. The first is to increase the use of energy, requiring more ATP production from the mitochondria. This results in the mitochondria using more fatty acids, reducing the concentrations and stopping the poisoning of the cells. Dr Cleland suggested that this strategy is not just about telling patients to go to the gym, which is not often a well-received suggestion. In practical terms, patients should walk more, or even just walk to the TV to change channel rather than using the remote control.

Another strategy for dealing with type 2 diabetes is to reduce energy intake, thus reversing the build up of fatty acid stores.

This can be achieved through a calorie restriction or dieting strategy.

Metformin is a useful strategy as it fools the body into thinking that it is exercising. This treatment option can improve mitochondrial dysfunction.

The final strategy suggested by Dr Cleland was the use of glitazones. They work on visceral adipocytes and stop secretion of fatty acids and cytokines into the circulation. They also divert a lot of the fat into subcutaneous rather than visceral stores. The overall effect is that the body believes that it is dieting.

### **Treatment in primary care**

Dr Cleland thought that over 80% of patients with type 2 diabetes should be seen in primary care. With the increasing prevalence he explained that secondary care cannot cope with any more type 2 diabetes patients. He also stressed the use of early pharmacological intervention. Metformin and glitazones have a good biochemical basis as long as they are used early enough before too much deterioration in  $\beta$ -cell function, he said. ■

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**Dr Cleland**

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