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DIABETES: A RISING TIDE

PROFESSOR CHRISTOPHER WHITTY

Diabetes is as old as medical records. It has been described since Egyptian texts in 1552 BC (Hesy-Ra). Others noticed ants attracted to the urine of sufferers, presumably due to the sugar in diabetic urine. It was famously described as 'the melting of flesh into urine' by Arateus in 150 AD, a vivid description of untreated Type 1 diabetes. Early diagnosis involved tasting urine to tell if it was sweet. From around the 1770s there was a recognition that there were at least two types of diabetic patients. One group often died within weeks; this is what we would call Type 1 diabetes. For the second, survival was much longer and diet might help, generally equivalent to what we call Type 2 diabetes.

The start of a proper scientific understanding of diabetes can probably be dated to when 1869 Paul Langerhans, a doctoral student, described clusters of clear cells in the pancreas, now called the 'Islets of Langerhans'. In 1889 von Mering and Minkowski showed that removing the pancreas from dogs causes diabetes. The breakthrough came when the Canadian team of Banting, Best, MacLeod and Collip extracted and purified insulin. This was given to Leonard Thompson, aged 14, in 1922, drifting in an out of diabetic coma. Thompson went on to live another 13 years. Banting and MacLeod were awarded the Nobel Prize.

Diabetes is common, in the UK and globally. An estimated 4.3 million people in the UK are living with diabetes, around 3.5m of whom are diagnosed. Around 415m globally have diabetes; they are in all walks of life including many successful and well known people. Diabetes has risen in prevalence (how many people have the disease) and in proportional importance for ill health as other causes of disease have reduced. Many people who listen to this talk will have diabetes, and almost all will know someone with diabetes even if they are not aware of it.

The detailed physiology of the control of glucose, which is at the heart of diabetes, is complicated, but the essence of it is simple. The body needs to keep glucose in a narrow range; either too much or too little is a problem. The pancreas ß cells secrete insulin in response to high glucose. Other cells including in the liver, fat cells and muscle respond to this by storing energy including as glycogen and fat. Without this feedback loop glucose is not stored and glucose in the blood increases. In all types of diabetes the feedback loop is damaged, or broken.

There are two major types of diabetes which will be covered in the lecture: what we currently call Type 1 and Type 2 diabetes. The pancreas Islets of Langerhans produce insulin from ß cells; in Type 1 disease these die off- probably due to an autoimmune disease. Without them the body cannot secrete insulin, and without insulin the body cannot regulate glucose and energy. Eventually there is almost no insulin. The problem in Type 1 is purely a lack of insulin; the cells in the body usually responds to insulin normally.

In Type 2 diabetes the pancreas produces insulin in response to glucose, although often not in sufficient quantities. The other cells in the body respond abnormally to this insulin, not reducing glucose as much as it should- this is called insulin resistance. The effect is glucose levels in the blood go up.

The age structure of Type 1 and Type 2 diabetes is also very different. Type 1 can come on at any point, but tends to present in late childhood through to early adulthood and is then lifelong. Type 2 tends to present in middle age or later and in some cases can reverse if people lose weight.

Along with these two major types of diabetes, a third, reversible form of diabetes is gestational diabetes, which occurs in women in around 5% of pregnancies, usually in the 2nd or 3rd trimesters and usually resolves after the child is born. There is however around a 7x increased risk of subsequently developing Type 2 diabetes, higher in those who are overweight. Diabetes is a serious challenge in pregnancy, with risks for the mother and the child, and in addition to gestational diabetes the number of women with prior diabetes (pre-gestational) is rising in pregnancy.

The cause of diabetes is an interaction of genetic factors and environment. There is a clear genetic component to Type 1 diabetes, although it is not 'inherited' in the way most people understand that. It is possible to look at Type 1 diabetes two ways: 85% have no first degree relatives affected, but the risk is about 15x higher if you do. People often worry about passing on diabetes, but there is only a 2-3% risk if someone's mother has diabetes and 6-9% risk with a Type 1 diabetic father, but 30% if both have Type 1 diabetes (still less than half). There is however a 30-70% for identical twins which provides evidence to support the strong genetic component.

Type 2 clusters loosely in families, but it is a complex relationship and the genetic basis is weak and poorly understood. It is 2-6x more likely if a family member has it, but as much of the risk of Type 2 diabetes is related to obesity which has both cultural and genetic components this is hard to disentangle. People living together tend to behave (and eat) more similarly than those who do not.

As striking as the genes from families is the impact of ethnic heritage on Type 2 diabetes. Childhood Type 2 diabetes is rare, but children of south Asian origin are around 8.9x more likely to have Type 2 diabetes than their White counterparts, children of African heritage were 5.8 times more likely. People of South Asian and African heritage are 2-4x more likely to develop Type 2 diabetes than White Europeans. Middle East heritage people are also high risk.

The major risk for developing Type 2 diabetes however is weight. 80-85% of Type 2 diabetes is accounted for by people being overweight or obese. This increases with deprivation (compared to Type 1 which does not). The relationship is causal: where people with Type 2 diabetes lose weight diabetes may go away. It is well known that the rates of obesity and being overweight in the UK are high, and have been rising; for this reason it is unsurprising that the rates of Type 2 diabetes, which now makes up 90% of diabetes, has risen.

There is no doubt that the prevalence of diabetes in the UK has risen over the last 4 decades and is still rising, but the situation is not quite as clear-cut as at first it appears. There are three possible drivers of this increase: rising rates of obesity and overweight people; changes in diagnosis and medical practice meaning it is more likely to be recorded; better survival. There is reasonable evidence all three have contributed over the last 4 decades, but in the last decade obesity and overweight increases have slowed, and if anything the number of new cases of diabetes (incidence) is falling. The survival of people with diabetes has however, significantly improved, and currently the rise in the number of people with diabetes is probably in large part explained by the fact they are living longer. Annual mortality rates are falling for Type 2 diabetes. Taking a recent major study: prevalence (people living with diabetes) rose from 3.2% to 5.3% from 2004-2014 but incidence (new cases) dropped from around 44/10,000 PYR in 2004, to 37 in 2014. Mortality rates fell from 319/10,000 per person year at risk to 216 over the same period (Zghebi et al 2017).

Before considering treatments, it is worth pausing on the symptoms of diabetes if untreated, both because they show what treatment can achieve, and because they are the warning signs to watch out for. For all types of diabetes the initial symptoms are going to pass urine frequently associated with thirst; tiredness; unplanned weight loss; skin infections, thrush and delayed wound healing. In the case of Type 1 diabetes this can (and without treatment will) progress to diabetic ketoacidosis: the blood glucose goes very high, ketones build up and the blood becomes acidic. Eventually patients lapse into coma, and if untreated die. There is a less common

complication of Type 2 diabetes called hyperosmolar hyperglycaemic state (HHS or HHNS) in which diabetics with either Type 2 or Type 1 have life-threateningly high glucose without ketones. Usually illness or infection triggers it. Both are medical emergencies, and one aim of treatment is to prevent them.

The main long-term aim of treatment of diabetes is to return blood glucose and the body's handling of glucose as close to normal for as possible for as long as possible. The mainstay of treatment of Type 1 diabetes, and to a much lesser extent Type 2, is insulin. Initial insulin was all short acting so needed repeated injections; the key to making a normal life possible was developing long-acting as well as short-acting insulin. Insulin can be given by injection, pen or pump. The ideal, not yet reached, is to have the artificial insulin mimic exactly what the body would have done if the pancreas was still behaving normally. Combining long-acting and short-acting insulin provides a rough approximation, but not a perfect match. Those on insulin need to be aware of hypoglycaemia, a significant risk of accidental overdose.

In Type 2 diabetes, where some insulin is still being produced, initial treatment is with diet, and if that does not provide control with oral drugs. Drugs can work through multiple pathways; these include stimulate insulin production from the pancreas directly (e.g. sulfonylureas, repaglinide); decrease liver glucose production (e.g. metformin); inhibit breakdown of gut enzymes GLP-1 and GIP which reduce glucose and stimulate the pancreas (e.g. DPP-4i). The routes by which these drugs were discovered were various. Metformin, the first line treatment is descended from French lilac used in traditional western medicine. Sulfonylureas were discovered accidentally from testing antibiotics against typhoid. DPP4-I drugs work via gut hormones and were discovered via more conventional science.

For both Type 1 and Type 2 diabetes, without very good glucose control there are several risks. These include: heart disease and heart attacks; stroke; eye disease and blindness; skin infections, peripheral vascular disease and nerve damage leading to ulcers and limb loss; kidney disease and renal failure; serious infections. There have been major advances in both the prevention and treatment of all these complications.

Diabetic eye disease takes many forms, but all have the potential if unchecked to lead to reduced vision and blindness. Three areas have led to improvement. The first is in prevention; there is good evidence that tight glucose control reduces the risks of eye problems, although it has to be balanced with the risk of hypoglycaemia (low blood sugar) if control is too aggressive. For those who develop problems, the mainstay of treatment has been laser treatment which has steadily improved, but new advances, especially the anti-VEGF drugs injected into the eye have led to better outcomes.

Foot disease in diabetes sounds trivial, but is not. It is caused by a combination of the tendency for people with diabetes to have vascular damage leading to poor blood supply, to have nerve damage reducing feeling and to have infections. Around 60,000 people with diabetes have foot ulcers at any time. It is a bad prognostic sign for their overall health. It costs the NHS and social care around £1Bn a year. It leads to around 7000 amputations a year in UK. Only half of the patients who have amputations survive more than 2 years. Again a combination of prevention and treatment can reduce the problem. Tight glucose control again reduces the incidence, and good foot care reduces it further. Early intervention with infections and on some cases vascular surgery can stave off amputations; there is still an unacceptably large variation in amputation in the UK.

Cardiovascular disease is one of the major causes of mortality in diabetes, and here the key is not tight glucose control, but strong intervention in all the risk factors for heart disease and stroke. Tight glucose control here is much less important. Reducing high blood pressure, cholesterol, stopping smoking, exercise and using a variety of drugs which protect the heart are more important in people with diabetes than those of the same age without diabetes. The impact of the cumulative effect of all these interventions is substantial and the outlook for those with diabetes in terms of cardiovascular health is much better than it was two decades ago.

One of the most common, and reasonable questions about diabetes is whether it can be cured or prevented. In the case of Type 1 diabetes, at the current state of scientific knowledge the answer is neither, although there are theoretical reasons for thinking both prevention and cure are realistic. For Type 2 diabetes some cases can be

cured, and a substantial proportion could be prevented with current science. The most extreme example of cure is gastric surgery. There is conclusive evidence that bariatric surgery can 'cure' (in the sense that no drugs are needed) diabetes in many of those who undertake it. Weight loss by other means can also reduce or remove the need for drugs. Neither are easy, or in the case if surgery risk-free, but they work.

Prevention is a more complex but in the long run more substantial issue. Put simply, being overweight or obese drives a lot of Type 2 diabetes which makes up around 90% of the total; current levels of overweight are very high by historical standards so biologically we can revert to historical norms. This is a balance between energy in (eat + drink) and energy out (basal rates + exercise). Exercise is good for many reasons and needs to be supported, but the even bigger issue is that people are consuming more energy. A political question is: should the state intervene? And if so how far up the ladder of state intervention from mild information-sharing to banning things is appropriate? Ultimately politicians, representative of and answerable to the public, will have to settle this. But at least two of the key points are settled: diabetes is a serious and growing public health problem: there are interventions available for state action, although the evidence-base is variable and sometimes weak. These include a sugar tax on fizzy drinks, traffic light labelling of foods, restricting direct advertising to children and restricting fast food outlets near schools. The aim should not be either to reduce pleasure, or profits, but to reduce energy intake. This is not scientifically impossible.

Finally this talk will consider the leading edge of practical science. This includes Islet cell transplants for Type 1 diabetes; an artificial pancreas; immunotherapy in early Type 1 diabetes; low calorie diets to put Type 2 diabetes into remission.

Diabetes prevalence is rising, but at this point mainly because survival is improving. Most areas of diabetes care are better than they were two decades ago, some substantially so. The outlook for treating diabetes is good; decisions around choices to prevent obesity, and therefore diabetes are ones for society.