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How does diabetes cause coronary artery disease?

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I was first introduced to the interaction between diabetes and coronary artery disease when I was a medical student sitting in the diabetes clinic run by my father, Professor Joseph de Bono, at St. Luke's Hospital. My group has retained an interest in diabetes, and in particular type II or non-insulin dependent diabetes, in relation to coronary artery disease because of its particular relevance to heart disease in our immigrant Indo Asian community in Leicester, UK.

From the cardiologist's viewpoint, we know that diabetes increases the rate of development of coronary atheroma, increases the risk of a coronary thrombosis, and has a deleterious effect on the outcome of myocardial infarction. For simplicity, I shall concentrate on ways in which diabetes may accelerate atheroma. Everyone accepts that both type I (primary insulin deficiency) and type II (insulin resistance + relative insulin deficiency) diabetes are associated with an increased risk of coronary atheroma, but there is controversy over the number of different mechanisms involved.

In type I diabetes, there is increasing evidence that hyperglycaemia itself plays an important part, although contributions from dyslipidaemia and from immune reactions to older non-human insulin cannot be excluded. There is good reason to believe that meticulous diabetic control, together with attention to conventional coronary risk factors will prevent, or at least reduce the risk of developing microvascular or macrovascular disease. The question of type II diabetes, which is a more important community cause of coronary disease because of its higher prevalence, is more difficult: not least because clinical non-insulin dependent diabetes is only the tip of an iceberg whose lower parts are formed from increasingly large populations with asymptomatic hyperglycaemia, glucose intolerance and insulin resistance.

"The insulin resistance syndrome" is a convenient short-hand for an association of central obesity, high fasting serum insulin concentrations, high plasma insulin concentrations following a glucose load or during glucose clamp studies, and a predisposition to hypertension and coronary heart disease. Also part of the syndrome is a trend towards high plasma triglyceride concentrations, a high concentration of "small dense" LDL particles, and a high plasminogen activator inhibitor type 1 (PAI-1) concentrations [1-3]. The fundamental cause of the syndrome is unknown. Without doubt, it can be exacerbated by overnutrition and physical inactivity, and conversely ameliorated by exercise and fasting [4,5]. Insulin-sensitive muscle glucose uptake has been shown to be abnormal in young relatives of patients with non-insulin dependent diabetes; exercise dramatically increases insulin sensitivity, but does not restore it to normal [6]. Several other studies have shown a strong correlation between physical inactivity and insulin resistance, on both an individual and a population basis. This raises, however, an interesting question as to whether it is physical inactivity which causes insulin resistance, or whether some fundamental defect in muscle glucose metabolism in itself predisposes to physical inactivity. The possibility that at least the susceptibility to insulin resistance is genetically determined, and/or influenced by foetal or neonatal nutrition, cannot be excluded and is currently the subject of active investigation.

Although the majority of patients with insulin resistance are 'normoglycaemic' by conventional standards, we cannot exclude the possibility that prolonged exposure to even very moderate hyperglycaemia can cause arterial damage. Glycosylated haemoglobin levels have been shown to be elevated in young non-diabetic relatives of patients with type II diabetes. A hypothesis which has been even more vigorously pursued has been the concept that insulin itself can be atherogenic [7]. In a variety of in-vitro models insulin can be shown to increase plasminogen activator inhibitor production by liver cells, and to alter the behaviour of smooth muscle cells from the vessel wall [8,9]. Whether these effects are enough, over a period of time, to cause atherosclerotic changes in the vessel wall, is unproven. Finally, an excess of insulin in the presence of normal or high concentrations of glucose, can lead to the excessive production of low density and very low density lipoprotein and hence to dyslipidaemia. Even if we do not know the precise causative mechanisms, there is now overwhelming epidemiological and clinical evidence that the metabolic environment of insulin resistance strongly encourages the development of coronary atheroma.

From our own work and that of others, insulin resistance emerges as a powerful independent predictor of coronary artery disease risk, and the magnitude of its effect is similar to that of differences in plasma cholesterol concentration. There is a strong correlation between the plasma insulin concentrations of patients with coronary disease, and those of their apparently unaffected children [10]. In the children of coronary disease patients we also found a strong negative correlation between plasma insulin concentrations and physical exercise [11].

What are the implications of insulin resistance for the prevention and management of coronary artery disease in diabetics? Perhaps the most depressing implication is

that by the time patients have developed clinically apparent non-insulin dependent diabetes, they almost certainly have also developed coronary artery disease whether or not this is clinically manifest at the same time. It is therefore very important in the initial management advice given to such patients that vigorous efforts are made to reduce other risk factors (smoking, high blood pressure, high cholesterol) which would contribute to the progression of coronary atheroma. The traditional emphasis on glycaemic control in these patients, though it may prevent the onset of severe hyperglycaemia and may, perhaps, have an impact on microvascular complications almost certainly has little relevance to the progression of coronary disease. For this to be prevented, or at least slowed, it is essential that insulin resistance is reversed, by increased physical activity and, where appropriate, by weight loss. It is interesting that, whereas most diabetic clinics are meticulous about maintaining records of patient weight, very few record physical activity in any standardised way, or use objective measures such as pedometers. Since we now recognise that type I and type II diabetes have different aetiologies, there is no reason why the two phenotypes should not co-exist in the same patient, and in populations with a high prevalence of insulin resistance this is indeed likely to occur. Patients who are often particularly difficult to manage are those who present with a combination of angina, obesity and insulin resistance. They tend to become locked into a vicious circle where angina prevents physical activity and inactivity results in increased obesity and insulin resistance. An aggressive approach to coronary revascularisation may be appropriate, but it needs to be emphasised to the patient that this will only be effective if he or she is prepared to make the effort to adopt a different lifestyle. An important implication of recent evidence on the inheritance of insulin resistance is that it is not only possible, but indeed essential, to look for the condition in asymptomatic young relatives of affected patients at an age where lifestyle modification is easier, and where it has a real chance of preventing the later development of coronary artery disease.

In summary, it can be a mistake to regard type II or non-insulin dependent diabetes as a 'mild' condition. Particularly in the presence of other cardiovascular risk factors, it can cause a major population burden of cardiovascular disease. Anticipation and prevention is important: waiting for the condition to become clinically manifest may seriously jeopardise long term outcome.

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