Atherosclerosis: Atherosclerosis and Diabetes Mellitus

Uptodate

Introduced by Professor Harry Keen.
Presented by Professor Harry Keen & Dr John Jarrett, Unit for Metabolic Medicine, Guy's Hospital.
With Professor Neville Woolf, Department of Histopathology, Middlesex Hospital; Mr Christopher Catterall, King's College Hospital; Dr Eishi Miki, University of Tokyo.

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Black-and-white
Duration: 00:33:53:08

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<Opening titles>

<**Opening film of commuters walking along crowded London streets, including men wearing bowler hats, interspersed with scenes of traffic. Brief close-up scenes in sequence of: exhaust fumes; mouth smoking cigarette; sausages, egg and bacon frying in pan; callipers measuring thickness of skin fat; blood pressure gauge; rotating molecular diagram**>

<Keen to camera>

Vascular disease is the major clinical problem in our day to day management of diabetics today. Since the introduction of insulin, perhaps microvascular disease as manifested by retinopathy and blindness has come to the fore, but well before that large vessel disease has been a problem which has identified the diabetic. Many

years before the clinical recognition of ischaemic heart disease as a distinct entity, gangrene of the foot was known to be associated with sugar in the urine, and this became almost a clinical reflex in those days. Levine[?] suggested an excess of ischaemic heart disease in the diabetic very shortly after the clinical syndrome was described in the population at large. Yet despite this almost historic association, the association between diabetes and large vessel disease, atherosclerosis, has been challenged and even to this day the relationship is not clear.

What we would like to do in this programme is to, first of all, consider the nature of the arterial lesion in the diabetic, to clarify this question of an excess prevalence and instance in the diabetic population, to look at the wider implications of glucose intolerance rather perhaps than diabetes mellitus, to talk about atherogenic mechanisms, and finally, to discuss the implications of these factors so far as treatment and prevention are concerned.

<Keen seated at table with Woolf. A display board for diagrams is set between them>

First of all, I'd like to ask Professor Woolf about the nature of the arterial lesion in the diabetic. Neville, is it the same as in the non-diabetic?

<Woolf to camera>

Well, we have the initial difficulty that though the clinical association between diabetes and coronary heart disease, peripheral vascular disease is well accepted, there is no such unanimity of opinion about the link between arterial wall disease and diabetes. It's a difficult matter measuring atherosclerosis; for one thing there's the irritating but inescapable fact that one has to be dead before the amount of atherosclerosis can accurately be assessed.

However, good studies have been carried out in the last few years and one of the best known of these is the International Atherosclerosis Project, which was carried out under the leadership of Professor Henry McGill of the New Orleans Medical

School. And this involved the accurate assessment of the amount of atherosclerosis in 23,000 sets of vessels – aortae, coronary artery disease, cerebral and carotid vessels – in patients from 19 different geographical locations and from several different racial groups.

<Woolf refers to diagrams and narrates over them>

Perhaps I could show you the results they obtained from this study. In this histogram, which shows us the percentage of intimal involvement by atherosclerotic lesions of various types in the aorta, the bottom portion of each column shows us fatty streaks, the upper portion shows us the raised lesions or fibro-lipid plaques. If we concentrate for a moment on the fatty streaks in the aorta, we will see that there is, in fact, no significant variation in the amount of fatty streaking between diabetic and non-diabetic populations in many of the locations we have mentioned.

As far as the raised lesions, or fibro-lipid plaques, are concerned, the picture is rather different and here in almost every instance, ranging from the affluent societies in North America like New Orleans to the rather less privileged societies such as Guatemala, Columbia, we find a significant increase in the amount of aortic surface involved by fibro-lipid plaques.

<*Next diagram*> This picture is even more strikingly seen in the all important coronary artery bed. Once again, fatty streaks at the bottom, the raised lesions in the upper part of each column. Here we can see that there is an increase in many areas between fatty streaking in the non-diabetic and diabetic populations, but it is the raised lesions which show the most significant rise in almost every one of these rather diverse populations.

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<**Woolf to camera**>

So, from these studies we have got some evidence about the amount of wall disease. Is it a different type of wall disease? I must say at once that we have to answer no, but it's a rather qualified no because it may well be that we're not asking the right questions and so we can't expect to have the right answer. But with the methods currently available to us, I don't think it's possible to distinguish an atherosclerotic plaque coming from a diabetic's vessel from one coming from a vessel of a non-diabetic. However, we do have some information on this vital matter of the natural history of atherosclerotic plaques, in particular the question of plaque necrosis and associated thrombosis. And there is no doubt that the IAP study shows us that there is a significant increase in complicated lesions such as ulcerated lesions with mural thrombosis, with calcified lesions and with necrotic soft plaques which are the ones most likely to be associated with a thrombotic episode.

However, this only tells us what diabetic artery wall disease is like in the postmortem room. Dr Jarrett, however, can tell us something about the situation in life.

<Jarrett to camera>

Well, Professor Keen mentioned in his introduction that the association between clinical arterial disease and diabetes has been challenged. Now we've heard Professor Woolf show the evidence that wall disease is certainly more common in the diabetic and in various parts of the world as well. And I want now to show you what I think is a convincing demonstration of the excess of clinical disease in diabetics. The data I want to show comes from the best known of the prospective studies, the one done in Framingham which is in Massachusetts in the United States, where virtually the whole population has been studied now for 20 years.

<Jarrett refers to series of diagrams and narrates over them>

And the histograms I have to show – the first one deals with mortality. And to explain the picture, the 100 line indicates what would be expected if the population conformed to the mortality seen in the general population. And if we look, first of all, at total mortality, we can see that there is an excess, a nearly 3 fold excess of total

mortality in the diabetics. There is an excess of coronary heart disease which is sudden in origin, an excess of coronary heart disease which is not sudden, an excess of cerebral vascular disease and also an excess of other forms of cardiovascular disease.

Now if we turn from mortality to morbidity, <*next diagram*> we see a similar sort of picture. And I want first of all to concentrate on the peripheral vascular disease shown here by intermittent claudication. And here we have the excess for the combined male female population. Here we see there is an excess in the male population and again an excess in the female population. So, this excess is rather greater than the excess due to coronary heart disease and cerebral vascular disease.

<Jarrett to camera>

Now, peripheral vascular diseases are a common clinical problem in diabetics and we made a visit to the foot clinic in the diabetic clinic of King's College Hospital and we asked Mr Catterall there whether arterial disease was the whole story in the problem of the diabetic foot.

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<Film shows Mr Catterall standing in a hospital ward speaking to Professor Keen>

<Catterall>

Oh no, indeed. We find that almost all these lesions are what we call combined lesions in that sepsis is added to a foot which is already desensitised by neuropathy and devitalised by ischaemia to greater or less degree.

<Keen off camera>

How do you recognise the element of arterial disease?

<Catterall>

Oh, this is the same, isn't it, as it is in any other arterial disease that as the circulation fails, the patient first of all complains of claudical pain on walking, which gradually gets worse and is classically worse at night, and then they get rest pain throughout the day which is very hard to control. And then on top of all that, there are the ordinary clinical appearances of the ischaemic foot, if we could look at Mr Peterson's leg?

<Catterall walks towards a male patient who is seated with his trousers rolled up. Catterall inspects patient's right leg>

<Catterall>

Mr Peterson is only 83 and I've known him for 5 or 6 years now. He started off with trouble in his left leg and now his right leg, as you see, is showing the dusky, dependent discolouration that one sees with an ischaemic leg, that the skin is not very elastic, the foot feels waxy. He's lost all his hair below the knee and, of course, there are no pulses to feel either on the dorsum of the foot or behind the medial malleolus and probably not below the popliteal.

<Keen off camera>

What about management in this stage?

<Catterall>

Well, at this stage one must merely prevent the foot from being damaged by seeing that he has proper instructions as to how to keep it clean, that he wears soft socks which are frequently changed at least daily, that it would be nice if they could be

made of wool but you can't buy woollen socks anymore, and that his shoes must be of adequate size with soft and pliable uppers so that nothing rubs on these feet.

<Keen off camera>

And the place of surgery?

<Catterall>

The place of surgery is when other conservative measures have failed and either the rest pain has become intolerable or else that an ulcer or a local area of gangrene has developed.

<Keen off camera>

And then what possibilities are there?

<Catterall>

Well, this sort of widespread arterial disease is very rarely susceptible to reconstructive arterial surgery and, in effect, one is left with an ablation of the leg, and as you can see on his left leg, he submitted to a below-the-knee amputation 5 years ago. He's now got his patella-bearing limb and that leg doesn't give him any trouble at all.

<End of film clip. Back to studio. Jarrett to camera, then refers to diagrams and narrates over them, interspersed with talk back to camera>

I like now to return to Framingham and to discuss coronary heart disease and remember this histogram shows the data on morbidity. And here we look at males first of all and we see that the excess morbidity in the diabetic males compared with the expectation is 1.64 times, whereas in diabetic females, the excess is 2.25. And this excess or morbidity is probably an underestimate because one of the things

which is known from other studies is that the mortality in diabetics who have a cardiac infarction is greater than in non-diabetic controls, so if we were to show a similar set of histograms for mortality from coronary heart disease, we would find a much greater excess. And this lack of the relative protection of the female who is diabetic is one of the features which remains unexplained, unfortunately amongst many others, in the association of diabetes and atherosclerosis.

Now, we have seen from this and from the other Framingham data that diabetics, at least in the Western world, have a great degree of atherosclerosis. This is not a universal phenomenon and I want to introduce now the topic of the Japanese diabetic and here we have data <*next diagram*> which compares two autopsy studies, one from the United States and one from Japan, and it shows the causes of death attributed at postmortem in these two populations. And the striking difference between the two is in the percentage of deaths attributed to coronary heart disease, in Japan only 6.5 %, in the United States over 53 %.

<*Jarrett to camera*> Recently Professor Keen interviewed a Japanese doctor who has experience of treating diabetics both in the United States and in Japan itself and he asked Dr Miki to comment on this striking difference that we've already seen.

<Cut to film of Dr Miki in conversation with Professor Keen>

<Miki>

In the United States I saw a lot of coronary disease and atherosclerotic disease compared with in Japan.

<Keen>

Would you say that it's a clinical rarity in Japan?

<Miki>

Not exactly, especially in diabetics we do have myocardial infarction, but the percentage of those with atherosclerotic disease is much less than in the United States.

<Keen>

What about gangrene of the extremities, for example, do you see that in Japan?

<Miki>

We very rarely see them, it's quite rare.

<Keen>

So this is a very distinct difference. I know we should not be too much impressed by the clinical impression in medicine…

<Miki off camera>

That's true.

<Keen>

…but I think this sort of difference sounds a very large one…

<Miki nodding>

Ah hah, yes.

<Keen off camera>

…especially if we look at the sort of figures that John Jarrett shows us about postmortem findings.

<Miki>

That's true.

<Keen>

Can I go on then to ask you about small vessel disease, microvascular disease, in Japanese and American diabetics. Is there the same sort of difference?

<Miki>

I don't think so. We do have a lot of problem about retina and kidney. If we have the same kind of operation[? unclear word] concerning duration or severity of diabetics, we do have, we almost have same percentage of retinopathy and nephropathies is one of the major killers, I should say, amongst diabetics in Japan.

<Keen>

So there seems to be a real dissociation between large and small vessel disease…

<Miki off camera>

That's true.

<Keen>

…in respect of Japan. To what do you attribute this comparative freedom of the Japanese diabetic?

<Miki>

I think this can be either dietary or racial, but I think dietary factor is much more important than racial.

<End of film clip>

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<Back to studio. Keen to camera, then refers to diagrams and narrates over them, interspersed with talk to camera>

The dietary factors that Dr Miki referred to are shown on this diagram for Japanese and Western diabetics. The diagram shows the proportion of fat, protein and carbohydrate as a proportion of total calories in the prevailing diabetic diets in these two areas of the world. Striking contrast really is between the very high proportion of carbohydrate in the Japanese diabetic diet, about 55 %, which reflects the generally culturally high level of carbohydrate in the Japanese diet as a whole, and by contrast the 52 % of fat calories in the Western diet. Not only is the amount of fat different in quantity but it's probably different in quality so the fat that the Japanese diabetic eats is more likely to be of vegetable or marine sources whereas most of the Western fat is of animal sources.

<*Keen to camera*> Now, how does diet influence the liability to atherosclerosis? Well, this, of course, is a most controversial question and the evidence will have been described and discussed in previous programmes. It seems very likely, of course, that the more saturated fat and cholesterol there is in the diet of a particular national group, the higher the levels of circulating cholesterol which themselves are, of course, risk factors for arterial disease. One of the factors that has to be considered, so far as the diabetic, is not so much the cholesterol level as the circulating triglyceride level. And this, I think, must bring us to the question of what the interaction is between the diet and the metabolic abnormality of diabetes. Some light may be cast on this by this next diagram.

<*Next diagram*> Now, this shows the components which go to make up the lipoproteins which, of course, carry triglyceride and cholesterol in the circulation. The free fatty acids, glycerol, cholesterol, phospholipid, all carried on an apoprotein, and these components all being put together in the liver to form the circulating lipoproteins. Once in the circulation, the lipoproteins are removed by lipoprotein lipase and deposited in depot fat against a time of need. From there they're liberated under the influence of tissue lipases and free fatty acid is discharged into the circulation where a proportion of it at any rate is carried back to the liver and once again contributes to the new synthesis of lipoproteins.

Now, the situation in diabetes is really quite complex. We have insulin acting to stimulate synthesis of lipoproteins from these precursors in the liver. We also have insulin stimulating the production of lipoprotein lipase and so the removal of lipoproteins from the circulation. Whether there is an elevation or a normal level of lipoproteins will then to some extent depend upon the balance of the effects of insulin in these two situations. And the complexity is further compounded by the fact that some of the actions of insulin may be antagonised in the diabetic, that's to say there is insulin resistance, whereas others of them may proceed unimpeded. A final action of insulin which may be of importance in this context is its effects in inhibiting the action of tissue lipase. This will have the consequence of increasing free fatty acid liberation from the depot and hence the concentration of free fatty acid approaching the liver, and to some extent governing the rate of lipoprotein synthesis. As I mentioned, it is the triglyceride rich lipoproteins which are usually elevated in the diabetic and, quite recently, it's been demonstrated that not only is the quantity of lipoprotein different in the diabetic but also perhaps the type: the constitution, the composition of the lipoprotein.

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<*Next diagram*> This slide shows the triglyceride concentration in three of the lipoprotein fractions – very low density lipoprotein, low density lipoprotein and high density lipoprotein – in diabetics, shown in black, and in non-diabetics, shown in the pale columns. What the slide shows is that in all three fractions, the proportionate

representation of triglyceride in each is higher in the diabetic than it is in the non-diabetic. And statistically significantly so in these two fractions <*indicates LDL and HDL*>

<Keen to camera>

So that we have a number of abnormalities in the circulation of the diabetic which in themselves are thought to favour the development of atherosclerotic lesion in the arterial wall. There are others, which I haven't mentioned – for example, the level of circulating insulin which may be raised in the presence of insulin resistance and even the elevated level of blood glucose itself. And Professor Woolf is going to describe to us one of the ways and others, perhaps, in which these changes in the circulating blood may influence the development of lesions in the arterial wall.

<Woolf to camera, then refers to diagram and narrates over it>

We are, of course, rather short of hard data on metabolic alterations in the vessel wall in diabetics but still there are a number of ways, one of which is shown in this diagram, in which the altered metabolic state in general may affect the arterial wall. When hyperglycaemia is present, we find an increased production of sorbitol and this is associated with increase in production of oxidised NADPH and reduced NADH. And the presence of this sugar within a tissue may, by virtue perhaps of osmotic changes, alter the permeability of that tissue. We know that this happens and is important in the production of cataract in the diabetic. We don't know yet what happens in the human arterial wall, but certainly in experimental situations, if we increase the blood glucose levels then we increase the amount of sorbitol which we can extract from the aortic wall of these animals.

<*Woolf to camera*> The changes in carbohydrate metabolism in diabetics may, of course, also affect the rate of production, perhaps the type of glycosaminoglycans or mucopolysaccharides in the vessel wall. And if there is a marked increase in the glycosaminoglycans, this may still further potentiate the entrapment of large plasma protein molecules, the lipoproteins and fibrinogen which we know are present in

increased amounts in atherosclerosis. An area of considerable potential interest is the question of metabolic changes in endothelial cells which up to now have been rather neglected. Dr David Slater, who works in Professor Crane's department in Sheffield, has developed an elegant technique for culturing endothelial cells from the aorta. And in cultures derived from the aortae of diabetics who've died, usually in ketosis, he has shown that the cells contain rather less acetyl-CoA enzyme carboxylase than do the endothelial cells of non-diabetics and that this is associated with an increase in triglyceride and an increase in non-esterified fatty acids.

Another area of considerable potential importance in the natural history of atherosclerosis in the diabetic is the question of plaque necrosis and whether metabolic alterations may influence this. Professor Arthur Harland and Dr Brooks have shown that tissue necrosis in general is influenced by the introduction into the tissues of certain minor sterols which they have been able to extract from certain necrotic atherosclerotic plaques. And it would be of the greatest interest to know whether these minor sterols occur with greater frequency and in greater concentration in the plaques of diabetics than they do in the plaques of their non-diabetic peers.

Lastly, we mustn't forget that arterial wall disease is only one, albeit perhaps the most important, component in clinical arterial disease and that we should look for possible functional changes in platelets and in the fibrinolysis system. On a group basis, the platelets in the diabetic tend to aggregate more rapidly when exposed to ADP than do those of non-diabetics. They are stickier than the platelets of non-diabetics and fibrinolysis is reduced in diabetics as opposed to non-diabetics. All these changes occur on a group basis and are not good individual predictors but they are there.

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<Jarrett to camera>

Prospective population studies have identified a number of so-called risk factors which, when looked at retrospectively, can be used to provide predictive statistics. Some of these appear to be independent to one another and these include the plasma lipids, and we've already heard about those in diabetics. They also include the level of blood pressure and the presence or absence of cigarette smoking.

What about diabetics and these two factors? Well, first of all, blood pressure. This is rather a complex topic in diabetics because there are certain specific features associated with the diabetic syndrome which can affect the level of blood pressure. One of these is renal disease and as we all know, renal disease is common amongst diabetics, and those with renal disease do tend to have elevated blood pressures. Secondly, diabetics are liable to develop neuropathy and those with significant neuropathy may develop lower blood pressures because of a postural hypotensive effect. Nevertheless, there does seem to be some evidence suggesting that the diabetics may have higher blood pressures than the controls. One strand of evidence comes from a study in the United States where employees of a commercial company were examined regularly. Some of them developed diabetes and it was shown that those who developed diabetes had significantly higher blood pressures prior to the diagnosis of the diabetes.

We have studied two populations in this country and in both of them we have found a correlation between the degree of glucose intolerance and the level of blood pressure, and this has also been found in another population in Finland. And if one segregates these people into diabetics and non-diabetics, then the diabetics have significantly higher blood pressures than the controls and this is at the onset of their diabetes. So, it may well be that blood pressure does contribute to the enhanced arterial disease of diabetics.

Now, cigarette smoking – unfortunately, we have very little data about this in diabetic populations. We ourselves have a little, and in our study in London we found no difference between the diabetics and non-diabetics in the percentage of current smokers or of non-smokers or of ex-smokers. There is some unpublished data from the United States, the Boston Collaborative Drug Programme in which, in fact, the

diabetics compared with controls, there were fewer smokers and more ex-smokers amongst the diabetics. So, it seems from the little evidence that we have that smoking is perhaps not an independent factor though, of course, we can't exclude the possibility that it may interact with other factors in the diabetic.

Now, thirdly, one can't discuss risk factors without mentioning obesity because, after all, in maturity-onset diabetics obesity does contribute to the aetiology of the condition. The studies which I mentioned earlier which have identified these risk factors seem to show that obesity per se is not an independent risk factor. It achieves its risk by being associated with other things like a raised blood pressure and raised plasma lipids and perhaps with glucose intolerance as well.

What about obesity in diabetic populations? Well, we do have a little evidence from the long-term study of therapy carried out by the University Group Diabetes Programme in the United States and the data from that is a little surprising because those diabetics who at the onset of the study were slightly overweight, in fact, had a better experience in terms of cardiovascular mortality than their lighter fellows. So, it may be that obesity, although contributing to the onset of diabetes, does not affect the arterial disease experienced by the diabetic.

<Keen to camera>

On the strength of this, I would like to state my own personal conviction that arterial disease in the diabetic is a preventable phenomenon. That's to say that it is not an inherent part of the diabetic syndrome. How should we set about trying to achieve this eradication of atherosclerosis in the diabetic? Well, the same question, I suppose, can be asked about the eradication of atherosclerosis in the general population, but so far as the diabetic is concerned, I think, there are some special points at which we should look. The first, perhaps, is our method of treatment. One of the more disturbing possibilities that we've been brought face to face with over these last few years is the possibility that the oral anti-diabetic agents themselves may contribute to sudden cardiovascular deaths in some of our diabetic patients who are receiving them. It must be said that there is evidence to the contrary and this whole

area is a very controversial one and I myself and many others are more concerned with the possibility that the nature of the diabetic diet, which we conventionally employ in the West, may itself have atherogenic potential. In terms of its composition, there is much to be said for the examination of the possibility of lowering the fat content and increasing the carbohydrate content and perhaps changing the nature of the fat in the diet. This really does focus much attention on the levels of lipids in the circulation in the diabetic, and I would like to suggest that we should perhaps be paying as much attention to plasma lipid levels in the diabetic as we traditionally have done to the blood glucose levels, and that the monitoring of plasma cholesterol and triglyceride and attempts at their correction by appropriate means should be as much part of the management of our diabetics as the maintenance of normal blood sugar levels.

At the same time, I think we should aim to correct those factors which we know in the general population to be related to an increased risk of atherosclerosis, that's to say elevation of blood pressure which might perhaps be rather more energetically treated, or our threshold of action might be rather lower in a diabetic with raised pressure than in a non-diabetic. I think we should exercise our influence in trying to stop our diabetic patients from smoking cigarettes and perhaps to try to induce them to take rather more physical exercise. If necessary, lipid lowering drugs should be employed in the therapeutic regimen in the management of the diabetic.

There are atherosclerosis-free, or virtually so, populations of diabetics in Japan, in Africa and elsewhere. I think on the strength of this, one can utter the hope that it is not impossible that we can hope to eradicate this source of misery, morbidity and mortality from our own Western diabetic populations.

<End credits>