

## **Understanding the link between high cholesterol and kidney disease**

It has been known for a very long time that people with chronic kidney disease (CKD) have a very much higher than normal incidence of cardiovascular disease, such as strokes and heart attacks. We've asked consultant nephrologist Dr Christopher Lawrence to explain just when the link between high cholesterol and renal disease was first discovered and how the conditions relate to one another.

### **What does research tell us about cardiovascular disease and CKD?**

One often quoted study from America showed the risk of dying of cardiovascular causes in patients receiving dialysis as strikingly higher compared to the 'healthy' or general population. The relative risk adjustment varied depending on age group but, for example, a middle-aged patient receiving dialysis is approximately 20 times more likely to die from cardiovascular causes than an age matched member of the general population.

In a population of patients who were not yet on dialysis but had advanced (CKD stage 4 and 5) kidney impairment, one study showed that in high risk patients the incidence of flow limiting coronary artery narrowing was 30%. This was in those who met at least one of the following three criteria: over 50 years of age; diabetic; or with symptoms or signs of heart disease.

It would seem then that the effect of high cholesterol on kidneys, or at least people with kidney problems is obvious, however it is not as straightforward as all that!

### **What's the role of statins in lowering cholesterol?**

In the general population, cholesterol lowering therapy with statins is thought to provide benefit in two ways. Firstly, conferring nearly immediate benefit by stabilising cholesterol plaques and making them less likely to rupture (resulting in blockage of the coronary artery). Secondly, by lowering cholesterol with time and therefore reducing the deposition of cholesterol plaques in the coronary arteries.

In the 1990s statins were shown to be effective at primary prevention, such as preventing heart attacks in people at risk of a heart attack but who had not yet had a heart attack. They also proved to be effective in secondary prevention, preventing further heart attacks in people who had already experienced one heart attack.

### **Are statins beneficial for CKD?**

It followed therefore that as people with kidney disease are more prone to cardiovascular events, such as stroke and heart attacks, and that cholesterol lowering drugs, like statins, prevent heart attacks (and strokes). This meant that people with kidney disease should take statins. Or did it?

In heart disease, as in many other things, it is rather more complicated for people with kidney disease than without.

Cholesterol causes atherosclerosis (fatty plaques in the blood vessels) but people with kidney disease also have accelerated arteriosclerosis (calcification of the arteries) as well as being more likely to have high blood pressure (due to salt and water overload, or the kidney disease itself) and a heart that pumps less well. It wasn't therefore obvious that cholesterol lowering drugs were of definite benefit to people with kidney disease.

Finally in 2011 the SHARP study was published showing that cholesterol lowering (using a combination of simvastatin and ezetimibe) did reduce the need for coronary revascularisation (angioplasties and bypass grafts); non-fatal heart attacks and ischaemic strokes. (The 85% of strokes that aren't bleeds)<sup>5</sup>.

The effect was bigger in patients with no history of vascular disease (surprisingly); diabetics; those aged over 50; non-smokers; those with a starting total cholesterol of more than 5.5 or an LDL more than 3; a body mass index of over 28; an eGFR of less than 60 ml/min but not yet on dialysis; and at least moderate albuminuria.

### **What are the risk factors for cardiovascular related CKD?**

Whilst there is statistically robust evidence from the SHARP study that cholesterol lowering can benefit many people with kidney disease preventing vascular events, it is worth remembering that age; being diabetic and being a current smoker are all more important risk factors than cholesterol for cardiovascular disease.

### **How does high cholesterol affect your kidneys?**

High cholesterol on its own does not directly affect the kidneys but it can affect the blood supply. Cholesterol plaque can clog the renal arteries and cut off blood flow to the kidneys, which can result in a loss of their function.

We've asked consultant nephrologist Dr Christopher Lawrence to explain how high cholesterol can put a patient at high kidney disease risk and whether any damage made to the kidneys can be reversed.

### **What kinds of kidney problems can high cholesterol lead to?**

The indirect effects of cardiovascular disease can lead to the heart working less well as a pump, providing the kidneys with insufficient blood, nutrients and oxygen resulting in kidney dysfunction.

The direct effects of cholesterol on the blood supply to the kidneys can result in what we term atherosclerotic renovascular disease (ARVD). This is a narrowing of the blood supply to the kidneys.

Atherosclerotic renovascular disease is more common in older, male, smokers. The condition can present with deteriorating kidney function with a 'bland urinary sediment.' In other words the urine does not normally contain blood and protein on the dipstick test.

Sometimes the condition is suspected when the kidney function deteriorates after certain blood pressure tablets are started. These are usually an angiotensin converting enzyme inhibitor, like ramipril, or angiotensin receptor blocker, like losartan.

### **Is this damage reversible?**

The damage caused to the kidneys by cardiovascular disease generally requires carefully

balancing the requirements of the heart and the kidneys. This is done through dietary salt restriction, superb control of diabetes and through a fine tuning of the relevant medicines used to improve the heart function.

Atherosclerotic renovascular disease can sometimes be treated with a balloon or a stent, very similar to how angina is treated. The process of atherosclerosis is usually considered to be a progressive condition. However, when a narrowing (like the one in the image above) occurs, it is possible, in carefully selected cases, to intervene by performing an angiogram to open up the blood supply, restore blood flow to the kidney. This hopefully reduces the requirement for blood pressure tablets and perhaps slow the deterioration in the kidney function.

The scientific evidence for intervening on renal artery narrowing is not particularly supportive. This does not mean that it is not helpful for some people, but it does mean that it will not be the right option for everyone.

### **How to manage high cholesterol with kidney disease**

In people with chronic kidney disease (CKD) heart disease is very common and it is therefore recommended that those with CKD should have their cholesterol tested every year.

We've asked consultant nephrologist Dr Christopher Lawrence to explain what risk factors increase the chance of developing high cholesterol and how these can be managed as a preventative for renal disease.

### **What advice would you give to someone with high cholesterol?**

In the setting of renal disease any advice is, by definition, not particularly well supported by evidence but is instead driven by practical approaches, experience and common sense. In these situations the advice I give patients is what I would follow myself if in the same situation. Before addressing high cholesterol I would make sure that I had addressed all of my other risk factors.

### **What are the risk factors?**

Smoking is particularly hazardous to vascular health amongst other recreational hazards. Diabetes must be brought under control. Excess weight should be addressed by following a low carbohydrate diet. Prioritisation of cholesterol over all other risk factors has led to a low-fat diet being advised in many countries around the world. One major problem with a low-fat diet is that they tend to be high in carbohydrates which results in excess weight gain, a preponderance to diabetes and consequently vascular complications!

### **After addressing risk factors, what else can I do?**

Once non-smoking, cured of diabetes (or prevented from becoming diabetic, or under excellent diabetic control), lean (or at least on the path to being lean) then I would consider my risk of cardiovascular disease from a personal perspective.

If I had no family history of vascular disease, mild kidney impairment, no albuminuria and no other risk factors for vascular disease, I would then assess my cholesterol. I would take into account my total cholesterol:HDL ratio. If my LDL cholesterol were over three and I had an adverse Total cholesterol:HDL ratio then I would consider taking a statin. It's important to be

aware that the 'numbers needed to treat' (that is the number of people in my position who would need to take a statin before one person benefitted) would be quite high.

Conversely, if I had multiple risk factors for vascular disease, had moderate to severe kidney impairment with moderate or worse albuminuria, then I might be tempted to take a statin no matter what my cholesterol reading was. I would certainly have a lower threshold for starting a statin and would consider treatment if my LDL cholesterol was more than 2 or if I had a poor Total cholesterol:HDL ratio.

### **Is aspirin beneficial for treating cardiovascular disease?**

The evidence for other preventative measures like aspirin are disproven for primary prevention in the general population. Aspirin can cause an equal amount of harm as good in people who have not had a heart attack. If, however, I had particularly strong risk factors for vascular disease then I might be tempted also to take an aspirin (75 (UK) or 81 (USA) mg daily), with of course a small dose of ranitidine (75mg daily, to protect my stomach lining from the effects of aspirin).

### **How long should I take statins for?**

Statin are not entirely without complications or side effects, although I feel the downsides of statins are somewhat overstated. As the benefits of taking statins accrue with time, it may be that there is an optimal age range during which to take them. I would be more permissive of a higher cholesterol level in elderly people as they are more prone to certain statin related side effects like memory loss and falls.

It is probably not advisable to stop taking statins suddenly once on them for a period of time, this is because of the risk of destabilising cholesterol plaques. However, if experiencing side effects, then it may be worth considering reducing the dose, or trying a different variety, rather than just stopping

*Do not hesitate to book an appointment with Dr Lawrence if you are concerned about your health.*

*Read more from Dr Lawrence on how high cholesterol affects the kidneys.*

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### References:

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<sup>3</sup> Pedersen TR for the Scandinavian Simvastatin Survival Study (4S) Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) Group. The Lancet 344(8934):1383-1389.

<sup>4</sup> Sacks FM et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. NEJM 335(14):1001-1009.

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