

## Vitamin B12 supplementation and Homocysteine

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**Norman Swan:** Now to that vitamin B12 story I promised you earlier. One risk factor for heart attacks, strokes and dementia is a substance in the blood called homocysteine. It's enormously controversial as you'll hear but in a recent editorial in the *Journal of the American Medical Association* (JAMA) -- David Spence, who's Professor of Neurology and Clinical Pharmacology at the University of Western Ontario in Canada, argued that there's more to homocysteine lowering than many doctors think -- but it's how you do it.

**David Spence:** Homocysteine is very clearly a risk factor. In the animal studies it's causal of atherosclerosis. The big discrepancy has been between the observational studies, the experimental research in animals and the failure of the clinical trials to show any benefit of vitamin therapy to lower levels of homocysteine.

**Norman Swan:** And the fact is that the vitamins such as folate B6 and B12 do lower homocysteine, but the lowering doesn't seem to flow through at least to coronary heart disease and dementia.

**David Spence:** Well actually no, there is pretty good evidence from Holland and the UK that vitamin therapy does improve dementia. The VITACOG studies by Helga Refsum and David Smith at Oxford do show improvements in dementia and a reduction of brain shrinkage on MRI, but the studies did not show what everybody expected which was a reduction of myocardial infarction and in fact it's much more complicated than everybody thought. So there is a trial from McMaster University in Canada called the HOPE-2 Study. That was the first study to use a decent dose of vitamin B12. They used a milligram of B12, that's 1,000 micrograms a day, which is the dose that is needed for elderly people with relatively poor absorption of B12. In the HOPE-2 Study the 1,000 micrograms of B12 along with folic acid and B6 significantly reduced strokes by 23%. But the authors, being cardiologists and therefore innocent of the circulation of the brain, they literally said 'well we couldn't think of a biological difference between heart attacks and strokes, so we concluded that this was a chance finding'.

**Norman Swan:** And the reason they said that was that the claim is that strokes occur because you get a clot, atherosclerosis in the artery in your neck, your carotid artery, which then breaks off and lodges in the brain which is analogous to what happens in a heart artery to get a heart attack or a myocardial infarction.

**David Spence:** Yes but it's different. Virtually all heart attacks are caused by an occlusion of a coronary artery. A plaque ruptures, the artery occludes, a clot forms that causes a heart attack. Most strokes on the other hand are caused by emboli to the brain, so chunks of plaque or clots break off from the heart or the arteries and they get thrown up into the brain arteries by the circulation of the blood.

And a high level of homocysteine, which is a clotting factor, more than quadruples the risk of stroke in patients who have a heart rhythm the surgeons called atrial fibrillation, because homocysteine is a clotting factor, so heart attacks and strokes are not the same and it shouldn't have been a surprise really that strokes were prevented when heart attacks weren't. What's transpired in the last several years is the juxtaposition of two studies that we did that have made it apparent that things were much more complicated than we thought.

So in 2005 we published a paper about a sub-group analysis of the VISP trial, vitamin intervention for stroke prevention trial.

**Norman Swan:** And just to explain: When you talk about sub-group analysis some epidemiologists raise the sign of the cross when people say sub-group analysis. This means that you've taken a group of people within the study with particular characteristics and said this is what happens to them. It might not happen to everybody else but this is what happens to them and the critics say you should never do sub-group analysis, in fact we've had them on the *Health Report* because you didn't design it for sub-groups to begin with and you've got no idea whether it's a real finding or not.

**David Spence:** Yeah, that's a very popular approach. The recent commentary that we wrote in the *JAMA* points out that sub-group analysis can be very informative.

**Norman Swan:** It gets pretty detailed but it's worth listening because given the huge volume of vitamin supplements that Australians consume each year, David Spence's work shows how the effects of vitamins differ hugely depending on our individual circumstances.

For example the VISP trial to prevent stroke failed to show an effect of B vitamins. David Spence believes that's because folate was added to the flour supply around that time which meant people weren't folic acid deficient. And the researchers also made the mistake of giving people who were B12 deficient vitamin B12 no matter whether they were in the placebo or treatment group.

**David Spence:** So we said let's look at what happens if we exclude these people who got the B12 injections and while we're at it we'll also exclude the people who had kidney failure. The reason we did that wasn't for what turned out to be probably the right reasons, we excluded them because we thought they would not respond to vitamin therapy. So in this sub-group analysis we had about two thirds of the patients from the VISP trial and in that group we showed a very significant reduction of strokes, heart attacks and death, there was a 34% reduction in strokes, heart attacks and death.

**Norman Swan:** So this is between those who had high vitamin B12 versus those who had low?

**David Spence:** Yes, that study suggested that vitamin B12 is probably pretty important in all this and we never realised that excluding the renal failure was the key to the benefits. So we published last year in *JAMA* a study in patients with diabetic kidney problems and we used a higher dose of B12 than we used in the VISP and we randomised these patients who had diabetic kidney disease to high dose vitamins versus placebo and when we got the results I was completely gobsmacked.

I thought we must have reversed the randomisation code because the high dose vitamins actually made things worse. The kidney function declined more quickly and they were twice as likely to have cardiovascular events, so death, myocardial infarctions, stroke, progression to dialysis and amputation, those were all combined. This meant that in patients with kidney failure the vitamins made things worse, so on the one hand in the VISP sub-group analysis where we excluded patients with kidney failure vitamins it made things better, but in patients with kidney failure vitamins made things worse.

**Norman Swan:** I apologise if this is making you go cross eyed but it's really important stuff. You see to go back to the beginning of this story it's still about homocysteine levels and the risk of blood clots and artery damage. It's just that in a country like Canada or Australia where we have folic acid in flour, vitamin B12 becomes the main way to bring homocysteine down. And if David Spence is right the kind of vitamin B12 you take is critical.

**David Spence:** But it's not just quite that simple. It's also another factor called ADMA, asymmetric dimethylarginine, and it depends on which B vitamin. The B vitamin that's harmful is high dose folic acid which increases the blood levels of this antagonist of the good stuff called nitric oxide which is increased in people who have high doses of folic acid and poor kidney function. And on the other hand the vitamin B12 that was used in all these trials was the usual form which is called cyanocobalamin, which has cyanide in it and it turns out that some work in Japan had shown about ten years ago that if you give cyanocobalamin to patients with kidney failure they get a build up of cyanide and cyanide consumes a factor that is good for the arteries called hydrogen sulphide. And researchers showed that if you give a different form of B12 called methylcobalamin, not only does it lower the levels of homocysteine but it also lowers the levels of asymmetric dimethylarginine, ADMA. You probably need to be using methylcobalamin in people with impaired kidney function, whereas in the VISP sub-group analysis we showed that ordinary B12 was beneficial when we excluded people with renal failure.

**Norman Swan:** So somebody is listening to us now to a very complicated story and a very important story, but a complicated story, how does that translate to what general practitioners, what consumers should be doing if they think well, should I be having my homocysteine level measured, should I be having my B12, what in fact is the right dose of vitamin B12, because you in your papers have argued that in fact what people are recommended as supplementation is probably really not adequate. Can you summarise what the consumer's story is here?

**David Spence:** Yes, so vitamin B12 deficiency is very common and missed much of the time.

**Norman Swan:** Why is it so common because when I was at medical school we were told the cause of low vitamin B12 is a condition called pernicious anaemia which is like an auto immune disease attacking the stomach and the stomach fails to absorb it from the diet.

**David Spence:** Yes that's an intrinsic factor and that's only one of the six ways that B12 can go wrong. B12 absorption is extraordinarily complex, to absorb B12 you need haptocorrin from saliva, you need stomach acid, you need intrinsic factor, you need pancreatic third factor...

**Norman Swan:** And what you're describing here are chemicals that are excreted by different parts of the intestinal tract, the stomach, the mouth and the pancreas which help chemically to absorb vitamin B12 from the bowel.

**David Spence:** Yes, there are about six ways for B12 absorption to go wrong and it turns out that when you measure serum B12 it does not do a good job of detecting the B12 deficiency, because only something between 6% and 20% of serum B12 is active. So in order to know if someone has metabolic B12 deficiency you have to measure either methylmalonic acid, which is hard to get done, or in people who are folate deplete you can measure homocysteine and it turns out when you do that the serum B12 below, either methylmalonic acid or homocysteine which begins to rise is 400 picomoles per litre and the normal range is from 160 to 600. So almost two thirds of the people in that normal range could have functional B12 deficiency and in order to know whether they do or don't you have to measure either their methylmalonic acid or homocysteine. And when you do that, metabolic B12 deficiency in my patients with vascular disease is present in 12% of those below age 50 and 13% of those between age 50 and 71 and 30% of patients above age 71. So it's very, very common and it's really important because B12 deficiency not only raises the levels of homocysteine, increases clotting of the blood, increases deep vein thrombosis, quadruples the risk of stroke and atrial fibrillation but B12 deficiency also causes damage to the peripheral nerves, the spinal cord and dementia. And so that's why Helga Refsum and David Smith at Oxford have shown that even in the normal range you can have shrinkage of the brain and dementia with B12 deficiency with normal serum B12 levels.

**Norman Swan:** So what's the practical, I mean this is very complicated and time consuming for a busy general practitioner to take on, is it such that you would almost put it in the water supply. I mean what's the story here?

**David Spence:** Well not cyanocobalamin.

**Norman Swan:** But you know what I'm saying here, what's the public health message here does everybody get it?

**David Spence:** Well the public health message is that vitamin B12 deficiency is way commoner than everybody thinks and in order to know if someone has B12 deficiency you can't just measure a serum B12. In Europe they measure something called holotranscobalamin, not readily available here and probably not in Australia. So if you have somebody who has a borderline B12 level you've got to measure the homocysteine level to know whether they have metabolic B12 deficiency.

**Norman Swan:** So that's after they've been fully replaced with folate, otherwise you don't know where you are?

**David Spence:** Yeah, so over here that's not an issue because we have folic acid fortification of the grain supply so we don't have folate deficiency anymore.

**Norman Swan:** Then the question becomes how -- you've already discussed the two forms of vitamin B12, but if you've got a problem absorbing it, I mean if you've got pernicious anaemia and you've lost this intrinsic factor as they call it from the stomach they say give vitamin B12 injections, don't swallow it because you're not going to absorb it.

**David Spence:** Most people don't need injections except maybe at the beginning so what's going on is that you need vitamin B12 for DNA synthesis, so the cells that get in trouble when you have a shortage of B12 are the cells that turn over quickly so we get anaemia because red cells turn over in 100 days, you get low platelet counts because platelets turn over in 10 days. And it turns out that the intestinal villi turn over in three days, so one of the things that happens in deficiency of either folate or B12 is that the intestinal villi shrivel and then you lose a huge amount of the surface area of the intestine and you become unable to absorb B12.

**Norman Swan:** It's a vicious cycle

**David Spence:** Yes, so some people need injections of B12 in the beginning to restore the intestinal villi and then they can absorb oral B12. And the doses that are used are way bigger than the recommended daily intake for people with normal absorption so you can absorb enough B12 from oral

B12 by mass transfer without the intrinsic factor but that's when you're getting up to these doses of 1,000 micrograms a day.

**Norman Swan:** Somebody is listening to this and they are 60 years old with no heart disease, feeling fine, good diet, do they go along to the GP and ask for a vitamin B12 level?

**David Spence:** Yes they should also have a TSH level to see if they have hypo-thyroidism.

**Norman Swan:** And if a GP is listening to this and has got somebody in front of them with the beginnings of heart disease you would argue they need a vitamin B12 level because that's the high risk group for vitamin B12 deficiency.

**David Spence:** Yeah, and homocysteine quadruples the risk of stroke and atrial fibrillation.

**Norman Swan:** And homocysteine is probably the best way of measuring it really in practical terms. How do you know whether or not they need an injection?

**David Spence:** What I usually go by is if the B12 level is very low, you know below 150 or something like that then they are probably going to need injections. You can sort it out by giving them oral vitamin B12 repeating the blood level in a month and seeing if it's come up above 400 and if it hasn't they might need injections.

**Norman Swan:** And putting your hand on your heart you feel the randomised control trial evidence is strong enough to recommend this course of action on a mass scale?

**David Spence:** Well the HOPE-2 trial and the VISP sub-group analysis yeah, I think so.

**Norman Swan:** There's a statistic in epidemiology called population attributable risk, and this is really saying look, if you take everybody who's had a stroke, or everybody who gets a stroke in a year, what percentage of those strokes could be blamed on low B12 and high homocysteine?

**David Spence:** Yes, so it's all related to age so if you take the attributable risk of stroke from atrial fibrillation, which is tightly connected to homocysteine I think, at age 50 only one and a half percent of strokes are due to atrial fibrillation.

**Norman Swan:** This is where the top two chambers of the heart kind of quiver, don't beat properly and you often get a little pouch growing off the left atrium which collects a clot which can then break off and lodge in the brain.

**David Spence:** Yeah and that causes one and a half percent of strokes at age 50, but it causes almost a quarter of strokes at age 80 and the homocysteine is a big factor in the older people. So I published in the *Lancet* a couple of years ago a nice graph showing that homocysteine levels above 14 which are reckoned to be a clotting factor are only present in about 10% of patients at age 30, but it's 40% of my patients at age 80. So I think that at the older age groups homocysteine accounts for a substantial proportion of strokes.

**Norman Swan:** Inevitably people will say 'oh, I don't like taking supplements can't I do this from my diet, can't I get the vitamin B12 from my diet'?

**David Spence:** No, vitamin B12 comes from meat and meat is bad for you.

**Norman Swan:** And you've got to eat too much of it?

**David Spence:** Yes.

**Norman Swan:** David Spence is Professor of Neurology at Clinical Pharmacology at the University of Western Ontario in Canada.

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