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Niacin and Risk of Cardiovascular Events: Deciphering the Paradox
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Guest: Dr. Rav Sodi from the Department of Clinical Biochemistry, Mid & South Essex NHS Trust in the United Kingdom.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. The "phrase too much of a good thing" can describe many things we ingest on a regular basis, but it may surprise you to hear that a B vitamin may soon be added to that list. Vitamin B3, or niacin, is a cofactor in many of the biological reactions required for energy production and a niacin deficiency results in pellagra, a fatal disease when left untreated. These observations led to food fortification with niacin in the 1930s, essentially eliminating pellagra in countries that implemented fortification programs.

In addition, niacin has been shown to reduce LDL, or bad cholesterol, while raising HDL, or good cholesterol, but despite its association with these desirable changes, niacin does not reduce the incidence of major adverse cardiovascular events. Known as the "niacin paradox," this discrepancy has baffled scientists for years. Other lipid-lowering medications have clear cardiovascular benefit, but niacin does not. So, why not? Were the early studies associating niacin with reductions in LDL incorrect? Or is niacin more complicated than originally understood?

A new perspective article, appearing in the November 2024 issue of *Clinical Chemistry,* summarizes a recent publication finding that niacin increases cardiovascular risk, raising questions about whether niacin food fortification should continue. In this podcast, we're excited to welcome the article's author. Dr. Rav Sodi is a Consultant Clinical Biochemist in the Department of Clinical Biochemistry, Mid and South Essex NHS Trust. His current research interests are home self-testing, particularly with regard to monitoring cancer, artificial intelligence, and genomic medicine.

So, doctor, let's get to the basics. What is the role of niacin in humans? What diseases are associated with niacin deficiency or excess?

Rav Sodi: So Bob, thanks for having me today. So, niacin, or nicotinic acid or vitamin B3, is a lesser-known B vitamin compared to say, for example, vitamin B12, or folate which is vitamin B9, or thiamine which is B1, or riboflavin which is B2. But yet, niacin has important roles in humans and animals. It is a

precursor of that ubiquitous molecule known as nicotinamide adenine dinucleotide, which all students know as NAD, and NAD is a coenzyme or a core substrate for many biological reactions in the body and is required for NAD metabolism. So it's a very, very important vitamin in humans.

What diseases are associated with niacin deficiency? So, severe deficiency of niacin causes the disease pellagra, which is derived from a language spoken in ancient Italy, I believe, and it means holly-like, from the Christmas tree plant. So you get a holly-like skin because those affected present with the dermatitis involving hyperpigmentation and thickening of the skin in sun-exposed areas, usually around the neck, and this has been likened to a necklace made of holly leaves or pearls. So other symptoms of pellagra include diarrhea, dementia, or delirium. So medical students tend to say the 3D's of pellagra.

Now, this disease pellagra was endemic with very, very high mortality rates until about 1950s, and in many parts of the world and the US, where corn or maize was the staple diet because there is no biologically available niacin in corn. So if that was your main meal then you would inevitably end up with niacin deficiency. However, in the late 50s or early 60s, the mandatory fortification of flour and cereals in many parts of the world, including the US, has almost eliminated this disease. And the other thing to mention is the niacin is also obtained from protein in the diet and specifically tryptophan, but there is a rare autosomal recessive condition known as Hartnup disease, in which several amino acids, including tryptophan, are poorly absorbed from the intestine and this also results in niacin deficiency. One of the rare condition that must be mentioned is the carcinoid syndrome, which is caused by neuroendocrine tumors, usually of the gut, and these secrete vast amounts of serotonin, which is derived from tryptophan. So in this condition, tryptophan is diverted away from niacin production, and so you have function deficiency.

Now, what about excess, Bob? There's very few conditions associated with the excess, but we do know that those who take niacin in vast concentrations present with skin flushing and liver disease, but otherwise, there is no major known adverse effects of niacin.

Bob Barrett: So, you can have a little bit of too much of a good thing there?

Rav Sodi: Absolutely, yes. Too much of a good thing is bad in life as it is in medicine and science.

Bob Barrett: So niacin has been used as a drug to treat lipid disorders mixed results in numerous studies on that. What's the latest guidance on the use of niacin?

Rav Sodi: Yes. So Bob, that's a bigger question, actually. Niacin at pharmacological doses was among the first lipid-lowering drugs used in world in the treatment of lipid disorders. Usually high cholesterol, high triglycerides. Niacin is well-known to significantly reduce low-density lipoprotein cholesterol that's so-called "bad" cholesterol. It also reduces triglycerides, and also increases the high-density lipoprotein, the HDL cholesterol. The so-called "good" cholesterol. However, somewhat paradoxically, Bob, many studies including one Cochrane meta-analysis, concluded that these changes do not result in reductions in major cardiovascular events defined as myocardial infarction or heart attacks, or strokes. And Bob, rather interesting as well, another meta-analysis showed that niacin actually increased the risk for all-cause mortality. Now this reduction in LDL cholesterol and triglycerides without corresponding decreases in major cardiovascular events, such as myocardial infarction or stroke, has been dubbed the "niacin paradox" and I think that this is the one thing which for many, many years, many investigators have found rather confusing, but I think, as it stands now, the niacin is not considered a first line drug such as statins and so, I think the jury is out whether its time has come and gone.

Bob Barrett: I want to go back to something you touched on a little. There's been great interest in the role of niacin in cardiovascular events. There was a recent landmark study that demonstrated that niacin is actually associated with increased risk of cardiovascular events. Could you please elaborate a bit on this?

Rav Sodi: Yes, definitely. So we know that despite major advances in the treatment of cardiovascular diseases, including the drug statin, the disease remains rather widespread and rampant in the world. Now, this suggests to me that there is substantial residual cardiovascular risk, and there must be other factors other than lipids that remain to be discovered and targeted. The landmark study you mentioned was undertaken by the Stanley Hazen's group at the Cleveland Clinic in Ohio and published in *Nature Medicine* earlier this year, and it identified two such factors that might partly explain the niacin paradox. So very briefly Bob, in their study, plasma samples were collected from a high-risk cohort of cardiac patients and they were analyzed using a technique we call metabolomics to identify candidate metabolites associated with incident, major cardiovascular events, independent of the traditional risk factors such as lipids.

Now, amazingly, they discovered that the terminal metabolites of niacin, Bob, who would have thought that a little-known vitamin B3 was carrying such loaded metabolites? And so, these metabolites, they've got quite

long names. I apologize--I have to spell them out initially. So two metabolites are methyl-2-pyridone-5-carboxamide, I'm sure I said that wrong, (2PY), and methyl-4-pyridone-3-carboxamide (4PY). They found these two metabolites of niacin were associated with cardiovascular disease risk, and so what they did was, the researchers then measured these two metabolites in two validation cohorts, one in the US and one in Europe. Of all the 3,000 individuals and their findings are quite striking. What they found was that those with 2PY or 4PY concentrations in the top 25% had up to double -- that's double the risk of major cardiovascular events over a three-year period compared to those in the bottom 25%, and this was after adjusting for the traditional established risk factors such as lipids.

They then went on to show that 4PY specifically, which is one of the metabolites of niacin, induced the expression of a very well-known molecule known as vascular adhesion molecule 1 or VCAM-1. This molecule is known to be involved in the promotion of vascular inflammation and hence atherosclerosis. Now we all know atherosclerosis is an inflammatory disease, and so taken together, the study showed that the terminal metabolites of niacin, i.e., 4PY and 2PY, promoted vascular inflammation and was associated with cardiovascular disease risk.

Bob Barrett: This is all pretty fascinating. So finally, if confirmed in further studies, what would the implications of these results be?

Rav Sodi: Yes. So, Bob, to put these new findings in perspective, the discovery that excess niacin is metabolized to 2PY and 4PY, leading to increased risk of major cardiovascular events, is very important. But first, we must state the limitations. All studies have limitations and in this study, the individuals were recruited from a highly selected cohort of high-risk patients, and so whether these findings are translatable to lower-risk cohorts or to other ethnic groups not examined in the study, remains to be established, and also it's important to remember that associations do not imply causality as there may be other confounding factors not considered in the study. But even so, Bob, these findings have major clinical ramifications affecting clinical practice or national health policies. So let me spell them out to you.

First and foremost, the mandatory fortification foods with niacin needs to be reconsidered, as niacin is almost ubiquitous in modern diets, and many widely available foods such as peanuts, have plentiful of niacin in them. I think it is questionable whether fortification is necessary in the modern era. Secondly, I think it is high time that there is scrutiny and regulation of the health and supplements industry. We know that the amounts of certain vitamins in some products is supraphysiological and given the finding from the study

that those with high niacin metabolites and higher risk of incident major cardiovascular events, I think the implication is quite alarming and I think it is time governments around the world looked at the supplements and health food industries, and started, I guess regulating what they're giving or selling to individuals. And then, thirdly, I think the continued residual cardiovascular risk in an era when we've got potent lipid-lowering therapies, suggests that there must be other risk factors that should be targeted, and this study by the Hazen group should galvanized efforts for us to continue searching for these molecules. I think finally the time has come to conclude that, despite its lipid-lowering ability, a role for niacin as a dyslipidemic drug has come and gone.

So as you say, Bob, in conclusion, further work is definitely needed to understand the role of niacin and its metabolites in the induction and developing of atherosclerosis. But as cardiovascular disease remains a major health burden, our search for other unknown factors must continue.

Bob Barrett: That was Dr. Rav Sodi from the Mid and South Essex NHS Trust, Essex, UK. He wrote a perspective article describing the paradoxical role of niacin in cardiovascular disease in the November 2024 issue of *Clinical Chemistry*, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.