B3 in the crosshairs—should you worry?

This past week we were regaled with headlines like:

- **High levels of niacin may increase heart risk**—*NBC News*
- **Too much niacin may be bad for the heart**—*U.S. News and World Reports*
- **Excess vitamin B3 linked to increased risk of heart disease**—*WebMD*

I must grudgingly extend my admiration to the folks at Cleveland Clinic for their awesome PR acumen! Biased media is notoriously willing to uncritically broadcast press releases about research that bashes supplements.

The authors of the study in question go so far as to suggest that we may have to rethink even the minimal amounts of B3 that we use to fortify grains—typically found in flour products and cereals.

If valid, this study might cause concern for consumers, like me, who consume multis, B complex supplements, and NAD boosters.

Though stories like these hit me like a gut punch, it’s worthwhile to put aside knee-jerk skepticism and calmly investigate the claims to determine what the real-world consequences might be.

High-dose B3—including niacin, niacinamide, nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN)—are *supra-physiologic pharmaceutical* applications of a vitamin normally found in small amounts in foods.

For example, steak provides just 4 to 6 mg of niacin per 100 grams. So even a hearty 12 oz. steak portion would furnish only about 15 to 20 mg of niacin; The recommended dietary allowance (RDA) of niacin for adult males is 16 mg per day and 14 mg per day for adult women who aren't pregnant.

If you don't get enough B3, you can develop pellagra, whose incidence in developed countries has virtually vanished with food fortification. The term "redneck" originated because of the characteristic collar rash that developed in poor white Southern farmers who subsisted on diets consisting largely of unfortified corn grits with minimal animal protein—their predilection for moonshine didn't help since alcoholism depletes B3. Pellagra also causes dementia.

The use-case for high-dose niacin is precisely for cardiovascular prevention: 1 to 3 grams daily of niacin reliably lowers total cholesterol, slashes "bad" LDL cholesterol and triglycerides, while helpfully raising "good" HDL.

Hearken back to the 80s when Robert Kowalski wrote a best-seller called "The 8-Week Cholesterol Cure". The book sold millions of copies until its popularity was dimmed by lawsuits from readers who developed liver problems, a known side effect of unsupervised use of high-dose niacin.

Studies on the efficacy of high-dose niacin for heart disease prevention, curiously, show diminishing efficacy, depending on when they were published:

1980s: Benefits
1990s: Equivocal effects
2000s: Neutral or harmful

Why should that be? It has to do with the adoption and ubiquity of statin drugs. Early studies were performed on drug-naive patients not yet prescribed statins. When statins became standard-of-care in the 90s, it was deemed *unethical* to deny at-risk patients the vaunted protection of statins, so studies looked only at the add-on benefits of niacin in patients whose cholesterol was already lowered by standard cholesterol drugs.

Subsequent studies sponsored by pharmaceutical companies teaming niacin with or without a drug designed to reduce niacin flush were a bust; the AIM-HIGH trial concluded:

"Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels."

It's kind of like a study designed to determine whether suspenders would augment the ability of people already wearing a belt to hold their pants up!

In 2012, a niacin/laropiprant combo drug designed to minimize niacin flushes called Tredaptive was abandoned by Merck because it didn't help and caused more side effects than statins alone.

Another drawback of high-dose niacin is that it can cause blood sugar to soar by as

much as 30%—augmenting the deleterious impacts of high insulin and glucose in the high percentage of heart patients with metabolic syndrome or diabetes.

Thus, niacin as a way to reduce cardiovascular risk has fallen by the wayside. I haven't used it or recommended it to lower cholesterol since the 90s. Now, with the Cleveland Clinic paper, comes research suggesting B3 is actually *bad* for the heart, even in modest amounts.

Without getting into the weeds of this rather technical study, what it established is that certain B3 metabolites—byproducts of normal breakdown of dietary B3—have pro-inflammatory effects on the arterial wall.

They also demonstrated that individuals with higher levels of these metabolites have a higher incidence of MACEs—major cardiovascular events.

Hence, there's *circumstantial evidence* that B3 accelerates cardiovascular risk.

What they *did not* establish is that people who take B3 supplements are at increased risk for heart problems. *The study did not include supplement takers.*

The people who had heightened risk from the B3 metabolites already had established cardiovascular risk, suggesting that the metabolites might not have been the *proximate cause* of their risk, but *simply a marker* of exaggerated susceptibility (i.e. "correlation is not causation").

It's even possible—and credit our resident nutritionist Leyla Muedin for this insight—that the increased MACEs thought to be attributable to higher dietary intake of B3 in this study might simply be due to excess consumption of B vitamin-fortified flour products (breads, waffles and pancakes, pastries, and pasta) and breakfast cereals—*their delivery of high glycemic index carbohydrates, acknowledged contributors to cardiovascular risk!*

The study doesn't make a conclusive case for me because we know that heart disease is not a matter of a single novel, or even a few, risk factor(s), but a concatenation of myriad influences—cholesterol, homocysteine, lp(a), obesity, glucose, insulin, C-reactive protein, apolipoprotein B, genetic variants, etc. and probably a whole lot of things that we haven't even yet discovered.

Moreover, previous research contradicts the B3/arterial inflammation hypothesis: "Niacin Suppresses Progression of Atherosclerosis by Inhibiting Vascular Inflammation and Apoptosis of Vascular Smooth Muscle Cells": *"In sum we demonstrated that niacin alleviates atherosclerosis through restraining the expression of adhesion molecules and inflammatory cytokines secretion in serum."*

Additionally, niacin has been found to reduce lp(a), a potent accelerator of cardiovascular risk: *"there has [sic] been cases reported in the literature with 60-80% reduction in Lp(a) levels by niacin alone."*

It's worthwhile to remember that Stanley Hazen, the lead author of the Cleveland Clinic study, has tried this before; Hazen is also the progenitor of another theory that indicts dietary and supplemental nutrients as risky for cardiovascular health—choline and carnitine. Around 10 years ago, he promulgated the theory that trimethylamine oxidase (TMAO), a gut-derived metabolite of choline and carnitine, is a novel metric for assessment of heart disease propensity. I wrote a skeptical article about TMAO in 2013—"Carnitine in the crosshairs: A fishy tale?"

Again, that didn't really make sense. Consumption of the major sources of

carnitine—red meat—and choline—fish, soybeans, and eggs—have mostly been exonerated as contributors to atherosclerotic disease; in fact, some may confer protection.

It's been disclosed that Dr. Hazen has profited from patents on blood tests used to detect TMAO as a heart disease risk factor, for which I don't begrudge him. Nevertheless, after 15 years TMAO hasn't really caught on, because of its unreliability. It seems TMAO has less to do with your diet and supplements than the state of your microbiome. It's even been proposed that the best way to lower TMAO is not via restricting intake of choline and carnitine, but by administering antibiotics!

The latest verdict on TMAO comes from a recent review that found *no causal link* in healthy individuals between TMAO and atherosclerosis: *"This showed TMAO is not the bad guy of heart attacks and stroke that we'd previously thought."* On the other hand, folks with *established heart disease* might have cause to worry about TMAO; higher levels contributed to "plaque instability".

So might B3 behave similarly—inconsequential for healthy people, but worthy of caution in people at high risk for cardiovascular events? We simply don't know without additional studies.

Other additional questions:

- Is the "toxic" biochemical pathway described in the Hazen study universal, or is it the consequence of certain genetic variants, or even dependent on the composition of the microbiome?
- Are there ways to mitigate the alleged adverse effects of high-dose B3 by teaming it with other supplements?
- Do the supposed harms of niacin extend to other forms of B3 like niacinamide, nicotinamide riboside, or nicotinamide mononucleotide? That would be surprising because proof-of-concept studies are underway to demonstrate the *benefits* of NR and NMN for heart disease and strokes, and they have been generally found to be *anti-inflammatory.*

For the millions who take high-dose niacinamide for its proven preventive effects in skin cancer, niacin for osteoarthritis or NAD supplements for cognitive and anti-aging purposes, these questions matter.

I, for one, am not ready to jettison my use of B-vitamin containing supplements and NAD-supporting nutrients on the sketchy basis of a single study, no matter how much it's been uncritically amplified by the media. But, as always, while keeping my powder dry, I'm open to additional research that will enhance our understanding of the risks and benefits of B3.