September 2012 Issue | William Harris, PhD Health Diagnostic Laboratory, Inc.

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Welcome to *Functional Medicine Update* for September 2012. Fish oils, omega-3 fatty acids. What a topic of discussion—literally thousands of articles have been published over the last 25 years since we first started hearing about the role that omega-3 fats have in cardioprotection and other immunological activities. We're very fortunate this month to have truly one of the renowned investigators in the omega-3 fatty acid/cardiovascular lipid area. And he, from his own experience, will help us to understand better both the history and where we are now, and how this relates to cardiovascular risk factors and their modification in the reduction of the burden of cardiovascular disease. Let's turn to our extraordinary authority for this focus on essential fatty acids.

INTERVIEW TRANSCRIPT

Researcher of the Month

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Here we are once again at the section of Functional Medicine Update that you and I and all of our listeners, I think, are most excited about. It's really the substance upon which we wrap each issue of Functional Medicine Update: our clinician or researcher of the month section. We're so privileged to have as our clinician/researcher this month an individual who I have gotten to know over the last several years who is really in the catbird seat in the area of nutritional therapeutics, this interface between pharmaceuticals and nutritionals and what's emerging in cardiovascular disease, lipidology, and the whole nature of risk. Bill Harris (William S. Harris).

Bill is a graduate in chemistry and went on and got his PhD at the University of Minnesota in nutritional biochemistry. He has been a Fellow in clinical nutrition at the Department of Medicine at Oregon Health Sciences, where we share a kinship; that was one of my early engagements, too, in the 60s. He is a member of the American Board of Nutrition. He is presently involved in a variety of different things: the Department of Internal Medicine at the Sanford School of Medicine at the University of South Dakota, where he is a research professor, and also he is working in the analytical area at Health Diagnostics Laboratory as a senior scientist. So he brings quite a bit of background both in the…I would call it the pure

science, looking at this relationship of omega-3 fatty acids, and also in the applied sciences as it relates to assessment, diagnosis, and how that relates to clinical medicine.

Bill, it's a tremendous pleasure to have you as a guest authority on Functional Medicine Update. Let's start with the question I ask virtually everyone first and that is: How did your path lead you into being one of the experts in omega-3 fatty acids?

Early Work Studying the Effects of Salmon Oil

BH: Jeff, that's a great question, and thank you for having me on the show, here. I really appreciate it. My path was certainly not planned. Hardly anybody's is, it seems. I did my first work in omega-3 as a post-doctoral fellow in the laboratory of Dr. William Connor at Oregon, as you mentioned. Dr. Connor's first assignment to me back in 1978 was to study the effects or to find out what the effects of salmon oil are on cholesterol levels in humans. Dr. Connor had a long tradition of studying the different kinds of dietary fats and their effects on blood cholesterol levels. Fish oils were kind of an odd duck. Fish oils were--like vegetable oils--liquid at room temperature, and we knew liquid oils (vegetable oils) lowered cholesterol. But on the other hand, fish oils are also from an animal, and animal fats had been known to raise cholesterol, although they typically are solid at room temperature because of saturated fats. Fish oils are somewhere in the middle. They were liquid animal fats, and Dr. Connor was interested in what happened to cholesterol levels. So that was my assignment, and we did a metabolic ward study feeding up to about a half a cup of salmon oil every day to a variety of paid volunteers (as you can imagine). That got us started. We really discovered the effects of omega-3 on triglyceride levels in that study. Cholesterol was not a particularly interesting outcome, but the triglycerides—and then platelet function—was improved, interestingly, as well.[1] That kind of got us beginning down the omega-3 road.

Dyerberg and Bang: Observations on the Diet of Greenland Eskimos

JB: I think that's a really important chapter in history, quite honestly. Bill Connor was, believe it or not, kind of a guide to me as well. He was kind of in his start at Oregon Health Sciences when I was there in the late 60s. He, I think, really pioneered so much of what we now have taken on as some of the tenets of the lipid hypothesis. On Functional Medicine Update we had the very high privilege of interviewing Dr. Dyerberg, who—I guess arguably—would be considered one of the first people to make the observations with Greenland Eskimos that this high seal and whale fat diet that they were consuming was leading to lowered incidence of vascular disease, which was entirely in opposition with the prevalent hypothesis or belief at the time that fat caused heart disease, and this concept that you could eat 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} or more of your calories as fat and have low incidence of heart disease was totally antithetical to the prevalent hypothesis at the time.[2] So you put the Dyerberg work together with the Connor work and then lay on all the work that you've done and it starts to develop a whole different model that's kind of very different than the Pritikin model of "fat is bad." I mean, I guess we have to ask the question: Who are the players? Tell us a little bit about how your model advanced and your work has advanced since Oregon Health Sciences days.

The Effects of Fish Oils on Lipoprotein Metabolism

BH: It's gone sort of fits and starts. I got interested in, of course, the effects of fish oils on lipoprotein metabolism. Connor's lab was quite good at doing some of the lipoprotein kinetic studies and certainly metabolic feeding studies, and so we went on to do a variety of other studies, giving people less and less fish oil. Of course, a half a cup of salmon oil is a lot of fish oil—around 25 grams of EPA and DHA a day is what we were giving in those days. We eventually backed it off as fish oil concentrates, as they were

called at the time, 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} omega-3 products, MaxEPA being the primary one—when they came onboard we could drop it down to 18 capsules and give 6 grams of omega-3 and we thought we were really reducing the dose. One of those studies actually showed that if you give fish oils to people who have high triglyceride levels you'll often see a rise in the LDL cholesterol (the bad cholesterol).[3] That was in the mid-80s and that observation got a fair amount of press and put a real kibosh on the fish oil for lipid lowering (advertising that was being done by a lot of fish oil companies). Things kind of went quiet for a while as people recoiled from seeing that cholesterol levels actually went up in some people given fish oil.

JB: Let me comment just as a brief side line. It's very interesting to reflect as I'm listening to you. In 1982, I was at the Pauling Institute on sabbatical, and I was asked if I would be a consultant to RP Shearer, the company that was bringing MaxEPA, the first omega-3 fatty acid concentrated supplement, to the United States from England. And I recall doing a variety of media for RP Shearer on their triglyceride form of MaxEPA and having all sorts of very critical comments made about, you know, feeding fat to people was going to create heart disease. I mean, it was quite a controversial media tour that I did for MaxEPA back in the early 80s. And then, of course, as you said, this suggestion that maybe in some individuals you get an increase in LDL cholesterol, which was considered very, very potentially dangerous, so it got a little bit of a negative stigma. How is it that we have woven ourselves out of that—or walked ourselves out—of that concern? Have we learned more about who the genetically sensitive individuals are? Or have we learned that the LDL elevation is marginal relative to its other benefits?

Publication of the DART Trial Results was Pivotal

BH: Yes, that's right. Actually what I think I can sayabout the field--what woke it up again--was the publication of the DART trial in 1989, which was really the first randomized trial in humans with heart disease that showed that increased omega-3 intakes reduced risk for total mortality and sudden death. That study, with only 2000 patients, came out of England, and was really what set the field back on fire.[4] You didn't really need high doses of omega-3—the kind we had been giving—to achieve a cardioprotective effect. Actually about a gram a day seemed—from that study—sufficient to actually reduce a very important end point: not LDL cholesterol, but actually mortality. That set us on a new path. It has still been a bit of a rollercoaster, but that was an exciting finding.

Explaining the Different Forms of Fish Oils

JB: It's interesting to me, and probably even more interesting to you as an expert in the field, that as we started to see industrial intervention to make higher degrees of concentration of these favorable omega-3s like the eicosapentaenoic and docosahexaenoic acids (EPA and DHA), that we started to see individuals go from the triglyceride delivery form into a resaponified and esterified ester form. Is there any difference that you see either in the absorption or activity of these, kind of the natural triglyceride versus the ester forms of these delivery omega-3s?

BH: That's a great question, and that's a question of increasing interest in the last several years. Yes, it appears that the ethyl ester form—which you are correct, was created so as to make as higher a concentration as possible per capsule—is not terribly well absorbed when taken without food (taken on an empty stomach). The ethyl ester form is the form that the current pharmaceutical products are in. It's not as well absorbed as the triglyceride form, which is the more natural form. This can be somewhat obviated by taking the ethyl ester with food, which stimulates, of course, hepatic and pancreatic secretions. It was somewhat of a surprise recently to see such a difference in ethyl ester absorption versus triglyceride.

JB: And when we go back and re-explore this LDL story, which has gotten a lot more information under it over the last 20 years, what are people now saying about the potential increased LDL that occurs with fish oil supplementation? Is the opinion changing? Where does the risk/benefit lie today?

What Do We Know About the Risks and Benefits of Fish Oil Supplementation Today?
BH: Yes, a couple of things on that. First of all, if people are taking omega-3 EPA and DHA in the neighborhood of one to two grams a day, there isn't an effect on LDL. And if the patients are not high triglyceride patients, there's not an effect on LDL by and large. Typically there really is just no change in LDL when you give fish oils in doses that we know reduce risk for cardiac advance, like one gram of EPA and DHA. That does not affect either triglycerides or LDL in any meaningful way. At that level, the LDL issue is a non-event. Where the LDL issue is an event is in people taking high doses; what we call lipid-lowering doses, 3 to 4 grams of EPA and DHA a day. In those patients, LDL can go up, and does if the patient is hypertriglyceridemic, which is the whole indication for giving that dose of omega-3. Interestingly, if you're on a statin at the same time this doesn't happen. A statin will block that effect. And there has been now some interesting data from a group that's selling an EPA-only product; Amarin is the name of the company and drug is Vascepa. It has been approved by the FDA just last week. It's a pure EPA product (EPA ethyl ester), and in its trials it does not raise LDL, whereas the combination of EPA plus DHA does seem to raise LDL.[5] We're beginning to think that the LDL-raising effect of high-dose omega-3 is related to the DHA component, not the EPA component. That's a new development and we don't really understand why. I think most people, again, don't really worry about this in terms of political effects, because, again, you can get significant cardiac protection at doses that do not affect LDL.

JB: Thank you. That's really helpful news to use. As I'm listening to you I'm thinking of, again, this concept of dose response or dose effect. Aspirin comes to mind as a classic example. Aspirin can be taken in three different doses with three different physiological outcomes. You can use baby aspirin for prevention of CVD and altering platelet adhesion. You can use a higher dose aspirin for headaches. And then there is the therapeutic dose of aspirin for arthritis and autoimmune disease, and they even used to use it for type-2 diabetes as a treatment. The problem is at those high doses, obviously the risk becomes quite high to gastrointestinal complications and bleeding. It seems like we need to be always be very mindful of dose effect, because one shouldn't assume that necessarily have the same physiology at different doses and also the same risks, so I think you brought that up very clearly with this EPA/DHA argument—that risk and effect are related to dose amount, it seems.

BH: Yes, and I would hasten to add that we really don't know, other than this effect on LDL in patients with high triglycerides, which really don't know is a clinically adverse effect. It's just that biochemically it changes the LDL levels. Whether that's a bad thing or not is another question. But other than that, we really haven't seen any adverse effects of fish oils, even up at…I think the most recent advice from the European Health Authority is that up to 5 grams of EPA and DHA a day is completely safe.[6] To continue your analogy with aspirin, we really do see an adverse effect on bleeding when you really get up to high doses of aspirin. We really haven't seen any downside to high doses of fish oil.

JB: I think that's a really important point for the clinicians because often we're led to believe that these numbers that relate to risk are directly related to clinical outcome. I think that risk factors and clinical outcome are correlated but they're not one-on-one. It's possible that one could have a marginal increase of a relative risk factor (in this case you're talking about LDL), but yet have an overall protective effect due to other influences on physiology that net it out to actually be net-positive on outcome. I think that's

a really interesting point you're making because sometimes I think we over-read a single biomarker or a single number and put too many eggs in that basket and not look at the composite effect of things that are pleiotropic and may have multiple influences on physiology.

BH: Very good point. I think back to your aspirin point. We know that aspirin lowers risk for cardiovascular events, but it certainly does not lower LDL levels. Athero risk is not one-to-one with LDL. It's not the beginning event.

The Signaling Effects of G-Protein-Coupled Receptors

JB: So there's another part of this story that, to me, is very fascinating. This is just a few years old. Jerrold Olefsky at UC San Diego I think might be credited with making these observations first (or you can correct me if there are other people that were earlier). This concept that these omega-3 long-chain polyunsaturated fatty acids like EPA and DHA have specific receptors that are called G-protein-coupled receptors that modulate intercellular signal transduction, so the effect of these fatty acids—at least in part, mechanistically—is through their activity in influencing specific GPCRs like GPCR120, and then that has a specific signaling effect that influences the expression of cassettes of genes that regulate inflammation, insulin sensitivity, and lipid dynamics.[7] It seems like that's a pretty remarkable part of the story—that fat can speak to our genes through these receptors (or certain types of fat).

Recent Discovery of New Metabolites Further Explain Omega-3 Fatty Acid Functionality

BH: Right. Exactly. And you're right to bring up Olefsky. He led the way in this. Because I think most of us have always thought: How do omega-3 fatty acids work? Well, they work via affecting eicosanoid synthesis, or being a substrate for cyclooxygenase that competes with arachidonic acid. And that sort of was as complicated or as simple as it was until studies such as Olefsky's showing that the omega-3s can actually activate specific receptors, and that's a whole new concept rather than just competing with arachidonic acid for some other enzyme. So I think the world is opening up. Along the same lines, we've now been able to discover that there are a whole host of metabolites of EPA and DHA that are made by cytochrome P450: epoxides, some mono- and di- and trihydroides, some ketones that are normal metabolites that we've just never been able to measure, and now we're discovering that a whole host of them exist, and the possibilities for how omega-3s actually are affecting health are continuing to expand as we discover these metabolites.

Low-Density Lipoprotein Cholesterol: Does Fish Oil Affect Count, Size, or Oxidation?

JB: Thank you. That's beautifully expressed. I think names like resolvins, which are some of these compounds, is a really interesting name, because then it says, "Well, what are you resolving? And why did these get the name 'resolvins'." They got the name 'resolvins' because of their effect on some of the untoward physiological things that occur with inflammation and disturbed metabolism. I think it's a really interesting story that you're describing. Let me ask a little bit about one of the themes that we see emerging with regard to lipid factors and risk, and we get into lipid particle count, and we get into various types of atherogenic particles. Steinberg, at UC San Diego (again),has brought up the concept of oxidized low-density lipoprotein cholesterol and how that plays as risk factor. Do fish oils, from your background, have any influence on particle count, lipid particle density, and/or oxidized LDL?

BH: They do have an effect on LDL size. The particle does get a little bit bigger, which is a good thing. I hasten to add that just because LDL particles are a little bit larger on fish oil than they are not, doesn't make—all of a sudden—LDL into a good player. It's maybe just not quite as atherogenic as it would

otherwise be. I sometimes hear people say, “LDL size is now larger, therefore now it’s a healthy particle.” You know, it’s not that, it’s just not as bad as it used to be. So fish oils can make that small change in LDL particle size, but as far as oxidation, that’s been a tricky field and actually it has kind of been quiet for some years now.

Fish Oils and the Oxidative Theory of Atherosclerosis

BH: The whole oxidative theory of atherogenesis really caught hold in the 1990s. Of course as you are well aware, a variety of randomized trials with vitamin E or other antioxidants failed to actually prevent atherosclerosis. That threw some of the foundation of that theory into a tailspin. But nevertheless, it’s still around that oxidation is playing a role. It’s exactly how we block it that’s the question. Fish oils can chemically increase the susceptibility of LDL particles to oxidizing, at least in the laboratory and the in vitro setting, because the omega-3 fatty acids are themselves very highly polyunsaturated—4,5,6 double bonds. And the more double you have the more places there are for oxygen to attack, and so in some model systems higher omega-3 levels in lipoprotein particles make those particles more susceptible to oxidation. But that has not translated into increased cardiovascular risk or increased atherosclerosis in vivo, so there’s a little bit of a disconnect between the oxidative theory and what omega-3s do.

JB: Thank you. That’s very helpful.

JB: Let me shift to another part of this story that I think is very timely and topical and that’s the HDL—what used to be considered the friendly cholesterol. There seems to be a lot of controversy about HDL right now and also HDL and its relationship to omega-3 oils. Can you kind of help bring us up to speed on that?

Raising HDL Levels May Not Be the Answer: What the Trials Tell Us

BH: Yes, boy, nobody’s betting on HDL anymore. We’ve all decided that we don’t know what the hell it does (pardon my French). Partly because of two or three trials that have taken new approaches to raising HDL cholesterol levels in people. Theoretically, high HDL cholesterol is protective against heart disease and there’s a lot of epidemiology and other studies that support that view, which is why we call it the good cholesterol. But these new trials have tested drugs that raise HDL cholesterol by a variety of mechanisms, and they are not proving to be beneficial. In the first case there were actually increased deaths in the treated group over the placebo group, so that drug has been killed.[8] The next drug to come along to try to achieve that same kind of thing didn’t actually end up killing anybody, but it was no different from placebo in terms of outcomes.[9] And so both these studies where HDL was raised significantly (almost doubling HDL levels—huge increases in HDL) did not produce a cardiovascular benefit. So now everybody in the field is sort of throwing their hands up and saying, “Well, we really don’t know what to do.” We know HDL is a predictor of risk, but we don’t know whether changing HDL levels changes risk. That’s the problem. The role of omega-3 and HDL is…HDL really isn’t affected much by taking omega-3 fatty acids (HDL levels). Whether HDL functionality is hasn’t really been studied.

JB: You know, I find this HDL controversy to be extraordinarily interesting both from the specific and general perspective, and that is that the drugs that have been used to raise HDL are cholesterol ester transport protein inhibitors (CETP inhibitors) and so one might ask: “Does that produce the same effect on vascular function as we would have in a normal kind of physiological mechanism of control of HDL without a drug that is hitting one specific protein effect (one enzyme effect) given that the HDL particle

has I think over 40 different proteins?" It's the most complex apolipoprotein particle in the whole family. Are we just looking at a specious effect of a pharmacological influence on a one-target protein out of a whole, or is it really an HDL personality problem? My intuition tells me it's not an HDL issue. It's a specific pharmacological impact on one component of the HDL that's producing these difficulties. But I think that's a hypothesis remaining to be proven, what's going on here.

BH: Jeff, I think you're right. I think many people in the field feel like the CETP-mediated rise of HDL may not have been the right strategy and we don't know what we're actually affecting. Just raising HDL cholesterol levels does not necessarily raise HDL particle numbers, and that is something that needs to be sorted out.

Diagnosing Omega-3 Status in a Patient

JB: So Bill I'd like to close with one last area that I know you're really an expert in, and that is: Okay, we've found this benefit from prophylactic administration of omega-3 fatty acids. There is large clinical outcome studies, we have some mechanistic work, we're talking about cell signaling from an mode of action (MOA) and its effect on inflammatory prostanoids. All of this is kind of an extraordinary body of literature of thousands of references. Then the question to the clinician is: "How do I know what the status of my patient is relative to their omega-3 status?" I think there is data saying that if your omega-3 fatty acid levels in your plasma membranes get to a certain level the relative risk of vascular disease is very low, so someone might want to know: How do we know where that risk is for the individual patient? Can you tell us, from a diagnostic perspective?

BH: Sure, sure. I appreciate that question. We did develop, some years ago, a test we call the Omega-3 Index, which is a blood test that is actually performed in red blood cells (not in the plasma, but in red blood cells) that measures the amount of EPA and DHA, which are the important omega-3s in this regard. And the higher the level of the EPA and DHA in the red cell the better (the higher the Omega-3 Index the better). I try to explain the Omega-3 Index as to being somewhat like a hemoglobin A1C in the control of diabetes. Hemoglobin A1C is a long-term marker of glucose control. Glucose goes up and down in plasma a lot, but the tissues see a very steady level of it. The Omega-3 Index is a similar thing. It is a stable biomarker of how much EPA and DHA are in tissues. It responds very well to taking omega-3 supplements. And as you mentioned, a high level of Omega-3 Index—up over 8{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, which is where we think the target should be—has been associated in other studies with reduced risk for sudden cardiac death, reduced risk for early aging, total mortality, and a variety of other endpoints. So, to your question of how does a doctor find out what his patient's omega-3 index is, as of about a year ago the Omega-3 Index test has been taken on and is now being offered by Health Diagnostic Laboratory (HDL) in Richmond, Virginia. That's a clinical lab that is really rather new, actually, but it is, I think, now the premier cardiovascular and metabolic risk assessment lab in the country. The HealthDyn HDL is the convenient name (or the abbreviation) for Health Diagnostic Lab. HDL is offering the Omega-3 Index test along with many other cardiovascular markers. It's really the first lab that has found a way to offer this test on scale. We're doing about 2500 tests a day now at HDL on the Omega-3 Index, and they are being submitted to third-party payers and insurance is covering the cost and that is really what has blown the door open and made the omega-3 test become much more popular.

JB: I think this is a fantastic breakthrough, and it reminds me very much of…I was a clinical chemist back in the days when the fingerstick cholesterol test first got approved (the Boehringer-Engleheim Test). Prior

to that, less than 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of people knew their blood cholesterol level, but after the technology became available for health fairs and shopping mall analysis suddenly almost everybody knew their blood cholesterol and the number was theirs, it wasn't somebody else's that their wife was reading about in a Good Housekeeping magazine and they were saying, "Well that's not me, I don't have a high cholesterol." Suddenly they had their number and that actually (probably) was the thing that fueled the growth in statin use and made it the number one prescribed drug family in America probably in the history of the pharmaceutical industry, actually. So I think this test, the OmegaQuant test that you're describing to look at the Omega-3 Index, is going to have a similar effect, I think, on allowing people to understand their own specific status, which is the motivator for complying with the interventions. So, congratulations, and that should revolutionize the field, I would think.

BH: I hope it does. I hope it does. I hope we get a lot of people who will pay attention to how much omega-3 they are eating because they know they are deficient.

JB: Bill, I want to thank you. Dr. Harris, as you can hear, obviously is an expert for decades in this area and has shared a lot of news to use in this last half hour. Bill, the best to you and thank you so much for bringing that high-level stuff down to a level that we can all understand and docs can use with their patients.

BH: Thank you for inviting me.

Bibliography

[1] Harris WS, Connor WE, McMurry MP. The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oils. *Metabolism*. 1983;32(2):179-184.

[2] Dyerberg J, Bang HO. A hypothesis on the development of acute myocardial infarction in Greenlanders. *Scand J Clin Lab Invest Suppl*. 1982;161:7-13.

[3] Dart AM, Riemersma RA, Oliver MF. Effects of Maxepa on serum lipids in hypercholesterolaemic subjects. *Atherosclerosis*. 1989;80(2):119-124.

[4] Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). 1989.*Lancet*;2(8666):757-761.

[5] Jacobson TA. A new pure ?-3 eicosapentaenoic acid ethyl ester (AMR101) for the management of hypertriglyceridemia: the MARINE trial. *Expert Rev Cardiovasc Ther*. 2012;10(6):687-95.

[6] http://www.efsa.europa.eu/en/efsajournal/pub/2815.htm

[7] Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell*. 2010;142(5):687-98.

[8] Bermudez, V, Cano R, Cano C, et al. Pharmacologic management of isolated low high-density lipoprotein syndrome. *Am J Ther*. 2008;15(4):377-88.

[9] Ghosh RK, Ghosh SM. Current status of CETP inhibitors in the treatment of hyperlipidemia: an update. *Curr Clin Pharmacol*. 2012;7(2):102-10.

[10] Kwak SM, Myung SK, Lee, YJ, Seo HG. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med*. 2012;172(9):686-94.

[11] Hu FB, Manson JE. Omega-3 fatty acids and secondary prevention of cardiovascular disease—is it just a fish tale? *Arch Inter Med*. 2012;172(9):694-696.

[12] Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006;296(15):1885-1899.

[13] Chisolm GM, Steinberg D. The oxidative modification hypothesis of atherogenesis: an overview. *Free Radic Biol Med*. 2000;28(12):1815-1826.

[14] Vita JA, Brennan ML, Gokce N, et al. Serum myeloperoxidase levels independently predict endothelial dysfunction in humans. *Circulation*. 2004;110(9):1134-1139.

[15] Meuwese MC, Stroes ESG, Hazen SL, et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk prospective population study. *J Am Coll Cardiol*. 2007;50(2):159-165.

[16] Shao B, Oda MN, Oram JF, Heinecke JW. Myeloperoxidase: an oxidative pathway for generating dysfunctional HDL. *Chem Res Toxicol*. 2010;23(3):447-454.p>