May 2009 Issue | Ralph La Forge, MSc Managing Director

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Welcome to *Functional Medicine Update* for May of 2009. As you know, this is a year of tremendous change in healthcare policy and planning, and in looking forward as to what our healthcare system will look like over the next years to come. As we are going through this dynamic process of contemplation, consideration, and reflection, data comes up that might be quite important as we start looking at the options for where the healthcare system might go. These data relate to disease prevalence, morbidity patterns and loss of work years, lowered quality of life, and trying to define the origin of conditions and then map them against certain physiological processes that relate to their etiology.

As I have said this, I have tied together quite a few disciplines of healthcare evaluation, including epidemiology, biostatistical evaluation and population-based studies (demographics), and even tissue pathology and cellular physiology. All of these are related, in part, to a drift-a warp and weft-of a change in function of people. This is a change in function in an individual as it relates to the impact the environment is having over time and how it translates through the physiological process into what we see as general health or disease patterns.

I think this is an interesting concept and it reminds me a little bit of tributaries coming together to form a major river that then flows to the oceans. With the gene pool, these considerations of uniqueness that we each have are locked into our genome and get bathed by and exposed to our environment (and our environment may be shared among all sorts of different genotypes), which then gives rise to-as we are heading down towards the sea-a confluence of those gene-unique interactions with the environment to produce patterns that we call diseases that appear in populations. Ultimately those tributaries collect into smaller rivers and into, finally, a major river, where we start shaping those major patterns that relate to healthcare expenditures

With this metaphor that I am describing of traveling to the sea, we can see some remarkable changes that have been occurring in disease patterns over the last 15 years, specifically with the rising prevalence of type 2 diabetes. As a student back in the 1960s, I recall that we were told that the incidence of diabetes had remained relatively constant in the population (somewhere between 2 and 3 percent of the population), giving us this view of it being determined and fixed somehow in our genes. Yet in the 21st century, we are witnessing a dramatic increase in the area of what used to be called adult-onset diabetes and is now called type 2 diabetes, which relates to not the changing of our genes, but the changing of epigenetic signals (the environmental interaction with our genes) to give rise to expression across many different genotypes of what we ultimately name as a disease (as if everyone who had that disease shared the same common background and etiology).

In my metaphor, the disease is the river, and the river comes from the individual tributaries. One of the contributors to this increasing prevalence of type 2 diabetes is the insulin resistance/hyperinsulinemia situation that we are seeing, is the change in how the message of insulin is and transmitted/transferred/transduced. The beta cells of the endocrine pancreas are still producing insulin, and maybe even working harder to produce extra amounts of insulin, but the message from that insulin is not being appropriately transmitted into cellular function. This is what we call syndrome X (from Gerald Reaven's nomenclature) or insulin resistance/hyperinsulinemia/metabolic syndrome.

Insulin is a Pleiotropic Hormone

The core signaling and intercellular signal transduction process that comes from interruption of insulin's responsiveness gives rise not just to an alteration in blood sugar, but it is now recognized that insulin is a very important pleiotropic hormone that influences many other aspects of gene expression; it overlaps with the cell physiological response that we associate with other diseases. In medical parlance, we call these co-morbidities, and included would be things like inflammatory diseases, osteoporosis, dementia, various kinds of cancer (like that of cancer of the colon, breast, and prostate), or cardiovascular diseases of certain types (small vessel disease). These co-morbidities really share common etiologies in this river of confluence that I am describing, as it pertains to the interaction of an altered environment with multiple genotypes to create an expression of outcome that we measure in a biomarker called blood sugar, from which is ultimately defined a disease called diabetes. The functional changes that occurred well before the onset of that diagnosis, however, are profound. Because insulin, in its high level, is insensitive at the cellular membrane in altering intercellular signal transduction, then affects many functions other than just the translocation of the GLUT4 receptor to the cell membrane, and glucose transport across the cell membrane into the cell. We recognize that people with metabolic syndrome/hyperinsulinemia present with biomarkers that are indicative of other changes, like hypertriglyceridemia or low levels of what is called the protective apolipoprotein that makes up HDL (so low HDL and a low apo A-I).

Graded Effect of Insulin Response was Not Recognized 30 Years Ago

There are obviously many other things that are going on other than just poor uptake of sugar across the cell membrane as one moves along the trajectory of this increasing degree of insulin resistance. I said something in that sentence that I think is quite important clinically. Nearly 30 years ago, I had the opportunity to speak at a conference on reactive hypoglycemia at the University of Washington School of Medicine in Seattle. At that conference, the then head of the endocrinology department-a world-renowned expert on diabetes-made the statement that there was no evidence (at that time) of a graded effect of insulin response (from optimal insulin sensitivity to the lack of insulin response that we call diabetes), and therefore one could not use a gradient effect logic to describe differing degrees of expression of insulin problems.

In the 30 years that have passed since that conference, this field has certainly changed considerably. If he were living today, I think Dr. Bierman, who was a fantastic contributor to our understanding of diabetes and actually authored the textbook that I had originally studied out of on diabetes, would probably say it is quite interesting how our understanding of insulin signaling has changed dramatically. We have started to now see that these gradient effects of degrees of insulin resistance are true and it is not "all patients are the same." Not every tributary that makes its way to the river of what we call type 2 diabetes is the same. Within that body of water that travels to the sea called type 2 diabetes, are different subgroups of individuals who really have different variations on a theme as it relates to how each presents with insulin resistance. That, then, is a very important clinical takeaway, because if we are looking for "the" type 2

diabetic, and we want to put everybody into a single kind of diagnostic criteria using univariant types of logic (which means looking for aberrant blood sugar on a fasting blood sugar level or elevated insulin on a fasting blood insulin level), we are probably going to miss many, many people who show different variations on this theme, who are still at risk as they travel down this river of life to various disorders that we associate with hyperinsulinemia/insulin resistance.

You might be saying I am going into this in greater detail than probably you really need because you are already aware of this, but sometimes I want to come back and revisit old things in new ways. We are starting to recognize that this interrelationship of insulin signaling to inflammatory signaling, to cell regulatory factors that relate to cell replication, to factors that relate to cell apoptosis and mitochondrial phosphorylation and bioenegetics-that all of those new kind of discoveries at the cellular level are about how insulin plays roles in each of these processes and ultimately even influences cellular redox (the reduction oxidation levels of cells) and how that relates to oxidative stress, and free radical pathology, and genomic damage and instability, which we learned about from Michael Fenech in a 2008 issue. All of the issues that I've just described could be put under the umbrella of insulin resistance or type 2 diabetes, but you can see-just by the way I stated it-that there may be different ways that individuals express each of those based upon their own specific interrelationship between their environment and their genes

There has been a longstanding question as to whether this insulin resistance/hyperinsulinemia/metabolic syndrome does or does not, in fact, correlate with increasing statistical risk of cardiovascular disease. I think it is important to point out that the term "cardiovascular disease" almost implies that it is a single condition, but as we know, it is really cardiovascular *diseases*. There are many different manifestations of disorders of the vascular system.

To give a gross type of differentiation, we could talk about large vessel disease and small vessel disease. In general, we would say that individuals with hyperinsulinemia/insulin resistance are individuals who have an increased risk for vascular endothelial dysfunction that ties together with small vessel disease. If we look at metabolic syndrome and its effect on predicting cardiovascular events in individuals who have normal fasting glucose, what happens if we go back and do a 15-year retrospective study of them? I want to emphasize again-these are people who present with normal fasting blood sugar, but who have elevated fasting triglycerides and low HDLs. We would say they have the underlying early stage of insulin resistance. They are pre-diabetic. They are metabolic syndrome patients. And they might easily be missed in a traditional assessment because they don't look like they are diseased; they look like they are metabolically dysfunctional.

Results of a 15-Year Follow-Up Study

What happens if we go back and evaluate them 15 years earlier? This was the question of a study that was actually done and published in the journal *Atherosclerosis* in 2008.[1] As I said, these were the results of a 15-year follow-up. These researchers found metabolic syndrome to be predictive of cardiovascular events regardless of the presence of impaired fasting glucose or type 2 diabetes. I'm trying to get us to recognize that looking at early warning precursor markers for later stage pathology is where we need to start focusing our attention in the new healthcare reform movement. By the time we get to overt pathology, the requirement for much more interventional drugs, surgery, and hospitalization becomes the principal tool we use to manage those conditions at their tertiary stage of pathology.

I think the view that is emerging is that biomarkers-the right biomarkers, validated biomarkers-that look

at functional disturbances early on that demonstrate a trajectory towards a later stage pathology (in this case, looking at derangements in insulin signaling) are very valuable as an inclusion criteria for the new medicine to create an appropriate mosaic of where that person's genes and environment interact to give rise to their function. Again, I want to emphasize this study looking at patients with normal fasting glucose, without type 2 diabetes, and following them for 15 years-and these are people who had elevated triglyceride/low HDL levels, meaning metabolic syndrome, with an increased waist-to-hip ratio-it was found that there was a very strong correlation, in the absence of impaired fasting glucose, of this condition with later stage cardiovascular disease.

Far-Ranging Questions and Opinions about Biomarkers

The biomarker questions that we are talking about can be far-ranging. We are going to hear about this issue from an expert in the area of lifestyle medicine and biomarker analysis as it relates to establishing risk to some of these metabolic dysfunctions, Ralph La Forge, and I think you are going to love his comments-very, very eloquent comments-from his work at Duke University Medical Center. But before we get to the discussion with Ralph La Forge, I would just like to review a few of the biomarkers that we often now employ for evaluating relative risk to these metabolic disturbances that we say are related to insulin signaling dysfunctions.

LDL-to-HDL Cholesterol Ratio

The first is the obvious LDL-to-HDL cholesterol ratio. I am reminded of a wonderful investigator from the department of nutritional sciences at the University of Connecticut, Dr. Maria Luz Fernandez. In some of her recent publications, Dr. Fernandez has talked about the importance of the LDL-to-HDL cholesterol ratio being a more reliable clinical tool than LDL cholesterol (itself) to evaluate cardiovascular disease risk, including HDL and LDL in the same analyte determinant.2 What you end up doing is looking at the risk to both large vessel disease and small vessel disease, because the HDL particles appear to be more related to aspects of insulin signaling, and the LDL particle seems to be more related to aspects of lipid dynamics. There is an interrelationship between those-I don't want to say they are totally independent variables-but HDL is a more sensitive mark of insulin signaling, and there LDL is a more sensitive mark of lipid biosynthesis and metabolism with LDL.

So controversy exists, as you know, regarding what the best method is for identifying those individuals who are at increased risk for coronary heart disease. We have recently seen from the JUPITER trial (the Paul Ridker trial that we talked about in a previous issue of Functional Medicine Update) that hsCRP (an inflammatory biomarker) has been suggested as another important indicator of the relative risk to cardiovascular disease. You'll hear Ralph La Forge talk about his view on hsCRP a little later, but for now we need to go back to these lipid biomarkers, and that leads us into recognizing that the National Cholesterol Education Adult Treatment Panel III (ATP III), guidelines have suggested that there should be specific targets for LDL cholesterol. People have now talked about cholesterol LDL levels below 70 milligrams per deciliter. For many people this target results in them being prescribed a statin, because to get their LDL to that level they often have to be on a statin. Maybe the more important thing is to look at the relative relationship between the LDL level and the HDL level. If we say the LDL level should be 120 or less and the HDL level should be 60 or more, then we would say that an LDL-to-HDL ratio should be 2-to-1 or less and the lower the LDL-to-HDL ratio, the lower the risk to both vascular disease of large vessels and small vessels.

Apolipoprotein B and Apolipoprotein A-I

In that ratio scheme, we have combined a little bit of the aspects of insulin signaling, inflammatory response and the lipid dynamic biosynthesis, and the so-called HMG-CoA-reductase pathway that leads to cholesterol biosynthesis. As you probably know, for the LDL particle, the protein carrying factor for that particle is apolipoprotein B. There is now evidence (as you will hear about-again-in greater detail later in this issue of Functional Medicine Update) that apolipoprotein B may be a more sensitive marker than LDL itself in picking up relative dyslipidemias associated with altered lipid biosynthesis metabolism and insulin signaling. In fact, there are now people who are saying the best risk factor might be to use the apolipo B particle and compare it to the apolipo A-I because apolipoprotein A-I is the principal apolipoprotein found in the HDL particle that relates to cholesterol efflux, meaning pulling cholesterol out of the artery wall, and it is very significantly associated with things like inflammatory mediation and insulin signaling. So as you have dysinsulinism and insulin resistance, apolipoprotein A-I goes down and apolipoprotein B goes up. Maybe the apo B-to-A-I ratio is even better than the LDL-to-HDL ratio. There is some controversy about that presently, I would have to say. At the Functional Medicine Research Center, we have worked with metabolic syndrome patients and published and article in Nutrition and Metabolism 2008.3 Our work indicated that insulin resistance was most reflective in the biomarker of the apo B-to-A-I ratio, and when that ratio became 0.7 to 1 or greater, that person had an increasing relative risk to vascular disease. It was seemingly a precursor to that of elevation of LDL itself, or the altered LDL-HDL ratio.

In panels of biomarkers that are trying to couple together insulin sensitivity, inflammatory markers, and lipid biosynthesis and metabolism, one might consider that the apo B-to-apo A-I ratio could be a very useful tool. In fact, Dr. Fernandez speaks about this in a number of her recent publications that are related to work that is going on now at the National Lipid Association in looking at the ratios of the two. We also recognize that the HDL particle, which exists in a number of different isoforms, is very complex because it is made up 44 different proteins. It is the most complex of the apolipoproteins. As we learned from Dr. Roger Newton in a previous issue of Functional Medicine Update, we should see HDL as a functional lipoprotein because it serves to transport things and be involved with metabolism. It has paraoxonase 1 as one component. That is an enzyme that is involved in detox; it has antioxidant potential-it is an antioxidant soaking up free radicals itself. It has myeloperoxidase as part of its particle composition. It has cholesterol ester transport protein, which is involved in how cholesterol is moving in and out of the artery wall. So it is a very complex lipoprotein that also has to do with the prevention of lipid peroxidation. When we are measuring things like the apolipo A-I, which is a surrogate marker for HDL function, and apolipo B, which is a surrogate marker for LDL function, we are getting a little bit more detail on evaluating the functional aspects of how these lipid particles operate within the vasculature.

LDL Oxidation

Let's just look at a quick snapshot of the work that Jay Heinecke and his colleagues are doing on HDL at the University of Washington Medical School in Seattle.4 We know that genetic, clinical, and pharmacological studies implicate elevated levels of LDL in the pathogenesis of atherosclerosis. Paradoxically, as Dr. Heinecke points out, native LDL fails to exert potentially atherogenic effects in vitro, suggesting that it must be modified to promote vascular disease. Indeed, many lines of evidence now support that.

This is the Daniel Steinberg hypothesis, as presented at the University of California, San Diego, by Dr. Steinberg many years ago, suggesting that oxidative damage to LDL is one important mechanism for

rendering lipoproteins atherogenic. So LDL in its native state may not be atherogenic until it gets oxidized. Then the question is: what oxidizes LDL and what prevents LDL from being oxidized? That leads to the HDL part of the story. In contrast to LDL, HDL (the beneficial form of blood cholesterol) protects the artery wall from atherosclerosis. Even in individuals whose LDL levels are low, HDL remains a strong, independent predictor of coronary artery disease, meaning you could have low LDL and a low HDL, and still have an elevated risk to heart disease.

The strong relationship between low levels of HDL and the risk of atherosclerosis and coronary disease has been attributed to many different mechanisms, and I think these mechanisms have been emerging over the last 30 years of discovery about HDL physiology. We now recognize that HDL transfers cholesterol from peripheral tissues to the liver, where the metabolites of the sterol cholesterol are then excreted into the bile, so we say HDL is involved with cholesterol efflux from the artery wall. That may then lead to its cardioprotective effects. Animal and human studies have the raised the possibility that HDL also slows vascular disease by blocking the inflammation (serving as an anti-inflammatory). For example, hypercholesterolemic mice deficient in apo A-I are known to develop systemic inflammation and recombinant HDL blocks vascular inflammation in atherosclerosis-prone rabbits. One potential mechanism involves the detoxification of lipid hydroperoxides, which are potentially atherogenic. And as I mentioned earlier, enzymes within the HDL particle, including paraoxonase 1, cholesterol HDL transferase, and lipoprotein-associated phospholipase A-2, have been proposed to degrade lipid oxidation products and actually help to protect LDL from being oxidized. As I said, oxidized LDL is apparently the atherogenic form of LDL.

Lipid hydroperoxides are the initial products when lipids are damaged by this oxidative process-the so-called free radical oxidation. HDL is the major carrier of these antioxidant properties and several factors might account for the fact that HDL contains more lipid hydroperoxides than LDL, including the greater susceptibility of HDL lipids to oxidation in vivo, the preferential accumulation of lipid hydroperoxides in HDL, and the apparent ability of HDL to degrade lipid oxidation products. So lipid oxidation can also generate advanced products of oxidation such as alkanes, aldehydes, and isoprostanes, and these can all participate, then, in the active promotion of free radical oxidative injury to other cells and tissues and biomolecules.

When put together, these observations, I think you can see, suggest that HDL plays a major role in the transport and metabolism of lipid hydroperoxides in vivo, and these processes contribute to the cardioprotective effects of HDL. I think we are seeing that HDL is a major lipoprotein carrier of things like isoprostanes, and aldehydes, and other oxidation products that tends to take them to the liver, where they can be degraded before they can have activity on other cell types, or other lipoprotein types. In some ways it is sacrificing itself for the game, right? The HDL is putting itself out there to be the preferential particle that soaks up these oxidants and then takes the peroxide products and transports them for their metabolism.

Lipoprotein-Associated Phospholipase A2

I think it is very important to look at HDL with a different eye than that with which we would look at LDL, and say, "As a biomarker for dyslipidemia, dysinsulinism, and free radical oxidative stress, we would put HDL in a pretty important category for evaluation." Now you probably recognize that this lipoprotein-associated phospholipase A2 (which I have referred to as the PLAC test)-that enzyme (protein/enzyme) is associated with HDL, and it has also developed its own ability to be seen as a

surrogate biomarker for atherosclerotic risk, particularly unstable plaque.

A recent study looking at the association of lipoprotein-associated phospholipase A2 (or Lp-PLA2) mass and activity with coronary and aortic atherosclerosis was published in Clinical Chemistry.5 The investigators found that Lp-PLA2 (or PLAC test) was strongly associated with coronary atherosclerosis in those who had unstable plaque. So it may be a surrogate marker for plaque instability as associated with inflammatory response, more so than just looking at atherogenesis itself. If you put the PLAC test together with an HDL evaluation and an apo A-I evaluation, you start to develop kind of a mosaic of understanding about things such as cholesterol efflux from the artery wall, the accumulation of lipid peroxides for processing, the protection against LDL oxidation, and the relative amount of inflammatory process that is going on in the artery wall that relates to unstable plaque.

Why Test for Nontraditional Biomarkers?

I think these are extended markers beyond the traditional biomarkers for evaluating relative risk to cardiovascular disease. They help us to differentiate the tributaries of this river that we call type 2 diabetes or cardiovascular disease. Now you might say, "Well, some of these sound like specialized tests (the PLAC test, or the apo A-I test, or the apo B test)-these are not traditional, standard, risk factor analytes." And that's true. So you might then say, "What good can I get from the things that are found in my standard blood chemistries, like the fasting triglyceride-to-HDL lipoprotein ratio (the TG-to-HDL ratio)?" Well, that's a pretty good first start, and certainly if you are not going to do specialized biomarker evaluation, it would be good to look at the triglyceride-to-HDL ratio. There are many, many different papers that have been published on the relationship of elevated triglyceride-to-HDL ratio and the association with insulin resistance and metabolic syndrome that show that it's a powerful predictor of all-cause mortality and cardiovascular events. In fact, one of the more recent studies in this area was published in the American Heart Journal in 2009.6 This was a study actually done with postmenopausal women, looking at their relative risk to cardiovascular events, knowing that heart disease is the number one killer in postmenopausal women. In this study it was found that the elevation of the triglyceride-to-HDL ratio predicted all-cause mortality in these women as they went on to have all kinds of different conditions, including that of myocardial infarction itself.

We would certainly say the TG-to-HDL-C ratio (HDL cholesterol ratio) is a very, very important independent predictor of all-cause and cardiovascular events that relates to more than just dyslipidemia; it also relates to dysinsulinism. You might say, "What level of ratio increase are we talking about that is a strong predictor?" In this particular study looking at the TG-HDL ratios, they found that when you got above 4, you got into the higher risk category, and that, as it went up monotonically from 4 up to as high as 18, there was increasing relative risk at a very dramatic statistical increase. Above 4-to-1 with your triglyceride-to-HDL ratio appears to be moving into an increasing relative risk category.

The Omega-3 Index

There is one other biomarker that I wanted to add to this list that may appear to some of you to be esoteric and not usual and customary, but I think it has a very potentially important additional value for assessing aspects that are modifiable pertaining to risk to dysinsulinism, so it is another way of evaluating and looking at the different tributaries of the river that we call type 2 diabetes. This biomarker is what Dr. William Harris calls the Omega-3 Index. The Omega-3 Index is evaluating the relative levels of omega-3 fatty acids found in red blood cell membranes in comparison to omega-6 fatty acids. For those of us who have been in this field for some time this doesn't sound remarkable. In fact, we can go all the way back to David Horrobin, back in the 1970s, who talked extensively about omega-3 fatty acids and their

relationship to cardiovascular incidence.

What has emerged recently is recognition that in our Western population, eating a standard Western diet, that we have seen a significant shift in the fatty acid profile of red cell membrane lipids (phospholipids), moving this Omega-3 Index more and more towards a low ratio of omega-3 to omega-6 fatty acids. Dr. Harris, who is at the Lipid and Diabetes Research Center at the American Heart Institute at St. Luke's Hospital and the University of Missouri in Kansas City, has been looking at this extensively over many years. His recent paper in Preventive Medicine I think really does a nice job of describing the Omega-3 Index as a new and cholesterol-independent risk factor for cardiovascular disease, and also for type 2 diabetes.7

In this study, the researchers looked at a number of individuals with a wide range of different functional characteristics and performed red cell membrane fatty acid analysis. They then looked at a content of EPA plus DHA in the red blood cell membranes (expressed as a percent of total fatty acids), which is what they call the "Omega-3 Index." They graded these individuals based upon that number (the fatty acid index, which is the combination of EPA-DHA divided by the total fatty acids, so looking at percentage). When they did this they found something very, very interesting: the individuals in the high-risk category had a very low Omega-3 Index, meaning their percent of DHA and EPA as a total percent of fatty acids in their red cell membranes was generally below 4{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} (somewhere in the range of 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} and below were in a reasonably high-risk group). There was a fairly significant correlation between the Omega-3 Index and this relative risk to cardiovascular disease, with low index being associated with increasing risk (so an inverse relationship). In individuals who had very low relative risk to vascular disease, they found that their cardiovascular Omega-3 Index was more in the range of 10 {56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} or higher (10-12{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the total fatty acids in the red cell membrane were that of DHA plus EPA). Here is, I think, another very interesting assessment that is cholesterol-independent that helps us to understand something about dynamics that relate to prostanoids and eicosanoids and the relative effects that these have on inflammatory processes, membrane construction, and intercellular signal transduction.

What happens if you supplement with EPA and DHA? What happens to the levels of these fatty acids in the red cell membrane? That was discussed in this particular paper. They gave graded doses of fatty acid supplements at a half-gram a day of EPA/DHA, at one gram a day, and at two grams a day. I want to emphasize for those of you that are deciding how much a patient needs to get to these levels, you need to look at the percentage of the total fatty acids in the supplement to determine what its relative percentage is of EPA/DHA. So the levels I gave you of 0.5 grams, one gram, and two grams is of the combination of EPA/DHA. If you had a supplement that was only 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} omega-3 fatty acids, you'd have to double these doses to get to these levels I'm describing.

When they did the graded dose study, what they found is that the omega-3 went up kind of monotonically with the increasing intake of DHA and EPA as a supplement. So you can, over a period of about 12 weeks, demonstrably indicate (or find) that there is a significant increase in the omega-3 fatty acid index in the red cell membranes of people who have been supplemented. If you then correlate all of this data

that I'm describing with the outcome in populations relative to their prevalence of cardiovascular disease (and this could be the GISSI study, the DART study, the Public Health Service Physicians' Study, the Seattle Heart Study), what you find (and this was described very nicely in Dr. Harris' article) is that those individuals in these large population-based studies who had the highest omega-3 index had the lowest incidence of vascular disease, both small- and large-vessel disease. I think the Omega-3 Index is another biomarker that can be used for tracking something that is modifiable.

A laboratory that does this testing has to be very capable of evaluating (accurately, sensitively, and reproducibly) the levels of fatty acids found in the red cell membrane. I'm not talking about plasma-free fatty acids; I'm talking about plasma-bound phospholipid materials that are found in the cellular membranes of red cells, so this is looking at red cell membrane phospholipid fatty acids, another indication. (By the way, we would probably like to get our omega-3 index up at 8 or above in individuals who are having this test done, so it is a way of marking where they start and following where they finish.)

We've talked about apo B and apo A-I. We've added the fatty acid index, and we've talked about HDL-C and LDL. All of these are relatively important markers for looking at how we differentiate patients who are in these tributaries that ultimately flow down into diseases that we call either cardiovascular disease or diabetes. The last thing I want to mention has to do with this metabolic syndrome and how it is influenced by central body fat, or visceral adipose tissue.

We now recognize that metabolic syndrome is a constellation of inter-related metabolic risk factors, as I mentioned, that appear to directly promote the development of both diabetes and cardiovascular disease. We now start looking at the confusion between the syndrome and obesity. Does metabolic syndrome get caused by obesity, or is obesity a manifestation of metabolic changes associated with some alteration in insulin signaling? What seems to be emerging now (and I'm taking from a review that just appeared in Hypertension Research in 2008 that I think is very well-written) is that we now would characterize metabolic syndrome as a condition associated with altered adipose tissue physiology, and obesity is really probably a result of (rather than the cause of) the condition.8 If we look in the fat mass itself--the central fat mass (the central adipose tissue)--it is characterized (on doing biopsy) by the association of activated macrophages and monocytes with activated adipocytes. They are sharing this imflammatory profile, and you actually start getting the death of adipocytes and macrophages that produce kind of a necrotic process in the fat that further amplifies and stimulates inflammatory processes, systemically. You see in the blood of people, then, elevated hsCRP levels and elevated TNF-alpha inflammatory cytokines, so we would say that there is an underlying process of inflammation as it pertains to this inter-relationship between the immune system and the fat mass adipocytes that is further a part of the complex etiology of this metabolic disturbance we call metabolic syndrome. To review, there is the hsCRP elevation, there is the increase in inflammatory markers, there is ultimately the increase in PLAC test values, and there is the oxidation of HDL. I want to emphasize that the emerging thought is that obesity, in and of itself, is not the cause of-but rather is the result of-metabolic disturbances that create these outcomes.

I hope this has given you some news to use in how you assess patients and actually start to use this understanding of the tributary that leads to the river that ultimately leads to the terms type 2 diabetes or heart disease. I think you are going to enjoy hearing more from our clinician of the month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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We are at that very interesting point in Functional Medicine Update, where, really, the tire meets the road and we look at the clinical applications of some of these recent investigations and published studies. Right now, as we are talking about changes in healthcare planning, policy, and delivery over the years to come, there is probably no more important area than that which we will discuss with our clinician of this month , Ralph La Forge. Ralph is an expert in what we will call therapeutic lifestyle changes. His work at Duke University Medical Center in the Division of Endocrinology, Metabolism, and Nutrition is, I think, really at the forefront of what's going on.

Ralph has his Bachelor's in Zoology from the University of Texas, and his Master's of Science from the University of Wisconsin, La Crosse. He has been at the Duke University Medical Center, Division of Endocrinology, Metabolism, and Nutrition for a number of years, really looking at the role that therapeutic lifestyle change (and specifically diet, exercise, and stress management) has on health outcomes. His background, obviously, is very strong in the area of exercise physiology and exercise prescription, but he has extended considerably into the area of diet and lifestyle and how it pertains to modulation of risk factors for major chronic diseases.

Ralph, it is really a pleasure to have you on Functional Medicine Update. I think the first question I would like to jump on is about cholesterol-the nature of the risk and this whole dyslipidemia issue. As a public health issue, once people knew their number (their cholesterol number) that they could get from a health fair, suddenly their interest in cardiac disease prevention changed from that of being somebody else's problem to being their own problem. What have you seen in the field as it relates to dyslipidemia being kind of the stepping stone into peoples' understanding of their relative risk?

The Role of Lifestyle Management in Reduction of Cardiovascular Disease Risk
RL: Well, after about 900 to 1000 clinical trials over the last two-and-a-half decades, I think we have hit the nail on the head multiple times: especially high LDL cholesterol (that's the bad cholesterol) is definitely correlated quite strongly with vascular disease (both cerebral vascular disease and cardiovascular disease). Of the other lipids (those other than cholesterol and LDL cholesterol), one that has really been getting a lot of attention in last couple of years is triglycerides, which are very much related to obesity and what we call the metabolic syndrome.

Lifestyle management (diet or physical activity or both) probably has a better focus (at least in the short term) on reducing triglycerides and perhaps increasing HDL a bit. After weight is lost, of course, LDL is reduced. There is no question that the large number of 100-million-dollar-plus clinical trials (mostly statin trials, drug trials) have shown us that even modest reductions in cholesterol, particularly LDL cholesterol, reduces risk of your first heart attack if you are a primary prevention-type patient. If you have had coronary disease already, or have already had a previous heart attack, certainly aggressive cholesterol therapy can reduce a recurrent event.

My big bone all along has been that lifestyle changes (even modest), if they are adhered to, clearly reduce risk of diabetes, but also cardiovascular disease, through mechanisms other than just lipids and cholesterol reduction. As a general rule, it takes quite an ardent following of lifestyle behaviors to reduce LDL cholesterol. Generally, diet and exercise don't hold the same power at reducing (especially in the speed of reducing) LDL cholesterol compared to some of the drugs; I don't think anybody will argue that. But I have always said diet and exercise have other benefits that have been, in some cases, even more attendant to the mechanisms of risk reduction than just myopically looking at LDL cholesterol.

JB: One of your recent articles that I think was very well-written is titled "Therapeutic Lifestyle Changes: Lost Horizons?" and talks about the pleiotropic benefits-the multiple benefits-of a therapeutic lifestyle change. You say, "One of the longest standing statin promotional advertisements reads, 'When diet and exercise fail, meet another candidate for lipid-lowering therapy.'"9 You go on to say it is almost subliminal that we are assumed to fail before we start, which then presupposes that a person needs to be on the cholesterol-lowering drug before they even give serious attention to therapeutic lifestyle changes. That really begs a question that relates to someone we interviewed last year in 2008, Dr. James Wright from the University of British Columbia School of Medicine. You probably know Dr. Wright authored (or actually co-authored) a very controversial paper in Lancet in which he and his colleague from Harvard did a retrospective analysis of the published primary prevention trials on statins and they came to the conclusion that the benefit to individuals on primary prevention of taking statins alone was probably far less than that which we recognize based on number-to-treat.10 They came to the view (based on the published intervention trials) that the NTT for statins in primary therapy (primary prevention) is probably greater than 60, which they said is, from a pharmacological model, kind of a crapshoot. When you talk about pleiotropic effects of a therapeutic lifestyle change program, it sounds to me like it may be much more efficacious than an NTT of 60 plus for individuals on statins.

Number-Needed-to-Treat Data is Open to Interpretation

RL: You know, the NTT (the number needed to treat) is dependent on the baseline risk to begin with. The higher your risk (the more risk factors you have) and the older you are affects the number needed to treat, and it can drop substantially down to as low as 6 or 7, as we saw with the Diabetes Prevention Program (again, they were not addressing first heart attack, they were addressing new onset diabetes). In other words, the higher the total cholesterol at baseline and the higher total global risk of the patient (including cholesterol, blood pressure, and all the other Framingham Risk Factors), the more efficacious and cost-effective statins are. I don't see anybody arguing that statement.

The option that I have always promoted is that within the lowest risk subsets (the majority of us are in the high-end of low-to-moderate risk level), many are taking prophylactic statins and other drugs to perhaps defer risk. That is where there is some question about the cost-effectiveness. For that group of people (including myself), sufficient energy expenditure per week/per day and the right choice of dietary behaviors (I'm not talking about a diet, per se, I'm just talking about the right choice of foodstuffs over the course of a day, a week, a month, or a year) would certainly be cost beneficial, especially from a cardiometabolic risk perspective. What I mean by that is that both the immediate risk of diabetes and metabolic disease and the later risk (usually it comes a little later) of cardiovascular disease are addressed.

The number needed to treat is certainly very high in some patient subsets, especially in primary prevention. We just saw in the JUPITER trial (one of the largest statin trials ever) with rosuvastatin in 18,000 older men and women that had absolutely normal total LDL the NNT averaged about 108. The

only risk factor the participants really had other than their age being around 66 years on average, was a high C-reactive protein (at around 4 or 4.1). The investigators stopped the main intervention at two years (it was supposed to be a five-year trial) and saw that there was unimpeachable statistical significant reduction in first event risk or around 44 to 45{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. If you looked at the number to treat needed to treat that many patients with that level of statin therapy (which happened to be 20 milligrams of rosuvastatin), the number needed to treat was around 100. But if you took the trial all the way out to five years and projected it, the number needed to treat was 25. So there is a lot of manipulation of the numbers. I try not to get too caught up in it other than what is...

You know, we have sort have lost our horizon, especially against some of the pharmacotherapies for people that are fairly average risk and not super-high risk. We have lost the horizon on the efficacy of modest but consistent lifestyle changes. For instance, just adding 1000 calories of exercise a week, and just making a couple of substitutions in diet would be equivalent to the risk reduction that we saw in the Diabetes Prevention Program, where the number needed to treat to prevent diabetes was 5 (5 to 7, depending on how long you take the trial out).

JB: You've raised some very, very important questions there, clinically. We went from the biomarker of LDL cholesterol and total cholesterol, then to hsCRP-are there other biomarkers that one would throw a net over that give us a better snapshot of relative risk?

Perspective on Biomarkers
RL: There are 47 biomarkers on my list. Biomarkers that independently score risk above the traditional risk factors are very few. Everybody says there are some, but nobody can provide sufficient data with multi-ethnic groups across all ages that stand out as an independent, added measure of risk.

One that is forthcoming that is probably (I'm going to take a guess, here) going to get some consensus with the next NIH guidelines on dyslipidemia, which will be out about a year from now (called ATP4), will be apoprotein B, which is very close to the same thing, but not identical, to what we call non-HDL. There is an apo B particle on every triglyceride-rich lipoprotein. In other words, on every lipid particle in the blood, (except HDL), there is an apo B particle on it. So if you're measuring apo B, or if you simply take your lipid profile that you get from the doctor's office and subtract HDL (the smaller number-HDL cholesterol) from the total cholesterol, you get non-HDL. Non-HDL and apo B are very close to the same thing. That measure (either non-HDL or, perhaps a little more specifically, apo B) will be looking at both cholesterol-rich and triglyceride-rich particles.

With apo B, you are talking about a measure that is going to be more reflective of lifestyle risk in more of an immediate fashion. For example, if you just stop drinking pop today (if you are someone drinking 3 or 4 Coca Colas each day), one thing that will be reflected in your blood test in the next 48 to 72 hours will be apo B or non-HDL, whereas LDL and total cholesterol HDL (if it's affected at all) may take some time. It is quite undisputable (just from the last two years of research and clinical trials) that apoprotein B and non-HDL may be as important, and in some cases, especially in diabetic patients and patients with metabolic syndrome, it is actually a better target of therapy for reducing cardiovascular risk than LDL cholesterol. We are not forgetting about LDL by any means, but we've now got a new measure that may supersede LDL by a small measure if the clinical trials continue to show that it is a great target for therapy.

I would have to say, C-reactive protein can also be an independent measure of risk-it has been shown in numerous studies-but when you add it to a traditional Framingham risk scoring tool, the consensus is divided that it is that much benefit-that it adds anything to it-with one exception: if you are in the moderate risk range (that means if your 10-year probability of having an acute, coronary event is 10 to 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}), high C-reactive protein can actually bump you up to the high risk classification, but it doesn't help much in predictive modeling if you are in the low risk or the high risk subset. The final analysis for CRP is not completely in yet, but the big question for the payers is, "Okay, don't tell me there are more biomarkers; tell me there is a biomarker that is better than what we have now and we'll identify more people over a 10-year period or longer that are going to infarct or have diabetes or whatever else." That's really what they are looking for and is of substantial importance to them.

JB: That really leads me to a very interesting collateral question that is related to the subtitle of your paper, "Therapeutic Lifestyle Changes: Pleiotropic Benefits." As you have already mentioned, the pleiotropic effects of a therapeutic lifestyle change might then have an effect on metabolism (such as to normalize a variety of metabolic disturbances that are associated with distorted physiology), and therefore what we need to look at is a pattern of biomarkers, not just put our eggs in a basket related to the biomarker of the month. Do you think we are getting into a pattern recognition kind of portfolio effect?

Biomarkers and Test-Retest Reliabilities
RL: Yes, that's a good question. I don't know what to make of all the biomarkers. I mean, all of them are, to some degree, more or less transduced by every thought you think, every minute of the day. What does that mean, is the big question?

Beyond weight loss and beyond total or LDL cholesterol reduction, all of the biomarkers are important, especially the inflammatory markers (the inflammatory cytokines, like interleukin-6 and CRP and others). But they have test-retest reliabilities that are very wide. You can do a biomarker litany test on an individual, split the sample and have one sample analyzed at one time of the day and then in the next aliquot have the next sample, and the lab bias can be anywhere-and this is true for LDL cholesterol-from 8 to 15 to 20 percent. It is very hard to grasp some of the biomarkers as standards that are stable enough to get our hands around so we won't get pre- and post-test changes due to lifestyle measures.

Probably the most noteworthy pleiotropic effect I can think of is AMP kinase activation. AMP kinase is an enzyme that is very much involved in energy production with every muscular contraction; it has to do with exercise, of course (even very low levels of exercise). AMP kinase activation is one of the principal foci of many of the anti-diabetic drugs, especially a wonderful drug-it is probably the drug in diabetes-and that is metformin, otherwise known as Glucophage. Glucophage and intentional types of exercise (I'm talking about walking for health, or that type of exercise) almost are duplicative of one another in their mechanisms in the muscle cell and in the liver. They almost have exactly the same responses. In fact, I've gone so far as to say that every step you take is an AMP kinase activator-you've taken small milligrams of metformin with every step you walk. But you are going to have to walk, and you are going to have to walk quite a bit. It is very close to the same effect, if not almost identical.

Does that mean we need to measure AMP kinase as a separate act? Absolutely not. It is so variable from minute to minute that you couldn't. If we look at apolipoprotein B, as I said earlier, that's a little bit more stable. It does need to be fasting, and depending on the assay you use (and they are narrowing down the

assay to just one, so everybody is on the same page). We're going to get a test-retest reliability that is plus or minus about a little under 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, which will be very good, whereas if you just measure triglycerides as a biomarker, triglycerides reflect a lot of lifestyle. In fact, it is probably the best single lifestyle marker you have that is on a traditional lipid profile in the doctor's office. It has a test reliability or variability co-efficient plus or minus about 35{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. It is like glucose; it goes up and down a lot.

Personally, I can't justify taking a whole litany of biomarkers (a collection of them) all at once, and then advising based on the average outcome to the assays, in terms of what someone should be doing by increasing their energy expenditure or eating more fish or whatever. But what I could do, perhaps, is take tier one of those biomarkers, which might be the most evidence-based ones, and do that-perhaps baseline and then every 8 to 12 weeks for the first year until we get the patient to where they think they should be. One of those targets would be lipids (apolipoprotein B, LDL cholesterol). Another target would be, perhaps, waist circumference. Of course, there is blood pressure-it's not a biomarker, but if it's measured correctly that would be another indicator. (I'm saying a lot there because I think sphygomometers often are not used correctly in physicians' offices-you've seen how people pump up the manometer in about 2 seconds and they drop it in about 1 second until you have 149 over 77.) And I would also use, perhaps, C-reactive protein. CRP is affected by weight loss and smoking cessation. It has also been shown in a number of studies recently that the fitter you are the lower your CRP (it doesn't mean it completely normalizes, but it does tend to come down with weight loss, and of course, improving your fitness).

Another measure that has gotten a lot of attention over the last five years is LDL particle number (not to be confused with the regular LDL cholesterol). LDL particle number is a great measure of modest lifestyle changes, especially moderate levels of exercise. LDL cholesterol that you'd have measured in your physician's office is not a very good marker (visit to visit) of how much exercise you are doing (it will be, ultimately, as you lose weight). LDL particle number is measured through nuclear magnetic resonance imaging (NMR). When you measure LDL particle number, it will drop in real time as you become more engaged in exercise, versus waiting for 6 to 12 months (if at all) to watch your LDL change. And LDL particle number probably is more meaningful than LDL cholesterol milligrams per deciliter.

That's my take on some of the more important markers that are pretty responsive to lifestyle changes, even modest levels of lifestyle changes.

JB: That was a fantastic review. I compliment you. That covered a huge body of literature very, very succinctly. You said something that I thought was quite interesting that I want to come back to pick up on, and that is the question concerning body mass index or central adiposity. There is a big question that continues to be controversial: how much weight does a person have to lose? Do they have get down to their ideal body height-to-weight ratio based on the Metropolitan Insurance Table Data? What is a realistic target/objective for a person with elevated BMI?

RL: We don't use BMI as a central measure for the metabolic syndrome. You use it in the clinic, of course, to measure someone's baseline, but it is not a targeted therapy, per se, for a pre-diabetic, or someone with the metabolic syndrome, which has, of course, consensus standards of risk factors that have cut points. For instance, one cut point for a male's waist circumference would be 40 inches or greater (this

would qualify for the metabolic syndrome), if you are measuring waist circumference correctly (which then takes some skill). In a woman, the measurement might be 35 inches or greater.

Waist circumference and BMI are very closely correlated, but central adiposity is a little easier to rationalize as a pre-diabetes equivalent, or a pre-diabetes risk factor, or a metabolic syndrome risk factor. Although in the last two years there have been several papers on large populations that said there wasn't that much discrimination of significance between measuring BMI and waist circumference. It's hard for me to hang my hat totally on one or the other, but one thing I will say: waist circumference or BMI don't give you a lot of real time feedback from doctor's visit to doctor's visit (that means every 6 to 8 weeks). I mean, they will change, but some of the biomarkers change a little bit faster and may be more responsive to modest lifestyle changes than weight. I still put adiposity or anthropometric changes in sort of a tier two class. They are in a tier one class in terms of predicting risk, no question; they are very, very important. But in terms of follow-up, I would rather measure behavioral follow-up than biomarker follow-up or anthropometric follow-up. Is not what we are trying to do from visit to visit measure the step count, the food choices, the stress and disease, someone's perception of their quality of life? Is that not the bottom line and does that not correlate as much (if not in some cases more) with heart vascular events or metabolic disease than the biomarkers do? You need both, is what I'm saying, but I think we need to put (as a biomarker) weekly step count on a reliable, well-engineered clinical pedometer as high as we would (if not more) than a lipid profile, for instance.

JB: That's very, very helpful. That's really clinical news to use. Could you give us some thoughts as to whether these concepts of therapeutic lifestyle change have been put to the test of trials, and if so, have the results looked favorable? People often ask about, "Show me. Give me the proof."

RL: Oh yes. It's funny because there is not as much consensus standard on how to walk and how to eat as there is how to measure lipids and waist circumference. It's coming of age, though. Let me just talk about one clinical trial that is going on now that had its first data published a little over a year ago called the Look AHEAD Trial. The Look AHEAD Trial is a very large trial of a little over 5000 diabetic patients. The Look AHEAD Trial is using absolutely the same lifestyle intervention as the big, head-turning, New England Journal of Medicine-published diabetes prevention trial that was published six years ago. A modest level of lifestyle changes in that diabetes prevention study delayed the onset of diabetes almost 60{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} compared to metformin, and metformin actually reduced new-onset diabetes itself.11

The Look AHEAD Trial is doing exactly the same study, except it is not using pre-diabetic or metabolic syndrome patients; it is using diabetic patients. The only difference is that rather than 150 minutes per week of exercise, they are doing 175 minutes per week of exercise, or what they are essentially doing is adding about 20,000 step counts per week to the patients' existing habits (over time; they don't do it all at once). It is one of the first trials that is actually measuring more judiciously and systematically the lifestyle changes (both diet and especially exercise). I don't have it right in front of me-but at the one-year mark they already lost just at 9{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of body weight. There are naysayers, including some of my own colleagues (not necessarily here at Duke, but just around the country and world) that say diabetics cannot lose weight (there's a huge mythology out there that diabetics have some mitochondrial dysfunction where they can't oxidize fatty acids sufficiently to lose weight); we've never subscribed to that, at least I haven't. The Look AHEAD Trial, at one year, showed just right

at 9{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} versus the control group that lost little or none. It also showed about a 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in many of the diabetes meds that participants were on at one year. I like to point at that one because that is a huge sponsored trial with adequate subject number with good statistical power. There are many much, much smaller lifestyle trials that have done the same thing, but they don't have the statistical power that you can argue with a little bit.

JB: Oh boy. I'll tell you, when we hear you speaking we wonder why this hasn't gotten more traction in medicine today. It is so overwhelming.

Do Clinical Studies Overlook Physical Activity?
RL: Dr. Bland, look at any package insert or any drug. Believe me, I'm hoping I'm not being too negative for drug therapy because we absolutely we have to have anti-lipemic drug therapy in my line of work, especially for people that already have disease. Clearly. First and foremost. Half of my work is with the National Lipid Association-with lifestyle changes there-but I certainly subscribe to the appropriate use of drug therapy for lipid disorders when it is necessary. But if you look at every anti-lipidemic, anti-cholesterol, or anti-triglyceride drug, in the package insert they will always have a lifestyle washout. It will show the list of clinical trials that were used to rationalize the efficacy of the drug to the FDA for approval. Of course, they always have 8, to 12, to 16 weeks of dietary intervention first. Nobody ever talks about physical activity. It is not in the vocabulary. It is always dietary intervention washout after so many weeks of diet, which, you know, actually has some efficacy, as they will show. But they leave it at that, with very modest dietary changes, and what is never, ever, posted in there is a behavior that probably has more far-reaching metabolic benefits in real time, and that is physical activity. And I'm not just talking about exercise, which is more systematic physical activity, I'm just talking about any physical activity.

In the article you read, Dr. Telford from Australia did a wonderful review: is it the physical activity or the weight loss that reduces risk?12 He says that 74 papers he reviews never quantify the effects of exercise. They always ruled in or ruled out dietary changes, and never calculated energy expenditure as a possible intervention or a possible contaminant to the outcomes of the study. It is virtually lost. That is just like these package inserts. They don't give credit for what would otherwise be a significant risk-reducer (not necessarily a significant LDL reducer, for instance, in statin therapy, but a significant risk reduction). Is not what we're trying to do reduce risk? Of course through reducing lipids, but isn't the bigger picture reducing risk? And if that is the case, why do we give such little accounting of physical activity in any of these studies, especially in the early phases of these drug trials?

JB: Yes, that's beautifully stated. Let me, if I can, just switch slightly over to the question of diet, nutrition, and food plans. We have a lot of controversy, obviously, floating around in discussion and in the literature about the most appropriate diet for inducing metabolic restoration. I think you made some very nice comments in your paper about studies that have been published-Esposito's work and others-as it pertains to a diet of variety and moderation. Could you tell us a little bit about your view on diet right now?

RL: I'm not a dietitian, but I've reviewed a lot of dietary trials and been involved in a number of them. If you rank order all the labeled diets-the more popular diets-over the last 15 years, without question

Mediterranean types of diets have, by far, the most evidence base in terms of cardiometabolic risk reduction, mostly on the vascular end (that is, reducing the risk of cardiovascular disease and maybe, to a little less extent, on metabolic disease like diabetes). I have to say the elements of a Mediterranean-type diet look like absolutely the best mix of nutrients from the fish, the nuts, the grains, and even the very, very modest/low consumption of alcohol. It looks like the most doable.

Of course, there is no one Mediterranean diet, per se. It is more of a concept that involves a variety of nutrients. A handful of investigators have spent their lives (and there are about 100 papers-published papers in refereed journals) on the biomarker responsivness to such dietary intervention. Clearly, if you look at the LYON Study from 15 years ago (one of the most important studies ever looking at Mediterranean-type diets reducing sudden death from coronary disease) and reflect back on that study and other studies like it, on the mechanisms of how such a balanced diet of fish, nuts, fruits and vegetables, whole grains could do such a thing, we clearly know that that type of diet is anti-inflammatory, tends to increase the threshold for ventricular arrhythmias (it doesn't mean that if you have extra heartbeats they all go away, but you have fewer of them), decreased synthesis of some of the cytokines, and clearly improved arterial wall motion (or what we call endothelial function). Also, it is anti-thrombotic. In other words, it is a little bit, if you will, like an aspirin effect. I shouldn't call it aspirin, but a little bit of an anti-platelet effect. Other diets have this too, but if you had to add and balance all of the nutrients of the Mediterranean concept, you'd probably have everything you need. There is enough flexibility in it to satisfy most peoples' craving for one nutrient over another.

JB: I noticed that you had been a co-author/collaborator in a very interesting paper I read that appeared in the journal Atherosclerosis in 2006 looking at diet and exercise versus pioglitazone in managing diabetogenic risk in patients with obesity and how that influences atherogenicity, lipoprotein particle size, and the like.13 Can you kind of review your conclusions?

RL: That was an original paper by the Mayo Clinic (some of our colleagues at the Mayo Clinic). I didn't have anything to do with the original paper in Diabetes Care some years ago, but I saw it and I called the investigators and I said, "Geez, can I get some of the bloodwork from that? You didn't mention much about the exercise and the lipid response. All you basically said is pioglitazone is a good drug." And it was a good drug; it increased sensitivity and it had a positive effect on the metabolic syndrome, although it did tend to increase fat stores a little bit like glitazones do, but they didn't do much analysis of the exercise. So I actually got the data from this study, along with Dr. Shadid, who was the lead author, and said, "Can I get the bloodwork? I want to do NMR, which will take a much harder look at all the lipoproteins and LDL particle numbers and all that." Well sure enough, when you looked at pioglitazone, at least 30 milligrams a day, versus the diet and exercise (and it was very modest), the exercise was adding about 1200 calories of exercise per week to these people (it was only about 40 people). Twelve hundred calories of exercise a week is about 10 miles of walking a week, so originally is was a very modest amount. And they decreased the total caloric intake by around 400-500 calories a day. What we found is that compared to pioglitazone, this modest dietary/exercise intervention in these patients with the metabolic syndrome, essentially in every category except for insulin sensitization, was remarkably more beneficial. And pioglitazone (otherwise known as Actos) was beneficial, definitely. It's a good drug-a great drug; it really is. But when you matched it against modest but systematic approach to consistent lifestyle changes... This did not come out in the original paper (it didn't even come out in my paper because I wasn't the lead author-it was a piogliatzone-focused paper). But in fairness to my co-authors, they did say that diet and exercise (the modest lifestyle change) was at least as good as the pioglitazone,

and one thing it did (over an above the pioglitazone course) is it prevented any further weight gain. In fact, participants actually lost weight rather than gained weight like you do on the glitazone meds. It had the same efficacy on increasing insulin sensitivity. The other thing diet and exercise did was it had a much more beneficial effect on the VLDL and reducing triglycerides. So it was a small study just saying that in many cases, for diabetes patients, if you can get the patients to walk more, lifestyle is a definite beneficial option to the medicine, or at least to be used in combination therapy with the medicine.

JB: I really want to compliment you. What you've covered in this last 40 minutes is just a spectacular landscape of clinical medicine taken down into the place where it really makes a difference and that's in patient management. I think your work is fundamentally important at this time when we are really contemplating cost-effective ways of improving the health of the world and certainly of the United States, specifically. I want to really encourage you in continuing this extraordinarily important work, and hopefully your voice will be heard in those decision-making quarters that are really going to decide how dollars are going to be spent on the way our healthcare system will look in the years to come. Mr. La Forge, thank you so much. It has been fascinating.

RL: Thank you so much, Dr. Bland.

JB: We'll be following your work very closely.

RL: Thank you.

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