FEATURE

The Heart and Medicine: Exploring the Interconnectedness of Cardiometabolic-related Concerns Through a Systems Biology Approach

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ABSTRACT

Patients do not just wake up one morning with cardiac disease. Instead there is an extended preclinical phase during which lifestyle choices determine outcome. Recent advances in our understanding of oxidative stress, endocrine signaling, immune/inflammatory balance, and energy production illuminate opportunities for efficacious intervention. A thorough exploration of these pathophysiologies will allow physicians the opportunity to offer their patients a journey away from illness and disease to optimal wellness.

摘要

罹患心脏病并非一夜之间。相反，这是一个潜伏期漫长的过程，在此期间生活方式的选择具有决定性的作用。近期我们对氧化应激反应、内分泌信号、免疫 / 炎症平衡及能量产生的理解更进一步，让我们看到有效干预的机会。对这些病理生理学方面的彻底探究将让医生有机会为他们的患者提供远离疾病保持健康的保健之道。

SINOPSIS

Los pacientes no se levantan de repente una mañana con una enfermedad coronaria. En cambio, existe una fase preclínica larga durante la cual la elección del estilo de vida determina los resultados. Los avances recientes en nuestro entendimiento sobre el estrés oxidativo, las señales endocrinas, el equilibrio inflamatorio/inmune y la producción energética abren las oportunidades para una intervención eficaz. Una exploración minuciosa de estas patofisiologías permitirá a los médicos ofrecer a los pacientes la oportunidad de un viaje lejos de su enfermedad hacia un bienestar óptimo.

The currently accepted understanding of cardiovascular disease views the signs and symptoms of angina, congestive heart failure, myocardial infarction (MI), and sudden death as acute episodes marking a disease process. A systems biology approach provides a different view, one in which there is an overlap among many conditions affecting many organ systems mediated by oxidative stress and immune/inflammatory dysregulation that contribute to the development of comorbidities.

It has been noted that rheumatoid arthritis and autoimmune inflammatory disease are associated with an increased risk for cardiovascular disease.[1] Sheng et al note in their 2012 *Journal of Rheumatology* article that treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) were associated with reduced total cholesterol levels in patients with osteoarthritis and rheumatoid arthritis.[2] More importantly, however, statins were associated with reduced cardiovascular events and all-cause mortality in rheumatoid arthritis patients and all-cause mortality in osteoarthritis. Thus we would be well suited to think about cardiovascular disease not as an isolated condition but rather to think about the pathophysiologies that underlie what many are now calling cardiometabolic syndrome. Cardiometabolic syndrome is a grouping of signs and symptoms including abdominal obesity, insulin resistance, elevated blood pressure, atherogenic dyslipidemia, a proinflammatory state, and a prothrombotic state.[3] Though controversy still exists as to whether or not the diagnosis of cardiometabolic syndrome allows for a differentiation of risks beyond the individual features, this diagnosis is useful in helping identify all the pathophysiologies that underlie the condition. We must consider that beyond the dyslipidemia, hypertension, atherosclerosis, and progression to type 2 diabetes, cerebral vascular disease, and cardiovascular disease, the consequences of cardiometabolic syndrome include type 3 diabetes, sleep apnea, malignancies, erectile dysfunction, nonalcoholic fatty liver disease, end-stage renal disease, and osteoporosis.

Though conventional wisdom frequently postulates that obesity is a cause for heart disease and diabetes, evidence would suggest instead that obesity may be a coexisting sign or indeed even a symptom of the underlying pathophysiology. It is very clear that metabolic syndrome is correlated with the presence of obesity. With an increase in the percentage of body fat and body mass index (BMI) from the normal range to the moderately obese, the prevalence of metabolic syndrome increases from 4.8% to greater than 90%.[4,5] As Ackermann et al[6] have noted, however, there is also a very interesting positive correlation between waist circumference and inflammatory cytokines including

high sensitivity C-reactive protein and interleukin 6.

As we witness the incidence of obesity increasing, we must consider some of the factors that also have changed in our society. Certainly one interesting component is that the way we live day to day is for most of us incongruent with our individual health goals. During in vitro experiments when cellular biologists wish to mature pre-adipocytes into mature adipocytes, they do so by exposing these cells to a cocktail of dexamethasone, insulin, and 3-isobutyl-1-methylxanthine. This cocktail is actually a real-life cocktail that many of us take each morning. The Monday morning stress of facing a new work week and racing at speeds well over the speed limit or being stuck in bumper-to-bumper traffic during our morning commute raise our endogenous cortisol levels. A highly sugared 4-shot latte provides the sugar needed to produce hyperinsulinemia, and the 4 shots of caffeine act as a phosphodiesterase inhibitor similar to the 3-isobutyl-1-methylxanthine.[7] And as Christakis and Fowler reported in *The New England Journal of Medicine* in 2007, obesity is socially contagious.[8] A person who has a friend who is obese has a nearly 100% increased risk for personal obesity. If a person has a mutual friend (meaning that each person regards the other as a friend) who is obese, then the risk approaches 200%. The difficulty involved in making lasting lifestyle changes increases the likelihood that obesity is here to stay. However, an interesting article by Ludwig et al in *The New England Journal of Medicine* in 2011 demonstrated that

> *the opportunity to move from a neighborhood with a high level of poverty to one with a lower level of poverty was associated with modest but potentially important reductions in the prevalence of extreme obesity and diabetes.*[9]

So why is it important to understand cardiovascular disease based on a systems biology approach rather than the standard signs and symptoms leading to a differential diagnosis? Wijeysundera et al reported that cardiovascular heart disease mortality in Ontario, Canada, decreased by 35% between 1994 and 2005.[10] They noted that improvements in medical and surgical care and reductions in risk factors including cholesterol and hypertension accounted for 43% and 48%, respectively, of the reduction. Yet diabetes prevalence and increasing BMI accounted for a 6% increase. So although the mortality may be dropping in established disease and some risk factors are being well managed, it appears the average patient really is not doing better. More and more of our patients are experiencing that long prodrome to clinical disease. The toxicity of our environmental, social, and cultural world creates the pathophysiologic disturbances that we call obesity, cardiometabolic syndrome, diabetes, and heart disease and that result in morbidity and mortality.

In a classic paper in 1980, Fries pointed out that lifestyle change could rectangularize the survival curve, resulting in more years of better quality of life and increased vitality.[11] The benefits of a healthy lifestyle realized by nonagenarians and centenarians living in the geographic regions characterized as "blue zones" by Dan Buettner[12] have suggested that this goal is achievable. Unfortunately, we in medicine are not achieving this compression of morbidity. Crimmins et al report that from 1998 to 2008, the length of life has increased, but the prevalence of disease has increased and mobility and functioning have declined.[13]

So what options can we offer our patients? Where do we find treatment approaches that incorporate this expanded understanding of physiology and provide answers? The classic approach for a new patient has been to conduct a standard history and physical, taking into account the history of present illness; past medical, social, and family histories; a review of systems; and finally a physical exam in the creation of a differential diagnosis list. The diagnosis at the top of this list is the name we give to the etiology of the symptoms and signs that we see. Then we blame this diagnosis and treat it in a linear pharmacologic fashion.

Understanding cardiovascular disease based on a systems biology approach and incorporating the functional medicine model of antecedents, triggers, and mediators allow us to see the connectedness between events and the connectedness between organ systems. Recognizing this interconnectedness allows us to effectively harness the latest science in a holistic model of care. As we plot a patient's history in the matrix taught by the Institute for Functional Medicine, we are given the opportunity to view pathophysiology in a fashion that offers new treatment opportunities.

A SYSTEMS BIOLOGY APPROACH TO CARDIOMETABOLIC DISEASE

Classically, we think about many conditions as being separate, both in their signs and symptoms as well as their etiology. Yet we now recognize the connectedness of the mechanisms of oxidative stress, endocrine signaling, immune/inflammatory balance, and energy production as underlying the pathophysiology of the named disease entity. Though some of our colleagues may be puzzled by the fact that inflammation and insulin signaling seem to overlap, these signaling pathways share a common developmental history in the teleologic expansion from the fat body of the *Drosophila*, the common fruit fly, to the unique organs and their metabolically active adipocytes, hepatocytes, and leukocytes that we see in mammals.[14] Zhang et al have gone even further and suggested that though

> *near instantaneous signaling of hypothalamic IKKb and NF-κB might once have been critical for survival in a pathogen-filled environment by helping innate immunity, this signaling might now be very responsive [overly] and truly detrimental in today's near constant calorie-rich environment.* [15]

Endoplasmic reticulum stress is now recognized as an early consequence of nutrient excess and perhaps a cause for insulin resistance and inflammation.[16]

Atherogenesis: How a Plaque Forms

Atherosclerosis traditionally has been characterized as the progressive laying down of cholesterol with subsequent narrowing of blood vessel leading to restricted blood flow. Though this might be a commonly held concept that informs our current model of care, early controversy existed as to whether cholesterol or inflammation was the primary risk factor for atherosclerosis. In a classic debate dating back to the early 1800s, pathologist Carl von Rokitansky and his counterpart Rudolph Virchow argued as to which was the primary risk factor. Despite Virchow's view on the irritation of the vessel wall, he did indeed acknowledge in 1856 that cholesterol was the prime etiologic agent in the development of atherosclerosis.[17] Anitschkow's experimental work in rabbit feeding studies in 1913 helped solidify the development of atherosclerosis as a consequence of a high-cholesterol diet.[18] In 1951, Duff and McMillian would mainstream this concept in an article in the *American Journal of Medicine*.[19]

Steinberg has very aptly noted that despite the key role that hypercholesterolemia plays as a major causative factor in atherogenesis, it is equally clear from the very beginning that atherogenesis has a strong inflammatory component.[20] Inflammation is the healing response of the body to an injury. It is only when triggers and mediators interfere with the switching off of inflammatory signaling that this process progresses in a feed-forward cycle to a pathophysiological condition. Our current model proposes that hypertensive stimuli and oxidized lipids lead to prooxidative changes in the endothelial cells that separate the lumen from the intima and media of the vessel well. The anatomical location of this single cell layer becomes crucial in our understanding of the dance that takes place between the consequences of hyperlipidemia, hyperglycemia, inflammation, and oxidative stress secondary to toxicity. Mayerl et al, in a review of actual atherosclerotic specimens examined by von Rokitansky, have demonstrated that proinflammatory cellular intralesional components and extracellular matrix proteins were indeed present.[21]

The Endothelial Layer: Where It All Begins

Endothelial injury is the initiating event that leads to the migration of oxidized low-density lipoprotein (oxLDL) particles through the endothelial layer into the intima. OxLDL increases lipoprotein phospholipase activity and upregulates the generation of inflammatory mediators that promote the recruitment and migration of monocytes through the endothelial layers and their activation into macrophages. These macrophages recruit additional monocytes and scavenge the deposited cholesterol. Lipid-laden macrophages transform into foam cells. These changes upregulate the secretion of inflammatory cytokines, cellular adhesion molecules, matrix myeloperoxidases, and reactive oxygen species. Ultimately, necrotic cell death of the macrophage is a final step in the formation of a cholesterol-laden atherosclerotic plaque with proinflammatory changes. This plaque is vulnerable to the accumulation of calcium and also vulnerable to plaque rupture with the subsequent pro-thrombotic state leading to development of flow-limiting blood clots. Hypertensive stimuli such as a high-salt diet and increased production of angiotensin II promote the production of reactive oxygen species, and these species contribute to hypertension and to the sequelae of this disease.[22]

Healthy endothelial cells in response to local stimuli produce nitric oxide (NO) from L-arginine. NO is the primary signaling molecule for the relaxation of the smooth muscles and the inhibition of monocyte adhesion and platelet aggregation. The primary stimulus for the production of NO is the sheer stress generated by blood flow across the endothelial lining. As blood pressure increases, as cardiovascular output increases, as systemic vascular resistance increases, increasing sheer stress activates the protein kinase Akt leading to upregulation of endothelial nitric oxide synthetase (eNOS) and a resultant increased production of NO.[23]

Interestingly, negative features like high blood sugar, oxLDL, and dysfunctional low-density lipoprotein (LDL) affect protein kinase C (PKC)b_{II}. This upregulation of $PKCb_{II}$ actually inhibits Akt and downregulates eNOS.[24] Ruboxistaurin (RBX), a $PKCb_{II}$ inhibitor, is undergoing clinical trials evaluating its ability to normalize eNOS function that has been decreased by glucose-induced $PKCb_{II}$ activation. In a multicentered, double-blind placebo-controlled trial of 123 subjects with type 2 diabetes and proteinuria, RBX significantly decreased albuminuria by 24% compared with 9% by placebo and RBX maintained renal function after 1 year.[25]

Flow-mediated vasodilation (FMD), a technique by which one looks at brachial artery dilation following an ischemia-induced hyperemic significant sheer stress, allows an insight into endothelial function. It has been demonstrated that FMD improves with reduction in cholesterol.[26,27] Highlighting the importance of endothelial function, FMD has been used to demonstrate that improvements in endothelial function are associated with a reduction in cardiovascular risks with treatment for hypertension.[28]

The role of nitrates and nitrites in the NO cycle has been evolving over the past decade. In an excellent review, Lundberg et al report that nitrates from food are reduced by bacteria in the oral cavity to nitrite.[29] In the gastric acidic milieu, a nonenzymatic reduction of nitrite to NO occurs. Both NO and nitrite are biologically active. It has been demonstrated that nitrite readily affects cyclic guanosine monophosphate production and may play a role in endothelial relaxation.[30] Indeed, mice fed a diet supplemented with nitrite in their drinking water exhibited both higher plasma levels of nitrite as well as a 48% reduction in infarct size.[31] Mice fed a cholesterol-enriched diet exhibit elevated

leukocyte adhesion. These mice were noted to have reductions in both the leukocyte adhesion and monocyte migration with the administration of nitrite in their drinking water.[32]

Omega-3 Fatty Acids: Looking Beyond Eicosanoid Balance

As we consider the biology of the endothelial layer, the role of lipids remains a significant one and indeed an evolving one. Close attention still needs to be made to the concentrations of LDL, high-density lipoprotein (HDL), and the very-low-density lipoprotein fractions. Yet, fatty acids are more than just building blocks for obstructive plaque. Fatty acids play integral roles in inflammatory processes and cell signaling. It has been demonstrated in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) study that low-dose fish oil significantly reduced the cumulative rate of all-cause death, nonfatal MI, and nonfatal stroke.[33] The individual components of fish oil docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been evaluated for their individual properties. DHA is the principal omega-3 fatty acid in fish and fish oils responsible for their blood pressure– and heart rate–lowering effects in humans.[34] EPA and DHA seem to be equally effective in lowering triglycerides with the caveat that while DHA leads to significant increases in HDL cholesterol, it may also lead to increases in LDL cholesterol not seen with EPA-containing supplements.[35]

Traditionally, supplementation of omega-3 fatty acids was conducted to restore balance between the proinflammatory omega-6 prostaglandins and the anti-inflammatory omega-3 prostaglandins. It is now recognized that DHA, by modulating mitogen-activated protein kinases, regulates the expression of transcription factors—a fact important in understanding the mechanism of action of this fatty acid on T-cell differentiation in disease and health.[36] Beyond this regulatory kinase role, omega-3 fatty acids bind to the G-coupled protein receptors (GPR) 120 and 140. When upregulated, these receptors increase insulin sensitivity by increasing glucose-dependent glucose-like peptide-1 secretion and by regulating adipocyte differentiation while downregulating inflammation.[37,38] GPR-120 functions as a receptor for unsaturated long-chain fatty acids and plays a critical role in modulating adipogensis and regulating appetite and food preferences. Ichimura et al have shown that GPR 120–deficient mice fed a high-fat diet developed many of the signs and symptoms associated with cardiometabolic syndrome, including obesity, glucose intolerance, and fatty liver disease.[39] It has been found that intravenous infusion of free fatty acids influences proliferation of the beta cell in people with type 2 diabetes.[40]

With an expanding database suggesting the benefits of marine oils containing omega-3 fatty acids, one would suspect that a consensus would have formed around the administration of omega-3 fatty acids in people with cardiometabolic syndrome and cardiovascular disease. A recent study by Kromhout et al, however, pointed out that

> *low dose supplementation with EPA/DHA or alpha-linolenic acid (ALA) did not significantly reduce the rates of major cardiovascular events among patients who had MI and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.* [41]

However, there were major flaws with the design of this study, and indeed, the study's 2x2 factorial design was inappropriate for the evaluation of 2 non-independent study drugs (the fish oil and the ALA). Additionally, the study was underpowered to detect differences among the 4 groups. One of the major physiological effects of omega-3 fatty acid supplementation is reduction in triglycerides, and the relevance of the low doses administered in this study are demonstrated by no change in triglycerides in any of the treatment groups. Despite this, in a post-hoc analysis, there was a significant reduction in cardiovascular risk for the diabetic participants taking fish oil in this study. Defilippis et al in a conservative opinion recommend "one serving (200-400 g) of fatty fish two times per week in a diet that includes foods rich in ALA for the primary prevention of cardiovascular disease."[42] Additionally, they recommended 1 serving of fatty fish or a fish oil supplement containing 900 mg of EPA/DHA every day as well as a diet rich in ALA for patients with known cardiovascular disease or congestive heart failure.

Environmental Toxicity

It is well recognized that, in addition to lifestyle changes that include increased carbohydrates in the diet and decreased exercise, environmental changes, specifically the exposure to persistent organic pollutants and toxic elements, contribute to the development of both atherosclerosis and diabetes. Menke has noted "the association between blood lead levels and increased all-cause and cardiovascular mortality was observed at substantially lower blood lead levels than previously reported."[43] Houston has recommended that evaluation for heavy metal toxicity should be conducted in all patients with hypertension, coronary heart disease, or other vascular disease, looking specifically for mercury and cadmium toxicity.[44] In an interesting study looking at arsenic in the drinking water in Michigan, a direct correlation has been noted between elevated arsenic levels and elevated mortality rates, both from males and females for circulatory diseases, diabetes mellitus, and kidney diseases.[45] In a study by Lim et al, the presence of high normal serum gamma-glutamyltransferase (GGT) activity is thought to be a marker for the presence of persistent organic pollutants.[46] Indeed, the risk for developing type 2 diabetes did not increase with increasing obesity except for the 2 quartiles with higher normal GGT levels, with the

risk being increased 6-fold for the group with moderate obesity and the fourth quartile of a normal GGT. Rejeb et al, looking at a Tunisian population, noted the increased liver enzyme activity associated with metabolic syndrome and noted that increased GGT and alanine aminotransferase seemed to be associated with an increase in coronary stenosis.[47] Barbara Corkey, in receiving her Banting Medal for Scientific Achievement Award in diabetes, noted that insulin resistance is caused by hyperinsulinemia, a consequence of increased beta-cell secretion due to toxicity. She has identified in her lab that monooleoylglycerol, iron, and saccharin may all be common dietary ingredients that are capable of producing hyperinsulinemia.[48] Hyperinsulinemia due to toxicity may be one of the predominant factors in the development of type 2 diabetes.

And It All Goes Back to the Gut

Research has highlighted a connection between gut function, cardiovascular disease, and diabetes. The function of our gut is certainly modified by the foods we eat. A high-fat meal induces low-grade endotoxemia, the passage of lipopolysaccharides (a cell-wall component of gram-negative bacteria) across the epithelial lining of the gut.[49] In a 2011 review, de Kort et al reported a connection between alterations in intestinal permeability, compromised barrier function, and immune responses leading to the upregulation of inflammation as playing a role in the development of type 1 and 2 diabetes.[50] Cani et al have demonstrated the changes in gut microbiota control inflammation in obese mice through a mechanism involving glucagon-like peptide-2 (GLP-2) activation.[51] Activation of endogenous GLP-2 production leads to improved gut barrier function. Direct evidence for the influence of endotoxemia upon insulin resistance in humans has confirmed that modulation of specific adipose inflammatory and insulin-signaling pathways by the administration of intravenous endotoxin to human subjects results in a 35% decrease in insulin sensitivity.[52]

While the foregoing examples have clearly demonstrated the connections among the pathophysiologies of inflammation, immune function, and oxidative stress as responses to our current lifestyle and environment, research has also shown that it is more than just the poor choices that we may make or the poor environment to which we may be exposed. Evidence suggests that the nutritional choices made by our parents and the environment to which they were exposed have an influence upon our physiologies. In a now classic experiment, Cooney et al demonstrated that agouti mice given nutritional support for methylation during pregnancy have changes in their offspring that are epigenetically driven.[53] Maternal agouti characteristics include yellow fur, the development of obesity and diabetes, and shortened lifespans. The offspring of the nutritionally supported mothers have brown fur, do not become obese, do not develop diabetes, and maintain normal life expectancies. The mechanism here is epigenetic modification. Epigenetic methylation of promoter and suppressor genes regulates which genes are expressed in response to environmental stimuli. These bookmarks allow for environmental changes within an organism's lifetime or across a few generations to create an adaptive response. Though obviously no prospective human studies have been completed, observational studies including those conducted after the Dutch famine of 1944 have demonstrated that children who were in utero during the time of the famine were born with low birth weights and thereafter had significantly different phenotypic expressions as they became obese in young adulthood. This obesity has been associated with increased morbidity and mortality secondary to cardiovascular disease, diabetes, and possibly schizophrenia.[54]

A SYSTEMS-BASED FUNCTIONAL MEDICINE TREATMENT MODEL

An appreciation of the interconnectedness of cardiometabolic syndrome and its associated conditions allows us to build a therapeutic model different from the traditional "naming and blaming" model. We are now able to intervene for our patients in that early clinical phase of being overweight, of being tired, of being fatigued, of showing some signs of inflammation (perhaps a rash, arthralgia, or gastrointestinal upset). The opportunity now is to reconsider therapeutic interventions, some of which have been mainstays and some of which are new, as options for treating these unique sets of problems.

Lifestyle Medicine Today

It has long been recognized that lifestyle is an important tool for our patients to use in their journeys to health and wellness. However, it has also been clearly recognized that this is in many regards an uphill journey for patients, one in which they struggle to adopt a lifestyle that they find to be healthy and yet rewarding. One of the difficulties in prescribing a healthy lifestyle for patients is that many patients have not experienced successful lifestyle changes in the past. Indeed, a Gallup poll demonstrated that the number of Americans who had attempted to lose weight more than 10 times had increased from 5% to 11% during 1990 to 2005. A couple of the major hurdles for our patients in adopting a healthy lifestyle are the lack of consensus in the medical community that lifestyle does indeed make a difference and determining which program will work.

The Diabetes Prevention Research Group reported in 2002 that a lifestyle intervention consisting of a goal of at least a 7% weight loss and at least 150 minutes of physical activity per week led to a 58% reduction in the incidence of diabetes compared with a 31% reduction with metformin as compared to placebo.[55] Given this fact, physicians should be comfortable knowing that lifestyle has a major contribution to make in addressing the concerns about a lack of consensus. However,

the question of which program will be efficacious remains. In a 2007 Cochrane Database systematic review, Nield et al noted, "there are no high quality data of the efficacy of the dietary treatment of type 2 diabetes."[56] There were 36 articles reporting a total of 18 trials looking at the macronutrient contents that varied from low-fat, high-carbohydrate diets to high-fat, low-carbohydrate diets to high-protein diets to very low–calorie diets and even to the American Diabetes Association Exchange Diet.

Obviously, something is missing here. It appears that no macronutrient profile led to an efficacious dietary treatment of diabetes, yet we have seen that the lifestyle program associated with weight loss in the Diabetes Prevention study worked. Light may be shed on this issue by the recognition in an article by Luoma in 2010 that "healthy living habits and gene-activating xenobiotics upregulate mechanisms that produce lipoprotein patterns typical of very old people and enhance longevity."[57] This suggests that it is important to consider the micronutrient content of the program. It is the phytonutrients in our foods speaking to our genes that modulate regulatory signaling. Jacobs et al note that "the complementary study of food and food patterns and of nutrients and specific food constituents will enhance the understanding of diet and health."[58]

The Mediterranean-style low glycemic–load food plan (Med LGL) has the features that one would ultimately apply for a healthy lifestyle. It is a food plan that is low in saturated fat, low in trans fats, low in cholesterol, low in sodium, and low in simple sugar. The Med LGL limits grains to those that are low glycemic, but it does ensure sufficient intakes of fruits, vegetables, and monounsaturated fats. This food plan, with a broad variety of fruits and vegetables, provides a phytonutrient content that works as a xenobiotic to modify the genes that we choose to express and to make them congruent with a healthy lifestyle. Med LGL has been specifically demonstrated in clinical studies to reduce oxLDL by 12% compared to baseline and that these changes in oxLDL were inversely correlated with plasma lutein, one of the plasma carotenoids.[59]

Mozaffarian notes in a recent opinion paper that "the relatively recent focus on nutrients parallels an increasing discrepancy between theory and practice: the greater the focus on nutrients; the less healthful foods have become."[60] This must be considered when we prescribe healthy food plans for our patients. We may well need to consider the benefits of medical foods and nutritional supplements as adjuncts as patients make their lifestyle changes.

Niacin: Beyond AIM-HIGH

Despite our expanded focus including inflammation and oxidative stress, we still need to consider what we would do as clinicians for a high LDL and a low HDL. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, treatment with fenofibrate plus simvastatin for a subgroup with an elevated baseline triglyceride greater than 204 mg/dL and an HDL cholesterol below 34 mg/dL resulted in a 31% reduction in the rate of primary outcome of fatal cardiovascular events, nonfatal MI, and nonfatal stroke.[61] Fenofibrate also has been shown to be beneficial when added to low- or moderate-dose statins in the reduction of the presence of metabolic syndrome more than low-, moderate-, or high-dose statin monotherapy.[62] However, when we start looking at other markers and other treatments beyond statins alone, we find that ezetimibe added to simvastatin failed to show a significant difference in the carotid intima-media thickness (cIMT) as compared with simvastatin alone.[63]

In a comparison of niacin and ezetimibe, each paired with a statin, niacin was found to be superior in causing a regression of cIMT.[64] The beneficial effects of niacin, however, are not simply limited to their cholesterol-lowering effects. Warnholtz et al noted in a post-hoc subgroup analysis of patients with low HDL cholesterol at baseline that there was a statistically significant improvement in FMD with niacin treatment.[65] Niacin has been demonstrated to inhibit vascular inflammation in human aortic endothelial cells by decreasing endothelial reactive oxygen species production and thus LDL oxidation and to have similar influences in downregulating inflammatory cytokine production. We can conclude that niacin is effective for the treatment of both lipidemia and endothelial dysfunction through its actions upon oxidative stress and inflammatory markers. The safety and efficacy of niacin, however, were recently challenged. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) Study, an investigation of 3500 patients with established vascular disease who were treated with up to 2000 mg per day of extended release niacin, failed to find a benefit despite favorable changes in HDL and triglycerides.[66] It is interesting to note that these patients were already being treated with statins to an LDL goal below 70 mg/dL. Also, during the course of the study, in order to ensure that all the benefits would be ascribed to HDL and triglycerides modification, statin doses were decreased if the addition of niacin further reduced LDL cholesterol. The study was discontinued early due to a small but unexplained risk for ischemic stroke. However, the stroke data need to be considered from the perspective that this was an intent-to-treat data set. In addition, of the patients in the treatment group, 9 had discontinued niacin treatment for 2 months to 3 years before the onset of their stroke. There is now general consensus that the AIM-HIGH Study failed to demonstrate a lack of benefit of niacin with this study design and failed to demonstrate the invalidity of attempting to raise HDL in people with low LDL cholesterol. We may thus conclude that the pleiotropic effects of niacin are well suited to inclusion in an integrative treatment plan.

Therapies for Healthy Endothelial Function

Specifically targeting therapeutics to endothelial dysfunction allows the practitioner an opportunity to intervene early in the treatment of preclinical cardiovascular disease. Niacin, CoQ_{10}, vitamin D, and dark chocolate all have favorable impacts upon endothelial function.[67-69] Foods that are rich in nitrites and nitrates are beneficial for improving endothelial function. Hord notes that "approximately 80% of dietary nitrates are derived from vegetable consumption; sources of nitrites include vegetables, fruit, and processed meats."[70] Interestingly, it has been noted that many of the traditional Chinese medicine botanicals used for therapeutic effect in patients with cardiovascular disease replete the biological nitrite and nitrate stores as well or provide a natural system for NO generation in both endothelial dependent and independent mechanisms.[71] Bondonno et al recently noted that nitrate-rich spinach and flavonoid-rich apples "can independently augment NO status, enhance endothelial function, and lower blood pressure acutely, outcomes that may benefit cardiovascular health."[72]

Rho-iso-alpha acids (RIAA), derived from the hop plant, have been shown to inhibit $PKCb_{II}$.[73] Given the activity of $PKCb_{II}$ inhibitors in restoring endothelial function, medical foods supplemented with acacia and RIAA are excellent choices for the nutritional support of individuals with cardiometabolic syndrome.[74,75] Our preliminary work conducted at the Functional Medicine Research Center at MetaProteomics with tetrahydro-iso-alpha acid (THIAA), another hop extract, and niacin has demonstrated efficacy in a statistically significant manner in endothelial function for subjects with dyslipidemia. The beneficial antiinflammatory effects of THIAA coupled with niacin indeed lead to the suggestion that the combination will outperform that of niacin alone.

CONCLUSIONS

Exploring the interconnectedness of cardiometabolic syndrome and its associated diseases provides an opportunity to better understand the mechanisms that underlie these personally and socially important conditions. Treatment directed at pathophysiological disturbances rather than diagnostic categories provide opportunities for patients to take a journey from illness to health and wellness. Our opportunity as practitioners is to help guide patients on this journey, and our reward is that our patients will experience better health. With respect to a systems biology approach, the following adage applies: "Do not go where the path may lead; go instead where there is no path and leave a trail."

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