Health Condition: Diabetes and Metabolic Syndrome

“There is a perception in many societies when you are *in utero* that you're going to be in an environment of low amounts of nutrition, etc. But we're finding now that we're in the land of plenty, so what is becoming epidemic throughout the whole world, not just in the United States or Western culture, are the problems of obesity, diabetes, and increased incidences of cancer. It is a mismatch that appears between what was perceived to be the environment that we are going to live in and the environment we find ourselves in. It is probably one of the first times--or maybe the first time--that's ever happened because usually an overabundance of food is not what our species has encountered.”

—Randy Jirtle, PhD
September 2010

What is Insulin Resistance?

“High triglycerides were as common as a high cholesterol concentration in patients who had a heart attack. Our initial goal was to figure out why people had high triglycerides. The one hint we had was based on results of a study showing that, for most individuals with high triglycerides, the more carbohydrate they ate, the higher their triglyceride concentration became. We formed a pretty fancy hypothesis, almost 40 years ago, that some people were very insulin resistant. When they ate carbohydrate, they had to make lots of insulin, and insulin would make the liver make more triglycerides. That’s why you had high triglyceride concentrations. We started looking at that hypothesis, step by step. Within about 10 years, we had evidence for the relationships I described a moment ago.

We then turned our attention to the fact that people with type 2 diabetes were probably also insulin resistant. We developed the first methods to actually measure that variable in patients with diabetes and point out that most patients with type 2 diabetes were also insulin resistant. That idea really caught on, because diabetes is such a major disease and people are so concerned about it.

In 1988, I was honored to receive the Banting Medal from the American Diabetes Association. As a result, I was required to address that group. As I was gathering my thoughts, I realized that, although everybody was now pretty convinced that insulin resistance was the basis and the primary lesion in patients with type 2 diabetes, most people did not realize that most individuals who were insulin resistant did not go on to get diabetes. They kept on making lots and lots of insulin, turning it out of their pancreas, and that ended up preventing the glucose from going up. What wasn't understood was that these people were at risk for a cluster of other abnormalities. One was a high triglyceride, clearly a low HDL cholesterol concentration. Hypertension was more common in this situation. I realized that none of this was well recognized; it had not been put together.

As part of the Banting address, I tried to point out that insulin resistance is a very common phenomenon. Some individuals could not keep up with resistance by making enough insulin, and they got type 2 diabetes. Most people, however, just kept on making lots and lots of insulin. They didn't get type 2 diabetes, but they had this whole cluster of abnormalities, which, since I thought was not well recognized or ‘unknown,’ I called syndrome X. That's a brief explanation for about 25 or 30 years of research.”

—Gerald Reaven, MD
Professor Emeritus, Stanford University School of Medicine
Author, *Syndrome X - Overcoming the Silent Killer that Can Give You a Heart Attack*
June 2001

Insulin resistance (also called hyperinsulinemia) is a physiological condition associated with premature age-related disease risk, including cardiovascular disease, stroke, and possibly colon cancer and certain other soft-tissue endocrine-related cancers. It also relates to autoimmune disorders. The hallmarks of insulin resistance, from a clinical assessment perspective, are elevated triglycerides, reduced HDL, increased levels of LDL-cholesterol (atherogenic particles), increased blood pressure, increased visceral adiposity (related to elevated waist-to-hip ratio), and increased plasma uric acid.

According to Dr. Gerard Reaven, a noted endocrinologist who brought the concept of insulin resistance to the attention of the medical field through his several decades of research, 20 percent or more of the nondiabetic population—the normal, apparently healthy population—carry some degree of insulin resistance. The insulin signaling pathway and all the variants tied to it include things like inflammatory signaling, lipid metabolism, and even oxidative chemistry. These connect to the insulin axis of regulatory control and insulin-like growth factor 1 and all the various types of other intermediary molecules and enzymes that are involved in the regulation of bioenergetics through glucose metabolism.

Insulin resistance has been demonstrated to increase the risk of congestive heart failure. It has a complex series of effects on vascular function, probably mediated through altered endothelial function. In 2005, the results of a study involving a large community-based sample of elderly men were published in the *Journal of the American Medical Association*[1]. These researchers found insulin resistance to be a predictor of congestive heart failure incidence, independent of other established risk factors, including diabetes.

In more recent years, insulin resistance has been found to potentially play a role in the etiology of Alzheimer's disease. In fact, there has been proposed a specific, insulin resistance condition of the brain which has been termed "Type 3 Diabetes by the group affiliated with Suzanne de la Monte, PhD, at the Department of Pathology at Brown Medical School in 2005 (see abstract below).

J Alzheimers Dis. 2005 Feb;7(1):63-80.

Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes?

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM.
Department of Pathology, Rhode Island Hospital and Brown Medical School, Providence, RI 02903, USA.

Abstract

The neurodegeneration that occurs in sporadic Alzheimer's disease (AD) is consistently associated with a number of characteristic histopathological, molecular, and biochemical abnormalities, including cell loss, abundant neurofibrillary tangles and dystrophic neurites, amyloid-beta deposits, increased activation of pro-death genes and signaling pathways, impaired energy metabolism/mitochondrial function, and evidence of chronic oxidative stress. The general inability to convincingly link these phenomena has resulted in the emergence and propagation of various heavily debated theories that focus on the role of

one particular element in the pathogenesis of all other abnormalities. However, the accumulating evidence that reduced glucose utilization and deficient energy metabolism occur early in the course of disease, suggests a role for impaired insulin signaling in the pathogenesis of AD. The present work demonstrates extensive abnormalities in insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) signaling mechanisms in brains with AD, and shows that while each of the corresponding growth factors is normally made in central nervous system (CNS) neurons, the expression levels are markedly reduced in AD. These abnormalities were associated with reduced levels of insulin receptor substrate (IRS) mRNA, tau mRNA, IRS-associated phosphotidylinositol 3-kinase, and phospho-Akt (activated), and increased glycogen synthase kinase-3beta activity and amyloid precursor protein mRNA expression. The strikingly reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, suggests that AD may represent a neuro-endocrine disorder that resembles, yet is distinct from diabetes mellitus. Therefore, we propose the term, "Type 3 Diabetes" to reflect this newly identified pathogenic mechanism of neurodegeneration.

Suzanne Craft, PhD, is a premier researcher in this area, based at the University of Washington in Seattle. She has published quite extensively on this topic, as some of her most recent paper abstracts are cited below:

J Alzheimers Dis. 2012 Aug 30. [Epub ahead of print]

Insulin and Alzheimer's Disease: Untangling the Web.

Craft S, Cholerton B, Baker LD.
Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA.

Abstract
The recognition of Alzheimer's disease (AD) as a heterogeneous disorder that results from incremental pathological changes in dynamic organismic systems is essential to move beyond the unidimensional approaches to prevention and therapy that have proven largely ineffective to date. Biological systems related to insulin metabolism are arguably the most critical regulators of longevity and corporeal aging. Our work has focused on identifying the relationship of the insulin network to brain aging, and determining the mechanisms through which insulin dysregulation promotes AD pathological processes. Candidate mechanisms include the effects of insulin on amyloid-β, cerebral glucose metabolism, vascular function, lipid metabolism, and inflammation/oxidative stress. It is likely that different nodes of the insulin network are perturbed for subgroups of AD patients, or that for some subgroups, pathways independent of insulin are critical pathogenetic factors. New methods from systems network analyses may help to identify these subgroups, which will be critical for devising tailored prevention and treatment strategies. In the following review, we will provide a brief description of the role of insulin in normal brain function, and then focus more closely on recent evidence regarding the mechanisms through which disruption of that role may promote AD pathological processes. Finally, we will discuss the implications of this area for AD therapeutics and prevention.

J Gerontol A Biol Sci Med Sci. 2012 Jun;67(7):754-9. doi: 10.1093/gerona/gls112. Epub 2012 May 8.

Session III: Mechanisms of age-related cognitive change and targets for intervention: inflammatory, oxidative, and metabolic processes.

Craft S, Foster TC, Landfield PW, Maier SF, Resnick SM, Yaffe K.
Department of Psychiatry and Behavioral Sciences, University of Washington, Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound, Seattle, USA.

Abstract
There is increasing evidence from basic science and human epidemiological studies that inflammation, oxidative stress, and metabolic abnormalities are associated with age-related cognitive decline and impairment. This article summarizes selected research on these topics presented at the Cognitive Aging Summit II. Speakers in this session presented evidence highlighting the roles of these processes and pathways on age-related cognitive decline, pointing to possible targets for intervention in nondemented older adults. Specific areas discussed included age differences in the production of cytokines following injury or infection, mechanisms underlying oxidative stress-induced changes in memory consolidation, insulin effects on brain signaling and memory, and the association between metabolic syndrome and cognitive decline in older adults. These presentations emphasize advances in our understanding of mechanisms and modifiers of age-related cognitive decline and provide insights into potential targets to promote cognitive health in older adults.

Mol Neurobiol. 2012 Aug;46(1):4-10. doi: 10.1007/s12035-011-8229-6. Epub 2011 Dec 29.

Brain insulin signaling and Alzheimer's disease: current evidence and future directions.

Schiöth HB, Craft S, Brooks SJ, Frey WH 2nd, Benedict C.
Department of Neuroscience, Uppsala University, Box 593, Husargatan 3, Uppsala, Sweden.

Abstract
Insulin receptors in the brain are found in high densities in the hippocampus, a region that is fundamentally involved in the acquisition, consolidation, and recollection of new information. Using the intranasal method, which effectively bypasses the blood-brain barrier to deliver and target insulin directly from the nose to the brain, a series of experiments involving healthy humans has shown that increased central nervous system (CNS) insulin action enhances learning and memory processes associated with the hippocampus. Since Alzheimer's disease (AD) is linked to CNS insulin resistance, decreased expression of insulin and insulin receptor genes and attenuated permeation of blood-borne insulin across the blood-brain barrier, impaired brain insulin signaling could partially account for the cognitive deficits associated with this disease. Considering that insulin mitigates hippocampal synapse vulnerability to amyloid beta and inhibits the phosphorylation of tau, pharmacological strategies bolstering brain insulin signaling, such as intranasal insulin, could have significant therapeutic potential to deter AD pathogenesis.

In 2010, Dr. Craft was interviewed by Dr. Jeffrey Bland and explained the relationship between glucose and brain chemistry this way:

"I think my interest in neuroendocrinology grew out of the appreciation that changes in cognitive function with aging were closely related to glucose metabolism, I think in a couple of ways. One, of course, is the very well-established finding that patients with Alzheimer's disease have hypometabolism in the brain. They have reduced cerebral glucose metabolism. This can be observed, actually, years before the diagnosis is made. So there is

something very fundamental about the changes in glucose metabolism that occur centrally, both with respect to aging and pathological aging, such as Alzheimer's disease.

“The brain is unable to synthesize or store glucose, so all of the glucose that it receives for its many functions, it receives from the periphery. The question I began to wonder about was the degree to which disorders that are associated with disrupted peripheral glucose metabolism may potentially impact the CNS, in that the brain may not be able to get adequate supplies of glucose in patients who have such disorders. That led me to the study of conditions like diabetes and insulin resistance and how those conditions might affect brain function and cognition.”

Dr. Craft was also very succinct in describing how insulin has both positive and negative effects in the body:

“I think the story with insulin, as I describe it, is very much what I consider a ‘Goldilocks’ story. Insulin, one of the most evolutionarily conserved of all peptides, is absolutely essential for a number of functions, and was early on best known for its critical role in promoting glucose uptake, peripherally. Removing insulin, either through a condition such as type 1 diabetes or in genetic models of insulin receptor knock-out transgenic rodent models, is lethal. So I think insulin has many beneficial roles to play. What I think is essential is the appreciation that optimal levels of insulin, in a healthy physiology, have many beneficial effects when insulin is secreted and cleared very quickly in a normal healthy individual (and I think this is the key to its positive effects). When, however, insulin is increased chronically or is increased to too great of a level, then I think negative effects begin to occur, of course- the insulin resistance, where tissues become resistance to the effects of insulin (insulin can no longer carry out its normal functions in tissues), or proinflammatory effects of chronic elevations of insulin. A number of negative effects occur when insulin is too high and around for too long a time.”

Metabolic Syndrome, Diabesity, & Metabolic Inflexibility: The Emerging Metabolic Disturbance

What is metabolic syndrome? According to Eckel, Grundy, and Zimmet, in an article published in the *Lancet:* "The metabolic syndrome is a common metabolic disorder that results from the increasing prevalence of obesity."[2] There are many people who might challenge that metabolic syndrome is simply a result of obesity, although most agree it is a factor. Metabolic syndrome also appears to have genetic factors, as well as other lifestyle factors, such as amount of exercise, involved in its etiology. It is not obesity or its covariables alone that cause metabolic syndrome, at least not in all people with the syndrome. If that were the case, how could we explain the individual who is very thin who has metabolic syndrome and insulin resistance? There are cases of people with low body weight, who are perhaps excessively lean and have metabolic syndrome, as well. It is not obesity alone that causes metabolic syndrome.

In 2002, the *Journal of the American Medical Association* published a study that estimated the prevalence of the metabolic syndrome in the United States. Data collected from more than 8800 individuals for the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) was analyzed and extrapolated to census data from the year 2000. The unadjusted and age-adjusted prevalences of the metabolic syndrome were 21.8% and 23.7%, respectively. The prevalence increased from 6.7% among

participants aged 20 through 29 years to 43.5% and 42.0% for participants aged 60 through 69 years and aged at least 70 years, respectively. Mexican Americans had the highest age-adjusted prevalence of the metabolic syndrome (31.9%). The age-adjusted prevalence was similar for men (24.0%) and women (23.4%). However, among African Americans, women had about a 57% higher prevalence than men did and among Mexican Americans, women had about a 26% higher prevalence than men did. Using the census data, it was estimated that about 47 million US residents have the metabolic syndrome.[3]

Metabolic syndrome is defined in various ways, but generally, an individual with this condition has slightly elevated fasting triglycerides and slightly lowered HDL levels, increased blood pressure (at least, marginal elevations of systolic pressure), elevated blood sugar, and often elevated blood uric acid levels. They generally have central obesity with increased waist-to-hip ratios and an elevated body mass index (BMI). They often have elevated dense LDL particles. None of those by itself is the *sine qua non* for metabolic syndrome. A constellation of variables is associated with the diagnostic markers of metabolic syndrome.

The principal diagnostic marker would be found by doing an insulin clamp study on an individual, the so-called euglycemic clamp. During this test, insulin and glucose are infused to evaluate the relative sensitivity of that person to the infusion. This is not a technique that is going to be routinely used in diagnosis, so the surrogate markers are used, such as triglyceride over HDL ratio, or various types of homeostasis models for glycemic or insulin response.

Another hallmark of metabolic syndrome is inflammation. This is a more recent emerging concept—that the pathophysiology of metabolic syndrome seems to be largely attributable to insulin resistance, with excessive flux of fatty acids through the liver inducing or associated with a proinflammatory state reflecting increased levels of proinflammatory cytokines and eicosanoids. The increased risk for vascular injury, endothelial injury, hypertensive dysfunction, renal problems, and cerebral vascular problems associated with metabolic syndrome, may be a consequence of the metabolic markers or mediators of inflammation. One of the surrogate markers for the assessment of the metabolic syndrome is evaluation of various inflammatory mediators, including high-sensitivity C-reactive protein (hsCRP).

Central obesity, or visceral adipose tissue, produces its own complex array of proinflammatory molecules, such as tumor necrosis factor alpha (TNF-a), interleukin 1 (IL-1), and interleukin 6 (IL-6). These messenger molecules also add to the production of proinflammatory signals, along with activated macrophages and an inflamed vascular endothelium. When a person has an occlusion, these are all sites or loci in the body where there is increased production of proinflammatory mediators. These mediators are also associated with the metabolic syndrome.

The prevalence of obesity is not the sole factor in the rising rate of the metabolic syndrome, but it is a contributing factor. The term “diabesity” has been used by researchers as early as 1980 to refer to the occurrence of metabolic syndrome in the context of rising rates of obesity. In his cutting-edge article published in 1994 entitled “Diabesity: the deadly pentad disease,” Dr. Daly comments:

“Insulin resistance and hyperinsulinemia are characteristic features not only of obesity and NIDDM, but are associated with the development of hypertension, hyperlipidemia, and atherosclerosis. DeFronzo et al has used the analogy that insulin resistance can be viewed as a large iceberg submerged just below the water. The physician recognizes only the tips of the iceberg--obesity, diabetes, hypertension, hypertriglyceridemia and low-HDL cholesterol, and atherosclerosis--which protrude above the surface, while the complete insulin-resistance syndrome may be missed. With the recognition that insulin resistance consists of a cluster of nutritional causes and biochemical abnormalities, it is important for the various subspecialties to work together closely to define the mechanism(s) responsible for the defects in insulin-mediated glucose metabolism and to discover effective strategies for prevention and treatment.”

In our modern society, we have had difficulty making the transition to the food of commerce, the food of convenience, the food of white sugar, white fat, and white flour, with nominal nutrient fortification. That diet, coupled with lowered exercise patterns and perhaps other factors such as stress, starts the clock ticking. The ticking clock indicates increasing atherosclerotic and diabetes risk. Microvascular outcomes occur as a consequence of metabolic syndrome, and this increases cardiovascular risk, as well as peripheral vascular injury, neurologic injury, peripheral neuropathies, and ocular injury. Nephropathic problems occur downstream with a loss of kidney function. These are big problems that occur over periods of time. Years before the person may be diagnosed as having diabetes, they may be experiencing these adverse effects.

More recently, the metabolic syndrome has been referred to as “lifestyle-induced metabolic inflexibility” signaling that its occurrence may be interconnected to the spectrum of inflexibility of oxidation of fuels with lesser degrees of oxidation of carbohydrate than that of lipid. Furthermore, and probably more concerning for long-term, metabolic inflexibility is seen as a rigid condition linked to accelerated aging. Some pertinent abstracts on this topic are listed below:

Obes Rev. 2011 Oct;12(10):859-65. doi: 10.1111/j.1467-789X.2011.00894.x. Epub 2011 Jun 21.

The relevance of increased fat oxidation for body-weight management: metabolic inflexibility in the predisposition to weight gain.

Astrup A.
Department of Human Nutrition, Centre for Advanced Food Studies, Faculty of Life Sciences, University of Copenhagen, Frederiksberg, Denmark. ast@life.ku.dk

Abstract

Cells, tissues and organisms have the ability to rapidly switch substrate oxidation from carbohydrate to fat in response to changes in nutrient intake, and to changes in energy demands, environmental cues and internal signals. In healthy, metabolically normal individuals, substrate switching occurs rapidly and completely; in other words, substrate switching is 'flexible'. A growing body of evidence demonstrates that a blunted substrate switching from low- to high-fat oxidation exists in obese individuals, as well as in pre-obese and post-obese, and that this 'metabolic inflexibility' may be a genetically determined trait. A decreased fat oxidation can lead to a positive energy balance under conditions of high-fat feeding, due

to depletion of glycogen stores that stimulates appetite and energy intake through glucostatic and glucogenostatic mechanisms, e.g. hepatic sensing of glycogen stores. Several genetic polymorphisms and single-nucleotide polymorphisms have been identified that are associated with low-fat oxidation rates and metabolic inflexibility, and genetic identification of susceptible individuals may lead to personalized prevention of weight gain using fat oxidation stimulants ('fat burners') in the future.

Nutr Metab (Lond). 2009 Apr 16;6:16. doi: 10.1186/1743-7075-6-16.

Lifestyle-induced metabolic inflexibility and accelerated ageing syndrome: insulin resistance, friend or foe?

Nunn AV, Bell JD, Guy GW.
Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, Du Cane Road, London, W12 OHS, UK. alistair.nunn@btconnect.com.

Abstract

The metabolic syndrome may have its origins in thriftiness, insulin resistance and one of the most ancient of all signalling systems, redox. Thriftiness results from an evolutionarily-driven propensity to minimise energy expenditure. This has to be balanced with the need to resist the oxidative stress from cellular signalling and pathogen resistance, giving rise to something we call 'redox-thriftiness'. This is based on the notion that mitochondria may be able to both amplify membrane-derived redox growth signals as well as negatively regulate them, resulting in an increased ATP/ROS ratio. We suggest that 'redox-thriftiness' leads to insulin resistance, which has the effect of both protecting the individual cell from excessive growth/inflammatory stress, while ensuring energy is channelled to the brain, the immune system, and for storage. We also suggest that fine tuning of redox-thriftiness is achieved by hormetic (mild stress) signals that stimulate mitochondrial biogenesis and resistance to oxidative stress, which improves metabolic flexibility. However, in a non-hormetic environment with excessive calories, the protective nature of this system may lead to escalating insulin resistance and rising oxidative stress due to metabolic inflexibility and mitochondrial overload. Thus, the mitochondrially-associated resistance to oxidative stress (and metabolic flexibility) may determine insulin resistance. Genetically and environmentally determined mitochondrial function may define a 'tipping point' where protective insulin resistance tips over to inflammatory insulin resistance. Many hormetic factors may induce mild mitochondrial stress and biogenesis, including exercise, fasting, temperature extremes, unsaturated fats, polyphenols, alcohol, and even metformin and statins. Without hormesis, a proposed redox-thriftiness tipping point might lead to a feed forward insulin resistance cycle in the presence of excess calories. We therefore suggest that as oxidative stress determines functional longevity, a rather more descriptive term for the metabolic syndrome is the 'lifestyle-induced metabolic inflexibility and accelerated ageing syndrome'. Ultimately, thriftiness is good for us as long as we have hormetic stimuli; unfortunately, mankind is attempting to remove all hormetic (stressful) stimuli from his environment.

In summary, the debate is no longer about the prevalence of metabolic syndrome and what its diagnostic criteria are; these are now well established. The debate is now about defining metabolic syndrome in such a way that it sounds like a discrete pathology and reducing the number of people who

are affected by underlying insulin resistance. These are people who may one day have premature heart attacks and strokes and wonder where they originated. We will have medicalization of those conditions with new stenting, new bypass surgeries, and new medications, but, we will not have asked the right questions early enough about the relative toxicity of the diet and its relationship to the incipient markers of later-stage vascular dysfunction, which is one possible outcome of metabolic syndrome.

Non-Alcoholic Steatohepatitis (NASH)

Until the rise in rates of obesity, insulin resistance, and metabolic syndrome use of the term “non-alcoholic steatohepatitis” (NASH) was generally confined to esoteric discussions about endocrinology. But the rate of cases of NASH is also on the rise. We are now learning NASH is a condition that derives from altered lipogenesis and hepatic function. When there is fatty liver infiltration in the absence of healthy diets, these kinds of conditions are the result. They are hormone-driven endocrine disturbances that relate to insulin resistance and metabolic syndrome. We now see young people showing up for routine medical examinations with marginally elevated liver enzyme profiles. They don't have hepatitis C infection; they don't appear to be abusing alcohol or drugs; yet they have elevated liver enzyme profiles. Why? The answer is NASH. They are suffering as a result of metabolic syndrome and hyperinsulinemia. It is correlated with obesity, but it is unknown if obesity causes NASH or whether they are both a consequence of other metabolic disturbances associated with insulin resistance, insulin signaling, and the whole nature of neuroendocrineimmune dysfunction.

Type 2 Diabetes

Type 2 diabetes, the most common form of diabetes in our culture, is an example of a functional disability. Type 2 diabetes used to be called maturity-onset diabetes, but that term has been changed because increasingly those who are getting type 2 diabetes are adolescents, not adults. Type 2 diabetes is not associated with low levels of insulin (as is the case with type 1 diabetes), but rather with high levels of insulin, or hyperinsulinemia. Type 2 diabetes is a complex metabolic disorder characterized by peripheral insulin resistance and impaired beta cell function. When we measure and monitor patients at risk for type 2 diabetes, we want to look at parameters that reflect the physiology/function associated with insulin’s role in cell signaling, not at blood sugar alone as a diagnostic determinant for diabetes.

Insulin resistance is inherited as a Mendelian trait, but due to its polygenic nature, the patterns can be quite complex. It is not a single gene that predisposes one to insulin resistance. In genetically predisposed individuals, resistance of skeletal muscle and adipose tissue to insulin action sometimes precedes the onset of clinical diabetes by decades. One of the genetic families of characteristics that appears to modify insulin sensitivity, giving rise to type 2 diabetes, are those genes found in the mitochondrial genome--extra nuclear DNA that has come principally from our mothers. Mitochondrial dysfunction and its association with type 2 diabetes is ever-increasing. Agents in the environment, drugs, excess alcohol, chemicals, or even radiation that would damage mitochondrial DNA, have been associated in animal and human studies with the onset of insulin resistance, hyperinsulinemia, and type 2 diabetes.

Researchers have worked to find an explanation for the increasing prevalence of this disease. It seems unreasonable to blame it on “bad genes” that are suddenly showing up. It seems more likely that we are witnessing an interaction between genes and a changing environment that alters gene expression and produces unique outcomes. We might suspect that variables associated with the environment/genotype connection (i.e., diet and lifestyle) may be regulating, or at least influencing, the prevalence of type-2 diabetes.

Another approach has been to examine the question of whether exposure to persistent organic pollutants (POPs) may play a role in the development of type 2 diabetes, POPs would include things like polychlorinated biphenyl (PCB), organochlorine pesticides, or dioxin (perhaps the most well known; dioxin was used in Agent Orange to defoliate Vietnam). These things enter into the body and then they sit there. They are difficult to metabolize. They are difficult to clear. They probably cause oxidative stress. They probably cause hormone disruption.

In 2010, Dr. Jeffrey Bland interviewed David R. Jacobs, PhD, of the University of Minnesota. Dr. Jacobs, along with his research collaborator Dr. Duk-Hee Lee in South Korea, has been investigating the potential link between accumulation of POPs in the body and type 2 diabetes. He said this:

“At least in our preliminary cross-sectional study of NHANES we had 2000 or more people, and I think we had 218 cases of diabetes that were prevalent (in other words, they existed at the time of measurement of the different POPs, persistent organic pollutants)…I think there were 463 people in the lowest quartile of the POPs. We actually took six POPs and we put them together, statistically, and so when I said a quartile of POPs that means that these were the people who had the least exposure to some combination of these six POPs, each of which had a pretty powerful relationship with diabetes. Among those 463 people, about one-third of them were obese, so a BMI (body mass index) over 30. There were only two cases of diabetes in those 463 people. One of them was in the middle BMI group (in the 25 to 30 group) and the 30-plus also had one, but that was a half a percent of the people who had diabetes, and overall, 218 people over about 2000 (it was about 10%). So in the top three quartiles, actually, I think we had 13% percent versus a half a percent in the bottom quartile of the POPs. As I just said, there was no gradient of the diabetes within that particular group of people who did not have very much in the way of POPs.[4]

Obesity has always been a difficult and an interesting thing to understand. The history of obesity and total mortality is a strong U-shape. And the history even with cardiovascular disease is sometimes on/sometimes off depending on the data set. For many years at the beginning of my career, we really thought that obesity was not a factor because if you regressed, say, cardiovascular disease on obesity and the triad of blood pressure, smoking, and cholesterol (sort of a Framingham score), the obesity would drop out of the model. Then over the years people got a little more sophisticated and they started to think that there are these secondary paths. So obesity causes hypertension. Obesity causes hyperlipidemia. It's related to smoking in that the smokers are thinner, and when they quit smoking they tend to gain quite a bit of weight. So it is really, in a certain way, a marker of all these things. It is an indirect player, and similarly (perhaps) with diabetes.

The third line of thought was that the obesity was actually sometimes leading to hypertension and hyperlipidemia and sometimes it was not. It's a little hard to know, and now with this added concept...there are two added concepts, which are really important with obesity. One is that adipose tissue is not only adipose cells. The adipose tissue also contains adipose cells that have died, and those will then be quickly surrounded by macrophages, a similar mechanism for body defense as happens in atherosclerosis. The macrophage colony will be throwing off IL-

6 (Interleukin-6) and a variety of other cytokines, so actually the adipose tissue is pretty interesting because it is more than just the adipocytes and the fat storage; it's also storage of some decaying and inflammatory matter. The other thing is that there are lots and lots of fat soluble substances that we encounter, and so where are they going to sit? Well, besides the fat in the adipocytes, there are going to fat soluble substances, and the pollutants that we have been talking about are basically fat soluble."

Diabetes is not a disease in search of a drug. It is a functional condition in search of the appropriate environment to create a gene expression profile that relates not to dysinsulinism, but to normal insulin modulation of cellular function. Insulin does not influence only blood sugar. It also influences gene expression—protein tyrosine kinases and other types of transcription factors that are modulated at both the genomic and post-genomic levels. The symphonic orchestration of these mediators influenced by environmental factors then creates a shift in metabolism that we later define as disease.

In 2005, an article was published in *Science* magazine about the search for genetic factors influencing the development of type 2 diabetes.[5] This quote appears in that article:

"The intensive search for genetic variants that predispose to type 2 diabetes was launched with optimism, but progress has been slower than was hoped."

It has been assumed that we would find just a few genes that might regulate the function of an individual who would, in the absence of proper regulation, present with the symptoms of type 2 diabetes. The more this is evaluated, the more genes are found that interrelate as a family. PPAR gene variants, mitochondrial genome variants, and the insulin signaling genes and their variations—there is tremendous variation in the different types of metabolic principles that cluster together with similar signs and symptoms that we call a disease. The proper treatment for those individuals may be better served by focusing on their individual genetic and metabolomic needs, rather than just on the class of disease management.

Assessment and Clinical Approach to Type 2 Diabetes

Type 2 diabetes is increasing in prevalence, not only in older people, but also in adolescents. Diabetes is the leading cause of blindness, renal failure, and non-traumatic amputations in adults. It is also a major cardiovascular risk factor, independent of LDL cholesterol. The disease accounts for about $1 of every $7 spent on health care in the United States and represents the highest cost expenditure in most HMOs.

Almost every medical group, hospital, insurance company, and managed care organization now realizes it must develop a plan to optimize diabetes care or prevent type 2 diabetes if it is going to improve cost effectiveness in medicine. More than 90 percent of the 16 million diabetics in the United States have type 2 diabetes. The number is increasing steadily, particularly among elderly and non-white populations.

We need to look at what insulin is signaling or not signaling. This means we need to make other clinical measurements, such as 2-hour postprandial insulin and glucose measurements. We need to measure C-peptide to see if it is elevated in the blood, indicating higher levels of insulin secretion in the range of

several units per milliliter of C-peptide. It is important to recognize that C-peptide, the peptide that is released when proinsulin is hydrolyzed to insulin, is an important indirect measurement of the amount of insulin that has been secreted.

Since the discovery of the first therapeutic administration of insulin as an injectable medication in 1922, individuals have been trying to develop an orally administered insulin that can mimic the body's own insulin function. This insulin mimetic has been considered the "Holy Grail" of diabetes research. In the years since 1922, oral therapies for type 2 diabetes have been developed and are widely used. Rather than acting by directly mimicking insulin signaling, these act by stimulating insulin release like the sulfonylureas, potentiating insulin action like the thiazolidinediones, or lowering hepatic glucose production by unclear mechanisms like the biguanides. None are effective in type 1 diabetics totally lacking insulin, and many type 2 diabetics respond weakly or not at all.

Optimizing insulin sensitivity plays an important role in the prevention of age-related dysglycemic events. The thiazolidinedione family of drugs has been used to improve insulin sensitivity through activation of the peroxisome-proliferated activated receptors (PPARs), but there are natural substances in the diet that are PPAR agonists. If diets are consumed consistent with physiological needs, some of the messages for PPAR agonists are sent free of charge. Medications may not be necessary.

As the mechanism of insulin resistance is explored, including some of the effects from certain drugs such as metformin, the sulfonylureas, or the thiazolidinediones, it is recognized that dietary factors play roles in the mechanisms the drugs are attempting to treat. They share common pathways. When we eat food that contains the right nutrients, it results in the right physiologic effects. Foods we frequently consume may send altered signals to dysfunctional pathways, for which we sometimes use various medications to modify, block, or alter.

Therapeutic Approaches

What do you do?

What are the therapies?

How do we stem the tide?

A provocative study was published in 2006 that helps with some path finding in this area. The Finnish Diabetes Prevention Study looked at sustained reduction in the incidence of type 2 diabetes.[6] There wasn't a drug or a specific pharmaceutical used in this particular intervention. What was used was lifestyle intervention with diet, exercise, and counseling.

In this particular study, 172 middle-aged men and 350 women with impaired glucose tolerance were randomly assigned to either an intensive lifestyle intervention or control group. After a median of 4 years of active intervention, patients who were still free of diabetes were further followed for a median of three years (with a total, then, of about 7 years). Diabetes incidence, body weight, physical activity,

and dietary intake of fat, saturated fat, and fiber were measured. The bottom line is that there was a statistically significant reduction in type 2 diabetes in the individuals who complied with lifestyle intervention as their primary mode of therapy. In fact, per 100-person-years, there was a statistically significant reduction in type 2 diabetes in the P< .0001 level, indicating a 43% reduction in relative risk (or almost approaching half reduction risk over those people that didn't engage). There is presently no drug therapy that will accomplish that outcome. Lifestyle intervention (the authors concluded), in people at high risk for type 2 diabetes, resulted in sustained lifestyle changes and a reduction of diabetes incidence, which remained after the individual lifestyle counseling was stopped for the duration of the 7 years of the study.

When we talk about the insulin signaling pathway, we talk about agents that can improve insulin sensitivity. Those agents include regular exercise, a diet low in sugars and balanced with protein and complex unrefined carbohydrate, and the appropriate amount and type of fats. (Those would be more polyunsaturated fats and low levels of saturated fat, increased omega 3 fatty acids, alpha-linolenic acid and the omega 3 oils like EPA, which are able to help improve cell membrane function and structure, and increased insulin sensitivity and glucose transport.) A variety of accessory nutrients also seem to improve insulin sensitivity and glucose transport. These accessory nutrients include chromium and vanadium, vitamin E, and antioxidants like lipoic acid.

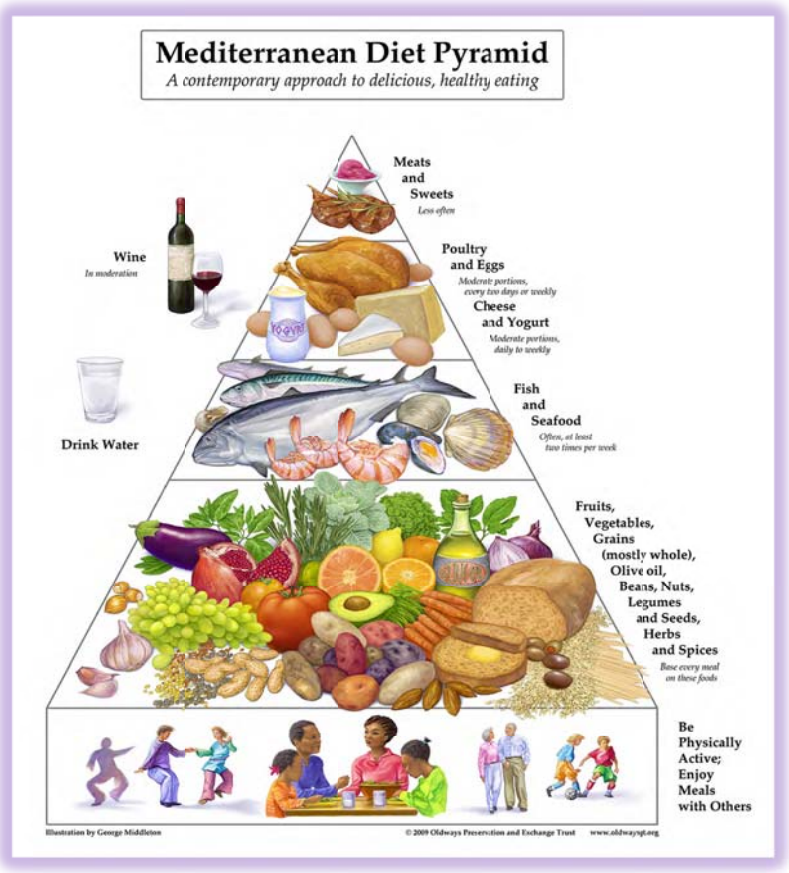
Dietary Approaches

One of the key aspects of lifestyle modification for metabolic syndrome and diabetes is dietary therapy; however, a consensus is lacking as to which dietary approach is most efficacious and, furthermore, how to tailor these therapies to individual risk factors. Since these conditions are implicated in the formation of cardiovascular disease, it might be worthwhile to examine traditional dietary recommendations such as those proposed by the National Cholesterol Education Panel (NCEP)-Adult Treatment Panel (ATP) III and the American Heart Association. These approaches have primarily emphasized the macronutrient content of the diet with their general recommendations to keep carbohydrate energy intake at 50-60%, protein to ≈ 15%, and fat to 25-35%, with saturated fat at <7%, in addition to the avoidance of trans fat and restriction on daily cholesterol intake (300 mg/d). As part of this recommendation for a low-fat, high-carbohydrate diet, NCEP-ATP III emphasizes the inclusion of fruits, vegetables, and whole grains.

Essentially, these pivotal opinion leader organizations are recommending following a higher carbohydrate, lower fat diet for reduction of cardiovascular disease risk. However, it could be debated that focusing solely on dietary macronutrient quantity without regard for the complexity and quality, may not be a comprehensive, individualized approach to metabolic syndrome and diabetes. Focusing on characteristics of healthy dietary patterns such as Glycemic Index (GI) and phytochemicals may provide other therapeutic opportunities.

Studies suggest that the Mediterranean dietary pattern may be effective for metabolic syndrome. Although it is not well defined, there is general consensus that the Mediterranean dietary pattern

includes the following features: (1) liberal quantities of minimally processed, fresh, plant-based foods such as fruits, vegetables, whole grains, seeds, spices, and nuts; (2) olive oil as the principal source of dietary fat; (3) minimal consumption of red meat and dairy products; and (4) high-polyphenolic wine in low to moderate amounts with meals.



Source: http://www.oldwayspt.org/mediterraneandiet, viewed July19, 2010

In a large meta-analysis that included 50 studies on the effect of the Mediterranean diet on indicators of metabolic syndrome (see abstract below), researchers concluded the following:

"…adherence to the Mediterranean diet was associated with reduced risk of MS (log hazard ratio: -0.69, 95% confidence interval [CI]: -1.24 to -1.16). Additionally, results from clinical studies (mean difference, 95% CI) revealed the protective role of the Mediterranean diet on components of MS, like waist circumference (-0.42 cm, 95% CI: -0.82 to -0.02), high-density lipoprotein cholesterol (1.17 mg/dl, 95% CI: 0.38 to 1.96), triglycerides (-6.14 mg/dl, 95% CI: -10.35 to -1.93), systolic (-2.35 mm Hg, 95% CI: -3.51 to -1.18) and diastolic blood pressure (-1.58 mm Hg, 95% CI: -2.02 to -1.13), and glucose (-3.89 mg/dl, 95% CI:-5.84 to -1.95), whereas results from epidemiological studies also confirmed those of clinical trials."

J Am Coll Cardiol. 2011 Mar 15;57(11):1299-313. doi: 10.1016/j.jacc.2010.09.073.

The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals.

Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB.
Department of Nutrition Science-Dietetics, Harokopio University, Athens, Greece.

Abstract

OBJECTIVES: The aim of this study was to meta-analyze epidemiological studies and clinical trials that have assessed the effect of a Mediterranean diet on metabolic syndrome (MS) as well as its components. BACKGROUND: The Mediterranean diet has long been associated with low cardiovascular disease risk in adult population. METHODS: The authors conducted a systematic review and random effects meta-analysis of epidemiological studies and randomized controlled trials, including English-language publications in PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials until April 30, 2010; 50 original research studies (35 clinical trials, 2 prospective and 13 cross-sectional), with 534,906 participants, were included in the analysis. RESULTS: The combined effect of prospective studies and clinical trials showed that adherence to the Mediterranean diet was associated with reduced risk of MS (log hazard ratio: -0.69, 95% confidence interval [CI]: -1.24 to -1.16). Additionally, results from clinical studies (mean difference, 95% CI) revealed the protective role of the Mediterranean diet on components of MS, like waist circumference (-0.42 cm, 95% CI: -0.82 to -0.02), high-density lipoprotein cholesterol (1.17 mg/dl, 95% CI: 0.38 to 1.96), triglycerides (-6.14 mg/dl, 95% CI: -10.35 to -1.93), systolic (-2.35 mm Hg, 95% CI: -3.51 to -1.18) and diastolic blood pressure (-1.58 mm Hg, 95% CI: -2.02 to -1.13), and glucose (-3.89 mg/dl, 95% CI:-5.84 to -1.95), whereas results from epidemiological studies also confirmed those of clinical trials. CONCLUSIONS: These results are of considerable public health importance, because this dietary pattern can be easily adopted by all population groups and various cultures and cost-effectively serve for primary and secondary prevention of the MS and its individual components.

Thus, it appeared from this analysis that the Mediterranean diet had positive benefit on multiple markers of the metabolic syndrome. If we look to the role of the Mediterranean diet on diabetes, there is some evidence to suggest that, indeed, there is a beneficial effect. Specifically, in a study by Esposito et al. published in the *Annals of Internal Medicine* in 2009 (see abstract below), they concluded the following:

"Compared with a low-fat diet, a low-carbohydrate, Mediterranean-style diet led to more favorable changes in glycemic control and coronary risk factors and delayed the need for antihyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes."

Ann Intern Med. 2009 Sep 1;151(5):306-14.

Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial.

Esposito K, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, Petrizzo M, Saccomanno F, Beneduce F, Ceriello A, Giugliano D.

Second University of Naples and ASLNA5, Vico Equense/Sorrento, Naples, Italy.

Abstract

BACKGROUND: Low-carbohydrate and low-fat calorie-restricted diets are recommended for weight loss in overweight and obese people with type 2 diabetes. OBJECTIVE: To compare the effects of a low-carbohydrate Mediterranean-style or a low-fat diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes. DESIGN: Single-center, randomized trial. Randomization was computer-generated and unstratified. Allocation was concealed in sealed study folders held in a central, secure location until participants gave informed consent. Participants and investigators were aware of treatment assignment, and assessors of the primary outcome were blinded. SETTING: Teaching hospital in Naples, Italy. PATIENTS: 215 overweight people with newly diagnosed type 2 diabetes who were never treated with antihyperglycemic drugs and had hemoglobin A(1c) (HbA(1c)) levels less than 11%. INTERVENTION: Mediterranean-style diet (<50% of daily calories from carbohydrates) (n = 108) or a low-fat diet (<30% of daily calories from fat) (n = 107). MEASUREMENTS: Start of antihyperglycemic drug therapy, defined by protocol as indicated for follow-up HbA(1c) level greater than 7% (primary outcome), and changes in weight, glycemic control, and coronary risk factors (secondary outcomes). RESULTS: After 4 years, 44% of patients in the Mediterranean-style diet group and 70% in the low-fat diet group required treatment (absolute difference, -26.0 percentage points [95% CI, -31.1 to -20.1 percentage points]; hazard ratio, 0.63 [CI, 0.51 to 0.86]; hazard ratio adjusted for weight change, 0.70 [CI, 0.59 to 0.90]; P < 0.001). Participants assigned to the Mediterranean-style diet lost more weight and experienced greater improvements in some glycemic control and coronary risk measures than did those assigned to the low-fat diet. LIMITATIONS: Investigators responsible for initiating drug therapy were not blinded to treatment assignment. Dietary intake was self-reported. CONCLUSION: Compared with a low-fat diet, a low-carbohydrate, Mediterranean-style diet led to more favorable changes in glycemic control and coronary risk factors and delayed the need for antihyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes.

The Glycemic Index

The glycemic index provides a measure of how quickly blood sugar levels rise after eating a particular type of food. Glycemic load is a number that estimates how much a food will raise a person's blood glucose level after eating it. In some quarters, the glycemic index and the glycemic load are still quite controversial. The debate centers on the importance of carbohydrate quality versus quantity in medical nutrition therapy. Often, we go astray by talking just generically about carbohydrate, protein, and fat, rather than talking about each type. Carbohydrate can either be high glycemic index or low glycemic index, depending upon its composition, form, and physical characteristics. If it is a component of highly unrefined roughage, including grains, it is generally low glycemic index. If it is very highly purified starch, it can be higher glycemic index. For instance, a potato, once mashed or fried, becomes a source of higher glycemic index than a baked potato. Rather than just talking about carbohydrate, we need to talk about the glycemic index of specific foods, and the total glycemic load that carbohydrate contributes to the daily diet.

The American Diabetes Association has no recommendations about the glycemic index. Some other groups, such as the Canadian Diabetes Association, do recommend a lower glycemic index diet, although they do not specify how that is to be achieved. The European Association for the Study of Diabetes has a fairly strong position on the low glycemic index component, and they define it more rigorously as it relates to its inclusion in the dietary management of diabetics.

What are the arguments for it? Glycemic index is a robust measurement. There is some variability in how food pertains to overall glycemic contribution to the diet versus its stand-alone glycemic index. That is why we often talk about the glycemic load of the total diet, not just the glycemic index of a food. Glycemic index is a physiological measurement. It therefore has some important values to correlate with the area under the curve of blood sugar after eating. Glycemic index of single foods has been shown to apply to mixed meals, and pooled glycemic index values of single foods are strongly correlated with the relative glycemic responses to mixed meals and can accurately predict the effects of mixed diets on glycemic control. Glycemic index is an easy concept to use, and can be employed by people who are not nutritional professionals. It has clinical utility because it correlates with HbA1C, fructosamine, fasting blood sugar, and fasting postprandial insulin levels.

What are the arguments against the glycemic index? People might say there is too much variability in the glycemic index. They might say that its calculation ignores glucose values below the fasting baseline, which is based on measurement of postprandial glucose over only two to three hours. They might say there are interactions among carbohydrate and other food factors, such as protein, fat, fiber, and the food form processing and preparation that complicate the accurate predictions of the glycemic response because of the way the food has been consumed in conjunction with the total meal. Last, criticisms of the glycemic index have shown that people feel there have not been enough randomized, clinical control data to make definitive clinical recommendations about how to apply the glycemic index of a food and appropriate cut-offs for what is high and what is low.

The PLMI supports of the glycemic load concept as being a good clinical indicator for doing diet evaluation and ultimate diet prescriptions for individuals with dysglycemia and dysinsulinism, and increasing relative risk to cardiovascular disease and diabetes. From many papers published over the past few years, it is now recognized that this may be the best clinical tool to apply to the construction of diets that will lower glycemic load and for the reduction of HbA1C, reduction of postprandial insulin, and improved insulin signaling.

Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, et al.
Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*. 2006;368:1673-1678.

Phytochemicals as Insulin Signaling Agents

Based on the benefits of the Mediterranean diet, one might propose that phytochemicals, or nonnutritive substances in plants that possess health effects, are an essential component of a diet for

metabolic syndrome and/or type 2 diabetes because of their effects on multiple cellular pathways. From an epidemiological perspective, fruit and vegetable consumption has stayed constant or slightly decreased since the late 1980s, and, in parallel, rates of syndromes like the metabolic syndrome have been on the rise, along with the steady climb of chronic diseases like type 2 diabetes and cardiovascular disease. Therefore, one could logically question as to whether consumption of the Western-style, "Standard American (now perhaps, All-Over-the-Planet) Diet", has resulted in a worldwide "phytochemical deficiency" due to its limited array of phytochemicals in the processed foods it contains.

Thousands of different plant pigments and other phytochemicals have been identified in whole plant food. Despite the focus on macronutrients and energy intake, it would seem that there should be increasing attention towards phytochemicals as they may play a larger role in our health than originally assumed. In the past years, the impact of dietary phytochemicals on protein kinases involved in pathways related to insulin signaling, inflammation, and stress responses continues to be elucidated. Some traditional food agents that have been researched for their molecular effects on processes related to defective insulin signaling include the following: cinnamon, green tea, bitter melon, and hops. For more details, please see the article by Minich and Bland in *Nutrition Reviews,* 2008 (abstract below):

Nutr Rev. 2008 Aug;66(8):429-44. doi: 10.1111/j.1753-4887.2008.00075.x.

Dietary management of the metabolic syndrome beyond macronutrients.

Minich DM, Bland JS.

Functional Medicine Research Center, MetaProteomics, LLC, Gig Harbor, Washington 98332, USA. deannaminich@metagenics.com

Abstract

Due to the complexity of chronic conditions like the metabolic syndrome (MetS), tailored dietary approaches beyond macronutrient ratio modification may be necessary to effectively address metabolic measures. Mounting data on whole foods-based, phytochemical-abundant dietary patterns, such as the Mediterranean diet, reveal that they contain constituents, such as phytochemicals, that may be beneficial for treating MetS. The role of food-based phytochemicals on underlying mechanisms of MetS, specifically as they impact insulin signaling, has yet to be investigated thoroughly. This review discusses various dietary approaches for MetS, with a focus on certain foods and dietary phytochemicals known to impact insulin signaling.

References

[1] Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA*. 2005;294(3):334-341.
[2] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415-1428.
[3] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. *JAMA*. 2002;287(3):356-359.

[4] Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, Jacobs DR Jr. A strong dose response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. *Diabetes Care*. 2006;29(7):1638-1644.
[5] O'Rahilly S, Barroso I, Wareham NJ. Genetic factors in type 2 diabetes: the end of the beginning? *Science*. 2005;307:370-373.
[6] Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*. 2006;368:1673-1678.

The information given and discussed in these materials is for research and education purposes only and is not intended to prescribe treatment.