June 2001 Issue | Gerald Reaven, MD

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Welcome to *Functional Medicine Update* for June 2001. This year we are focusing on applied functional endocrinology and neuroendocrinology. Following our May symposium, it is appropriate to begin this month with a focus on insulin resistance/hyperinsulinemia. In addition to type 2 diabetes, insulin resistance is related to a variety of degenerative diseases, including coronary heart disease, vascular stroke, certain forms of cancer, such as colon cancer, possibly dementias of aging, and autoimmune disease.

Dr. Gerald Reaven, this month's Clinician of the Month, originated the term "syndrome X" to describe the insulin resistance/hyperinsulinemia syndrome. He began using the term several years ago to describe the triad of hypertension, hypertriglyceridemia, low HDL, and insulin resistance with the appearance of hyperinsulinemia observed after fasting for two hours following a standard glucose challenge

In the past year we have been discussing the gene/environment concept, which is central to what we call functional medicine. Functional medicine originates with the concept of biochemical heterogeneity, diversity, and functional genomics—genes and environment interacting to give rise to the phenotype, the outcome of the individual's performance over decades of living. This is a new concept in medicine. Within the genome are pleuripotentialities, or alternative outcomes in the way we function. Those functions depend, in part, on the environment into which the genes are plunged. A harmful environment for an individual, based on his or her genome, gives rise to a phenotype that may be associated with the onset of early-stage morbidity. Plunging that same genome into a different, more optimal environment, on the other hand, can lead to extending the health span, reducing premature morbidity, and even increasing life span itself.

The phenotype, therefore, is the result of interaction between the genome and the environment. Nutrients are among the most important environmental components that alter the phenotype through life. A recent article in *Nutrition Reviews* discusses the implications of the Human Genome Project for understanding gene/environment interactions. This same topic was the theme of a book I wrote a couple of years ago. That book, *Genetic Nutritioneering*, discusses the interaction of genes and environment, giving rise to the appearance of either health or dysfunction as we age.

Polymorphic and Pleomorphic Characteristics and the New Medicine

Extensive genetic variability exists both within and between human populations. These distinct genotypes respond differently to environmental variations, giving rise to distinct norms of reaction that are individualized to that person. In the past, many studies have drawn conclusions based on an average

response of participants, rather than on cohort analysis, in which we look for individual responses in smaller groups differentiated by their unique genotype and biochemistry. Advances in molecular genetics have made it possible to start to analyze the way the 50,000 or so different genes respond to different environmental stimuli, and how they functionally interact to produce what we call the phenotype.

This new concept will have a tremendous impact on the future practice of medicine. Using a few drops of blood we will be able, for pennies per gene, to analyze an individual's genomic messages under certain environmental conditions and considerations. This will allow the tailoring of a program for the individual based on his or her own genomic expression pattern. We will then be fully able to realize the dream of Dr. Roger Williams in the 1950s when he originated the concept of biochemical individuality, and Dr. Linus Pauling's discussion in the 1940s of molecular medicine.

Proteomics

We are finally starting to understand the DNA message and its ultimate expression into proteins and enzymes. This so-called proteomics connection gives rise to the expression of function. It relates to epigenetic effects like phosphorylation and glycation, the reaction of proteins with sugars, for example, and how they influence the function of these molecules over the course of living. This is the design of a new epistemology of molecular medicine, molecular aging, molecular gerontology. It is the intersection of many disciplines that will provide new tools for the clinician.

The implications of the Human Genome Project for understanding the gene/environment interactions are creating the potential for this new medicine to evolve. This new medicine has a rich, deep clinical observational history built on centuries of good observation, but it is now tied together with these new tools that help us tailor the program to the individual—called personalized medicine

Cholesterol itself if an example. We know that increased LDL cholesterol is associated with increased risk of coronary heart disease. This has been well established through multi-centered trials in lipid clinic centers in different areas of the world. Those research centers have helped us learn that a 1 mg percent cholesterol increase can result in a 2 percent increase in the statistical probability of heart disease, after you get to a certain threshold, say above 200 mg percent total cholesterol and above 120-130 mg percent LDL cholesterol.

Interestingly, in individuals who are age 80 or older, high total cholesterol concentrations are associated with longevity. This seems paradoxical, but is due to lower mortality from cancer and infection. Self-selection may be occurring. At younger ages, those individuals with high cholesterol may be at risk, due to their harmful environment, for early-stage coronary heart disease and coronary myocardial infarction. If they survive that period, however, some beneficial effects may be associated with the modulating processes that cholesterol affords that control cell signaling, reduce inflammation, and help in cell repair and other membrane-related phenomena.

Overcoming Cholesterol's Bad Reputation

It is interesting that we sometimes lock onto a molecule and give it a bad name. Cholesterol is considered a bad molecule in the minds of most individuals on the street today, but we know it plays some important roles. It is a critical element in the lipid bilayer of membranes. It plays an important role as the precursor

to cholic acid, deoxycholic acid, and chenodeoxycholic acid, bile acid components used for solubilizing cholesterol and assisting in the digestion of fats. It is also the central precursor to an array of steroid hormone molecules—the stress hormones, the glucocorticoid hormones, the mineral corticoids, and the sex steroid hormones. Perhaps cholesterol should not be called a bad molecule. It is a molecule with information that, in fact, is involved in a series of sophisticated processes throughout the course of aging. It may be that the outcome of these reactions, rather the fate of cholesterol than cholesterol itself, determines some of our health risk relationships.

The article in the *Lancet* discusses people age 85 or older whose high total cholesterol concentrations were associated with longevity and lower incidence of mortality to cancer and infection. Therefore, the authors of this article conclude, we need to reassess the effects of cholesterol-lowering therapy in older-age populations. In a younger-age group, we may be lowering the risk of heart disease with these drugs, but in an older-age group, giving them cholesterol-lowering therapy may increase their risk of cancer and infection. These are more subtle questions related to messages in the genotype/phenotype connection and expression throughout the different phases of aging

Another interesting part of this story has to do with the genotype of apolipoprotein E. We have discussed three different kinds of apolipoproteins—apoE2, E3, and E4. If you are homozygous for apoE4, inheriting one copy of E4 from your mother and one from your father, a so-called double E4 genotype, you have a characteristic associated with significant increased prevalence of cardiovascular disease and Alzheimer's dementia. Some people have said you would not want to know if you are an apoE4 homozygote because you might get depressed and there is nothing you can do about it. You can't change your genes.

We are learning, however, that the apoE4 allele is very saturated-fat-sensitive. It may be possible, therefore, to remove or significantly reduce the expression of these adverse phenotypic outcomes of heart disease and Alzheimer's by recognizing this genetic susceptibility and putting a person in those situations on a rigorously modified or restricted saturated fat diet. Perhaps these individuals need to be placed on rigorous programs like those of Dr. Dean Ornish or Dr. McDougal. These are very high unrefined complex carbohydrate modest protein/low fat dietary regimes with most of the fat coming as polyunsaturated, unrefined vegetable oils. Again, certain genotypes may lead us into the selection of specific diet and lifestyle environments that then wash over the genes through decades of living, to give rise to the phenotype that is not going to express morbidity and premature risk to death

Not too many years ago, we were told there was virtually no difference between normal vegetable oils and the partially hydrogenated vegetable oils that contain the so-called trans fats. In America, we had no regulation on the inclusion of trans fats in vegetable oil products. Europe, Japan, and other regions of the world, however, have had rigorous controls over their inclusion. Not more than .1 percent of trans fats could be included because of concerns about their safety. In the United States the burden of proof was on those individuals who, like Dr. Mary Enig, criticized trans fats, rather than on those who put it in the food.

In the past five or six years increasing evidence has begun to indicate that the trans fats that result from the partial hydrogenation of vegetable oils are, in fact, anti-metabolites (to use the term advisedly). They have adverse effects on specific metabolic functions that we normally associate with unsaturated fatty acids. One paper that has contributed to the groundswell of concern about partially hydrogenated vegetable oils was "Effects of Different Forms of Dietary Hydrogenated Fats on Serum Lipoprotein

Cholesterol Levels," published in the *New England Journal of Medicine.*

Individualized Responses to Trans Fats in the Diet

The study looked at 18 women and 18 men consuming each of six diets in random order for a 35-day period. It found that consumption of products that were low in trans and saturated fats had beneficial effects on serum lipoprotein concentrations, whereas those that were higher in trans fats elevated lipoprotein concentrations associated with increased risk to coronary heart disease. The study also found these fats can be selectively sensitizing, in certain genotypes, toward that cholesterol-elevating effect. Again, not everyone responds in the same way. Asking the right question of the right individual about his or her genotype/environment relationship may give a more specific answer as to how that patient should be monitored, controlled, or counseled.

For some time we have believed that individuals should be very concerned about their dietary cholesterol if they have elevated LDL. In a Florida restaurant not many years ago I observed an older woman surgically dissecting her egg to separate every trace of yolk from the white, which she then proceeded to eat. I couldn't help, when I encountered her later at the checkout counter, telling her I had noticed her dissecting her egg to remove the yolk and that I wondered why she had done so. She replied that her cardiologist told her if she ate any egg yolk at all she would die of a heart attack.

Egg Yolks—Good Protein Source or Villain?

She had obviously gotten the message, but was it the right message? How much do a person's blood and LDL cholesterol go up when she eats 300 mg of cholesterol from an egg yolk each day? In most cases, modest dietary cholesterol has very little impact upon LDL cholesterol. For some individuals, however, particularly apoE4 individuals, modest cholesterol increases can lead to significant increases in plasma LDL cholesterol. These are cholesterol-sensitive individuals.

How do we determine who should receive the strict dietary cholesterol control recommendation? In a public health recommendation, everybody is affected, but that recommendation may actually prevent many people from eating a pretty good, high-protein food that is an inexpensive source of protein. I'm not recommending excessive egg consumption. I am just trying to bring this discussion back into perspective. You may remember a report in the *New England Journal of Medicine* of an 87-year-old man who consumed 88 eggs a week and had no coronary atherosclerosis. One needs to be very cautious about specific public health recommendations and how they may affect the individual, based upon this genomic uniqueness concept.

Pros and Cons of Salt Consumption

Salt has a similar reputation. Although we hear most about sodium sensitivity, the chloride in salt may actually be causing the problem. The chloride ion may have an adverse impact on blood pressure. Most individuals with essential hypertension do not suffer from sodium sensitivity. That is not the principal reason their blood pressure is elevated. Putting them on a rigorous salt-restricted diet has little impact on their blood pressure.

Some individuals, however, are very sodium sensitive. For them, restriction of sodium or sodium chloride

intake can have a profound effect on blood pressure. The future of personalized medicine requires using the right dietary management program for the right genotype

One genetic uniqueness that is causing increasing concern in our population is related to insulin resistance/hyperinsulinemia and perhaps later-stage 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 nonwhite populations.

Insulin as Messaging Molecule

More than 30 years ago, when I was in school, I learned that type 2 diabetes is a consequence of inability of the b -cells in the pancreas to secrete enough insulin. This theory is now under some scrutiny, because many type-2 diabetics are hyperinsulinemic, not hypoinsulinemic. The b -cells are still secreting a considerable amount of insulin, perhaps even an excessive amount, but the message is not being received. As a messaging molecule, insulin somehow has lost its ability to have its signal transduced by the various insulin-signaling mechanisms. The result is the insulin resistance, a refractory insulin communication system. In response, the pancreas ramps up message production and increases the secretion of insulin until eventually it can no longer do so. The reserves are exhausted, and you now have a true frank insulin deficiency. A paper in *Postgraduate Medicine* discusses the difference between a type 1 insulin-deficiency type of diabetes and a type 2 hyperinsulinemic/insulin-resistance type of diabetes.

Financial and Quality of Life Implications of Type 2 Diabetes Management

The primary problems and secondary side effects associated with type 2 diabetes have a tremendous economic impact. Some effects are less tangible, quality-of-life issues. People become functionally disabled, with low energy, fatigue, inability to concentrate, headaches, muscular aches, pain of unknown origin, and kidney problems of modest difficulty. These quality-of-life issues sometimes precede by decades the onset of severe symptoms.

In a paper published in the *Journal of the American Medical Association*, investigators looked at health economic benefits and quality of life achieved during an improved glycemic control among patients with type 2 diabetes. They found a considerable cost saving was realized by placing individuals on a glycemic management program with rigorous control of their blood sugar and insulin in terms of the healthcare expenditures that occurred downstream. They also found these individuals' quality of life was substantially improved in the short term. There are both long-term health economic benefits and short-term patient satisfaction benefits associated with implementation of an appropriate program to improve insulin sensitivity and glucose management.

Characteristics of Type 2 Diabetes

Type 2 diabetes is a complex metabolic disorder characterized by peripheral insulin resistance and impaired b -cell function. Most individuals with this condition have impaired insulin resistance and hyperinsulinemia. It is not just a condition of low insulin output. 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 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. Therefore, if we wait for the onset of diabetes, we may have missed decades of potential adverse effects of inappropriate insulin signaling. I want to reemphasize the polygenic nature of the disease. It is not due to alterations of a single gene. Defects in insulin management can result from mutations in a large number of genes and produce symptoms with varying degrees of severity.

Genes and Environment in Insulin Sensitivity

It is not clear whether b -cell and insulin sensitivity relationships are strictly genetic or whether they are more likely to be environmental. Research is going on in this area. What we have seen in human genetics work at present is a clear illustration that impaired b -cell function, increased hepatic glucose production, and decreased insulin peripheral sensitivity are a strict genetic disorder. This does not mean that there is no room to maneuver, rather it means that phenotype is a consequence of plunging the susceptible genes into a harmful environment. It is the environment that becomes important, because environment is modifiable. We cannot clinically modify the genes, but we can modify the environment into which the genes are placed, thereby altering phenotype. This is the area in which functional medicine can play a major role.

A study published in *Nature Genetics* presents the hypothesis that insulin resistance in muscle and fat is sufficient to cause type 2 diabetes in the absence of intrinsic b -cell function in liver abnormalities. The researchers examined this hypothesis in various animals that had become insulin resistant due to transgenic manipulation. These animals developed all the prodromal features of type 2 diabetes. Despite the compounded effect of peripheral insulin resistance and mild impairment of b -cell function, however, they failed to become diabetic.

Measuring Insulin Sensitivity

This study suggests another series of events may have to occur, a second-level effect, to produce diabetes after insulin resistance. Therefore, individuals may never go on to be insulin resistant, but have this insulin-signaling defect that increases the risk to vascular disease, dementias, cancer, and inflammatory disorders, even in the absence of diabetes. I want to emphasize that the *sine qua non* for insulin resistance is not diabetes itself—an important part of our clinical observations.

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.

A Glucose Assessment Panel

C-peptide is another determinant one can use, along with hemoglobin A1C, glycated hemoglobin, glycated albumin, which is probably even more sensitive than glycated hemoglobin for determining defects in glucose management, and then the 2-hour postprandial insulin and glucose measurements. You can also tie this together with triglycerides and HDL, recalling that elevated triglycerides and reduced HDL are also hallmarks of hyperinsulinemia and insulin resistance. We just set up a panel. Increased triglycerides, reduced HDL, increased blood pressure, increased 2-hour postprandial insulin and glucose, increased C-peptide, and increased glycohemoglobin are all associated with the insulin resistance/dysglycemia situation.

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. A major discovery was made in 1999. 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

It has been 28 years since the insulin receptor was identified as a functional entity, 16 years since it was identified as an insulin activated tyrosine kinase, and 14 years after it was cloned molecularly. Recently, Zhang et al. from Merck have been able to identify a molecule that seems to mimic insulin that is orally administered. The discovery of this molecule offers insight into the methods of drug discovery. It involved screening of more than 50,000 different compounds against a hamster ovary model for molecules with specificity toward the insulin receptor. Orally administered, this molecule was found to have selectivity toward insulin receptors instead of the closely related and more mitogenically active IGF-1 receptors that are 84 percent identical in the kinase domain. The catalytic activities of this mimetic molecule and insulin were very close, but it failed to interact with IGF-1, which turns out to be helpful if you are trying to reduce cell proliferation and to improve glucose management. IGF-1 stimulants will increase cell cycling, which may then increase the risk of certain malignancies or neoplasias.

This molecule is a fungal metabolite that has been identified in nature, a phenolic compound (actually a quinone), found to have a positive effect on the insulin-mediated cell signaling process. It stimulates glucose transport by activating the cell signaling pathways of insulin through the glut4 receptors (glucose transporter receptors). This lowly fungus was found in the African forest near Kinsasha. This fungal metabolite is a molecule with a low molecular weight. It is not broken down by proteases in the gut and can be transported across the gut barrier into the blood, having insulin-like activity.

Food Substances and Insulin Control

Considerable research will have to be done before this substance can be introduced to the marketplace. It must demonstrate its safety and effectiveness. The theme in all of this is that natural substances can

impact the complex cascade of events that we call insulin signaling and, ultimately affect glucose removal, or glucose transport. It would not be surprising as we look at the influence of foods on the expression of genes that control insulin management and glucoregulation, to find constituents of various foods that people have historically eaten have salutary effects on certain processes associated with glucoregulation and insulin management. In fact, it would be more surprising to find there were not such things.

As the research proceeds, we see there are nutrients, both essential nutrients (vitamins and minerals) and phytonutrients (specific plant-derived substances) that seem to influence gene expression in the area of insulin signaling. This may be one of the major breakthroughs that allows us to tailor diets for genetically susceptible individuals in such a way as to decrease the risk of type 2 diabetes and/or hyperinsulinemia/insulin resistance. It will involve more than just the gross macronutrients. It will be necessary to consider specific micronutrients, or components in a complex diet, which will speak to certain genes that have regulatory effects on the complex cycle of glucose transport.

The pharmaceutical industry has developed a number of selective medications to manage type 2 diabetes that operate at different levels within this cascade. The American Diabetes Association recently changed the diagnostic criteria for type 2 diabetes from a fasting blood sugar level to 126 mg per deciliter or less, from the previous criteria, which was 140 mg per deciliter. This tightened standard for what constitutes type 2 diabetes and fasting sugar is supposed to help us identify patients at risk. However, according to comparative studies published in the *Lancet* in 1998, the World Health Organization criteria, which uses 2-hour postprandial sugar and insulin, appears better able to predict those individuals at risk to coronary vascular disease as a consequence of dysinsulinism. These measurements appear preferable to relying on fasting blood sugar, even at the 126 mg per deciliter criteria level.

Therefore, I urge you as a clinician to consider the whole array of variables for assessing insulin sensitivity—the triglycerides, the HDL, C-peptide levels, glycosylated hemoglobin, and the 2-hour post prandial sugar levels after an oral glucose load of 75 grams. All of these together give a better understanding of the complex response a person has to carbohydrate in his or her diet.

Drug Therapy and Diabetes Management

The five drugs of choice in diabetes management include insulin, acarbose, metformin, sulphonylureas, and the thiazolidinedione drugs. Those are the most common classes of medications being employed. The most recent advances are the thiazolidenediones, drugs like peoglitazone and rosiglitazone**.** Until recently, troglitazone was also in this class. It was removed from the market as a consequence of its hepatotoxicity potential. When this drug first came out on the market, many of us were concerned because it was known to be a very powerful peroxisome proliferated activated receptor *alpha* (PPAR-a) activator, as well as a PPAR-g receptor activator.

PPAR-a is a peroxisomal upregulated effect that can lead to lipid peroxidation and potential oxidative stress to the liver. Those of us who looked at the original data on troglitazone were concerned that it may have adverse impact on liver function in certain susceptible individuals through increasing liver oxidative reactions. Rosiglitazone and peoglitazone appear to be much more sensitive/selective as PPAR-g agonists rather than PPAR-a . We need to watch liver function in patients on these medications, however.

The First Step in Blood Sugar Management

You may wonder about the different uses of these various medications for individuals with type 2 diabetes. A review article in *Patient Care* covered this topic. In recent onset of blood sugar dysregulation, or insulin dysregulation, according to the authors, the first step a clinician should pursue is a 6-12 week course of diet, exercise, and non-drug intervention for the patient. I want to emphasize the importance of this step. Many practitioners jump immediately to pharmacological therapy when they see an individual above 126 mg per deciliter on a fasting blood sugar. They immediately take the prescription path.

All evidence published in the past two to three years indicates that the first step in patients with marginal elevations of blood sugar who do not have glucose toxicity, meaning 250 mg/dl blood sugars, should be intervention with a diet, exercise, and lifestyle program. This intervention can help determine not only if the patient will comply, but also what the level of sensitivity to that program will be. Somehow, we often miss that important step in medicine. If a patient can achieve a balance at that point, he or she is in self-regulation. The cost to the healthcare system is significantly reduced. The individual is an active participant in his or her own program, and perhaps the patient's blood sugar difficulties were there to teach a lesson about self-control and genotypic understanding. The patient can tailor his or her phenotype to be a health functional phenotype.

Acarbose as the Second Step

Pursuing a 6- to12-week course of diet, exercise, and lifestyle management, without resorting to drugs, seems to be the first step. If that doesn't work, obviously, as a clinician, you would move into other alternatives. If it is recent onset with minimum fasting blood sugar elevations, predominantly postprandial, not fasting blood sugar, you might consider blocking the release of sugar from carbohydrate across the GI, which is done with a starch blocker called acarbose. Acarbose is a starch-inhibiting molecule that enzymatically inhibits the release of sugar. It might be the mildest approach for that kind of patient.

If there is recent onset with minimum to severe blood sugar elevations that are fasting and not postprandial (above 126 but lower than 200 mg per deciliter), you should determine if the person has impaired renal function. If so, he or she probably should be on the thiazolidenedione drugs. If not, the patient should probably go into metformin, particularly if they have no abnormal liver enzymes or history of alcohol abuse.

Metformin would be the drug of choice.

Stronger Medications for More Severe Problems

However, if they have problems with liver enzymes and/or alcohol abuse, then low-dose insulin might be a preferable, according to this article. If they have severe fasting blood sugar elevations above 200 mg per deciliter but no significant obesity or other co-morbidity, then at that point they can be put into the sulfonylurea compounds and be managed on those.

Last, if they have glucotoxicity above 250-300 mg per deciliter of fasting blood sugar, they need to go immediately into human insulin, together with oral antidiabetic agents such as the sulfonylureas. There

are different graded therapies, but I want to emphasize the place to begin is with a diet, exercise, and lifestyle program, unless they have glucotoxicity above 200 mg per deciliter fasting blood sugars. These drugs—insulin, acarbose, metformin, sulfonylureas, and thiazolidenediones—affect function in different ways. There are different instances in which to use these different drugs depending on what is needed for the patient's management. Each has its own potential adverse side effects and inherent expense. If we can avoid them by having the patient self-regulated, that would be the most desirable.

Tailoring Management Programs to Individual needs

There is a significant observed difference in efficacy from patient to patient among the different agents I just described. That is what makes this an artful approach toward medicine. One size does not fit all. If you are managing insulin resistance or type 2 diabetes, you do not just jump in with a formula.

You must tailor the program to the individual because of the variety of genotypic variations that give rise to the outcome we see as type 2 diabetes. There is not a single cause for type 2 diabetes. Multiple paths with differing metabolic implications lead to that condition. It is not just one drug therapy for all patients. It is graded to the severity of their problem, their genotypic uniqueness, and their response. I refer to an article titled "Effects of Diabetes on Cardiovascular Drug Metabolism."

Evaluating how the patient will respond to various medications is an important part of the approach, but emphasizing that the first step is to intervene with diet and lifestyle changes is an important takeaway from this discussion, unless the patient has true glucotoxicity.

Sulfonylureas have been available since the 1950s, tolbutamide being one of the best examples. These drugs can have adverse cardiovascular side effects in certain individuals over time, however, because of their effect on ATP-dependent potassium channels. Caution should be exercised, therefore, in using these drugs in individuals who have certain types of cardiovascular problems.

Different Drugs, Different Potentials for Side Effects

The thiazolidenediones influence the peroxisome-proliferated activated receptors (PPARs). Therefore, we want to follow liver enzyme function because of their potential adverse effects on liver peroxidation. Metformin has been available in the United States for only about five years, but it was previously used for many years in other parts of the world. It has been shown to reduce hepatic glucose overproduction. It may increase muscle glucose utilization and decrease intestinal glucose absorption. A worrisome side effect of metformin is lactic acidosis. Worldwide experience with metformin suggests this risk is very low when the drug is used at appropriate doses. Although it is better than fenformin, it does have some risk in that area that needs to be of some concern. Different drugs have different modes of action and different activities on glucose and insulin regulation.

Many studies have demonstrated the value of these medications in managing patients who are at risk to macro- and microvascular problems. One may never get type 2 diabetes, but he or she still may be at risk for cardiovascular disease or peripheral vascular disease. A paper in the *Lancet* looks at intensive blood sugar control with sulphonylureas or insulin compared with other therapies and the complications of type 2 diabetes. Another article in *Diabetes Care,*titled "Effects of Metformin on Insulin Resistance, Risk Factors for Cardiovascular Disease, and Plasminogen Activator Inhibitor in NIDDM Subjects," shows

that proper regulation of blood sugar lowers plasminogen activator inhibitor and therefore improves vascular dynamics.

Identifying the Patient's Genotype

We recognize there are powerful benefits for these interventions, but they may be seen as a second line after first trying to modify genotypic expression through diet and lifestyle intervention in these patients. The syndrome X patient or the hyperinsulinemic individual may be a person whose cells are starving for lack of fuel, because glucose is one of the principle fuels to power up ATP formation. Dr. A.M. Fournier, in a recent paper titled, "Intracellular Starvation in the Insulin Resistance Syndrome and Type 2 Diabetes Mellitus," explains that hypertension, type 2 diabetes, and dyslipidemia are causally linked in many patients to insulin resistance, beginning long before clinically detectable type 2 diabetes is seen.

This linkage occurs at a cellular level and is related to insulin's key role in insuring an adequate delivery of fuel for metabolic activities such as active transport and energy- requiring enzyme reactions. Lack of proper glucoregulation can result in altered intracellular calcium levels, reduced levels of ATP, decreased phagocytic function, and increased oxidative stress. The hypothesis is that the effects of insulin resistance are those of intracellular glucose starvation due to defective insulin signaling. Insulin is a gene response modifier. It is not solely a glucoregulatory hormone, so it has effects elsewhere on genetic expression that control cell cycling and other functions within the cell that we see as the secondary effects of insulin dysregulation.

We are at a point in our discussion where we need an expert to guide us in understanding how all these things fit together in controlling the specific insulin-signaling mechanism and the role of diet, both macro- and micronutrients, in normalization in genetically susceptible individuals. This is the genotype/phenotype interconnection.

What is the ability for glycemic control and insulin control to occur through the modulation of carbohydrate, protein, lipid metabolism, and its relationship to dietary fiber? That was described in a recent review article in *Diabetes Spectrum*, in which the author explains that diet may play an important role, well before the implementation of medications, in management of this insulin resistant/hyperinsulinemic syndrome. By appropriately tailored dietary intervention using a proper balance of macronutrients and unrefined fibers, one might be able to achieve regulation of these genes and their expression well before one gets into pathophysiology from poor glucoregulation or insulin imbalances. Clinical experience has shown that dietary intervention can play a profound role if the patient is appropriately educated. It must also be easily applied and fit in with the patient's lifestyle so it does not seem to him or her to be "cruel and unusual dietary punishment.

INTERVIEW TRANSCRIPT

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Evolution in Understanding Insulin Resistance

JB: We are privileged to have Dr. Gerald Reaven as our Researcher of the Month in this issue of FMU. Dr. Reaven has published more than 500 research and review articles, 117 books, numerous chapters of books, and results of many conference proceedings. He has won awards for his research on diabetes, and for his excellence in teaching. He currently serves on the editorial boards of the American Journal of Physiology: Endocrinology & Metabolism and the Journal of Internal Medicine. Welcome to Functional Medicine Update, Dr. Reaven. How has the understanding of insulin resistance evolved under your leadership during the past 40 years?

GR: 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.

Banting Medal Speech and the Origin of Syndrome X Term

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.

Seeking Acceptance of the Syndrome X Concept

JB: Given the 500 papers, your 30-plus years of experience, and all the clinical support from other groups for this concept, why has it not yet woven itself into standard practice in medicine?

GR: This is going to sound cynical, and I apologize for that, but I think it's true. Several very prestigious groups in this country, including the American Heart Association and the National Cholesterol Education Program, have been pretty much fixated on cholesterol as the only issue worth talking about. I won't be so cynical as to suggest it may be because a lot of drug companies are currently interested in drugs that lower LDL cholesterol. The thought leaders, who are paramount in these kinds of programs, were people who grew up totally focused on cholesterol lowering as the only issue worth addressing. Despite the fact there is ample evidence to show that has not been the case, I think it still continues, although it is slowly changing.

Much of the education of practitioners in this country is supported by drug companies. If drug companies have good drugs that lower cholesterol, that's a good thing. I'm not trying to denigrate the importance of that, but if that's where they're making their money, then clearly they're not sponsoring talks at CME meetings on issues other than lowering cholesterol.

Diet and Insulin Resistance

JB: In your recent book on syndrome X, you talk about the diet relationship to management of insulin resistance. We are all aware that diet and nutrition are not major topics in medical school education. Do you feel this plays a role as well?

GR: I think it's terribly important. It's another example of the power of these various organizations, despite the scientific evidence, which is certainly out there. It's so straightforward. If you increase the amount of carbohydrate in your diet, you have to secrete more insulin to compensate. There's nothing more fundamental than that. If you're very insulin sensitive, that's a nice thing to be if you have the right genes, you're not overweight, and you're very physically active. If you are insulin sensitive and you increase your dietary carbohydrate, that's almost an irrelevant issue, because the amount of insulin you need to compensate for that change is not so great, and you're not at the beginning secreting much insulin.

On the other hand, if you are insulin resistant an increase in dietary carbohydrate can cause problems. You either have to secrete even more insulin, your insulin goes up more, and the problems of syndrome X get worse, or you can't secrete more insulin, your glucose goes up, and you have hyperglycemia. There's nothing very fancy about that.

Low-Fat, High-Carbohydrate Diet Recommendations

Americans have been told for years they should eat low-fat, high-carbohydrate diets. That recommendation is based on the idea that if you eat a low-fat diet, you'll eat less saturated fat and keep your low-density protein, or LDL cholesterol, low. I have absolutely no problem with that. I think that's a good thing to do.

The real question concerns what to substitute for that saturated fat. If you substitute carbohydrate for it,

and you are insulin resistant, as I said, bad things happen. But if you simply substitute saturated fat with unsaturated fat, the improvement in LDL cholesterol is every bit as powerful and you don't have any of the problems of high carbohydrate diets. I think it's almost to a point now where no one can seriously defend the alternative, and we're already beginning to see the American Diabetes Association and the American Heart Association acknowledge this fact. They have come out recently with guidelines that take this into consideration.

Differences between Saturated and Unsaturated Fats

JB: For the sake of our listeners, who are principally clinicians, could you be a bit more specific about the difference between saturated and unsaturated fats? Are we talking about mono- versus polyunsaturated fats, omega-3s versus 6s, or does it not matter?

GR: It probably doesn't matter a great deal. One’s LDL cholesterol concentration is primarily regulated by his or her genetic background. The ability to modify LDL cholesterol concentration by dietary intervention is real, but modest. Of all the factors that play a role in modifying LDL cholesterol concentration, the greatest is the kind of fat. I think there is no disagreement about the fact that saturated fat is probably the major dietary modulator of LDL cholesterol. The more saturated fat you ingest, the higher your LDL cholesterol will be. Now, again, your baseline will depend upon other things. There are some arguments about whether monounsaturated or polyunsaturated fat is better to replace saturated fat in reference not so much to LDL cholesterol (they seem to be pretty equal in that context), but in reference to HDL cholesterol concentration.

Given the relative difficulty in getting any patient to follow a diet, I try to make things as simple as I can. I figure if I can have them do just a couple of things, they may actually follow the suggestions. My general thought has been to focus not so much the fine details, but just to replace saturated fat with mono/poly, and we tend to try to make that proportionate. For example, in the book I wrote, we recommended in general that a diet containing approximately 40 percent of calories of fat would not be unreasonable. It should contain no more than 10 percent saturated fat, with the rest divided between polys and monos, but I don't think there's a major difference.

Protein and Carbohydrate Types and Differences

JB: How about if we look at protein and carbohydrate types, say vegetable versus animal protein, or different unrefined carbohydrates versus refined. Is there any difference in those categories?

GR: One thing I'd like to make really clear is the misconception that carbohydrate is insulinogenic, but protein is not. That is just not so. If you look at any textbook on physiology, it's very clear that protein is broken down into amino acids, and the amino acids are highly insulinogenic. In a recent paper in the Journal of Endocrinology & Metabolism, Frank Nuttal's group in Minnesota showed that if you eat protein, plasma insulin levels go up. The idea that you can avoid hyperinsulinemia by giving high protein/low carbohydrate diets is without any scientific basis.

On the other hand, there are differences in the kinds of carbohydrate you eat. This is uniquely the case when you are ingesting only the pure carbohydrate. For example, 100 grams of potato versus 100 grams of rice would be different. However, when you begin to put those things into meals, you obviously

attenuate these differences on the basis of other constituents in the diet.

My own feeling is that if you're going to go through a list of dietary modifications, the first thing is to make sure people are of normal body weight. That may be the most important. Next is to replace saturated fat with unsaturated fat. The third is, don't increase your carbohydrate and eat low-fat/high carbohydrate diets. If one wants to get involved at a fourth level with the kind of carbohydrate, how much fiber, and so forth, I have no problem with that. It is just less powerful than the first three.

Protein Glycosylation

JB: One question clinicians have asked me is whether protein glycosylation is influenced by insulin resistance. Do you see any change in glycohemoglobin or glycosylated albumen?

GR: The question of glycosylated proteins and how important they are in the pathogenesis of various diseases is not totally clear to me yet. There's ample evidence from in vitro studies that one can change a lot of metabolic behavior of glycosylated proteins. How much of this happens in vivo and how important it is in terms of various complications, certainly in non-diabetic individuals, is not clear to me at all. There's more evidence that they may play a major role in patients with hyperglycemia. I don't have a good feeling yet as to how important these issues are.

Effects of Insulin

JB: How about insulin's effect? Most of us in our early schooling learned that insulin is a glucoregulatory hormone, and we saw it exclusively as that kind of hormone. Now we are starting to see that glucose transport is a much more complex signal transduction process and that insulin may have influences in gene expression—protein tyrosine kinase activities. Are there things you're starting to see as they relate to insulin's personality beyond the simple concept that it just works at the insulin receptor?

GR: I think it is even more important to point out that hyperinsulinemia in individuals who are insulin resistant comes about primarily because of resistance to the ability of insulin to stimulate glucose uptake by muscle. It is also unable to regulate normal adipose tissue metabolism so there's somewhat increased lipolysis. Those are the two tissues that are insulin resistant in the strict sense.

Many complications or manifestations of being insulin resistant come about because the hyperinsulinemia in insulin-resistant individuals acts upon tissues in those same individuals who are insulin sensitive. A classic example is the kidney. The kidney remains (retains?) normal insulin sensitivity. Individuals who have insulin resistance and compensatory hyperinsulinemia also have excessive or accentuated sodium retention by the kidney. They also have difficulty in uric acid excretion. They have a decrease in uric acid clearance. Both of these come about through insulin’s acting on a normally insulin-sensitive kidney in the face of insulin-resistant muscle and adipose tissue.

Manifestations of Insulin Resistance

The hypertriglyceridemia in insulin-resistant individuals comes about through the combined effects of the compensatory hyperinsulinemia due to muscle insulin resistance, and the increased fatty acids in the plasma due to the adipose tissue insulin resistance going back to a liver that is normally insulin-sensitive,

and making you secrete more triglyceride.

Polycystic ovary syndrome, which is the most common reproductive abnormality in premenopausal women, is another example of the ovary responding to a high insulin level secondary to the insulin resistance. The ovary makes more testosterone and plays a major role in the manifestations of the polycystic ovary syndrome. A multitude of manifestations of abnormal metabolism are evident in individuals who are insulin resistant. They come about because the insulin levels, which have become high to prevent diabetes, are having untoward effects on tissues that remain normally insulin sensitive.

Widespread Nature of Insulin Resistance

JB: That should cause clinicians to look at other variables than diabetes. You have stated that the prevalence of various degrees and manifestations of insulin resistance is more significant than most clinicians realize. I believe you stated that 20 percent of the non-diabetic population may be insulin resistant. Is that what you've found in your work?

GR: There's no simple way to say who is resistant and who is not, because it's clearly a continuum. We have now shown in several publications the results of measurements of insulin resistance, or insulin-mediated glucose uptake by muscle, to be specific, in healthy, non-diabetic volunteers for a finite period of time. In the lower third, the third of the population that is least insulin-resistant, we've yet to see a case of type 2 diabetes, hypertension, coronary heart disease, or stroke developing. If you now go to the upper tertile, you begin to see a lot of bad things happening.

We recently published a paper where we studied roughly 150 individuals who were between the ages of 40 and 50 when we started the study. We followed them for approximately five years. One out of 7 individuals in each tertile of 49 volunteers had a coronary. Using figures like that, we're talking about 25 to 30 percent. Twenty is probably a modest estimate of the number of the population at large which is insulin resistant enough to be at risk to develop type 2 diabetes, hypertension, stroke, and coronary heart disease.

I'm sure you're aware of the fact that in the last couple of years, there have been increasing reports of hyperinsulinemia’s being a marker, at least in association with increased risk of cancer. How this evolves, who knows, but it's a new notion. In the common chronic diseases of Western civilization—high blood pressure, type 2 diabetes, coronary heart disease—we literally can say that a third of the population has increased risk to half of those things because of insulin resistance.

Genotype and Risk for Insulin Resistance

JB: That leads me to the question of genotypes that may have more than the average risk. I'm thinking, for instance, of the apoE genotype, the 2, 3 and 4 single or double allele types. We think of the apoE4s as being at high risk to coronary heart disease. Are there certain genotypes that you have seen that are more at risk to insulin resistance?

GR: Unfortunately, no one has found evidence of any genetic regulation of insulin resistance per se. There are clearly ethnic differences, but no one has found a relevant gene for their association with genotypes. There are certainly genetic changes that can modulate the manifestations of insulin resistance.

You mentioned the apoE gene. There's no doubt that that can modify triglyceride concentration, but it's modifying the fundamental abnormality that takes place in terms of increased production of triglycerides.

Another good example is that there are people who are heterozygous for mutations in the lipoprotein lipase gene. These individuals, if they're heterozygous, unless they're making too much triglyceride, have no problem. But if you are heterozygous and also have certain LPL mutations, you're also insulin resistant, and you're also making more triglyceride, the height of your triglyceride will certainly be modulated by whether or not you have specific mutations in the LPL gene. Things like that are evolving, but for insulin resistance per se, there has been no convincing evidence so far of any major genetic regulation. There's evidence of genetic regulation, but there has been no interesting information on the genotype so far.

Multigene Implications in Chronic Degenerative Diseases

JB: That falls in line with the emerging understanding that a lot of our chronic degenerative diseases seen in mid- and late-age are really multigene and we're not going to find any single genotype

GR: Absolutely. This is not going to be like cystic fibrosis.

Exercise and Insulin Resistance

JB: You conducted a study of exercise and insulin resistance, which was published in JAMA in 1999. It showed that moderate exercise improved insulin sensitivity. If you were to contrast modest exercise to diet intervention, which has a greater ability to help improve insulin sensitivity?

GR: They're probably equally good. The problem with exercise is that if you look at the variables that affect insulin action in a healthy volunteer population, roughly 25 percent of the variability from person to person is due to differences in weight and roughly 25 percent due to differences in physical activity. If you're insulin resistant and lose weight, for example, the benefits you have gained from the weight loss will stay as long as you maintain that weight loss and don't gain it back. If you exercise, there's no doubt you can improve your insulin sensitivity, but it's fairly transitory. If you exercise faithfully for six months and everything is terrific and then stop for a couple of weeks, you've pretty well lost the benefits. I'm not putting down physical activity, but I think in a pragmatic sense, diet may be more powerful than activity level.

The Zone Diet Concept

JB: The idea of balancing protein and carbohydrate has been made popular by diets like the Zone Diet approach. I think your name is mentioned as someone who helped design this approach. Do you have an assessment of the Zone concept?

GR: Yes, very straightforward. First of all, I think the physiology is basically sheer nonsense. As I said earlier, protein is insulinogenic, so giving people high protein diets is going to increase their insulin levels as compared to substituting unsaturated fat. Second is the notion that glucagon modulation is crucial. If you actually measure glucagon levels throughout the day, they barely change. Glucagon, I think, is very important in preventing us from getting fasting hypoglycemia. The idea of substituting protein for

carbohydrate makes no sense. It's a lot simpler just to substitute unsaturated fat for saturated fat. Don't increase carbohydrate; don't increase protein. Protein is insulinogenic so I don't see any reason to eat something which makes insulin go up.

Conclusion

JB: That's very helpful. I want to tell you how much we appreciate the years of contributions you've made to this field, opening doors of understanding. We wish you continued success, and we look forward to following your work.

Dr. Reaven is a leader in the field of endocrinology related to insulin signaling and glucose management. We honor him as the Linus Pauling Functional Medicine award winner at our Eighth International Symposium on Functional Medicine. As the sixth winner of this award, he joins Dr. Glenn Doman, Dr. David Jones, Dr. Leo Galland, Dr. Sidney Baker, and Dr. Kilmer McCully. This is a big year for Dr. Reaven, because in the year 2000 he also received the Novartis Award for long-standing achievement in diabetes. He has made tremendous contributions and we thank him for being our guest on Functional Medicine Update.

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