November 2014 Issue | Osama Hamdy, MD, PhD

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Welcome to *Functional Medicine Update* for November 2014. This is the second of our three-part series on diabesity. We've been so privileged to have as our lead-off presenter in October Dr. Philip Kern, as you recall, who is the director of the Barnstable Diabetes and Obesity Center at the University of Kentucky School of Medicine, and an endocrinologist (both clinician and researcher). I think Dr. Kern did a fantastic job of tipping us off as to what does the landscape of diabetes and diabesity look like (this interconnection between obesity and diabetes). And what types of parameters do you use to evaluate patients, and what are some of the difficulties that you have in managing this complex condition, and what are the available tools that sit in traditional medicine today and their strengths and limitations. I think that that was a very good landscape analysis as to the state of affairs as it pertains to type 2 diabetes and obesity.

In this issue—in the November issue—we're going to move this on to the next level with our clinician/researcher/expert of the month, Dr. Osama Hamdy. Dr. Hamdy, as you will learn, is from the Joslin Diabetes Center at the Harvard Medical School and is a respected world expert in this area of the behavioral management of type 2 diabetes and the diabesity area. And so without further ado, let's jump right in with Dr. Hamdy and get his perspective on how lifestyle medicine is an approach towards the management (both prevention and treatment) of type 2 diabetes.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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As you know, we're doing this three-part series on the epidemic that we call type 2 diabetes, insulin resistance, and all the panoply of clinical affairs and effects that are a result of the downstream inappropriate modulation of insulin and the disturbances of glucose transport, and we're very privileged to have as one of our three top global opinion leaders, Dr. Osama Hamdy, who is at the Joslin Obesity Clinical Program. He's actually the medical director of that program at Harvard Med School. He's an endocrinologist (both a research and a clinical endocrinologist—MD, PhD). Remarkable publication record. You probably would have heard of work indirectly in that his group made the outstanding discovery a number of years ago—I think it was back around 2002—that individuals who were obese that lost about seven percent of their body weight had a significant improvement in their vascular endothelial function as measured by flow-mediated dilation, and that translates, obviously, to a very significant contribution to the prevention of atherosclerotic disease and coronary artery disease in individuals with insulin resistance.[1] It helped us understand you don't have to get to your ideal body mass index to have improved clinical and metabolic function, and that was a very nice contribution of Dr. Hamdy and his group's work.

He has had many publications over the years and you're going to hear about a number of them over the course of this discussion. Osama, we want to welcome you to Functional Medicine Update and thank you both for being able to share your insight with us and also for the years of contribution you've made to the field.

OH: Jeff, it is my pleasure. Your program, I hear, is enriching thousands and thousands of physicians. I will be more than happy to add a little from the amount of knowledge that we have about obesity and diabetes.

JB: Well, thank you. Let's start down the road and let you tell a little bit about yourself. What led you into your work as both a combination researcher and clinical endocrinologist? I know you did your medical work in Egypt, and then you did a fellowship and postdoctoral work at Harvard. How did you travel down your path to this point?

OH: You'll be surprised. This is my passion, you know? I grew up in a family. All my family are overweight and all of them have type 2 diabetes, and many of them died at a very young age. My father died at age 48, and I wished that we were able to help them. I had been almost craving for knowledge about obesity and diabetes—what is the core of the problem and why people develop diabetes when they gain weight. What is the role of body fat distribution in this problem? So I decided to move to the US in the early 90s to complete my research, and my study, and my clinical work as well around that area, and I found that Joslin is the best place to be and I have been with Joslin for almost 17 years.

Why WAIT: Weight Achievement and Intensive Treatment Program

JB: Yes, and I think you've made really remarkable contributions to our body of knowledge, and I'm sure contributed significantly to your patients at the Joslin Clinic. You've developed this program with your colleagues at Harvard Joslin that I'm very interested in knowing more about. It's called "Why WAIT" that really stands for Weight Achievement and Intensive Treatment program. Tell us a little bit about where that came from and how it uniquely provides opportunities for the patients there.

OH: For almost 15 years we have been doing research around the impact of weight management on the cardiovascular outcomes, and on diabetes control, and many of the fundamentals of the theology and pathogenesis of type 2 diabetes. We decided in 2005 to start this program, which as you mentioned is Weight Achievement and Intensive Treatment, which means that we are trying to target diabetes from its core problem. We believe that the core problem of type 2 diabetes is body weight. If someone has a genetic background that will dispose the person to diabetes and that person gains weight—especially the weight gain in the central area, especially the increase in the intra-abdominal visceral fat—those people become very high risk not only for diabetes but also for coronary artery disease. And we found, interestingly, that there are many ways that we can review that risk and help those people to lose weight—not only to lose weight but to maintain that weight loss for a long duration. When we started the Why WAIT program in 2005, we implemented the method that we thought at the time would be very effective in weight loss, but over time we have been fine tuning this program, and we're reaching the point where this program is very, very successful. Everyone who participated in the program lost a very good amount of weight, but the most important [thing] is that they maintain the weight loss for a long duration and they reduce their medication by around 50 to 60 percent. And of course this will be translated into huge savings.

JB: Well, I know that you have done a really nice job of capturing some of the concepts in that program in your new book, The Diabetes Breakthrough: Based on the Scientifically Proven Plan to Lose Weight and Cut Medications.[2] I had the privilege of reading your book. I think it's a very nice summary for the general reader on some of the details of the program in providing some news-to-use as to how to get going on it. The interest I have is this word "intensive," because I think a lot of people feel that they can just back into these programs and just put their toe in the water, but the word "intensive" in "Why WAIT" (Weight Achievement and Intensive Treatment) I think is very important. Could you tell me why you chose the word "intensive" and what it means?

Maintaining Muscle Mass During a Weight Loss Program is Very Important

OH: Yes, "intensive" means that we are developing every single tool that we know that will be effective with management and in diabetes control. So it is a multidisciplinary approach. It is not a dietary intervention or exercise intervention or behavior intervention, but it is a multidisciplinary approach that includes the diet part, the exercise part, the behavior part, the education part, and also it includes modification and adjustment of diabetes medication. The program is very interactive. Over 12 weeks, every week we keep changing medication and also adjust the program to fit the individual who is in the program. And as you mentioned, we explain that in a very clear way in The Diabetes Breakthrough. It is a 12-week program, and the main philosophy in the program is that during weight loss we would like to maintain the muscle mass. We realize that if people, during weight loss, are able to maintain a very good amount of their lean muscle mass, the chances for them to maintain the weight loss for longer duration is usually the case.

JB: So let me, if I can, just go down a little bit of a laundry list of certain questions that I know you discuss in more detail in your book and in the program. First is, what about diet composition and a source of nutrients? Is there some guidance on the overall composition of the diet?

Dietary Composition is More Important that Calorie Count

OH: Yes, we believe seriously that dietary composition is the most important factor in weight loss in comparison to the general belief that it is all around calories. We don't believe that calorie-in-and-calorie-out is the case. There are several clinical trials that have shown that changing dietary composition can have huge impact not only on weight loss, but also on diabetes control. We implemented Joslin Nutrition Guidelines, which we developed in 2005, where the amount of carbohydrates and type of carbohydrates had been dramatically changed. We reduced the amount of carbohydrates down to around 40-to-45 percent, an also we reviewed the significance of the glycemic index of carbohydrates. But at the same time, we increased the amount of protein and the type of protein that people consume, and aim to maintain the muscle mass. As I mentioned, this is very important. People with diabetes, in general, lose nearly around one pound of their muscle mass every single year. During weight loss, when the protein intake is lower because of the reduction in the caloric intake, people lose even more muscle mass, and this will lead to rebound weight gain. At the same time, we give our patients a very high quality fat, and we give a fiber, and we review the sodium, and provide them with a meal replacement designed specifically to match the Joslin Nutrition Guidelines. We find that this intervention is extremely successful and easy for people to follow with an instructional plan.

JB: So let me talk a little bit about this protein. I know that you've been involved in some research about composition of proteins, both in terms of bioactive peptides and also certain amino acids (maybe some of the branched chain amino acids and even proline). Can you tell us a little bit about the composition of protein and how it interrelates to insulin management?

Protein Composition and Insulin Management

OH: Yes, we have found recently that protein in the body will ultimately be in the form of glucose, so every time you eat 100 grams of protein it will be translated to around 56 or 60 grams of glucose inside your body. The only difference is that blood glucose will not go up with protein, and—contrary—blood glucose will go down every time you add protein. And the reason is very simple. Many of the amino acids are very strong stimuli for insulin secretion, but we also know that several amino acids accumulate GLP-1 hormone. This is the same hormone that we use now to treat type 2 diabetes. So for example, glutamine is a strong stimulus for GLP-1 hormone. Arginine is a very strong stimulus for insulin secretion. So even if the pancreas or the beta cell loses sensitivity to the glucose stimuli, they retain their sensitivity to the protein stimuli. And many of the good research has shown that people who increase the protein intake from 15 percent up to 30 percent showed significant reduction in the A1c, even within a short period of time, which would signify that we have been missing that part for a long time—adding protein in a good amount to the diabetes diet. The fear has been always for the kidney, but data shows definitely that if someone has normal kidney function, increasing protein intake will never cause any damage in the kidney or increase microalbumia. At the same time, reduction of protein has not shown, in any clinical trial and in a very big data analysis, that there is any impact in preserving kidney function. So I think we have been in a mess around protein for a long time and it is time for us to correct that mess and give our patients enough amounts of protein.

JB: Now, I notice when you said glutamine and arginine, that those, as I recall, are in the ratio to, say, lysine are higher in vegetable proteins than in animal proteins on a per-gram basis. Is there any difference in the sparing effect of muscle between vegetable and animal protein as far as you know, at given equivalents?

OH: Yes, that's a very good point. In reality we know that plant protein is more beneficial. The only problem with plant protein is that it is deficient in essential amino acids. So many of the trials that have been done among the vegetarians showed that actually a vegetarian diet reduces the risk for type 2 diabetes and also has some good impact on lipid profile and cardiovascular risk in general. But the problem is that it put people at higher risk for deficiency or abnormality in some of the coenzymes and hormones that are dependent on essential amino acids. On the other side, protein that comes from meat and processed meat is a problem. This is the protein that has a higher amount of heme, or iron, and that amount of iron actually increases insulin resistance to a higher level and makes diabetes, in general, worse. Plus the fat in this type of protein—the meat and processed meat—is actually the worst type of saturated fat.

JB: That's very helpful. And now let me shift, if I can, to micronutrients for a second. There are a few micronutrients that I have read that seem to be associated prominently with the important role they play in glucose management. Those include biotin, thiamine, chromium, inositol, and magnesium. I'm sure there are many other vitamins and minerals as well, but those are the ones I've seen kind of prominent. Is there any experience that you have had about the ratio or balance of these pivotal micronutrients in managing blood sugar?

OH: Yes, there is a lot of research. None of that research, I would say, rates to the quality that we can use it as a guideline. The only two micronutrients that I will trace on is the magnesium and vitamin D. There is data to show that higher magnesium and higher vitamin D actually reduce the risk for type 2 diabetes. But the rest, you know, there is some little data about chromium, some little data about thiamine and others, but I would say that magnesium and vitamin D are most associated. In many meta-analyses they have been shown to be associated with a reduction in the risk for type 2 diabetes.

Fiber Intake Can Have A Huge Impact on Diabetes

JB: So now let's talk about the topic that you mentioned, which is fiber. We know that there are different kinds of fiber from the soluble and insoluble family, and different types of oligosaccharides that make up different kinds of non-digestible carbohydrate. Are there any guidelines as to the type of fiber? Or as long as it is non-digestible carbohydrate it is good?

OH: Yes. In general, the US population is eating very little amounts of fiber. If you look to the Canadian guidelines or the European guidelines, they recommend fiber close to 30-40 grams per day. Our recommendation had been staggering around 25, 30 grams per day. The reality is if we were to increase fiber and to raise fiber up to 50 grams per day, it has a huge impact on diabetes, because it slows gastric absorption, it slows transit time in the GI tract, and it reduces the sudden spike in the blood glucose in response to carbohydrates. But regarding the soluble and insoluble fiber, in reality soluble fiber is a major fiber that has huge impact on LDL and also on the risk for diabetes. You know, when data analysis compared fiber from leafy green vegetables and fiber from fruits, which is soluble fiber mostly, they found that there is always a reduction in risk of diabetes with a soluble fiber. So people who will be able to increase the amount of soluble fiber get two benefits. The first benefit is a reduction in the risk for diabetes, but the second benefit, which is also very important, is the reduction in LDL.

JB: Yes, I'm very interested in watching the evolution of this story. Fiber has been around in my life as a topic since the oat bran craze about 25 years ago. Now we start seeing things of the soluble fiber

families—like inulin, for example and other oligosaccharides—where the gut microbiome can make the short-chain fatty acids (proprionic, butyric, acetic acid) and how they influence aspects of glucose regulation, so this interaction between fiber and the microbiome and insulin signaling appears to be a very fascinating chapter that is evolving in this field.

OH: You are absolutely right, Jeff. You know, there is new data which is still fresh but I hope it can be confirmed, that when you give any slowly digested carbohydrates, the fermentation that is caused by the microbiota in the intestine could be the reason for the assimilation of the GLP-1 hormone production in the intestine. What I have seen in many of the diabetes is a specific formula that use a resistant starch which is not digested in the GIT and remains, you know, in the GIT for longer duration to reach the terminal part of the ileum and the large intestine. There is data to show that giving them increases actually GLP-1. I have seen the same with monounsaturated fat and also with saturated fat. So it is a very interesting concept, how the microbiota react and may be beneficial for people with diabetes, but time will tell us more because this is a fresh and new area of research.

JB: Let's move over to a huge study that you've been involved with as a principal investigator. It's a very important study—the Look AHEAD study. For those that are not familiar with that could you tell a little bit about the design of that study, where we are and what the results have been? You've, I know, published progress reports on this very interesting, forward-looking study.[3]

The Look AHEAD Trial: A Successful But Misunderstood Study on Lifestyle Intervention

OH: Yes, Look AHEAD is probably the third largest study that has been done in the history of diabetes research, after the DCCT trial and the Diabetes Prevention Program. The whole idea of the Look AHEAD study is to see if people with diabetes lose and maintain weight loss (7-to-10 percent weight loss) for 10 years or more, and will this intervention lead to reduction in the mortality and cardiovascular events (fatal and nonfatal heart attacks and so on). The first data results of the study were very promising after one year and four years, but unfortunately the study had been terminated earlier because of futility (there is no difference between the intensive intervention arm and the control arm). It sent a shock of the wrong message to many in the community when the study was stopped because people started to feel that lifestyle intervention would have no impact on cardiovascular mortality and cardiovascular events, but in reality, people who know the design of the study and how the study had been conducted can easily understand what is the impact. When the study was initially designed, there was a calculation of the rate of mortality per year from cardiovascular reasons, but over the last decade, actually the deaths from cardiovascular events went down in the entire nation by close to around 50 percent. So the study, in reality, started to lose its power over time. The other part, which is very important, is that the other arm of the study, the control group, had been freely increasing and changing their lipid-lowering medication and antihypertensive medication. Both of them are very strong in protection from coronary events. The intervention arm, in reality, would use this medication and they use also diabetes medication, so when we see there is no difference between the two, we can actually conclude that you can prevent coronary artery disease either by adding more medication, as had been shown in the control arm, or by lifestyle intervention, and it is the choice for the individual to choose between increasing medication or losing weight and maintaining that weight loss. The study, in reality, showed many, many benefits of the weight loss. Hospitalization had been less. Cost had been less. Risk for depression had been less. Risk for chronic kidney disease had been less. Quality of life improved significantly as well. So I will say the study had been very successful, but the design of the study and the conduct of the study was not

controlled enough to make the difference show up over time.

Opinions on Surrogate Biomarkers

JB: Thank you. So that raised a question for me from a clinical perspective, and that is we have a variety of surrogate biomarkers that are used to track the progress of a patient, knowing that not everyone is going to have some type of a vascular analysis done, either EBT, or FMD, or something, so we use things like hemoglobin A1c, or hs-CRP, or adiponectin. What surrogate biomarkers do you think are clinically useful in tracking the progress of these therapies in individuals at risk.

OH: This is a very good point. I personally believe that the core of the problem of both type 2 diabetes and atherosclerosis is subclinical inflammation going on. That subclinical inflammation is not manifested in the form of fever or white cell count, but you can easily assess that subclinical inflammation by measuring the cardio CRP. They have showed over and over that any intervention that reduces CRP actually reduces the risk for heart attack. To our knowledge, two major interventions can reduce CRP. One of them is the statin, and this has been seen in the JUPITER trial, even in patients with normal LDL. When the CRP was high and reduced by rosuvastatin, the risk for cardiac events and mortality had been lowered. The other intervention that we know for sure and we have data to show that clearly is lifestyle intervention. Lifestyle intervention has been very, very effective at reducing CRP. Some newer medications like GLP-1 analogs also have been shown to reduce many markers of inflammation. So I think markers of inflammation are very important. Adiponectin indicate improvement in insulin sensitivity, but the measurements are a little bit complicated or a little bit difficult and costly, and it is not suitable for clinical practice. I believe CRP is easy—very simple—a non-fasting sample can be done and you can get very good results.

The Strengths and Limitations of Measuring Hemoglobin A1c

JB: So can you give us the state-of-the-art right now as it relates to the use of hemoglobin A1c for measuring glucose, what it's strengths and limitations are?

OH: Yes, the problem with A1c is that A1c has very low sensitivity and very high specificity, which means that when the A1c is high it always signifies there is a problem going on, or even diagnose diabetes in a very effective way. But when A1c starts to go down, it doesn't exclude that there is damage going on and people may still have diabetes even with A1c in the pre-diabetes range, between 5.7 and 6.4. But in general, A1c is a simple, easy tool that can be used for diagnosis, for screening, because it doesn't require fasting and it is also summary of every three months because it's not just one measurement.

Diabetes is a Continuum and Numbers are Arbitrary

JB: You know, I'm taking a little bit of a look back with you here for a second. I was in school in the late 60s and I recall that the course I had in discussing diabetes and endocrinology said something like diabetes started when the fasting blood sugar was greater than 200. And so at that point in the sequelae of events, many people that presented with diabetes already had nephropathic or neurological injury. They might have had ocular problems. And so you had a whole bunch of attendant secondary pathologies that were involved when a person was diagnosed with diabetes. Today, the definition for a diabetic patient is, I think, a blood sugar (fasting) greater than 126 milligram per deciliter. So it seems like we should be

getting people earlier, which would make them more of a candidate for these lifestyle intervention therapies, yet we see our dialysis centers just filling up with more and more patients that are in renal failure. How does this all fit together? It seems like there is something that I'm missing.

OH: Yes, you are absolutely right. The problem is that diabetes, in relation to complication and risk, is a continuum. We created those arbitrary numbers of 200 or 126 or 140, but in reality the risk is a continuum, and the risk starts very, very, very early, even before people develop pre-diabetes, which means that if we would be able to identify those people of higher risk early enough, we should immediately intervene. The problem right now is that we wait until the car makes a crash and then rebuild the car. We need to protect the car from getting into that crash. Most people wait until the patient develops diabetes and confirm the diabetes to treat them, but studies show that actually people with pre-diabetes, or even relatives (first degree relatives) of people with type 2 diabetes have exactly the same risk, so intervention should be started very, very early once those people have been identified that they have a family history of diabetes. You know, using the blood glucose level as a parameter for diagnosis is a problem by itself.

JB: So that leads us to where the tire meets the road right now. We have these increasing numbers of patients that are coming in in early-stage diabetes. We know that over the course of therapy that they'll probably be started on metformin as the first pharmacotherapy and then they'll be graded up with maybe TZDs or with incretins and GLP-1 agonists and then they might go through ultimately ending up in insulin therapy. How does this all compare to an effective intervention of lifestyle therapy? If we had to go on the basis of the data today and we didn't have to worry about the behavioral determinants and the compliance and adherence components, which would win? Does the lifestyle intervention win, or does the graded pharmacotherapy win in preventing the terminal states of diabetes?

OH: Yes, Jeff, this is a very, very important question. We have to understand that the major problem in type 2 diabetes is insulin resistance. I personally believe it is more than 90 percent of the problem, is the insulin resistance in people with type 2 diabetes. So unless we improve insulin sensitivity, we cannot control diabetes in a very efficient way. To our knowledge, the best and the most effective [approach] in improving insulin sensitivity is not medication like metformin and TZDs, it is the weight loss. And the subject you referred to earlier showed that when people lose seven percent of their body weight, insulin sensitivity improves by 57 percent. Fifty-seven percent is equivalent to two medications for diabetes at maximum dose. Metformin improves insulin sensitivity, but was not able to prevent type 2 diabetes in comparison to lifestyle and the Diabetes Prevention Program. In the Diabetes Prevention Program, people who lost weight and maintained weight loss reduced risk of full conversion to type 2 diabetes by 58 percent, while with metformin it was only 51 percent. So you can see there is a big difference. If lifestyle is done very, very early and people lose that seven percent and maintain that weight loss, this is a glorious period of diabetes because during this period people are still making enough amounts of insulin, and that insulin can put into function back and diabetes can be reversed entirely or maybe it will go into remission. In the Why WAIT program, we have seen around 17 percent of our patients stop their medication and back to partial or complete remission from diabetes. So it is a time factor—when to start—and how aggressive you are, but the key also is to maintain that weight loss for longer duration.

JB: That was beautifully stated, and I guess one of the things that you imply in this is that when you talk to a diabetes cell biology researcher they will tell you it's all around beta cell preservation. If you can preserve beta cells, which is what you're telling us, that you're going to be able to prevent the onslaught

of this progressive diabetes. Is there any evidence that you're aware of that lifestyle intervention, when successfully applied, such as the Why WAIT program, does preserve beta cell function, or do we just assume that from surrogate evaluation?

OH: You know, the reason for the strain on the beta cells is to try to overcome the insulin resistance. So the best preserver of the beta cell is actually the improvement in insulin sensitivity. So any intervention that improves insulin sensitivity actually put beta cells to some rest, and we have seen this after bariatric surgery, after nonsurgical weight loss—insulin levels start to go down and there is improvement in insulin sensitivity. So, in my personal view, the best way to preserve the beta cell or to prevent further loss function of the beta cell is to improve insulin sensitivity, and the best way, of course, is the weight loss.

JB: Well I can tell you that this has been extraordinarily helpful and informative for all of our listeners and certainly me as well. I want to thank you both for the time you've spent with us today, but also for the extraordinary work and commitment you've made over the last 15 to 20 years in helping to better understand. And it sounds to me—if I can do a sound bite takeaway—that this type 2 diabetes epidemic that we're experiencing is really a lifestyle disease, and that you need to treat a lifestyle disease with a lifestyle intervention. It's not an infectious disease that you treat with antibiotic; it's a lifestyle disease that you treat with the proper lifestyle. That's kind of my takeaway from what we've talked about.

OH: Yes, Dr. Bland, you framed it very, very nicely. I would like to call it lifestyle diabetes. It is not type 2 diabetes—lifestyle diabetes. You know, during the time of Elliott Joslin, in the old days, they used to call it fatty diabetes because they understand that the core problem of type 2 diabetes—the bacteria of the disease—is the body weight. The fever is the blood sugar. So if we spend all our effort, our time, our money just treating the fever by drugs without dealing with the core problem, which is the body weight, I think we're wasting time and effort. This is a lifestyle disease. For prevention, for management, for prevention of complications—primary, secondary, tertiary—it is a lifestyle disease.

JB: That's a fantastic place to leave this. I'm thinking it's an optimistic message because lifestyle is modifiable, genes are not. I think you've done a wonderful job in your book, The Diabetes Breakthrough, in laying this down in a way that people can understand. Dr. Hamdy, thank you so much for the time spent and continue on with your great work and we'll be following it very closely.

OH: Thank you very much for inviting me.

JB: Appreciate it. Bye-bye.

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