February 2013 Issue | Jeffrey Mechanick, MD Sinai School of Medicine

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Welcome to *Functional Medicine Update* for February, 2013. Complex metabolic disease: how does it relate to systems biology in medicine and the functional medicine model? Well, we're going to have the opportunity to explore that in some depth with a leading expert in this month's issue, a practitioner who bridges the gap between what I would call the standard of care/practice and the development of standard procedures in medicine, and that of opening the mind to this future of medicine—a systems biology-based approach—looking at emergent structures. I think you'll find this discussion is both interesting from a philosophical perspective, but probably more importantly from a patient management and evidence-based perspective. So, with that in mind, let's turn to our clinician/researcher of the month, Dr. Jeffrey Mechanick.

INTERVIEW TRANSCRIPT

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Here we are once again at that part of our Functional Medicine Update each month that we look forward to because I'm sure you're asking, "Who will Jeff Bland have the privilege of talking to this month?" And for me it's always, "Wow, what a great opportunity to speak to one of the great leaders in establishing a platform and landscape of medicine in the 21st century." Today I have the fortune of speaking with Dr. Jeffrey Mechanick, who is a clinical professor of medicine and a director of Metabolic Support, Division of Endocrinology, Diabetes, and Bone Disease at the Mount Sinai School of Medicine. He has an MD degree with an endocrinology focus from Baylor College of Medicine, and an endocrine fellowship at Mount Sinai. He has authored more than 200 publications on endocrinology, metabolism, and nutrition.

Dr. Mechanick is the past president of the American Board of Physician Nutrition Specialists, and is currently the president-elect of the American Association for Clinical Endocrinologists, and the section

editor of Current Opinion in Clinical Nutrition and Metabolic Care in Current Opinion in Endocrinology and Diabetes. As I've reviewed his publications—as I mentioned, over 200 of them—his breadth of impact and expansive interest spreads throughout all of his publications, so we're very, very pleased to have an expert in the field that we might call personalized lifestyle medicine, or functional endocrinology, or let's call it just good, plain old medicine.

Dr. Mechanick, thanks so much for being with us on Functional Medicine Update, and what a privilege and pleasure it is to have a chance to talk to you about the exciting work that you're doing.

JM: Thanks, Jeff. It's a pleasure to be here.

A Transcultural Approach to Optimizing Diabetes Care and the Need for Clinical Practice Guidelines

JB: So let's—with no necessary priority or ranking of order of importance of what you've done--let's start with one of your recent contributions, which I found absolutely fascinating, that speaks directly to this rising global burden of chronic disease or chronic illness that we're seeing. A recent Lancet issue was entirely focused on global trends in disease, and that is looking at your work on this diabetes-specific nutrition algorithm—this transcultural approach towards optimizing diabetes and pre-diabetes care, which I think has been a very big question in the minds of many people.[1] How do you translate discoveries or programs that might be developed for one population group to another knowing that there are very significant differences in ethnicity, regionalism, cultural habits, and so forth? You've really done a creative and innovative job in this transcultural approach. Could you tell us a little bit about its origin and its development and what it can do?

JM: Sure, Jeff, and thanks for that introduction because I think you hit the nail on the head. One of the things to bear in mind is that sometimes it's better to approach clinical problems from a systems perspective. Certainly when you have an individual patient in front of you, say somebody with a nutritional disorder or diabetes, you want to address that individual person, and it's very scientific and very empirical. But when you want to ask a research question, sometimes you need to zoom out and take a wider look, so from my standpoint I have always been interested in optimizing lifestyle. You know, in this country, one of the overt shortcomings in the delivery of health care is this de-emphasis, even absence, of formal training in nutritional medicine or lifestyle medicine. Clearly, there is a very important role for that, so how on Earth are you going to be able to learn about lifestyle and the role that it plays in treating a metabolic disease such as diabetes, and you can even include obesity, and the whole spectrum of prediabetes and diseases of dysglycemia? How on Earth are you going to address that just focusing on the narrow, single patient, or maybe a single disease, without really gleaning a lot of rich information from the diversity of human biology?

So that was the set-up for this, and I was actually requested to propose a research project, and it occurred to me that in the development of clinical practice guidelines—and I participated on a number of these clinical practice guidelines as part of my role with the American Association of Clinical Endocrinologists—as part of those clinical practice guidelines, let's say in diabetes, it's great to put something together and have something that is very academic, and very evidence based, and very scientific, but it really falls short of the mark if you can't implement it. And beyond that, how are you going to implement it on a generally wider scale when you're not even taking into account the diversity of your patients?

This diversity can be viewed two ways. It's the diversity in your own particular clinic, so in my office practice here in Manhattan I don't just see the average or standard patient; I have patients from all sorts of ethnicities and socioeconomic classes, and from different nations of the world, and then you can ask questions—well, what about treating diabetes and nutrition? How are those disorders expressed with the different genomics and epigenomics and cultures in Ghangzhou in China, or in Brazil, or in some of these other countries that really represent points along a broad spectrum? So that was the set up: that we have these very good, evidence-based clinical practice guidelines, but they are not portable. They are just not portable in order to implement them in different patient populations.

JB: We've experienced that same challenge in our work, touching with Functional Medicine Update more than 35 countries with practitioners who are listeners. They have often come back to us and said: "How can you regionalize this or how can you take this message that you are transmitting—this systems biology approach to health care—and focus it in on our area of specific interest or need based on our culture?" Can you tell us a little bit how you approach that with regard to taking the general and making it specific to a cultural need?

Solving Clinical Problems within a Narrow Time Constraint

JM: I think the first step is to recognize that human disease is complex, and it's not complex just from the standpoint of science. I mean, it certainly is complex scientifically, but you have a lot of other platforms that need to be integrated into a complete or successful solution. You have factors such as economic factors, and cultural factors, and socialization factors, and psychological factors, and when you try to bring all these complex factors into play, you need a different way to solve it. Bear in mind that there are these imperatives of solving clinical problems that are within a narrow time constraint: you have somebody in front of you, and you need to be able to come up with some sort of a solution, or advice, or counseling, and you don't really have hours to do that and you need to have some framework—some approach that takes into account that complexity. So I think that's where the common ground is, Jeff, between what you're doing in functional medicine, and when you're dealing with the interaction of environment on biology, with what I'm doing with a specific problem, which is the role of nutrition for a specific disorder—diabetes—but both have a very large scope.

JB: So let's take that as a specific example, now, into the area of metabolic syndrome, pre-Type 2 diabetes. You've authored some very interesting work in that area. One of the papers I saw is with Dr. Potenza titled, "The Metabolic Syndrome: Definition, Global Impact, and Pathophysiology" in Nutrition in Clinical Practice a couple of years ago.[2] Tell us how using the metabolic syndrome/insulin resistance concept relates specifically to your thoughts.

The Best Disease Management Plan Will Be Preventive

JM: Right. So I think what I would like the listeners to consider is not that obesity and diabetes exist as solitary, isolated, or insular pathophysiologic states, but rather they are points along a timeline, which begins with someone's preprogramming, or basic biology and genomics, and then migrates through these states—these physiologic states, for lack of better word—that we now call a pre-disease, so pre-hypertension or pre-diabetes. We have overweight, which is really a pre-disease state for obesity. And to recognize those—to understand that they exist, to understand that they identify patients who are "at risk." And just to segue from there, Jeff, I think it's a very important concept to understand the differences

among primary, secondary, and tertiary prevention, because they correlate to where you are along that timeline for an individual patient as they migrate through a latent phase into a pre-disease state, into frank disease, then into complications that eventually exceed our ability to manage them.

I think the other point of the paper is that we in the US, as well as others around the world, we need to migrate from this disease management paradigm more into a preventive medicine or a health promotion paradigm; we can ill afford all the disease that we're seeing now. Our treatments really just can't keep pace, and as it turns out, the best management plan is going to be one that is preventive.

JB: You know, what you just said, I actually had a goosebump experience, and the reason for it was not only the clarity of what you express, but I reflected back immediately in my own life to 1979. I'll just give a quick vignette. In 1979 I was asked to speak at a symposium that was sponsored by the University of Washington School of Medicine, and it was actually chaired by (then) the head of the Department of Endocrinology at the Medical School who had actually authored the book on endocrinology that I had studied as a student. I had a great amount of respect for him—a tremendous diabetologist/endocrinologist, and the topic of this was hypoglycemia (so-called reactive hypoglycemia), which was, in the 70s, kind of a very big thing around consumers (low blood sugar). I was a young guy back then—early-stage academic professor—and really prepared, I thought, for a presentation, and I was the presenter right before he was to present. So I went up and gave my presentation and I thought I did a pretty good job, and then he got to the stage and he said, "You know, this gentleman, Dr. Bland, that just spoke obviously was very enthusiastic and gave a lot of very interesting information, but I do want to say one thing about his presentation: there is no such thing as a gradient effect between optimal glycemic regulation and diabetes. It's a step function; you either have it or you don't." And that was 1979, so clearly, from what you've said, we've come a long way in understanding this gradient transition into different stages of metabolic dysregulation.

JM: Yes, I would agree.

Integrative Physiology and Bone Disease

JB: So let's, if we can, take that concept and look at how it spreads out into what you called 'integrated physiology' in several of your articles. I really like that term integrated physiology because it really puts what some people call integrative medicine on a more evidence-based foundational footing in that integrative physiology is really another term for a systems biology approach to examining health and disease. The article I'd like to review with you is one of your recent publications in an area of your deep expertise, which is bone disease/osteoporosis, and this article appeared in Current Osteoporosis Reports in 2011 on "Nutrition, Bone, and Aging: An Integrated Physiological Approach."[3] In this, you talk about how bone is more than this thing that is a skeleton we hang up in the closet that seems like a piece of dead physiology. You talk about it as a very live, dynamic part of the interface among other organs in a systems biology approach. Can you tell us a little bit about that?

JM: Yes, and thanks so much for giving me the opportunity to do this. This has really been a pet project of mine, and I'm very passionate about it, and here's a little bit of the history. Going back to the early 90s, I became very involved in recognizing this state of chronic critical illness, which is sort of a later truncated part of the timeline when patients are critically ill. These patients who are critically ill don't die from their critical illness; they are essentially technologically immortalized, and eventually receive a

tracheostomy, and it's a very difficult pathophysiologic state to treat, and I don't know if we're going to have time to discuss this concept of allostasis, but basically through the process of adaptation they enter into a stage where there is no evolutionary precedent for what's going on, and the cost of adapting to prolonged stress—eventually you can't pay off that metabolic debt. So here we find these patients, and I was noticing some electrolyte abnormalities, some abnormalities with calcium phosphorus and urinary calcium. We put together a model that these patients were hyper-resorbing calcium, not only as a result of immobilization, but as a result of the influence of cytokines, and we actually in parallel started to investigate this in spinal cord injury patients, where we were able to demonstrate that this bone hyper-resorption was not dependent on the level of injury but rather the completeness, and that was also consistent with an inflammatory model.

We started a study and we found these very high prevalence rates of vitamin D deficiency, upwards of 92 to 96 percent bone hyper-resorption. We started to intervene with activated vitamin D and intravenous bisphosphonates like pamidronate. We were getting some biochemical responses. And then fast-forward a good ten years or so, and through corroborations at Mount Sinai, mainly with Mone Zaidi—he's a personal friend of mine, extremely active and productive in the field of molecular biology as it applies to bone—and what they found in their lab really was a paradigm shift. It was always believed that, for instance, it was thyroid hormone, or the end-organ endocrine hormones that have this direct effect on coupling of osteoblasts and osteoclasts, but instead it was the pituitary hormones: TSH, and LH, and FSH (primarily FSH). But the pituitary glycoproteins were affecting bone, along with cytokines, and then paracrine effects, the effects of monocyte macrophages, and now you've built up this complex system. Now, you have the results of Karsenty over at Columbia showing this amazing feed-forward loop with fat, and now you can see how this applies to bariatric surgery. Fat to brain, via leptin, through the sympathetic nervous system, through beta adrenergic receptors in the bone, clock genes in the bone, a feed-forward system, and now you start to see that the bone is intimately integrated with multiple organs. There were then some subsequent studies looking at enterochromaffin cell metabolism, of tryptophan to tryptamine to serotonin, and effects that that mechanism has indirectly on bone, the effects of osteocalcin and osteopontin from bone on beta cell activity, which then affect insulin, and diabetes, and insulin then affecting bone and fat, and now you have a complex system. This is not simply a motif of A-to-B, B-to-C, C-to-A. This is now a complex network that really requires a higher level of mathematics to solve it, and if you talk to the systems biologists, the threshold effect for our ability to solve these problems has been the advent of the supercomputers and the accessibility of the supercomputers using this top-down type of research where you build up these models, you build up these networks, based on information at hand, and then you discover these emergent motifs, and then based on those discoveries you can then feed hypothesis-driven component research, and that was the point of these papers. The point of these papers was to say, "Look, you have a disease like critical illness, or rather a pathophysiologic state—a state, not necessarily a disease, but a pathophysiologic state like critical illness—and what if we explore? What's the rule of thumb?" Now who on earth would start working up bone, or discussing bone, on rounds in an ICU? But when you start to look and examine the integrated physiology, you then learn. And where that helps is when patients simply don't behave the way they should a priori. You give a certain medicine, they're supposed to get better, but when they don't—and many times they don't—that's when you need to zoom out, consider these physiologic networks, and try to come up with alternate hypotheses.

JB: That was unbelievably eloquent and it hit on so many of the areas that we have been exploring in Functional Medicine Update over the last 25 or so years. We could obviously use this as a springboard for hours and hours of discussion, but I'll try to keep it succinct, so let's talk first about this concept of stress

that we call allostasis. I'm reminded of our discussion—in my case, going way back to the extraordinary luxury that I had a chance to meet Hans Selye at the end of his life and have conversations with him about his so-called general adaptation syndrome (or GAS). A lot of patients, he said, would run out of gas (run out of GAS) because they would go through arousal, adaptation, and then exhaustion of their endocrine system, and so he used to talk about adrenocortical fatigue and how that related to long-term adaptation to unremitting stress. And then later, that was really transitioned into a more robust concept of allostasis that you mentioned. The concept of allostatic load and how the body responds to it, and how it affects the whole of the system means you're not just affecting one organ, or gland, or one tissue, you're really putting an environmental perturbant into the system that then disturbs the whole web. So in the network, you can't just affect one tendril of the net without affecting the whole. This model that you've developed ,how it applies to bone, and ultimately to bone disease, ultimately leads to a better understanding of early-stage changes in the bone because it uncovers different predictive biomarkers for physiological disturbances that associate with allostatic load. And then from that, earlier intervention with hopefully lifestyle personalized characteristics. This seems like a whole new paradigm for health care to me. Am I on the right track?

JM: I think you are. The only thing I would add, Jeff, is that these are not mutually exclusive. And remember, I've sort of been a student of this. I've only been introduced to this over the last five, six, seven years, and the way I was introduced to it is really the way your listeners are being introduced to things: they hear things, they think, they take notes, and then they move forward. And one of the things that I was struggling with early on is I thought this was an either/or type scenario, but it's not. The systems biology paradigm, with these complex networks, actually acts to inform the component biology/traditional scientific method. Then the results of the scientific method feed back to inform the network, and what you have is an iterative process that learns. So what I would do is just add to what you've said for the benefit of the listeners to realize that network analysis or network-based classifiers can work together with component biology or statistical-based classifiers, and the two can resonate.

Emergence: A New Concept Starting to Inform Medicine

JB: That's very, very helpful. Thank you, that's a really great insight. You mentioned a term, which is a term that seems to be getting a little bit of lift in the medical vocabulary recently, and that's "emergent structures"—that you start to get these things happening cooperatively across structures in a network, that is, an emergent new steady state. We used to call it homeostasis, but homeostasis kind of defines a healthy state, but actually you could have a steady state, or an emergent structure of a disturbed metabolism, like diabetes, for instance, or osteoporosis, that would appear from this model, so maybe we have to redefine what we mean by "steady state," always implying that homeostasis means good.

JM: Yes, I think emergence…you could sit around a coffee table and talk about this for a long time. I can share with you an anecdote of how I got involved in it. I was seeing a patient, and the night before I had just read Brian Green's book on string theory. I was talking to this patient and I found out he was a theoretical physicist, so I thought: "Wow, we can have a little bit of discussion, here, on string theory," and when I finished he said, "You know what, that's just nonsense. What you really need to read about is emergence." As a result of that brief conversation, I went to Amazon and got some books and started reading about emergence, and it really fit in well with a lot of the issues that I've written about, going back to medical school, and creativity, and incompleteness in medicine. Medicine—perhaps other than the military—is probably the only profession, or field, where one must act based on incomplete knowledge.

And when you look at evidence-based medicine, there's this tremendous resistance against that philosophical tenet that you have incomplete knowledge, and bearing in mind the issues of Godel's proof, and the fact that we live in an incomplete world, we just need to reconcile ourselves to the fact that information is incomplete, and the way we solve problems is by trying to capture those emergent data. On rounds, when we are trying to solve a problem, it isn't so much that we need to guess the problem. It's not that you have to get that problem right off the bat—that you guessed three or four things and hopefully one or two of those things will be the right answer. The target is actually to create a state—a network, or a state, or a framework—where eventually that correct answer will emerge. And it's a different way of thinking. It's a different way to approach problems. But it is the way that I find that I approach medicine in my own practice.

The Interrelationship between Bone and the Gut

JB: I think that is an extraordinary insight. This is the example, isn't it, of being a life-long learner, being a seeker, being able to give yourself the permission to broaden your field of vision and to feel comfortable with going outside your disciplinary definitional biography into areas that help pull you into unexpected discoveries that can really make meaningful differences either in the communication you have with patients to help them along their path, or maybe even open up doors for new therapeutic avenues that might be extraordinarily important that were previously not understood. So I want to really compliment you. That's a characteristic that you have that is a very unique and is a precious characteristic that really leads to advancements. Let me if I can go back to your discussion about bone for a second, and you threw out a whole bunch of really important news-to-use, there, but one that stuck with me that ties together with some things that we've discussed in FMU over the last few years has to do with serotonin. As most of our listeners know if they've been following us, it's recognized that two-thirds of the body's serotonin is produced by the enterochromaffin cells from the gastrointestinal mucosa, so this concept that the gut talks to bone and bone talks to the beta cells in the endocrine pancreas may have sounded like a very ridiculous concept a decade ago, but now it seems to be emerging that it's interrelated and it may help us to understand things like inflammatory bowel disease and its comorbidity and disease adjacency with osteoporosis. Is this part of what your systems biology approach to bone disease is telling us?

Bariatric Surgery and Remission of Diabetes

JM: Right. I think there's two ways to look at it. You build up the model, just like I think you and the listeners have all appreciated and you're running with, and then you look to substantiate that model. You look to find clinically relevant examples of that model to sort of bring it home; to have context. Now, one way to do that is to say, "Okay, let's look at inflammatory bowel disease or celiac disease, where bone loss is part of it, and try to explore that mechanism." But there's another way. The other way is to look at either natural or man-made experiments, and to substantiate that concept, what we've done is looked at bariatric surgery. If you examine the literature on bariatric surgery and some of the history of the way it's been managed, and we had our first clinical practice guidelines on this published in 2008, and we're actually just finishing up our update now.[4] We know that there is bone loss; there is unloading. In fact, probably as a result of obesity—just the mechanical forces, but also some of the hormonal effects. There's also concomitant vitamin D deficiency due to sequestration of vitamin D in the adipose tissues. And then the patient loses weight and unloads. The bone mass goes down, and the clinical question was: Do you intervene? Do you now treat, at one year, when that bone density shows bone loss, are you obligated to treat? And what we found is that bone recovers, and there is really this complex network of interactions

that we still haven't figured out, but that is really a man-made experiment that can be very fruitful for us to understand what's happening in this complex physiology.

JB: That is an absolutely fascinating example of emergent structure, isn't it? So you put a perturbation, which is bariatric surgery, in the system. It responds to develop its immediate kind of traumatic response. That leads to bone loss through this changing web. And then, over time there is a self-correction as the emergence of the steady state occurs and then you're saying that bone starts to accrete back again, so that's a very, very interesting example of adaptation, it seems, in response to a changing environment.

JM: Right. I mean, there are other examples, for instance the "cure"—let's use the word "remission"—of diabetes after a Roux-en-Y gastric bypass. Far beyond what you would expect from the weight loss, because we see the differences in the remission rates for the same amount of weight loss between a Lap band, for instance, or one of those adjustable gastric banding procedures, and the Roux-en-Y gastric bypass, and for that matter, a biliopancreatic diversion with duodenal switch, where you could have 100 percent, in some series, remissions (long-term remissions) of diabetes. Now bear in mind long-term is not really long-term the way everybody else defines it. It may be only for several years, and that's what the critics are looking at. But this effect of bariatric surgery on diabetes was emergent. That was not something that was predicted or designed a priori when bariatric surgery was being innovated.

JB: I think that's, again, another really powerful example, isn't it? It's interesting how we keep coming back to the gut, here. We've talked about gut and bone; now we're talking about altering the gastrointestinal environment and its influence on beta cell function and insulin sensitivity. It seems like there is a pretty interesting signaling network around gut-related neurology, immunology, and endocrinology.

JM: Right. We're learning all of these interactions, and then for the benefit of your listeners, the next step afterwards is the validation process to see if this can actually become relevant and we can implement it in routine daily care in clinical practice. So for instance, even though it's very sexy that bariatric surgery "cures" diabetes, whether these procedures should actually be offered as a primary intervention for diabetes is very controversial. If you look at our clinical practice guidelines, in 2008 for bariatric surgery we didn't recommend them at all; in 2011, that is for diabetes (not for obesity, but for diabetes), we actually had some stipulation that there was a role for bariatric surgery in certain very recalcitrant cases of diabetes; and now in our updated version that will be coming out we have even more attention devoted to this controversy. There's a lot more data, and some long-term information about the role of bariatric surgery in diabetes remission. The problem is in the interpretation of the clinical trials. So, Jeff, you start off with the network that you build up, which is theory-based, and then you do an analysis, but ultimately this must be translated to an individual patient with the help of actual clinical trials to see if something really works, and there the listeners need to be able to read these studies and make sure that the comparator groups are appropriate, that the risks and benefits are appropriate, that an intent-to-treat analysis was done, that they are generalizable, and in fact that the treatment is durable. And for that matter, we still don't know whether this anti-diabetic effect is a durable effect with a net benefit.

Thyroid Function and Subclinical Hypothyroidism

JB: Very, very helpful. Thank you, that's really good news-to-use. I'd like to finish up with two areas in the range of the many, many things we could talk about with you. One is related to thyroid function

evaluation, and the other is this recent paper you've published about vitamin C and its relationship to bones loss, which I thought was quite fascinating. Let's start with you being a member of this clinical practice guidelines group for hypothyroidism in adults and a recent paper that you were a co-author of in Endocrinology in Practice in 2012.[5] This is a big area of discussion—maybe even controversy—within the field of docs in the functional medicine milieu. Could you tell us a little bit, what is coming out of this in terms of assessment of thyroid function, subclinical hypothyroidism, where are we in this whole area right now?

JM: Right. You have to recognize that clinical practice guidelines, by their very definition, need to be evidence-based, and there is a level of transparency where you can track the recommendations through the evidence and the evidence levels. What is missing—and this is what causes a lot of the controversy—is anecdote. So, we incorporate subjective opinion, but it is not based on subjective opinion. It is based on evidence. So many times the evidence changes and recommendations can change. So let me offer that just as a preface to my remarks. What I've learned in working with the clinical practice guidelines—and Jeffrey Garber was the chair of this, this was co-sponsored between ACE and the American Thyroid Association—is that contrary to maybe 10 or 15 years ago, where the interpretation of TSH really needed to adhere to very strict cut-offs for upper limit and lower limit based on clinical chemistry, we're recognizing that some of those cut offs may change again based on—and you're hearing this term again—different physiologic states. For instance, in pregnancy, a TSH of 2.5 or higher might indicate—and in fact, the recommendation is that it does indicate—the need for supplementation or treatment with Levothyroxine. The way in which we manage patients who are older, the way in which we interpret thyroid function tests in patients who are critically ill, or patients who are on different medications, can change the way in which we interpret thyroid function testing. But still, the TSH test reigns supreme when you look at the evidence. Now, when you look at controversial topics, those controversial topics are obvious. One of them is the use of T3. And that's a big area. Right now, our opinion, based on these clinical practice guidelines and based on the evidence, is that there is insufficient evidence for the widespread, general use of T3. And that stems from lack of studies. The T3 preparations that are available are short acting, and really, is there truly a need to add T3 when you're giving T4 and the TSH is in the normal range? The critics would say, "Well, the blood tests really don't give you the whole story, and if somebody still has symptoms then you should treat those symptoms with an intervention, and then the evidence would indicate." But that's an unproven claim, because a lot of those symptoms are not specific, and, in fact, my experience is that I've had a number of patients who have come in with dramatically suppressed TSH levels who have been given escalating doses of T3 that have been titrated against the metric, which is "I don't feel well" or "I'm tired" or "I'm lethargic," and then as a result, you do witness some of the adverse effects of T4 overdosage. I think the bottom line is—and clearly I have a biased and polarized view because I'm really preferentially putting weight on the evidence—is that I would go by what the evidence is, but individual doctors can still use their judgment in managing individual patients. I think that your listeners are going to go on the internet and they're going to find contrary opinions, and certainly patients have the right to seek out the management that they desire, but we felt that there was a need to express this evidence-based perspective, and again bearing in mind that the evidence can change, that there should be better studies looking at the effect of T3 (I'm just picking that out as one of the controversies), and then if the data are different, then we can change. For instance, there are polymorphisms as you are well aware and you may have discussed it on some of your other tapes, that there are polymorphisms in deiodinase, where some patients just are not efficiently converting T4 to T3 that well. This isn't necessarily Refetoff-type thyroid hormone resistance syndrome, but there might be some inefficient conversion. I've had patients in the ICU where I have treated, from time to

time, with low dose T3, and there is some mainstream literature on the use of T3 in critically ill patients. So there is a gray area, and I think ultimately there is this philosophical issue of whether you base your clinical practice—and I'm speaking as a physician now—do base your clinical practice on evidence, do you base it solely on anecdote, or do you base it on what I would term informed judgment?

Is Hashimoto's Thyroiditis on the Rise?

JB: Thank you. Once again, very, very helpful. I want to just ask your opinion. We have the impression from watching the literature and feedback that we've gotten from docs in the field that there is a rising tide (a rising prevalence) of Hashimoto's thyroiditis. If that's true, it begs a question—why? I don't think thyroid glands are suddenly being born that are imperfect. Is it true that that's an increasing problem, and if so do you have any idea what its origin is?

JM: Right. In large part it's due to increased detection. That's one of the reasons why we've seen this increase, for instance, in capillary thyroid cancer, particularly these microscopic forms, because we're just detecting them easier. We have better high resolution ultrasounds. In the case of Hashimoto's thyroiditis, a lot of practitioners are sending off antibodies more commonly. But there are pitfalls. For instance, just because you have the presence of antibodies does not mean that you have Hashimoto's thyroiditis. Hashimoto described a goiter. There has to be lymphocytic infiltration and hypothyroidism. And just the simple presence of an antibody as a marker of some autoimmune process is not equal to a diagnosis of Hashimoto's thyroiditis. On the other hand, if you want to zoom out and look at autoimmune disease in general, that's something worthwhile studying. In the environment, there are endocrine disruptors; there are various pollutants and chemicals that have been associated with some increased rates of autoimmune disease. We don't really have mechanisms and whether these are, again, a consequence of increased detection modalities, or whether there really and truly is some underpinning of some mechanism remains to be seen. We like to detect things early because we like to prevent disease instead of, as I said before, being in a disease management paradigm, so it's laudable to look for these diseases, but I would caution that you don't want to draw a test, or look for a particular disease, unless you have a sufficiently high pre-test probability using a little bit if Bayesian inference. Otherwise, your posterior distribution, as you know, can be very confounded, and the likelihood of actually making that diagnosis if you don't really suspect it at the beginning can be quite low. One of the things that we discussed in the guidelines was the appropriate use of screening, and the appropriate use of aggressive case finding, and that's another important take home message from those clinical practice guidelines. I think one of the interesting points that I came across when I was working with our committee and we were updating our bariatric surgery guidelines is, do you have to screen patients who are obese with a TSH? That's a very interesting question. And it turns out that the evidence doesn't support it. That obesity is not a physiologic state that warrants—just by itself, just having a high BMI—doesn't warrant screening with TSH. Now, if you have symptoms—if you have some symptoms that make you think of it—then that's fine. That's an indicated test. But just by virtue of a BMI being high is not sufficient to justify screening with a TSH, and one of the reasons is that TSHs physiologically run a little bit high in obesity. And we know that after bariatric surgery those TSHs normalize. That was a very interesting observation—something that I learned in the process of developing those guidelines.

Iodide and the Management of Thyroid Disease

JB: Thank you. Another point of great news-to-use. Let me close—and you've been very kind, by the way,

and gracious in giving us so much time—but I want to close on this thyroid connection to iodine. Everyone knows that iodine or iodide is incorporated into the formation of T4 and ultimately deiondated form, T3, and the important role that that plays, as you indicated in regulating nuclear orphan receptor activation of certain gene expression patterns that are associated with metabolism. What is not so well understood, I think, and there seems to be a swirling controversy, is whether we are, as a general rule, getting enough iodide, or too much iodide, or whether iodide can be used as treatment for things like thyroid-related dysfunctions as a nutritional agent. What's the general sense right now of iodide in this whole picture?

JM: Well, there are certainly certain endemic areas that have iodine deficiencies as a result of geologic issues and the amount of iodine in the earth, and then in vegetation, and making it along the food chain into adults, and those areas have been recognized and foods have been supplemented with iodine, and TSH levels, on average, have come down, and goiters have improved. But I think the point that you bring up is a very interesting point, which is the use of iodine in the management of thyroid diseases. One of the problems that I see is patients who are flocking to use iodine as a dietary supplement to "boost" their thyroid. Number one, there is no evidence that in the absence of an iodine deficiency, that using iodine pharmacologically can boost thyroid function. And in fact, iodine has a pharmacologic effect of inhibiting thyroid hormone release, and then we use it in medicine to inhibit the formation of thyroid hormones, something that's called the Wolff-Chaikoff effect, where iodine somehow inhibits the activation in free radical activation that's necessary to attach an activated iodine molecule to an activated carboxyl residue in thyroglobulin and in the formation of thyroid hormone. So you see these detrimental effects of iodine in patients in theory. Now, in practice, you probably don't see that much of an adverse effect, and when we use it in medicine we're really using iodine to treat hyperthyroid (overactive thyroid) conditions. If you have a normal thyroid and you're taking iodine you're probably just urinating it out and it's excreted, but it's unlikely to have a salutary or beneficial effect unless you truly have an iodine deficiency.

JB: I think, again, that's extraordinarily helpful news for many of our listeners. We've exceeded our goodwill with you. This has been a very, very rich discussion. Obviously we could go on for hours with the background and information you have at hand, but we want to thank you so much, Dr. Mechanick, for your extraordinary work and sharing it with us. You know, this bridging of the gap—you're really a translational medicine expert from your background in nutrition, and endocrinology, and internal medicine, and really I would call it systems biology. This is the pattern characteristic of the physician of the 21st century. Thank you so much for kind of being our standard. We appreciate everything you've shared with us, and wish you the best and look forward to revisiting you in the future.

JM: Great. Jeff, thanks so much for having me. I enjoyed it.

JB: Likewise. Take care of yourself.

Bibliography

[1] Lim SS, Vos T, Flaxman AD, Danai G, Shibuya K, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-2260.

[2] Potenza MV, Mechanick JI. The metabolic syndrome: definition, global impact, and pathophysiology. *Nutr Clin Pract*. 2009;24(5):560-577.

[3] Schulman RC, Weiss AJ, Mechanick JI. Nutrition, bone, and aging: an integrative physiological approach. *Curr Osteoporos Rep*. 2011;9(4):184-195.

[4] Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Obesity* (Silver Spring). 2009;17 Suppl 1:S1-70.

[5] Garber JR, Cobin RH, Gharib H, Hennessey JV, et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012:1-207.

[6] Pauling L. Orthomolecular psychiatry. Varying the concentrations of substances normally present in the human body may control mental disease. *Science*. 1968; 160(3825):265-71.

[7] Zhu LL, Cao J, Sun M, Yuen T, Zhou R, et al. Vitamin C prevents hypogonadal bone loss. *PLoS One*. 2012;7(10):e47058.

[8] Lambert JK, Zaidi M, Mechanick JI. Male osteoporosis: epidemiology and the pathogenesis of aging bones. *Curr Osteoporos Rep*. 2011;9(4):229-236.p>