

FUNCTIONAL MEDICINE UPDATE

November 2013

Vol. 33, No. 11

The theme of this month's issue is the pleiotropic effects of both pharmaceutical drugs and natural molecules, and the challenges of designing effective clinical trials in the case of the latter. In the area of systems biology, it is complicated to use a univariate type of hypothesis to prove a point.

Statins—as Dr. Bland points out—are an excellent example. He says: “We were told that these drugs worked by blocking the synthesis of cholesterol. And by the way, they do that, so that's not to be corrected. However, with more, now, 30 years of experience with these statins, both the original Lovastatin and then the later developments of other derivatives, like the more potent statins of today, we find that they have pleiotropic effects. They have biological effects other than just the inhibition of this enzyme HMG-CoA reductase. In fact, these other effects may be as or more important in their efficacy than was the singular belief that they worked solely by blocking HMG-CoA reductase.”

Obesity and Diabetes: Fatness versus Fitness

As another example of the complexity of developing an understanding of mechanism and therapeutic approach, Dr. Bland discusses the long-perceived correlation between elevated Body Mass Index (BMI) and type 2 diabetes risk. He cites a recently published article from researchers at Winston-Salem State University titled “Fitness, Fatness, and Survival in Adults with Pre-diabetes.” This was a large study involving 17,044 individuals. Dr. Bland points out that this study included individuals who were reasonably fit (as determined by a standard submaximal cardiac stress test), overweight, and pre-diabetic, yet the data indicate there was no difference in their health outcomes than in lean, fit individuals who participated in the study. He asks: “So can we say that fatness causes diabetes?” And answers: “No, we can't. We say it is associated, but there are other factors that we have to take into account as part of the system disturbance to really understand personally how that individual has a risk to diabetes.” He calls the association between fatness and diabetes an oversimplification, with the result being a huge number of people put on weight loss diets and not responding very effectively due to the assumption that obesity is the cause of their diabetes. Dr. Bland goes on to mention studies in top-tier medical journals in which diabetics whose blood sugars were controlled by precise use of the pharmacology of the day did not have ideal response when outcome-based levels were examined. The answer, as Dr. Bland discusses, is personalization and stratification. REF #1-7

Microbes, Metabolism, and Medications

Nature Medicine published an article in a recent issue titled “Metabolic Disease Puts Up A Fight: Microbes, Metabolism and Medications.” Dr. Bland takes great pleasure in discussing this article

because he feels a focus on this topic—the gut as the central therapeutic focus for improving insulin sensitivity and treating type 2 diabetes—is frame shifting and long overdue. And—as he points out—it also complements his point about considering pleiotropic effects. He states: “This again shows you the nature of thinking from a systems biology approach, that you need to get beyond thinking of one agent for one outcome. Your agents may have multiple effects. Particularly when you start talking about lifestyle intervention or diet intervention, you’re not just hitting one target. You’re hitting many, many different targets, so you wouldn’t just put a person on a program solely for their gut mucosal effects. You would put a person on a good nutrition program that would re-nourish the gut mucosa, but it would also simultaneously have positive effect upon multiple other factors, systemically, really, that relate to physiology.” REF #8

Dr. James A Levine and Non-exercise Activity Thermogenesis (NEAT)

Dr. Bland recently attended a lecture by Dr. James Levine, a well-respected clinician at the Mayo Clinic, and is intrigued by his concept of Non-exercise Activity Thermogenesis (NEAT), which, in the subtitle of a 2006 publication, Dr. Levine and colleagues describe as “The Crouching Tiger Hidden Dragon of Societal Weight Gain.” Dr. Bland describes the concept in greater detail, and cites the numerous studies and findings Dr. Levine has published on the topic. REF #9-10

Clinician/Researcher of the Month

Jay Udani, MD, CPI, FACN

CEO and Medical Director, Medicus Research

CEO, SysteMedicus, Inc.

Medical Director, Northridge Hospital Integrative Medicine Program

www.medicusresearch.com

Dr. Jay Udani is the founder and CEO of Medicus Research. He is a board-certified internist who served as Chief Resident at Cedars-Sinai Medical Center in Beverly Hills before completing two fellowships in Health-Services Research and Integrative Medicine at Cedars Sinai/UCLA. He was among the first physicians in America to become a Certified Physician Investigator for clinical trials through the American Academy of Pharmaceutical Physicians.

Medicus Research is a contract research organization for the natural health products industries, including botanical drugs, dietary supplements, and functional foods. SysteMedicus Inc. is an innovative mobile health company that creates technologies to serve patients, clinicians, CROs, and clinical trials sponsors. Dr. Udani has filed nine patents and has been an invited speaker within the pharmaceutical, nutraceutical, and technology industries. His unique background has given him valuable insights into the way technology is changing clinical trials and medical practice.

Dr. Udani was introduced to integrative medicine and natural products during his time as Chief Resident at Cedars Sinai Medical Center. His interest had already been sparked, and then was cemented when Dr. David Eisenberg—author of a well-known study of interest in complementary and alternative medicine in the US—came to lecture. With experience and interest in the area of designing and running clinical trials, Dr. Udani eventually founded Medicus Research to focus on the field of natural products, where he perceived a need. He describes his view this way: “Clinical trials for natural health products, but in the context of always knowing that these products have a certain risk-benefit ratio, which is that the benefit may not be as immediate or abrupt as pharmaceutical, but the risk profile is—in my opinion—so far superior that it is worth doing.”

Dr. Udani has performed in excess of 125 clinical trials and published more than 40 articles. Dr. Bland cites several of his published studies and they discuss the challenges and variables of working with natural products in a world that tends to favor the classic design of a randomized, double-blind, placebo-controlled trial. REF #11-15

References

1. McAuley PA, Artero EG, Sui X, Lavie CJ, Almeida MJ, Blair SN. Fitness, fatness, and survival in adults with pre-diabetes. *Diabetes Care*. 2013 Sept 23. [Epub ahead of print]
2. Helrich SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of onset of insulin-dependent diabetes mellitus. *N Engl J Med*. 1991 Jul 18;321(3):147-152.
3. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. *Diabetologia*. 2003 Mar;46(3):359-364.
4. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010 Jul 28;304(4):411-418.
5. Mitka M. Aggressive glycemic control might not be the best choice for all diabetic patients. *JAMA*. 2010 Mar 24;303(12):1137-1138.
6. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, et al. Long-term effects of intensive glucose-lowering on cardiovascular outcomes. *N Engl J Med*. 2011 Mar;364(9):818-828.
7. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol*. 2011 Jan;68(1):51-57.
8. Maratos-Flier E. Metabolic disease puts up a fight: microbes, metabolism and medications. *Nat Med*. 2013 Oct 7;19(10):1218-1219.
9. Levine JA, Vander Weg MW, Hill JO, Klesques RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. *Arterioscler Thromb Vasc Biol*. 2006 Apr;26(4):729-736.
10. Manohar C, Levine JA, Nandy DK, Saad A, Dalla Man C, et al. The effect of walking on postprandial glycemic excursion in patients with type 1 diabetes and healthy people. *Diabetes Care*. 2012 Dec;35(12):2493-2499.
11. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med*. 1993 Jan 28;328(4):246-252.

12. Shrestha S, Volek JS, Udani J, Wood RJ, Greene CM, et al. A combination therapy including psyllium and plant sterols lowers LDL cholesterol by modifying lipoprotein metabolism in hypercholesterolemic individuals. *J Nutr.* 2006 Oct;136(10):2492-2497.
13. Udani JK, Singh BB, Barrett ML, Preuss HG. Lowering the glycemic index of white bread using a white bean extract. *Nutr J.* 2009 Oct 28;8:52.
14. Udani JK, Singh BB, Barrett ML, Singh VJ. Proprietary arabinogalactan extract increases antibody response to the pneumonia vaccine: a randomized, double-blind, placebo-controlled pilot study in healthy volunteers. *Nutr J.* 2010 Aug 26;9:32.
15. Udani JK, Ritz BW. High potency fish oil supplement improves omega-3 fatty acid status in healthy adults: an open-label study using a web-based, virtual platform. *Nutr J.* 2013 Aug 8;12(1):112.

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