November 2019

Thank you for subscribing to Dr. Jeffrey Bland's newsletter. Enjoy and share this information, which is for educational purposes only and is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always consult with a qualified healthcare professional when you are in need of advice regarding a medical condition.

In this issue: Medical Milestone: JAMA Study Demonstrates Efficacy of Functional Medicine; BDNF Metabolism Reflects Lifestyle and Vitality; Meet and Greet Kinases--AMPK & PI3K; Another Example of Microbiome-Transplantable Dysfunction?

Medical Milestone: JAMA Study Demonstrates Efficacy of Functional Medicine

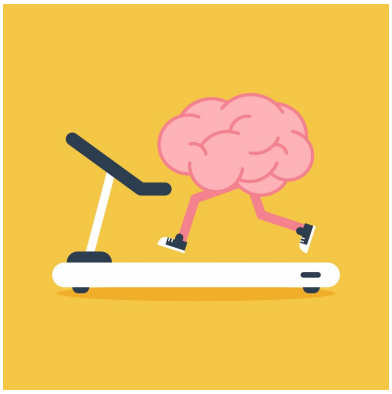
At present, around 90% of US health care expenditures arise from chronic disease and 12% of US adults have five or more chronic health conditions. Nutrition and lifestyle contribute to many of these, yet related interventions remain on the sidelines of treatment. Conventional care focuses on managing symptoms and abnormal test values, largely disregarding the roots of chronic disease—what Dr. Mark Hyman of the Cleveland Clinic's Center for Functional Medicine (CFM) has called "the social determinants and food-driven causes of health." Results from the first study to systematically investigate how Functional Medicine (FM) impacts health-related quality of life and compare it to a more conventional approach have just been published in JAMA Network Open, and are sure to increase appreciation for the efficacy of FM and the way it deals with the causes of chronic dysfunction.

This large-scale retrospective study of 7252 patients compared the outcomes of those receiving care at the CFM with those receiving standard care from one of the Cleveland Clinic's family health centers (FHC). It employed PROMIS questionnaires for Global Physical Health (GPH) and Global Mental Health (GMH) developed and validated by the National Institutes of Health to detect treatment effects over time on physical, mental, emotional, and social functions, overall health, and quality of life. After 6 months of care, participants receiving FM treatment demonstrated significantly greater improvements in GPH and GMH than those receiving standard treatment, and FM patients with data at 12-month as well as 6-month time points also showed significantly greater increases in their GPH scores (indicating improvement) at 12 months compared to FHC patients.

According to the Cleveland Clinic's press release announcing the study, in about 31% of CFM patients, GPH scores increased by 5 or more points—a clinically meaningful degree of change that is noticeable to patients in their daily lives. CFM patients were also more likely to raise their GMH scores by 5 or more points compared to FHC patients. CFM patients see a health coach and a dietitian as well as a primary care clinician, and the CFM emphasizes patient engagement and self-care as part of a partnership approach to enhancing health and function.

The Functional Medicine 'operating system' is based on optimizing function in order to promote well-being and reverse illness by considering behavioral and lifestyle inputs, including crucial factors not definitively addressed by conventional treatment like sleep, exercise, eating habits and nutrient intakes, stressors, social relationships, genomics, digestive and metabolic functions, the microbiome, and the exposome. Few health care practitioners have been prepared by their training to assess and treat this broader 'systems biology' range of health-related function in their patients, and the Institute for Functional Medicine (IFM) has provided continuing medical education to 15,000 practitioners. To date, over 1,000 care providers have received comprehensive IFMCP designation as certified practitioners of Functional Medicine, and IFM CEO Amy Mack expects this number to multiply over the coming years. She explains that "One of the things that we see happening with some Functional Medicine concepts is they get adopted into standard of care and they no longer are called Functional Medicine, but the concept is embraced…that's a win." You can read more about the rapid growth of Functional Medicine education, practice, and business in this article from Crain's Cleveland Business: https://www.crainscleveland.com/health-care/surpassing-expectations.

BDNF Metabolism Reflects Lifestyle and Vitality



Brain-derived neurotrophic factor (BDNF) is a valuable regulator of the life, connection-making, and death of neurons (especially notably within the hippocampus during aging), and reduced circulating BDNF levels may be a biomarker for cognitive impairment. Maintaining neuroplasticity is a major focus in successful aging—and a key part of neurologist Dale Bredesen, MD's ReCODE protocol, described in his book The End of Alzheimer's. BDNF is inducible by new mental, physical, and emotional challenges, but is also suppressible, and BDNF levels depend greatly on stage of life, state of health, and lifestyle behaviors.

Here is a sampling of recent research findings:

- In healthy individuals aged 65-85, even a single 35-minute bout of exercise can significantly raise BDNF levels, and a meta-analysis found this true for the general population, and especially men; regular exercise is even more effective.
- Curcumin supplementation significantly increases serum BDNF levels, according to a meta-analysis of four studies.
- In young people, supplementation with lutein, zeaxanthin, and meso-zeaxanthin significantly increased serum BDNF levels while improving some measures of cognitive processing.
- In an animal model of brain trauma, astaxanthin was seen to increase levels of BDNF and other nerve growth factors following injury.
- An in-depth review of herbs and food plants cites research showing that several (many of which are considered adaptogens) contain phytonutrients that can upregulate BDNF production. These plants include ashwagandha, bacopa, rhodiola, saffron, Siberian ginseng, Panax ginseng, St. John's wort, perilla, olives, green tea, grapes, ginkgo, Chinese salvia, and coffee.
- In a 2019 study, dialysis patients with depression receiving one *Lactobacillus* and three *Bifidobacterium* strains plus prebiotics showed significant increases in serum BDNF compared to those receiving only the probiotics or placebo; the synbiotic combination also appeared to improve measures of mood in dialysis patients whether or not they were depressed.
- Neurons exposed to *Bifidobacterium bifidum* TMC3115 or the Brassica vegetable

metabolite sulforaphane showed upregulation of BDNF production.
- A review of neurocognitive and cardiovascular mechanisms of action for resveratrol cites research showing how it may variously upregulate BDNF production or trigger its release to increase serum levels.
- The polyamine spermidine (found in many foods) increased levels of BDNF in neurons, in a lab study.
- In an animal model of diabetes, the bitter herbal principle berberine rescued disease-related downregulation of BDNF.
- Preclinical research suggests that anthocyanins such as cyanidin-3-glucoside may beneficially influence BDNF signaling in the central nervous system.

On the other hand:

- Impaired glucose metabolism and insulin resistance are linked to lower serum BDNF levels.
- Adverse experiences or exposure to bisphenol A early in life can alter BDNF gene methylation patterns in the hippocampus, which may increase risk for disorders such as depression, autism, or schizophrenia.
- Chronic arsenic exposure may lower serum BDNF levels while negatively impacting cognitive function.

In this FMU interview, Dr. Bland and Dr. Bredesen discuss prion biochemistry, synapse formation, how exercise supports BDNF while opposing formation of abnormal proteins in the brain, and other factors influencing long-term cognitive wellness.

Meet and Greet Kinases--AMPK & PI3K

Kinases are perhaps *the* archetypal enzyme, comprising a dynasty of hundreds of hardworking proteins that accelerate processes enabling human metabolism. At the most basic level, they constitute a sort of energy transfer system in that their specialized molecular configuration allows them to convey highly reactive and unstable phosphate groups from high-energy molecules to substrates—and thus, they are considered phosphotransferases rather than phosphorylases. Most kinases act on proteins, and can activate, stabilize, deactivate, or tag them for further regulation, and their phosphorylation (typically at a protein's tyrosine, serine, or threonine residues) facilitates a broad range of metabolic events ranging from aiding mitochondrial energy production to influencing cell life and death. Other kinases act on lipids, carbohydrates, or other substrates. Here we introduce a few members of this stalwart family.

AMPK—Adenosine monophosphate-activated protein kinase

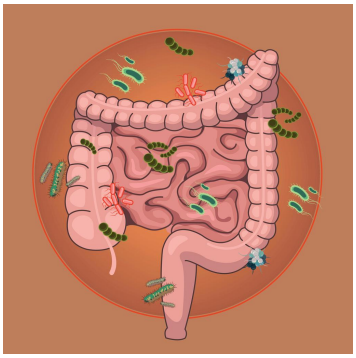
Even among kinases, AMPK stands out. This protein kinase helps organize body responses related to physical crisis, cellular aging, and survival at bodily and cellular scales. It is exquisitely responsive to changes in diet and lifestyle, and reconfiguring energy usage with every change in circumstance is its very reason for being. Whether you're observing a fasting-mimicking diet or indulging in fries, AMPK is busy coordinating insulin sensitivity and fat metabolism for immediate as well as possible future needs. Whenever you are aerobically working, AMPK is there, remolding metabolism to optimize balance between adenosine triphosphate (ATP) and adenosine monophosphate energy currency forms and to maximize mitochondrial efficiency through parting out or recycling old cellular apparati and reordering production of "new equipment" when feasible. AMPK is a master networker, and in order to carry out its functions, it cooperates with a large posse of other cell signaling networks including sirtuins, mTOR, PPARs/PGC1α, HMG-CoA, FOXOs, and many others. Physical activity and diet are the premiere influences on AMPK activation, but a few known dietary activators include cocoa flavonoids, berberine, capsaicin, and genistein. AMPK is the body's math whiz in balancing out equations ruling anabolism and catabolism, which makes it a prime target for personalized lifestyle medicine and drug development.

PI3K—Phosphoinositide-3-kinase

PI3K is an example of a lipid kinase, and it is a major player in regulating insulin

homeostasis. Upon activation by interactions at the insulin and insulin-like growth factor receptors, PI3K instigates numerous downstream kinases (like Akt/protein kinase B, the mammalian target of rapamycin/mTOR, and glycogen synthase kinase) to orchestrate cellular, nuclear, and mitochondrial actions that govern the glucose response, muscle growth, and other insulin-dependent aspects of metabolism. Dysregulation at any of these steps can result in insulin resistance and dysglycemia, but additionally, as these pathways can influence autophagy, cell proliferation, and cellular survival, their inappropriate stimulation via cytokines and other messengers of chronic stress can potentially encourage tumorigenesis. In addition, PI3Ks exert some control over T-helper cell differentiation and therefore affect balance among Th1, Th2, Th17, and T-regulatory cells, which modulates overall immune tone—whether normal or predisposed towards inflammation or autoimmunity. In this interview, oncologist D. Barry Boyd, MD, MS and Dr. Bland discuss how chronically impaired insulin signaling can impact cancer through altering cytokine production and balance between cell growth and apoptosis—and all of which may be moderated by eating patterns and managing chronic stressors that influence dietary choices.

Another Example of Microbiome-Transplantable Dysfunction?



The vigilant and always-active news, communications, signal-producing, gene-regulating, and response-mediating organization known as the gut microbiome has been found capable of transmitting wellness, inflammation, and illness from one organism to another in animal research. Obesity/leanness and immune tolerance/allergy are a couple of recent examples, though preclinical findings are not always replicated in clinical study, as shown by this relatively brief 12-week study of fecal microbiome transplantation (FMT) in obesity.

Recent human and animal research into gut microbiome involvement in SLE (systemic lupus erythematosus) has found that microbiota composition is altered during the pathogenesis of this condition, with reduced overall diversity and different abundance of Bacteroidetes phylum members like *Odoribacter* or *Reikenella* species and Firmicutes members like *Blautia* despite similarity in overall Bacteroidetes/Firmicutes balance. One of the chief clinical diagnostic and prognostic markers of SLE and its renal complications is the presence of antibodies to double-stranded DNA (dsDNA), which can activate an autoimmune response. An August 2019 study using the same model of SLE has discovered that FMT from affected animals resulted in the production of anti-dsDNA antibodies, initiation of intestinal mucosal inflammation, and, upregulation of SLE-related gene expression in germ-free animals.

The etiology and course of immune, structural, and functional derangements in SLE is far from well understood, and the results of these experiments indicate that changes in gut microbiome composition may predate overt manifestation of SLE and potentially be involved in its pathophysiology--in which case, future FMT research might also examine whether or not beneficial dietary inputs are able to offset the diversion of immune function towards SLE.

Connect with Dr. Jeffrey Bland

Newsletter Team
Jeffrey Bland, PhD - Publisher
Cheryl Kos, ND - Content Developer and Writer
Kirsten Miller - Content Editor
Annette Giarde - Subscription Manager