The Microbial Origin of Fibromyalgia: Getting to the "GUT" of Myalgenic Mitochondrial Dysfunction and Microglial Activation

Alex Vasquez DC ND DO FACN, International College of Human Nutrition and Functional Medicine (ICHNFM.ORG) and Biotics Research Corporation (BioticsResearch.com)

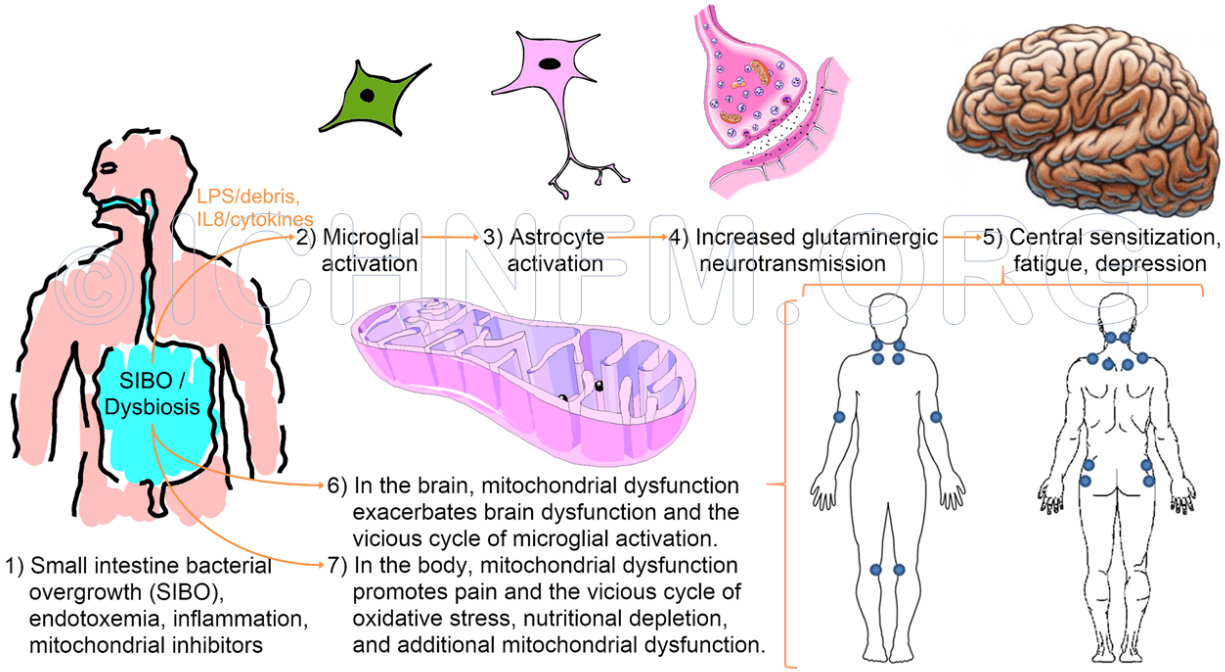
Introduction: For the accurate understanding and effective treatment of any disease, all components of the disease should first be integrated into a cohesive and consistent model that explains all aspects of the disease ranging from risk factors to pathophysiologic findings to responses to treatments. For fibromyalgia (FM), the most cohesive model centers on the disease's genesis in the gastrointestinal tract, resulting from overgrowth and/or imbalance of intraluminal bacteria. This short article will present gastrointestinal dysbiosis as the GUT—grand unified theory—of all aspects of fibromyalgia based on previous and recent reviews by this author.[1,2,3,4,5] The pathophysiology is illustrated and described sequentially in the sections that follow.

1. Patients with FM have high rates of gastrointestinal dysbiosis in proportion to the severity of musculoskeletal pain: Small intestine bacterial overgrowth (SIBO)—also referred to as "intestinal bacterial overgrowth" or simply "bacterial overgrowth"—provides the single best model for explaining the clinical and pathophysiological manifestations of fibromyalgia, as well as irritable bowel syndrome (IBS). Although commonly underappreciated by many clinicians, SIBO is common in clinical practice, affecting for example approximately 40% of patients with rheumatoid arthritis, 84% of patients with IBS, and 90% to 100% of patients with fibromyalgia. In a study of 42 fibromyalgia patients, all 42 FM patients showed laboratory evidence of SIBO, and the severity of the intestinal bacterial overgrowth correlated positively with the severity of the fibromyalgia, thus indicating the plausibility of a causal relationship.[6] The links between fibromyalgia and IBS are also strong; many IBS patients meet strict diagnostic criteria for fibromyalgia, and many fibromyalgia patients meet strict criteria for IBS. Lubrano et al[7] showed that fibromyalgia severity correlated with IBS severity among patients who met strict diagnostic criteria for both conditions. The high degree of overlap between these two diagnostic labels suggests that these conditions are two variations of a common pathophysiological process—SIBO.[8] SIBO causes altered bowel function, immune activation, and visceral hypersensitivity, and it is the best causative explanation for the clinical and pathophysiological manifestations of IBS; for more details and citations, see the excellent review by Lin published in *JAMA* in 2004.[9] IBS is characterized by *visceral* hyperalgesia (hypersensitivity to pain), just as fibromyalgia is characterized by *musculoskeletal* hyperalgesia. Given that strong evidence indicates that IBS is caused by SIBO and that IBS and fibromyalgia are variations of the same pathophysiological process, then fibromyalgia may therefore be caused by SIBO. Small intestine bacterial overgrowth is highly prevalent in fibromyalgia. Several studies have shown that 90% to 100% of fibromyalgia patients have evidence of SIBO; such strong correlations and the dose-response relationships imply causality and must be integrated into any science-based model of fibromyalgia. As generally expected with gastrointestinal dysbiosis, FM patients show evidence of increased intestinal permeability, so-called "leaky gut."[10] Successful treatments for gastrointestinal dysbiosis include monotherapy with berberine from *Berberis vulgaris*[11] and *Origanum vulgare* (emulsified oil of oregano time-released for proper dispersion)[12] and combined use of *Artemisia dracunculus, Tinospora cordifolia, Equiseturn arvense, Thymus vulgaris, Pau D'Arco, Anethum graveolens, Brucea javanica, Pulsatilla chinensis, Picrasma excelsa, Acacia catechu, Hedyotis diffusa,* and *Achillea millefolium*.[13]
2. Microbial molecules from the gut account directly and indirectly for nearly all of the clinical manifestations of FM: Bacterial LPS and other antigens absorbed from the intestine during SIBO contribute to a subclinical inflammatory state that results in pain hypersensitivity and increased cytokine release, both of which are characteristics of fibromyalgia. In animal models and in human research studies, exposure to bacterial endotoxin/LPS has been shown to increase the brain's sensitivity to and perception of pain. Immune-mediated and inflammation-mediated pathways that promote pain sensitivity and pain perception include increased production of nitric oxide with increased production of prostaglandins and cytokines, resulting in the sensitization of peripheral and/or central neurons to pain perception/transmission. In support of this concept, Lin (op cit) wrote, "The immune response to bacterial antigen in SIBO provides a framework for understanding the hypersensitivity in both fibromyalgia and IBS." A 2008 paper by Othmanm, Agüero, and Lin[14] stated, "…a recent animal study demonstrated that exposure to endotoxin increased the production of prostaglandins and simultaneously decreased nitrous oxide production, resulting in inflammatory hyperalgesia" and "These observations suggest that SIBO is a common feature in both [IBS and FM] disorders and that altered gut microbiota in SIBO may play a role in the induction of somatic or visceral hypersensitivity, with affected patients meeting the diagnostic criteria for IBS, fibromyalgia or both disorders."

3. Small intestine bacterial overgrowth leads to systemic absorption of toxins that impair brain/nerve and muscle/mitochondrial function: SIBO is associated with overproduction and absorption of bacterial cellular debris (e.g., lipopolysaccharide [LPS], bacterial DNA, peptidoglycans, teichoic acid, exotoxins) and antimetabolites—substances which are directly toxic to cellular energy/ATP production and muscle and nerve function—such as D-lactic acid, tyramine, tartaric acid, hydrogen sulfide (H2S). Intestinal gram-negative bacteria produce endotoxin (also known as lipopolysaccharide, LPS), which impairs skeletal muscle energy/ATP production. Endotoxin also raises blood lactate under aerobic conditions in humans.[15] Thus, via direct and indirect effects on cellular metabolism, chronic low-dose bacterial LPS/endotoxin exposure can result in impaired muscle metabolism and reduced ATP synthesis via impairment of mitochondrial function.[16] Intestinal bacteria also produce D-lactate, a well-known metabolic toxin in humans; SIBO often results in variable levels of D-lactate acidosis, severe cases of which can progress from fatigue and malaise to encephalopathy (e.g., confusion, ataxia, slurred speech, altered mental status) and death.[17] Supporting the proposal that bacterial overgrowth with D-lactate-producing bacteria is a contributor to the chronic fatigue syndromes including fibromyalgia is an excellent study published in 2009 showing that patients with chronic fatigue syndrome have intestinal overgrowth of bacteria that produce the cellular toxin D-lactate; specifically the research showed that these chronic fatigue patients have a 7-fold increase in D-lactate producing *Enterococcus* and 1,100-fold increase in D-lactate producing *Streptococcus*. Energy/ATP underproduction and lactate overproduction cause muscle fatigue and muscle pain. An additional cellular toxin produced by intestinal bacteria is hydrogen sulfide (H2S), which causes DNA damage[18] (noted previously to be increased in fibromyalgia patients) and which impairs cellular energy production, a finding relevant to *but not limited to* the pathogenesis of ulcerative colitis.[19,20] Bacteria and yeast in the intestines produce H2S, which can bind to the mitochondrial enzyme cytochrome c oxidase (part of Complex IV of the electron transport chain), thereby impairing oxidative phosphorylation and ATP production; this may partly explain the association of gastrointestinal dysbiosis and small intestine bacterial overgrowth (SIBO) with conditions such as chronic fatigue syndrome (CFS) and fibromyalgia.[21] Mitochondrial dysfunction in muscle leads to the cellular/cytologic and histologic/tissue changes that are typical and well-documented in cell and muscle samples of patients with fibromyalgia.[22] These peripheral (eg, non-brain) changes in muscle also prove beyond any doubt that fibromyalgia is not a "brain disease" or solely a "disorder of pain processing." Oral supplementation with coenzyme-Q10 (ubiquinone) has repeatedly proven to be the most effective mitochondrial-supportive nutritional intervention in fibromyalgia.[23,24]
4. Central sensitization in fibromyalgia is caused by microbial debris and secondary metabolic and inflammatory effects: As a result of SIBO, fibromyalgia patients suffer increased sensitivity to pain due to heightened sensitivity of the brain and spinal cord—as well as from peripheral sensitization and impaired muscle function due to the previously detailed mitochondrial dysfunction. SIBO leads to intestinal absorption and systemic distribution of low levels of bacterial endotoxin (endotoxemia) and other *inflamm*ation-*gen*erating molecules (inflammogens); this results in low-grade inflammation (including release of cytokines, prostaglandins and other inflammatory mediators and oxidants).[25] Microbial inflammogens cause systemic inflammation, and cytokines and prostaglandins produced peripherally (ie, outside of the central nervous system [CNS], which is the brain and spinal cord) can readily traverse the blood-brain barrier (BBB) and enter the CNS to promote glial activation—brain inflammation.[26] Some of these microbial inflammogens may be able to bypass the BBB directly, when the BBB becomes permeable/leaky following induction of systemic inflammation. In the brain, mitochondrial dysfunction exacerbates brain dysfunction and the vicious cycle of microglial activation.[27] Microglia are immune cells in the brain that respond to cytokines, prostaglandins, and microbial inflammogens; when microglia become stimulated or "activated" by inflammatory triggers/signals, the microglia signal/activate/irritate the nearby astrocytes, which are cells in the brain that respond by causing an increase in neuron-to-neuron communication (neurotransmission) via the neurotransmitter glutamate, which is stimulatory to neurons.[28] While glutamate is necessary in small and regulated amounts, higher levels of glutamate promote central sensitization, pain amplification, "brain fatigue", depression and anxiety; when very elevated, glutamate can promote migraine headaches, seizures and epilepsy.[29] High levels of glutamate cause excitation of brain neurons, and this increased activity leads to increased production of free radicals, which cause additional local inflammation and mitochondrial dysfunction within the brain, leading back to microglial activation for a vicious cycle. The brain is now in a "positive feedback loop" which promotes additional pain/fatigue/depression independently from ongoing stimulation from the original trigger. Excess or prolonged microglial activation promotes neurodegeneration via hyperexcitation of neurons, basically causing them to "burn out" in a process that has been described as "brain on fire."[30] The exception to this occurs after a period of particularly protracted microglial activation, which can cause damage or "burn out" of the astrocytes, too; this "astrocyte degeneration" leads to neurodegeneration when the astrocytes become impaired and cannot perform their supportive functions to the

neurons. Persistent pain is also facilitated by concomitant vitamin D deficiency, which promotes pain sensitization[31] as well as myalgia and bone pain (osteomalacia). Human clinical trials have shown that vitamin D supplementation can alleviate inflammation[32], intestinal hyperpermeability[33], FM pain[34] and other neuromusculoskeletal pain. Vitamin D reduces experimental microglial activation[35], a component of neuroinflammation and central sensitization.

5. Clinical improvements in FM following eradication of SIBO prove causality: In 1999, Pimentel et al[36] showed that oral administration of antibiotics lead to alleviation of pain and other clinical measures of FM. In 2004, Wallace and Hallegua[37] showed that eradication of SIBO with antimicrobial therapy lead to clinical improvements in FM patients in direct proportion to the antimicrobial efficacy.



A simple integrated model of fibromyalgia, emphasizing dysbiosis-induced glial activation and mitochondrial dysfunction: Small intestine bacterial overgrowth (SIBO) elaborates endotoxin/lipopolysaccharide (LPS) with other inflammogens and mitochondrial inhibitors (including D-lactate and hydrogen sulfide [H2S]). Microglial activation can be triggered directly by LPS or indirectly by peripheral and central cytokines (especially IL-8), and it then triggers astrocyte activation and results in increased glutaminergic neurotransmission, which promotes central sensitization and the resulting depression, central fatigue, and pain sensitivity. In the brain, mitochondrial dysfunction exacerbates brain dysfunction and the vicious cycle of microglial activation. In the body, mitochondrial dysfunction promotes pain and the vicious cycles of oxidative stress, nutritional depletion, and additional mitochondrial dysfunction. Vitamin D deficiency, common in many conditions of persistent pain, exacerbates central pain by allowing increased microglial activation while also contributing to peripherally-sourced pain from muscle (myalgia) and bone (osteomalacia). Illustration by Vasquez A, *Inflammation Mastery, 4th Edition* (ICHNFM.ORG, 2016); image of brain by IsaacMao per Flickr.com via creativecommons.org/licenses/by/2.0. Image licensed to Naturopathic Doctor News & Review (NDNR); no other use, replication or derivation permitted without written permission from the author.

Conclusion: Per this data, we see very clearly that 1) FM patients have a high prevalence of gut dysbiosis, and that 2) microbial molecules from the gut can create the pathophysiology noted in FM, specifically 3) mitochondrial toxicity and 4) pain sensitization; 5) eradication of SIBO alleviates FM. As such, fibromyalgia in its classic form can be easily explained/understood as SIBO-induced central sensitization and mitochondrial dysfunction, resulting in pain and fatigue. Other conditions such as vitamin D deficiency, hypothyroidism, hemochromatosis, persistent infections and viral (re)activations, chemical overload and heavy metal toxicity can mimic and/or contribute to the clinical picture of FM. Treatment of SIBO can be accomplished with berberine, emulsified oregano, and combination botanicals while supplementation with vitamin D and ubiquinone alleviate mitochondrial dysfunction and the central and peripheral

contributions to pain, respectively. Most FM cases will respond favorably to this pathophysiology-based approach, while others may require more intensive therapy.[3,5]

[1] Vasquez A. *Musculoskeletal Pain*. Institute for Functional Medicine, 2008
[2] Vasquez A. *Fibromyalgia in a Nutshell*. CreateSpace, 2012
[3] Vasquez A. *Naturopathic Rheumatology v3.5*. International College of Human Nutrition and Functional Medicine, 2014
[4] Vasquez A. The Microbiome Arrives to Prime Time in Primary Care, Implications for the Anti-Dysbiotic Treatment of Fibromyalgia. *Nutritional Perspectives* 2015 Oct, 45-50
[5] Vasquez A. *Inflammation Mastery, Fourth Edition*. International College of Human Nutrition and Functional Medicine, 2016 in press. ISBN-10:0990620484
[6] Pimentel et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. *Ann Rheum Dis*. 2004 Apr;63(4):450-2
[7] Lubrano E, et al. Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder. *Int J Colorectal Dis*. 2001 Aug;16(4):211-5
[8] Veale et al. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. *Br J Rheumatol*. 1991 Jun;30(3):220-2
[9] Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA*. 2004 Aug 18;292(7):852-8
[10] Goebel et al. Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome. *Rheumatology* 2008 Aug;47(8):1223-7
[11] Han J, Lin H, Huang W. Modulating gut microbiota as an anti-diabetic mechanism of berberine. *Med Sci Monit*. 2011 Jul;17(7):RA164-7
[12] Force M, Sparks WS, Ronzio RA. Inhibition of enteric parasites by emulsified oil of oregano in vivo. *Phytother Res*. 2000 May;14(3):213-4
[13] Chedid V, Dhalla S, Clarke JO et al. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Glob Adv Health Med*. 2014 May;3(3):16-24
[14] Othman M, Agüero R, Lin HC. Alterations in intestinal microbial flora and human disease. *Curr Opin Gastroenterol*. 2008 Jan;24(1):11-6
[15] Bundgaard et al. Endotoxemia stimulates skeletal muscle Na+-K+-ATPase and raises blood lactate under aerobic conditions in humans. *Am J Physiol Heart Circ Physiol*. 2003 Mar;284(3):H1028-34
[16] Scirocco et al. Exposure of Toll-like receptors 4 to bacterial lipopolysaccharide (LPS) impairs human colonic smooth muscle cell function. *J Cell Physiol.* 2010 May; 442-50
[17] Vella A, Farrugia G. D-lactic acidosis: pathologic consequence of saprophytism. *Mayo Clin Proc*. 1998 May;73(5):451-6
[18] Attene-Ramos MS, Wagner ED, Gaskins HR, Plewa MJ. Hydrogen sulfide induces direct radical-associated DNA damage. *Mol Cancer Res*. 2007 May;5(5):455-9
[19] Magee et al. Contribution of dietary protein to sulfide production in large intestine: in vitro and controlled feeding study in humans. *Am J Clin Nutr*. 2000 Dec;72(6):1488-94
[20] Babidge W, Millard S, Roediger W. Sulfides impair short chain fatty acid beta-oxidation at acyl-CoA dehydrogenase level in colonocytes. *Mol Cell Biochem*. 1998 Apr:117-24
[21] Lemle MD. Hypothesis: chronic fatigue syndrome is caused by dysregulation of hydrogen sulfide metabolism. *Med Hypotheses*. 2009 Jan;72(1):108-9
[22] Cordero et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther*. 2010;12(1):R17. Olsen NJ, Park JH. Skeletal muscle abnormalities in patients with fibromyalgia. *Am J Med Sci*. 1998 Jun;315(6):351-8
[23] Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, Cotán D, Gómez Izquierdo L, Bonal P, Campa F, Bullon P, Navas P, Sánchez Alcázar JA. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther*. 2010;12(1):R17
[24] Cordero MD, Alcocer-Gómez E, Culic O, Carrión AM, de Miguel M, Díaz-Parrado E, Pérez-Villegas EM, Bullón P, Battino M, Sánchez-Alcazar JA. NLRP3 inflammasome is activated in fibromyalgia: the effect of coenzyme Q10. *Antioxid Redox Signal.* 2014 Mar 10;20(8):1169-80
[25] Patel et al. Human experimental endotoxemia in modeling pathophysiology, genomics, and therapeutics of innate immunity in complex cardiometabolic diseases. *Arterioscler Thromb Vasc Biol* 2015 Mar:525-34.
[26] Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc*. 2002 Dec;50(12):2041-56
[27] Nguyen et al. A new vicious cycle involving glutamate excitotoxicity, oxidative stress and mitochondrial dynamics. *Cell Death Dis*. 2011 Dec 8;2:e240
[28] Béchade C, Cantaut-Belarif Y, Bessis A. Microglial control of neuronal activity. *Front Cell Neurosci*. 2013 Mar 28;7:32
[29] Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. *Trends Neurosci*. 2013 Mar;36(3):174-84
[30] Cohen G. The brain on fire? *Ann Neurol*. 1994 Sep;36(3):333-4
[31] von Känel R, Müller-Hartmannsgruber V, Kokinogenis G, Egloff N. Vitamin D and central hypersensitivity in patients with chronic pain. *Pain Med*. 2014 Sep;15(9):1609-18
[32] Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM*. 2002 Dec;95(12):787-96
[33] Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, Meddings J, O'Sullivan M. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study. *United European Gastroenterol J.* 2015 Jun;3(3):294-302
[34] Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, Hahne J2, Friedrich M. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. *Pain*. 2014 Feb;155(2):261-8

[35] Hur J, Lee P, Kim MJ, Cho YW. Regulatory Effect of 25-hydroxyvitamin D3 on Nitric Oxide Production in Activated Microglia. *Korean J Physiol Pharmacol*. 2014 Oct;18(5):397-402
[36] Pimentel M, Hallegua DS, Wallace DJ, et al. Improvement of symptoms by eradication of small intestinal overgrowth in FMS: a double-blind study [abstract]. *Arthritis Rheum* 1999, 42:S343
[37] Wallace DJ, Hallegua DS. Fibromyalgia: the gastrointestinal link. *Curr Pain Headache Rep*. 2004 Oct;8(5):364-8