The Commensal Relationship of the Normal Human Colonic Microbiome: We supply them with vitamin D they supply us with B vitamins.

Vitamin D deficiency has produced a pandemic of the "wrong" colonic microbiome.

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ABSTRACT: This is the second in a series of three reports describing the effects of vitamin D supplementation as a treatment for sleep disorders in neurology patients. It extends the clinical observations to 6 years and proposes a link between vitamin D and the colonic microbiome. The improvement in sleep achieved by vitamin D levels of 60-80 ng/ml reported in our first article was not permanent. In the second year the sleep began to worsen again and new symptoms of neuropathy and pain appeared. This report proposes that vitamin D deficient patients have a second, linked deficiency of a B vitamin, pantothenic acid which arises from a change in the supply from its natural source, the intestinal bacteria. There are recent articles describing a pandemic of the "wrong" colonic microbiome. Patients with this condition have a higher incidence of sleep apnea, obesity, autoimmune disease, hypertension, heart disease and stroke. There are also recent reports that 7/8 of the B vitamins are made by the normal colonic bacteria and are absorbed there. Appropriate doses of vitamin D and all 8 B vitamins, given for three months returned the colonic microbiome to normal in over 1000 patients. Based on these observations I hypothesize that we have a commensal relationship with our normal colonic bacteria; we provide them a source of vitamin D, they provide us with the B vitamins. I also suggest that the four species that make up the normal human colonic microbiome; Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria exist naturally as a foursome because they are commensal with one another. Each requires a vitamin D source and at least one B vitamin in order to thrive. Epidemically low vitamin D levels throughout our sun-sheltered human population have produced a change in the colonic microbiome that results in accompanying B vitamin deficiencies. Pantothenic acid becomes coenzyme A, a metabolic cofactor used in over a hundred enzymatic processes throughout the body including the production of melatonin, acetylcholine and cortisol. Pantothenic acid deficiency and deficiencies of the other B vitamins should be considered as possible etiologic agents in the diseases reported to occur in parallel with the "wrong" colonic microbiome. (Also, see accompanying article.)

Key words: vitamin D deficiency, microbiome, sleep, pantothenic acid, neuropathy, pain

Introduction:

This is the second of three reports (see companion article) linking vitamin D deficiency to abnormal sleep, extending the clinical observations reported in 2012. (1) The improved sleep achieved with sustained vitamin D levels of 60-80 ng/ml lasted only two years, then the sleep began to fail and different symptoms appeared. In this and the accompanying third report I hypothesize that these new symptoms and the return of sleep disruption are caused by pantothenic acid (B5) deficiency. The B5 deficiency manifests in most patients during the 2nd or 3rd year of vitamin D replacement, probably from a combination of decreased supply of B5 from the altered intestinal bacterial population, and increased demand for B5 as the brain attempts to stay in deep sleep longer to make repairs. In order to permanently normalize sleep and the colonic microbiome we must understand how the sleep disorder, the vitamin deficiencies, and the abnormal microbiome are linked to one another.

The colonic bacterial flora of normal, healthy mammals is made up of four predominant species; Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria. (2) There has been an epidemic change in our colonic microbiome that is thought to be linked to our declining health and our increasing obesity. (3-7) Observations regarding the negative effects of abnormal intestinal flora go far beyond bowel symptomatology. There are reports linking changed intestinal flora to high blood pressure, heart disease, high cholesterol, diabetes, colon cancer and autoimmune diseases such as psoriasis, asthma, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, crohn's disease, and ulcerative colitis. (3-7)

Within this context I hypothesize four novel ideas. 1) The 4 predominant bacterial species of healthy, outside-living mammals require a vitamin D source provided by the host. 2) A commensal relationship exists between host and bacteria wherein the sun-exposed, vitamin D producing, host animal provides vitamin D for the intestinal bacteria, and they, in turn make B vitamins that are absorbed and used by the host. 3) The four species that predominate in the colon of healthy animals exist as a foursome because species "A" makes thiamine that "B" needs, species "B" makes riboflavin that "A" needs; they are commensal with one another. 4) The change in the make-up of the intestinal bacterial population due to epidemically low vitamin D levels has resulted in an accompanying pandemic of B5 deficiency. (See accompanying article.)

Patient Selection:

The patients reported here presented to my general neurology practice over a six year period from 2010 to 2015 and do not include patients with primary brain cancer, amyotrophic lateral sclerosis or Alzheimer's disease. Occasional patients presented for a primary sleep disorder, but most came for neurologic complaints of headache, vertigo, epilepsy, tics, pain, multiple sclerosis, neuropathy, Parkinson's disease, tremor, dystonia, cerebellar degeneration, depression, fatigue or memory loss. The vitamin regimen described herein is used to improve the patient's sleep in order to improve their neurologic complaints. Some patients have had sleep studies, some have not, but all patients with documented sleep apnea were encouraged to continue positive pressure masks and patients with insomnia used a variety of sleep medications.

Vitamin D: The seasonal control of sleep and weight:

Our first report referenced articles showing that the periaqueductal gray brainstem nuclei that are responsible for the timing and paralysis of sleep are heavily invested with vitamin D receptors. (1,8,9) Vitamin D is an endocrine hormone produced by sun exposure. Light of only a specific wavelength, UVB converts cholesterol on our skin to a pre-hormone, which is then absorbed through the skin. This hormone allows us to adapt to seasonal changes in food supplies. Vitamin D controls the endocrine functions of feeding, reproduction and sleep, allowing all three to change with the seasons at latitudes where the UVB wavelength of light does not pass through the earth's atmosphere in winter. (1,8,9) Animals living far from the equator where there is no winter food source must either migrate or hibernate. Humans hibernate in a modified way; lower vitamin D levels cause us to sleep more in winter. As the pituitary is heavily invested with vitamin D receptors, lower winter vitamin D levels slow our metabolism by lowering thyroid hormone production. (10-12) Saving calories as fat also improves survival in winter, and recent studies suggest that specific bacterial species in the colon play a role in determining whether the calories we consume go to energy production or fat storage. (13,14) Therefore it seems logical that there would be a link between vitamin D levels and colonic bacterial populations. Winter bacterial species favored by lower D levels would promote fat deposition, higher spring and summer D levels would favor the "healthy four" bacterial species that direct consumed calories into muscle to build strength and burn energy.

Three symptoms that were not improved by vitamin D supplementation:

There were three complaints that never improved with vitamin D supplementation even with improved sleep; 1) Weight gain, which was present in about half of the patients, did not improve with D supplementation. Several patients reported that they slept better, felt better and were exercising but were not losing weight; 2) Approximately 30% of the patients had irritable bowel syndrome (IBS), which showed no improvement with D supplementation, and; 3) 75% of patients complained of joint pain, neuropathic pain or muscle pain, especially on awakening, which seemed to be worsening by the end of the second year. (See companion article.)

In addition, there were two young headache patients who, after two years of vitamin D and B12 supplementation, developed a new complaint of burning in the hands and feet.

Do the sleep nuclei need something else?

Because of the improvement in sleep followed by decline I wondered if the brainstem sleep nuclei were now appropriately supplied with vitamin D but required something else to produce the coordinated, carefully timed, neurotransmitter changes needed to complete normal sleep. Serendipitously one of my patients brought me a book called "Overcoming the Pain of Inflammatory Arthritis, *the Pain Free Promise of Pantothenic Acid*". (15) The authors reported that rheumatoid arthritis sufferers given 400 mg of B5 had improvement in both joint pain and sleep. They referenced a series of 1950's experiments where artificially induced B5 deficiency rapidly caused insomnia. (16-19) Preliminary studies had been done in animals fed B5 deficient diets. Within weeks pigs began to walk oddly as though they had a neuropathy. Rats made B5 deficient died of adrenal hemorrhage. It was proposed that the rats' inability to make cortisol, due to the lack of B5, was linked to the adrenal injury. (16-19) Human experiments were two small groups of prison inmates. One group was tube-fed a fully synthetic B5 deficient liquid diet, the other group was tube-fed the same diet with an additional blocker of pantothenic acid called omega methyl pantothenic acid. Within 2 weeks all subjects complained of an inability to sleep, abdominal

discomfort, balance difficulties, and tingling and burning in the hands and feet. (16-19) Although there was no reference made to joint pain in these reports, cortisol is widely used as a therapeutic agent to treat a variety of autoimmune disorders suggesting that a chronic deficiency of cortisol resulting from B5 deficiency might lead to a chronic inflammatory state and the development of arthritic pain.

Pantothenic acid supplementation in D replete patients:

In hopes of improving my patients' sleep I recommended 400 mg of pantothenic acid to approximately 50 patients with good vitamin D levels who still awoke with muscle, joint or neuropathic pain. (Pantothenic acid blood levels were not commercially available and I made no attempt to measure other B vitamin levels aside from B12 which was replaced when deficient, see also, companion article.) The two patients who had recently developed burning in the hands and feet reported resolution of their symptoms within 2 days suggesting that B5 deficiency was probably the cause. However, 90% of the patients given the 400 mg dose of B5 reported that their sleep was immediately worse. Many reported that they felt "agitated" and "couldn't sleep at all" and therefore stopped the supplement in 1-2 days.

We have been taught that "B vitamins are safe in large doses, we urinate out the excess". However, B5 in a large dose had an immediate, very negative effect on sleep. Assuming that the 400 mg dose was too high, I recommended a dose of 100 mg in a B complex called B100. Within days of starting B100 patients reported a marked improvement in sleep and pain. (B100 is an over the counter, nonproprietary supplement with 100 mg each of thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, 100 mcg each of biotin, and cyanocobalamin, and 400mcg of folate.) I was puzzled by the fact that after 2 years of vitamin D supplementation my patients appeared to be manifesting new symptoms that were improved by B vitamin supplementation. Why would they be B vitamin deficient and why would the symptoms appear two years after starting vitamin D supplementation?

Scientific literature concerning pantothenic acid deficiency ended in the 1980's when the accepted dogma became: "pantothenic acid deficiency doesn't exist because it's ubiquitous in food".(20) My patients were taking a multivitamin, why would they be deficient in any B vitamin, let alone one that was in every food? (20) An excellent 2011 review of the absorption of water soluble vitamins made a very thought provoking observation: 7/8 of the B vitamins, (not niacin) have a *colonic bacterial source and a food source*.(20) We have been taught that the B vitamins come from food, but if all of the B vitamins are made by the colonic bacteria and absorbed from the colon, then the animals that hibernate, animals that do not find food for several weeks, and animals that have not been taught the importance of a "well rounded diet" have probably always relied on their colonic bacterial source. This second supply also explains how animals have survived without the ability to make 7 chemicals that are absolutely necessary for normal cellular function; we never needed to make them because we have always carried a source within us. Could it be that my patients were B5 deficient because their colonic bacterial source was "wrong"?

What is the "right "dose of pantothenic acid for normal sleep?

If the 400 mg dose of B5 was too high and made sleep worse, but B100 made it better what dose did the brain use to sleep normally before the epidemic of the "wrong" bacteria? Though no one has measured the hourly B5 production of the "healthy foursome" of colonic species, it probably would be the "right" dose and maybe if we fixed the microbiome the sleep would normalize too. But some questions remained;

if the colonic bacterial source was wrong all along, causing my patients' IBS symptoms, why did it take two years for the B5 deficiency symptoms to appear? Also, if vitamin D deficiency caused the change in the intestinal microbiome why hadn't two years of vitamin D replacement fixed the bowel symptoms and returned the bacteria back to normal?

Vitamin D plus B100 repair the microbiome:

If the wrong microbiome was affecting my patients' health and perhaps their sleep, how could I correct it? The two available treatments; probiotics and fecal transplant both assume that we need to re-supply the "good bacteria". Many of my patients were already taking probiotics without much success. (3,4) But what if the *supply* was not the problem? Studies show that the "healthy four" bacterial species appear spontaneously in the colon of normal 3 month old children without the use of probiotics or fecal transplant. (3,4) Perhaps my patients had the "right " bacteria in small numbers but the environment of the colon did not favor their growth? Maybe there were always four specific species because as the bacteria grew side by side they excreted growth factors (vitamins), creating a sort of "B vitamin soup" that favored their growth but did not support other species? If vitamin D supplementation alone did not bring the healthy bacteria back, perhaps vitamin D plus B100 would recreate the "D and B vitamin soup" that favored the healthy four and promote their return.

In the 4th month of B100 supplementation most patients had return of sleep issues and pain, both of which disappeared immediately when the B complex was stopped. My interpretation was that after three months the dose of B5 became a combination of the oral supplementation *plus* the bacterial supply, and the increased dose caused sleep interruption similar to the 400 mg dose. This suggested that the "normal" species had grown back in three months and were supplying B5 now. Also in support of this hypothesis, the majority of patients had complete resolution of their IBS symptoms by the end of the third month, including several adults who had been constipated since childhood. Also, patients who added back B100 a second time months later, against my advice, had sleep difficulties, pain or IBS symptoms immediately. I believe that this suggests that B5 has a very narrow dose range and the amount made by the healthy intestinal bacteria is the "normal" daily dose. This also suggests that high dose B vitamin supplementation is not necessarily "good" for the normal colonic microbiome or the normal human who has not experienced prolonged periods of vitamin D deficiency. (See companion article.)

Why the epidemic change in the microbiome?

The epidemics of obesity and of the "wrong" colonic microbiome have occurred together over the last 40 years as increasing use of air-conditioning and sunscreen have produced a population with chronically low vitamin D levels. This does suggest a link between vitamin D levels and the colonic microbiome, however, the "healthy four" bacterial species did not return with just vitamin D supplementation. They appeared to need two things to grow back; "extra vitamin D" (big enough doses that all is not completely absorbed by the host and some is passed down to the intestinal bacteria) and "extra B vitamins" supplied in large dose and in a full complement of 8. I therefore hypothesize that the "healthy foursome" of colonic bacteria need both a vitamin D supply from the host and at least one B provided by other, nearby bacteria. It is important to note that I am not able to find references supporting the idea that the healthy microbiome requires vitamin D as a growth factor. However, despite our extensive knowledge of the "DNA footprints" of 100 species of colonic bacteria, only 2% of the species known to be present in the colon have ever been grown in a petri dish. (3) Perhaps using vitamin D as a growth factor for bacteria

has never been considered. Clearly microbiological experiments confirming this hypothesis will need to be performed, as will experiments supplementing just B100 for three months without vitamin D.

Health, inflammation and the intestinal microbiome:

It has become clear that certain bacteria and fungi, commensal organisms living on and in us, are not only advantageous to our health, but should actually be viewed as one of the organs of our body. (3-6, 13,14) Many of the diseases shown to be related to the abnormal microbiome have an "inflammatory" basis and range from autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease, to atherosclerotic heart disease, hypertension, and stroke. But does the "wrong" microbiome produce this pro-inflammatory state or do the two observations occur together from a shared cause? In view of the fact that normal daily cortisol production is necessary for a normal immune system, and in view of the many articles linking vitamin D to the function of the immune system I hypothesize that it is a combined deficiency of both vitamin D and B5 (and perhaps other B vitamins) that results in the pro-inflammatory state described above. (21-24) Thus, to correct the vitamin deficiencies and normalize both the sleep and the immune system the vitamin D level must be in range *and* the colonic microbiome must be normal.

Vitamin D deficiency is linked to obesity through its effect on sleep and the colonic microbiome:

Obesity is a world-wide problem in all nations where air conditioning has arrived, and it appears that vitamin D deficiency is always present where obesity and sleep disorders are common. (25-30) But vitamin D supplementation alone did not result in easy weight loss in my patients. Though there is much evidence suggesting that sleep disruption of any cause can produce weight gain, my patients only began to report weight loss once the sleep and the colonic bacteria had both returned to normal. (31-36) It is now clear that the bacteria that make up the colonic microbiome have direct effects on weight gain. Certain bacterial species, through the generation of short chain fatty acids, stimulate hunger and determine whether the calories consumed go to fat or energy production. (13,14) There would seem to be a logical survival advantage to winter weight gain at latitudes where winter food sources are few, therefore I suggest that falling winter D levels induce a change in the bacterial species resulting in weight gain into the winter. Increasing D levels in the spring bring about a return of the summer bacterial species that encourage consumed calories to go into energy production and strength.

Keeping the colonic microbiome normal:

I have made the assumption that before air-conditioning, humans who lived outside and had the normal seasonal changes in their vitamin D levels probably maintained levels from 40-90 ng/ml and the microbial species in their colon varied from a summer population to a winter population following the D level. Most patients with neurologic disorders present with vitamin D levels below 30 ng/ml and my patients who maintained vitamin D levels of 60-80 ng/ml for two years were still not able to spontaneously revert to the normal microbiome. Thus it seems likely that for the "wrong" microbiome to recur the vitamin D level would have to drop below 30 ng/ml for sustained periods again. Those studies have yet to be performed, but so far my patients who carefully monitor their vitamin D blood levels have not had return of their IBS symptoms during two years of follow up.

Conclusions:

I propose that the parallel epidemics of sleep disorders and abnormal colonic microbiome are linked to one another through vitamin D deficiency. The vitamin D that we produce by sun exposure is passed down to our colonic bacteria in the bile. They, in turn provide us with the normal daily doses of 7/8 B vitamins. Proper supplemental doses of vitamin D plus all 8 B vitamins returns the colonic microbiome to normal in three months. Reinstating the normal colonic microbiome not only cures IBS symptoms, it returns the supply of 7/8 B vitamins to their natural daily doses. Returning to restorative sleep with a normal supply of the eight building blocks of cellular repair has the potential of curing several diseases that have become epidemic in air-conditioned, sun sheltered populations over the last fifty years.

Addendum: Concerns about vitamin supplementation:

Vitamin D supplementation is now quite common and vitamin D is no longer the misunderstood "bone vitamin" that it was when our first article was published. However, five years of supplementing this hormone in over 5000 patients has made me concerned about its increasing use. Vitamin D replacement is difficult, the dosing is very individualized and the blood levels must be monitored carefully to produce an improvement in sleep and health. Vitamin D levels over 80 ng/ml can produce fibromyalgia-type pain (see companion article). The pain can begin years after beginning D supplementation as the blood levels rise slowly over years with small daily doses. Also, vitamin D supplementation, even when the blood levels are carefully maintained, has eventually produced a pain syndrome in most of my patients. (See companion article for the hypothesized mechanism.) In addition, there is abundant misinformation about "vitamin D" and the scientific nomenclature is very flawed. Ergocalciferol (D2) is a different chemical than cholecalciferol (D3), but is still called "vitamin D". Ergocalciferol is still available as a prescription and, unfortunately, still recommended as a replacement by pharmacists and physicians. Non-nocturnal mammals, birds, reptiles and insects do not make or use D2. Only nocturnal animals such as rats use D2. Ergocaliciferol is probably a more primitive form of D hormone, made by fungus. It is indeed, eaten (thus the misnomer "vitamin") by nocturnal animals who still need a D source but do not make D3 because they sleep in the day. Ergocalciferol appears to have agonist and antagonist effects at the vitamin D receptor and caused severe worsening of sleep, suggesting that it may displace whatever little D3 remains. Therefore in order to see the above described positive effects of supplementation one must pay close attention to the dosing and the type of vitamin D recommended. Also, many of my patients who started on B100 found the dose to be too high and had either diffuse pain on awakening or agitation and insomnia suggesting that B5 also has very specific dose requirements. One must understand these specifics to use the B vitamins safely. Most patients do well on either B100 or B50 for three months and correct the colonic microbiome with no side effects, but once that second source returns the B5 dose must be reduced and the amount needed in the months following is very personalized. (See companion article.)

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