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Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a "pro-inflammatory" state associated with atherosclerosis and autoimmunity

S.C. Gominak M.D.

1635 NE Fremont St., Portland, OR 97212, United States

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ABSTRACT

Study objectives: Vitamin D blood levels of 60–80 ng/ml promote normal sleep. The present study was undertaken to explore why this beneficial effect waned after 2 years as arthritic pain increased. Pantothenic acid becomes coenzyme A, a cofactor necessary for cortisol and acetylcholine production. 1950s experiments suggested a connection between pantothenic acid deficiency, autoimmune arthritis and insomnia. The B vitamins have been shown to have an *intestinal bacterial source and a food source*, suggesting that the normal intestinal microbiome may have always been the primary source of B vitamins. Review of the scientific literature shows that pantothenic acid does *not* have a natural food source, it is supplied by the normal intestinal bacteria. In order to test the hypothesis that vitamin D replacement slowly induced a secondary pantothenic acid deficiency, B100 (100 mg of all B vitamins except 100 mcg of B12 and biotin and 400 mcg of folate) was added to vitamin D supplementation.
Methods: Vitamin D and B100 were recommended to over 1000 neurology patients. Sleep characteristics, pain levels, neurologic symptoms, and bowel complaints were recorded by the author at routine appointments.
Results: Three months of vitamin D plus B100 resulted in improved sleep, reduced pain and unexpected resolution of bowel symptoms. These results suggest that the combination of vitamin D plus B100 creates an intestinal environment that favors the return of the four specific species, Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria that make up the normal human microbiome.
Hypotheses: 1) Seasonal fluctuations in vitamin D levels have normally produced changes in the intestinal microbiome that promoted weight gain in winter. Years of vitamin D deficiency, however, results in a permanently altered intestinal environment that no longer favors the "healthy foursome". 2) Humans have always had a commensal relationship with their intestinal microbiome. We supplied them vitamin D, they supplied us B vitamins. 3) The four species that make up the normal microbiome are also commensal, each excretes at least one B vitamin that the other three need but cannot make. 4) Improved sleep and more cellular repairs eventually depletes body stores of pantothenic acid, causing reduced cortisol production, increased arthritic pain and widespread "pro-inflammatory" effects on the immune system. 5) Pantothenic acid deficiency also decreases available acetylcholine, the neurotransmitter used by the parasympathetic nervous system. Unopposed, increased sympathetic tone then produces hypertension, tachycardia, atrial arrhythmias and a "hyper-adrenergic" state known to predispose to heart disease and stroke.

Introduction

Vitamin D deficiency is a global epidemic and has been linked to numerous diseases including sleep disorders [1–11]. There has been a parallel change in the human intestinal microbiome thought to be linked to the increasing incidence of obesity, hypertension, high cholesterol, autoimmune disorders, and atherosclerotic heart disease [12–17]. Recent reports documenting that 7 of the 8 B vitamins have a colonic bacterial source *and* a food source suggest that a population with the "wrong" intestinal microbiome might have unexpected B vitamin deficiencies,

E-mail address: sgominak@yahoo.com

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unrelated to food sources, that might play a role in the etiology of those diseases [18].

In 2012 we reported a successful, uncontrolled trial of vitamin D supplementation (in doses to maintain a blood level of 60–80 ng/ml) as treatment for sleep disorders [1]. This current report documents the continued treatment of the same patient population for another four years. Despite maintaining a vitamin D blood level of 60–80 ng/ml, most patients' sleep complaints began to return by the end of the second year. Because of 1950s reports of insomnia produced by pantothenic acid (B5) deficiency B100 (a non-proprietary over-the-counter B complex of 100 mg of thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, 100 mcg of cyanocobalamin, 100 mcg biotin, and 400 mcg of folic acid) was added to the vitamin D regimen [19–22]. Vitamin B5 is needed to make Coenzyme A, a metabolic cofactor used in over one hundred metabolic processes, including the production of cortisol, melatonin and acetylcholine [23–25]. Acetylcholine is a neurotransmitter responsible for our level of alertness during the day as well as the normal completion of rapid eye movement (REM) sleep at night [26–28]. The addition of B100 led to rapid improvement in sleep as well as an unexpected resolution of irritable bowel syndrome (IBS) symptoms.

Methods

Over 1000 neurology patients took part in an uncontrolled treatment trial with a regimen of vitamin D and B100 for sleep disorders. Patients with primary brain cancer, amyotrophic lateral sclerosis, or Alzheimer's disease were excluded. Occasional patients presented for primary sleep disorders such as insomnia or sleep apnea, 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 described regimen was used to improve the patient's sleep in order to improve their neurologic complaints. All patients with documented sleep apnea were encouraged to continue positive pressure masks, and patients with insomnia used a variety of sleep medications. Because of B12's known effects on sleep, all patients with B12 blood levels less than 500 ng/L were supplemented orally with 1000 mcg of B12 [29–31]. Patients also took a multivitamin that had 50–100% minimum recommended dose of all 8 B vitamins. The patients with IBS continued all probiotic supplements or medications used for those symptoms. Vitamin D supplementation was given as an individualized dose to guarantee a blood level of 60–80 ng/ml. Observations regarding the patients' neurologic symptoms, sleep habits, and IBS symptoms (abdominal pain, gas, bloating, diarrhea, constipation) were recorded by the author during regular clinical follow ups with the patients. There was no attempt to quantitate the exact number of patients with IBS symptoms, but it was estimated to be approximately one third of the population. The patients have been followed for a total of 1–6 years.

Results

Vitamin D replacement, in combination with a specific, high dose B vitamin supplementation (B100 or B50, 1/2 of B100) brought about complete resolution of all IBS symptoms in the majority of patients by the end of three months. This included many patients who had been constipated since childhood. The high dose B supplement was stopped at three months, the vitamin D level was maintained at 60–80 ng/ml, and patients observed for a maximum of three years had no return of IBS symptoms. The combination of vitamin D and B100 also brought about a rapid improvement in sleep complaints as well as a marked improvement in pain. The sleep interruption and pain usually returned if the high dose B complex was continued past four months.

Discussion

The changed intestinal microbiome

There is a pandemic of the "wrong" intestinal microbiome, the cause of which is unknown. The current treatments; probiotics and fecal transplant, are intended to provide the "missing" bacterial species but they are only partially successful [12–17]. Observations regarding the negative effects of abnormal intestinal flora go far beyond the bowel symptomatology of IBS. There are reports linking the "wrong" intestinal flora to hypertension, 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, all diseases that also have reported links to sleep disorders [3–17,31–34]. The changed intestinal microbiome has become epidemic in parallel with the epidemic of vitamin D deficiency, suggesting that they might be linked.

Vitamin D, the seasonal control of sleep and weight

The periaqueductal gray brainstem nuclei that are responsible for the timing and paralysis of sleep are heavily invested with vitamin D receptors [1,35,36]. Vitamin D is an endocrine hormone produced by sun exposure. Light of only a specific wavelength, UVB, converts cholesterol on the skin to a pre-hormone, which is then absorbed through the skin. This hormone allows adaptation 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 [1,35,36]. 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 [37–39]. Saving calories as fat also improves survival in winter, and recent studies suggest that specific bacterial species in the intestine play a role in determining whether the calories we consume go to energy production or fat storage [40,41]. Therefore, it seems logical that there would be a link between vitamin D levels and intestinal 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. It was therefore our expectation that vitamin D supplementation would improve IBS symptoms and lead to weight loss, but during two years of careful vitamin D supplementation and improved sleep, there was still no improvement in patient-reported IBS symptoms and no significant weight loss.

Pantothenic acid, sleep and pain

Improvements in sleep achieved by a vitamin D level of 60–80 ng/ml began to wane at the end of two years, and there were an increasing number of patients with new complaints of pain. References were found linking B5 deficiency to insomnia and pain in the form of a series of 1950s experiments [19–22]. Two small groups of prison inmates were tube-fed a fully synthetic B5 deficient, liquid diet. The second group was tube-fed the same diet with an additional blocker of pantothenic acid called omega

methyl pantothenic acid. Within two weeks, all subjects complained of an inability to sleep, abdominal discomfort, balance difficulties, and tingling and burning in the hands and feet [19–22].

Based on studies reporting the use of B5 for the treatment of rheumatoid arthritis the original dose of B5 that was tried was 400 mg/day [42]. That dose produced unexpected complaints of immediate agitation and insomnia in approximately 30 patients, so a lower dose, of B100 (100 mg B5) or B50 (50 mg B5) was recommended. The addition of B100 to the vitamin D regimen produced an improvement in both sleep and pain within days, suggesting that a vitamin B deficiency state had somehow been induced by the D supplementation and was now responsible for worsening sleep and pain. The patient reports of insomnia induced by the higher, 400 mg dose confirmed that B5 had a marked effect on sleep but also suggested a very narrow dose range.

The intestinal bacterial source of B vitamins

An excellent review of the production and absorption of the B vitamins states (as do most modern references) that "pantothenic acid deficiency doesn't exist because it's ubiquitous in food" [18]. But that same review makes a very thought provoking observation: 7 of the 8 B vitamins, (not niacin, which can made from tryptophan) have an intestinal bacterial source *and* a food source. If all of the B vitamins are made by the intestinal bacteria and absorbed there, then 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 always relied on their bacterial source. This second supply would also explain how animals have survived without the ability to make seven chemicals that are absolutely necessary for normal cellular function; we never had to make them because we have always carried our source within.

The B100 supplement was stopped at three months after many patients reported a return of their sleep and pain issues during the fourth or following months. This, in addition to the complete resolution of IBS symptoms by three months, suggested that the original "healthy foursome" of bacterial species had returned, and the sleep disruption was from a double dose of B5, one from the now-normal bacterial production and a second from the supplement.

Pantothenic acid deficiency due to depletion of body stores

Despite the current belief that all B vitamins are water soluble and are not stored, the majority of patients treated with vitamin D supplementation began to develop new symptoms by the end of the second year: sleep disruption, arthritic pain, new allergic symptoms of hives, rash, or diffuse itching. All symptoms cleared within days or weeks of starting B100, suggesting that they were related to a new deficiency of one or more of the B vitamins. Despite the lack of published information regarding spontaneous human B5 deficiency there are two studies showing changes in B5 urinary excretion rates in human subjects given low doses of B5 followed by high doses [43,44]. Both studies reported that the B5 blood level did not change significantly with changes in B5 dosing but that the rate of urinary excretion of B5 changed significantly. Both studies also concluded that there were "body stores of B5" and that the rate of urinary excretion was a more accurate measure of those stores than the B5 blood level. Perhaps, as the B vitamins are the building blocks of all cellular repairs, the improved sleep and increased repairs that occurred during the first two years of D supplementation eventually caused a depletion of the B5 stores. Decreased coenzyme A production in the brain due to lack of B5 could lead to decreased acetylcholine production, resulting in sleep disorders. Decreased coenzyme A in the adrenal glands might result in lower cortisol levels (adrenal fatigue) producing increased inflammation, allergy, and arthritis.

Converting the microbiome back to normal

The epidemics of obesity, sleep disorders, and the "wrong" intestinal 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 intestinal microbiome; however, based on patient-related IBS symptoms, the "healthy four" bacterial species did not return with just vitamin D. The normal microbiome appeared to need two things to grow back: "extra vitamin D" (presumably big enough doses that all is not completely absorbed by the host) and "extra B vitamins" supplied in large dose and in a full complement of 8. There are no 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 the 100 species of human intestinal bacteria, only 2% have ever been grown in a petri dish, suggesting that there may be species that have never been grown in vitro, because they require vitamin D as a trophic factor [12]. Clearly, microbiological experiments confirming this hypothesis will need to be performed, as will experiments supplementing with 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 [12–17]. 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. In view of the many articles linking vitamin D to the normal function of the immune system, and the fact that B5 is needed for the production of cortisol, it is my hypothesis that a sustained deficiency of both vitamin D and B5 result in this abnormal, pro-inflammatory state [45–48].

Obesity and the colonic microbiome

Obesity is a worldwide problem, and it appears that vitamin D deficiency is always present where obesity and sleep disorders are common [32–34]. However, vitamin D supplementation alone did not result in easy weight loss. Though there is much evidence suggesting that sleep disruption from any cause can produce weight gain, patients only began to report weight loss once the sleep and the intestinal bacteria had both returned to normal. It is now clear that the bacteria that make up the intestinal 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 [40,41]. There would be a logical survival advantage to winter weight gain at latitudes where winter food sources are few; therefore it is probable 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.

Historical mistakes regarding B5

Despite the claim that "pantothenic acid is ubiquitous in food", it is actually coenzyme A, not B5, that is ubiquitous in food, and coenzyme A must be converted to B5 to be absorbed [18,49–52]. There is one published article documenting the intestinal conversion of coenzyme A to pantothenate [53]. The conversion required

several enzymatic steps and the products of conversion; dephosphocoenzyme A, phosphopantetheine, pantetheine, and pantothenate were found in the small intestine of the live rat, so it was assumed that coenzyme A could be converted to pantothenate and absorbed. However, if the source of the converting enzymes were not the animal itself, but instead, the bacteria inhabiting the animal's intestine, then the ability to make pantothenate from coenzyme A might change with the bacterial population. More recently, it has been shown that B5 does not passively diffuse into the intestinal mucosal cells. A specific sodium dependent multivitamin transporter (SMVT) has been described and cloned [54–56]. The SMVT transports three separate vitamins: biotin, pantothenate, and alpha lipoic acid (vitamin like substance), all of which are made by the normal intestinal microbiome [18,54–56]. Each vitamin competitively inhibits the absorption of the other two, suggesting that the amount of biotin or pantothenate given as an oral supplement could significantly alter the absorption of the other two vitamins [18,54–56]. Also, B5 is a chiral molecule. The form that is biologically active for all organisms, including bacteria, is the D isomer [49,56]. Some bacterial species are able to convert coenzyme A to the D enantiomer of B5, which is then excreted and used by neighboring bacteria, as well as the human host. The S enantiomer of B5 is not transported by the SMVT, so if there were luminal enzymatic conversion of coenzyme A to a racemic mixture of equal amounts of the D and S forms of B5, half of the product made would not be biologically active [56]. In summary, there were several incorrect assumptions made in the statement "B5 deficiency does not exist because it is ubiquitous in food". Despite the ubiquitous presence of coenzyme A in food one cannot assume 1:1 conversion of coenzyme A to B5, especially in the setting of a pandemic change in the human intestinal microbiome. Also, the bacterial species in the intestine that are not able to make B5 compete with the host for the available amount of D isomer of B5, so probiotic supplementation with species such as lactobacillus that compete for the available B5 might paradoxically decrease the amount of pantothenate available for host absorption.

Once B5 is pumped into the mucosal cells of the intestine, it moves into the blood and is pumped into the brain as B5 at the choroid plexus [57]. B5 given as a supplement has profound, dose-related effects on the nervous system the day it is taken. Patients have consistently reported a difference the following morning (for better or worse) and can perceive changes in doses as small as 5 mg. If the primary source of B5 were from the food, it would imply that large changes in day-to-day food intake would produce the same effects on sleep as those observed with B5 supplement, and sleep would be very unpredictable.

Decreased acetylcholine production

The normal function of the autonomic nervous system depends on balanced activity of paired reciprocal nervous systems. The parasympathetic nervous system known by the "rest-digest" moniker uses acetylcholine to slow the heart rate, dilate the cardiac blood vessels, encourage gastrointestinal tract motility, and empty the bladder. The adrenergic, sympathetic nervous system's "fight-flight" function speeds the heart, constricts the blood vessels, and slows the GI tract [58]. If a change in the intestinal microbiome led to decreased production of B5 and the eventual depletion of B5 brain stores, there would be a reduced ability to make acetylcholine resulting in a relatively "hyper-adrenergic" state. Heart rate variability, an accepted method of measurement of autonomic function, has documented abnormally low parasympathetic tone in patients with several disorders including diabetes, sleep disorders and IBS [59–61]. A reduction in parasympathetic tone would leave the sympathetic nervous system unopposed producing hypertension, coronary artery vasoconstriction, tachycardia, atrial dysrhythmias, reduced gastrointestinal motility, gastric reflux, and poor bladder emptying, all of which are seen in the elderly as part of "normal aging" but have, more recently started to present in much younger age groups.

Future studies

What we have been taught about the biology of B5 and B5 deficiency needs to be reevaluated in the setting of these new clinical observations. More study should be given to the hourly production of the B vitamins by the normal intestinal microbiome; probably a very difficult undertaking but one that would teach us much about the "normal "doses. Since the contents of the colon are eliminated daily, it is more likely that the primary source of the B vitamins is the microbiome of the small intestine. The bacterial population of the small intestine is much harder to sample but would logically provide a much more stable, hourly, vitamin source with a much larger absorptive area. Attempts to confirm the bacterial species of the small intestine before and after the above described regimen should be undertaken. Confirmatory studies measuring cortisol levels and other measures of inflammation should be performed in patients before and after normalization of D and B vitamin levels. Because the B5 blood level does not appear to reflect the body stores of B5 better methods of assessing B5 body stores should be investigated. Because the B vitamins are so biologically intertwined it's likely that it is not just B5 that is deficient and causing increased inflammation. Studies of other B vitamin levels, especially pyridoxine, comparing before and after return of the normal microbiome would be very helpful. B12 deficiency may in some cases be related to vitamin D deficiency as well, though through a different mechanism. There are vitamin D receptors in the salivary cells that secrete haptocorrin, which binds and protects B12 during its transport through the stomach, and D receptors on the stomach cells that encourage secretion of intrinsic factor [62–64]. Some of the patients in the current study normalized their B12 levels over a period of years suggesting that vitamin D deficiency may play a role in the accompanying B12 deficiency. Further confirmatory studies following haptocorrin, intrinsic factor and B12 levels before and after the vitamin D blood levels have been normalized would be needed for confirmation.

Conclusion

I hypothesize that the parallel epidemics of abnormal sleep and abnormal intestinal microbiome are linked to one another through vitamin D deficiency. Proper supplemental doses of vitamin D plus all 8 B vitamins appears to return the intestinal microbiome to normal in three months. Reinstating the normal microbiome not only treats IBS symptoms, it returns the supply of B vitamins to their natural daily doses. The B vitamins are neither "good for us" nor "unnecessary"; they are good for the person who needs them and only until the normal source picks up again. Both sleep disruption and pain can be caused by large doses of B vitamins once the intestinal microbiome has returned to normal. The B vitamins are very biologically intertwined, both in their intestinal production and cellular use. This suggests that B vitamins, aside from B12, were not meant to be used individually. Returning to restorative sleep with a normal supply of the building blocks of cellular repair has the potential to repair the "pro-inflammatory" state seen in association with atherosclerosis as well as the "hyper-adrenergic" state associated with hypertension, heart disease and stroke. It appears that given the proper essential elements for normal sleep, the body is designed to repair every physical injury that occurs during normal daily use and may even retain a memory of long-deferred repairs. It also appears that many of the manifesta-

tions of "normal aging" have always been linked to this cascade of events and may therefore be reversible or at least prevented by careful maintenance of normal sleep into advanced age.

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