

Review Article

May Fibromyalgia be caused by Long-Standing Vitamin D Deficiency?

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Submitted: 26 October 2016

Accepted: 21 February 2017

Published: 23 February 2017

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Abstract

Fibromyalgia is a chronic disease belonging to the spectrum of fatiguing illnesses. It goes along with severe wide-spread pains, severe fatigue and many neuro-psychiatric symptoms. Personal clinical observations suggest a most probable connection between these diseases and along-standing, yet untreated vitamin D3 deficiency which becomes a chronic and may-be not fully reversible condition due to consecutive calcium and phosphate deficiency and overall mineral dysregulation.

New scientific research shows that vitamin D3 deficiency results in alteration of cellular calcium handling, and in elevated intracellular calcium level, with consecutively reduced clearance of free radicals and toxins. As a consequence, generalized and progressive signal alteration and functional instability are supposed to evolve, with slow transition to overt structural damage (co-morbidity). Cognitive, mental, immune and muscular-skeletal dysfunctions in fatiguing illnesses would fit to this hypothesis. Fibromyalgia could be viewed as a late manifestation in this process because already substantial co-morbidity exists.

The presented article is only a clinical observational study, but offers a critical dealing with still existing interpretations and prejudices. This paper tries to align my personal observations with elucidating recent bio-molecular research data.

OBJECTIVE

Fibromyalgia is a term coined 40 years ago [1]. However, the disease is supposed to be as old as human beings exist. Yet it was termed differently. Very often diagnosis of fibromyalgia is missed. Instead it is categorized as a psychiatric and/or orthopedic disease [2]. Until nowadays, fibromyalgia and chronic fatigue syndrome are still described in separated sections in medical textbooks in spite of many common overlapping symptoms, such as chronic unexplained fatigue, cognitive difficulties, sleeping disorder, concomitant depression, and widespread pains [3-7]. Whereas fibromyalgia is enlisted as a muscular-skeletal disorder, chronic fatigue syndrome is, presumably falsely, listed as a euro-psychiatric one.

The aim of this article is to compare a putative unifying disease model outlined by recent research with my personal observations. Maybe still ongoing misconceptions about fibromyalgia and related diseases will become eradicated in future.

Misconception 1: Chronic fatigue syndrome and fibromyalgia are different diseases

From the year 1990 up to 2006, I worked in my practice as

internist and psychotherapist. Thanks to spending more time by listening to the complaints of my patients, I learned a lot about functional disorders, and how my patients experienced them. I realized that psychotherapy did not really cure my patients. They only learned to handle these disorders in a better way. During the first three years in my practice, I merely searched for deficiency of iron and vitamin B12, and for thyroid disorders, if patients complained of chronic fatigue. Only in case of abnormal or borderline calcium serum levels, I also looked for parathormone because I knew from my medical textbook that both hypo- and hyperparathyroidism may induce neuro-psychiatric manifestations [8,9].

In the year 1991, I began to treat a female patient by psychotherapy. She complained of severe chronic fatigue and depression after the death of her mother. Instead of recovering by psychotherapy, she suffered from increasing fatigue, sleeping disorder, difficulty concentrating and remembering, as well as lack of drive and interest. She complained also of abdominal bloating and watery diarrhea. In the year 1993, she lost almost completely her hairs, and developed a seemingly paradoxical urticarial skin rash after the prescription of a cortisol inhaler applied because of a slightly pathologic pulmonary function test. At that time she reported to find no longer any sleep, and

obviously she forgot immediately what I just had spoken to her. Her motions became extremely restless, and her palms were covered with cold sweat. She laughed and wept for no reason at all, and complained about not feeling the respective emotion. Referral to an endocrinologist, a gastroenterologist, and an allergy specialist did not yield any useful diagnosis.

Because I suspected that this patient probably might suffer from chronic fatigue syndrome, a disease, I only knew from lay press at that time, I began preparing a referral to the university hospital. By checking her laboratory flow sheet, I realized that in 1991, serum calcium level was near the upper limit, whereas in 1993, calcium had decreased to the lowest normal level. This was the clue to the final diagnosis of secondary hyperparathyroidism due to severe vitamin D3 deficiency. Whereas the serum level of 25-hydroxyvitamin D3 (25OHD3) was initially 4 ng/ml (10nmol/ml), 25OHD3 was no longer measurable at the time of a second control in hospital. So I learned that vitamin D deficiency might induce chronic fatigue.

Fortunately, by finding the underlying cause and installing a targeted treatment, the severe fatigue, difficulty sleeping and the neuro-psychiatric symptoms disappeared promptly. After adding a magnesium, potassium and phosphate containing compound, hair loss was reversible as well. I was reluctant to prescribe a calcium compound at that time, because I assumed that milk products combined with such a high dose of colexicaliferol (10,000 IU/d initially, 250 mcg respectively) would be sufficient to restore calcium and phosphate deficits. However, she recovered not fully, and did not regain her pre-morbid intellectual performance. Concentration and stress tolerance remained diminished. She lost her job as a secretary due to her frequent spelling mistakes. One year later she complained of chronic bone and joint pains, sicca syndrome, and still of overall weakness of more moderate intensity than in the beginning of her disease. A maintenance dosage of 5,000 IU per day (125 mcg) was instituted under which 25OHD3 levels stabilized by about 50 ng/ml (125 nmol/ml). Control of serum calcium showed always normal values.

Of note, in the beginning I considered a diagnosis of depression, then chronic fatigue syndrome, and during extremely low 25OHD3 levels even a beginning psychosis, then after one year treatment fibromyalgia, and 10 years later osteoporosis. This course of disease told me that chronic fatiguing illnesses can pass over to different clinical diagnoses and that vitamin D deficiency might induce long-lasting effects. By seeing other patients with chronic fatigue who recovered by vitamin D treatment, I also learned that it can occur in distinct severities, and that it is always associated with many functional disturbances.

Misconception 2: Interpersonal conflicts and violence experiences induce fibromyalgia

The textbooks are right when pointing to a host of stressful life events preceding fibromyalgia. However, most severe stress, such as violence, neglect or abuse, could be found only in a very small minority of patients. Yet, many patients reported preceding frequent infections, often since childhood, or other chronic illnesses, frequent surgical interventions, and/or traumatic body lesions by an accident, as well as harsh life events such as early

chronic under nutrition, poverty, war affairs, or loss of a caregiver or spouse. However, these events were not generally associated with most negative emotional relationships. Many patients recalled their parents as loving and careful. Interestingly, many patients reported that their mother suffered from chronic disease as long as they could remember. On the other hand, off-springs of fibromyalgia mothers were often more severely affected than their mothers. Many off-springs developed psychiatric-like diseases with social dysfunction (no training or education, no job, no motivation) in spite of sufficiently caring parents, suggesting possible genetic or more probably, some epigenetic causal factors [10].

In contrast to patients with fibromyalgia, those with chronic fatigue syndrome and myalgicencephalopathy, mostly had not suffered from major negative preceding life events. Many of them had been very privileged due to family and educational conditions, before they got ill. But they often had overworked, or got ill after an infection, or a documented intoxication, for instance.

Misconception 3: The multiple symptoms of fatiguing illnesses make no sense

The symptoms of vitamin D deficiency and those of patients who had found out by themselves that they might suffer from chronic fatigue syndrome appeared to be identical. Both diseases showed a clear-cut pattern, demonstrating "overall functional instability" (Table 1 and 2). The dysfunctions involved all organ and regulation systems. Severity of fatigue and of dysfunctions, and also of disability appeared to correlate with each other. Therefore I began to categorize my patients grossly into putative four major disease stages which differed also with respect of reversibility after targeted treatments. Different clinical diagnoses were used in order to express the most prominent symptoms in the respective stage (Table 3). In order to learn more about vitamin D deficiency, I checked textbooks about rickets in children and osteomalacia in adults. However, both diseases seemed to be described incompletely. Bone pains, abnormal childhood sweating with hair loss, and impaired infection resistance were mentioned, but not explicitly fatigue, neither dysfunctional disease. Maybe it was not asked for, or patients assessed their symptoms as their "normal" conditions or in case of children, they might be not able to tell.

As radio-graphic evidence of pseudo-fractures and Looser's zones are late clinical events, and coexisting secondary hyperparathyroidism may confound radiological results, less objective and earlier occurring clinical symptoms such as otherwise unexplainable fatigue and dysfunctions appeared more use ful in order to suspect vitamin D3 deficiency.

Slightly affected patients were grouped into stage I. They merely suffered from so-called "idiopathic chronic fatigue". Many of them do not mention fatigue spontaneously, but they visit a doctor due to dysfunctional symptoms. Even these mildly fatigued patients show already a clear-cut pattern of disease, such as frequent infections, allergy-like manifestations, headaches, intermittent muscular discomfort, and of notice, augmented occurrence of unwanted intolerance reactions against drugs such as analgesics, antidepressants and antibiotics, or against drugs prescribed against allergies.

Table 1: Conventional view on fibromyalgia.

| Core symptoms | Main associated syndromes | Comorbidities |
|---|--|---|
| Widespread musculo-skeletal, tissue pains and tenderness ("neuropathic-like"). Increased evoked pain with or without tender points. Neuro-psychological symptoms such as chronic unexplained severe fatigue, post-exertional malaise, un refreshing sleep and other sleep disorders, cognitive dysfunction, and many more functional symptoms. Stress intolerance. | Chronic fatigue syndrome. Chronic headaches. Irritable bowel syndrome. Painful pelvic/bladder/perineal Syndrome. Temporo-mandibular disorder. Restless legs syndrome. Regional myofascial pain syndrome. | Chronic inflammatory and/or degenerative joint syndromes, such as arthritis, bursitis, tendinitis. Chronic infections, such as chronic bronchitis, borreliosis, Epstein-Barr virus infection. Chronic rheumatic diseases. Metabolic syndrome or other specified metabolic conditions. Endocrinopathies, in particular of the thyroid, and/or hyper- or hyperparathyroidism. |

Table 2: Proposed description of fibromyalgia in "short-cut" by considering more recent scientific research.

| Symptoms | Presumable pathophysiology | Proposed pathogenesis |
|--|--|--|
| Generalized "functional instability". (Pains, neuropsychiatric symptoms, and associated syndromes, all interpreted as dysfunctions). Comorbidities interpreted as slowly emerging clear-cut physical damage evolving from continuously increasing signaling alterations. | Generalized instability of signaling and phenotypic organization (53). Main affected signals: Small molecules (second messengers) such as NO, phosphate, calcium, reactive oxygen substrates (ROS), nitrated ROS (NROS), and their binding to bigger molecules affect all signaling pathways. Further-on dysregulation of: Transcription factors. Cytokines. Neurotransmitters. Hormones. Receptors. Cyclins. | Chronic vitamin D3 deficiency induces compromise of: Gene transcription (55) Cell signaling (53,54) Calcium and phosphate metabolism (55) Free radical clearing (28,53) Detoxification (28,53) Overall mineral metabolism (24,28) Reduced stress resistance (53) Many other biologic functions. (28,39,53-55,58,59-64) |

Table 3: Postulated hierarchical classification of disease course correlated to degree of disability and observed response after treating vitamin D-deficiency and mineral dysbalance.

| Proposed clinical diagnosis | Most prominent symptoms | Observed degree of disability | Observed degree of reversibility |
|--|--|---|---|
| STAGE I: Idiopathic chronic fatigue | Chronic unexplained fatigue. Non-refreshing sleep. Frequent infections. Headaches. Some dysfunctional symptoms. | < 25% - 40% Patients can still compensate by longer rest periods and avoidance of more stressful activity. | 100% |
| STAGE IIa: Chronic fatigue syndrome | Prominent and severe fatigue. Sleeping disorders. Multiple dysfunctions, more severe than in idiopathic chronic fatigue. Fatigue more prominent than pains. | > 40%, up to 75% Patients are no longer able to compensate the high degree of chronic fatigue. | Not in any case fully reversible. Reversibility mainly determined by duration and severity of symptoms. |
| STAGE IIb: Fibromyalgia | Severe pains overall. Severe fatigue in many cases. Detoxification defects, sometimes severe. Multiple dysfunctions similar to those in chronic fatigue syndrome. However more severe depressive-like symptoms. Most patients older than 40 years. More females affected than men. | 50% up to 80% | Less reversible than Chronic fatigue syndrome, mainly due to: Prominent orthopedic problems. Frequent surgical interventions. Increasing number of immunological, metabolic, degenerative, and/or endocrine comorbidities. |
| Stage III: Myalgic encephalopathy | Very prominent fatigue. Severe pains of neuropathic character. Severe detoxification defects (chemical and overall hypersensitivity, "pseudo-allergies"). Patients mostly bedridden. | 80% up to 100% | Most often not reversible. Often intolerance even against vitamin D3, multi-minerals, -vitamins, and other complementary supplements. |

| | | | |
|--|--|---|--|
| <p>Stage IV: Overt and defined somatic diseases. Neuro-psychiatric dysfunctions are accepted as disease-related in this stage.</p> | <p>Key symptoms are disease-specific. Fatigue and pains are viewed as disease-inherent. Fatigue and dysfunctional symptoms may become reduced by disease-specific treatment.</p> | <p>Severity of fatigue determines the extent of disability in most cases. Severity of fatigue seems to be associated with unfavorable disease course and drug resistance.</p> | <p>Sometimes, specific disease course can be ameliorated by vitamin D3 and multi-mineral supplement therapy.</p> |
|--|--|---|--|

More severely affected patients were grouped into stage II. They suffer from chronic muscular, mental and overall physical fatigue and weakness which interferes with work and life quality. Persistent symptoms of musculoskeletal pains, substantial sleeping disorder, multiple intolerances, overall sickness feeling, and stress intolerance with protracted occurrence of so-called "post-exertional fatigue" are present. According to the most disabling symptoms which mostly are pains or fatigue, either a diagnosis of so-called "chronic fatigue syndrome" or fibromyalgia appeared as adequate. Misclassification by physicians who do not know the course of fatiguing illnesses is supposed to occur very frequently. Isolated diagnoses such as sleeping, pain, or psychiatric disorder should be scrutinized closely by asking for additional symptoms. Debilitating fatigue and post-exertional malaise bother patients with chronic fatigue syndrome more than muscular-skeletal pains, whereas debilitating pains, mostly of neuropathic character bother patients with fibromyalgia more, although if asked for, chronic fatigue and a full array of functional symptoms usually coexist, often even with higher severity compared to patients with chronic fatigue syndrome. Wide-spread hypersensitivities and intolerance reactions, such as intolerance against sunlight, food, chemicals and drugs are common in both diseases. However, fibromyalgia is accompanied more frequently with obvious co-morbidities, such as chronic inflammatory, autoimmune or degenerative illness suggesting more ongoing tissue damage compared to chronic fatigue syndrome [5].

When treating people over years, one can observe the slow progress from chronic fatigue syndrome to fibromyalgia in most cases which might explain the substantial overlap between both diseases. Average age, co-morbidity, disability, and burden of disease appear to be much higher in patients with fibromyalgia. Frequent co-morbidities are in particular, thyroid, gynecological and joint diseases.

Patients with so-called "myalgic encephalopathy" are the most severely affected and were grouped to stage III. They share the typical symptom pattern of chronic fatigue syndrome, however all symptoms are excessively severe. Very prominent are high grade of general intolerance against food, drugs, chemicals, heat, light, noise and odors, and a most pronounced post-exertional malaise following minor activities. Diet and treatment options become extremely restricted. Many of these patients are strikingly young. Most patients are no longer able to visit the doctor and are totally bedridden. Unfortunately most physicians believe in a psychiatric origin of this most debilitating disease.

A putative stage IV seems to be reached when apparent organic disease has developed. When asking such patients about previous fatigue in their life they report very often about substantial chronic fatigue and dysfunctions for many years before outbreak of the organic disease.

Misconception 4: Treatment of deficiencies results in total recovery in any case

I began to understand that any deficiency, metabolic or endocrine disorder, as well as many hidden intoxications begin with chronic fatigue and minor depression-like and "multi-system" dysfunctional symptoms [11]. Deficiency-specific physical symptoms are supposed to be late events. However, most of those disorders are much less frequent than vitamin D3 deficiency due to western life-style.

According to my observations, people with duration of disease less than one year get symptoms of fatigue and dysfunction when 25OHD3 drop lower than 30 ng/ml (75nmol/ml). Early treatment showed complete reversibility in these cases. So I guessed that it should be an "optimal level" [12,13]. 25OHD3 levels between 15–30 ng/ml (50 - 75 nmol/ml) might indicate insufficiency, whereas those of lower than 15 ng/ml (37 nmol/ml) might indicate clear-cut deficiency. Symptoms are severe enough to compromise health quality substantially. If physicians take these symptoms not for serious they put their patients at risk to progress to more severe stages in which the correlation between 25OHD3 level and disease severity becomes less tight and reversibility more difficult to achieve.

Some authors argue that measuring vitamin D3 levels mirrors not necessarily what is going on in the body as, for instance, short-term sun bathing could elevate the level thus pretending a sufficient vitamin D status [14,15]. Indeed, it is true that laboratory results will undulate according to the season. And it is also true that all severely affected patients show very low levels due to their disabilities which keep them house-bound. However, without monitoring vitamin D levels, I would have missed this putative biomarker for fatiguing illnesses, and it would have been nearly impossible to convince the patients that a targeted therapy is indicated. In addition, I would not have learned that a colecalciferol dose of at least 4,000 IU (100 mcg) per day seemed to be necessary to maintain a symptom-free condition in already recovered patients. This dosage corresponded to an average 25OHD3 level of more than 30 ng/ml (75 nmol/ml). Also, I would not have found out that patients with high severity and long duration suffer from more or less vitamin D resistance. Rise of 25OHD3 is no longer associated with clear-cut recovery in these patients, as could be observed in stage I.

Thus, my own observations are in clear contrast to the opinion that low vitamin D levels might be merely "a confounding biological interplay" [16], and a useless "misapplication" causing "escalating health care costs" [17]. One has to interpret the test results by considering life style, season time, duration and course of disease. I learned not to control 25OHD3 during the first year, except when there was no response at all. After one year of substitution, most patients showed 25OHD3 levels about 100

ng/ml (250 nmol/ml). If patients did not yet reach this value, I treated for a more prolonged time with 10,000 IU (250 mcg) colecalciferol because this serum level seemed to be correlated to maximal response. Maintenance therapy was done with 5,000 or 4,000 IU (125 or 100 mcg) colecalciferol. One additional control under this regimen showed mostly serum levels between 30-50 ng/ml (75-125 nmol/l) when investigated during sun-deficient months. It is true that in case of stable health, no further tests should be done under life-long substitution [15]. Only if life events promise more availability of sun, substitution should be discontinued, such as during vacation in sunny regions.

Though vitamin D3 insufficiency or deficiency appears to be the most frequent event, other more infrequent deficiencies are worth to check, in particular if no or only minor recovery can be achieved. Unfortunately, many deficiencies cannot be diagnosed for sure.

Though I did not observe obvious iron deficiency anemia in my patients who usually had gone through multiple former health checks, I found somewhat low ferritin levels between 25-50 ng/ml very frequently. Iron substitution did not show big effect with respect to fatigue reduction, and levels dropped whenever substitution was discontinued. My hypothesis was that there might be some metabolic blockade against higher iron storage, a condition which seemed to persist instead of vitamin D treatment.

The same could be observed in case of vitamin B12 substitutions. Patients with low normal serum levels showed only limited response by oral or parenteral high dose substitution and some reported unwanted weight gain, where as those with clearly diminished B12 showed a better response though they needed concomitant vitamin D therapy as well.

Oral folic acid and vitamin B6 seemed to have slightly positive additional effects in some patients though serum vitamin levels and homocysteine did not indicate overt deficiencies. Oral substitution of a mixture of B vitamins appeared to be ineffective, maybe due to the low dosages provided in these compounds. One patient reported to feel less depressed after ingesting 15 mg folic acid/day, and one by ingesting 100 mg riboflavin/day. Both showed lowered serum levels of the respective vitamin before treatment. Two of my patients felt less fatigued when ingesting 2 g levo-carnitine per day.

If patients could afford to buy Q10 drops I encouraged them for a while to test the effects because I hoped to see a positive additive effect. However, I did not see any response. Meanwhile some papers report a favorable response to Q10 [18,19] or B12 and folic acid substitution [20] in fibromyalgia patients. My failing response to Q10 might have been caused by too low doses or by some lack of manufacturing quality. And I did not treat patients with a parenteral mixture of B12, folic acid and B6 which maybe would have been more effective.

One interesting paper reports about a positive effect by treating with metformin and caloric restriction [21]. This regimen activated adenosine-monophosphate kinase [AMPK]-dependent restoration of mitochondrial dysfunctions in fibroblasts from fibromyalgia patients. Interestingly, vitamin D3 and elevated intracellular calcium are reported to activate AMPK as well

[22], and vitamin D3 and metformin are reported to potentiate growth inhibition of prostate cancer cells, an effect mediated by an AMPK/mTOR signaling pathway [23].

Spoken in general, I was rather reluctant to treat with isolated vitamins or other supplements if not clearly proved by laboratory results, because a healthy diet should contain all necessary components for health, except vitamin D3 which is mostly incorporated by means of UVB-radiation. Western food, low sunlight availability due to latitude, life-style, burden of working hours and sun protection are the main causes for the so-called "pandemic. Indeed, vitamin D deficiency seems to be a most probable "every-day condition". The same is true for calcium intake. Ingestion of 1200 mg elementary calcium is not easily achieved, and many patients do not like or tolerate milk products.

I treated less symptomatic patients with induction doses of 5,000 IU (125 mcg), and those with severe symptoms with 10,000 IU (250 mcg) colecalciferol per day. Vitamin D3 levels did rise, after months of treatment. Those treated with 5,000 IU (125 mcg) reached a plateau of about 50 ng/ml (125 nmol/ml), and those treated with 10,000 IU (250 mcg) about 100 ng/ml (250 nmol/L). In addition, I detected that patients, substituted with multi-minerals, containing citrate, carbonate and phosphate salts of calcium, magnesium, sodium, zinc, copper, sodium molybdate, chromium chloride, and sodium selenite showed a better response to colecalciferol than those who were not substituted. Some patients who were very ill and could not afford the expense, I treated only with calcium carbonate, magnesium citrate and sodium-hydrogen phosphate powder. When taken in a high amount (3 x 2 teaspoons per day) symptoms ameliorated as well.

However, a minority of patients did not recover. One cause of treatment failure is supposed to origin from my former ignorance about the probably high impact of concomitant calcium and phosphate deficiency which is supposed to be a major cause for vitamin D resistance [24,25].

Meanwhile I speculate if my first patient would have done better, if calcium and phosphate would have been substituted from the very beginning. Maybe, fibromyalgia and osteoporosis would have been prevented [26,27]. At that early time of my detection, I feared too much to induce extra-osseous calcification. I did not yet know that adequate calcium, phosphate and vitamin D3 will counteract extra-osseous calcification [28-30].

In children and adults, chronic fatigue syndrome was fully reversible, if disease duration was less than one year, in particular if the grade of fatigue was not yet maximal. Even children with clinical signs of prominent fatigue and apparent monarthritits, though without inflammatory laboratory evidence, were able to recover completely.

Adult patients with more pronounced symptoms of chronic fatigue syndrome, and longer overall disease duration, had mixed treatment results. Most patients recovered substantially, after one to three years of treatment. But some few patients, in particular those who showed borderline low serum calcium levels, paradoxically combined with inadequately high urinary calcium loss, did not recover at all. A small trend of amelioration could be achieved by adding 1,000 mg calcium per day to the

regimen, later-on. Viewed retrospectively, I suspect that some sort of parathormone resistance due to calcium and phosphate depletion might have played a role and might have induced hypercalciuria [27]. They probably would have needed additional vitamin K substitution, because vitamin K is described to prevent renal calcium loss [31,32].

As I supposed that long disease duration might reduce treatment results, I did not expect that patients with fibromyalgia would take much profit, because many reported lifelong symptoms. However, to my surprise, they reported substantial, though partial, relief of pains and general weakness after one year of treatment with doses of vitamin D3 up to 10,000 IU (250 mcg) per day and ingesting calcium-rich diet. If patients could afford the expense, they combined this regimen with multi-minerals. They usually reported: "Now I can live with my pains. They are now tolerable." Some patients recalled that they had been treated as a child with 10,000 IU (250 mcg) colecalciferol per day. Thus they seemed to have been treated exactly with the same amount which I estimated as upper safe treatment dose in adults.

In sharp contrast to fibromyalgia patients, the few patients seen with myalgic encephalopathy seemed to be resistant and intolerant against vitamin D3 and a multi-mineral therapy. Severe phosphate deficiency which is described to elicit multiple intolerance reactions, such as against lactose and fructose, probably contributed to treatment resistance [25,33]. However, I was very reluctant to add phosphate because I had knowledge about phosphate toxicity, but not yet enough knowledge about phosphate regulation and deficiency.

In summary, vitamin D deficiency is supposed to be not fully reversible in any case. It may leave its persistent mark on a patient. Age, disease duration and severity are presumed to affect the clinical outcome. But further studies about potential further metabolic effectors are warranted.

Misconception 5: The actually recommended therapies are sufficient and efficient

Psychotherapy, physiotherapy, psycho-pharmaceuticals and symptom-targeted interventions are usually recommended in case of fibromyalgia and other fatiguing illnesses [1,6]. Because they are all targeted against symptoms, not against a potential cause, therapeutic success is assumed to remain restricted.

Cognitive and behavioral psychotherapy can be supportive if the therapist tries to understand and respect the patient's history and to acknowledge the really existing disabilities [34]. The underlying hypothesis of psychotherapy is that patients overrate their symptoms, and that they should become encouraged to neglect their sickness feelings. This approach ignores that the patient suffers from a "real" disease, and that he is unable to overcome his substantial energy and functional deficit by effort. That is why pacing is supposed to be not really effective. Disease aggravation results when the individual's energy reserves become exhausted. This symptom is called post-exertional malaise [35-37]. I myself was not able to notice overrating and pretending of symptoms, or any gain of illness. Instead, patients seemed to long for recovery, or at least, for reduction of symptoms.

In particular, physical therapy can help slightly against

fibromyalgia pains, when applied wisely. Like the psychotherapist, the physiotherapist has to respect the reduced energy reserves of these patients. Patients usually are unable to take profit of active training because they are unable to augment their physical power. The neuropathic-like or mixed pains are limiting as well [3,5,7,38]. But some passive treatments may alleviate muscle and overall tissue tenderness for a short period. Warmth and to my surprise, also cold chambers were usually quite well tolerated.

Psycho-pharmaceuticals can alleviate pains and sleeping disorders. Yet drugs which induce somnolence will augment the pre-existing functional disability. Therefore these drugs should be applied only in the lowest effective doses. According to my experience patients tolerate only minor drug dosages. One possible explanation may be that vitamin D deficiency results in reduced gene expression of drug-metabolizing enzyme CYP3A4 which is most important for drug processing and detoxification [39].

At present only balanced serotonin-norepinephrine re-uptake inhibitors (amitryptiline, duloxetine, milnaciprane) and ligands of the alpha-2-delta subunit of voltage gated calcium channels (gabapentin, pregabalin) promise some pain relief [40,41]. Unwanted sedation, drug tolerance, even dependence, and other side effects may limit their long-term use [42-44].

Though amitryptiline is an "old drug", the long experience with the drug and the availability of very low doses seems to be favorable [45]. If only a maximum dose of 25 mg is ingested early in the evening, it will be tolerated even by very drug-sensitive patients according to my observations. This minor dosage, and the specific timing of intake, will reduce the excessive morning fatigue which is caused due to its long half-time. Newer, more recently developed drugs are not always available in minor dosages. On the other hand, anti-depressive drugs which are believed not to induce drug-related fatigue are reported to induce more suicidal and paradoxical effects, at least according to some authors [46,47].

Use of non-steroidal anti-inflammatory drugs and corticosteroids cannot be recommended in general due to the special pain character in fibromyalgia. Furthermore, these drugs favor gastric discomfort. Subsequent treatment with proton pump inhibitors put at risk for unwanted reduced enteral calcium absorption due to the augmented pH of gastric juice [48]. Thus long-term use should be discouraged.

In contrast to all these symptomatic treatments, correction of vitamin D deficiency would be part of a putatively causal therapy which is supposed to be well comprehensive. Yet one should consider that long-standing vitamin D deficiency will induce bone loss which implicates loss of all minerals and micro minerals which are stored in bone, and also loss of bases, such as citrate, carbonate and phosphate. Repletion of bone stores might be important for therapeutic success, as well.

This treatment regimen is not too much expensive and is well tolerated by many patients. Higher doses, such as 5,000 (125 mcg) up to 10,000 IU (250 mcg) colecalciferol per day, combined with up to 1,000 mg calcium, were well tolerated and not associated with unwanted side effects, according to my own observations. These colecalciferol doses are in line with more

recent publications [49,50]. Addition of up to 1200 mg calcium did not induce hypercalcemia or hypercalciuria, even when augmenting colecalciferol dosage beyond 10,000 IU (250 mcg). Treatments were observed for months, up to a maximal time of 52 weeks [38,51,52]. According to my own personal experience, doses higher than 10,000 IU (250 mcg) per day were not tolerated without some side effects, such as tachycardia, severe headaches or bone pains. At present, and to my best knowledge, no studies using pharmacologic doses of colecalciferol for more than one year and also no studies about combination with multi-minerals are published.

Misconception 6: Fibromyalgia is an unexplained disease

My presented observations have to be aligned with more recent vitamin D research results (Table 4).

It is well known, that vitamin D, in its activated biochemical form (1,25-dihydroxyvitamin D3 [1,25] (OH)2D3)), controls calcium and phosphate metabolism by acting on bone, muscle, bowel, and kidney [53-58]. Less well-known are the multiple

effects on cells in immune [58,59] and nervous system [29,53,55], and on cells and their functions in organs such as pancreas, heart muscle, endocrine glands, and other organs and tissues [28, 55,56,60, 61].

1,25 (OH) 2D3 is a transcription factor, comparable to steroid hormones, such as estrogen, cortisol, or thyroid hormone. Like other transcription factors, it regulates and modulates multiple gene expressions, hence, multiple functional systems, and contributes to overall homeostasis, stress resistance and "phenotypic stability" [28,53,54,60].

Gene expression of calcium transporters and calcium binding proteins, cell-cycle proteins, DNA-demethylases and histone-acetylases, some anti-oxidative enzymes, and the detoxifying enzymes Cyp3A4 and p-glycoprotein are positively regulated by 1,25 (OH)2D3 [53]. In addition, vitamin D3 induces gene expression of important key transcription factors, such as Nrf2 and FOXO which are strongly engaged in anti-oxidation defense, detoxification, and stress resistance [28,53].

Most importantly, vitamin D supports calcium entry into cells, on the one hand, but on the other hand, prevents cytosolic

| Main bio-molecular effects | Main patho-physiologic consequences |
|---|---|
| Reduced cathelicidin expression (28,53,55,56,58,59) Impaired autophagy (55,56,58,63) | Defective clearance of pathogens and cell debris resulting in latent, persistent, or chronic infection/ inflammation, tissue degeneration, autoimmunity. |
| Reduced anti-inflammation and augmented pro-inflammation (53,56,58-60) | Chronic inflammation. Sickness-behavior. |
| Reduced gene expression of calcium transporting proteins (53,55,56) | Reduced enteral uptake of calcium and phosphate. Reduced renal re-absorption of calcium. Parathormone rise due to calcium deficiency. Parathormone-induced phosphate deficiency. Reduced bone mineralization due to calcium and phosphate deficiency. |
| Reduced expression of membrane calcium ATPase (53,55) | Cytosolic calcium overload. |
| Reduced regulation of cytosolic calcium entry (27,29, 53,54) | Cytosolic calcium overload. |
| Reduced gene expression of calcium binding proteins (53,55) | Elevated ratio of free to bound calcium in cytosol and in organelles affecting cell functions and cell signaling. |
| Reduced Nrf 2 gene expression (28,53,54) | Reduced clearance of free radicals results in signal alteration, hypersensitivity and membrane damage. Membrane damage causes "calcium leak". Vicious mutual augmentation of elevated free calcium and free radicals. Impaired detoxification. |
| Reduced FOXO gene expression (28,53) | Reduced overall stress intolerance. Reduced gene expression of Fos and Jun, resulting in decreased gene expression of vitamin D receptor and retinoid X receptor, which both mediate vitamin D's transcriptional activity. |
| Reduced alpha-Klotho gene expression (24,28-30,53,60) | Disturbed mineral regulation and augmented renal calcium loss. Extra-osseous calcification. Reduced antioxidant reserve. Altered signal pathways: derepression of phospho-inositide kinase3/AKT/mTOR. Alteration in p23/p21, cyclic AMP and protein kinase C signaling. |
| Reduced gene induction of histon-acetylases and DNA-demethylases (28,53) | Altered gene expression due to epigenetic modification. Alterations become inheritable ("gene imprinting"). |
| Non-genomic actions (58,61) | Rapidly acting alterations of pathway activities (phospholipase C, phospholipase A2, phosphatidyl-inositol-3 kinase, p21ras, Scr, proteinkinase A, proteinkinase C, mitogen-activated protein kinase, Ca-calmodulin kinase II). Alteration of second messenger signals (Ca2+, cyclic AMP, fatty acids, 3-phospho-inositides). Altered opening of calcium-and chloride channels. |

calcium overload [28,54]. This is managed by down-regulating of voltage-gated calcium channels, by reducing calcium release from the endoplasmic reticulum, and by enhanced gene expression of membrane calcium-ATPase which transports calcium out of the cell, by an energy-dependent process [28,53,55].

A so-called “anti-aging” protein, named alpha-klotho, is induced by vitamin D3. It protects against vitamin D-toxicity by counteracting both calcium and phosphate overload via renal effects on tubular transporters, and by counteracting extra-osseous calcification [28,53,55,60]. Of importance, alpha Klotho regulates many ion channels, supports anti-oxidation and detoxification besides many further modulatory effects on cell function and signaling [28-30,53].

Other counteracting vitamin D-dependent gene products, such as FGF23 and calcium-sensing receptor, are also important for regulation of the “bone-energy-metabolism-axis” [24,28,53,55].

The effects of vitamin D are not restricted to modified gene expression. Rapidly elicited non-genomic actions of 1,25 (OH)2D3 modulate cell signaling and functions, as well, thus further augmenting the complexity of biologic effects [61-63].

The proposed model would imply that untreated vitamin D deficiency compromises cell signaling and intracellular regulation of free calcium which is a key second messenger. Due to uncontrolled inflow of extracellular free calcium and deficient binding of calcium to calcium binding proteins in cytoplasm and cell organelles, free intracellular levels are supposed to rise which is followed by reduced clearance of free radicals [28,53]. In turn, elevation of free radicals damage cell and organelle membranes. They become leaky, resulting in further rise of free intracellular calcium. A self-perpetuating vicious cycle is supposed to be initiated which would explain the observed relentless disease progression from early signal alteration to late oxidative damage of membranes and cell organelles [28,53]. Functions of membrane channels, transporters, exchangers and many membrane receptors are supposed to be affected by membrane damage [53]. Since ATP is generated in mitochondria at the price of elevated ROS production, reduced ATP production could be viewed as a useful and protective counter-regulatory effect. However, endoplasmic reticulum is supposed to develop defective protein folding and induction of endoplasmic reticulum stress response due to reduced calcium binding by effect or proteins [64].

CONCLUSIONS

Postulating a multi-system involvement and a hierarchical disease course which is likely to occur in vitamin D deficiency may open a much better approach to fatiguing diseases. Other pathological conditions might elicit a rather similar scenario, yet frequently occurring causes will dominate over rare events. That is why vitamin D3 deficiency and resulting mineral disturbance might be a major cause for hitherto unexplained diseases. Fatigue, wide-spread pains, overall dysfunctional disease with hypersensitivities and intolerance reactions, paradox sleeping disorder, and the enigmatic symptom of post-exertional malaise would become explainable by elevation of cytosolic free calcium and free radicals, and by consecutive stress responses of closely interacting cell organelles, such as

mitochondria and endoplasmic reticulum. Disease induction by means of severe and unfavorable life conditions, but also high engagement in duties and interests, and also home-bound and shift work would become explainable as well. Reflecting the slow transition from altered cell signaling (causing dysfunction) to cellular and tissue damage (causing overt physical disease) would explain why fibromyalgia presents with substantial co-morbidity.

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Cite this article

Hoeck AD (2017) May Fibromyalgia be caused by Long-Standing Vitamin D Deficiency? *J Chronic Dis Manag* 2(1): 1007.