

Vitamin D deficiency results in chronic fatigue and multi-system symptoms

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Initially, all metabolic disorders cause nonspecific symptoms combined with fatigue

It was in 1993, when I detected, that not only such common metabolic disorders, like thyroid diseases, iron and vitamin B12 deficiencies, cause nonspecific symptoms like chronic fatigue and functional disorders, but as well vitamin D deficiency (1). Not only these symptoms could be observed in vitamin D deficiency, but as well frequent infections, allergies and widespread intolerances, pains, sleep disorder, mood and personality changes (1,2).

In these early days, I found out an optimal treatment dose of 5,000 – 10,000 IU (125-250 mcg) cholecalciferol by dose-response trials (2). Initially, I hesitated to combine such high doses with calcium, because of potential hypercalcemia and hypercalciuria. But addition of a base powder, containing multi-minerals, and calcium as well, seemed to optimize treatment results (2).

The striking resemblance between the symptoms of vitamin D deficiency and chronic fatigue syndrome (CFS/ME), as well as the low levels of the meanwhile accepted biomarker for vitamin D deficiency, 25-hydroxyvitamin D₃, which is named as well 25-hydroxycholecalciferol (25OHD₃), induced me to treat CFS/ME patients with cholecalciferol (vitamin D₃). However, though patients with mere chronic fatigue recovered soon, most with full-blown CFS/ME did not respond remarkably to treatment. In particular patients with calcium serum levels near the lowest or highest normal range seemed to be the most vitamin D resistant (2).

When I realized that combination with calcium is mandatory for treatment response, I substituted with 500 to 1,000 mg elementary calcium per day, which might have been, in retrospective view, a perhaps too low dose for assumed severe calcium deficiency following chronic vitamin D deficiency (3-10).

Vitamin D deficiency is a hidden disorder of high frequency

Vitamin D deficiency is by no means rare (3,11-15). In particular, highly gifted and engaged people working most of time indoors, but as well poor and socially deprived people are at high risk, due to their common problem, the lack of sunlight.

Vitamin D insufficiency, showing 25OHD3 levels from 20-30 ng/ml (50-80 nmol/L) even in summer time, is quite common, but already entailing the threat of chronic depletion of body calcium stores, and chronic infections (11-14). Levels from 10-20 ng/ml (25-50 nmol/L) are measured frequently in winter season. This aggravates calcium deficiency substantially.

Severe vitamin D deficiency with levels below 10 ng/ml (25 nmol/L) causes severe fatigue and personality changes, depression-like symptoms, chronic sleep disorder, multiple intolerances, obvious immune dysfunctions and in the long time, multi-system symptoms and multi-system diseases (1,2).

Vitamin D deficiency leads inevitably to calcium and other mineral deficiencies

Long lasting or chronically repeated 25OHD3 levels beneath 30 ng/ml (80nmol/L) result in compromised calcium absorption in the bowel, and inefficient fixation of calcium and phosphate, as well as all other minerals, stored in bone (4-10). This means, chronic vitamin D deficiency can not be separated from the clinical consequences of calcium and phosphate, and overall mineral and base deficiency (11-15).

Due to lowered body stores of calcium, a special “calcium rescue-hormone”, synthesized in little glands (parathyroidea) positioned very closely (“para”) to the thyroid, augments its production and secretion. This hormone is called parathormone (PTH) (5,7,8,10).

PTH enhances calcium absorption in the bowel and tubular calcium “re-uptake” (re-absorption) in the kidney (5,7). Thus PTH helps to compensate for net calcium deficiency. However, PTH mobilizes as well bone calcium stores thus acting as a so-called “osteolytic” hormone (5,7). That means, at the costs of bone calcium, PTH tries to normalize appropriate serum levels of calcium which are mandatory for proper neural and general cellular function (5,7,8,10,14).

If enough stores of 25OHD3 and calcium circulate in blood, PTH levels are undulating with peaks and troughs. In case of low stores, in contrast, PTH will be constantly elevated. As PTH enhances the conversion from the pro-hormone 25OHD3 to the more metabolically active hormone 1,25-dihydroxycholecalciferol [1,25(OH)₂D₃] (5,7,8), the latter will also be constantly elevated, as long as any 25OHD3 will be available. Due to the high conversion

rate, 25OHD₃ stores become depleted more quickly. Moreover, depleted stores compromise a constant rate of conversion. It is important to realize that a persistent elevation of PTH and low stores of 25OHD₃ are no healthy conditions, and disturb profoundly cell functions and metabolism. Normally, 1,25(OH)₂D₃ is converted only when the cell needs it. Furthermore, persistent elevation of PTH augments constantly the relation of free to protein-bound calcium in the cells (3-15). This as well is detrimental for cells, finally causing multisystem diseases (3-15).

The multiple actions of vitamin D become more and more acknowledged in research

Besides the classical and well known actions on bone, gut and kidney, most tissues possess nuclear vitamin D receptors (11,12,15-18,20). More than 200 genes are now known to be influenced by vitamin D (11,12). Besides these actions on gene expression, it acts as well on cell signalling by multiple mechanisms (8,15,19,20). Many common and frequent diseases, like heart problems, diabetes, hypertension, Parkinson's disease, multiple sclerosis, and colon, prostate and breast cancer, as well as chronic inflammatory and autoimmune diseases, are now discussed as co-induced by vitamin D deficiency (8,21-34). This points to the impact of vitamin D deficiency and vitamin D resistance for the general population (8,21-34), and to the importance to substitute vitamin D and calcium in many chronic health problems (21-34).

In particular, immune system takes profit from treatment (22-30). Vitamin D supports the primary (innate) immune answer strongly (22-27), but regulates, modifies and mitigates the secondary (cognate) immune answer (22,26-29), and inhibits the nuclear factor kappa-B (NF-KB) which is an important pro-inflammatory switch signal in cells (30), thus preventing chronic inflammation and autoimmunity by multiple mechanisms (22-30). Meanwhile, recent new research about immune regulatory cells elucidates more clearly the connection between chronic fatigue and chronic inflammation (35). These insights fit very well to already existing results of vitamin D research (22).

Chronic fatigue syndrome, a condition of vitamin D resistance?

As sufficient stores of vitamin D and calcium are mandatory for general health (8-15), CFS/ME as a severe health problem, accompanied by immune dysfunctions and high grade disability, should be focussed as well (11), though not yet broadly discussed in literature (3). In case of chronic disease, lifetime-stabilization of seasonal fluctuations of vitamin D level will enhance calcium absorption (11,12); calcium substitution will restore already existing calcium body deficits (5,8,11,12), thus reducing high turnover of vitamin D (8,38,39) and vitamin D resistance (8,38,39).

Vitamin D de- or insufficiency can be easily identified by serum 25OHD3 levels. However, it is difficult to prove chronic calcium deficiency by serum measurements. The well known osteolytic actions of parathormone and inflammatory cytokines result in misleading rise of serum calcium levels obscuring the real whole body calcium deficits (4-6,14).

Furthermore, it must be kept in mind that both calcium deficits (36) and high oxidative-nitrosative stress (37) result in altered protein shapes (secondary structure) which highly compromise enzymatic and other biologic functions. Both mechanisms may substantially contribute to the observed vitamin D resistance of patients with CFS/ME.

In order to overcome this resistance, substitution doses should be high enough. 25OHD3 levels should be higher than 40 ng/ml (100 nmol/L) (13,38). As ergocalciferol is less potent, but nevertheless raises 25OHD3 levels, cholecalciferol would be the preferred compound, if locally available (9). At least 2,000 IE (50 mcg) cholecalciferol, but often higher doses up to 10,000 IE (250 mcg) per day, are necessary (38,39). The daily amount of calcium should be at least 1200 mg, given 3-4 times a day, in divided single doses between 300 - 600 mg (5,8). Calcium needs in severe diseases are reported to be as high as 2400 mg per day (5,8,10,39).

Last, but not least, it should be mentioned that cholecalciferol as chemical derivative of cholesterol is an important antioxidant (40), and is able to restore redox balance (36). Both actions are supposed to be of additional usefulness in CFS/ME.

Summary

Physicians should realize that chronic fatigue is not a primary mental disease. Vitamin D de- or insufficiency seems to be the most frequent cause. If untreated, calcium depletion and vitamin D resistance, presumably further deficiencies, and for instance, chronic fatigue syndrome will develop, later on followed by other more obvious diseases. Vitamin D resistance of chronic fatigue syndrome should be treated with much higher doses of vitamin D and calcium, than applied in osteoporosis prophylaxis.

Clinical high quality studies would be helpful to get an overview which doses of calcium and vitamin D will be optimal and appropriate in CFS/ME, and reveal the rate of treatment responses. Possibly, further micronutrient co-medications will be necessary in severe cases of CFS/ME.

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