

## Role of phosphate dysmetabolism in the pathogenesis of chronic fatigue syndrome

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### Abstract

Oxidative phosphorylation is a fundamental process of brain energy metabolism. It provides nearly all of the ATP used then in multiple phosphorylation cycles, including glucose phosphorylation. Moderate (40%) efficiency of the glucose-ATP cycle requires a continuous extracellular supply of phosphates which deficiency is manifested as chronic fatigue syndrome. In this minireview, I present the potential causes of phosphate dysmetabolism in brain disorders resulting in all spectrum symptoms of chronic fatigue syndrome.

### Keywords

Chronic fatigue syndrome; Phosphate metabolism; Myalgic encephalomyelitis.

### Case Report

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease characterized by profound fatigue, cognitive dysfunction, sleep abnormalities, autonomic manifestations, pain, and other symptoms that are made worse by an exertion of any sort [1-3]. The global prevalence of ME/CFS ranges between 0.4 and 2.5% and it predominantly affects young adults between the ages of 20 to 40 years, with a higher proportion of females affected compared to males [1]. It is a heterogeneous condition of unknown etiology and there are currently no therapies or medications approved to treat the cause of the illness [1,3]. Chronic fatigue is a common symptom of neurological and metabolic diseases that cause failure to activate and sustain motor behavior [4]. The neural correlates of fatigue are dysfunction in the central, peripheral, and autonomic nervous systems, particularly in the basal ganglia, thalamus, limbic system, and higher cortical centers [3]. Such a broad spectrum of physiological, cognitive, and affective changes makes the diagnosis of ME/CFS particularly complicated. Full clarification of the mechanisms underlying ME/CFS is essential for the development of preventive and therapeutic methods for this syndrome. One of the proposed pathomechanisms is energy metabolism deficiency. This claim is strongly supported by observed reduced levels of glucose and two major energy molecules, ADP and ATP in ME/CFS [1]. These results, in turn, allow concluding that energy dysmetabolism and related fatigue symptoms may result from phosphate homeostasis disorders.

Phosphate has important functions in the body and several mechanisms have evolved to regulate phosphate balance including vitamin D, parathyroid hormone, and phosphatonins such as fibroblast growth factor-23 (FGF23) [5]. FGF23 is expressed and secreted predominantly by bone osteoblasts and endothelial cells surrounding venous sinusoids in the bone marrow [6]. Its main task is the reduction of circulating phosphate levels. The excess of FGF23 may have pathological effects due to intracellular depletion of phosphate which in turn leads to a decrease in energy metabolites such as ATP in neurons and 2,3-bisphosphoglycerate (2,3DPG) in blood red cells [5]. The observed symptoms of fatigue are the brain's reactions to the deficient metabolic processes, and especially to the decline of energy metabolism relying mainly on glucose and oxygen supply [7]. Here the main suspect is phosphate which participates in all processes of protein phosphorylation while in the brain acts as a 'metabolic booster'. On the cellular level, the uninterrupted process of glucose phosphorylation, tuned by neuronal activity, allows utilizing a controlled glucose stream as an energy fuel in the process of cellular respiration [7]. The products of respiration, especially CO<sub>2</sub>, control in turn phosphate activity boosting the cellular metabolic cycles. In the brain, each massive disturbance of the cellular life cycle is signalized as fatigue [4].

Intensive brain and muscular activity result also in a rapid decrease in serum phosphate due to its intensive use for sustaining high cellular metabolism. Phosphate deficiency due to FGF-dependent hypophosphatemia is unable to meet the metabolic needs of the brain, resulting in a permanent feeling of fatigue. Hypophosphatemia can also be evoked by increased blood glucose levels and respiratory alkalosis, two substrates vital for cellular metabolism [5]. It results in intracellular depletion of phosphate which in turn leads to a decrease in metabolites such as ATP and 2,3DPG. This causes the mitochondrial production of ATP from ADP and a consequent increase in AMP which additionally disturbs cellular energy metabolism. Chronic hypophosphatemia was shown to cause respiratory muscle weakness, respiratory deficiency, and even rhabdomyolysis [5]. All these taken together contribute to extreme susceptibility to fatigue. Importantly, ME/CFS patients also typically present disorders of the immune system characterized by tender lymph nodes. Such symptoms suggest the leading pathogenic impact of increased FGF23 expression in the thymus and lymph nodes e.g., as a result of the previous viral infection and/or its treatment [2].

The maintenance of phosphate homeostasis plays an important role in the brain and muscles. Blood circulating active form of vitamin D has a major role in the simultaneous control of calcium and phosphate concentration and storing them in bones [5]. On this level, the FGF23 downregulates serum phosphate concentration by reducing renal phosphate reabsorption [5]. In physiological conditions, FGF23 is mostly secreted by osteoblasts, however, what seems the most relevant for the pathogenesis of the ME/CFS, FGF23 can be also secreted in the thymus and lymph nodes, which excessively decreases levels of phosphate [5].

## Conclusion

Concluding, the up-to-date knowledge allows us to point out the most probable cause of chronic fatigue, and taking into account fact that the large doses of vitamin D may safely restore serum phosphate levels by increasing its intestinal absorption, we can undertake the very first attempts to cure ME/CFS.

**Conflicts of interest:** The author declares no conflict of interest.

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**Manuscript Information:** Received: December 01, 2022; Accepted: January 06, 2023; Published: January 10, 2023

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**Citation:** Błaszczuk JW. Role of phosphate dysmetabolism in the pathogenesis of chronic fatigue syndrome. *Open J Clin Med Case Rep.* 2023; 1963.

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