Creatine in Post-Viral Fatigue Syndrome

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Post-viral fatigue syndrome (PVFS) is a widespread chronic neurological disease with no definite etiological factor(s), no actual diagnostic test, and no approved pharmacological treatment, therapy, or cure.

post-viral fatigue syndrome | chronic fatigue syndrome | creatine | GAA | creatine kinase

1. Introduction

Post-viral fatigue syndrome (PVFS) is a medical condition that is categorized among other disorders of the nervous system (Code: 8E49) in the eleventh revision of the International Classification of Diseases [1]. According to the current codification system published by the World Health Organization in 2019, PVFS covers chronic fatigue syndrome (CFS) and benign myalgic encephalomyelitis (ME), puzzling conditions previously designated as individual entities, and now systematized under the PVFS umbrella. Although some CFS/ME cases are not preceded by a viral infection[2], all conditions share clinical features that allow for a mutual medical/scientific exploration. Mainly characterized by a prolonged severe post-exercise malaise, an impairment in various cognitive functions, non-inflammatory myalgia and joint pain, and unrefreshing sleep, PVFS has an unknown cause, no pathognomonic diagnostic criteria, and no approved medical treatment (for a detailed review see[3][4][5]). Various viral infections have often been reported before the first appearance of PVFS, including Epstein–Barr virus, cytomegalovirus, coxsackieviruses, and coronaviruses, and the onset might be sudden or gradual [6]. Besides viruses, many physiological and psychological factors appear to work together to predispose an individual to PVFS and to precipitate and perpetuate the illness[7], making this ailment even more baffling and hard to tackle. Beyond other risk factors, creatine shortfall may be one of the hallmarks of PVFS pathology, with compensating for the lack of creatine perhaps seen as an adjunct management strategy in this mysterious disease[8]. This review paper outlines the irregularities of creatine metabolism in PVFS, summarizes studies on creatine supplementation in PVFS and similar syndromes, and discusses new frontiers of using creatine by emphasizing COVID-19 pandemics and post-COVID-19 convalescence and nutritional care.

2. Biomarkers of Creatine Metabolism in Post-Viral Fatigue Syndrome

A pioneering biochemical and muscle study from the late 1980s and early 1990s on patients with PVFS revealed minimal changes in surrogate markers of creatine turnover/muscle physiology. A mildly elevated creatine kinase (CK) and indistinguishable muscle biopsies were found in 96 patients who had suffered from the PVFS, although enterovirus RNA was present in the skeletal muscle of some patients up to 20 years after the onset of disease[9].

Preedy and co-workers[10] reported only minor abnormalities or expected outcomes after a quantitative morphometric analysis of skeletal muscle fibers in 22 patients with PVFS. Mean muscle RNA composition (mg RNA/mg DNA) was reduced by 15% in acute onset PVFS, implying lower muscle protein synthetic potential (but not muscle bulk), while plasma carnosinase and CK levels were within normal ranges. Another study demonstrated mostly regular electromyographic and muscle histopathology studies, and normal plasma CK levels in 35 patients with chronic fatigue[11], yet abnormal fiber density was found in several patients who did not have acute-onset PVFS. Wassif and colleagues[12] confirmed that the conventional biochemical markers (e.g., albumin, liver enzymes, CK, and carnosinase) are insensitive to discriminate patients with CFS and other myopathies, while histological examination revealed relatively mild abnormalities in 3 out of 10 patients with PVFS (e.g., macrophage infiltration and muscle fiber atrophy). An exciting trial found that stress-induced neutrophil mobilization might be disrupted in CFS, with healthy women demonstrating a strong correlation between exercise-induced neutrophilia and plasma CK while this link was not observed in the CFS patients[13].

Studies following those seminal trials brought a somewhat better understanding of tissue metabolism of creatine in PVFS by using magnetic resonance spectroscopy (MRS). Wong and co-workers[14] were arguably the first who evaluated skeletal muscle metabolism in CFS during rest and exercise using ^{31}P MRS to reflect minute-to-minute intracellular high-energy phosphate metabolism. The authors found that CFS patients and normal controls have similar skeletal muscle metabolic patterns during and after exercise. However, CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have relatively reduced intracellular concentrations of ATP (adenosine triphosphate), while no intergroup differences were found for muscle phosphocreatine levels. A follow-up study confirmed that no significant metabolic abnormalities are associated with fatigue in CFS patients, although abnormalities may be present in a minority of patients[15]. However, other ^{31}P MRS trials reported significantly reduced the maximal rate of post-exercise phosphocreatine resynthesis in CFS patients compared to sedentary controls[16], or decreased resting values of phosphocreatine-to-phosphocreatine plus phosphate and increased pH levels during exercise in the CFS population[17]. This implies CFS-driven perturbation in energy metabolism, although not all studies reported an impaired rate of phosphocreatine resynthesis after exercise[18][19]. Finally, Brooks and colleagues[20] demonstrated a trend of reduced levels of hippocampal creatine in CFS patients as compared with controls (8.6 mM vs. 10.9 mM), suggesting an impaired creatine metabolism in the brain as well.

Chronic fatigue syndrome in childhood also appears to be characterized by vascular and metabolic alterations in the brain[21], with lower blood flow in the temporal and occipital lobes and markedly higher blood flow in the basal ganglia and thalamus in patients with CFS as compared to healthy children. This was accompanied by a notable elevation of the choline-to-creatine ratio in children with CFS, which was arguably the first time that a possible creatine alteration in CFS in the young brain has been described, although no individual levels for brain metabolites were reported. A choline-to-creatine ratio is a well-known surrogate ^{1}H MRS biomarker of altered brain metabolism, with elevated levels perhaps demonstrating a reduction in brain creatine (or an elevation in brain choline). Soon afterward, an elevation in the choline-to-creatine ratio in the basal ganglia and white matter was found in patients with histologically mild hepatitis C suffering from CFS[22]. Altered cerebral metabolism was also found in patients with CFS who demonstrated higher *N*-acetyl aspartate-to-choline and choline-to-creatine ratios in the occipital

cortex, as compared to healthy controls[23][24]. Various cardiac bioenergetic abnormalities were found in 12 CFS patients, with the mean phosphocreatine-to-ATP ratio in the CFS group tending to be lower than that seen in the control group, with values consistent with significant cardiac impairment [25]. In addition, the half-time for phosphocreatine recovery from end-exercise to baseline levels was prolonged in CFS patients. Van der Schaaf and co-workers[26] used functional brain imaging in 89 women with CFS, evaluating the possible link between the brain metabolism and clinical features of CFS. They found that more pain in CFS was associated with reduced gray matter volume and decreased *N*-acetyl aspartate-to-creatine ratio in the dorsolateral prefrontal cortex. Nevertheless, most of the studies provided no absolute levels of creatine in relevant tissues, making the case for creatine alterations in CFS incomplete.

Widespread metabolic abnormalities in CFS were corroborated in a recent whole-brain magnetic resonance spectroscopy trial[27]. A notably elevated choline-to-creatine ratio was found in the left anterior cingulate, with metabolite ratios correlated with fatigue in seven brain regions. Specifically, creatine levels in the parietal cortex were lower in CFS patients than in the control group (6.4 mM vs. 7.3 mM, $p = 0.03$), while in the putamen, creatine was higher in patients t[30]han in controls (6.3 mM vs. 5.7 mM; $p = 0.01$), suggesting location-specific variation in brain creatine in CFS. Patients with CFS also showed higher brain temperatures than healthy controls in several brain regions, suggesting that neuroinflammation, mitochondrial dysfunction, and aberrant neuronal communication may contribute to metabolic perturbations in the CFS brain. An elevated creatine excretion via urine has been identified as a metabolomic signature of fibromyalgia syndrome, a chronic condition similar to PVFS, with creatine urinary loss correlating well with fatigue and pain severity[28]. The increased utilization of creatine to form ATP in CFS has been suggested in a metabolomics trial[29], as illustrated by elevated urinary creatinine (an end product of creatine metabolism) and decreased serum glycine (a precursor of creatine) in blood and urine samples from 34 women with ME/CFS.

In the search for valid diagnostic/prognostic biomarkers of CFS, Nacul and co-workers[30] recently reviewed lab tests from 272 people with CFS and 136 healthy controls participating in the UK ME/CFS Biobank. The authors reported that patients with severe CFS actually have lower CK levels compared to healthy controls and non-severe CFS patients, with differences persisting after adjusting for sex, age, body mass index, muscle mass, disease duration, and activity levels. This interesting discovery was corroborated in a consecutive trial where among the 30 clinical parameters evaluated at the UK ME/CFS Biobank, only blood CK levels showed statistically significant differences between groups, with levels lower in CFS patients than in healthy controls (59.93 U/L vs. 88.67 U/L; $p = 0.006$)[31]. This was accompanied by a CFS-driven dysregulation of microRNA profiles, which represent genes interconnected with neuronal and endocrine-metabolic system pathways, including an upregulation of *NTRK1*, which is essential for the development and survival of neurons, and downregulation of *MECP2* and *AGO2* genes, which provide instructions for modifying chromatin and RNA-mediated silencing, respectively. Low CK activity in CFS is perhaps another indicator of an inadequate turnover of a key enzyme involved in creatine utilization and may be a symptom of the low availability of cellular energy that might involve both mitochondrial and cytosolic pathways[32][33].

3. Dietary Creatine and Alternatives in Syndromes with Prolonged Fatigue

Keeping in mind the fact that supplemental creatine has been investigated in a plethora of neurological, neuromuscular, and immune disorders characterized by creatine deficit or perturbation, it is odd that PVFS mainly remained outside of the scope of the creatine research community. A single clinical trial on creatine supplementation in CFS was registered at ClinicalTrials.gov in 2015 (NCT02374112), and the study is still on going, with no results published so far. Besides, only a handful of trials evaluated the effects of supplemental creatine and/or other guanidino compounds in the PVFS population or similar disorders with prolonged fatigue of unknown source.

Almost 20 years ago, Brouwers and co-workers[34] assessed the effect of a polynutrient supplement on the fatigue severity, clinical symptoms, and physical activity of patients with CFS. The authors conducted a prospective randomized placebo-controlled, double-blind trial in 53 CFS patients who received a multi-component product specifically developed to have a high antioxidative capacity for ten weeks. The product contained protein, carbohydrates, fat, trace elements, minerals, vitamins, and other components, including creatine (1200 mg per 100 mL). The authors found no significant differences between the placebo and the treated group on any of the outcome measures. Besides other methodological limitations of this study (e.g., no assessment of the nutritional status of CFS patients prior to the treatment, some components of the mixture having potential contrasting effects), the creatine dosage used here appears to be insufficient as compared to traditional supplementation regimens.

A research group from the University of Sao Paolo evaluated the effects of creatine supplementation in fibromyalgia, a condition similar (if not equivalent) to CFS and characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory, and mood issues[35]. The authors supplemented creatine (20 g of creatine monohydrate for five days followed by 5 g per day throughout the trial) to 43 fibromyalgia patients in a randomized, double-blind, placebo-controlled, parallel-group design, and monitored muscle performance, cognitive function, sleep, and tissue metabolism at baseline and 16-week follow up. Creatine intervention provoked higher muscle phosphoryl creatine levels when compared with the placebo group, accompanied by greater dynamic and isometric muscular strength. The mental health domain from the 36-item Short-Form Health Survey was also improved following creatine supplementation, along with incidental memory from the Delay Recall Test, while the other markers of cognition, quality of life, or sleep remained unchanged. Another randomized controlled crossover trial evaluated the effects of supplemental guanidinoacetic acid (GAA), a natural precursor of creatine, in 21 mid-age women with CFS [36]. Three months of oral GAA (2.4 g/day) induced a significant elevation of total muscle creatine levels compared with the placebo group (36.3% vs. 2.4%; $p < 0.01$), complemented by a superior rise in quadriceps isometric strength and maximal oxygen uptake. GAA also attenuated several aspects of fatigue, such as activity, motivation, and mental fatigue, and improved both physical and mental domains of health-related quality of life assessed through the 36-item Short-Form Health Survey. However, GAA demonstrated no effects on the main clinical outcomes, such as general fatigue and musculoskeletal soreness at rest and during activity.

An interesting cross-sectional study assessed the dietary habits and food avoidance-behaviors in women with CFS[37]. Although no homogeneous pattern of food habits was established in this trial, CFS patients appear to often avoid many foods rich in creatine (e.g., meat, milk, and dairy products). A connection between dietary intake of creatine and clinical features of CFS has not been established so far; however, low creatine consumption from food sources may play an essential role in the creatine metabolism irregularities associated with CFS, and perhaps calls for creatine compensation through the prescription of creatine-rich foods and/or creatine supplementation. Jenkins and Raymen also reported intakes below the reference values for animal-based nutrients (e.g., vitamin D, vitamin A, calcium, zinc, and iron) in CFS patients[38]. To understand this under-investigated disorder will require careful nutritional approaches.

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