

Proposal of a food supplement for the management of post-COVID syndrome

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Abstract. – A vast majority of COVID-19 patients experience fatigue, extreme tiredness and symptoms that persist beyond the active phase of the disease. This condition is called post-COVID syndrome. The mechanisms by which the virus causes prolonged illness are still unclear. The aim of this review is to gather information regarding post-COVID syndrome so as to highlight its etiological basis and the nutritional regimes and supplements that can mitigate, alleviate or relieve the associated chronic fatigue, gastrointestinal disorders and continuing inflammatory reactions. Naturally-occurring food supplements, such as acetyl L-carnitine, hydroxytyrosol and vitamins B, C and D hold significant promise in the management of post-COVID syndrome. In this pilot observational study, we evaluated the effect of a food supplement containing hydroxytyrosol, acetyl L-carnitine and vitamins B, C and D in improving perceived fatigue in patients who recovered from COVID-19 but had post-COVID syndrome characterized by chronic fatigue. The results suggest that the food supplement could proceed to clinical trials of its efficacy in aiding the recovery of patients with long COVID.

Key Words:

Post-COVID syndrome, Acetyl L-carnitine, Hydroxytyrosol, Vitamin, Food supplement.

Introduction

The new coronavirus responsible for the coronavirus disease 19 (COVID-19) is the severe acute respiratory syndrome 2 (SARS-CoV-2), a

member of the subfamily of β -coronaviruses¹. COVID-19 is an acute multi-system disease, which in rare cases can result in bilateral pneumonia and collapse of internal organs and systems, leading to death. About 40% of person contracting SARS-CoV-2 infection remain asymptomatic. Of the symptomatic 60%, about 80% show mild symptoms, such as dry cough, sore throat, anosmia and ageusia, 15% need hospitalization and 5% require intensive care and ventilation¹⁻¹².

At the beginning of the pandemic, it seemed that the illness lasted only a few days, after which patients could resume their normal lives². This turned out to be incorrect. A proportion of patients experience post-COVID fatigue, persistent enervating symptoms and post-exertional neuro-immune exhaustion similar to that observed in SARS patients. This condition was consequently named post-COVID syndrome (PCS)¹³. It is characterized by persistent multi-organ damage due to severe inflammatory responses, oxygen deprivation, thrombotic microangiopathy and venous thromboembolism⁶.

Some patients have very slow recovery with persistent fatigue resembling chronic fatigue syndrome/myalgic encephalomyelitis, similar to that observed in health workers in Toronto and Hong Kong who contracted SARS-CoV during the SARS epidemic 2002-2003 and were unable to return to work for up to 20 months⁴⁻⁷. The implication is that PCS might last for weeks to years and its mechanism needs to be clarified by further research.

Post-viral fatigue is not uncommon and has been reported after infection by other viruses and proteobacteria, such as those causing influenza, herpes, brucellosis, Ebola disease¹⁰, Ross River fever¹¹ and Q fever. The mechanism underlying the chronic fatigue caused by these infections might help to elucidate PCS. However, there are currently few reports on the mechanisms underlying PCS and it remains extremely difficult to understand why some people recover quickly while others develop the syndrome. In certain cases, prolonged illness seems to be linked to older age and multiple chronic medical conditions¹².

The aim of this study was to evaluate the effects of a food supplement containing hydroxytyrosol, acetyl L-carnitine and vitamins B, C and D on perceived fatigue in patients recovering from COVID-19, and to assess any side effects of the supplement.

Patients and Methods

Subjects

Twenty subjects (11 females and 9 males) who recovered from COVID-19 (mean age \pm SD: 52.25 ± 12.07 ; range 28 to 76 years), complained of fatigue and were offered the food supplement. We collected the informed consent from the participants. They filled in an Activation-Deactivation Adjective Check List self-assessment questionnaire¹⁴ at the beginning and end of the study period. They confirmed taking the supplement at a dose of one pill a day. Twenty other subjects (10 females and 10 males), who did not have COVID-19 and did not take the supplement, filled in the self-assessment questionnaire to detect any perceived changes in fatigue in the study period (mean age \pm SD: 53.3 ± 13.48 ; range 29 to 73 years). The study period lasted 15 days. The food supplement users also filled in another self-assessment questionnaire at the end of the study to monitor side effects of the supplement, although it was impossible to know whether reported effects were related to the syndrome or to the supplement.

Food Supplement Composition

The food supplement contained: 160 mg vitamin C, 150 mg acetyl-L-carnitine, 100 mg hydroxytyrosol/olive polyphenols, 12.5 mg thiamine, 5 mg vitamin B6, 0.2 mg folic acid, 0.025 mg vitamin D3 and 0.005 mg vitamin B12.

Questionnaire

The Activation Deactivation Adjective Check List (AD ACL) is a validated questionnaire that has been applied in a wide range of studies, including drug and exercise studies^{14,15}. It is a multidimensional test of various transient arousal states, including energy and nervous arousal. The AD ACL Short Form consists of 20 self-descriptive adjectives divided into four subscales (energy, tiredness, tension and calmness), each with five adjectives to score. The respondent scores each adjective from 1 to 4 (no, cannot decide, feel slightly, definitely feel, respectively) and the five scores are summed or averaged for each subscale. The possible score of a subscale is therefore between 5 and 20, and possible totals are between 20 and 80. Participants were instructed to rate each adjective according to how they felt while answering the questionnaire at the beginning and at the end of the study. The analysis compared differences in fatigue symptoms before and after the 15-day use of the supplement.

Results

The energy and psychological status of users and non-users of the food supplement were compared on the basis of the questionnaire results. After taking the supplement for 15 days, supplement users recorded more improvement in energy and psychological status than non-users. The latter did not show any significant change (Table I). Self-reported energy levels doubled after 15 days on the food supplement (+123%), whereas levels of tiredness and tension halved, -51% and -48% respectively. The non-user group reported an increase in energy and calmness and a decrease in tiredness and tension but both were much less than those recorded by the user group (Figure 1).

Possible side effects of the supplement reported by users were stomachache (25%), lack of appetite and headache (20%), nausea and diarrhea (15%) and vertigo (10%) (Figure 2). Although these percentages seem high, one should consider that such symptoms are also typical of post-COVID syndrome, and therefore cannot be regarded as true side effects of the supplement¹⁶. The side effects are gastrointestinal or neurological origin. Fifty-five percent of volunteers reported that the supplement had a pleasant taste, 30% perceived it as tasteless, and 30% reported an unpleasant taste.

Table I. The initial status of the supplement users group (patients recovered from COVID-19) showed lower scores for energy and calmness and higher scores for tiredness and tension than the non-users group. After 15 days of taking the food supplement, the supplement users group showed a greater improvement than the non-users group.

	Food supplement users' group						Difference %
	Day 0			Day 15			
Energy	Active	32	155	Active	73	345	+123%
	Energetic	31		Energetic	69		
	Vigorous	32		Vigorous	68		
	Lively	31		Lively	70		
	Full-of-pep	29		Full-of-pep	65		
Tiredness	Sleepy	59	260	Sleepy	26	127	-51%
	Tired	65		Tired	28		
	Drowsy	55		Drowsy	25		
	Wide-awake	29		Wide-awake	20		
	Wakeful	52		Wakeful	28		
Tension	Tense	65	244	Tense	31	126	-48%
	Intense	43		Intense	24		
	Fearful	33		Fearful	20		
	Clutched-up	44		Clutched-up	26		
	Jittery	59		Jittery	25		
Calmness	Placid	36	184	Placid	68	257	+40%
	Calm	37		Calm	70		
	Still	33		Still	67		
	At-rest	50		At-rest	29		
	Quiet	28		Quiet	23		
	Non-users group						Difference %
	Day 0			Day 15			
Energy	Active	66	273	Active	70	300	+10%
	Energetic	65		Energetic	67		
	Vigorous	51		Vigorous	56		
	Lively	50		Lively	59		
	Full-of-pep	41		Full-of-pep	48		
Tiredness	Sleepy	39	174	Sleepy	29	137	-21%
	Tired	40		Tired	30		
	Drowsy	31		Drowsy	25		
	Wide-awake	22		Wide-awake	20		
	Wakeful	42		Wakeful	33		
Tension	Tense	41	177	Tense	29	138	-22%
	Intense	43		Intense	33		
	Fearful	26		Fearful	24		
	Clutched-up	36		Clutched-up	29		
	Jittery	31		Jittery	23		
Calmness	Placid	50	213	Placid	57	226	+6%
	Calm	49		Calm	59		
	Still	55		Still	60		
	At-rest	29		At-rest	25		
	Quiet	30		Quiet	25		

Discussion

Our preliminary results show that a multivitamin food supplement containing B group vitamins, vitamin C, vitamin D, acetyl L-carnitine and hydroxytyrosol might be able to help patients to recover from fatigue and tiredness. Interest-

ingly, the self-reported levels of energy increased much more in food supplement users than in non-users, whereas self-reported tiredness and tension decreased much more in the users group. Although our population was not large and we were unable to determine whether there were statistically significant gender- and age-specific dif-

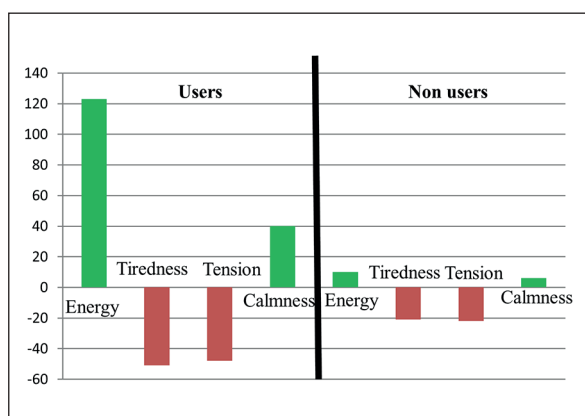


Figure 1. Graphical representation of energetic status changes from the initial status. Supplement users show a higher increase in energy and calmness scores and a higher decrease in tiredness and tension scores when compared with the non-users group.

ferences in response to the food supplement, the results were a good basis for extending the study to a larger population in a randomized placebo-controlled clinical trial. Possible side effects of the supplement were gastrointestinal (75%) and neurological (30%), however, these symptoms are also typical of post-COVID syndrome and cannot therefore be regarded as definite side effects of the supplement. Furthermore, 70% of volunteers found that the supplement had a pleasant taste or was tasteless.

Food supplements which are able to reduce persistent inflammatory responses, scavenge free radicals, improve energy levels by boosting mitochondrial function, protect against progressive organ damage, and improve the overall health of

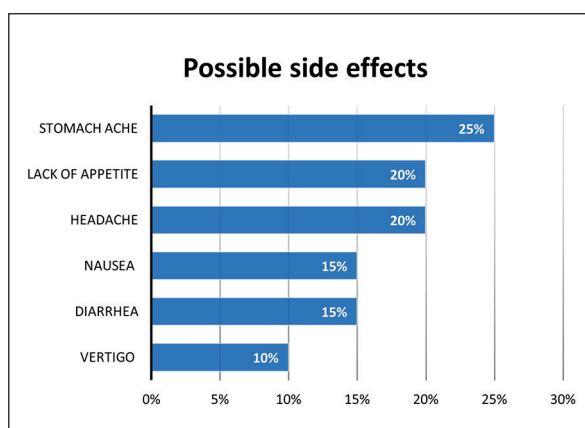


Figure 2. Side effects and taste perception self-reported by the volunteers that took the food supplement.

COVID and PCS patients are currently investigated in observational studies and clinical trials¹⁷. For instance, there is strong evidence¹⁸ that thiamine, vitamin C and vitamin D supplements are beneficial in respiratory diseases, such as COVID-19 and acute respiratory distress syndrome, and in sepsis. In addition, vitamin D supplementation has been reported to be effective in preventing acute respiratory tract infections and influenza¹⁹⁻²¹, and in improving chronic fatigue^{22,23}.

Likewise, vitamin B complex, specifically folate, vitamin B12, thiamine, riboflavin and pyridoxine, have been shown to help improve this condition. These vitamins support mitochondrial function, regulate inflammation, improve digestion and help eliminate toxins, thus bringing benefits to patients with viral infections²⁴.

Vitamin C has antiviral, antioxidant, anti-inflammatory and immunomodulatory effects, which make it attractive in the management of PCS²⁵.

Acetyl L-carnitine (LC) is an amino-acid-derived quaternary ammonium compound involved in metabolism in most mammals, plants and some bacteria. It transports long-chain fatty acids into mitochondria for oxidation and energy production²⁶. It also helps remove metabolic by-products from cells. It is widely used in the management of cardiovascular diseases, diabetes, neurological disorders, such as Alzheimer's disease, hepatic encephalopathy and other painful neuropathies, and has been associated with overall improvement of health, thereby reducing fatigue²⁷⁻³². Administration of LC to elderly patients has been linked to an overall reduction in total fatty tissue, improvement in lipid profiles and reductions in physical and mental fatigue²⁸. There is evidence³¹ that LC reduces inflammatory mediators in intestinal and coronary artery disease, as well as inactivating the hepatitis C virus, which is an RNA virus like SARS-CoV-2. LC is also an immunomodulator that downregulates pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1³³.

In PCS, LC can improve fatigue by helping mitochondrial oxidation of fatty acids to produce energy for the body. The importance of LC in cell energy generation is indicated by a study that revealed that chronic fatigue patients have 30-40% lower levels of LC than healthy subjects³². Other randomized controlled trials^{34,35} reported that administration of 3000 mg/d carnitine for 4-8 weeks significantly improved fatigue.

Hydroxytyrosol is a powerful antioxidant phenol compound obtained from the fruit and leaves

of the olive tree³⁶. It also has anti-inflammatory properties³⁷. One study³⁸ highlighted this property by effective inhibition of NO and PGE2 production, leading to a decrease in secretion of cytokines (IL-1 α , IL-1 β , IL-6, IL-12, TNF- α) and chemokines (CXCL10/IP-10, CCL2/MPC-1). Another study³⁹ reported that hydroxytyrosol modulates activation of the transcription factor NF- κ B, which in turn activates expression of genes encoding cytokines (TNF- α , IL-1, IL-6 and IL-17), chemokines and adhesion molecules associated with physiological and pathological inflammatory responses. By virtue of these properties, hydroxytyrosol has recently received special attention in the prevention of COVID-19 infection and to alleviate PCS-related symptoms⁴⁰⁻⁴³.

Post-COVID fatigue and tiredness may be linked to continuing inflammation, mitochondrial dysfunction, accumulation of damaged mitochondria and protracted infection due to prevention of cytotoxic killing of infected cells⁴⁴. Food supplements, such as vitamin B and L-carnitine, that restore mitochondrial function and help remove damaged mitochondria, can be used to enhance energy production^{45,46}. Vitamin C is also beneficial for alleviating fatigue and stress⁴⁷.

Food supplements having antioxidant and anti-inflammatory activities, such as acetyl L-carnitine, hydroxytyrosol, vitamins C and D, not only help the body fend off viral infection but also boost immunity and prevent prolonged post-COVID fatigue and gastrointestinal problems. In this way, they promote overall health and improve the quality of life of patients who have managed to recover from SARS-CoV-2 infection¹⁷.

Our study showed that a food supplement containing vitamin C, acetyl-L-carnitine, hydroxytyrosol, thiamine, vitamin B6, folic acid, vitamin D3 and vitamin B12 may bring about an improvement in self-perceived physical and mental status in volunteers recovering from COVID-19 with respect to healthy volunteers who did not take the supplement.

Conclusions

Post-COVID syndrome is an emerging long-term condition. Although efforts have been made to discover the mechanism by which the virus causes these deleterious effects, few papers on the mechanisms underlying PCS have been published. Research-based evidence on specific food supplements as adjuvant therapy in the man-

agement of PCS is also limited. A plethora of literature supports the use of food supplements and natural compounds on the basis of their immunomodulatory, anti-inflammatory, antioxidant and antiviral properties, however, their efficacy in treating PCS has yet to be evaluated in well-structured clinical trials¹⁸. Although natural compounds, such as acetyl-L-carnitine and hydroxytyrosol, offer many potentially beneficial properties, a blend of carefully selected supplements in the right proportions is more likely to prove beneficial in management of PCS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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