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Multivitamin mineral supplementation in patients with chronic fatigue syndrome

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Background: Chronic fatigue syndrome (CFS) is characterized by medically unexplained persistent or reoccurring fatigue lasting at least 6 months. CFS has a multifactorial pathogenesis in which oxidative stress (OS) plays a prominent role. Treatment is with a vitamin and mineral supplement, but this therapeutic option so far has not been properly researched.





Material/Methods: This prospective study included 38 women of reproductive age consecutively diagnosed by CDC definition of CFS and treated with a multivitamin mineral supplement. Before and after the 2-month supplementation, SOD activity was determined and patients self-assessed their improvement in 2 questionnaires: the Fibro Fatigue Scale (FFS) and the Quality of Life Scale (SF36).

Results: There was a significant improvement in SOD activity levels; and significant decreases in fatigue ($p=0.0009$), sleep disorders ($p=0.008$), autonomic nervous system symptoms ($p=0.018$), frequency and intensity of headaches ($p=0.0001$), and subjective feeling of infection ($p=0.0002$). No positive effect on quality of life was found.

Conclusions: Treatment with a vitamin and mineral supplement could be a safe and easy way to improve symptoms and quality of life in patients with CFS.

MeSH Keywords: **chronic fatigue syndrome • oxidative stress • quality of life • vitamins**

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Background

Fatigue is one of the most common complaints. It is defined as a lack of energy and its causes are numerous. About 10% of people experience fatigue that lasts for more than 6 months. Chronic fatigue syndrome (CFS) is characterized by medically unexplained persistent or reoccurring fatigue lasting at least 6 months [1]. This disease is often accompanied by numerous symptoms involving various body systems, including headache, joint pain, gastrointestinal (GI) disturbance, sore throat, painful lymphadenomegaly, cognitive disturbances, and paresthesia [1–3]. The debilitating fatigue and the accompanying symptoms significantly influence everyday activities, thus patients with CFS generally experience a lower quality of life [4–7].

There have been reports that only approximately 20% of people living with CFS have been diagnosed [8]. The disease is more frequent in females in all epidemiological studies but the prevalence varies depending greatly on CFS definition, method of assessment and country (region) observed, and range from 0.03% to over 3% [8–10].

CFS most likely has a multifactorial pathogenesis in which oxidative stress (OS) plays a prominent role. Evidence supporting the pivotal role of OS in CFS is strong and extensive. Symptoms such as fatigue, pain, gastrointestinal problems, and cognitive impairment can all be connected to either direct toxic effects or indirect effects of reactive oxygen species [12–15]. Although most of the exact mechanisms by which OS causes some of the symptoms are yet to be defined, increased lipid and protein oxidation has been established in patients with CFS compared to controls. In these studies the degree of lipid and protein oxidation correlated with symptom severity. There is also some evidence of DNA damage due to OS in patients with CFS. Currently, there is general consensus that CFS is characterized by low-level inflammation and oxidative and nitrosative stress pathways [12–18].

Oxidative stress in CFS is due to diminished antioxidant capacity and/or decreased activity of antioxidant enzymes. Treatment with a vitamin and mineral supplement could be a safe and easy way to improve symptoms and quality of life in patients with CFS. However, this therapeutic option thus far has not been properly researched. In this study, we aimed to determine objective parameters of antioxidant capacity in patients with CFS before and after multivitamin mineral supplementation, as well as subjective parameters of treatment success.

Although CFS is a well-recognized condition world-wide, this is the first study of this condition in our region.

Material and Methods

Study population and clinical examinations

The research was conducted at the Infectious Diseases Clinic at the Clinical Center of Vojvodina during 2011. This was a prospective study of 38 women of reproductive age (18–50 years old) who were consecutively diagnosed and treated for CFS at the clinic. CFS diagnosis was established according to the CDC definition [19]. Before starting treatment, all the patients signed a written consent to participate in the study.

All patients were treated for 2 months with the multivitamin mineral supplement Supradyn® (Bayer Schering Pharma). Its contents are shown in Table 1. Patients purchased the supplement themselves and kept the boxes for inspection. We selected Supradyn® by Bayer Schering Pharma because at the time of the investigation, this supplement was one of the most affordable and its composition suited the purposes of the study. The study was a part of a regional project approved of and funded by the provincial Ministry of Science and was not in any way sponsored by a pharmaceutical company.

We did not include patients who had known allergies to any of the components of the supplement, who were pregnant or lactating, who had current chronic or acute diseases, or who were taking antidepressants, antipsychotics, and/or anxiolytics.

Before and after the treatment, laboratory and clinical tests were performed to exclude active inflammatory syndrome.

To assess antioxidant status, superoxide dismutase (SOD) activity was measured in all patient plasma samples before and after treatment. SOD activity was determined using a commercial ELISA test based on the spectrophotometric principle. The signal strength correlated to activity of the enzyme. The SOD activity was expressed as both a percentage (%) and in equivalents (mEq).

Two self-rating scales were used to determine treatment outcome. Patients were questioned before and after treatment with multivitamin mineral supplement.

The Fibro Fatigue Scale (FFS) was used as an instrument to assess symptom severity and change after treatment in patients with CFS. The 12-item questionnaire included questions on aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances, irritable bowel, headache, and subjective experience of infection. Based on the information obtained from a clinical interview, each item was scored 0 (absence of symptom) to 6 (maximum degree of symptom). To assist in scoring, a short description (anchoring point) was

Table 1. Ingredients of the multivitamin mineral supplement Supradyn® (Bayer Schering Pharma).

Vitamin B6	6 mg	Calcium	120 mg
Vitamin A	800 µg	Phosphorus	120 mg
Beta-carotene	0.72 mg	Iron	5.6 mg
Vitamin D	5 µg	Magnesium	45 mg
Vitamin E	10 mg	Zink	6 mg
Vitamin C	180 mg	Iodine	60 µg
Vitamin B1	4.2 mg	Copper	1 mg
Vitamin B2	4.8 mg	Chrome	0.05 mg
Vitamin B3	54 mg	Manganese	1.4 mg
Folic acid	600 µg	Potassium	20 mg
Vitamin B12	3 µg	Selenium	28 µg
Biotin	450 mg	Silica	2 mg
Vitamin B5	18 mg	Molybdenum	60 µg
Vitamin K	0.03 mg	Chloride	18.5 mg

given for scores 0, 2, 4, and 6. If the patient's condition fell somewhere in between the anchoring points, a score of 1, 3, or 5 (which were not defined) was given.

The short-form Quality of Life Questionnaire (QOL SF-36), which is widely used to measure disability in CSF research, was used to assess the impact of illness on everyday physical, psychological, and social functioning. The 36 items on the questionnaire are aggregated in 8 scales: physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE), and mental health (MH). These are then aggregated into 2 summary measures (physical and mental health). Three scales (PF, RP, and BP) are strongly correlated with the physical component and contribute most to the scoring of the Physical Component Summary (PCS). The psychological component is most strongly correlated with MH, RE, and SF scales, which also contribute most to the scoring of the Mental Component Summary (MCS) measure. Three of the scales (VT, GH, and SF) have noteworthy correlations with both components.

Statistical methods

Data were analyzed using SPSS 8.0 software. Differences between 2 groups were assessed by the Mann-Whitney test and ANOVA. The relationship between the various parameters was assessed by correlation. Data are expressed as means and 2-tailed p-values less than 0.05 were considered statistically significant.

Results

Out of the 38 women who entered the study, 36 completed the 2-month treatment. Two patients decided not to continue taking the supplement, so they were excluded from the study. No adverse effects of treatment were observed.

Observed SOD parameters are shown in Table 2.

SOD activity was 313.81 mEq (16.67%) before the treatment and 70.53 (4.01%) after the treatment, which suggests a significant improvement in the activity of the antioxidant enzyme ($p < 0.005$).

The FFS score did not change after treatment, but several aspects of the scale did differ between the 2 groups. Significant decreases in fatigue ($p = 0.0009$), sleep disorders ($p = 0.008$), autonomic nervous system symptoms ($p = 0.018$), frequency and intensity of headaches ($p = 0.0001$), and subjective feeling of infection ($p = 0.0002$) were observed.

At the baseline and after treatment, CFS patient health-related quality of life did not differ from the general population ($p = 0.23$ and $p = 0.25$, respectively). Supplementation did not influence any aspect of health-related quality of life ($p > 0.05$). CFS diagnosis alone had an effect on diminished vitality (median value 49.74 at both time points).

The antioxidant capacity parameter did not correlate with the total FFS score. Mildly statistically significant correlations

Table 2. Observed parameters before and after treatment with multivitamin mineral supplement.

	Before supplementation (mean ±SD)	After 2 month supplementation (mean ±SD)	p value
SOD activity			
[mEq]	313.81±102.98	70.53±15.48	<0.005
[%]	16.67±1.74	4.01±0.9	<0.005
Fibro fatigue score			
Aches and pain	1.97 (±1.17)	1.57 (±1.20)	0.15
Muscular tension	1.29 (±1.06)	1.6 (±0.95)	0.19
Fatigue	3.53 (±1.19)	2.31 (±1.35)	0.0009
Concentration difficulties	1.34 (±1.10)	1.03 (±1.04)	0.21
Failing memory	0.82 (±1.01)	0.8 (±0.90)	0.94
Irritability	1.89 (±1.27)	1.4 (±1.14)	0.08
Sadness	0.84 (±0.92)	0.46 (±0.89)	0.07
Sleep disturbances	1.87 (±1.26)	1.14 (±1.00)	0.008
Autonomic disturbances	2.23 (±1.07)	1.6 (±1.44)	0.018
Irritable bowel	1.11 (±1.41)	1.37 (±1.86)	0.491
Headache	2.29 (±1.31)	1.2 (±0.96)	0.0001
Experience of infection	2.53 (±1.01)	1.6 (±0.98)	0.0002
Total FFS score	21.6 (±5.99)	16.08 (±8.08)	0.001
Quality of life			
Physical health	69.05±10.06	67.48±11.56	0.85
Mental health	66.32±12.79	67.42±14.03	0.91

were found after the treatment between SOD activity and the physical aspect of the HR QoL parameters: physical function (r=0.330, p=0.053), physical role (r=0.365, p=0.031), bodily pain (r=0.429, p=0.01), and total score (r=0.399, p=0.018). Also, SOD and some parameters of mental aspects of the HR QoL correlated after the treatment: vitality (r=0.370, p=0.029), mental health (r=0.412, p=0.014), and total score (r=0.427, p=0.010).

Discussion

Chronic fatigue syndrome is a multisystem disease that requires a multidisciplinary approach. This condition has a complex pathogenesis that includes oxidative stress and oxidation of macromolecules [11–16,20,21]. Thus far, treatment options have included psychotherapy and physical conditioning, with varying results. Multivitamin mineral supplementation could be a safe additional therapeutic option that could diminish patient symptoms by improving antioxidant status.

Up until now, few studies have investigated supplementation as a treatment option for patients with CFS. One of the earliest studies was done by Kaslow et al. [22] using cow liver extract containing folic acid and cyanocobalamin. The group found an improvement in all patients' overall condition, but it lacked statistical significance. Ten years later, Heap, Peter, and Wessley confirmed vitamin B deficiency in CFS patients [23]. Several studies experimented with adding vitamin B to improve cognitive function in deficient patients, with promising results [24–27], but thus far it has not been studied in CFS patients.

Until now, the only microelement well studied in CFS is magnesium. The studies began after Cox found lower magnesium levels in erythrocytes of CFS patients [28]. As magnesium levels in erythrocytes correlate well with serum levels, studies then followed on magnesium supplementation. In a randomized, double-blind study, Cox found a significant improvement in patients receiving a magnesium supplement. Patients reported higher energy levels, diminished pain, and

better mental state. Two later, similar studies were not able to replicate these results, but magnesium has remained as an important mineral in our understanding of CFS pathogenesis. There have been suggestions that lower magnesium levels can be associated with diminished ATP, the consequent muscle weakness, and fatigue, which are characteristic of CFS. Also, lower magnesium levels have been implicated in lipid peroxidation in conditions like diabetes and atherosclerosis [29–32]. Oxidative stress and magnesium have been studied in CFS as well. In a study done by Keenoy et al., patients with CFS who had low magnesium levels were supplemented with 10 mg/kg/day of oral magnesium [33]. Before this treatment, lower magnesium levels correlated with total antioxidant capacity. At the end of the study, there was an increase in the levels of vitamin E and transferrin and a decrease in lipid peroxidation products (TBARS).

Besides magnesium, low vitamin E levels also correlate with increased lipid peroxidation and this has been demonstrated in CFS patients by several authors [34–36]. Vecchiet et al. showed a significant correlation of low vitamin E levels to fatigue [34]. Similar results were achieved by a group of Japanese authors in 2 studies [35,36]. They also claim that the independent risk factors are low for coronary heart disease in CFS patients and a good indicator for the intensity of lipid peroxidation in these patients. There have been several proposals that CFS patients should be supplemented with vitamin E, but the only literature available is on multivitamin supplementation that included this vitamin as well. CFS patients were also shown to be deficient in zinc [37]. In the present study, zinc correlated with $\alpha 2$ globulin level (inflammatory response indicator) and with a subjective experience of infection.

Besides the scientific rationale behind supplementation, many patients decide to take a multivitamin with or without a physician's advice. In this study, we aimed to investigate the effects of a widely available multivitamin mineral supplement on oxidative stress levels and subjective complaints in CFS. We wanted to study a supplement that would be available for other patients later on if proven to be effective. Supradyn® contains a safe, below therapeutic dose of vitamins and minerals. Some of them have been used in previous studies in patients with CFS, such as vitamin B, magnesium, zinc, and selenium [23,28,29] and/or have been shown to be decreased in CFS (vitamin E, magnesium, zinc) [28,34–37].

To get the most complete results, we decided to determine both objective and subjective parameters in CFS. As the objective parameter of supplement efficiency, the activity of the most important antioxidant enzyme – superoxide dismutase (SOD) – was used. SOD has previously been used as a marker of oxidative stress in numerous studies, including CFS animal models [38–41]. Higher SOD activity is considered a measure

of good antioxidant status and lower SOD activity is considered a sign of increased oxidative stress [42–44]. We are aware of only 1 group of authors who have measured SOD activity in CFS patients [38]. In that study, muscle biopsies were performed to detect oxidative damage to DNA and lipids in muscle specimens of CFS patients in comparison to age-matched controls. No difference in SOD activity was found between the 2 groups. In our study, we found a significant decrease in SOD activity after the treatment. We also found several significant correlations between quality of life measures (physical function, physical role, bodily pain, vitality, and mental health) and SOD activity, but only after treatment. This is one of the reasons we believe a drop in SOD activity may be an indication of normalized SOD activity.

In the literature on CFS, the only other objective marker of antioxidant supplement activity was erythrocyte fragility [45]. In that study, Öckerman used a pollen extract with well-documented antioxidant activity and showed a significant improvement in erythrocyte fragility. He also noted decreased symptoms like fatigue, sleep disturbances, and digestion in most CFS patients.

Most of the previous studies on supplementation in CFS used different questionnaires to evaluate treatment effect. In the first study on multivitamin use in CFS, from 1994, Martin et al. used a supplement on 42 patients [46]. Treatment effects were evaluated every month for 6 months, with a general health questionnaire sent by mail and used previously only with patients with depression. The study had a high drop-out rate (almost 50%) and although the initial results showed improvement in most of the patients who finished the study, the variance analysis failed to show change. In a much larger study on 242 people taking Pharmaton® capsules containing ginseng, investigators demonstrated diminished fatigue after a 6-week course of treatment [47]. The only randomized clinical study on supplementation in CFS was carried out in 2002 by a Dutch group on 16 men and 37 women. The treatment effect was determined using 2 questionnaires, a pedometer, and a daily diary of fatigue. At the end of study, the group found a complete lack of treatment effects. Although it was a randomized, double-blind study, there were no biochemical markers of treatment success and the participants were asked to focus on the symptoms during the whole course of the study.

In our study, we asked the participants to answer 2 questionnaires. One was the FFS, which is one of the tests used for assessing symptom severity in CFS. Similarly to some of the studies previously mentioned [45–47], we also found a reduction in some symptoms' intensity after 2 months of supplementation. Patients were less fatigued, had fewer sleep disturbances, less pronounced vegetative disorders, headaches were less frequent, and the subjective feeling of infection declined. There

is now a considerable body of evidence on immune activation, as suggested by an elevation of pro-inflammatory cytokines increased expression of T lymphocyte activation markers such as CD26 and CD38, and decreased function of natural killer (NK) cells [48]. Because some of the improved symptoms like fatigue, feeling of infection, headaches, and vegetative disorders can be caused by low-level inflammation, we believe that, in correlation with decreased SOD activity, this could be an indicator for diminishing levels of inflammatory cytokines and could be a basis for further investigation of this type of supplementation.

Quality of life is a goal for all treatments and is usually decreased in chronic diseases [49–52]. Contrary to most other studies, we did not find evidence of decreased quality of life in our CFS population. This is an unusual finding because most of the previous studies found a low quality of life in CFS patients compared to general population [53–55]. This may be because due of lack of SF36 standards in Serbia we used Croatian standards based on the geographic, cultural, and historical similarities of the 2 countries. This could have been an incorrect assessment because, of course, there are many differences between the observed and the standard Croatian population.

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Conclusions

This study is only the second study done on multivitamin mineral supplementation in CFS that used both biochemical and subjective markers of treatment success. Similar to other experimental studies on CFS, this one was also done on a relatively small number of patients. In our case this was due to the small number of patients diagnosed with the condition in our region, where CFS is rarely diagnosed and the incidence is unknown. We believe the power of this study lies in promising results in normalization of antioxidant enzyme activity and improvement of symptoms. Since immune activation and oxidative stress are now well documented in CFS, we believe this type of supplementation could be a safe addition to other therapeutic options for CFS patients.

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