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Improvement of fatigue in patients with systemic lupus erythematosus (SLE) and undifferentiated connective tissue diseases (UCTD) with the use of a SOD-enriched whey protein formula

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TITOLO
Miglioramento dell'astenia in pazienti affetti da lupus ertematoso sistemico e da connettivite indifferenziata con l'impiego di una formulazione di proteine da siero di latte arricchita con superossido-dimutasi

KEY WORDS
Systemic lupus erythematosus, undifferentiated connectivite tissue, asthenia, supplementation of whey protein

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Lupus eritematoso sistemico, connettivite indifferenziata, astenia, integrazione con proteine da siero di latte

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Summary
In this work we report the results of our study on fatigue in a cohort of 100 patients with systemic lupus erythematosus (SLE) and undifferentiated connective tissue disease (UCTD). We evaluated the efficacy on fatigue, of a preparation of way proteins characterized by high content of cysteine and cystine (Prother™ SOD). The results showed that this preparation is effective in controlling fatigue in this group of patients.

Riassunto
In questo articolo riportiamo i risultati del nostro studio, condotto su 100 pazienti affetti da lupus eritematoso sistemico (LES) e da connettivite indifferenziata, con lo scopo di valutare l'efficacia, sull'astenia, di una preparazione a base di proteine da siero di latte, ad elevato contenuto di cisteina e di cistina (Prother™ SOD). I risultati ottenuti dimostrano che la formulazione è efficace nel controllo di tale sintomo nei pazienti presi in considerazione.

Fatigue and SLE

Fatigue is a common complaint in patients with Systemic Lupus Erythematosus (SLE) and it is reported in more than 80% of them while in 30-50% it is s the most disabling symptom (1). The cause of fatigue is not known but it is associated to mood disorders, poor sleep patterns, low levels of aerobic fitness and to myalgia and diffuse arthralgia, as in patients with fibromyalgia. Kaiser et al, in a study of patients with medium-moderate SLE, observed that fatigue is associated with aerobic insufficiency, which is the reason of the reduced activity of patients (2). On the other side Tench et al observed, in 93 patients with SLE without active disease in any major organ, that fatigue improves when appropriately prescribed graded aerobic exercise (3). Anyhow it is difficult, for patients with fatigue to make aerobic exercise. Therefore it is important to explore other ways to reduce the severity of fatigue in order to make patients able to conduct aerobic exercise.

Consequences of fatigue

In patients with SLE fatigue causes a poor quality of life, affecting social life and working activity. The relationship between fatigue and activity of disease is controversial, in fact, also if it is a consensus that patients with a quiescent disease continue to experience this symptom (4), authors reported a correlation between fatigue and disease activity index (5). Fatigue and mood disorders strongly affect quality of life in patients with SLE, in particular contributes to depression (6). Patients with fatigue are unsure about their physical performance and working activities, which in turn complicates the relationship with other people and the ability to execute the normal-life activities. Fatigue is also present when the disease is quiescent and therefore the patient's malaise is often seen by relatives and colleagues as unjustified; the patient's physical conditions may be good and accompanied by modest or even absent clinical symptoms and therefore the patient is often considered an absentee or as simply being bone-idle.
Fatigue disrupts normal daily activities, which often leads to disability. In a population of 1248 patients with SLE from the German Collaborative Arthritis Centres only 40.8% of them were gainfully employed and 18.5% early retired. In this population of patients the percentage of employed patients with sick leave during the past 12 months, because rheumatic disease, was 35.7% (7). Treatment of SLE does not improve fatigue, although hydroxychloroquine is a widely considered a useful treatment for this symptom. Hence the need to experiment new strategies in support of conventional therapies, based, for example, on targeted nutritional supplementation (8), able to control oxidative stress.
The oxidative stress is the result of breakdown of the physiological balance between production and elimination, by antioxidant defence systems, of Reactive Oxygen Species (ROS) (9).

SLE and oxidative stress

An increase of oxidative stress is reported in patients with SLE (10, 12). Oxidative stress is one of the pathogenic factors of early onset cardiovascular damage observed in patients SLE and it is more frequently associated to anti-phospholipid syndrome. In fact these patients have an high incidence of early vascular damage and early atherosclerosis (13).

Oxidative stress and fatigue

Oxidative stress is also increased in patients with chronic fatigue syndrome (14). The musculoskeletal pain, which is often associated to the syndrome, is related to an alteration of nociception, which in turn is a consequence of increased oxidative stress (15). Increased production of ROS induces isoprostane which stimulates nociceptors C and, consequently, pain (16).
Avalos et al. observed that in patients with moderate SLE the oxidative stress, evaluated with urinary excretion of isoprostane F, is correlated to fatigue score, according the Fatigue Severity Score (FSS), and to a poor quality of live, but not to disease activity measured with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) (17).
The underling hypothesis of our work was that fatigue in SLE is a consequence of ROS accumulation, so that a nutritional strategy for reducing ROS could, al least theoretically, improve this symptom.

Instrument to evaluate fatigue

The most commonly used instrument to evaluate fatigue in SLE is the "Krupp Fatigue Severity Scale" (FSS) (18). FSS has been recommended by the Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue (19), because it is based on its vali-

date psychometric properties. In FSS are evaluated nine points. For each of them we have a score from 1 (no fatigue) to 7 (maximum of fatigue). The final score is the average of the results obtained from every point. The Committee suggest that a 15% of decrease of FSS score has to be interpreted as an important improvement of fatigue (Table 1).

Whey proteins

In the control of oxidative stress, the enzymatic axis responsible for elimination of ROS generated by activation of NADPH oxidase, present on the membranes of cells involved in inflammatory response, is represented by superoxide dismutase (SOD) and peroxidase system, such as catalase and, in particular, glutathione peroxidase, whose coenzyme is the tripeptide glutathione (GSH), consisting of glutamic acid, cysteine and glycine (20). It is known that milk whey proteins, for their high content of cysteine and cysteine residues promote the endogenous synthesis of GSH, allowing glutathione peroxidase to reduce peroxides, markers and amplifiers of the oxidative insult, to innocuous alchols (9). This mechanism of antioxidant defence, however, although effective on peroxidases already formed, is not active against superoxide anion, generated directly by NADPH oxidase, whose inactivation is responsible, however the SOD (9). For these reasons, the addition of SOD to a formula based on whey proteins – providing the necessary substrate for the conversion of superoxide anion to water – is a very attractive and innovative strategy to rebalance the oxidative balance which alteration contributes to the genesis of the observed symptoms of fatigue in SLE and in disease related to it. Moreover, the proteins from whey have always been favourable properties on metabolism and muscle physiology in general (21).

Based on these considerations we performed a longitudinal open-label study in patients with SLE or UCTD with the aim of assessing the effectiveness, on the symptom of fatigue, of a preparation of whey proteins – with an high content of cysteine and cystine – obtained through a controlled process of ultrafiltration and spray drying at low temperature, with the addition of vegetable SOD (activity). This formulation is duly registered with Italian Ministry of Health as a dietary food for special purposes (Prother™ SOD).

Table 1 - The Fatigue Severity Scale

Items:
1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

Individuals chose a number from 1 to 7 (where 1 = strongly disagree and 7 = strongly agree).

Results of the study

From January 2005 to December 2010 were enrolled 100 patients, all previously treated for this disease and whose state of fatigue was present for at least three months prior to administration of the integrator and had not been changed with the medical therapy used. Disease status (active or quiescent) did not correlate with the fatigue reported by patients (data not shown).

The formulation, which is in powder form, was assumed after it dissolved in yogurt, fruit juice or cold milk, in the morning during breakfast, for a minimum period of 3 months.

Sixty-six/100 patients, took the supplement continuously for 3 months and were evaluated with the FSS. Thirty-four assumed the supplement for less than three months and were not included in this preliminary analysis. Median age was 46 years (range 15 to 95 years), with a prevalence of females (ratio F: M 58:8, ie 88% vs. 12%). Of these, 27 had a diagnosis of SLE based on ARA criteria, and 39 of undifferentiated connective tissue (UCTD).

The FSS questionnaire was assessed at time 0 and 3 months. We considered as non-responsive patients who have had a change of the score less than 10%; for those with a higher response, we evaluated the response as "satisfactory" when the variation of the scores was between 10 and 30% and "good" over 30%. Only 15% of patients were non-responsive, while 64% of them showed a "satisfactory" response, compared with 12% attributable as "good" responders. Ultimately, 76% of patients showed a significant global response to treatment, which was related to a better quality of life.

The nutritional supplementation with the new formula was well tolerated. Only 2 patients decided to stop taking it for a sense of nausea, which have reported related to the low palatability of the product.

This trial has several limitations, including lack of a control and the absence of biochemical assessments of oxidative stress. On the whole, however, remained confined only to fatigue symptom, for which it was designed.

In conclusion this study suggests that the intake of a formula based on whey proteins with the addition of SOD may be effective in controlling fatigue in patients with SLE and with UCTD, in up to levels that have a positive impact on quality of life, without interfering with the specific treatments used to control the disease.

Further studies should confirm these encouraging preliminary results.

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