letter

Carnitine deficiency in scleroderma

In a recent *Trends* article, Rose and Leskovsek suggest the use of antioxidant drugs to treat scleroderma (SSc), although they do not discuss the rationale of this strategy[1].

Patients with SSc have unbalanced redox metabolism and oxidant stress, as most are deficient in antioxidant micronutrients such as ascorbic acid, selenium and carnitines[2–5].

Carnitines are present in all tissues and act as essential cofactors in the system that transports long-chain fatty acids across the inner mitochondrial membranes, where they undergo β-oxidation and energy production[6]. Thus, a balanced pool of carnitines is crucial to the normal energy metabolism of cells and, as a consequence, alterations in metabolism or levels of carnitines might substantially affect energy production and severely impair mitochondrial function. Importantly, it has been demonstrated that impaired mitochondrial function with disrupted transmembrane potential is an early and irreversible step in the effector phase of apoptotic cell death[7]. This supports recent evidence that the anti-depolarizing action at the mitochondrial level and antioxidant activity of carnitines participate in their anti-apoptotic effect[8]. Taken together, it appears that carnitine deficiency or altered carnitine metabolism, regardless of the cause, should be regarded as a potentially relevant factor contributing to tissue injury and functional organ impairment.

The clinical subgroup of SSc might have an important impact on the carnitine status of SSc patients. In our study, the vast majority of patients with diffuse cutaneous involvement had reduced concentrations of total and/or free carnitine in their sera but patients with limited cutaneous SSc had normal or elevated levels. However, we found no other correlation between carnitine concentration and disease duration, internal organ involvement (lung fibrosis and oesophageal hypomotility) and laboratory parameters (IgG, IgM and IgA levels, antinuclear antibody titer and erythrocyte sedimentation rate) of the disease. Furthermore, we found no difference in serum carnitine levels between SSc patients receiving treatment with prednisolone and untreated patients, but it is unclear whether long-term administration of corticosteroids can affect carnitine metabolism.

The mechanisms leading to carnitine deficiency in SSc patients are not yet fully understood. Causes might include: reduced dietary intake due to decreased appetite or dysphagia; reduced absorption, attributed to a subclinical malabsorption syndrome due to the intestinal involvement by SSc; or even changes in carnitine metabolism. Interestingly, malabsorption has been ruled out as a cause of the reduced circulating levels of ascorbic acid in SSc patients[9]. Subclinical renal disease and bacterial overgrowth in the gut lumen could be additional factors contributing to carnitine depletion in these patients.

Because free radicals and oxidant stress appear to play a role in SSc pathology[2–4], deficiencies in carnitines as well as in other antioxidant micronutrients might predispose towards irreversible tissue injury over the course of SSc. As carnitines interfere with the transduction of apoptotic signals to lymphocytes[10–12], the depletion of the carnitine pool is implicated in lymphocyte activation and unregulated cytokine production, which are ongoing features of SSc (Refs 13–15).

To our knowledge, no other data are available on carnitine levels and metabolism in SSc patients. It should be noted that our conclusions are based on a study of a limited number of SSc patients, therefore, caution should be used when extrapolating these results to the broad population of SSc patients. Information obtained through investigating a larger sample of patients could be of value in delineating new therapeutic strategies that might improve the clinical status of SSc patients or perhaps alter the course or slow the progression of disease. The hypothesis that carnitine administration could be helpful in the clinical management of SSc patients should be tested in formal clinical trials. Interestingly, early uncontrolled studies reported that the administration of L-carnitine had a favourable impact on the course of the disease (reviewed in Ref. 5) and this improvement was paralleled by a reduction in serum immunoglobulin levels[16].

References

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