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Clinical Nutrition and Metabolism Group Symposium on 'Nutrition in the severely-injured patient'

Part 2

Micronutrients in the severely-injured patient

Alan Shenkin
Department of Clinical Chemistry, University of Liverpool, Duncan Building, Daulby Street, Liverpool L69 3GA, UK

The trace element and vitamin requirements of severely-ill injured patients depend on a complex interaction of the status of the patient at the time of admission, ongoing losses and the potential benefit of supplying large amounts of individual micronutrients. Characteristic clinical deficiency states are now uncommon, but subclinical deficiency is of growing concern. The main effects of subclinical deficiency are: (1) an altered balance of reactive oxygen species and antioxidants, leading to oxidative damage of polyunsaturated fatty acids and nucleic acids, and possibly to increased activation of the transcription factor nuclear factor-κB, with increased production of pro-inflammatory cytokines; (2) impaired immune function with increased likelihood of infectious complications. Laboratory tests to optimize intake in such critically-ill patients lack sensitivity and specificity, this situation being made worse as a result of the acute-phase response. Recent studies have indicated the clinical benefit of providing large amounts of certain micronutrients in burned and head-injured patients. Further clinical studies are now required to define optimal levels of provision in different disease states, with a particular emphasis on markers of tissue function and clinical outcome.

Micronutrients: Severely-injured patients: Subclinical micronutrient deficiency

Despite the increasing interest in micronutrients in recent years, evidence remains too sparse to permit confident recommendations for dietary intakes. Difficult though this situation is in health, the problems are magnified several fold when considering disease states where the acuteness and severity of the illness and the associated patho-physiology may all affect requirements for individual micronutrients. Attention has been progressively shifting away from the relatively simple objective of prevention of obvious clinical deficiency states to the much more complex concept of achieving optimal tissue or organ function.

The micronutrient requirements of a patient depend on the net effect of three considerations:

(1) the status of the patient with respect to that micro-nutrient, i.e. the extent to which the intake has been sufficient to meet losses from the body and the requirements for growth or repair in the recent past, and hence whether the concentration of the micronutrient is adequate to maintain normal biochemistry in all cells and fluid compartments where it is biochemically active;

(2) the ongoing consumption or losses of each micronutrient;

(3) whether there is any benefit from supplying a micronutrient in amounts substantially greater than those required to meet normal nutritional functions.

Abbreviation: ROS, reactive oxygen species.

Corresponding author: Professor Alan Shenkin, fax +44 (0) 151 706 5813, email shenkin@liverpool.ac.uk

Factors affecting the micronutrient status of a severely-injured patient

The status on admission

Most patients admitted to hospital after an acute severe injury will have relatively normal micronutrient status, at least initially. This status will depend on the adequacy of their oral diet during daily living, and by definition, this status should be adequate for most healthy individuals. Certain groups of individuals are at risk of depletion of certain micronutrients as a result of their atypical diets or lifestyles. In particular, individuals with depleted status who are also especially at risk of injury are those consuming excess alcohol (at risk of vitamin B and C depletion), or the elderly, especially if institutionalized (risk of Fe, Zn, folate and vitamin C depletion; Finch *et al*. 1998).

Increased requirements to meet metabolic demands

Hypermetabolism associated with severe injury such as burns or multiple trauma will inevitably be associated with an increased requirement for cofactors involved in metabolic pathways. Requirements for thiamine and niacin are linked to energy metabolism, that of vitamin E to polyunsaturated fatty acid intake and metabolism, and that of pyridoxine to amino acid metabolism (Department of Health, 1991). Although requirements for other micronutrients have not been linked as closely, it seems logical to assume that their requirements increase at least proportionately with those of the macronutrients.

There is increasing interest in the altered requirements for micronutrients to cope with reactive oxygen species (ROS) generated as part of oxidative metabolism (see p. 453). Since ROS production is increased following severe injury, certain micronutrients will be consumed, and moreover most will be required in greater amounts to cope with the oxidative challenge (Furst, 1996).

An important feature of micronutrients is that the increased requirement may be present not only during the period of hypercatabolism which is associated with severe illness, but it may also continue into the prolonged period of tissue anabolism and recovery which follows. Deficiency states have frequently been observed during this period of anabolism, during which new cells and tissues are formed and micronutrients are incorporated and utilized within them (Kay *et al*. 1976).

Increased losses

Severely-ill patients are likely to lose substantial amounts of micronutrients, especially water-soluble nutrients. Thus, after severe burns losses of trace elements, and probably of certain water-soluble vitamins, in burn exudate fluid are markedly increased (Berger *et al*. 1992). Moreover, patients with substantial blood loss, those who require haemodialysis or peritoneal dialysis, or who develop complications of surgery leading to gastric aspirate or intestinal fistula losses, will all lose trace elements such an Mg, Zn and Cu, and water-soluble vitamins such as vitamin C and folate.

Reduced provision

Although the factors mentioned earlier all increase the requirement for micronutrients, severely-ill patients often have reduced levels of provision. This situation results partly from the delay in provision of a full nutrition regimen whilst stabilization of the condition of the patient is achieved, or whilst attempts are made to introduce enteral nutrition, and partly from the fact that provision of the nutrition regimen itself is frequently interrupted as part of other clinical or diagnostic procedures, so that the prescribed amounts are not provided in each 24 h period.

Consequences of impaired micronutrient status

Clinical deficiency states

Classically, severe micronutrient deficiency leads to a characteristic deficiency state, with specific structural or functional changes which are reversible on provision of the individual micronutrient. An intriguing feature of this type of deficiency is the extent to which the deficiency state can be recognized as a result of the features of presentation being fairly consistent. For example, Zn deficiency is typically associated with anorexia, diarrhoea, alopecia and eczematous skin rash in body flexures, whereas folate and vitamin B_{12} deficiency are associated with megaloblastic anaemia. On the other hand, thiamine deficiency may present as quite different syndromes, as a highly aggressive form of dilated cardiac failure with lactic acidosis (Shoshin beri-beri), as high-output cardiac failure (wet beri-beri) or as neurological beri-beri (with facial nerve palsy, possibly together with Korsakoff psychosis; LaSelve *et al*. 1986). Se deficiency may present with skeletal myopathy, cardiomyopathy, hair or nail changes, or anaemia (Vinton *et al*. 1988). Intriguingly, only a small proportion of patients with severe Se deficiency develop obvious clinical signs, suggesting that some other factor, e.g infection or stress, may be a necessary factor in leading to one of the clinical Se deficiency states (Shenkin *et al*. 1986).

Subclinical deficiency

It is now increasingly recognized that clinical deficiency states are the end point of a progressive process extending over days, weeks or months, the duration depending on the extent of stores of individual micronutrients and the magnitude of the daily shortfall in provision. During the course of development of a deficiency state, patients pass through a series of stages (Fig. 1). Initially there is depletion of stores and of tissue content, with attempts to compensate either by increased absorption from the gut or by reduced excretion, where this process is possible. This stage is followed by a period of reduced intracellular concentration, leading to some impairment of biochemical functions. This stage in turn may lead on to a period of non-specific functional defects where there may be identifiable problems in metabolism, immune function, certain types of cognitive function, or in fatigue and work capacity. It is only after a further variable period of time that these non-specific defects give rise to a characteristic clinical deficiency state.

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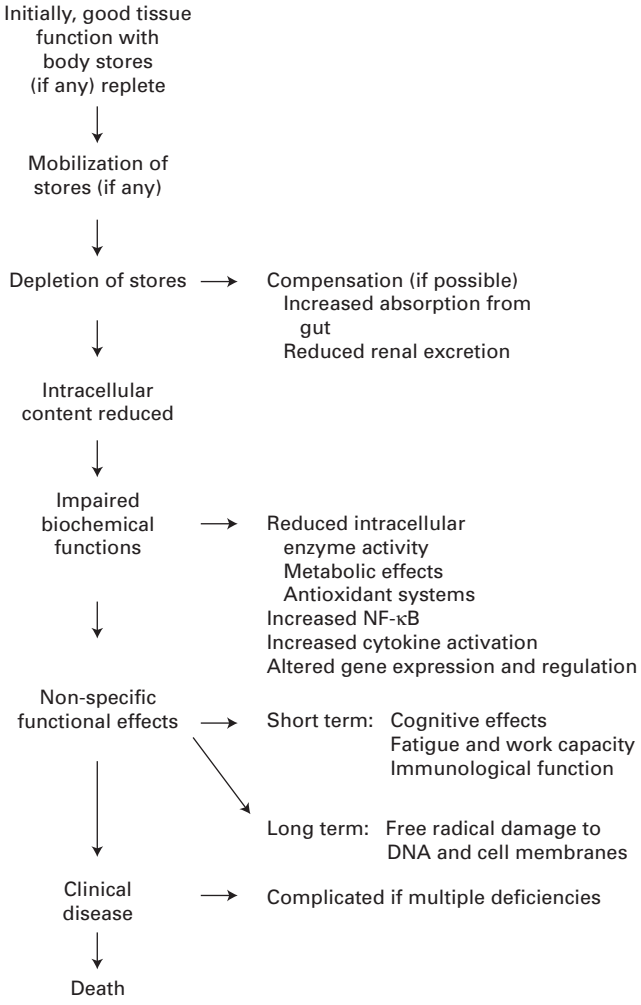

Fig. 1. Consequences of inadequate vitamin and trace element intake in serious illness. NF-κB, nuclear factor κ-B.

These states which lead up to clinical deficiency are sometimes defined as subclinical deficiency, since vitamin or trace element status is poor but the overt signs of deficiency are not yet present. Part of the challenge in the critically-ill patient is to identify the progressive development of subclinical deficiency and prevent its progression to more severe states.

Biochemical changes associated with subclinical deficiency may not be apparent against the background of severe illness. Thus, there may be impaired glucose tolerance or worsening of N balance. One specific example may be the low triiodothyonine syndrome which is found in critical illness. This syndrome may at least in part result from impaired Se status, leading to a reduction in the selenoprotein type I 5′-deiodinase, with consequent reduction in peripheral thyroxine deiodination (Berger & Shenkin, 1998).

The clinical penalty associated with a subclinical micronutrient deficiency is particularly difficult to define, since effects may be mild and non-specific, and only become apparent after a long period or when a particular stress is superimposed. In patients admitted to the intensive care unit at Glasgow Royal Infirmary a few years ago, those with impaired thiamine and riboflavin status were more likely to die in the unit than those with relatively normal biochemical status (Cruickshank *et al*. 1988; Shenkin *et al*. 1989). None of the patients had clinical signs of vitamin deficiency, and there were no other significant differences in biochemical or nutritional status between those who survived and those who died in the unit. The mechanism of this association was by no means clear, but possible ways in which subclinical deficiencies may alter cellular or tissue function will be described.

Possible effects of subclinical deficiency

Altered balance of reactive oxygen species and antioxidants

Increased reactive oxygen species in acute illness. A number of ROS have been observed to increase in acute illness. These species include not only free radicals such as superoxide, hydroxyl and nitric oxide, but also non-radical species H_2O_2 and HOCl. Their production is associated with increased oxidative metabolism associated with the hypercatabolism of severe illness (Halliwell & Gutteridge, 1999). Clinical conditions associated with increased ROS therefore include sepsis, acute respiratory distress syndrome, renal failure and various forms of trauma including burns, bony fractures, brain injury and reoxygenation after a period of ischaemia (Berger & Shenkin, 2000).

Reduced antioxidants in critically-ill patients. Many studies have demonstrated low plasma and intracellular concentrations of the various antioxidants. For example, α-tocopherol has been shown to be reduced in patients with acute respiratory distress syndrome (Richard *et al*. 1990), plasma vitamin C concentrations are low in patients in the intensive care unit despite large doses of vitamin C (Schorah *et al*. 1996), and poor Se status with concomitant low GSH peroxidase activity has been found in many forms of critically-ill patients, including those with burns, trauma, dialysis and sepsis (Forceville *et al*. 1998). Although not as well characterized, it would seem likely that other aspects of the intracellular antioxidant systems, such as superoxide dismutase (which is Mn dependent in mitochondria, and Zn and Cu dependent in cytoplasm) vitamin A or β-carotene, and glutathione are also significantly reduced in critically-ill patients.

Some of the effects on total antioxidant activity may be ameliorated by the use of Propofol®, a widely-used anaesthetic agent. Propofol® has a structure which is chemically similar to α-tocopherol, and various studies have indicated that some of the effects of $_2O_2$ on lipid peroxidation and also on left ventricular function can be attenuated by the use of Propofol® in typical pharmacological concentrations (Kokita & Hara, 1996). When the antioxidant capacity of Propofol® in plasma has been measured, it has been found to provide about one-third to half the activity of vitamin E, and may therefore be of value in situations where the vitamin E concentration is limiting (Aarts *et al*. 1995).

Effects of altered balance of reactive oxygen species and antioxidants The increase in ROS coupled with reduced antioxidant activity inevitably means that intracellular oxidative damage is likely. This damage is particularly

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directed at polyunsaturated fatty acids within mitochondrial membranes, nuclear membranes and cell membranes, with the probable result of altering their permeability, deformability and protein-binding characteristics (Halliwell, 1997). Products of oxidative metabolism of polyunsaturated fatty acids increase in plasma and urine, and various studies have demonstrated increased urinary malonyldialdehyde or other oxidative products (Halliwell & Gutteridge, 1999).

Oxidative damage within the nucleus is potentially of greater long-term significance, although perhaps less relevant in the acutely-ill patient. Oxidation of guanine residues within DNA may lead either to mutagenesis with potential neoplastic change, or may prevent further replication of DNA and hence tissue growth and regeneration (Ames, 1998). The reaction of free Fe^{2+} with superoxide radicals converts them to the highly-reactive hydroxyl radical which is most likely to cause damage to DNA.

An interesting example of probable oxidative damage to genetic material has been identified by Beck *et al*. (1995) in relation to Se deficiency. They demonstrated that when Se-deficient mice were infected with a normally benign strain of Coxsackie virus B_3 which was not expected to cause any damage to the myocardium, the virus genome underwent mutation. Six base changes in the RNA genome occurred, and these changes led to the strain of virus becoming virulent with respect to causing heart damage in the Se-deficient mice. The precise mechanism of this change is under study, and it remains to be demonstrated whether Se deficiency may result in alteration in the genome of other viruses so that they may become more virulent. Moreover, studies are required to determine whether this effect may also be associated with deficiency of other antioxidants.

A further example of the effects of the altered balance of ROS and antioxidants may be found in the effect on cytokine activity. With the altered redox state of the cell, there is increased activation of the transcription factor nuclear factor κ-B by many stimuli including lipopolysaccharide, viruses and cytokines. This process stimulates increased synthesis of pro-inflammatory cytokines, such as interleukin 1 and tumour necrosis factor, which will cause increased metabolic rate, protein catabolism and further production of ROS. The activation of this factor, on the other hand, may be inhibited by a variety of antioxidants, so that optimization of micronutrient antioxidants may reduce the severity of the inflammatory response (Christman *et al*. 1998).

Subclinical deficiency and infection

One of the most important subclinical effects of micronutrient depletion is to alter some aspects of immune function. *In vitro* studies demonstrated that most micronutrients have some effect either on T-cell function, B-cell function, or on neutrophils (Chandra, 1997). Severe Zn deficiency, for example, not only reduces T-cell numbers and T-cell responsiveness to mitogens, but is also associated with reduced primary antibody responses, and a reduced delayed hypersensitivity response (Keen & Gershwin, 1990). Nonetheless, it has proved remarkably difficult to determine the clinical consequences of impaired function of individual aspects of the immune system. Better evidence has come from supplementation studies where reducing or preventing the subclinical deficiency has led to clinically-measurable benefits.

An important trial was performed by Berger *et al*. (1998) who studied the effects of provision of intravenous Cu, Zn, and Se in doses between two and six times the normal intravenous supply for the first 8 d after severe burns. This treatment led to a reduced incidence of pulmonary infections over the 30 d period following the burn injury. The amount of the trace elements was calculated to meet the increased losses through burn exudate. Although the pulmonary infection rate was reduced, the mechanism of this reduction was not apparent in terms of standard tests of lymphocyte cell number or function, although total leucocyte numbers were increased between days 10 and 20 following burn in the group given supplements.

In a separate study Young *et al*. (1996) demonstrated that provision of large amounts of Zn in patients who had suffered head injury led to significant improvements both in mortality and in Glasgow Coma Score over a 28 d period. Again the mechanism for this change is not clear, and the study was complicated by the fact that more patients in the low-Zn group underwent craniotomies than those in the high-level supplementation group.

Zn supplements have been found to reduce the severity of diarrhoea and respiratory infection in infants (Lira *et al*. 1998), and vitamin A supplements reduce complications of measles infection (Glasziou & Mackerras, 1989).

Clinical studies in seriously-ill patients are complicated by the many major factors which influence outcome. The studies mentioned above do suggest, however, that outcome may be modified by appropriate micronutrient supplements, especially when these supplements are designed to minimize subclinical deficiency, and further studies in different clinical groups are required.

Optimization of intake

It is clear, therefore, that prevention of deficiency states cannot be regarded as the only end point in terms of provision of micronutrients. Some measure of functional benefit would appear to be most valuable (King, 1996), and it seems probable that the two areas of greatest clinical benefit would be improved immune function in the short term, and perhaps improved antioxidant function in the long term.

Laboratory tests are of relatively little value in this group of patients with regards to assigning optimal levels of intake. Most of the laboratory tests are affected by illness, either by the acute-phase reaction with changes in carrier proteins, or by altering the distribution of the trace elements or vitamins themselves. Thus, an acute-phase reaction causes a marked fall in serum Zn and Fe, and a rise in serum Cu (Shenkin, 1995), and also significant falls in vitamins C, A and D in plasma (Louw *et al*. 1992).

Laboratory tests are only of value in this group of patients when used sequentially, and when interpretation is linked to changes in the magnitude of the acute-phase response, e.g. by measuring C-reactive protein concentration in serum. The main value, however, of measuring

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blood concentrations is to prevent the extremes of under- or over-provision of micronutrients.

Suggested provision of micronutrients in critically-ill patients

Ideally, most critically-ill patients will meet their micronutrient requirements by the enteral route. Not only might this provision be beneficial in maintaining the structure and function of the intestinal mucosa, but it will also involve the normal safety mechanism of selective gut absorption, especially of trace elements.

In practice, however, intake of nutrients by the enteral route will be limited in this group of patients, and hence intravenous supply should be considered. Patients in intensive care almost certainly have increased requirements for all micronutrients. Berger & Shenkin (2000) have suggested provision of approximately 10 mg Zn, 1·3 mg Cu and 100 μg Se in the intensive care patient, this level of provision rising to 40 mg Zn, 3·75 mg Cu and 375 μg Se in burn patients. As far as vitamins are concerned, although the usual intravenous requirement for thiamine and vitamins C and E are 3 mg, 100 mg and 10 mg respectively in typical intensive care patients, these amounts may rise to about 250 mg (for the first 2–3 d), 250 mg and 50 mg respectively for the typical intensive care unit patient, possibly with very high requirements of > 1000 mg for vitamin C and 100–200 mg for vitamin E in patients with severe burns. These levels of provision will vary with the severity of the injury and the subsequent clinical progress, and it is evident that further clinical studies are required with both clinical and laboratory end points.

Summary

There is a greatly increased micronutrient requirement in critical illness. This increase results partly from the increased metabolic requirement in such patients, and partly from the increased losses which such patients are likely to suffer. Methods of assessing requirement, however, are poorly defined, especially since most of the biochemical tests are affected by the acute-phase response. The best methods of assessment would appear to be the clinical response to particular supplements. Clinical trials of such supplements are beginning to be performed, and further trials investigating different levels of provision are now urgently required to define optimal provision in different disease states.

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