Supplementation with selenium and coenzyme Q10 in critically ill patients

ABSTRACT

Multiple organ dysfunction and resultant mortality in critically ill patients has been linked with impaired cellular energy supply and oxidative stress. Clinical studies supplementing selenium, on the basis of its role as a key cofactor of antioxidant enzymes, have reported variable outcomes in critically ill patients. However, the synergistic interaction between selenium and coenzyme Q10, which has essential roles in cellular energy supply and as an antioxidant, has not been considered in such studies. This article reviews the link between selenium and coenzyme Q10, and the potential role of their co-supplementation in critical illness.

Multiple organ dysfunction in the critically ill has been linked to mitochondrial dysfunction, oxidative stress and inflammation. Critically ill patients have been supplemented with selenium in order to enhance their antioxidant capacity, although results have proven equivocal. However, in view of the synergistic relationship between selenium and coenzyme Q10 (CoQ10) at the cellular level, the co-supplementation of selenium and CoQ10 may be of therapeutic benefit to critically ill patients.

Mortality in critically ill patients is linked to multiple organ dysfunction; this in turn has been linked to a self-reinforcing destructive cycle of mitochondrial dysfunction, impaired cellular energy supply, oxidative stress and inflammation (Mantzarlis et al, 2017; Pool et al, 2018). To address this problem, critically ill patients have been supplemented (intravenously or orally) with selenium, primarily because the latter is an essential component of antioxidant enzymes protecting against free radical-induced oxidative stress (Mertens et al, 2015; Steinbrenner et al, 2016). The results from such studies supplementing selenium in critically ill patients have been equivocal with one review suggesting that selenium supplementation is unwarranted (Manzanares et al, 2016). However, one issue which has not been considered is the interaction between selenium and CoQ10, which plays a key role in the cellular energy production mechanism; if levels of CoQ10 are deficient then the effect of supplementation with selenium is likely to be sub-optimal. This article reviews the link between selenium and CoQ10, and the potential role of their co-supplementation in critically ill patients.

Pathogenesis of multiple organ dysfunction

Major causes of critical illness include sepsis, trauma (head injury) and burn injury. These in turn result in immune system activation, inflammation, oxidative stress and ultimately multiple organ failure and possible death – it has been estimated that up to 50% of critically ill patients do not survive sepsis. Treatment to minimize the risk of multiple organ dysfunction is based on prevention of tissue hypoxia. However, despite the early optimization of oxygen haemodynamics, delivered oxygen may not be adequately used at the cellular level. Mitochondria consume approximately 90% of cellular oxygen during oxidative phosphorylation to generate energy in the form of ATP, on which the normal functioning of all cells depends; mitochondria are also both a source of and target for free radicals (Al Shahrani et al, 2017). Inflammation results in oxidative stress, which induces mitochondrial dysfunction and impaired cellular energy supply; this in turn leads to further inflammation and oxidative stress, resulting in a self-reinforcing cycle of mitochondrial dysfunction, impaired energy supply and multiple organ dysfunction (Zhang et al, 2018). The incidence and mortality of sepsis increase with increasing age, and this may be linked to known age-related depletion of CoQ10 and selenium levels (Knoop et al, 2017).

Role of selenium in cell metabolism and antioxidant defence

Selenium is a trace element obtained from the normal diet. In the UK, a deficiency of selenium in soil is manifest upwards through the food chain, and the average UK diet contains only about half of the recommended selenium intake of 70 mcg/day. Selenium is an essential component of some 25 selenoproteins involved in the regulation of the inflammatory response, proliferation and differentiation of immune cells, and in antioxidant activity (Steinbrenner et al, 2016); examples include selenoprotein P (selenium transport) and the enzyme glutathione peroxidase which is an antioxidant. One of the major functions of selenium is as a component of the selenoenzyme thioredoxin reductase which is required for recycling extra-mitochondrial ubiquinol from CoQ10 (Xia et al, 2003) (*Figure 1*); this in turn is essential for maintaining cellular antioxidant defence, as outlined below.

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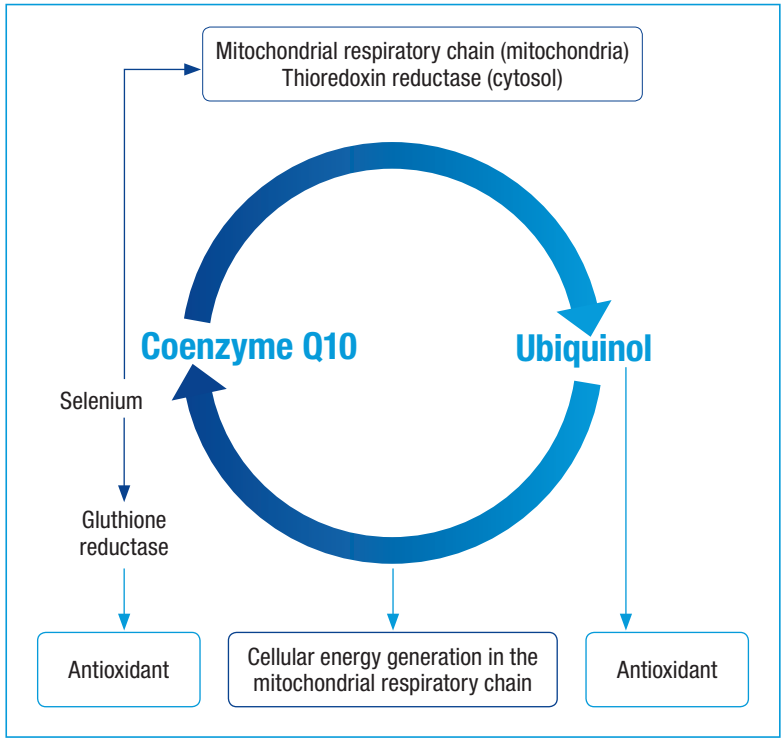

Figure 1. The potential cellular targets of selenium supplementation and the major functions of coenzyme Q10 and ubiquinol within the cell.

Clinical studies of selenium supplementation in critically ill patients

In critically ill patients, selenium levels are reported to correlate inversely with the severity of sepsis, oxidative stress, inflammation and organ failure (Heyland et al, 2005; Manzanares et al, 2009). This is because distribution of selenium from the liver to other tissues by selenoprotein P is inhibited by sepsis (during which plasma selenoprotein P levels are substantially reduced).

Clinical studies have shown variable outcomes of selenium supplementation in critically ill patients. Four randomized controlled clinical studies were identified (via Medline) in which the effect of supplemental selenium alone (intravenous or parenteral) *vs* placebo was determined on clinical outcome (via effects on disease severity or mortality). Two studies reported significant benefit, and two studies no significant benefit, on clinical outcome. Thus in a study of some 200 critically ill patients with sepsis, supplementation with selenium (1000 mcg/day as initial bolus injection, followed by 1000 mcg/day intravenous infusion for 14 days) reduced the mortality rate to 42% compared to 57% in the placebo group (Angstwurm et al, 2007). Similarly in a study of 70 critically ill patients with sepsis, intravenous administration of selenium (initial bolus of 2000 mcg followed by 1600 mcg/day for 10 days) significantly improved outcome, assessed via SOFA (sequential organ failure assessment) score (Manzanares et al, 2011). Conversely, in a study of 60 critically ill patients with sepsis, intravenous infusion of selenium (4000 mcg first day followed by 1000 mcg/day for 10 days) had no significant effect on mortality rates compared to placebo (Forceville, 2007). In addition, a study of 500 critically ill patients receiving parenteral selenium (500 mcg/day for 7 days) found no significant effect on mortality (Andrews et al, 2011).

Several meta-analyses (including more wide-ranging studies than the four identified above) have examined the effect of selenium supplementation in critically ill patients. A meta-analysis comprising nine randomized controlled studies including a total of 800 critically ill patients with sepsis demonstrated a significant reduction (odds ratio 0.73) in mortality rate following selenium supplementation (Alhazzani et al, 2013). In a meta-analysis by Huang et al (2013) including 12 randomized controlled studies and 900 critically ill patients with sepsis, parenteral administration of selenium significantly reduced mortality (relative risk 0.83). However, a meta-analysis by Manzanares et al (2016) including some 21 randomized controlled studies concluded that administration of intravenous selenium in critically ill patients does not improve clinical outcome or reduce mortality. A recent meta-analysis by Zhao et al (2019), based on some 19 randomized controlled studies, reported variable outcomes with regard to total mortality and 28-day mortality and length of hospital stay or stay in intensive care following intravenous administration of selenium in critically ill patients. Furthermore, a meta-analysis by Li et al (2019) found no association between selenium treatment and decreased mortality in patients with sepsis, although a reduced period of vasopressor therapy and length of stay in intensive care were reported following selenium supplementation.

Role of CoQ10 in cellular metabolism and antioxidant defence

CoQ10 is a vitamin-like substance (although by definition not a vitamin, since it is synthesized within the body) that plays a key role in the biochemical process within mitochondria that supplies all cells with the energy required for their normal functioning. Specifically CoQ10 transfers electrons between complex I and complex II to complex III of the mitochondrial respiratory chain (Hargreaves, 2003). An adequate supply of CoQ10 is of particular importance in tissues with a high energy requirement, such as the heart, skeletal muscles, kidneys, liver and brain (*Figure 1*). CoQ10 is also important as a lipid-soluble antioxidant which protects cellular membranes and lipoproteins, but especially mitochondria, against the toxic effect of free radicals generated during normal cellular metabolism (Hargreaves, 2003) (*Figure 1*).

The antioxidant function of CoQ10 is attributed to its fully reduced ubiquinol form which, in addition to acting as an antioxidant in its own right, is also involved in the regeneration of other antioxidants such as α-tocopherol and vitamin C (Crane, 2001). The mitochondrial respiratory chain ensures that CoQ10 is reduced to ubiquinol within the mitochondria (Åberg et al, 1992). Within the cytosol, thioredoxin reductase plays an important role in reducing

CoQ10 to ubiquinol and maintaining extra-mitochondrial antioxidant defence (Xia et al, 2003) (*Figure 1*). In addition, CoQ10 directly affects the expression of a number of genes, including some of those involved in inflammation (Mantle, 2015).

An adequate supply of CoQ10 is essential for normal functioning of mitochondria. Although some CoQ10 is obtained from the normal diet (approximately 5 mg/day), most of the daily CoQ10 requirement (estimated at 500 mg) is synthesized within the body. As people age, the capacity of the body to synthesize its own CoQ10 decreases; optimal production occurs around the mid-twenties, with a continual decline in tissue levels thereafter. In addition to the normal ageing process, CoQ10 levels are also depleted by intense exercise, statin-type drugs and illness. Dietary supplementation with CoQ10 therefore provides a mechanism to maintain adequate levels within the body.

Clinical studies on CoQ10 supplementation in critically ill patients

CoQ10 plasma levels have been reported to be significantly depleted in critically ill patients, both with septic shock (Donnino et al, 2011) and without septic shock (Coppadoro et al, 2013). In addition, low plasma CoQ10 levels have been correlated with increased mortality in critically ill patients with cardiovascular disease (Shimizu et al, 2017).

In contrast to the situation with selenium, few clinical studies have investigated the effect of CoQ10 supplementation in critical illness. Only one randomized controlled study was identified, which studied 38 critically ill patients with sepsis. Of these patients 19 received 400 mg ubiquinol (the reduced form of CoQ10) per day for 7 days with the remaining patients in the placebo group. After 7 days of treatment, although there was a significant increase in the level of circulatory CoQ10 compared to the placebo group, there was no noticeable benefit to the clinical outcome of the patients or any other secondary outcomes of endothelial function, inflammation or mitochondrial injury that were also assessed in this study (Donnino et al, 2015).

Statins have been used to treat sepsis in critically ill patients (Dobesh and Olsen, 2014; Zhang et al, 2015), but this may result in further depletion of CoQ10 levels, since statins are known inhibitors of endogenous CoQ10 synthesis (Okuyama et al, 2015).

Evidence for selenium and CoQ10 synergism

CoQ10 occurs in cells in two closely related forms, oxidised (ubiquinone) and reduced (ubiquinol); continual inter-conversion between these CoQ10 forms is required for normal mitochondrial function, including cellular energy generation and antioxidant protection. Selenium is a component of the enzyme thioredoxin reductase, which catalyses the reduction of ubiquinone to ubiquinol. Thus a deficiency of either selenium or CoQ10 can impact on this inter-conversion process, and subsequent mitochondrial function. In addition, CoQ10 has an important role in the synthesis of selenocysteine, which in turn is required for the production of selenoproteins, including thioredoxin reductase (Moosmann and Behl, 2004). Therefore deficiency of selenium can result in reduced CoQ10 synthesis, and deficiency of CoQ10 can result in reduced selenoprotein synthesis.

A randomized controlled trial (KISEL-10) was carried out in normal elderly subjects, who were supplemented with CoQ10 (200 mg/day) and selenium (200 mcg/day) for 5 years. The levels of a number of biomarkers for inflammation and oxidative stress were significantly reduced in the supplemented group *vs* placebo; these included SP-selectin, C-reactive protein, copeptin and adrenomedullin (Alehagen et al, 2015a,b). In addition, cardiovascular-related mortality was reduced by more than 50% in the supplemented group compared to placebo (Alehagen et al, 2013).

These data provide a rationale for the co-supplementation of selenium with CoQ10 to reduce inflammation and oxidative stress, and optimize mitochondrial function and cellular energy generation in critically ill patients. To date there have been no randomized controlled clinical studies to investigate the effect of selenium/CoQ10 co-supplementation in critically ill patients, but based on the studies of Alehagen et al (2015a,b), a daily dose of at least 200 mcg selenium and 200 mg CoQ10 would be required. Selenium can be administered intravenously or orally; supplemental CoQ10 is usually administered orally, although it has been administered intravenously in some clinical studies (Okamura et al, 1984; Tsubaki et al, 1984).

Importance of supplement quality and bioavailability

Oral selenium supplements can vary considerably in stability, selenium content and bioavailability. This is important because the therapeutic window for supplemental selenium is relatively narrow, and it is important to be able to control precisely how much selenium is given to the patient. In this regard, supplemental selenium in the organic form of selonomethionine and selenocysteine, produced to pharmaceutical standards, has the highest degree of stability and bioavailability.

Similarly, the quality and bioavailability of supplemental CoQ10 may vary considerably between manufacturers. When supplemental CoQ10 is first produced (via a yeast fermentation process), it is obtained in the form of crystals that cannot be absorbed from the digestive tract. It is essential that these crystals are dispersed into single CoQ10 molecules (and remain dispersed during the product shelf-life) to enable optimum bioavailability; adding CoQ10 crystals to a carrier oil without such dispersal, a cost-saving technique used by some manufacturers, is inadequate. Disparity in the findings of clinical trials supplementing CoQ10 may result from a number of factors, including insufficient CoQ10 dosage or study duration, variation in

KEY POINTS

- Selenium and coenzyme Q10 have key roles in cellular energy production, as antioxidants, and as mediators of oxidative stress and inflammation.
- Levels of both selenium and coenzyme Q10 are significantly reduced in critically ill patients.
- Clinical studies in critically ill patients supplementing selenium or coenzyme Q10 individually have been equivocal or have shown no benefit respectively.
- Because of the synergistic interaction between selenium and coenzyme Q10 at the cellular level, optimum clinical benefit in critically ill patients may be obtained by supplementing selenium and coenzyme Q10 in tandem. To date there have been no randomized controlled trials to investigate the combined effect of supplementary selenium and coenzyme Q10 in critically ill patients.

the capacity of individuals to absorb CoQ10, as well as the use of CoQ10 supplements with inadequate bioavailability (Mantle and Hargreaves, 2019).

Safety of CoQ10 and selenium supplementation

CoQ10 is generally well tolerated, with no serious adverse effects reported in long-term use. Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed (Hosoe et al, 2007; Hidaka et al, 2008). The safety of CoQ10 has been confirmed in more than 200 randomized controlled trials on a wide range of disorders. Several case studies have suggested that CoQ10 may interfere with the action of warfarin, but a randomized controlled clinical trial showed CoQ10 supplementation at 100 mg/day had no effect on the clinical action of warfarin (Engelsen et al, 2003).

With regard to selenium, there is a relatively narrow therapeutic window, since administration of too high a dose may be toxic. Rayman et al (2018) have suggested that selenium supplementation in the general population should be restricted to 300 mcg/day, although a daily dose of 1000 mcg/day has been routinely used in critical care patients (Heyland, 2007).

Laboratory measurement of CoQ10 and selenium

Neither CoQ10 or selenium is usually included in routine biochemical analysis of blood by hospital pathology laboratories. The most common laboratory procedures used to assess CoQ10 status are based on high-pressure liquid chromatography with either ultraviolet or electrochemical detection (Yubero et al, 2014). CoQ10 levels are usually determined in blood, with normal plasma levels typically in the range 0.5–1.5 mcg/ml. Because CoQ10 levels are dependant on lipoprotein status (as the major carriers of CoQ10 in the circulation), it has been suggested that plasma CoQ10 levels should be expressed as a ratio with respect to total plasma cholesterol (Hargreaves, 2003).

Selenium status is generally determined by atomic absorption spectrometry in blood, using either whole blood, erythrocytes, plasma or serum (Ashton et al, 2009; Gudmundsdottir et al, 2012). The normal range for serum selenium levels is typically of the order 60–160 mcg/litre. However, it is considered that in order to get a 'true measure' of selenium status, the amount of selenium that is available for the activity of the selenoproteins should be determined (Thomson, 2004). Therefore, the determination of the concentrations of individual selenoproteins such as selenoprotein P is thought to provide more appropriate information than the circulatory levels of this trace element (Thomson, 2004). Furthermore, the activities of plasma, erythrocyte or platelet glutathione peroxidase have also been reported as a useful indicator of functional selenium status (Thomson, 2004).

Conclusions

This article has reviewed evidence to provide a rationale for the use of supplemental selenium and CoQ10 in combination to improve patient outcome in critical illness; this is in contrast to conventional treatment of such patients with selenium alone. Intensive care staff may wish to consider the proposed therapeutic strategy as a novel approach to the future management of critically ill patients. **BJHM**

Conflict of interest: Dr IP Hargreaves: none; Dr D Mantle is a medical consultant to the company Pharma Nord (UK) Ltd.

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