British Journal of Nutrition (2018), **120**, 1–2

British Journal of Nutrition

Invited Commentary

Invited commentary in response to: selenium supplementation lowers insulin resistance and markers of cardio-metabolic risk in patients with congestive heart failure: a randomised, double-blind, placebo-controlled trial

Mounting evidence supports the consensus that health benefits of Se supplementation depend mainly on the status of this nutrient in the body. Supplementation of subjects with sub-optimal to deficient status produces increases in the expression of Se-dependent proteins; supplementation of Se-adequate subjects does not further increase the expression of those already optimised proteins, but can increase tissue Se levels, particularly if the dominant food form of Se, selenomethionine, is used. Beneficial effects of Se supplementation have been reported for non-deficient subjects: stimulation of immune functions in healthy elderly and in patients with squamous cell carcinoma or HIV infection[1–3]. Effects on type 2 diabetes risk among non-deficient subjects have been mixed; no effects were observed among adult subjects of the Selenium and Vitamin E Cancer Prevention Trial (SELECT)[4] and among younger adult subjects of the Selenium Trial with selenised yeast[5], but there was an increased risk among older adults in both the Selenium Trial[5] and the Nutritional Prevention of Cancer (NPC) trial[6]. Similarly, the risk of prostate cancer among non-deficient subjects was reduced in response to Se supplementation in the NPC trial[7] but not the SELECT trial[4]. Rayman[8] pointed out the similarly mixed results from prospective studies exploring associations between health status and Se status. Although a meta-analysis concluded that there was an inverse association between Se status and CHD risk, the PREvention of Cancer by Intervention with SElenium pilot trial found modest improvements in plasma cholesterol levels among older adults supplemented with a yeast containing selenomethionine[9,10], and Se supplementation did not affect CVD in another study[11]. Despite these seemingly inconsistent outcomes, these results collectively suggest that subjects entering a clinical trial with low Se status are likely to benefit from supplementation with selenomethionine (either as L-selenomethionine or selenium-enriched yeast).

In this issue of the *British Journal of Nutrition*, Raygan *et al.*[12] report findings from a cohort of fifty-three participants diagnosed with congestive heart failure at 45–85 years of age in Kashan, Iran. In a randomised, double-blind, placebo-controlled trial, twenty-six subjects were given selenised yeast at the level of 200 μg Se/d, and twenty-seven were given a placebo. At baseline, and again after 12 weeks, each subject was assessed by analysis of metabolic profiles in serum samples. On the basis of changes in several metabolic and cardiovascular parameters (e.g. decreased insulin, LDL-cholesterol and C-reactive protein concentrations; increased HDL-cholesterol, total antioxidant capacity and glutathione concentrations), the authors concluded that Se supplementation benefited the treatment group, suggesting a protective role of Se supplementation in alleviation of the metabolic syndrome in patients with congestive heart failure.

The fact that either Se deficiency or Se in excess may instigate a common pathological consequence has been shown in studies of type 2 diabetes[13–15]. This phenomenon is thought to relate to two noteworthy features of Se metabolism. First, at deficient to nutritionally adequate levels of intake, Se is prioritised to support the expression of a relatively small number of selenoproteins. Second, at adequate and greater intakes, Se is increasingly incorporated non-specifically into all proteins by replacement of methionine with selenomethionine residues[16]. In this way, the biochemical targets of supplemented Se are fundamentally influenced by the basal Se status of the subject. Se supplementation of Se-deficient subjects may result in health benefits through optimal selenoprotein expression; however, Se supplementation of subjects already of adequate Se status may produce adverse effects. This U-shaped response was pointed out by Waters *et al.*[17]. For this reason, health claims for Se supplementation must be referenced according to the baseline Se status of the subjects in question.

Unfortunately, Raygan *et al.*[12] failed to provide any definitive measure of the baseline Se status of their subjects – for example, serum/plasma Se concentration – nor did they report the results of Se analyses of their intervention agents. These critical omissions leave it uncertain as to whether the effect they show may actually have been because of changing Se status. Although they provided estimates of dietary intakes of Se, those values were imputed on the basis of very old food Se data that were not produced in Iran. It is not likely that the actual intakes of food Se were lower than suggested, as the Se contents of Kashan soils do not seem to be low; in fact, Iran is known to have relatively high levels of soil Se[18], and it is again uncertain as to whether the subjects of this Iranian cohort were indeed adequate in body Se status before the supplementation. Even if these subjects were actually consuming a background intake of about 55 μg/d, their plasma Se levels should have been in the 60–75 μg/l range, which would have corresponded to nearly full selenoprotein expression – that is, nutritional selenium adequacy. Further, if their subjects actually received a daily supplement of 200 μg Se, their plasma levels would have gone to

>150 μg/l, and most of the increase in their plasma Se would have been in non-specific Se in albumin[16], indicating similar increases in proteins of other tissues.

Nonetheless, because the Se supplementation resulted in decreased serum insulin level in this Iranian cohort with congestive heart failure, one might speculate that these patients were low in basal Se status and/or co-conditioned with diabetes. Such possibilities are suggested by reports of diabetes prevention and alleviation of symptoms in diabetic patients by maintaining nutritionally adequate levels of Se[13,14,19].

It is of great practical interest to know whether Se supplementation can be useful in reducing risk of type 2 diabetes, or any other disease. However, as we have pointed out, this question must be addressed in reference not only to health status but also to subject Se status, as both can affect the metabolic utilisation of this essential nutrient. Therefore, such trials must be careful to characterise subject baseline Se status, as well as the specific identity of the intervention and control agents. Not to do so is to severely limit the inferential value of any findings.

Acknowledgements

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

W.-H. C. and G. F. C. wrote the paper.

The authors take responsibility for its content and declare no conflicts of interest.

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doi:10.1017/S0007114518001228

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