Selenium supplementation and selenoenzyme activity

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Brown et al. [1] have recently described the effects of selenium supplementation on selenoenzyme activity. They claim that inverse relationships between baseline enzyme activities and percentage change in activity indicate that pre-treatment activity may be sub-optimal. However, there are two problems with this supposition, the first statistical and the second conceptual.

The authors noted the wide variability in selenoenzyme activity. In such a situation, if a variable is measured twice, the second measurement is likely to demonstrate ‘regression to the mean’ [2], even if there is no real change in that variable. Thus, if the first measurement was low, simply by chance the second measurement is likely to be higher, even if there is no true trend; conversely, high values are likely to be followed by lower ones. Thus if change is measured, low values are likely to be associated with positive changes and high values with negative changes. This effect is well recognized in hypertension research. Such a statistical phenomenon is likely to have contributed to the ‘inverse relationship’ seen in Figure 3 in [1], where low-baseline values are associated with positive changes and high-baseline values with negative changes.

By using percentage change, the authors have compounded the problem. Baseline values are plotted against a function of themselves. A relationship is therefore expected, whose nature will depend on the function of the baseline values, in this case, a simple inverse one that is dependent on the ratio of follow-up to baseline. In effect, the authors have plotted the reciprocal of a variable against itself; a negative relationship is therefore expected, since the value of follow-up/baseline will decrease as the baseline score increases. Furthermore, percentage change is not informative if there is reasonable variability in the baseline score, particularly if the change in one unit is considered to be equal anywhere along the scale. For example a change in one unit from 1 to 2 represents a 100% increase, whilst that from 10 to 11 represents a 10% increase. To compare directly these percentage increases is not very informative. Probably of more interest and use is to compare absolute change.

We took fifty pairs of random normally distributed numbers and plotted percentage change against the first (baseline) value (Figure 1). It can be noted how closely this resembles Figure 3 in [1]. Indeed, as in the analysis of Brown et al. in Table 2 [1], a strong regression can be calculated, \( r = -0.6 \) in this case, although it is probably not valid to fit a linear regression to a relationship that is clearly curvilinear. The curve found with change in selenoenzyme activity cannot, therefore, be interpreted as demonstrating the dependence of response upon baseline selenoenzyme status as is claimed.

The conceptual problem with the argument proposed in this paper is the premise that a rise in a measured variable (in this case selenoenzyme activity) with an intervention (selenium supplementation) can be taken as evidence that the variable was sub-optimal prior to that intervention.

Key words: selenium, selenoenzymes, statistical artefacts, regression to the mean.

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This is clearly not valid; we would not argue that the diet is deficient in salt because a high-salt intake was found to increase mean blood pressure. To argue that a physiological variable is sub-optimal requires either knowledge of what is optimal and the measurement of a value below such an ideal, or else the demonstration of deleterious consequences as a result of values in that range. Neither of these seem to have been demonstrated in this study.

The impact of falling selenium intake is clearly an important issue which requires investigation but in order for such an impact to be investigated, it must be separated from confounding statistical and conceptual artefacts.

REFERENCES


Selenium supplementation and selenoenzyme activity: authors’ reply

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In response to the commentary of Macallan and Sedgwick we would like to clarify that in our paper, Brown et al. [1], we do not make any claim which indicates that pre-treatment enzyme activity is sub-optimal. Rather, we suggest that pre-treatment activity may be sub-optimal.

To evaluate the effect of any treatment, a variable must always be measured twice. The mathematical argument that measurement of a variable twice simply represents a regression to the mean does not necessarily apply to our data. Figure 2 in our paper shows that placebo-treated controls demonstrate no increase in cytosolic glutathione peroxidase (GP1) or phospholipid-hydroperoxide glutathione peroxidase (GP4) activity between baseline and day 28 of treatment [1]. Moreover, in placebo-treated controls the extent of any variation in enzyme activity between baseline and day 28 was significantly lower (P<0.001) compared with selenium (Se)-treated subjects (see Table 1 in [1]). This suggests that the relationship shown in Figure 3 of our paper may indeed represent a treatment effect rather than a mathematical one [1].

Although we agree that there may be an element of mathematical chance associated with any observation, we should not ignore the fact that changes in response to any treatment may be of biological significance. The significant variation in the extent of increased enzyme activity is most concisely demonstrated when presented as percentage change. Moreover, the fact that the greatest increase in activity occurred in subjects with a baseline GP1 activity of 0.2 unit/mg of protein or less, suggests that baseline activities in our group of subjects may have influenced the extent of response to supplementation. This data is reported cautiously on an understanding that the biological implications of low or high levels of selenoenzyme activity are not clear.

The concept that an increase in enzyme activity may be a consequence of an increase in dietary intake of Se is sound. Our data shows such a response. It is not unreasonable to suggest that low levels of selenoenzyme activity in platelets, granulocytes and lymphocytes might reflect sub-optimal activity since there are no data reported from human studies to suggest otherwise.
In our current research, which is nearing completion, we examine the \textit{in vivo} intracellular distribution and activity of GP\textsubscript{x}4 in subjects of varying Se status, and determine the extent to which Se status influences the essential roles of GP\textsubscript{x}4.

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