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Clinical Study

Selenium Status in Patients Receiving Short-Term Parenteral Nutrition: Frequency of Deficiency and Response to a Standard Supplementation Regimen

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Background. This study aimed to determine the prevalence and correlates of Se deficiency in patients referred for parenteral nutrition (PN) and to assess the response to a standard supplementation regimen. *Methods*. Adult patients (53) were recruited prior to commencing a PN regimen delivering 32 μg (0.4 μmol) Se per 24–36 h. Serum Se concentrations were measured before and daily during PN. *Results*. At baseline 49 (92%) patients had serum Se concentrations below the reference range (0.9–1.65 μmol/L). Se concentrations climbed during PN from 0.49 ± 0.23 (mean ± SD) to 0.57 ± 0.22 μmol/L ($P < 0.05$), but in 48 (91%) patients the concentrations remained low at post-PN. Taking a Se concentration below 0.6 μmol/L as indicative of depletion in the presence of an acute phase response (APR), 37 (70%) patients had Se depletion at baseline and in 27 (51%), levels remained low at post-PN. Baseline serum Se predicted the length of hospital stay ($r = -0.36$, $P < 0.05$). Increased "malnutrition universal screening tool" score predicted low Se ($r = -0.93$, $P < 0.05$). *Conclusions*. Patients referred for PN have a high prevalence of Se deficiency, even when the APR is taken into account. Se supplementation of 32 μg Se per 24–36 h is insufficient for most patients. Baseline serum Se may have prognostic value.

1. Introduction

Selenium (Se) is a trace element essential to human health [1]. It is present within selenoproteins which include glutathione peroxidase (GPx), a family of enzymes which catalyse the reduction of hydrogen peroxide to water. GPx accounts for 10–16% of serum Se [2, 3]. The UK Reference Nutrient Intake (RNI) is 75 μg (0.96 μmol) Se per day for males and 60 μg (0.77 μmol) per day for females. This intake is required to maximize plasma GPx activity which occurs at a Se concentration of 89–114 μg/L (1.14–1.46 μmol/L) [4]. Concentrations lower than this are thought to compromise the activity of Se dependent enzymes. Studies of European populations have shown intakes to be considerably less than the RNI [5].

There is ongoing debate about how best to assess Se status, but serum Se is the most commonly used test, its concentrations being thought to reflect short-term changes in dietary intake [6]. Concentrations less than 0.8 μmol/L correlate with dietary Se intake but at higher concentrations tissue selenoproteins plateau as requirements have been met [7]. Serum GPx has also been proposed as a measure of Se status [6]. It responds promptly to changes in intake, being thought to reflect relatively short-term Se status. Its activity correlates with plasma Se and falls in established Se deficiency [8]. In hospitalized patients the interpretation of serum Se concentrations is complicated by the effect of the acute phase response (APR). Both serum Se and GPx have been reported to fall 40–60% during acute illness [9]. This is thought to

reflect redistribution of Se to vital organs though acutely ill patients may have true Se deficiency as well [10]. In an effort to account for the APR, the authors of this study suggested that, in the presence of inflammation, as indicated by an elevated C-reactive protein (CRP) level, Se concentrations below 0.6 μmol/L (46.9 μg/L) indicate true Se deficiency.

Patients receiving parenteral nutrition (PN) are at risk of developing Se deficiency if their needs are not fully met. This can adversely affect outcome [11]. Clinical Se deficiency has been observed where Se supplementation of the feed was inadequate [12] and several cases of low plasma Se and GPx activities have been reported [13–15]. Se deficiency in the context of PN has been associated with a higher mortality rate [16]. Whilst it is clear that Se supplementation is required to avoid deficiency, the optimal amount required in PN is debated. There have been relatively few studies of Se in postsurgery patients. One study showed that 32 μg per day was sufficient for maintaining Se status over short periods of PN [17], but variable amounts are required postop to prevent decline in Se status [18]. In 1998, ASPEN recommended that 20–60 μg/day Se should be added to adult PN [19], and it has also been recommended that trace elements be given from the first day of PN and daily thereafter [20]. Some patients clearly require higher doses, including those with upper gastrointestinal or fistula-associated losses or severe postoperative stress [16]. Their requirements are probably at least as high as those of patients on home PN (60 μg per day) [21]. Critically, ill patients in the intensive therapy unit (ITU) are likely to have much higher requirements.

Patients referred for PN in our hospital generally receive Se supplementation of 32 μg per 24–36 h. Since many are malnourished at referral, it was considered likely that a significant proportion would be Se deficient at the outset and respond poorly to supplementation. This study therefore aimed to assess the prevalence and correlates of Se deficiency in patients referred for PN, accounting for the APR and to assess the response to the current supplementation regimen.

2. Methods

2.1. Subjects. Patients referred to the nutrition support team (NST) for PN were recruited to the study between August 2006 and January 2007. All were in-patients on the surgical, medical, and oncology wards of the Royal Surrey County Hospital NHS Trust (RSCH). PN was prescribed until it was possible to meet the patients' nutritional requirements by the oral or enteral route. The PN admixture was supplemented with trace metals as "Additrace" (Fresenius Kabi, Runcorn, UK) containing 32 μg Se as sodium, selenite. The feed was delivered initially over a 24–36 h period depending on the clinical situation and thereafter over 24 h. Length of hospital stay (LOS) and duration of PN were recorded. In total 53 patients were recruited (33 male, 20 female) with a mean age of 67 years (range 17–92). Twenty five patients had malignant and 28 nonmalignant conditions. The mean duration of PN was 8.7 days (range 3–27). All patients except two received PN for five days or more. The mean LOS was 20 days (range 8–55). No patient had features suggestive of clinical Se deficiency. Participation in the study was subject to informed written consent. The study was approved by the South West Surrey Local Research Ethics Committee (LREC) (study no. 06/Q1909/70).

2.2. Nutritional Risk Screening. On referral to the NST, patients were screened using the malnutrition universal screening tool (MUST) [22]. This allocates a risk score ranging from 0 to 6 based on the body mass index (BMI), recent percentage weight loss, and the presence or absence of acute disease. A score of 2 or above indicates high nutritional risk which means that malnutrition is either already present or likely to develop imminently unless nutrition support is commenced.

2.3. Specimen Collection. Se and GPx analysis were carried out on serum specimens taken for routine clinical monitoring. These were collected at baseline, daily during PN and on the day following discontinuation of PN ("post-PN"). Serum was separated by centrifugation for 10 minutes at 3.4 krpm in a bench-top centrifuge. An aliquot of each serum specimen was stored at −20°C in a glass vial for later Se and GPx analysis. These vials had previously been shown to be free from Se contamination.

2.4. Analyses. Se analysis was by graphite furnace atomic absorption spectroscopy using a Thermo Fisher Scientific, M6 series atomic absorption spectrometer. The reference range for serum Se in the laboratory is 0.9–1.65 μmol/L (69.5–128.9 μg/L). Serum GPx was assayed using a Randox kit based on a method based on the one by Paglia and Valentine (1967) [23]. This utilises the ability of GPx to catalyse the oxidation of glutathione by cumene hydroperoxide. Oxidised glutathione is converted back to the reduced form in the presence of glutathione reductase and NADPH. The concomitant oxidation of NADPH to $NADP^+$ was followed by absorbance at 340 nm on a Siemens Advia 1650 analyser (Camberley, Surrey, UK). CRP was measured on serum by an immunometric method on a Siemens Advia 1650 autoanalyser, and albumin was measured by a BCG succinate method on the same analyser [24].

2.5. Data Analysis. t-Tests were performed using Analyze-IT for Excel. Correlation and linear regression analyses were performed using Excel for Windows. Statistical significance was taken as $P < 0.05$.

3. Results

3.1. Baseline Levels and Response to PN. Because patients received PN for different periods of time, data analysis was carried out on observations made at baseline, day five, and post-PN, that is, the day following discontinuation of PN. Baseline serum Se concentrations were below the reference range in 49 (93%) patients. Se concentrations had responded significantly to supplementation at post-PN (Table 1). However, in 48 (91%) patients, concentrations failed to reach the lower reference limit at post-PN. The mean Se concentration at post-PN remained 50% less than that believed necessary to maximize plasma GPx activity (1.14 μmol/L). For the

Table 1: Serum Se and GPx concentrations at pre- and post-PN.

Analyte	Pre-PN	Post-PN	Day 5
Se (μmol/L)	0.49 ± 0.23	0.57 ± 0.22 ($P < 0.05$)	0.52 ± 0.23 ($P = 0.33$)
GPx (U/L)	336 ± 165	338 ± 143 ($P = 0.94$)	330 ± 147 ($P = 0.74$)

Results are shown of Se and glutathione peroxidase (GPx) concentrations at baseline (pre-PN), on the day following completion of PN (post-PN) and on day five of PN for 53 patients. Data are mean ± SD. In each case, P values refer to comparison with baseline concentrations.

Table 2: Subgroup analysis of Se and GPx concentrations at pre- and post-PN.

Subgroup	Analyte	Pre-PN	Post-PN	P value
Malignancy	Se (μmol/L)	0.47 ± 0.21	0.58 ± 0.26	<0.05
	GPx (U/L)	330 ± 164	336 ± 138	<0.05
Other conditions	Se (μmol/L)	0.53 ± 0.24	0.55 ± 0.22	0.7
	GPx (U/L)	334 ± 171	318 ± 145	0.7

Results are shown of Se and glutathione peroxidase (GPx) concentrations at baseline (pre-PN) and on the day following completion of PN (post-PN). Data are mean ± SD. In each case, P values refer to comparison with baseline concentrations.

five patients whose Se concentrations reached the reference range, baseline levels were 0.86 ± 0.16 μmol/L (mean ± SD). No significant differences were observed in Se or GPx concentrations at day five compared to at post-PN.

3.2. APR. As 45 (85%) patients had an elevated CRP at baseline, an attempt was made to account for the APR upon Se levels. A serum Se concentration below 0.6 μmol/L was taken as representing true Se depletion in the presence of APR. Based on this criterion, 70% of patients were Se depleted at baseline and 51% had levels which remained low at post-PN. Supplementation was therefore successful in 49% of patients.

3.3. GPx. Baseline GPx activities ranged from 59 to 684 U/L. There was no significant increase in activities at day five or at post-PN (Table 1). Two patients who received PN for less than five days were omitted from this comparison.

3.4. Subgroup Analysis. A subgroup analysis of the data was carried out on the patients with malignancy versus those with other conditions. Table 2 shows the mean serum Se and GPx concentrations at baseline and at post-PN for the two groups. Se climbed significantly at post-PN in those with malignancies but not in patients with other conditions. GPx also increased significantly during PN in patients with malignancies alone. This finding was further investigated by means of correlation analyses of the subgroups, the results of which are shown in Table 3. Se and CRP results correlated more strongly in patients with malignancies than in the other patients.

3.5. Regression Analysis. Correlation analyses were carried out to assess the correlates of Se and GPx and to determine whether these parameters had prognostic value. Results are shown in Table 3. When all results were considered together, Se concentrations were negatively related to CRP. Baseline Se considered alone did not correlate with CRP but did correlate with LOS and MUST score. Se correlated with GPx activity in patients with baseline Se below 0.6 μmol/L but not at higher Se concentrations.

4. Discussion

This study observed a high prevalance of serum Se concentrations below the reference range in patients referred for PN. Using a more stringent criterion for Se deficiency (<0.6 μmol/L) in the presence of an APR, the prevalence of deficiency was considerably lower and the success rate of supplementation 40% higher than previously. The low Se concentrations observed were presumably due to a combination of the APR and reduced intake and increased losses, for example, via fistula or upper gastrointestinal aspirates. Overall Se correlated negatively with CRP and positively with albumin in line with levels falling in response to an APR. The absence of a correlation between baseline Se levels and CRP suggests that nutritional factors may contribute more than the APR to baseline Se status. This contention is supported by the strong correlation observed between baseline Se and MUST score. It should be emphasised that this study did not include critical patients in ITU. Such patients are generally iller than those elsewhere in the hospital and would be expected to have poorer Se status than those studied here.

The Se supplementation given to the patients in this study was towards the lower end of the range recommended by ASPEN [19]. It was therefore anticipated that concentrations would respond poorly to supplementation. Although Se concentrations increased significantly during PN, supplementation appeared to be inadequate for the majority. Half had post-PN concentrations insufficient to optimise GPx activity. Similar findings have been observed in other studies of Se supplementation in patients receiving postsurgical PN. A recent review concluded that patients receiving postsurgical PN require at least as 60–80 μg/day with some requiring more [21]. It is uncertain why the patients with malignancies appeared to respond better to supplementation than those without malignancies.

Whilst none of the patients had clinical features of Se deficiency (cardiomyopathy, myositis) their levels may still have been sufficiently low to adversely affect outcome. Prospective studies need to investigate how suboptimal Se status relates to outcome and to determine which subgroups

Table 3: Correlation analyses.

Dependent variable	Independent variable	r value	P value
GPx	Albumin	−0.11	0.08
GPx	CRP	0.03	0.62
GPx	Se	0.41	<0.05
Se	Albumin	0.38	<0.05
Se	CRP	−0.27	<0.05
Se	CRP (baseline results)	−0.07	0.07
Se	CRP ("malignancy" subgroup)	−0.37	<0.05
Se	CRP ("others" subgroup)	−0.17	<0.05
Se	GPx ("malignancy" subgroup)	0.54	<0.05
Se	GPx ("others" subgroup)	0.26	<0.05
Albumin	CRP	−0.38	<0.05
MUST score	Se (baseline results)	−0.93	<0.05
Se	GPx (patients with baseline Se < 0.6 μmol/L)	0.37	<0.05
Se	GPx (baseline results) in patients with baseline Se < 0.6 μmol/L	0.29	0.29
Se	CRP (baseline results) in patients with baseline Se < 0.6 μmol/L	0.2	0.22
LOS	Se	−0.36	<0.05
LOS	GPx (baseline results)	−0.24	0.08
LOS	Albumin	−0.38	<0.05

Key: GPx: glutathione peroxidase; CRP: C-reactive protein; LOS: length of stay.

of patients should be targeted for Se monitoring and additional supplementation. If improved outcome is observed in response to greater Se supplementation, there may be a place for assessment of baseline Se status with a view to more aggressive supplementation. However, these studies are difficult to carry out and interpret because of the numerous factors influencing outcome in patients receiving PN.

As there was no local reference range available, it was not possible to establish whether the serum GPx levels of patients were low or high relative to the normal population, but low values would be expected in patients with an APR and Se depletion. In practice the absolute GPx value may be of less importance than changes in activity observed during treatment. Mean GPx results did not change at post-PN, suggesting that the increase in Se levels was not sufficiently large to increase activity. There is evidence that when Se supply is limited, selenoprotein P synthesis may take priority over GPx synthesis [25]. Data were analysed to determine whether GPx predicted Se concentrations and might act as a functional indext of Se status. The two were weakly correlated ($r = 0.41$, $P < 0.05$) in agreement with the findings of other studies [26, 27]. This finding is consistent with serum GPx representing a weak indicator of short-term Se status. A previous study observed significant differences between individuals in their selenoprotein response to supplementation [28]. This may explain why the overall correlation is weak. The measurement of serum GPx does not appear to be of value in the assessment of Se status in patients receiving PN.

Several adverse effects of radio- and chemotherapy have been linked to oxidative cell damage. It was therefore considered likely that the patients with malignancies would have greater GPx depletion and that Se and GPx would respond differently to supplementation in these patients. However, subgroup analysis of the patients with malignancies and those without malignancies observed that GPx levels were not significantly different between the groups. This observation does not support the contention that patients with malignancies have higher levels of oxidative stress leading to GPx depletion. The patients with malignancies did however have significantly higher Se and GPx results in response to PN. The reason for this is not clear but may relate to greater Se reserves in these patients or reflect changes in Se distribution.

It is well recognised that low serum albumin levels predict increased morbidity, mortality, and length of hospital stay (LOS) in acutely ill hospitalised patients [29], a finding confirmed by the present study. This is thought to reflect the status of albumin as a negative APR marker rather than a link with nutritional status. The strength of this association and low cost of the assays have supported the use of serum albumin as prognostic tool in identifying high-risk patients [30]. Low Se correlated with longer LOS and high nutritional risk score. Low Se should therefore be anticipated in patients at high nutritional risk and appears to have prognostic value. This is likely in part due to the APR which will be most severe in the illest patients. This finding is in line with a previous study where depleted Se status in patients receiving PN was associated with a higher mortality rate [11]. Se supplementation in patients with burns, sepsis, and trauma was associated with significantly reduced LOS [31]. Baseline GPx did not predict LOS suggesting that it has no prognostic value.

Our findings have implications for monitoring of Se. The NICE nutritional guidelines [32] recommend that baseline assessment of trace element status should be carried out in patients at risk of depletion, though our own data demonstrates this to be the majority. Measurement of baseline Se analysis in all patients referred for PN would place a

significant burden on the laboratory, particularly as a rapid turnaround time would be required if the regimen were to be altered accordingly. The approach adopted at RSCH is to measure baseline serum Se only in patients in whom PN is anticipated to be required long term (>2 weeks) or where losses are of an extent considered to put the patient at risk of clinical deficiency.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper. The authors have no direct financial relation that might lead to a conflict of interests.

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