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Research Article

Relationship of Selenium, Zinc and Copper with Inflammatory and Nutritional Markers and Impact on Clinical Outcome in Malnourished Patients

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Abstract

Aim: The study evaluates the relationship between Se, Zn and Cu with inflammatory and nutritional markers and their impact on clinical outcome in malnourished patients.

Methods: This retrospective observational study was carried out in 109 patients with underlying gastrointestinal disorders and poor nutritional status. Serum Cu, Zn and Se, pre-albumin, albumin and C-reactive protein (CRP) concentrations were recorded.

Results: Study patients were split into two groups: survivors (n = 65) and non-survivors (n = 44). Serum Se, Zn and Cu concentrations were lower in non-survivors compared to survivors. There was no significant difference in CRP, albumin and Pre-albumin between the two groups.

Serum Se and Zn showed a significant negative correlation with CRP in survivors and non-survivors. A significant negative correlation with Cu and CRP was only seen in survivors.

Serum Se, Zn and Cu showed significant positive correlation with albumin in both groups. Serum Se showed a significant positive correlation with pre-albumin where as serum Zn showed significant positive correlation with pre-albumin only in non-survivors.

There was a significant negative correlation of CRP with albumin and pre-albumin.

Conclusion: Our study suggests that serum Se, Zn and Cu should be interpreted in malnourished patients with the inflammatory markers as metabolic stress influences their concentration in blood.

Keywords: *Selenium; Copper; Zinc; Malnourished; Inflammation*

Introduction

Trace elements (TE) are present at very low concentrations (equal to or less than 0.005% of body weight) in the human body. Copper (Cu), zinc (Zn) and selenium (Se) are essential trace elements that form part of the functional groups of several antioxidant enzymes such as glutathione peroxidase, superoxide dismutase and catalase [1]. Zn plays a role in a variety of enzymatic, metabolic, and immunologic functions. Se due to its antioxidant role has been postulated to protect from oxidative tissue damage in many inflammatory conditions. Cu plays a role in hematopoiesis, connective tissue synthesis, and oxidative enzymes. Therefore, TEs have an important protective role in illness.

Serum TE estimation is commonly carried out to assess the status of TE in body. Nevertheless, serum concentration of these TE on their own do not accurately reflect total body status, their serum concentration may be measured in combination with other indices, for example enzyme activities or tissue content, to assess deficiency, toxicity or inborn errors of metabolism [2-5].

Latter are difficult to estimate and therefore not used routinely.

TEs are transported in blood by plasma proteins. Albumin is a carrier protein for Zn, Se and Cu. Acute phase response in illness has a substantial effect on the blood concentration of TE [6]. The acute-phase or inflammatory response is a coordinated sequence of reactions involving biochemical and physiological changes whose aim is to limit damage and aid repair [7]. Zn and Se are negative acute-phase reactants whereas Cu concentration increases as part of the acute-phase response [8,9].

Chronic illness associated with systemic inflammatory response causes nutritional and functional decline presenting with malnutrition. Serum albumin and pre-albumin are widely used as markers of nutritional status [10,11]. Nevertheless, it is now well known that acute phase response or inflammation influence the serum albumin and pre-albumin levels [11,12]. Since albumin is a carrier for TE in blood, the acute phase response mediated changes in albumin may account for some of the changes in serum TE concentration. Therefore, plasma proteins and acute phase response influence the serum TE estimation.

Malnutrition is commonly seen in patients with gastrointestinal conditions such as short bowel syndrome, high fluid output enterocutaneous fistulas, and chronic diarrhea due to poor oral intake. Malabsorption leads to increased losses of nutrients and inflammation. Low TE status in malnourished patients can be either related to poor nutritional status or acute phase response related to plasma protein changes. This poor TE status in malnourished patients may adversely affect the clinical outcome in such patients. We assessed the relationship between serum Zn, Cu and Se with a marker of inflammation (CRP) and nutritional status (albumin and pre-albumin) in malnourished patients with chronic gastrointestinal disorders. We also assessed the impact of TE status on the survival of these patients.

Methods

Study Patients

This retrospective observational study was carried out in 109 hospitalised patients with chronic gastrointestinal disorders. Nutritional status was evaluated by malnutrition universal screening tool (MUST) in all the study patients [13]. Since MUST suggested high risk of malnutrition (MUST score ≥ 2) patients were referred for nutritional support. Due to the underlying gastrointestinal conditions, these patients were not suitable for oral or enteral nutritional support. Hence all these patients were commenced on parenteral nutrition support. Baseline blood samples were collected for TE (Se, Zn, Cu), inflammatory (CRP) and nutritional markers (Albumin and Pre-albumin) before commencing the study patients on parenteral nutrition support.

The study patients were divided into survivors (n = 65) and non-survivors (n = 44).

Data Extraction and Collection

Serum copper (Cu), zinc (Zn) and selenium (Se), pre-albumin (PA), albumin (ALB) and C-reactive protein (CRP) concentrations were collected from the laboratory information system (LIMS) (TelePath).

Biochemical Analysis

Serum Cu, Zn and Se were measured using inductively coupled plasma mass spectrometry (ICP-MS) (Thermo, Hemel UK). Inter-assay CVs were < 5%. PRA, ALB and CRP were measured using automated colorimetric and turbidometric assays (Roche Diagnostics Inc., Lewes, East Sussex, UK), inter-assay CVs were < 5%.

Statistical Analysis

All statistical analysis was performed using Analyse-it for Microsoft Excel (Analyse-it Software Ltd, version 2.20, Leeds, UK). Student t-test and Mann-Whitney tests were used to compare the groups and spearman correlation was used to evaluate relationships between the biochemical parameters measured.

Results

Patient demographics

Patients were split into two groups' survivors and non-survivors. Survivors (n = 65) had a mean age 57 years, female (n = 27), men (n = 38). Non-survivor (n = 44) had a mean age 69 years, female (n = 25), men (n = 21).

Comparison of Serum Zn, Cu, Se, CRP, ALB and PA between Survivors and Non-survivors

Analytes measured in serum (Reference range)	Survivors (n = 65) Median (SD)	Non-survivors (n = 44) Median (SD)	p
Se (0.6 - 1.5 µmol/L)##	0.63 (0.21)	0.49 (0.26)	0.05
Zn (12 - 25 µmol/L)##	9.3 (3.34)	8.65 (3.87)	0.17
Cu (12 - 25 µmol/L)#	17.7 (4.31)	13.8 (8.65)	0.07
CRP (< 5 mg/L)##	90 (98.7)	97 (82.21)	0.74
Albumin (35 - 50 g/L)#	27 (7.10)	22 (8.43)	0.09
Pre-albumin (0.2 - 0.4 g/L)#	0.11 (0.07)	0.11 (0.06)	0.32

Table 1: *Comparison of serum trace element, inflammatory and nutritional markers between survivors and non-survivors. Cu: Copper; Zn: Zinc; Se: Selenium; CRP: C-Reactive Protein. A student t-test was used when analytes were parametrically distributed# and a Mann-Whitney test was used for non-parametrically distributed results##. *Deemed significant when p = <0.05.*

Serum Se, Zn, Cu was lower in non-survivors compared to survivors but a borderline significant difference was seen only with serum Se (p = 0.05). There was no significant difference between serum CRP, PRA and ALB between the two groups.

Relationship of serum Zn, Cu, Se with inflammatory marker (CRP)

	Survivors (n = 65)		Non-survivors (n = 44)	
Variables	**r**	**P**	**r**	**p**
Cu vs. CRP	-0.28	0.04*	-0.09	0.6
Se vs. CRP	-0.34	0.001*	-0.44	0.009*
Zn vs. CRP	-0.43	0.001*	-0.35	0.04*

Table 2: *Spearman's rank correlation analysis between Trace elements and CRP.*

Cu: Copper; Zn: Zinc; S: Selenium; CRP: C-Reactive Protein

**Deemed significant when p = <0.05*

Serum Se, Zn and Cu showed a significant negative correlation with CRP except in the non-survivor group where correlation was not significant between copper and CRP.

Relationship of serum Zn, Cu, Se with nutritional markers (ALB, PA)

	Survivors (n = 65)		Non-survivors (n = 44)	
Variables	**r**	**p**	**r**	**p**
Cu vs. PA	0.09	0.52	0.25	0.15
Cu vs. ALB	0.41	0.002*	0.6	<0.0001*
Se vs. PA	0.47	0.0006*	0.56	0.0006*
Se vs. ALB	0.67	<0.0001*	0.74	<0.0001*
Zn vs. PA	0.3	0.03*	0.31	0.07
Zn vs. ALB	0.38	0.003*	0.59	<0.0001*

Table 3: *Spearman's rank correlation analysis between Trace elements and nutritional markers.*

Cu: Copper; PA: Pre-Albumin; ALB: Albumin; Se: Selenium; Zn: Zinc.

**Deemed significant when p = <0.05*

Serum Se, Zn and Cu showed a significant positive correlation with serum ALB. Se showed a positive correlation with PA, Zn showed a positive correlation with PA in survivors but not in the non-survivors. Cu did not show any correlation with PA.

Relationship of CRP with ALB and PA

	Survivors (n = 65)		Non-survivors (n = 44)	
Variables	**r**	**p**	**r**	**p**
CRP vs. PA	-0.68	< 0.0001*	-0.39	0.03*
CRP vs. ALB	-0.52	< 0.0001*	-0.38	0.02*

Table 4: *Spearman's rank correlation analysis between CRP and nutritional markers.*

PA: Pre-Albumin; ALB: Albumin.

Serum CRP showed a significant negative correlation with albumin and pre-albumin in both survivors and non-survivors.

Discussion

Our study showed a significant negative correlation of TE with CRP and positive correlation with ALB in malnourished patients. Another significant finding in our study was inverse correlation between markers of inflammation and nutritional status suggesting that nutritional markers such as ALB and PA are influenced by inflammation and may not be reflective of nutritional status in malnourished patients.

Acute phase response is an inflammatory response to illness characterised by release of cytokines, which propagate the release of free radicals and thereby removing the pathogenic stimuli. This limits the damage to tissues and promotes the repair and healing of tissues [7]. Nevertheless, if illness continues and inflammation is aggravated, increased production of free radicals will inflict damage through lipid peroxidation and inducing oxidative stress [14].

The acute phase response in the short-term is beneficial but in the long-term it can be deleterious. This action of free radical induced oxidative damage in illness is limited by antioxidants, which scavenge or limit the production of free radicals in illness. TEs have an important role as antioxidants as they are part of antioxidant enzymes, e.g. Cu, Zn are co factors for superoxide dismutase and Se dependent glutathione peroxidase. In malnourished patients antioxidant activity is compromised either due to poor nutrient intake, gastrointestinal loss of TE or redistribution of TE due to inflammation. Since we observed a negative correlation between TE and CRP, the lower concentration of TE levels in our study patients was due to inflammation resulting in the reuptake of TE by tissues as a part of body defence mechanism. Similar findings have been reported by studies, which have assessed the relationship between TE and inflammation. Serum Zn levels were shown to fall after major surgery, by 40 ± 50% within 6h [8] and with lesser degrees of trauma (CRP up to 20 ± 30 mg/L) the reduction in Zn concentration was smaller, around 10% [15].

The fall in serum Zn is mediated by cytokines [interleukin-1 (IL-1) and interleukin-6 (IL-6)], which promote the uptake of zinc into the liver where it is complexed to metallothioneins involved in the production of new proteins [16]. Studies using radiolabelled Zn show increased tissue concentrations at sites of inflammation, which suggests localized roles in tissue regeneration [17]. Hence low serum Zn concentrations are beneficial to host defense by depriving microorganisms of a TE essential for growth and replication.

Se is a negative acute-phase reactant and in a series of intensive-care patients admitted for various clinical conditions, circulating selenium concentrations were on average 40% to 60% lower than in healthy individuals.

This is suggested to be due to redistribution of selenium, which is beneficial as it participates in the synthesis of antioxidant enzymes. Also, several studies have reported an inverse relation of serum selenium with CRP levels [18], suggesting that redistribution may be responsible for low levels of selenium. Compared to Zn and Se, which are negative acute phase reactants, Cu is a positive acute phase reactant. After major trauma or surgery, serum Cu concentration increases steadily and by day seven are 30% higher. Such changes are a direct result of increased hepatic synthesis of caeruloplasmin, the major Cu binding protein, mediated by cytokines IL-1 and IL-6. Higher caeruloplasmin concentration during illness are postulated to be beneficial since caeruloplasmin scavenges free radicals and helps to maintain iron in the reduced state, i.e. it functions as an antioxidant. Contrary to this, in our study we found that serum Cu levels reduced with increase in CRP. There can be a few reasons for this as our study cohort included patients with underlying gastrointestinal conditions and Cu is primarily absorbed in duodenum and most endogenous copper is lost via bile [19]. Therefore, malabsorption resulting in gastrointestinal loss of Cu may be a possible cause of low serum copper levels in our study cohort.

Inflammation, which accompanies illness further, contributes to the low TE levels by altering the plasma proteins such as ALB. The possible mechanism of reduction in ALB levels in blood in malnourished patients can be due to decreased hepatic synthesis, increased rates of degradation or loss from the body and redistribution between the vascular and extravascular compartments. Since the TEs are bound to ALB, any change in ALB levels will alter their levels in blood. Therefore, in our study patients who were malnourished and had gastrointestinal losses; inflammation had a significant contribution to low TE levels besides poor nutrition and losses incurred by underlying gastrointestinal condition. Thus, both inflammation and plasma proteins have an affect on TE levels in blood.

PA has been shown to be useful as a screening marker of nutritional status and in monitoring nutritional support [11,20]. Studies have shown that PA rather than albumin to have greater sensitivity in the detection of malnutrition [21]. However, PA has been shown to have poor specificity as its level in blood is affected by acute phase response. We observed a significant negative correlation of PA with CRP in our study patients. In acute phase response, there is redistribution of PA as well as reprioritization of protein synthesis (reduced synthesis of visceral proteins) in liver, leading to its low levels in blood. Therefore, PA levels are depressed during inflammation and may not accurately assess the nutritional status [22].

Our study showed that Zn, Cu and Se levels in blood are not prognostic markers in malnourished patients. Nevertheless, the concentration of TE was lower in non-survivors compared to survivors but this was not significant. This may be because there was no difference in degree of inflammation (CRP) or nutritional status (ALB and PA) between survivors and non-survivors. Nonetheless we did observed a significant positive correlation of Se with PA in both the survivors and non-survivors and borderline significant reduction in Se levels in non-survivors compared to survivors. Studies in critically ill patients show an inverse correlation of Se with mortality rate [9,23], thus suggesting that Se may have a prognostic role in our study patients who were not only malnourished but also had underlying gastrointestinal losses contributing to low Se levels.

The strength of our study is that inflammation affects the markers of nutritional status such as albumin and Pre-albumin in malnourished patients compromising the nutritional assessment in these patients.

One of the limitations of this study is that, there was no significant difference in severity of inflammation and degree of malnutrition between the survivors and non-survivors in our study patients. Similarly, to albumin, plasma concentration of Pre-albumin falls in the acute phase response. Thus, a low concentration of serum albumin and Pre-albumin may reflect a poor nutritional intake or inflammation, though both of these are risk factors for the development of malnutrition.

Conclusions

Low TE levels in malnourished patients should be interpreted in relation to the severity of inflammation The TE levels in blood does not predict the clinical outcome in malnourished patients.

Declarations

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Contributorship: ASD performed data collection and analysis. VM conceived ideas and designed study. All authors contributed to writing the manuscript.

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