Incidence and Predictors of Zinc Deficiency in Stable Peritoneal Dialysis Patients

Zinc is an essential trace element which plays many vital roles in cellular metabolism, growth, tissue repair, neurotransmitter production, and inflammation (1). Zinc deficiency has major clinical effects, particularly in children, ranging from poor appetite, weight loss, growth retardation, delayed healing of wounds, to loss of taste and mental slowness (2). Generally, zinc intake correlates well with dietary protein intake, as the major dietary sources of zinc are meats, dairy products, legumes, and whole grains. Nevertheless, zinc may bind to phytates, oxalate, iron, or medicines such as phosphate binders prescribed to chronic kidney disease (CKD) patients, leading to the formation of less absorbable insoluble complexes in the small intestine. Once absorbed from the gastrointestinal tract, zinc is transported in the plasma predominately by albumin, and stored intracellularly. Zinc is largely excreted in the feces, with urinary excretion accounting for less than 10% of daily losses.

As zinc excretion is principally through the gastrointestinal tract, dialysis patients are at no greater risk of zinc toxicity than the general population. However, in dialysis patients, several factors may contribute to altered body zinc storage. Poor appetite and restriction of dietary protein may lower zinc intake. Many medicines, including ion exchange resins, may interfere with zinc absorption. As such, several studies have measured plasma zinc levels in hemodialysis (HD) patients (3), reporting no effect with HD (4), although a meta-analysis reported HD patients were more likely to have low plasma zinc levels (5). In theory, peritoneal dialysis (PD) patients are more likely to have zinc deficiency than HD patients due to reduced appetite, lower serum albumin, and peritoneal protein losses. As there are limited small studies with differing results investigating zinc deficiency in PD patients, we audited plasma zinc levels in a stable PD population.

PATIENTS & METHODS

Plasma zinc levels were measured in 152 chronic stable PD outpatients, mean age 58 years (23 – 89), 51.3% male, 28.9% diabetic, and median dialysis vintage 11 months (1 – 157). Plasma samples were collected in specially prepared tubes designed to minimize external trace element contamination, and zinc, copper, and selenium were measured by atomic absorption spectroscopy. Serum biochemistry and hematology samples were analyzed with standard multi-channel analyzers. Body composition analysis was performed with multi-frequency bioelectrical impedance analysis (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea) (6,7).

This retrospective audit complied with the UK NHS guidelines for clinical audit and service development.

STATISTICAL ANALYSIS

Data are presented as a mean ± standard deviation or median and interquartile range unless otherwise stated. Statistical analysis used SPSS version 20 (SPSS, Chicago, IL, USA) and Prism version 6.0 (GraphPad, San Diego, CA, USA) employing Mann Whitney U test, and Kruskal-Wallis test was performed to identify racial differences in zinc level. Multiple linear correlation analysis was performed to determine which variables were associated with plasma zinc level, with nonparametric variables log transformed, then using a step backward model, initially including all variables with $p < 0.1$, and then eliminating variables that were not significant, or 95% confidence limits crossing the line of unity unless they did not increase the statistical fit of the model. Statistical analysis was taken at $p < 0.05$.

RESULTS

The mean patient age was 58 years (range 23 – 89 years), 51.3% male, 28.9% diabetic, and median PD vintage 11 (1 – 157) months. The most common ethnic group was Caucasian (48%), followed by African/Afro-Caribbean (17.1%), and South Asian (17.1%). A total of 60.6% were treated by overnight cycler (automated PD). Median weekly total Kt/V_{urea} was 2.28 (1.71 – 2.98), and median urinary creatinine clearance was 5.6 (1.7 – 10.8) mL/min/1.73 m^2.

Nutritional status was assessed by body mass index (BMI), median 26.2 (23.8 – 29.9) kg/m^2, and measurement of body cell mass, skeletal muscle mass, and percentage body fat. Dietary protein intake was calculated from 24-hour urine and PD effluent collections, using the normalized protein nitrogen accumulation (nPNA), median 0.85 (0.71 – 1.03) g/kg/day, and mean serum albumin was 37.9 ± 3.9 g/L. Mean total cholesterol and low density lipoprotein (LDL) were 4.69 ± 1.29 and 2.36 ± 0.98 mmol/L, respectively. In total, HMG CoA reductase inhibitors (statins) were prescribed to 66.4% of patients. The median serum C-reactive protein (CRP) was 3 (1 – 7) mg/L.

Altogether, 64.6% of patients were prescribed oral phosphate binders; 31.8% calcium-based binders, 16.4% lanthanum carbonate, and 16.4% sevelamer hydrochloride. No patient was prescribed oral iron.

The mean plasma zinc was 11.01 ± 2.83 umol/L (normal range 11 – 24 umol/L), with 57.2% of patients having low zinc levels (defined as < 11 umol/L). Mean serum copper was 16.9 ± 4.04, with 5.1% having low copper levels (defined as serum copper < 11 umol/L), and mean selenium was 0.86 ± 0.22, with 37.6% having low selenium (as defined as selenium < 0.8 umol/L).

There were positive correlations between plasma zinc and serum albumin ($r = 0.212$, $p = 0.014$), as well as for body fat mass corrected for body surface area ($r = 0.274$, $p = 0.01$), and a negative correlation with skeletal muscle mass ($r = -0.365$, $p = 0.01$). On multiple linear correlation, plasma zinc correlated both positively with serum albumin (β coefficient 0.113, 95% confidence interval (CI) 0.009 – 0.217, standard error (SE) 0.052, t statistic 2.150, $p = 0.034$) and negatively for skeletal muscle mass/body surface area (β -0.273, 95% CI -0.516 to -0.029, SE 0.123, t statistic 2.219, $p = 0.029$), r2 for model 0.173, and adjusted r2 0.143. There were no significant differences between patients with low and normal zinc levels (Supplemental table 1). Similarly there was no correlation between plasma zinc and copper ($r = -0.053$, $p = 0.54$) and selenium levels ($r = -0.081$, $p = 0.356$). Sevelamer prescription did not affect plasma zinc, copper, or selenium compared with other phosphate binders ($p = 0.978$) (Supplemental tables 1 and 2). Independent Kruskal-Wallis test identified no significant differences in zinc level across different ethnic groups.

DISCUSSION

In our cohort of chronic stable PD patients, the incidence of zinc deficiency was as high as 57.2%. The majority of previous studies have reported that PD patients are likely to have similar zinc levels compared with non-dialyzed CKD patients and healthy controls (5), but on the other hand some studies have reported low zinc levels (5). However, it is unclear in some of these reports how samples were prepared and whether external contamination could have occurred.

We looked for possible causes of zinc deficiency. As zinc is protein-bound, we compared peritoneal protein losses in the zinc deficiency group and the normal zinc group, but these were not different. This is supported by an earlier study which measured zinc in spent peritoneal dialysate effluent and found no significant peritoneal zinc losses (8). Poor dietary intake has been previously described as a cause of low zinc levels. However, from our study, estimation of dietary protein intake by nPNA did not show any association with low zinc level, and, similarly, there was no co-association with copper or selenium concentrations. Dietary sources of zinc are widespread, as zinc is present in meats, whole grains, legumes, and shellfish. Copper also has a ubiquitous distribution among food sources and has a low daily requirement, so deficiency is rare. Although some foodstuffs, such as liver, are high in selenium, dietary sources of selenium are also widespread in meats, cereals and other grains, and dairy products. As such, if zinc deficiency were to be secondary to dietary intake, we would have expected to find lower levels of both copper and selenium in this cohort. Similarly, we found no association between plasma zinc and body weight, BMI, or nPNA. Indeed, we found a negative association between body muscle and zinc levels, suggesting that zinc levels cannot simply be predicted from measures of dietary protein intake or body composition. Our finding parallels those of earlier smaller studies. Therefore, nutritional status of patients *per se* is not a sensitive predictor for zinc deficiency.

It has been suggested that plasma zinc may be reduced by inflammation. Whether this is related to malnutrition and inflammation syndrome is unclear from previous studies (5). In our cohort, C-reactive protein was not different between subjects with low and normal plasma zinc levels. Although there was a statistical correlation with serum albumin, the strength of the correlation was very weak and, rather than being linked to a relationship with lower albumin and inflammation, was more likely confounded by zinc being transported by albumin in plasma. We found no effect due to diabetes in the 2 zinc groups.

Another possibility is that zinc could be bound in the gastrointestinal tract, leading to decreased absorption. Sevelamer hydrochloride, an ion exchange resin prescribed as a phosphate binder to patients with CKD, has been reported to have an adsorptive property to zinc and copper. In our study, there were no significant differences in zinc and copper levels between sevelamer and non-sevelamer groups. The lipid profiles between sevelamer and non-sevelamer groups were also not different. However, this may have been due to a high prevalence of lipid lowering drugs prescribed, with some 64% prescribed statins. Similarly standard calcium-based phosphate binders also did not affect zinc levels. However, caution must be exercised in interpreting these data, as the number of patients prescribed sevelamer in this study was relatively low (16.4%) and therefore our results could be biased by the small numbers of measurements in the sevelamer group. Oxalate and phytates could also potentially bind zinc in the gastrointestinal tract, reducing absorption. Diets differ between ethnic groups, so we compared zinc and other trace elements between our main ethnic groups of Caucasians, South Asians (many of whom were vegetarian), and Afro-Caribbeans and Africans. However there were no differences in plasma zinc and either copper or selenium between our racial groups.

One difference between PD patients and those treated by HD is that many PD patients are prescribed cathartics to treat constipation, and, as zinc is excreted through the gastrointestinal tract, this may increase zinc losses in the feces. Zinc excretion differs from that of copper, which is predominately excreted into bile, and selenium, which is primarily excreted in the urine. As such, the explanation of the lower zinc levels in our PD cohort may lie in increased fecal zinc loss, but this would require conformational studies.

DISCLOSURES

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