Zinc Status is Related To Dialysis Adequacy In Peritoneal Dialysis Patients: A Cross-Sectional Study In Central China

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Abstract

Background: Zinc displays an essential role in regulation of inflammation and redox oxidative stress and patients on peritoneal dialysis (PD) are prone to develop zinc deficiency due to decreased dietary intake and losses via PD effluent and urinate. This study was aimed to evaluate the prevalence rate of zinc level in Chinese patients on PD and the relationship between zinc level and total Kt/V (tKt/V) on PD;

Methods: A cross-sectional study of a cohort of 116 patients with end-stage kidney disease (ESKD) receiving PD was conducted. Peritoneal dialysis Kt/V were identified and patients were grouped as high tKt/V (≥1.7) (n=78) group and low tKt/V（＜1.7）(n=38) group. The zinc level in whole blood were measured using atomic absorption spectroscopy（AAS）;

Results: The zinc level in whole blood showed significantly higher values in patients with high tKt/V than those with low tKt/V (5.47±0.47 and 5.02±0.35, p=0.031, respectively). Age, zinc, albumin and cholesterol level were identified as independent predictors of Kt/V in PD patients by multivariate analysis. The prognostic value of zinc of high tKt/V was revealed as an area under the curve (AUC) of 0.799 (95% CI :0.717-0.881, p＜0.001) with a sensitivity of 80.8% and specificity of 73.7%. Compared with albumin and cholesterol, Delong'test was empolyed and the results showed that zinc in whole can predict the better adequacy of PD significantly (p＜0.05);

Conclusions: Zinc level in whole blood are low in patient undergoing peritoneal dialysis. Low zinc concentration is associated with low tKt/V in PD patients, suggesting that zinc level in whole blood may serve as an independent factor of dialysis quality of PD patients.

1. Introduction

Zinc is an essential trace micronutrient for human and considered to be vital for physiological activities, for instance tissue repair, growth, vision, immunity and cognition[1, 2]. Zinc takes part in various important cellular metabolism as an important cofactor of many neurotransmitters, enzymes and transcriptional factors[3]. Zinc deficiency is associated with growth retardation, delayed would healing, decreased taste, cardiovascular disease or immune system disturbances[4–6].

Peritoneal dialysis (PD) patients are in poorer nutrition situation compared to patients on hemodialysis (HD) due to the loss of albumin in the PD effluent[7, 8]. Zinc deficiency is common and prevalent in PD patients due to inadequate dietary intake, tubular reabsorption impairment, hypo-proteinemia, reduced gastrointestinal zinc absorption and remove from the PD effluent[9]. There are several cross-section studies revealing the prevalence of zinc in peritoneal dialysis patients worldwide including Japan, Mexico, United states and European countries[9–11]. In contrast, there are few reports on dietary zinc intake and zinc concentration in patients on PD in China. Given the dietary habit and food structure is totally different in China compared to those in western countries, even in Japan, it is essential to investigate the prevalence of zinc deficiency in Chinese patients and appropriate zinc supplementation may be beneficial in the peritoneal dialysis population.

Peritoneal fibrosis and ultrafiltration failure has been considered as the major complications for patients to withdraw peritoneal dialysis[12]. Accumulating evidences demonstrated that inflammation and reactive oxygen species (ROS) are involved in the progression and pathogenesis of peritoneal fibrosis[13, 14]. Several studies have revealed that zinc supplement ameliorate inflammation via interfering NF-kB pathway and inhibiting ROS via activating Nrf2 antioxidant pathway[15, 16]. However, there is limited studies on the relationship between zinc level in whole blood and the efficiency of peritoneal dialysis. Therefore, we conducted this study to investigate whether low zinc level in whole blood is associated with low efficiency of peritoneal dialysis in PD patients in central China.

2. Materials And Methods

A total of 116 patients who were on maintenance peritoneal dialysis at the second hospital of Anhui Medical University from May 2020 to May 2021 were recruited. This study was approved by the ethics committee of the second hospital of Anhui Medical University (PJ-YX2019-013). Patients who were older than 18 years of age and received PD more than 3 months were enrolled. Patients with malignancy, obvious infectious diseases, concomitant steroid or immunosuppressant medication, gastrointestinal disturbance and zinc supplementation within previous 6 months were excluded.

Analysis of Biochemical Parameters

Demographic and biochemical parameters, including age, sex, body mass index (BMI), duration of dialysis, smoke, diabetes, cause of ESKD and comorbid cardiovascular disease (CVD) were collected from the medical records. The blood samples were obtained after 8 hours fasting in the morning. Biochemical parameters, including serum creatinine, blood urea nitrogen, total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, calcium, phosphorus, serum iron, total iron binding capacity, intact parathyroid hormone (iPTH), serum ferritin level and C-reactive protein (CRP) were measured using routine clinical chemistry procedures with commercial kits in the general lab in our hospital.

The zinc concentrations in whole blood were measured by atomic absorption spectroscopy (AAS). AAS methods were based on those of Meret and Henkin. All experiments were performed using an atomic absorption spectrometer and the kit (BH5100S1, Bohui innovation biotechnology company, Beijing, China). Zinc was measured at a wavelength of 213.9 nm, using a slit width of 1.0 nM and lamp current of 5.0 mA. For calibration, a 612 μmol/L zinc nitrate standard was added in volumes of 0, 20, 50 and 75 μL to 1 mL pooled human blood to produce concentrations of 0, 13.9, 27.8 and 41.7 μmol/L.

Assessment of the adequacy of Peritoneal Dialysis

The adequacy of PD was evaluated by weekly total urea clearance (Kt/V). Weekly total Kt/V (tKt/V) comes from residual kidney function (rKt/V)and weekly Kt/V urea from PD (pKt/V) which were calculated from a 24-h collection of dialysate and urine with the use of standard methods17.

Statistical Analysis

Quantitative data were expressed as mean ± standard deviation or as the median (interquartile range) as appropriate. Continuous variables were compared between the study groups using the Student's *t*-test. Categorical variables were compared between different groups using chi-square test. Factors associated with the zinc level were sought using the Spearman rank correlation. Multiple linear regression analysis was then performed to analyze the association between tKt/V and other parameters. The receiver operating characteristic curve (ROC) was performed to access the potential predictive value of zinc for the higher efficiency of peritoneal dialysis. All statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL,USA). Additionally, part of ROC analysis was performed using MedCalc 20.015 software. A two tailed $p \leq 0.05$ was set to indicate a statistical significant difference.

3. Results

3.1. Biochemical and Anthropometric parameters of PD patients

3.1. Biochemical and Anthropometric parameters of PD patients

A total of 116 PD patients (72 women and 44 men; mean age, 53.4±13.5years, Mean PD vintage, 37.0±31.2 months) were enrolled in this study. In addition, there were 61 healthy controls in the control group. As shown in Table 1, there is no significant difference in age or gender between the two groups (p>0.05). The level of hemoglobin and serum albumin of PD patients are significantly lower than those of healthy control (p<0.05). Moreover, the zinc of whole blood of PD patients were 5.57 mg/L and significantly lower compared with that of healthy people (8.78±0.74mg/L).

All the PD patients were divided into two groups for further comparisons. Group 1 patients had high tKt/V (n= 78), and group 2 included patients with low tKt/V (n =38). As shown in Table 2, patients with low tKt/V had significantly lower serum albumin, alkaline phosphatase, HDL cholesterol and zinc in whole blood. In addition, patients with low tKt/V had fewer female patients than those of high tKt/V (p□0.05). Moreover, compared to patients with high tKt/V, patients with low tKt/V had significantly higher serum creatinine , CRP, Ferritin, BMI and heart rate (p□0.05). With regard to PD associated parameters, patients with high tKt/V drained more dialysate (p□0.05) than patients with low tKt/V, while the exchange bags and the glucose dialysate were similar between the two groups.

Table 1
The comparisons of Clinical characteristic between PD patients and control group

Variables	PD group (n = 116)	Control group (n = 81)	T/z/x^2	*p*-Value
Female (n,%)	30,62%	47,58%	0.622	0.615
Age (Years)	52.3(45,57)	50.6 (44,55.8)	-0.913	0.420
Hb (g/L)	101.97 ± 17.25	136.5 ± 12.57	-9.230	< 0.001
Alb(g/L)	34.67 ± 6.80	46.02 ± 2.64	-3.165	< 0.001
Zinc (mg/L)	5.57 ± 0.65	8.78 ± 0.74	-5.614	< 0.001
Hb,hemoglobin; Alb, albumin;				

Table 2
Patients' characteristics at baseline in patients on peritoneal dialysis

Variable	High tKt/V (n = 78)	Low tKt/V (n = 38)	*p*-Value
Female(n %)	55 (70.5%)	17 (44.7%)	0.08
Age (years)	51.9 (45,61.3)	53.8 (41,61.8)	0.529
BMI(m/kg^2)	21.7 ± 3.5	24.2 ± 3.6	< 0.001
PD vintage (months)	37.2 (12,52.2)	53.6 (12,66.3)	0.490
Cause of ESRD			
Glomerulonephritis	50(64.1)	10 (26.3%)	< 0.001
Hypertension	6(7.7%)	1 (2.6%)	0.382
Diabetes	15(19.2%)	27(71.1%)	< 0.001
Cystic kidney disease	6(7.7%)	0 (0%)	0.152
Others	3(3.8%)	0(0%)	0.087
Comorbidity			
Cardiovascular disease	6(7.7%)	5(13.2%)	0.348
Hypertension	35(83.3%)	33 (86.8%)	0.625
Diabetes	24(30.8%)	31 (81.6%)	0.010
Smoke	4 (5.1%)	5 (13.2%)	0.131
Auria	40(51.3%)	29(76.3%)	0.010
PD treatment time, h/day	15.6 ± 3.2	16.4 ± 2.0	0.312
PD fluid drain volume, mL/day	356.8(96.5,659.5)	616.36(434.8,769.)	0.003
1.5% glucose dialysate, L/day	5.2 ± 1.8	2.7 ± 0.9	0.396
2.5% glucose dialysate, L/day	2.6 ± 1.9	1.4 ± 1.1	0.859
Systolic BP, mmHg	138.3 ± 23.1733	142.9 ± 25.1	0.331
Diastolic BP, mmHg	83.9 ± 16.7	88 ± 16.5	0.202
Heart rate,(bpm)	79.0 ± 6.5	82 ± 8.7	0.04

3.2. Independent predictors of tK/tv in PD patients

In order to predict the adequacy of peritoneal dialysis, we further analyzed the independent determinants using multiple linear regression, and found out that age, zinc, anuria, albumin and cholesterol level were

independent predictors of tKt/V in PD patients (Table 3).

Table 3
Laboratory parameters in the PD groups of high tKt/V and low tKt/V

Variable	High tKt/V (n = 78)	Low tKt/V (n = 38)	*p*-Value
Albumin, g/L	32.6 ± 3.7	31.1 ± 2.3	0.005
Hemoglobin, g/L	100.5 ± 20.4	91.6 ± 16.2	0.012
Urea nitrogen, mmol/L	15.6 ± 5.5	18.9 ± 5.9	0.004
Creatinine, μmol/L	687 ± 298	953.2 ± 332.7	< 0.001
Corrected calcium, mg/dL	2.2 ± 02	2.2 ± 0.4	0.052
Phosphate, mmol/L	1.4 ± 0.5	1.7 ± 0.6	0.16
Alkaline Phosphatase, IU/L	112 (71,123)	94 (76,113)	0.01
iPTH, pg/mL	272.1 (78.3,322.75)	258.0 (100.1,403.3)	0.15
Zinc, mg/L	5.47 ± 0.47	5.02 ± 0.35	0.031
Total cholesterol,mmol/L	4.2 ± 1.2	4.4 ± 1.1	0.647
HDL cholesterol,mmol/L	1.2 ± 0.4	1.0 ± 0.2	0.01
LDL Cholesterol,mmol/L	2.7 ± 0.8	2.8 ± 0.8	0.419
Triglycerides, mmol/L	1.5 ± 1.0	1.8 ± 1.0	0.10
CRP ,mg/dL	3.4 ± 3.2	7.5 ± 5.1	0.01
Ferritin, ng/mL	170.5 (57.2, 226.5)	227.5(89.8,299.2)	0.034
Transferrin saturation	24.1(12.2,31.5)	23.0 (15.9,30.1)	0.991

Table 4
Independent determinants for high tKt/V using multiple regression analysis in patients on PD

Variables	**0.623** **20 and < 0.001**	**R^2(adjusted R^2)** **F and *p***	
	t	**β**	**p**
Age	0.000	0.003	< 0.001
Dialysis duration	5.490	0.013	0.94
Anuria	2.828	0.256	0.06
Zinc	3.132	0.457	< 0.001
CRP	0.94	-0.034	0.621
Hemoglobin	1.162	0.078	0.248
Albumin	7.377	-0.015	< 0.001
Total Cholesterol	3.915	0.245	< 0.001
Triglycerides,	1.449	0.095	0.15

3.3. Factors affecting the zinc level in whole blood

As presented in Table 5, Zinc level exhibited negative correlation with CRP(r=-0.277, p = 0.003), anuria（r=-0.183, p = 0.05）, BMI (r=-0.337, p = 0.00) and albumin in PD fluid(r=-0.215, p = 0.2). Furthermore, positive associations with albumin (r = 0.202, p = 0.03), hemoglobin (r = 0.288, p = 0.02), rKt/V (r = 0.243, p = 0.02) and tKt/V(r = 0.515, p = 0.00) were observed for zinc level.

Table 5
Spearman correlation coefficients between study variables and zinc level in patients on peritoneal dialysis

Variable	Zinc	
	Estimate	p-Value
CRP	-0.277	0.003*
Albumin	0.202	0.030*
Hb	0.288	0.002*
BMI	-0.337	0.000*
rKt/V	0.243	0.009
tKt/V	0.515	0.000*
Anuria	-0.183	0.05*
Albumin in PD fluid	-0.215	0.020*
Total cholesterol	-0.066	0.481
L-LDL	-0.061	0.518
Triglycerides	-0.206	0.026*
CRP, C-reactive protein; BMI, body mass index; PD, peritoneal dialysis; *p□0.05		

3.4 Zinc level in whole blood is predictor of high tKt/V

The ROC curve analysis was performed to access the potential predictive values for the high efficiency of peritoneal dialysis. As shown in Fig. 1, the prognostic power of zinc was revealed as an Area Under the Curve (AUC) of 0.799 (95% CI:0.717–0.881= with a sensitivity of 80.8% and specificity of 73.7%. Similarly, the sensitivity of albumin and cholesterol were 60.3% and 64% respectively, Meanwhile, specificity of them are 73.6% and 72.1% respectively. In order to compare the overall diagnostic performance, Delong's Test was employed to analyze the AUC of zinc, albumin and cholesterol and suggested that zinc level in whole blood can predict efficiency of PD treatment better than serum albumin and cholesterol (Zinc vs Alb, p 0.00, Zinc vs CHO, p 0.04).

Table 6
Comparison the predictive capability among zinc, cholesterol and Albumin.

Variable	Cutoff	Sensitivity	Specificity	Area under curve (95%CI)	*p* (95%CI)
Zinc	5.11	80.8%	73.7%	0.799 (0.707,0.881)	
CHO	3.55	64%	83.6%	0.541 (0.446 ,0.634)	0.04 *(0.005,0.253)
Alb	31.5	60.3%	72.1%	0.670 (0.576 ,0.754)	0.00* (0.120,0.396)
CHO, cholesterol; Alb, albumin					

4. Discussion

To the best of our knowledge, our study is the first study to investigate the zinc level in whole blood in peritoneal dialysis patients in central area in China. Among studied patients, the average level of zinc in whole blood in PD patients is lower than that of healthy control were observed. Based on our findings, patients on chronic stable peritoneal dialysis with low level zinc in whole blood are prone to have decreased peritoneal dialysis efficiency as there is a negative correlation between zinc level and tKt/V. Furthermore, zinc concentration was negatively correlated with C-reactive protein, which is essential marker of inflammation. The ROC curve analysis showed that zinc level could be a diagnostic value as a biomarker with proper sensitivity and specificity. Our clinic study suggested that low zinc level in whole blood were associated with high risk of decreased peritoneal dialysis efficiency.

Although there is only 1% of total zinc existing in circulation, approximately 80% of the zinc is distributed in erythrocytes and 20% in serum. Most of previous studies evaluated the zinc level in either serum or plasma in CKD patients [18, 19], there is limited data revealing the statue of zinc in whole blood. Given ESKD patients prone to develop anemia[20], it is of great importance to reflect the accurate and true zinc homeostasis using samples from whole blood rather than in plasma or serum. Our present project first time uncovered the overall distribution and homeostasis of zinc in patients on PD. The result demonstrated that the zinc concentration in whole blood were significantly lower compared to the healthy population from the same region in where people having the diet habit in common, indicating that low level of zinc concentration in whole blood is prevalent among peritoneal patients in central area of China. Furthermore, previously published data revealed that there was no significant correlation between serum zinc and hemoglobin in hemodialysis patients[21], however, our study identified that there was a positive association between hemoglobin and zinc concentration in whole blood, implying that the hemoglobin level has an impact on zinc hemostasis in ESKD patient and suggesting that in future there should be

more attentions on measuring zinc level in whole blood to evaluate the zinc status in this special population.

Several studies has already demonstrated that ESKD patients are prone to develop zinc deficiency due to various factors, including decreased food intake, uremic toxicity, increased loss through urine [19, 22–24]. One of the most essential factors which impact the zinc intake is diet habit. Seafood such as oyster and scallops were reported to known as food containing abundant zinc and are the main resource of zinc intake of human[25]. The patients observed in our study inhabit the center part of China and seldom consume seafood mentioned above, which can partly explain the shortage of zinc intake. Furthermore, due to approximately 60–80% of serum zinc is bound to albumin, the amount of zinc might decrease not only because of the protein restriction and decreased absorption of zinc from the intestinal tract in ESKD patients, but also albumin being excreted via PD effluent fluid and protein urea. Our data are in accordance with previous studies suggesting that the zinc concentration in whole blood is significantly corelated with albumin level in PD patients [26]. Furthermore, our study identified inverse negative correlation between zinc level and the albumin concentration in the PD effluent, indicating that the more albumin lost in the PD effluent the lower zinc concentration is. Moreover, there is significant negative correlation between zinc level and anuria, indicating that the less protein loss from urine the higher zinc concentration in whole blood. A similar relationship was also observed in the study in which Zn bound to albumin and globulin in spent CAPD fluid[22]. Damianaki et.al reported that CKD patients had higher 24h urinary zinc excretion than non-CKD participants and impaired tubular activity account for zinc deficiency[27]. However, some studies did not show the significant correlation between zinc loss and lower serum zinc levels[28]. From clues mentioned above, our study further provided more evidences on the opinion that the losses of protein through peritoneal effluent and urea have impact on the zinc level in whole blood in patients on PD.

In recent decades emerging evidences demonstrated that there is a crosstalk between zinc and free fatty acid (FFA) including total cholesterol, LDL-Cholesterol and triglycerides[29, 30] and albumin mediate this crosstalk. This is due to the fact that binding site of zinc ion (Site A) and FFAs (FA2) both lie at the interface between domains I and domians II[31]. Briefly speaking, Zn-Site A is only available in FFA-free albumin, but is disrupted when an FFA molecule occupies site FA2[32]. Numerous intriguing interaction with regard to FFA-Zn crosstalk have been observed for energy metabolism and metabolic diseases[33, 34]. A statistically significant inverse correlation was found between zinc in whole blood and triglycerides but no significant relationships were found with LDL and total cholesterol. Nevertheless, the results of our study demonstrated that the total cholesterol positively correlated with tKt/V in PD patients. However, the mechanism underlying the crosstalk between FFA and zinc with regard to chronic kidney disease is unclear, implying more studies related should be conducted in future.

Inflammation is one of the major risk factors that contributes to the pathological process of PD ultrafiltration failure[35, 36]. Zinc plays an important role in regulating inflammation. Voelkl, Jet al demonstrated that zinc finger protein-TNFAIP3 is a suppressor of the NF-κB transcription factor pathway by inhibiting phosphorylation and degradation of IκB[37]. Furthermore, another study reported that

TNFAIP3 overexpression inhibits LPS induced NF-κB activation, TRAF6 and CD40 expression in rat peritoneal mesothelial cells[38]. Some clinic investigations also showed that zinc supplements ameliorates TNFα,IL-1beta and Hs-CRP in hemodialysis patients[39]. However, in those studies, no significant correlation was found of serum zinc levels with peritoneal dialysis adequacy[9, 40]. In this study we found that zinc levels in whole blood are significantly different between patients with high tKt/V patients and those with low tKt/V patients. Moreover, a moderate inverse association was found between zinc level in whole blood and C-reaction protein (CRP), indicating zinc deficiency is related with inflammation in long-term peritoneal dialysis patients and may result in chronic fibrosis of peritoneal membrane tissue. In addition, given the result of ROC analysis that compared with other risk factors such as albumin and cholesterol, zinc level in whole blood is the more proper biomarker to indicate the efficacy of peritoneal dialysis with higher specificity and sensitivity.

Several limitations in our study should be acknowledged. First of all, we could not evaluate the zinc intake from diet. Three-days dietary recall questionnaires were designed and supposed to evaluate nutrient intake among the PD patients, however, due to the Chinese diet habit of dining together, it is difficult to calculate the weight of food and then evaluate the zinc intake. In further more studies are required to access the zinc intake in patients and for developing strategies to improve nutrition status. Secondly, although our study measured the total amounts of albumin in PD effluent, the amount of zinc in PD effluent and urine were not measured due to the limited technique, therefore further investigations are required to access the loss of zinc particularly in PD patients and the association of the zinc loss via PD effluent and tKt/V is needed to be clarified. Last but not the least, our study could not observe the efficacy of zinc supplementation. A plethora of studies suggested that deficiency of the micronutrient zinc is also associated with CVD risk and overall mortality in CKD patients[12, 41]. Random clinical trials in multiple centers should be performed to further confirm the preliminary efficacy of zinc supplementation in patients on long-term dialysis with zinc deficiency.

5. Conclusions

The low zinc level in whole blood is common in patient undergoing peritoneal dialysis in the central region in China. Moreover, lower zinc concentration in whole blood is associated with low tKt/V in PD patients, suggesting that zinc level in whole blood may serve as an independent factor of dialysis quality of PD patients. Micronutrient trace zinc supplementation should be advised and further studies of zinc supplementation in zinc-deficient patients on PD are in huge demand.

Declarations

Author Contributions: Conceptualization, D.Z; methodology, software and formal analysis, D.Z; resources, L,L; data curation X,Z. Preparation and writing of the original draft, D.Z; review and editing of the manuscript, G.L and D,W. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

Data available on request due to privacy/ethical restrictions.

Ethical approval and Consent to Participate: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Second Hospital of Anhui Medical University. All of the participants provided written informed before their entry into the perspective study.

Consent for publication

Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. King, J. C., Shames, D. M. & Woodhouse, L. R. Zinc homeostasis in humans. *The Journal of nutrition* **130**, 1360s-1366s, doi:10.1093/jn/130.5.1360S (2000).
2. Fukada, T., Yamasaki, S., Nishida, K., Murakami, M. & Hirano, T. Zinc homeostasis and signaling in health and diseases: Zinc signaling. Journal of biological inorganic chemistry: JBIC : a publication of the Society of Biological Inorganic Chemistry **16**, 1123–1134, doi:10.1007/s00775-011-0797-4 (2011).
3. Prasad, A. S. Zinc: role in immunity, oxidative stress and chronic inflammation. Current opinion in clinical nutrition and metabolic care **12**, 646–652, doi:10.1097/MCO.0b013e3283312956 (2009).
4. MacDonald, R. S. The role of zinc in growth and cell proliferation. *The Journal of nutrition* **130**, 1500s-1508s, doi:10.1093/jn/130.5.1500S (2000).
5. Alker, W. & Haase, H. Zinc and Sepsis. Nutrients **10**, doi:10.3390/nu10080976 (2018).
6. Grüngreiff, K., Gottstein, T. & Reinhold, D. Zinc Deficiency-An Independent Risk Factor in the Pathogenesis of Haemorrhagic Stroke? *Nutrients* **12**, doi:10.3390/nu12113548 (2020).
7. Tonelli, M. *et al.* Trace elements in hemodialysis patients: a systematic review and meta-analysis. BMC medicine **7**, 25, doi:10.1186/1741-7015-7-25 (2009).
8. Kiebalo, T., Holotka, J., Habura, I. & Pawlaczyk, K. Nutritional Status in Peritoneal Dialysis: Nutritional Guidelines, Adequacy and the Management of Malnutrition. Nutrients **12**, 1715, doi:10.3390/nu12061715 (2020).
9. Shimizu, S. *et al.* Prevalence of Zinc Deficiency in Japanese Patients on Peritoneal Dialysis: Comparative Study in Patients on Hemodialysis. Nutrients **12**, doi:10.3390/nu12030764 (2020).

10. Martín-del-Campo, F. *et al.* Dietary micronutrient intake in peritoneal dialysis patients: relationship with nutrition and inflammation status. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis **32**, 183–191, doi:10.3747/pdi.2010.00245 (2012).
11. Panorchan, K. & Davenport, A. Incidence and Predictors of Zinc Deficiency in Stable Peritoneal Dialysis Patients. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis **35**, 597–599, doi:10.3747/pdi.2014.00134 (2015).
12. Williams, J. D. *et al.* Morphologic changes in the peritoneal membrane of patients with renal disease. Journal of the American Society of Nephrology: JASN **13**, 470–479, doi:10.1681/asn.V132470 (2002).
13. Noh, H. *et al.* Oxidative stress during peritoneal dialysis: implications in functional and structural changes in the membrane. Kidney international **69**, 2022–2028, doi:10.1038/sj.ki.5001506 (2006).
14. Zhang, Z., Jiang, N. & Ni, Z. Strategies for preventing peritoneal fibrosis in peritoneal dialysis patients: new insights based on peritoneal inflammation and angiogenesis. Frontiers of medicine **11**, 349–358, doi:10.1007/s11684-017-0571-2 (2017).
15. Jarosz, M., Olbert, M., Wyszogrodzka, G., Młyniec, K. & Librowski, T. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. Inflammopharmacology **25**, 11–24, doi:10.1007/s10787-017-0309-4 (2017).
16. Fan, Y. *et al.* Zinc inhibits high glucose-induced NLRP3 inflammasome activation in human peritoneal mesothelial cells. Molecular medicine reports **16**, 5195–5202, doi:10.3892/mmr.2017.7236 (2017).
17. Teehan, B. P., Schleifer, C. R. & Brown, J. Assessment of dialysis adequacy and nutrition by urea kinetic modeling. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis **14 Suppl 3**, S99-104 (1994).
18. Xiang, S. *et al.* Comparative Study on Trace Element Excretions between Nonanuric and Anuric Patients Undergoing Continuous Ambulatory Peritoneal Dialysis. Nutrients **8**, doi:10.3390/nu8120826 (2016).
19. Shen, Y. *et al.* Plasma element levels and risk of chronic kidney disease in elderly populations (≥ 90 Years old). Chemosphere **254**, 126809, doi:https://doi.org/10.1016/j.chemosphere.2020.126809 (2020).
20. Stevens, L. A. & Levin, A. Anaemia, cardiovascular disease and kidney disease: integrating new knowledge in 2002. Current opinion in nephrology and hypertension **12**, 133–138, doi:10.1097/00041552-200303000-00002 (2003).
21. Takic, M. *et al.* Zinc Deficiency, Plasma Fatty Acid Profile and Desaturase Activities in Hemodialysis Patients: Is Supplementation Necessary? Frontiers in nutrition **8**, 700450, doi:10.3389/fnut.2021.700450 (2021).
22. Ščančar, J., Milačič, R., Benedik, M. & Križaj, I. Total metal concentrations in serum of dialysis patients and fractionation of Cu, Rb, Al, Fe and Zn in spent continuous ambulatory peritoneal dialysis fluids. Talanta **59**, 355–364, doi:https://doi.org/10.1016/S0039-9140(02)00522-2 (2003).

23. Esmaeili, M. & Rakhshanizadeh, F. Serum Trace Elements in Children with End-Stage Renal Disease. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation **29**, 48–54, doi:10.1053/j.jrn.2018.05.005 (2019).
24. Tonelli, M. *et al.* Concentrations of Trace Elements and Clinical Outcomes in Hemodialysis Patients: A Prospective Cohort Study. Clinical journal of the American Society of Nephrology: CJASN **13**, 907–915, doi:10.2215/cjn.11451017 (2018).
25. Maret, W. & Sandstead, H. H. Zinc requirements and the risks and benefits of zinc supplementation. Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS) **20**, 3–18, doi:10.1016/j.jtemb.2006.01.006 (2006).
26. Tsutsumi, R. *et al.* Albumin-normalized serum zinc: a clinically useful parameter for detecting taste impairment in patients undergoing dialysis. Nutrition research (New York, N.Y.) **34**, 11–16, doi:10.1016/j.nutres.2013.10.009 (2014).
27. Damianaki, K. *et al.* Renal handling of zinc in chronic kidney disease patients and the role of circulating zinc levels in renal function decline. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association* **35**, 1163–1170, doi:10.1093/ndt/gfz065 (2020).
28. Wallaeys, B., Cornelis, R., Mees, L. & Lameire, N. Trace elements in serum, packed cells, and dialysate of CAPD patients. Kidney international **30**, 599–604, doi:10.1038/ki.1986.227 (1986).
29. Coverdale, J. P. C., Khazaipoul, S., Arya, S., Stewart, A. J. & Blindauer, C. A. Crosstalk between zinc and free fatty acids in plasma. Biochimica et biophysica acta. Molecular and cell biology of lipids **1864**, 532–542, doi:10.1016/j.bbalip.2018.09.007 (2019).
30. Lu, J. *et al.* A molecular mechanism for modulating plasma Zn speciation by fatty acids. Journal of the American Chemical Society **134**, 1454–1457, doi:10.1021/ja210496n (2012).
31. Barnett, J. P. *et al.* Allosteric modulation of zinc speciation by fatty acids. Biochimica et biophysica acta **1830**, 5456–5464, doi:10.1016/j.bbagen.2013.05.028 (2013).
32. Handing, K. B. *et al.* Circulatory zinc transport is controlled by distinct interdomain sites on mammalian albumins. Chem Sci **7**, 6635–6648, doi:10.1039/c6sc02267g (2016).
33. Foster, M. & Samman, S. Zinc and Regulation of Inflammatory Cytokines: Implications for Cardiometabolic Disease. **4**, 676–694 (2012).
34. Zahid, H. *et al.* Zinc-induced oligomerization of zinc α2 glycoprotein reveals multiple fatty acid-binding sites. The Biochemical journal **473**, 43–54, doi:10.1042/bj20150836 (2016).
35. Zhou, Q., Bajo, M. A., Del Peso, G., Yu, X. & Selgas, R. Preventing peritoneal membrane fibrosis in peritoneal dialysis patients. Kidney international **90**, 515–524, doi:10.1016/j.kint.2016.03.040 (2016).
36. Raby, A. C. & Labéta, M. O. Preventing Peritoneal Dialysis-Associated Fibrosis by Therapeutic Blunting of Peritoneal Toll-Like Receptor Activity. Frontiers in physiology **9**, 1692, doi:10.3389/fphys.2018.01692 (2018).

37. Voelkl, J. *et al.* Zinc Inhibits Phosphate-Induced Vascular Calcification through TNFAIP3-Mediated Suppression of NF-κB. Journal of the American Society of Nephrology: JASN **29**, 1636–1648, doi:10.1681/asn.2017050492 (2018).
38. Zou, X. L., Pei, D. A., Yan, J. Z., Xu, G. & Wu, P. A20 overexpression inhibits lipopolysaccharide-induced NF-κB activation, TRAF6 and CD40 expression in rat peritoneal mesothelial cells. Int J Mol Sci **15**, 6592–6608, doi:10.3390/ijms15046592 (2014).
39. Guo, C. H. & Wang, C. L. Effects of zinc supplementation on plasma copper/zinc ratios, oxidative stress, and immunological status in hemodialysis patients. International journal of medical sciences **10**, 79–89, doi:10.7150/ijms.5291 (2013).
40. Kaneko, S. *et al.* Serum Zinc Concentration Correlates With Ferritin Concentration in Patients Undergoing Peritoneal Dialysis: A Cross-Sectional Study. Frontiers in medicine **7**, 537586, doi:10.3389/fmed.2020.537586 (2020).
41. Nakatani, S., Mori, K., Shoji, T. & Emoto, M. Association of Zinc Deficiency with Development of CVD Events in Patients with CKD. Nutrients **13**, doi:10.3390/nu13051680 (2021).

Figures

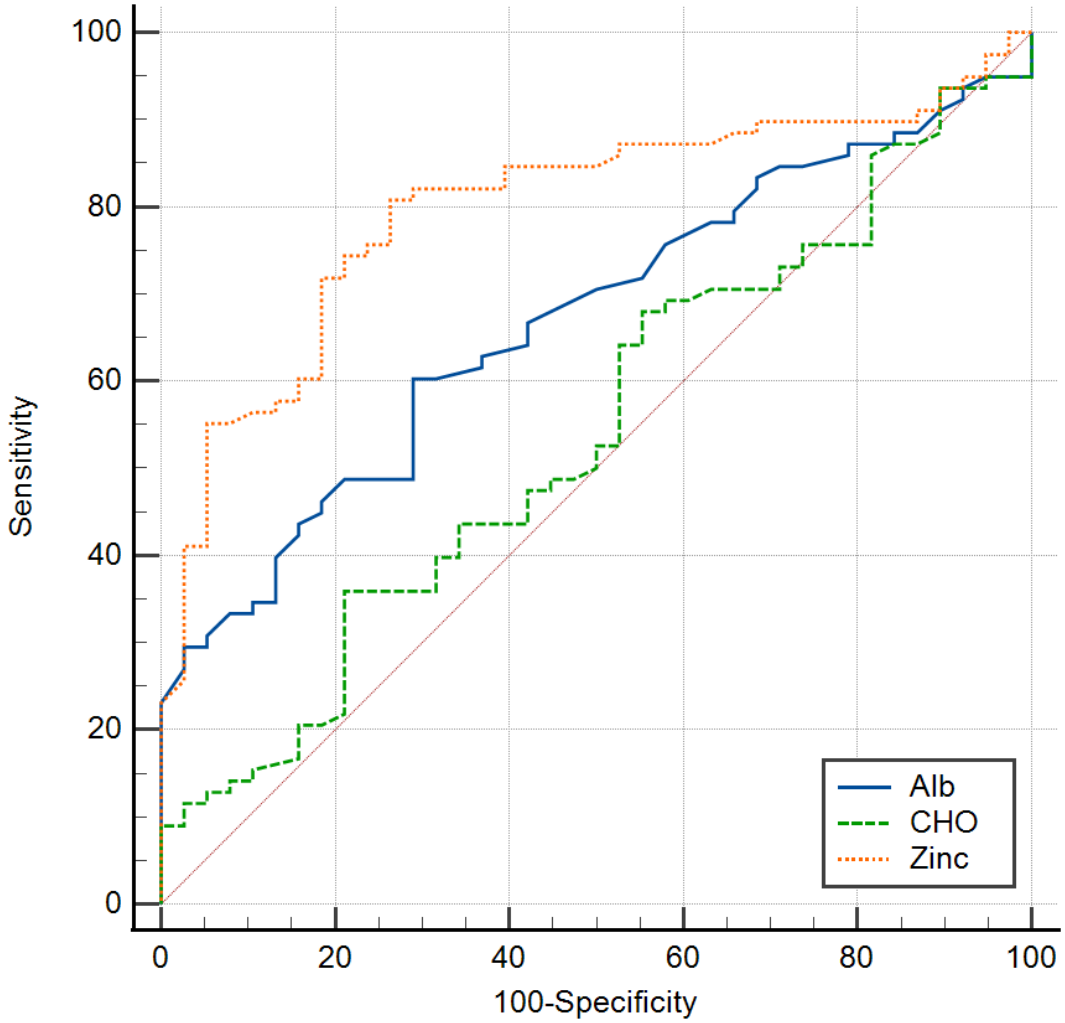

Figure 1

Comparison of ROC curve of predictive capability among Zinc, Cholesterol and Albumin