

Zinc (II) Induced Renal Functional Activities for Inhibitory Chronic Kidney Disease Progression

Dr. Sci. Tsuneo Ishida

2-3-6, Saido, Midori-Ku, Saitama-Shi, Saitama-Ken, 336-0907, Japan

Abstract

Zinc(II) induced chronic kidney disease (CKD) prevention is involved that zinc supplementation with 30 mg/day may benefit a metabolic improvement, a decrease in cardiovascular diseases (CVD), and the neurologic functional CKD prevention. Zinc induced renal functional activity for mild stage of CKD is involved that zinc supplementation of 30 mg/day may be beneficial for nutritional status in CKD children and adolescents, serum albumin, zinc and C-reactive protein (CRP) levels. Zinc(II) may reduce urinary protein excretion that is composed of albumin, urinary protein excretion is considered at high risk for renal disease progression and the minimized proteinuria excretion is an important therapeutics.

Zinc induced renal functional activity for moderate stage of CKD is involved that zinc fractional excretion is stable in the early stage of CKD, then a sudden and strong increase was seen in stage 3 patients, in which urinary zinc excretion was significantly higher in CKD patients that this factor of urinary zinc excretion is caused by that an increase in zinc's binding to alpha2-macro-globulin may reduce the amount of ultra-filterable zinc.

Zinc induced renal functional activity for severe stage and end-stage renal disease (ESRD) of CKD is involved that zinc is actively bound to several proteins such as albumin, a-macroglobulin and transferrin, that zinc intake has been shown to be lower in patients with advanced stage CKD, that ESRD in CKD has the baseline subject characteristics were divided according to baseline serum zinc levels at the first HD. Further, Zinc 15 mg/day and Selenium 50–70 µg/day are recommended such as micronutrient supply in adult patients on haemodialysis and peritoneal dialysis. Zinc induced NAD(P)H oxidase (Nox) activation occurring ROS generation in CKD cell involves assembly that ROS include the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$), in which Zn^{2+} bioavailability induces Nox upregulation, thereby promoting oxidative stress and subsequent kidney damages.

Zinc(II) ions-binding protein molecular mechanism is clarified that Zn^{2+} ions-several protein complexes coordinated binding model of ligands of such as albumin, a-macroglobulin and transferrin in several proteins have been found on the binding specificity by Zn^{2+} ions-centered tetrahedral geometric coordination, in which causing zinc-activated serine, histidine and aspartate hydrogen residues enhance renal function activity and resulting inhibition of CKD progression is proceeded.

Keyword: CKD prevention, Serum zinc and creatinine levels, Urinary protein and glycoprotein, ESRD prevention, Zn^{2+} ions-centered coordinated pattern.

Abbreviations: ACR=albumin-to-creatinine ratio, AH=arterial hypertension, AKI=acute kidney injury, BMI=body mass index, BP=blood pressure, CKD=chronic kidney disease, CAPD=continuous ambulatory peritoneal

***Corresponding Author:** Dr. Sci. Tsuneo Ishida, 2-3-6, Saido, Midori-Ku, Saitama-Shi, Saitama-Ken, 336-0907, Japan.

dialysis, **CRF**=chronic renal failure, **CRP**=C-reactive protein, **CVD**=cardiovascular disease, **DM**=diabetes mellitus, **DN**=diabetic nephropathy, **eGFR**=estimated glomerular filtration rate, **ESRD**=end-stage renal disease, **FE**=fractional excretion, **HD**=hemodialysis, **MHD**=maintenance hemodialysis, **NADPH**=nicotinamide adenine dinucleotide phosphate, **Nox**=NADPH oxidase, **OS**=oxidative stress, **PEW**=Protein-Energy Wasting, **RCTs**=randomized controlled trials, **RDA**=recommended dietary allowance, **ROS**=reactive oxygen species, **ZnD**=zinc deficiency.

INTRODUCTION

Severe COVID-19 infection may enhance chronic kidney disease (CKD) and acute kidney injury (AKI) developments that are susceptible to occur in preexisting CKD patients with the severity of COVID-19 increasing. CKD patients in non-dialytic stage exhibit a vulnerability to COVID-19 disease comparable to that of patient on kidney replacement therapy. More attention should be paid to decrease in COVID-19 pandemic, seek effective clinical pathways for CKD patients, and avoid CKD end stage renal disease (ESRD) [1]. CKD is a major global public health issue that common causes include hypertension, glomerulonephritis and autosomal dominant polycystic kidney disease, and many individuals have no known cause of CKD [2]. CKD have therapeutic patients clinical symptoms such as gross hematuria, a sign of albuminuria, nocturia, flank pain, or decreased urine output and CKD steps as glomerular filtration rate (GFR) less than 60 mL/min/1.73 m², albuminuria (ie, urine albumin ≥ 30 mg per 24 hours or urine albumin-to-creatinine ratio [ACR] ≥ 30 mg/g), imaging suggestive of kidney damage, renal tubular disorders [3].

CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² or the presence of structural or functional abnormalities [(micro)albuminuria] for at least 3 months [4]. Arterial hypertension (AH) was defined as mean office blood pressure (BP) $> 140/90$ mmHg measured at more than one occasion, or an office BP $> 140/90$ mmHg while taking one or more antihypertensive drugs [5]. The CKD Practice Guide of Nephrology recommendation referral meets any of the following 3 criteria: 1) 0.5g/g creatinine or higher, or proteinuria ($\geq 2+$), 2) an eGFR of less than 50 mL/min/1.73m², or 3) positive results ($\geq 1+$) for both proteinuria and hematuria tests [6].

While, zinc element is important essential for human body. According to the opinions on zinc homeostasis and zinc deficiency, the recommended dietary allowance (RDA) for zinc is of 11 mg/day for men and 8 mg/day for women, lower zinc intake is recommended for infants (2–3 mg/day) and children (5–9 mg/day) [7]. Zinc deficiency has been proven to deteriorate the symptoms associated with renal insufficiency, high-dose zinc (150 mg/day) following stem cell transplantation, and a weekly dose of 70 mg zinc not only reduced the incidence of death from pneumonia but also lowered the incidence of diarrhea, with overall mortality reduced by 85% [8]. Due to the fact that zinc is liable to be bound to proteins in the plasma [9], glomerular filtration and consecutive urinary excretion are limited [10] that the zinc-protein binding complexes function as Zn-protein enzymes in the human body.

Serum zinc levels tend to decrease with CKD progression and become lower in maintenance dialysis patients that patients on hemodialysis frequently develop zinc deficiency due to zinc removal during hemodialysis, inadequate dietary intake. Serum zinc level is low and serum leptin level is high in patients with CKD that serum zinc level of the studied patients (mg/dL) 60.9 ± 13.3 before and 95.0 ± 9.84 after zinc supplementation [11]. Optimal serum zinc level as normal zinc status is given as $80\text{--}120$ $\mu\text{g/dL}$ such as Japanese Practical Guidelines > 80 $\mu\text{g/dL}$, National Health and Nutrition Examination Survey ≥ 100 $\mu\text{g/dL}$, and in stroke in participants ≥ 120 $\mu\text{g/dL}$ [12]. Low zinc intake has significantly increased risk of incident CKD that mean eGFR was 92.1 ± 16.1 mL/min/1.73m². The mean daily zinc intake and zinc intake density were 86 ± 3.4 mg and 4.4 ± 0.944 mg/1000 kcal, respectively [13].

Zinc supplementation may be beneficial for nutritional status in children and adolescent with CKD, especially with 30 mg/day of zinc supplementation that is bound to several proteins such as albumin, α -macroglobulin and transferrin that the decrease of circulating zinc levels in CKD is partly caused by renal losses of zinc, becoming zinc-deficiency in CKD and possibly due to impairment in tubular reabsorption [14]. Moreover, zinc supplementation reduces urinary albumin excretion in patients with type 2 diabetes mellitus (DM) with micro-albuminuria and zinc supplementation may protect against the exacerbation of renal dysfunction, in which CKD is a significant risk factor for end-stage kidney disease (ESKD) and cardiovascular disease (CVD), hence, prevention of CKD progression

is an important strategy to improve poor prognosis and avoid deterioration in quality of life [15]. The other, uremia-induced alterations in protein metabolism and gastrointestinal tract function can result in poor nutritional status and Protein-Energy Wasting (PEW) become clinically manifest at an advanced stage, which increases the risks of CVD and infection, in which the non-traditional factors which increase the cardiovascular risk in CKD patients [16].

In this semi-review article, zinc(II) induced renal functional activities for CKD prevention and regulatory CKD development with mild stage, moderate stage, and severe stage are investigated, and subsequently, zinc(II) ions-binding molecular mechanism is clarified.

CKD (CHRONIC KIDNEY DISEASE) DEVELOPMENT

CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². The classification of CKD depending on GFR value consists of stage 1 — normal GFR (above 90 mL/min/1.73 m²) with persistent microalbumin, stage 2 — GFR 60–89 mL/min/1.73 m² with persistent microalbumin, stage 3 — GFR 30–59 mL/min/1.73 m², stage 4 — GFR 15–29 mL/min/1.73 m², and stage 5 — GFR below 15 mL/min/1.73 m² or end-stage renal disease (ESRD) [17].

CKD also can be classified into five stages based on the eGFR levels of individuals. eGFR is categorized into stages 1 to 5 of CKD as follows: stage 1 (eGFR ≥90 mL/min/1.73 m²), stage 2 (60–89 mL/min/1.73 m²), stage 3A (45–59 mL/min/1.73 m²), stage 3B (30–44 mL/min/1.73 m²), stage 4 (15–29 mL/min/1.73 m²), and stage 5 (< 15 mL/min/1.73 m²) [18].

The other, CKD stages have 1, 2, 3, 4, 5 stages / First stage, middle stage, final stage / Mild stage, moderate stage, severe stage that zinc induced CKD stages of mild stage, moderate stage, and severe stage have the probability of CKD regression and mortality far exceeded the risk of progression or kidney failure that CKD regression may be at least as common as CKD progression or kidney failure for mild to severe CKD [19].

Accordingly, CKD has been defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². Stage 1 CKD; eGFR 90 or greater, Stage 2 CKD; eGFR between 60 and 89, Stage 3 CKD; eGFR between 30 and 59, Stage 4; eGFR between 15 and 29, and Stage 5 CKD; eGFR less than 15. Low dietary zinc

intake for normal renal function may increase the risk of CKD development.

ZINC INDUCED CKD PREVENTION

Zinc(II) could prevent to CKD that zinc can prevent the oxidative stress and the inflammatory response, the intensification of the immune response, especially zinc deficiency (ZnD) is a risk factor for CKD progression with the recommended zinc dose ranges from 1.5 to 7.7 mmol/day or 1 mg/kg/day and absorption is decreased in oral intake going from the dietary 40% - 90% to the supplementary 8% - 38% [20]. ZnD also serves an important role in the pathogenic mechanisms of renal interstitial fibrosis during the development of diabetic nephropathy (DN) and suboptimal zinc status induces renal tubulointerstitial injury associated with the development of DN, in which 30 mg/day of zinc supplementation may benefit in the medication and prevention of the CKD [21].

Renal effect of zinc-activated metallothionein is involved that a significant positive correlation between metallothionein and eGFR in vivo in case of Zn administration, which could indicate a protective role of metallothioneins in a setting of reduced kidney function, which is possibly influenced by Zn [22]. As low zinc intake has been associated with a significantly increased risk of incident CKD, the mean daily zinc intake and zinc intake density are assumed to be adapted to 8.6 ± 3.4 mg and 4.4 ± 0.9 mg/1000 kcal, respectively [23].

ZINC INDUCED MILD STAGE OF CKD PROGRESSING

In the patients with different degrees of chronic renal failure, a statistically significant negative relationship was found between plasma zinc and serum creatinine concentrations. These data confirm that plasma zinc levels are reduced in patients with chronic renal failure and suggest that zinc deficiency may be related to the degree of renal insufficiency. Many factors could contribute to the decrease of plasma zinc levels in these patients [24]. The effect of zinc intake on serum zinc level 76 mg/dL, eGFR 30–59 and serum creatinine concentration at CKD mild stage becomes that Zinc intake <11 mg/Day and ≥11 mg/Day are Serum creatinine 0.99 and 0.97 mg/dL, respectively [25]. ZnD may result in apoptosis, oxidative stress, inflammation, and uncontrolled blood pressure, all of which are risk factors for CVD that approximately 60–80% of zinc is combined with albumin in serum, with an

increase in urinary albumin levels, while serum albumin and serum zinc levels decrease in patients with advanced CKD patients are also susceptible to ZnD owing to an inadequate dietary intake and reduced gastrointestinal zinc absorption that poor outcomes in maintenance hemodialysis (HD) patients were attributed to ZnD [26].

Patients excreting large amounts of urinary protein which the proteins in the urine are comprised of albumin and globulin from the plasma, should be considered at high risk for renal disease progression that the upper limit of normal for total urinary protein excretion is 150 mg/24 h, in which the normal amount of albumin excretion is <30 mg/day (<20 g/min). Persistent albumin excretion between 30 and 300 mg/day (20–200 g/min) is considered microalbuminuria. Values >300 mg/day are considered overt proteinuria or macroalbuminuria. The minimized proteinuria is an important therapeutics that reduce urinary protein excretion [27].

Specific glycoprotein alterations might be useful in predicting CKD progression that urinary glycoproteins unique to CKD patient having body mass index 30.5(kg/m²), serum creatinine 1.75(mg/dL), eGFR 52.0 (mL/min), protein/creatinine ratio 2.15, allow depletion of albumin and other abundant plasma proteins while providing a more thorough analysis of a subfraction of the urine proteome [28]. The other, NADPH oxidases (Noxs) play a critical role in kidney damage and Nox2-containing Nox plays a role in cyclosporine induced kidney damage, while Nox4-containing Nox is involved in diabetes-induced kidney damage [29].

ZINC INDUCED MODERATE STAGE OF CKD PROGRESSING

Low dietary zinc intake may increase the risk of CKD development in individuals with normal renal function that the mean serum Zn concentration in patients on maintenance HD was significantly with the cut-off point of 70 µg/dL [30]. Serum zinc is 52.8 µg/dL at eGFR 30–44 that the serum zinc level is shown to be at moderate stage [26]. Zinc-deficiency at stage 2–3 is that urinary zinc excretion was significantly higher in CKD patients and zinc fractional excretion was stable in the early stage of CKD, then a sudden and strong increase was seen in stage 3 patients [12]. Urinary protein excretion with CKD patient at moderate stage occurs that zinc supplementation reduces urinary albumin excretion in patients with type 2 diabetes mellitus (DM) with microalbuminuria that zinc

supplementation may protect against the exacerbation of renal dysfunction [15].

Zinc may reduce proteinuria in diabetic patients that zinc levels are lower in CKD and account for zinc imbalance in CKD that CKD patients had lower circulating zinc levels and higher 24-h urinary zinc excretion than non-CKD participants (612.4 versus 479.2 µg/day) and the fractional excretion (FE) of zinc increases with more advanced CKD stages, in which this factor of urinary zinc excretion may be involved that an increase in zinc's binding to alpha2-macroglobulin may reduce the amount of ultra-filterable zinc, thus altering the urinary zinc excretion and reduced albumin excretion in microalbuminuric type 2 diabetic patients [31, 32].

Thus, zinc may reduce proteinuria excretion in CKD patients that the urinary protein excretion composed of albumin becomes decreasing for an important therapeutics of proteinuric CKD.

ZINC INDUCED SEVERE STAGE FOR CKD AND END-STAGE RENAL DISEASE (ESRD)

Zinc induced severe stage of eGFR=15~29.

In CKD 4–5 stage, risk of CVD becomes higher [33] that Zn supplementation in the process of recovery from CVDs would be most beneficial primarily for the prevention and appropriate dietary recommendations, food fortification, and agronomic biofortification strategies can attain sufficient levels of dietary Zn in daily diets and potentially diminish the risk of developing CVDs [34] and zinc supplementation of 25 mg/day in zinc homeostasis has a beneficial effect for CVD in vascular dysfunction [35].

Factor of ZnD in CKD is depended on that zinc ions are present predominantly as being bound to proteins such as albumin, α-macroglobulin, and transferrin with approximately 60–80% of zinc in serum bound to albumin related to low zinc levels in CKD patients that zinc intake has been shown to be lower in patients with advanced stage CKD, in which ZnD in CKD progressing occurs by decreased food intake, increased urinary excretion that the effect of zinc supplementation on kidney function in pre-dialysis CKD is needed to determine that zinc supplementation greater than 45 mg/day may be necessary to increase the serum zinc level in HD patients [12]. Zinc balance in uremia by nutritional zinc represents the major factor in the development of negative zinc balance in zinc deplete animals after the onset of renal insufficiency, in which

the inverse association between urinary zinc excretion and uromodulin could partly account for zinc imbalance in CKD and zinc levels are lower in CKD by reduced renal zinc excretion [36]. As zinc levels are lower in CKD, and not compensated by reduced renal zinc excretion and uromodulin possibly points which could partly account for zinc imbalance in CKD [31].

Thus, zinc intake of 30 mg/day and serum zinc level of 60~76 µg/dL could slow down CKD progression.

Urine Zinc-Deficiency with Urinary Zinc Excretion in CKD (Can be Reduced and Stopped in Renal Activity)

Factor of zinc-deficiency in CKD is involved that zinc ions are present predominantly as being bound to proteins such as albumin, α -macroglobulin, and transferrin, with approximately 60–80% of zinc in serum bound to albumin several hypotheses related to low zinc levels in CKD patients have been proposed, such as low dietary intake due to protein restriction and decreased gastrointestinal absorption of dietary zinc due to impairment and zinc intake has been shown to be lower in patients with advanced stage CKD.

Urinary zinc excretion was significantly higher in CKD patients (612.4 µg/24 h) as compared with non-CKD patients with preserved kidney function (479.2 µg/24 h) and from uromodulin, a protein produced by tubular cells identified as a marker of tubular mass and function in the general population, urinary zinc loss may be linked to the low number of functional tubules associated with CKD [12, 31].

Plasma zinc and urine zinc contents decrease with CKD progressing that the plasma zinc content in healthy controls exhibits normal values (14.2 ± 1.1 mmol/l) while it showed moderately decreased values in CRF patients on conservative treatment (9.7 ± 0.9 mmol/l) and on CAPD treatment (9.1 ± 1.2 mmol/l) and The urine zinc content of healthy controls (8.5 ± 0.5 mmol/day) and conservatively treated chronic renal failure (6.3 ± 0.6 mmol/day) [37].

Zinc-Induced ESRD (Stage 5, Egfr < 15), ESRD Prevention

Zinc supplementation benefits the nutritional status of maintenance hemodialysis (MHD), leads to an anti-inflammatory and antioxidative effect in MHD, and there is a need for the effects of zinc supplementation on clinical endpoint events and on race [38]. Serum zinc concentration

is baseline serum zinc levels: tertile, <45, 45–59, and ≥ 60 µg/dL that the baseline subject characteristics were divided according to baseline serum zinc levels at the first HD and that serum zinc and serum albumin levels are 37.4 ± 5.4 and 2.6 ± 0.6 µg/dL, respectively, for as eGFR 6.6 (5.2–8.3) [26].

Serum zinc (Zn) levels tend to be low in chronic kidney disease (CKD) patients that Zinc induced ESRD is involved in eGFR below 15 mL/min/1.73 m² or ESRD that the mean Zn level was 59.6 µg/dl and the median eGFR was 20.3 ml/min/ 1.73 m² [15].

Zinc supplementation greater than 45 mg/day may be necessary to increase the serum zinc level in hemodialysis patients that in children with hemodialysis patients aged between 5 and 18 years old, given daily zinc supplementation of 50–100 mg for 90 days found that serum zinc was significantly increased from 53.2 ± 8.15 to 90.75 ± 12.2 µg/dL ($p=0.001$) [12]. In addition, zinc 15 mg/day and Selenium 50–70 µg/day are recommended such as micronutrient supply in adult patients on haemodialysis and peritoneal dialysis [39].

Thus, zinc induced ESRD functional activity is involved that serum zinc concentration is baseline serum zinc levels: tertile, <45, 45–59, and ≥ 60 µg/dl, Zn level was 59.6 µg/dl and the median eGFR was 20.3 ml/min/ 1.73 m², serum zinc and serum albumin levels are 37.4 ± 5.4 and 2.6 ± 0.6 µg/dL, respectively, in which Zinc 15 mg/day and Selenium 50–70 µg/day are recommended such as micronutrient supply in adult patients on haemodialysis and peritoneal dialysis and In children with hemodialysis patients aged between 5 and 18 years old, given daily zinc supplementation of 50–100 mg for 90 days found that serum zinc was significantly increased from 53.2 ± 8.15 to 90.75 ± 12.2 µg/dL ($p=0.001$). In addition, serum zinc level in HD patient has been recommended as a serum zinc range (≤ 78.3 µg/dL) [26].

Accordingly, zinc can prevent ESRD, in which serum zinc range (≤ 78.3 µg/dL) and daily zinc supplementation of 50–100 mg for 90 days found that serum zinc was significantly increased from 53.2 ± 8.15 to 90.75 ± 12.2 µg/dL ($p=0.001$), and Zinc 15 mg/day and Selenium 50–70 µg/day are recommended as micronutrient supply. Thus, Zinc intake of 45–75 mg/day and serum zinc level of ≤ 78.3 µg/dL could prevent ESRD stage.

ZINC INDUCED ROS GENERATION IN CKD PROGRESSION

Zinc induced Nox activation occurring ROS generation in CKD cell involves assembly of enzyme's membrane-associated subunits with cytosolic subunits that ROS are by-products of aerobic metabolism and include the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$), and in the kidney, mitochondria and the Nox family are the major sources of endogenous

ROS. For Nox, Seven different Nox homologues have been characterized (Nox1–Nox5, DUOX1, and DUOX2) with different activation mechanisms, heterogeneous tissue distribution and subcellular localizations. Nox4 is the principal Nox isoform in the kidney [40].

Nox is activated by ROS production in endothelial vascular smooth muscle and renal parenchymal cells that zinc induced NADPH oxidase activation can reduce chronic inflammation and oxidative stress in CKD [41].

Table 1. Zinc induced immune renal functional effect on chronic kidney disease development

Zn ²⁺ ions	Zinc induced renal functional activities on CKD prevention, mild stage, moderate stage, and severe stage, ESRD			
	CKD Prevention	Mild Stage, eGFR= 45~60	Moderate Stage eGFR= 30~44	Severe Stage eGFR=15~29, ESRD(Stage 5) < 15
Zn ²⁺ →	→ → Zn²⁺ -Zinc effect for decrease in oxidative stress and inflammatory response, immune Daily zinc intake and zinc intake density are assumed to be adapted to 8.6 ± 3.4 mg and 4.4 ± 0.9 mg/1000 kcal, respectively. -Zinc supplementation benefits hormones and parathormone -Zn; 52 ages, 8.6 mg/day, eGFR= 92.8 -Zinc; beneficial 30 mg/day	→ Zn²⁺, O₂⁻, H₂O₂, .OH, Nox2 -ZnD is a risk factor for CKD progressing -Nox2-derived oxidative stress and Nox4 NADAPH can reverse ZnD-induced kidney damage -Serum zinc 76 mg/dL, eGFR 30-59 -Serum zinc ≥60 µg/dL, eGFR 45-59 -Serum creatinine 1.75(mg/dL), eGFR 52.0 (mL/min), protein/creatinine ratio 2.15, eGFR 52.0 (mL/min) at urinary glycoproteins -Zinc 15 and 30 mg/day for 12 month -Zn level; 1.57-7.7 m mol/day, or 1mg/kg/day -Zinc; 30 mg/day for beneficial nutritional status	→ Zn²⁺, O₂⁻, H₂O₂, OH, Nox2 -Low dietary zinc intake increases the risk of CKD progress -Nox2-derived oxidative stress can reverse ZnD-induced kidney damage -Urinary zinc excretion 612.4 µg/24 h, ZnD risk factor -Serum albumin 3.1 ± 0.5 (g/dL)	→ Zn²⁺, O₂⁻, H₂O₂, .OH, Nox2 -Decreased plasma and urine zinc contents -Higher and increased zinc urinary excretion (> 612.4 µg/24h) and zinc FE (higher 0.9%) -Zn 71.6 µg/dl, Creatinine 1.98 µg/dl, eGFR=22.7 Zn 48.2 µg/dl, Creatinine 2.55 µg/dl, eGFR=18.2 -NADPH oxidase activation reduce chronic inflammation and oxidative stress -NADPH oxidase-2 can reverse ZnD-induced kidney damage -Zn level=59.6 µg/dl, eGFR=20.3 -Zinc; more than 45 mg/day ESRD < 15 eGFR -Serum zinc and serum albumin levels are 37.4 ± 5.4 and 2.6 ± 0.6 µg/dL, respectively, for as eGFR 6.2(5.2–8.3) -Serum zinc and albumin; 52.8 µg/dL and 3.1 g/dL, eGFR; 5.3. -Higher doses of zinc (≥75 mg/d) and higher doses of selenium (≥100 mcg/d) with control. -In children Zinc 50–100 mg for 90 days serum zinc from 53.2 to 90.75 µg/dL, cut-off point of 70 µg/dL -Serum zinc level ≤78.3 µg/dL, and zinc 45-75 mg/day in HD

Zinc-binding protein molecular mechanism; Zn²⁺ ions-several protein complexes coordinated binding model of ligands of such as albumin, a-macroglobulin and transferrin had been found on the binding specificity by Zn²⁺ ions-centered tetrahedral geometric coordination for this Zn²⁺ ions-centered coordination pattern that the decrease of circulating zinc levels in CKD is partly caused by renal losses of zinc, becoming zinc-deficiency in CKD, and possibly due to impairment in tubular reabsorption.

ZINC IONS-PROTEINS BINDING MOLECULAR MECHANISM WITH CKD DEVELOPMENT

Zinc induced zinc ions-proteins interaction complexes are formed that Zn^{2+} ions tend to bind many proteins by zinc ions-protein interaction in CKD blood. The zinc ions complexes may play important role that Zn^{2+} ions-protein complexes are liable to form for this Zn^{2+} ions-centered coordination pattern that the zinc-coordinating inhibitor of tetrahedral zinc sites is tetrahedrally coordinated binding to such as the catalytic triad of zinc-activated Serine, Histidine and Aspartate Hydrogen Residues.

Thus, Zinc(II) ions-binding protein molecular mechanism is involved that Zn^{2+} ions-several protein complexes coordinated binding model of ligands of such as albumin, a-macroglobulin and transferrin in several proteins had been found on the binding specificity by Zn^{2+} ions-centered tetrahedral geometric coordination for this Zn^{2+} ions-centered coordination pattern that the decrease of circulating zinc levels in CKD is partly caused by renal losses of zinc, becoming zinc-deficiency in CKD, and possibly due to impairment in tubular reabsorption.

Accordingly, as mentioned above, renal functional activities of zinc induced CKD development with CKD prevention and inhibitory progression with mild stage, moderate stage, and severe stage, respectively, are represented in Table 1, including with Zinc(II) ions-binding protein molecular mechanism caused by Zn^{2+} ions-several protein complexes coordinated binding model of ligands of such as albumin, a-macroglobulin and transferrin in several proteins.

CONCLUSIONS

Zinc(II) induced renal functional activities for inhibitory chronic kidney disease (CKD) progression with mild stage, moderate stage, and severe stage are elucidated, subsequently the zinc induced binding protein molecular mechanism has been clarified.

Zinc induced CKD prevention is involved that zinc supplementation with 30 mg/day may benefit a metabolic improvement, a decrease in cardiovascular diseases (CVD), and the neurologic function in the medication and prevention of the CKD.

Zinc induced renal functional activity for mild stage of CKD is involved that zinc supplementation of 30 mg/day may be beneficial for nutritional status in CKD children and adolescents, serum albumin, zinc and C-reactive protein

(CRP) levels. Zinc(II) may reduce urinary protein excretion that is composed of albumin, urinary protein excretion is considered at high risk for renal disease progression, and the minimized proteinuria excretion is an important therapeutics.

Zinc induced renal functional activity for moderate stage of CKD is involved that zinc fractional excretion is stable in the early stage of CKD, then a sudden and strong increase was seen in stage 3 patients, in which urinary zinc excretion was significantly higher in CKD patients ($612.4 \pm 425.9 \mu\text{g}/24 \text{ h}$) as compared with non-CKD patients with preserved kidney function ($479.2 \pm 293.0 \mu\text{g}/24 \text{ h}$). This factor of urinary zinc excretion is considered that an increase in zinc's binding to alpha2-macroglobulin may reduce the amount of ultra-filterable zinc, thus altering the urinary zinc excretion.

Zinc induced renal functional activity for severe stage and end-stage renal disease (ESRD) of CKD is involved that zinc is actively bound to several proteins such as albumin, a-macroglobulin and transferrin that the decrease of circulating zinc levels in CKD is partly caused by renal losses of zinc, becoming zinc-deficiency in CKD and zinc intake has been shown to be lower in patients with advanced stage CKD, and that ESRD in CKD has the baseline subject characteristics were divided according to baseline serum zinc levels at the first HD and that serum zinc and serum albumin levels are 37.4 ± 5.4 and $2.6 \pm 0.6 \mu\text{g}/\text{dL}$, respectively, for as eGFR 6.6 (5.2–8.3). Further, Zinc 15 mg/day and Selenium 50–70 $\mu\text{g}/\text{day}$ are recommended such as micronutrient supply in adult patients on haemodialysis and peritoneal dialysis.

Zinc induced ROS generation in CKD progressing is that ROS are by-products of aerobic metabolism and include the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$). Reduced Zn^{2+} bioavailability induces NADPH oxidase upregulation, thereby promoting oxidative stress and subsequent kidney damages.

Zinc(II) ions-binding protein molecular mechanism is involved that Zn^{2+} ions-several protein complexes coordinated binding model of ligands of such as albumin, a-macroglobulin and transferrin in several proteins had been found on the binding specificity by Zn^{2+} ions-centered tetrahedral geometric coordination. The decrease of circulating zinc levels in CKD is partly caused by renal losses of zinc, becoming ZnD in CKD, and possibly due

to impairment in tubular reabsorption, in which causing zinc-activated serine, histidine and aspartate hydrogen residues enhance renal function activity and resulting inhibition of CKD progression is proceeded.

Conflicts of Interest; The author declares there is no conflicts of interest.

Sources of funding; No source funding for this article, author's own expenses.

REFERENCES

1. Ya-Fei Liu, Zhe Zhang, Xiao-Li Pan, Guo-Lan Xing, Ying Zhang, Zhang-Suo Liu, Sheng-Hao Tu (2021); The chronic kidney disease and acute kidney injury involvement in COVID-19 pandemic: A systematic review and meta-analysis *PLOS ONE* 16(1): 1-13.
2. Sarah Elshahat, Paul Cockwell, Alexander P. Maxwell, Matthew Griffin, Timothy O'Brien, Ciaran O'Neill (2020); The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review *PLOS ONE* 15(3): 1-19.
3. Teresa K. Chen, Daphne H. Knicely, Morgan E. Grams (2019); Chronic Kidney Disease Diagnosis and Management: A Review *JAMA*. 322(13): 1294–1304. doi:10.1001/jama.2019.14745
4. Paun S, Tudosie M, Petris R, Macovei R (2015); The effects of Zinc on human body, including on renal failure and renal transplantation *Journal of Medicine and Life* 2015; Special Issue:137-140.
5. Hassan Askari, Nima Sanadgol, Asaad Azarnezhad, Amir Tajbakhsh, Hossein Rafiei, et al (2021); Kidney diseases and COVID-19 infection: causes and effect, supportive therapeutics and nutritional perspectives *Heliyon* 2021;7:1-15.
6. Kunitoshi ISEKI (2011); Role of Urinalysis in the Diagnosis of Chronic Kidney Disease (CKD) *JMAJ, January/February* 54, No.1: 27-30.
7. Barnett JP, Blindauer CA, Kassar O et al (2013). Allosteric modulation of zinc speciation by fatty acids. *Biochim Biophys Acta* 1830: 5456–5464.
8. King JC, Shames DM, Woodhouse LR (2000). Zinc homeostasis in humans. *J Nutr* 2000; 130: 1360S–1366S.
9. Levey AS, Eckardt KU, Tsukamoto Y et al (2005); Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 67: 2089–2100
10. Mancia G, De Backer G, Dominiczak A et al (2007); 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
11. Ghada M. El Mashad, El Sayed I. El Gebally, Sally M. El Hefnawy, Asmaa M. El Sayed Saad (2018); Effect of zinc supplementation on serum zinc and leptin levels in children on regular hemodialysis *Menoufia Medical Journal* 2018; 31, No.2: 1-7.
12. Shinya Nakatani, Katsuhito Mori, Tetsuo Shoji, and Masanori Emoto (2021); Association of Zinc Deficiency with Development of CVD Events in Patients with CKD *Nutrients* 2021; 13: 1-21.
13. Young Su Joo, Hyung Woo Kim, Sangmi Lee, Ki Heon Nam, Hae-Ryong Yun, et al (2021); Dietary zinc intake and incident chronic kidney disease *Clinical Nutrition* 2021; 40(3): 1039-1045.
14. Marlene Fabiola Escobedo-Monge, Guido Ayala-Macedo, Graciela Sakihara, Silvia Peralta, et al (2019); Effects of Zinc Supplementation on Nutritional Status in Children with Chronic Kidney Disease: A Randomized Trial *Nutrients* 2019; 11: 1-20.
15. Atsuyuki Tokuyama, Eiichiro Kanda, Seiji Itano, Megumi Kondo et al (2021); Effect of zinc deficiency on chronic kidney disease progression and effect modification by hypoalbuminemia *PLOS ONE* 2021; 16(5): 1-13.
16. Alice Bonanni, Irene Mannucci, Daniela Verzola, Antonella Sofia, Stefano Saffioti et al (2011); Protein-Energy Wasting and Mortality in Chronic Kidney Disease *Int. J. Environ. Res. Public Health* 2011; 8: 1631-1654.
17. Stanisław Niemczyk, Longin Niemczyk, Katarzyna Romejko-Ciepielewska (2012); Basic endocrinological disorders in chronic renal failure *Polish Journal of Endocrinology* 2012; 63(3): 250–257.

18. Jeewoo Kim, Juyeon Lee, Kyoung-Nam Kim, Kook-Hwan Oh, Curie Ahn, et al (2018); Association between Dietary Mineral Intake and Chronic Kidney Disease: The Health Examinees (HEXA) Study *Int. J. Environ. Res. Public Health* 2018; 15: 1-14.
19. Ping Liu, Rob R. Quinn, Ngan N. Lam, Huda Al-Wahsh, et al (2021); Progression and Regression of Chronic Kidney Disease by Age Among Adults in a Population-Based Cohort in Alberta, Canada *Nephrology* 2021; 4(6): 1-13.
20. L. C. Neto, M. R. Bacci, L. C. Sverzutt, M. G. Costa¹, B. C. A. Alves, F. L. Fonseca (2016); The Role of Zinc in Chronic Kidney Disease Patients on Hemodialysis: A Systematic Review *Health* 2016; 8: 344-352.
21. Xiuli Zhang, Dan Liang, Xu Lian, Zhi-Hong Chi, Xuemei Wang, Yue Zhao and Zhang Ping (2016); Effect of zinc deficiency on mouse renal interstitial fibrosis in diabetic nephropathy *Molecular Medicine Reports* 2016;14: 5245-5252.
22. Moritz Schanz, Lea Schaaf, Juergen Dippon, Dagmar Biegger, Peter Fritz et al (2017); Renal effects of metallothionein induction by zinc in vitro and in vivo *BMC Nephrology* 2017; 1: 1-8.
23. Young Su Joo, Hyung Woo Kim, Sangmi Lee, Ki Heon Nam, Hae-Ryong Yun, Jong Hyun Jhee et al (2021); Dietary zinc intake and incident chronic kidney disease *Clinical Nutrition* 2021; 40:1039-1045.
24. P. Gill, F. Fagioli, E. De Paoli Vital, A. Farinel (1985); Is Zinc Status a Problem in the Dietary Treatment of Chronic Renal Failure? *Nephron* 1985;40: 382.
25. Yiyang Zhang, Yan Liu and Hongbin Qiu (2018); Association between Dietary Zinc Intake and Hyperuricemia among Adults in the United States *Nutrients* 2018; 10: 1-12.
26. Tatsunori Toida, Reiko Toida, Shou Ebihara, Risa Takahashi, Hiroyuki Komatsu, Shigehiro Uezono, Yuji Sato and Shouichi Fujimoto (2020); Association between Serum Zinc Levels and Clinical Index or the Body Composition in Incident Hemodialysis Patients *Nutrients* 2020; 12: 1-11.
27. Biff F. Palmer (2007); Proteinuria as a Therapeutic Target in Patients with Chronic Kidney Disease *American Journal of Nephrology* 2007; 27: 287-293.
28. Anuradha Vivekanandan-Giri, Jessica L. Slocum, Carolyn L. Buller, et al (2011); Urine Glyco-protein Profile Reveals Novel Markers for Chronic Kidney Disease *International Journal of Proteomics* 2011; 2011:1-19.
29. Mirandy S. Li, Sherry E. Adesina, Carla L. Ellis, Jennifer L. Gooch, Robert S. Hoover, and Clintoria R. Williams (2017); NADPH oxidase-2 mediates zinc deficiency-induced oxidative stress and kidney damage *Am J Physiol Cell Physiol* 2017; 312: C47-C55.
30. Simin Dashti-Khavidaki, Hossein Khalili, Seyedeh-Maryam Vahedi, Mahboob LessanPezeshki (2010); Serum Zinc Concentrations in Patients on Maintenance Hemodialysis and its Relationship with Anemia, Parathyroid Hormone Concentrations and Pruritus Severity *Sauji J. Kidney Diseases and Transplantation* 2010; 21(4): 641-645.
31. Katerina Damianaki, Joao Miguel Lourenco, Philippe Braconnier, Jean-Pierre Ghobri et al (2020); Renal handling of zinc in chronic kidney disease patients and the role of circulating zinc levels in renal function decline *Nephrol Dial Transplant* 2020;35(7):1163-1170.
32. Mahmoud Parham, Massoud Amini, Ashraf Aminorroaya and Esfandiar Heidarian (2008); Effect of Zinc Supplementation on Microalbuminuria in Patients With Type 2 Diabetes: A Double Blind, Randomized, Placebo-Controlled, Cross-Over Trial *The Review of Diabetic Studies* 2008; 5: 102-109. DOI 10.1900/RDS.2008.5.102
33. Joachim Jankowski, Jürgen Floege, Danilo Fliser, Michael Böhm, Nikolaus Marx (2021); Cardiovascular Disease in Chronic Kidney Disease Pathophysiological Insights and Therapeutic Options *Circulation*. 2021; 143: 1157-1172.
34. Yukinori Tamura (2021); The role of zinc homeostasis in the prevention of diabetes mellitus and cardiovascular diseases *J Atheroscler Thromb*. 2021; 28: 1109-1122.
35. Marija Knez and Maria Glibetic (2021); Zinc as a biomarker of cardiovascular health *frontiers in nutrition* 2021; 8, Article 606878:1-7.
36. AUL L. KIMMEL, DON W. WATKINS, ELIZABETH B. TELLER, Rsjiv KHANNA, STEFAN DOSA, and TERENCE

- M. PHILLIPS (1988); Zinc balance in combined zinc deficiency and uremia *Kidney International* 1988; 33: 1091-1099.
37. Yonova, Vazellov, Tzatchev (2012); Zinc status in patients with chronic renal failure on conservative and peritoneal dialysis treatment *HIPPOKRATIA* 2012; 16(4): 356-359.
38. Ling-Jun Wang, Ming-Qing Wang, Rong Hu, Yi Yang, Yu-Sheng Huang, Shao-Xiang Xian, and Lu Lu (2017); Effect of Zinc Supplementation on Maintenance Hemodialysis Patients: A Systematic Review and Meta-Analysis of 15 Randomized Controlled Trials *BioMed Research International* 2017; 2017:1-12.
39. Anne-Elisabeth Heng and Noel J. M. Cano (2010); Nutritional problems in adult patients with stage 5 chronic kidney disease on dialysis (both haemodialysis and peritoneal dialysis) *NDT Plus* 2010; 3: 109-117. doi: 10.1093/ndtplus/sfp147 Advance Access publication 19 October 2009 109-117.
40. Maria V. Irazabal, and Vicente E. Torres (2020); Review Reactive Oxygen Species and Redox Signaling in Chronic Kidney Disease *Cells* 2020; 9(6):1-17.
41. Yonova, Trendafilov, Georgieva, Dimitrova, Arabadjieva and Velkova (2018); Oxidative stress (OS) in chronic kidney disease (CKD): A mini review *Nephrology and Renal Diseases* 2018; 3(3):1-3.

Cite this article: Dr. Sci. Tsuneo Ishida. Zinc (II) Induced Renal Functional Activities for Inhibitory Chronic Kidney Disease Progression. *International Journal of Research in Medical and Clinical Science*; pp: 01-10.

Copyright: © 2023. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.