Evaluation of the Effect of Zinc supplementation on the Health Status of Hemodialysis Patients

A Thesis submitted for fulfillment of Master Degree in Pharmaceutical Science
(Clinical Pharmacy)

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List of abbreviations

ACE	**Angiotensin Converting Enzyme**
ACEI	**Angiotensin Converting Enzyme Inhibitor**
ACM	**All Cause Mortality**
ACR	**Albumin to creatinine ratio**
ADMA	**Asymmetric dimethyl-arginine**
AER	**Albumin Excretion Rate**
AFB	**Acetate-free biofiltration**
Ag II	**Angiotensin II**
AKI	**Acute Kidney Injury**
ALA	**Aminolevulinic acid**
APD	**Automated Peritoneal Dialysis**
ARB	**Angiotensin II Receptor Blocker**
BP	**Blood Pressure**
BSA	**Bovine Serum Albumin**
CAPD	**Continuous Ambulatory Peritoneal Dialysis**
CKD	**Chronic Kidney Disease**
CKD-BMD	**Chronic Kidney Disease- Bone Mineral Disease**
CKD-EPI	**Chronic Kidney Disease Epidemiology Collaboration**
Cu^{++}	**Cupric ion**
CUA	**Calcific uremic arteriolopathy**
CV	**Cardiovascular**
CVD	**Cardiovascular Disease**
CVM	**Cardiovascular Mortality**
DM	**Diabetes Mellitus**
DN	**Diabetic Nephropathy**
DNA	**Deoxyribonucleic acid**
DTRPs	**Drug Therapy Related Problems**
ECV	**Extracellular volume**
eGFR	**estimated Glomerular Filteration Rate**
ELISA	**Enzyme Linked Immunosorbant Assay**
EPO	**Erythropoietin**
ESA	**Erythropoiesis-Stimulating Agent**
ESCP	**European Society of Clinical Pharmacy**
ESRD	**End Stage Renal Disease**
ET-1	**Endothelin-1**
Fe^{++}	**Ferrous ion**
FSS	**Fatigue Severity Scale**
GFR	**Glomerular Filteration Rate**
GSH	**Glutathione peroxidase**
H_2O_2	**Hydrogen Peroxide**
Hb	**Hemoglobin**
HCl	**Hydrochloric acid**
HD	**Hemodialysis**
HDF	**Hemodiafiltration**
HF	**Hemofiltration**
HNS	**Hypertensive Nephrosclerosis**

HRP	**Horseradish peroxidase**
hs-CRP	**high sensitive - C Reactive Protein**
HTN	**Hypertension**
IDH	**Intradialytic Hypertension**
IQR	**Interquartile Range**
IL-6	**Interleukin-6**
KDIGO	**Kidney Disease Improving Global Outcome**
KDOQI	**Kidney Disease Outcome Quality Initiative**
LDL	**Low Density Lipoprotein**
LVH	**Left Ventricular Hypertrophy**
MDA	**Malondialdehyde**
MDRD	**Modification of Diet in Renal Disease**
MRI	**Magnetic Resonance Imaging**
NADPH	**Nicotinamide adenine dinucleotide phosphate oxidases**
NHP	**Nottingham Health Profile**
NK	**Natural Killer**
$\dot{O}^-_2$	**Superoxide anion**
$\dot{O}H$	**Hydroxyl radical**
PD	**Peritoneal Dialysis**
PEM	**Protein Energy Malnutrition**
pmp	**Per million population**
PTH	**Parathyroid Hormone**
QOL	**Quality of Life**
RA	**Renal Anemia**
RAAS	**Renin Angiotensin Aldosterone System**
RBCs	**Red Blood Cells**
RDI	**Recommended Daily Intake**
RHDx	**Regular hemodialysis duration**
RO	**Renal Osteodystrophy**
ROS	**Reactive Oxygen Species**
RRT	**Renal Replacement Therapy**
RT	**Renal Transplantation**
SCr	**Serum Creatinine**
SD	**Standard deviation**
SF-36	**Medical outcomes study short form health survey**
SH	**Sulfhydral**
sHPT	**secondary Hyperparathyroidism**
SLE	**Systemic Lupus Erythematosis**
SOD	**Super Oxide Dismutase**
TAC	**Total Antioxidant Capacity**
TMB	**tetramethylbenzidine**
TNF-α	**Tumor necrosis factor - α**
U.S.	**United States**
USRDS	**United States Renal Data System**
VSMC	**Vascular Smooth Muscle Cell**
WST-1	**Water soluble tetrazolium salt**
Zn	**Zinc**

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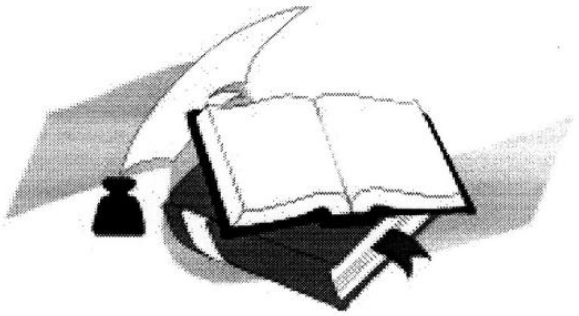
Abstract



Abstract

Introduction:

Dialysis has improved the life expectancy of End Stage Renal Disease (ESRD) patients, yet the mortality rate still remains disappointingly high. Oxidative stress and inflammation together with their complications such as cardiovascular diseases, protein-energy wasting and erythropoietin-resistant anemia are prevalent in hemodialysis (HD) patients and increase their mortality. The prevalence of zinc (Zn) deficiency in patients with HD is about 40–78%, which has been found to predispose them to oxidative stress, inflammation and anemia. Fatigue is one of the most common symptoms experienced by dialysis patients, with its prevalence ranging from 60% to 97%. Zinc supplementation appears to ameliorate fatigue in chronic fatigue syndrome patients.

Aim of the work:

The aim of this study was to evaluate the role of zinc as an adjunctive therapy on oxidative stress, inflammation, anemia and fatigue in hemodialysis patients.

Patients and methods:

Patients on long-term hemodialysis with lower than normal serum zinc concentration (< 80 μg/dL) were randomized in to 2 groups; group 1 received 25 mg/day oral Zn supplement (n = 28) and group 2 received placebo (n = 24) for twelve weeks. Serum Zn, malondialdehyde (MDA), total antioxidant capacity (TAC), superoxide dismutase (SOD) activity, high sensitive-CRP (hs-CRP), interleukin-6 (IL-6) and hemoglobin (Hb) were assessed before and after the supplementation period. Quality of life was assessed using Fatigue Severity Scale (FSS) at baseline and at the end of the study.

Results:

The results obtained showed that there was a significant increase in both serum Zn and Hb levels from baseline values in patients of group1 with ($p<0.001$) and ($p=0.002$) respectively. Also these levels were significantly different from post-study levels of both Zn and Hb in patients of group 2 with ($p<0.001$) and ($p=0.005$) respectively. Moreover, there were significant changes in serum MDA and TAC levels in group1 at the end of the study ($p< 0.05$) without significant change between the two groups. There were no significant changes in SOD activity within groups or between the two groups at the end of the study.

Concerning serum levels of inflammatory marker, it was found Zn supplementation did not affect serum hs-CRP or in IL-6 levels with no significant difference within or between both groups. Using FSS, there were a significant decrease in fatigue in group 1 ($p = 0.001$) with a significant difference between the two groups in percent change ($p < 0.001$) at the end of the study.

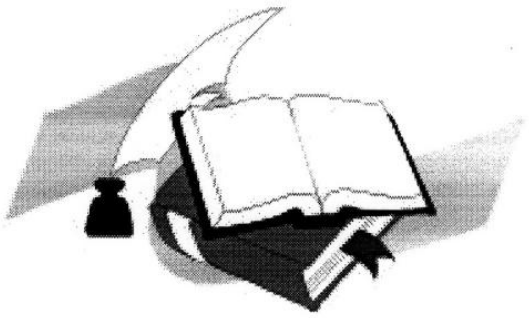
Conclusions:

From the results found it was concluded that, zinc supplementation at dose of 25 mg/day for 12 weeks ameliorates low serum Zn and Hb levels, improve fatigue and may reduce oxidative stress in Zn deficient HD patients suggesting that Zn supplementation may be considered an adjunctive treatment in HD to reduce morbidity and mortality risk factors. Zinc supplementation at dose of 25 mg/day for 12 weeks does not ameliorate inflammation in these patients.

Key Words

Anemia – Chronic kidney disease – End Stage Renal Disease – Fatigue – Hemodialysis – Hemoglobin – Inflammation – Oxidative stress – Zinc supplementation

Review of Literature



Renal Failure

Kidney failure is classified into two broad categories: acute kidney injury and chronic kidney disease. The basic difference between them is the rate of disease progression, which is rapid for acute kidney injury (usually within days or weeks) and gradual for chronic kidney disease (usually in the range of years) **(Chawla et al., 2014)**.

Both acute and chronic kidney disease can lead to complete loss of kidney function, causing the patient to depend on renal replacement therapy either dialysis or transplantation **(Tammen et al., 2014)**.

Acute Kidney Injury (AKI):

It is characterized by abrupt decline in glomerular filtration rate (GFR). Many definitions for AKI are present with the most popular one is the elevation of serum creatinine > 0.3 mg/dL over a baseline creatinine below 2 mg/dL **(Kellum et al., 2011)**.

Chronic Kidney Disease(CKD):

It is a life-threatening condition characterized by progressive and irreversible loss of kidney function. The growing inability of the kidneys to adequately clear the blood of waste products finally results in the implementation of dialysis (or kidney transplant) in order to prevent azotemia, systemic organ damage and death **(Lopez-Novoa et al., 2010).**

The Kidney Disease Improving Global Outcome (KDIGO) has defined CKD as:

Abnormalities in kidney structure or function persist for 3 months or longer, with implications for health **(KDIGO, 2013)**.