



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# بسم الله الرحمن الرحيم



**MONA MAGHRABY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



**MONA MAGHRABY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**MONA MAGHRABY**

# **The role of Zinc supplementation as anti-inflammatory in prevalent Hemodialysis patients**

## **Thesis**

Submitted for partial fulfillment of Master degree  
in Internal Medicine

**By**

**Elham Atitallah Mansour**

**(M.B.B.Ch)**

**Under supervision of**

**Prof. DR. Eman Ibrahiem Sarhan**

Professor of Internal Medicine and Nephrology  
Faculty of Medicine, Ain Shams University

**Dr. Mohamed Saeed Hassan**

Lecturer of Internal Medicine and Nephrology  
Faculty of Medicine, Ain Shams University

**Dr. Moustafa Abdelnassier Abdelgawad**

Lecturer of Internal Medicine and Nephrology  
Faculty of Medicine, Ain Shams University

Faculty of Medicine  
Ain shams University

**2020**



## Acknowledgments

*First and foremost, I feel always indebted to **Allah**, the **Most Beneficent** and **Merciful**, Who gave me the strength to accomplish this work,*

*My deepest gratitude to **Prof. Dr. Eman Ibrahiem Sarhan**, Professor of Internal Medicine and Nephrology, Faculty of Medicine, Ain shams University, for her valuable guidance and expert supervision, in addition to her great deal of support and encouragement. I really have the honor to complete this work under her supervision.*

*I would like to express my great and deep appreciation and thanks to **Dr. Mohamed Saeed Hassan**, Lecturer of Internal Medicine and Nephrology, Faculty of Medicine, Ain shams University, for his meticulous supervision, and his patience in reviewing and correcting this work,*

*I can't forget to thank with all appreciation **Dr. Moustafa Abdelnassier Abdelgawad**, Lecturer of Internal Medicine and Nephrology, Faculty of Medicine, Ain shams University, for the efforts and time he has devoted to accomplish this work,*

*Special thanks to my **Parents**, my **Husband** and all my **Family** members for their continuous encouragement, enduring me and standing by me.*

 **Elham Atitallah Mansour**

## **List of Contents**

<i><b>Subject</b></i>	<i><b>Page No.</b></i>
<b>List of Abbreviations.....</b>	<b>i</b>
<b>List of Tables.....</b>	<b>ii</b>
<b>List of Figures .....</b>	<b>iv</b>
<b>Introduction .....</b>	<b>1</b>
<b>Aim of the Work.....</b>	<b>3</b>
<b>Review of Literature</b>	
Zinc.....	4
Zinc Deficiency and Chronic Diseases .....	26
Zinc and Renal diseases .....	44
<b>Patients and Methods.....</b>	<b>56</b>
<b>Results.....</b>	<b>59</b>
<b>Discussion .....</b>	<b>74</b>
<b>Summary .....</b>	<b>81</b>
<b>Conclusion.....</b>	<b>84</b>
<b>References .....</b>	<b>85</b>
<b>Arabic Summary .....</b>	<b>—</b>

---

## List of Abbreviations

<b>Abbr.</b>	<b>Full-term</b>
<b>Cd</b>	Cadmium
<b>CD</b>	Cluster of differentiation
<b>DCs</b>	Dendritic cells
<b>EEA</b>	Early endosome antigen
<b>ESRD</b>	End stage renal disease
<b>FOXP3</b>	Forkhead box p3
<b>Hg</b>	Mercury
<b>HSCR</b>	High sensitive proteins
<b>IFN</b>	Interferon
<b>IGE</b>	Immunoglobulin E
<b>IL</b>	Interleukin
<b>LPS</b>	Lipopolysaccharide
<b>MHC</b>	Major histocompatibility complex
<b>MMPS</b>	Matrix metalloproteinase
<b>MT</b>	metallothioneine
<b>NAPDH</b>	Nicotinamide adenine dinucleotide phosphate
<b>NF.KB</b>	Nuclear transections factor
<b>NK</b>	Natural killer
<b>NO</b>	Nitric oxide
<b>PI3K</b>	Phospholipid phosphatidylinositol 3 phosphate
<b>PMNS</b>	Polymorph nuclear neutrophils
<b>RA</b>	Rheumatoid arthritis
<b>ROS</b>	Reactive oxygen species
<b>SOD</b>	Superoxide dismutase
<b>STST</b>	Special tertiary admission test
<b>VSMC</b>	Vascular smooth muscles cells
<b>WHO</b>	World health organization
<b>ZIP4</b>	Zinc transporter precursor
<b>Zn</b>	Zinc
<b>ZnT1</b>	Zinc transporter



## List of Tables

Table No.	Title	Page No.
<b>Table (1):</b>	Dietary Reference Index (DRIs) of trace elements .....	7
<b>Table (2):</b>	Zinc content of selected foods .....	8
<b>Table (3):</b>	Major Zn-proteins and their function on the immune system .....	25
<b>Table (4):</b>	Clinical manifestations of zinc deficiency .....	31
<b>Table (5):</b>	Chronic inflammatory diseases characterized by Zn-deficiency and models of Zn supplementation .....	42
<b>Table (6):</b>	Demographic Characteristics of both study groups .....	59
<b>Table (7):</b>	Etiology of ESRD .....	60
<b>Table (8):</b>	Comparison of baseline Zinc level in each group .....	61
<b>Table (9):</b>	Comparison between routine labs of ESRD patients who had zinc deficiency (N35) before and after zinc supplementations .....	62
<b>Table (10):</b>	Correlations between baseline zinc level with demographic data and routine laboratory tests of ESRD patients who had zinc deficiency (N35) .....	64
<b>Table (11):</b>	Correlation between baseline zinc level and inflammatory markers (HS CRP and IL6) in ESRD patients who had zinc deficiency (N35) before zinc supplementation .....	65



<b>Table (12):</b>	Zinc level before and after zinc supplementation in ESRD patients who had zinc deficiency (N35).....	67
<b>Table (13):</b>	Correlations between zinc level at end of study with demographic data and routine laboratory tests after zinc supplementations of ESRD patients who had zinc deficiency (n=35) .....	69
<b>Table (14):</b>	Correlation between zinc level and inflammatory markers (HS CRP and IL6) after zinc supplementation in ESRD patients who had zinc deficiency (N 35).....	70
<b>Table (15):</b>	Comparison between HSCRP and IL6 levels at baseline and after zinc supplementations for 3 MS.....	72

## List of Figures

Figure No.	Title	Page No.
<b>Figure (1):</b>	Subcellular localization of human ZIP/ZnT Zn .....	10
<b>Figure (2):</b>	Schematic representation of the innate and adaptive immune system acute response in a normal versus Zn-lacking system .....	20
<b>Figure (3):</b>	A schematic diagram illustrating the antioxidant, antiapoptotic, and antiinflammatory properties of zinc. ....	46
<b>Figure (4):</b>	(A) Systolic blood pressure (SBP), measured by tail-cuff technique, and (B) creatinine clearance ( $C_{cr}$ ) determined at 15, 30, 45, and 60 d of the dietary treatment in the control .....	50
<b>Figure (5):</b>	Zinc level in each group.....	61
<b>Figure (6):</b>	Hb before and after zinc supplementations.....	63
<b>Figure (7):</b>	Ca before and after zinc supplementations.....	63
<b>Figure (8):</b>	Correlation between zinc level and CRP in ESRD patients .....	66
<b>Figure (9):</b>	Correlation between zinc level and IL6 in ESRD patients.....	66
<b>Figure (10):</b>	Zinc level before and after zinc supplants .....	68
<b>Figure (11):</b>	Correlation between zinc level and CRP after zinc supplementation in ESRD patients. ....	71

<b>Figure (12):</b> Correlation between zinc level and IL6 after zinc supplementation in ESRD patients.....	71
<b>Figure (13):</b> HS CRP level before and after zinc supplementation .....	73
<b>Figure (14):</b> IL6 level before and after zinc supplementation .....	73

## Abstract

**Background:** Zinc is an essential micronutrient for human beings and its deficiency affects their normal growth and development. Although the prevalence of zinc deficiency is still unclear in patients with maintenance hemodialysis (MHD), some data show adverse outcomes that may attribute to zinc deficiency. **Aim of the Work:** to assess if zinc supplementation has a role in decreasing the inflammatory markers levels in hemodialysis patients with zinc deficiency; 60 patients (20 healthy people as control – 40 patients ESRD on regular hemodialysis). **Patients and Methods:** A cohort prospective interventional study was conducted on 60 patients (20 healthy people as control – 40 patients ESRD on regular hemodialysis) at Dialysis unit of Ain Shams University during a period of 6 months. **Results** that zinc level was significantly lower in ESRD ( 8.33 )  $\mu\text{mol/l}$  compared to the healthy control group (13.33 )  $\mu\text{mol/l}$  ( normal level of zinc 12.5-18.5  $\mu\text{mol/l}$  the inflammatory markers were significantly higher in ESRD who had zinc deficiency HSCRP (9565.7) $\text{mg/l}$  , IL6 ( 57.8 )  $\text{pg/ml}$  compared to the ESRD patients who had normal zinc After zinc supplementations to ESRD patients who had zinc deficiency we found that The zinc level increased significantly from ( 7. 1 $\pm$  1.1 )  $\mu\text{mol/l}$  to ( 14.3 $\pm$  1.8 )  $\mu\text{mol/l}$  . inflammatory markers level was significantly decreased, HS CRP Level from ( 9565.7  $\pm$  259307 )  $\text{mg/l}$  to (4708  $\pm$  2235.4)  $\text{mg/l}$  , IL6 level from (57.8  $\pm$  16.5 )  $\text{pg/ml}$  to (28.0  $\pm$  9.1 )  $\text{pg/ml}$  **Conclusion:** Zinc deficiency in ESRD on regular hemodialysis is more than in normal population which increase the inflammation response and, high HSCRP and IL6 as a inflammatory markers, after correction of zinc deficiency in ESRD, the inflammatory markers is decreased and the inflammations is improved , and has a positive effect to Hb and Ca.

**Key words:** zinc supplementation, inflammatory markers, hemodialysis, deficiency, ESRD

# Introduction

**Z**inc (Zn) nutritional importance has been known for a long time, but in the last decades its importance in immune modulation has arisen. This review aims at describing the mechanisms involved in the regulation of Zn homeostasis and their effects on the immune response focusing on those which are implicated in the physiopathology of rheumatoid arthritis. Zn functions as a modulator of the immune response through its availability, which is tightly regulated by several transporters and regulators (*Lönnnerdal, 2000*).

When this mechanism is disturbed, Zn availability is reduced, altering survival, proliferation and differentiation of the cells of different organs and systems and, in particular, cells of the immune system. Zn deficiency affects cells involved in both innate and adaptive immunity at the survival, proliferation and maturation levels. These cells include monocytes, polymorphonuclear-, natural killer-, T-, and B-cells (*Maywald et al., 2017*).

T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in Zn status. While acute Zn deficiency causes a decrease in innate and adaptive immunity, chronic deficiency increases inflammation. During chronic deficiency, the production of pro-inflammatory cytokines increases, influencing the outcome of a large number of inflammatory diseases, including rheumatoid arthritis (*Domellöf et al., 2009*).

The 24<sup>th</sup> most abundant element in the earth's crust, zinc (Zn), is a metallic chemical element, which has “exceptional biologic and public health importance”. Zn is referred to as a trace element with a minor plasma pool (13.8–22.9 µmol/L) and a rapid turnover. Because of the absence of specialized Zn storage in the body, a Zn daily intake (20– 40% of daily intake depending on diet) is required to achieve the steady-state, maintain it and support all its functions (*Shankar and Prasad, 1998*).

Zn is involved in numerous aspects of cellular metabolism and is an integral component of proteins involved in cell structures and stabilization of cell membranes (*Maret, 2017*).

It plays a role in cellular respiration (carbonic anhydrase), immune functions, protein synthesis, wound healing, DNA synthesis, and cell division. For these reasons, Zn nutritional defect or over-absorption is linked to a large number of diseases and particularly to immune diseases (*Prasad, 1998*).

## **Aim of the Work**

**T**his study assessed if zinc supplementation has a role in decreasing the inflammatory markers levels in hemodialysis patients with zinc deficiency.