

# **The Effect of Two Types of Intravenous Iron on Phagocytic Function of Neutrophils in Hemodialysis Patients**

**Thesis**

*Submitted for Partial Fulfillment of Master Degree  
In Internal Medicine*

**By**

**Ahmed Lotfy Latif Mahmoud**

*M.B.B.Ch*

*Faculty of Medicine –Ain Shams University*

***Under Supervision of***

**Prof. Dr. Iman Ibrahim Sarhan**

*Professor of Internal Medicine and Nephrology*

*Faculty of Medicine - Ain Shams University*

**Dr. Maha Abd El Moneim Behairy**

*Lecturer of Internal Medicine and Nephrology*

*Faculty of Medicine - Ain Shams University*

**Dr. Doaa Mohamed Abd ElAziz**

*Lecturer of Clinical pathology department*

*Faculty of Medicine - Ain Shams University*

**Faculty of Medicine**

**Ain Shams University**

**2016**

## *Acknowledgement*

First and foremost, I would like to begin by thanking **ALLAH**, Most Strong, All Almighty, for providing me the strength and perseverance required to achieve this work.

I would like to express my deep gratitude to **Prof. Dr. Iman Ibrahim Sarhan**, Professor of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University, for her helpful and constructive suggestions, and for the continuous encouragement that she generously offered during this work.

I am also very grateful to **Dr. Maha Abd El Moneim Behairy**, Lecturer of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University, for her great and smart guidance and supervision of this work; also she devoted much of her precious time and effort in order to achieve this work in a successful form.

I would like to thank to **Dr. Doaa Mohamed Abd El Aziz**, Lecturer of Clinical pathology department, Faculty of Medicine, Ain Shams University, for her guidance and suggestions which were of great value to me.

Special thanks to my family and my Friends who helped me and provided me the personal support in completing this work.



*Ahmed Loify*

# Contents

List of Abbreviations .....	I
List of Tables .....	V
List of Figures .....	VII
<b>Introduction .....</b>	<b>1</b>
<b>Aim of the Work.....</b>	<b>6</b>
<b>Review of Literature.....</b>	
• Chapter (1): Iron therapy in ESRD Patients .....	7
• Chapter (2): Immune Dysfunction in ESRD Patients .....	39
• Chapter (3): Effect of Iron Therapy on Immune Cells .....	62
<b>Subjects and Methods.....</b>	<b>76</b>
<b>Results .....</b>	<b>85</b>
<b>Discussion.....</b>	<b>110</b>
<b>Summary.....</b>	<b>128</b>
<b>Conclusion.....</b>	<b>133</b>
<b>Recommendations.....</b>	<b>134</b>
<b>References .....</b>	<b>135</b>
<b>Arabic Summary.....</b>	<b>--</b>

## ***List of Abbreviations***

---

<b>Abb.</b>	<b>Description</b>
<b>AGEs</b>	Advanced glycation end products
<b>AOPPs</b>	Advanced oxidation protein products
<b>ARIC</b>	Atherosclerosis Risk in Communities
<b>AVF</b>	Arterio-venous fistula
<b>BAAF</b>	B cell activating factor
<b>BMI</b>	Body mass index
<b>BUN</b>	Blood urea nitrogen
<b>Ca</b>	Calcium
<b>CAPD</b>	Continuous ambulatory peritoneal dialysis
<b>CERA</b>	Continuous erythropoiesis receptor activator
<b>CHF</b>	Congestive heart failure
<b>CHOIR</b>	Correction of Hemoglobin and Outcomes in Renal Insufficiency
<b>CHr</b>	Reticulocyte Hb content
<b>CKD</b>	Chronic kidney disease
<b>CREATE</b>	Early Anemia Treatment with Epoetin Beta
<b>CRP</b>	C-reactive protein
<b>CVD</b>	Coronary vascular disease
<b>DBP</b>	Diastolic blood pressure
<b>DCs</b>	Dendritic cells
<b>DHE</b>	Dihydroethidium
<b>DHR</b>	Di-hydro-rodamine
<b>DMT1</b>	Divalent metal transporter
<b>DRIVE</b>	Dialysis Patients' Response to IV Iron with Elevated Ferritin

---

<b>Abb.</b>	<b>Description</b>
<b>EDTA</b>	Ethylene diaminetetraacetic acid
<b>eGFR</b>	Estimated glomerular filtration rate
<b>EPO</b>	Erythropoietin
<b>ERBP</b>	European Renal Best Practice
<b>ESA</b>	Erythropoietin-stimulating agents
<b>ESRD</b>	End stage renal disease
<b>EUTox</b>	European Uremic Toxin Work Group
<b>FBC</b>	Full blood count
<b>FGF23</b>	Fibroblast growth factor 23
<b>fMLP</b>	N-formyl-methionyl-leucyl-phenylalanine
<b>Hb</b>	Hemoglobin
<b>HCV</b>	Hepatitis c virus
<b>Hcy</b>	Homocysteine
<b>HD</b>	Hemodialysis
<b>HDL</b>	High-density lipoprotein
<b>HDL</b>	High-density lipoprotein
<b>HIF</b>	Hypoxia-inducible factor
<b>HLA</b>	Human leukocytes antigen
<b>HOCl</b>	Hypochlorous acid
<b>ICAM-1</b>	Intercellular Adhesion Molecule 1
<b>ID</b>	Iron dextran
<b>IgLCs</b>	Immunoglobulin light chains
<b>IL</b>	Interleukin
<b>IS</b>	Iron sucrose
<b>IV</b>	Intravenous
<b>K/DOQI</b>	Kidney Disease Outcomes Quality Initiative

<b>Abb.</b>	<b>Description</b>
<b>KDIGO</b>	Kidney Disease Improving Global Outcomes
<b>LVH</b>	Left ventricular hypertrophy
<b>LVMi</b>	Left ventricular mass index
<b>MDA</b>	Malondialdehyde
<b>MGO</b>	Methylglyoxal
<b>MPO</b>	Myeloperoxidase
<b>NICE</b>	National Institute for Clinical Excellence
<b>NO</b>	Nitric oxide
<b>NTBI</b>	Non-transferrin-bound iron
<b>nTreg</b>	Natural regulatory T cell
<b>oxLDLs</b>	Oxidized low-density lipoproteins
<b>PAA</b>	Phenylacetic acid
<b>PAA</b>	Phenylacetic acid
<b>PBMCs</b>	Peripheral blood mononuclear cells
<b>PLT</b>	Platelet
<b>PMA</b>	4-beta-phorbol 12-beta-myristate 13-alpha-acetate
<b>PMNLs</b>	Polymorphonuclear leukocytes
<b>PTH</b>	Parathyroid hormone
<b>RBC</b>	Red blood cell
<b>RBP</b>	Retinol binding protein
<b>RBPs</b>	Retinol-binding proteins
<b>RENAAL</b>	Reduction of Endpoint in NIDDM with the Angiotensin II Antagonist Losartan
<b>RES</b>	Reticuloendothelial system
<b>ROS</b>	Reactive oxygen species

<b>Abb.</b>	<b>Description</b>
<b>RR</b>	Relative risk
<b>SBP</b>	Systolic blood pressure
<b>SFG</b>	Sodium ferric gluconate
<b>SLE</b>	Systemic lupus erthymatosis
<b>SQ</b>	Subcutaneously
<b>TFTs</b>	Thyroid function tests
<b>THP</b>	Tamm-Horsfall protein
<b>TIBC</b>	Total iron binding capacity
<b>TIBC</b>	Total iron binding capacity
<b>TIR</b>	Transferring receptor
<b>TLC</b>	Total leukocytic count
<b>TLRs</b>	Toll-like receptors
<b>TNF<math>\alpha</math></b>	Tumor necrosis factor alpha
<b>TSAT</b>	Transferrin saturation
<b>UF</b>	Ultrafiltration
<b>URR</b>	Urea reduction ratio

## ***List of Tables***

<b>Table</b>	<b>Title</b>	<b>Page</b>
<b>1</b>	Guideline recommendations for Ferritin/TSAT thresholds to guide use of iron therapy	31
<b>2</b>	Immune dysfunction associated with different uremic toxins	51
<b>3</b>	Demographic data	86
<b>4</b>	Clinical data	87
<b>5</b>	Basal lab investigations	88
<b>6</b>	Comparison between neutrophil oxidative burst index and CRP titre before and after introduction of iron sucrose in (group I):	89
<b>7</b>	Comparison between neutrophil oxidative burst index and CRP titer before and after introduction of iron dextran in (group I)	91
<b>8</b>	Comparison between neutrophil oxidative burst index and CRP titre before and after introduction of iron dextran in (group II)	93
<b>9</b>	Comparison between neutrophil oxidative burst index and CRP titre before and after introduction of iron sucrose in (group II)	95
<b>10</b>	Correlation between age, weight, height, BMI and basal neutrophil oxidative burst index	97
<b>11</b>	Relation between sex, smoking status and	98

<b>Table</b>	<b>Title</b>	<b>Page</b>
	basal neutrophil oxidative burst index	
<b>12</b>	Correlation between duration of dialysis, blood pressure and basal phagocytic function	100
<b>13</b>	Relation between clinical data and basal phagocytic index	100
<b>14</b>	Relation between lab investigations and basal phagocytic index	101
<b>15</b>	Comparison between group I and group II regarding demographic data	103
<b>16</b>	Comparison between group I and group II regarding clinical data	104
<b>17</b>	Comparison between group I and group II regarding basal lab investigations	105
<b>18</b>	Comparison between group I and group II regarding basal neutrophil oxidative burst index and basal CRP	106
<b>19</b>	Comparison between the two types of iron regarding their effects on neutrophil oxidative burst index in all patients groups	108
<b>20</b>	Comparison of phagocytic index before and after introduction of each type of IV iron	108
<b>21</b>	Two way ANOVA test	109

## ***List of Figures***

<b>Figure</b>	<b>Title</b>	<b>Page</b>
<b>1</b>	Different mechanisms of iron uptake	10
<b>2</b>	Role of hepcidin in regulation of iron level	12
<b>3</b>	The spectrum of iron deficiency	14
<b>4</b>	Consequences of anemia and cardiovascular complications with progression of CKD	15
<b>5</b>	Risk factors and immune dysfunction in chronic kidney disease	41
<b>6</b>	Different mechanisms promoting infections in patients with chronic kidney disease	42
<b>7</b>	Chronic kidney disease and cardiovascular disease are unified by oxidative stress	43
<b>8</b>	Metabolic abnormalities associated with renal failure and its relation with immune dysfunction	46
<b>9</b>	Effect of different uremic toxins on exerting antagonistic effects predisposing to infection and inflammation	50
<b>10</b>	Neutrophils oxidative burst index	81
<b>11</b>	Comparison between phagocytic index before and after introduction of iron sucrose in group I	90
<b>12</b>	Comparison between phagocytic index before and after introduction of iron dextran in group I	92

<b>Figure</b>	<b>Title</b>	<b>Page</b>
<b>13</b>	Comparison between phagocytic index before and after introduction of type dextran in group II	94
<b>14</b>	Comparison between phagocytic index before and after introduction of iron dextran in group II	96
<b>15</b>	Relation between sex and basal phagocytic index	99
<b>16</b>	Correlation between post-dialysis urea level and basal neutrophil oxidative burst index	102
<b>17</b>	Correlation between URR (%) and basal neutrophil oxidative burst index	102
<b>18</b>	Comparison between group I and group II regarding basal neutrophil oxidative burst index	107
<b>19</b>	Phagocytic index as regard to type and time of introduction of IV iron	109

# **The Effect of Two Types of Intravenous Iron on Phagocytic Function of Neutrophils in Hemodialysis Patients**

## **Abstract**

**Background:** Untreated anaemia of CKD is strongly associated with cardiovascular and renal complications, resulting in increased hospitalisations and mortality. Therefore, correcting anaemia is considered an important part of slowing or even stopping the progression of CKD. Intravenous (IV) iron preparations are widely used in the management of anemia in ESRD populations. **Aim:** To evaluate the effect of IV iron sucrose and iron dextran on phagocytic function of neutrophils in hemodialysis patients. **Subjects:** This study was including 20 ESRD patients on regular hemodialysis. Patients were divided into 2 groups: Group I: 10 ESRD patients on regular hemodialysis received 100 mg iron sucrose with the assessment of the phagocytic function of neutrophil cells by flow cytometry before and after giving it. Group II: 10 ESRD patients on regular hemodialysis received 100 mg iron dextran with the assessment of the phagocytic function of neutrophils before and after giving it. **Results:** All patients were subjected to the following: Full history and clinical examination including (age, sex, BMI, smoking, duration of hemodialysis, cause of renal failure, type of vascular access, symptoms or signs of active inflammation). **Conclusion:** The use of either IV iron dextran or iron sucrose maintenance dose in regular hemodialysis patients is associated with highly significant increase in neutrophil oxidative burst with worsening of the neutrophil phagocytic function and no significant difference between both types regarding this effect. **Recommendations:** Importance of tests of neutrophil function in hemodialysis patients regularly as to follow up the hazardous effects of iron therapy.

---

**Keywords:** CKD: chronic kidney disease, IV: intravenous, ESRD: end stage renal disease, BMI: body mass index.



---

# Introduction

---





---

# *Aim of the Work*

---





---

## Chapter (1)

# **Iron Therapy in ESRD Patients**

---

