Effect of Zinc Supplementation on Glucose Homeostasis in Patients with β-Thalassemia Major Complicated with Diabetes Mellitus

Thesis

Submitted for the Partial Fulfillment of Master Degree in Pediatrics

Presented By

Veronia Philip Serour Banoub

M.B., B.Ch. 2012 Faculty of Medicine, Ain Shams University

Under Supervision of

Prof. Dr./Randa Mahmoud Asaad Sayed Matter

Professor of Pediatrics
Faculty of Medicine –Ain Shams University

Prof. Dr. / Nancy Samir Elbarbary

Professor of Pediatrics
Faculty of Medicine –Ain Shams University

Dr. / Eman Abdel Rahman Ismail

Consultant of Clinical Pathology Faculty of Medicine – Ain Shams University

Faculty of Medicine - Ain Shams University 2019



سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to AUAH, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr./Randa Mahmoud Asaad Sayed Matter**, Professor of Pediatrics - Faculty of Medicine-Ain Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.

I am also delighted to express my deepest gratitude and thanks to **Prof Dr.** / **Mancy Samir Elbarbary**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her kind care, constant help and great assistance throughout this work.

I am deeply thankful to **Dr.** / **Eman Abdel Rahman Ismail**, Consultant of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her great help, active participation continuous supervision and valuable instructions.

I wish to introduce my deep respect and thanks to Dr. VJasser Wagih Darwish, Consultant of Clinical Pathology, Faculty of Medicine, Ain Shams University, Dr. Ahmed Shafik Mada, Professor of Drug Radiation Research, Drug Radiation Research Department, National Center for Radiation Research and Technology, Egyptian Atomic Energy Authority, Cairo, Egypt for their kindness and cooperation in this work.

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Veronia Philip Serour

List of Contents

| Title | Page No. |
|---|----------|
| List of Tables | i |
| List of Figures | iv |
| List of Abbreviations | x |
| Abstract | xiiiiii |
| Introduction | 1 |
| Aim of the Work | 5 |
| Review of Literature | |
| Thalassemias | 6 |
| Effect of Zinc | 51 |
| Glucose homeostasis in patients with beta that major complicted with Diabetes | |
| Patients and Methods | 84 |
| Results | 94 |
| Discussion | 136 |
| Summary | 152 |
| Conclusion | 158 |
| Recommendations | 159 |
| References | 160 |
| Arabic Summary | |

List of Tables

| Table No. | Title I | Page No. |
|--------------------|--|--------------|
| Table (1): | Hemoglobin types in the different developmental stages of human life | |
| Table (2): | Types of thalassemias. | |
| Table (3): | Iron chelators | |
| Table (4): | Recommended Dietary Allowance | |
| | (RDAs) for Zinc | |
| Table (5): | Selected Food Sources of Zinc: | |
| Table (6): | Descriptive baseline clinical data of a | |
| - (-) | patients with β-TM | |
| Table (7): | Descriptive baseline hematological ar | |
| | biochemical data of all patients with | |
| | <u>-</u> | 96 |
| Table (8): | Descriptive baseline glycemic profi | le |
| | and zinc level of all patients with β -TM | |
| Table (9): | Baseline clinical data among β-T | \mathbf{M} |
| | patients with and without zi | nc |
| | supplementation | 98 |
| Table (10): | Baseline hematological and biochemic | al |
| | data among β-TM patients with an | nd |
| | without zinc supplementation | 99 |
| Table (11): | Baseline glycemic profile and zinc lev | el |
| | among β-TM patients with and witho | ut |
| | zinc supplementation | 100 |
| Table (12): | Comparison of clinical data among β-T | \mathbf{M} |
| | patients with zinc supplementation | |
| | baseline and at 12 weeks | 101 |
| Table (13): | Comparison of hematological ar | nd |
| | biochemical data among β-TM patien | its |
| | with zinc supplementation at baseling | ne |
| | and at 12 weeks | 103 |

List of Cables (Cont...)

| Table No. | Title | Page 1 | Vo. |
|--------------------|---|------------------|-----|
| Table (14): | Comparison of glycemic profile and z level among β-TM patients with z supplementation at baseline and at | zinc 12 | 106 |
| Table (15): | weeks | TM . at | |
| Table (16): | Comparison of hematological a biochemical data among β-TM patie without zinc supplementation | and nts at | |
| Table (17): | baseline and at 12 weeks | inc zinc | 110 |
| Table (18): | weeks | ory and 12 | |
| Table (19): | weeks | inc and | |
| Table (20): | without zinc supplementation at 12 weed Percent change of the studied variate among β-TM patients with and with | oles .out | |
| Table (21): | zinc supplementation at 12 weeks Percent change of glycemic profile a zinc level among β-TM patients w and without zinc supplementation at | and rith | 121 |
| Table (22): | 1 | the | 123 |
| | Zinc supplementation at baseline | | 124 |

List of Cables (Cont...)

| Table No. | Title | Page No. |
|-------------|--|-----------------------------|
| Table (23): | Correlation between Zinc level and studied variables in β-TM pati | |
| Table (24): | without Zinc supplementation at base Multivariable linear regression and for independent variables affect baseline zinc level in patients wit | eline 129 lysis eting |
| Table (25): | TM receiving zinc supplementation. Multivariable linear regression and for independent variables affect baseline zinc level in patients wit | 134 lysis eting |
| | TM without zinc supplementation | • |

List of Figures

| Fig. No. | Title F | age No. |
|---------------------|---|-----------|
| Figure (1): | Hemoglobin Molecule with Glob | |
| Figure (2): | The changes in human globin chair synthesis during developmental stag of life | es |
| Figure (3): | Geographical distribution of, thalassemia around the world | 3 |
| Figure (4): | Pathophysiology of β-thalassemia | 21 |
| Figure (5): | Difference between normal and thalassemia ineffective erythropoiesis | • |
| Figure (6): | Cellular mechanisms by whi decreased iron uptake into erythro precursors may promote survival an | ch oid |
| | differentiation | 27 |
| Figure (7): | Hair on end appearance. Coar osteopenia, and widening marrow cavi | |
| Figure (8): | Iron chelation therapy for patients with thalassemia naïve to iron chelation | |
| Figure (9): | Zinc molecule may play a role in chror diseases such as cardiovascular disea (CVD) and type 2 diabetes mellit | se us |
| E' (10) | (DM). | |
| Figure (10): | Cellular zinc homeostasis. | |
| Figure (11): | Subcellular localization of zinc (Z transporters and metallothionei (MTs). Localization and potenti | ns ial |
| Figure (12): | functions of Zn | ar |
| | pancreatic islet β-cells. | 62 |
| Figure (13): | Shows zinc anioxidant effect | 65 |

| Fig. No. | Title | Page No. |
|---------------------|---|-----------------------|
| Figure (14): | Zinc anti-inflammatory effect | 66 |
| Figure (15): | Insulin metabolism in Bcell | 68 |
| Figure (16): | Zinc sources | 74 |
| Figure (17): | Amelioration of free iron species and LCI) by iron chelators antioxidants | and |
| Figure (18): | Glycemic abnormalities in TM | |
| Figure (19): | Transfusion index among β -TM path with zinc supplementation at base | ents eline |
| Figure(20): | and at 12 weeks. LDH among β-TM patients with supplementation at baseline and a weeks. | zinc t 12 |
| Figure (21): | HbF, total cholesterol, HDL- and I cholesterol among β -TM patients zinc supplementation at baseline ar 12 weeks. | LDL- with nd at |
| Figure (22): | UACR among β-TM patients with supplementation at baseline and a weeks. | zinc t 12 |
| Figure (23): | FBG, RBG and fructosamine amor TM patients with zinc supplements at baseline and at 12 weeks. | ng β- ation |
| Figure (24): | HbA1c, fasting C peptide, fasting seinsulin and HOMA-IR among patients with zinc supplementation | erum 3-TM |
| Figure (25): | baseline and at 12 weeks Serum zinc among β-TM patients zinc supplementation at baseline ar | 107 with |
| | 12 weeks | 108 |

| Figure (26): | LDH among β -TM patients without zinc | |
|---------------------|---|-------|
| | supplementation at baseline and at 12 | |
| | weeks. | . 111 |

| Fig. No. | Title | Page No. |
|---------------------|---|----------------|
| Figure (27): | Serum ferritin among β-TM patr without zinc supplementation at bas and at 12 weeks. | eline |
| Figure (28): | Triglycerides, total cholesterol, HDL-LDL-cholesterol among β-TM pat without zinc supplementation at bas and at 12 weeks. | ients eline |
| Figure (29): | Transfusion Index among β-TM pati with and without zinc supplements at 12 weeks | ation |
| Figure (30): | HbF among β -TM patients with without zinc supplementation at weeks. | |
| Figure (31): | Serum ferritin among β-TM pati with and without zinc supplements at 12 weeks | ation |
| Figure (32): | Triglycerides, total cholesterol, H and LDL-cholesterol among β patients with and without supplementation at 12 weeks | -TM zinc |
| Figure (33): | UACR among β -TM patients with without zinc supplementation at weeks. | and 12 |
| Figure (34): | FBG, RBG, fructosamine among β patients with and without supplementation at 12 weeks | -TM zinc |
| Figure (35): | HbA1c, fasting C peptide, fasting seinsulin and HOMA-IR among patients with and without | erum 3-TM |
| Figure (36): | supplementation at 12 weeks | 119 ents |
| | at 12 weeks. | 120 |

| Fig. No. | Title | Page | No. |
|---------------------|---|-----------------------|-----|
| Figure (37): | Correlation between baseline se zinc and total cholesterol among patients with Zinc supplementation. | 3 -TM | 125 |
| Figure (38): | Correlation between baseline sezinc and UACR among β -TM pat with Zinc supplementation. | ients | 126 |
| Figure (39): | Correlation between baseline sezinc and fasting blood glucose amor TM patients with Zinc supplementate | erum ng β- | |
| Figure (40): | Correlation between baseline se zinc and random blood gluocse amo | erum ng β- | |
| Figure (41): | zinc and HbA1c among β-TM pat | erum ients | |
| Figure (42): | zinc and fasting C peptide among [| erum B-TM | |
| Figure (43): | patients with Zinc supplementation. Correlation between baseline se zinc and triglycerides among [| erum 3-TM | |
| Figure (44): | patients without Zinc supplementation Correlation between baseline se zinc and total cholesterol among | erum | 130 |
| Figure (45): | patients without Zinc supplementation Correlation between baseline sezinc and LDL-cholesterol among | erum | 131 |
| Figure (46): | patients without Zinc supplementation. Correlation between baseline set zinc and fasting blood glucose amount TM patients without supplementation. | erum ng β- Zinc | |

| Fig. No. | Title | Page No. |
|--------------|---|-------------|
| Figure (47): | Correlation between baseline serum and random blood glucose among patients without Zinc supplementation | β-ТМ |
| Figure (48): | Correlation between baseline sezinc and HbA1c among β -TM pat without Zinc supplementation | ients |

List of Abbreviations

| Abb. | Full term |
|----------|------------------------------------|
| AGEs | . Advanced Glycation end Products |
| AHSP | α-hemoglobin-Stabilizing Protein |
| AKT(PKB) | Protein kinase B |
| BM | . Bone marrow |
| BMD | Bone mineral density |
| BMI | |
| | Beta-thalassemia major |
| | . Beta-thalassemia intermedia |
| BW | Body weight |
| CVD | Cardiovascular disease |
| D.bil | Direct bilirubin |
| DEXA | . Dual Energy X-ray Absorptiometry |
| DFP | Deferiprone |
| DFX | Deferasirox |
| DM | Diabetes mellitus |
| DNA | Deoxy Nucleic Acid |
| EC | Enothelial cell |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| EPO | Erythropoietin |
| | Eendoplasmic Rreticulum |
| Fig | Figure |
| GDF15 | Growth differentiation factor 15 |
| γGT | Gamma-glutamyl transpeptidase |
| GLUT | Glucose transporter |
| GSH | Glutathione |
| Нь | Hemoglobin |
| HbA | Adult Hemoglobin |

List of Abbreviations (cont...)

| Abb. | Full term |
|---------------|---|
| | |
| | Fetal Hemoglobin |
| HBV | |
| HCV | Hepatitis C virus |
| HFD | High Fat Diet |
| | Human leukocyte antigen |
| | Heme oxygenase-1 |
| HOMA-IR | Homeostasis Model Assessment Insulin |
| | Resistance |
| HPLC | high performance liquid chromatography |
| HU | Hydroxyurea |
| | Impaired Fasting Glucose |
| | Impaired Glucose Tolerance |
| IL-6 | |
| | Insulin-responsive aminopeptidase |
| Kb | Kilo Bite |
| MCH | Mean corpuscular Hb |
| | Macrophage Chemoattractant Protein 1 |
| | Mean corpuscular volume |
| MDA | Malondialdehyde |
| MTs | |
| MUFA | Monounsaturated fatty acid |
| NADPH-oxidase | Nicotinamide Adenine Dinucleotide |
| | phosphate-oxidase |
| NF- k B | Nuclear factor -KB |
| Nrf2 | Nuclear factor erythroid 2-related factor 2 |
| | Oxidative Stress index |
| | Peroxisome proliferator-activated receptor |
| | (NR1c3) |
| PRDX2 | |