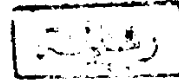




AIN SHAMS UNIVERSITY
FACULTY OF MEDICINE



BETA₂-MICROGLOBULIN-RELATED AMYLOIDOSIS IN CHILDREN WITH END-STAGE RENAL FAILURE

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF
THE M.D. DEGREE IN PAEDIATRICS

By

Dr. MOHAMED HESHAM M. EZZAT ABDEL HAMEED

M.B., B.Ch., M.S. in Paediatrics

Assistant Lecturer of Paediatrics

Faculty of Medicine - Ain Shams University

Supervised by

Prof. Dr. FARIDA AHMED FARID

Professor of Paediatrics

Faculty of Medicine - Ain Shams University

Prof. Dr. MOHAMED ABDEL
AALA EL-SHAWARBY

Professor of Pathology

Faculty of Medicine

Ain Shams University

Dr. KHALED SALAH AWWAD

Assistant Professor of Paediatrics

Faculty of Medicine

Ain Shams University

Dr. ASHRAF ABDEL BAKY
SALAMA

Lecturer of Paediatrics

Faculty of Medicine

Ain Shams University

Dr. HALA AHMED TALKHAN

Lecturer of Clinical Pathology

Faculty of Medicine

Ain Shams University

1998





To

The Soul of My Father

*My Mother With Love
And Affection*



ACKNOWLEDGMENT

First and foremost thanks to **Allah**, the most beneficent and merciful .

I am greatly indebted to **Prof. Dr. Farida Ahmed Farid**, *Professor of Paediatrics and Paediatric Nephrology, Ain-Shams University* for her constructive remarks and valuable advice. Working under her supervision is all at once both pleasurable and educational. Her motherly attitude towards me is unique and memorable.

To Prof. **Dr. Mohamed Abdel Aala El-Shawarby**, *Professor of Pathology, Ain-Shams University*, I would like to express my sincere gratitude; he gave me an excellent example of how a true scientist should guide and supervise his student's work. He has provided me with all the available facilities so that the histopathologic work; the corner stone of this thesis, would never see light without his constant, generous and faithful supervision.

Any expression of thanks would ever fail to give **DR. KHALED SALAH AWWAD**, *Assistant Professor of Paediatrics, Ain-Shams University*, his worth of gratitude for his precious time and moral support throughout the course of this work. He has spared no effort so that this work would have been completed. He has been a faithful director and a meticulous supervisor. I owe his excellency a lot, yet no words can express my feelings towards him but all what can I say, which is the best, is asking God to bless him.

I am sincerely thankful to **Dr. Ashraf Abdel Baky Salama**, *Lecturer of Paediatrics, Ain-Shams University*, for his endless encouragement and cooperation especially during choosing the topic of this thesis. Actually, he is the engineer of this work.

This work would have never been completed without the great help, close supervision and the meticulous lab work offered by **Dr. Hala Ahmed Talkhan**, *Lecturer of Clinical Pathology, Ain-Shams University*.

I would like to convey my warmest gratitude to **Dr. Mahmoud Tarek Abdel Moneim**, *Lecturer of Paediatric, Ain-Shams University* and to **Dr. Hany Mohamed Amin**, the highly expert specialist in the *Cardiology and Echocardiography Unit, Children's Hospital, Ain-Shams University* for their thankful cooperation at any time despite this work was not under their supervision yet they did the best as if they were.

Finally, I acknowledge my *patients* and their *parents* for their cooperation and their sincere feelings. I also acknowledge the team of the *Paediatric Dialysis Unit, Children's Hospital, Ain-Shams University* as well as the technician team of the *Radiology Department* for their endless cooperation.

MOHAMED HESHAM M. EZZAT

* * * * *

CONTENTS

List of abbreviations	i
List of tables	iv
List of figures	vi
Introduction	1
Aim of the work	2
Review of Literature	3
* <i>Chronic renal failure</i>	3
* <i>Beta₂-microglobulin</i>	19
* <i>Amyloidosis (B-Fibrillosis)</i>	44
* <i>Dialysis-Related-Amyloidosis (DRA)</i>	74
Subjects and Methods	99
Results	108
Discussion	156
Recommendations	168
Summary and Conclusion	169
References	174
Arabic Summary	

LIST OF ABBREVIATIONS

μg	: microgram
Å	: Angstrom
AA protein	: Amyloid A Protein
ACE	: Angiotensin Converting Enzyme
ADH	: Antidiuretic Hormone
AEF	: Amyloid Enhancing Factor
AGEs	: Advanced Glycation End Products
AIDS	: Aquired Immodeficiency Syndrome
AL	: Amyloid Light Chain
ANP	: Atrial Natriuretic Peptide
ARC	: AIDS Related Complex
B-amyloid	: Beta-amyloid
B₂-m	: Beta ₂ -microglobulin
C	: Control
Ca	: Calcium
CAPD	: Continuous Ambulatory Peritoneal Dialysis
CBD	: Clinical Bone Disease
CCPD	: Continuous cycler-Assisted Peritoneal Dialysis
Ccr	: Creatinine Clearance
CGN	: Chronic Glomerulonephritis
CJD	: Creutzfeldt-Jakob-Disease
CNS	: Central Nervous System
Cr	: Creatinine
Cr⁵¹EDTA	: Chromium 51-Ethytenediamine Tetracetate
CRF	: Chronic Renal Failure
C-RP	: C-Reactive Protein
CSF	: Cerebrospinal Fluid
CTS	: Carpal Tunnel Syndrome

CVD	: Collagen Vascular Disease
CVS	: Cardiovascular System
Da	: Dalton
DCT	: Distal Convoluted Tubules
2D-ECHO	: Two Dimensional Echocardiography
DRA	: Dialysis Related Amyloidosis
ECF	: Extracellular Fluid
ECG	: Electrocardiogram
EIA	: Enzyme Immuno-assay
EMG	: Electromyogram
ESRD	: End Stage Renal Disease
F	: Female
FAC	: Familial Amyloid Cardiomyopathy
FAN	: Familial Amyloid Nephropathy
FAP	: Familial Amyloid Polyneuropathy
FFI	: Fatal Familial Insomnia
FMF	: Familial Mediteranean Fever
GAGs	: Glycosaminoglycans
GFR	: Glomerular Filtration Rate
GSS	: Gertsman-Straussler-Scheinker
HCHWA-D	: Hereditary Cerebral Haemorrhage With Amyloid-Dutch Type
HD	: Haemodialysis
HIV	: Human Immunodeficiency Virus
HLA	: Human Leucocyte Antigen
I-DOX	: 4-iodo-4-deoxydoxorubicin
IGF-1	: Insulin-like Growth Factor-1
IGF-2	: Insulin-like Growth Factor-2
Igs	: Immunoglobulins
IL₁	: Interleukin 1
IL₂	: Interleukin 2
K	: Potassium
Kg	: Kilogram

KUF	: Ultrafiltration Coefficient
L	: Liter
L_K	: Kappa Light Chain
L_λ	: Lambda Light Chain
M	: Male
M²	: Meter Square
MEN -2A	: Multiple Endocrinal Neoplasia Type 2a
MHC	: Major Histocompatibility Complex
Min	: Minute
mL	: Milliliter
MRI	: Magnetic Resonance Imaging
Na	: Sodium
ng	: nanogram
NS	: Not Significant
N-terminus	: Amino-terminal
O₂⁻	: Superoxide anion
OH	: Hydroxyl
PAN	: Poly Acryl Nitrile
P-Component	: Plasma Component
PCT	: Proximal Convoluted Tubules
PDU	: Pediatric Dialysis Unit
PGL	: Persistent Generalized Lymphadenopathy
PGs	: Proteoglycans
Ph	: Phosphorus
PI	: Isoelectric Point
PMMA	: Polymethylmethacrylate
PrP	: Protease-Resistant-Protein
PS	: Patient serum
PTH	: Parathyroid hormone
PU	: Patient urine
RB	: Reagents Blank
RFLP	: Restriction Fragment Length Polymorphism
ROD	: Renal Osteodystrophy

S	: Standard
SAA	: Serum Amyloid Associated Protein
SAP protein	: Serum Amyloid Protein
SCD₄	: Soluble CD ₄
SCD₈	: Soluble CD ₈
Scr	: Serum creatinine
SD	: Standard Deviation
sIL_{2r}	: Soluble IL ₂ receptors
SN	: Serial Number
T	: Tricuspid
TSEs	: Transmissible Spongiform Encephalopathies
TTR	: Transthyretin
UK	: United Kingdom
US	: United States
UTI	: Urinary Tract Infection
Y	: Year

LIST OF TABLES

Table (I):	Aetiology of CRF in Children of US	4
Table (II):	Aetiology of CRF in Egyptian Children	5
Table (III):	Stages of progressive loss of renal function	6
Table (IV):	Clinical features of uremic encephalopathy	12
Table (V):	Common clinical problems during HD therapy	17
Table (VI):	The physiochemical properties of B₂-m	20
Table (VII):	Classification of Amyloidosis	46
Table (VIII):	B₂-m involved in formation of amyloid fibrils protein	75
Table (IX):	Prevalence of shoulder pain and/or CTS in patients on regular HD	86
Table (X):	Rheumatologic manifestations of DRA	86

TABLES OF RESULTS

Table (1):	Individual clinical and laboratory data of the control group	108
Table (2):	Individual clinical data of children with ESRD on regular HD	109
Table (3):	Individual laboratory data of children with ESRD on regular HD	111
Table (4):	Individual radiological signs of children with ESRD on regular HD	113
Table (5):	Individual echocardiographic findings of children with ESRD on regular HD	115
Table (6):	Aetiology of ESRD among children on regular HD ..	117
Table (7):	Clinical manifestations suggestive of DRA among children with ESRD on regular HD	119
Table (8):	Comparison between serum B_{2-m} concentration in the control group and children on regular HD	121
Table (9):	Serum B_{2-m} concentration in both males and females children with ESRD on regular HD	123
Table (10):	Correlation between mean concentration of serum B_{2-m} and different causes of ESRD	126
Table (11):	Correlation between B_{2-m} and parameters of chemical profile in both the control group and children on regular HD	129
Table (12):	The effect of unsubstituted cellulose and synthetic polysulfone dialyzer membranes on clearance of B_{2-m} in children on regular HD	130
Table (13):	Radiological signs in children with ESRD on regular HD	132
Table (14):	Echocardiographic findings of children with ESRD on regular HD	142

LIST OF FIGURES

Figure (I):	Pathogenesis of Renal Osteodystrophy	14
Figure (II):	Structure of B ₂ -microglobulin	21
Figure (III):	Schematic outline of some mechanisms involved in cellular activation during haemodialysis and their possible relation to the development of dialysis-related amyloidosis via a limited proteolysis of B ₂ -m	82

FIGURES OF RESULTS

Figure (1):	Aetiology of ESRD among children on regular HD ..	118
Figure (2):	Clinical manifestations suggestive of DRA among children with ESRD on regular HD	120
Figure (3):	Comparison between mean serum B ₂ -m concentration in the control group and children with ESRD on regular HD	122
Figure (4):	Correlation between serum B ₂ -m and age in control group	124
Figure (5):	Correlation between serum B ₂ -m and age in children with ESRD on regular HD	125
Figure (6):	Serum B ₂ -m concentration in children on regular HD with and without clinical bone disease	128
Figure (7):	The effect of dialyzer membranes on clearance of B ₂ -m	131

Figure (8):	Radiological signs in children with ESRD on regular HD	133
Figure (9):	B ₂ -m concentration in children with ESRD on regular HD with and without radiological bone disease	134
Figure (10):	Plain X-ray, right shoulder joint, AP view, showing multiple punched out cysts in the humeral head. ...	135
Figure (11):	Plain X-ray, right shoulder joint, AP view, showing extensive cystic changes in the humeral head.	136
Figure (12):	Plain X-ray, left wrist joint, AP view, showing multiple subchondral subarticular bone cysts in the distal ends of radius and ulna.	137
Figure (13):	Plain X-ray, right knee joint, AP view, showing sub-articular cystic changes, erosions and lucent areas in the distal ends of long bones.	138
Figure (14):	Plain X-ray, cervical vertebrae, lateral view, howing spondyloarthropathy more evident in C3-C4, C4-C5, and C5-C6. The vertebral end plates are irregular, eroded with osteophytes formation	139
Figure (15):	Plain X-ray, lumbar vertebrae, AP view, showing severe osteopenia, multiple cysts, erosions and irregularities most prominent at L3-L4.	140
Figure (16):	Plain X-ray, lumbar vertebrae, lateral view, showing erosions and destruction of the intervertebral disc (L2-L3) with subarticular cysts and synostosis at their anterior margin.	141
Figure (17):	Echocardiographic findings of children with ESRD on regular HD	143
Figure (18):	B ₂ -m concentration in children with ESRD on regular HD with and without echocardiographic findings	144
Figure (19):	2D-ECHO, showing granular sparkling in the inter-ventricular septum.	145
Figure (20):	2D-ECHO, showing granular sparkling in the inter-ventricular septum with hypertrophied both inter-ventricular and interatrial septa.	146

Figure (21):	2D ECHO, showing symmetrical ventricular wall thickness and mild to moderate pericardial effusion.	147
Figure (22):	2D-ECHO, showing hypertrophied interatrial septum with the characteristic bilobed configuration	148
Figure (23):	2D-ECHO, showing hypertrophied interventricular septum with granular sparkling and diffuse thickening of the mitral valve.	149
Figure (24):	2D-ECHO, showing diffuse thickening of the tricuspid valve.	150
Figure (25):	2D-ECHO, showing mitral flow pattern with mitral regurge.	151
Figure (26):	2D ECHO, showing tricuspid flow pattern with tricuspid regurge.	152

COLOUR PLATES

Colour plate (1):	Diffuse, fine, granular amyloid deposition in the subcutaneous abdominal fat seen under the polarized light. Congo red. X100. Patient number (3)	154
Colour plate (2):	Diffuse heavy amyloid deposition in the abdominal pad of fat under the polarized light. Congo red. X100. Patient number (6)	155