

٢٠١٣

URINARY TRANSFORMING GROWTH FACTOR BETA-1  
AS A MARKER OF RENAL DYSFUNCTION IN SICKLE  
CELL DISEASE

Thesis  
Submitted for Partial Fulfillment of Master  
Degree  
**in Pediatrics**

By

*Amany El-Nady Bayoumy*  
*M.B.C.H, Ain Shams University, ٢٠٠٦*

Supervisors

**Prof. Dr. Galila Mohamed Mokhtar**

*Head of Pediatric Department*  
*Professor of Pediatrics*  
*Faculty of Medicine - Ain Shams University*

**Dr. Nevine Gamal Andrawes**

*Lecturer of Pediatrics*  
*Faculty of Medicine - Ain Shams University*

**Dr. Abeer Attia Saad**

*Assistant Professor of Clinical Pathology*  
*Faculty of Medicine - Ain Shams University*

Faculty of Medicine  
Ain Shams University

# بسم الله الرحمن الرحيم

إقرأ باسم ربك  
الذي خلق {١} خلق  
الإنسان من  
علق {٢} إقرأ  
وربك  
الأكرم {٣} الذي  
علم بالقلم {٤} علم  
الإنسان ما لم  
يعلم {٥}

صدق الله العظيم  
سورة العلق





*First thanks to **ALLAH** to whom I relate any success in achieving any work in my life.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Dr. Galila Mohamed Mokhtar**, Professor & Head of Pediatric Department for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Dr. Nevine Gamal Andrawes**, Lecturer of Pediatric for her sincere efforts and fruitful encouragement.*

*I am deeply thankful to **Dr. Abeer Attia Saad**, Assistant Professor of Clinical Pathology for her great help, outstanding support, active participation and guidance.*

***Amany El nady***

# List of Contents

Title	Page No.
<i>Introduction</i> .....	١
<i>Aim of the Work</i> .....	٤
<i>Review of Literature</i>	
▪ <i>Sickle Cell Disease</i> .....	٥
▪ <i>Sickle Cell Nephropathy (SCN)</i> .....	٥١
▪ <i>Transforming Growth Factor Beta-١ (TGF-<math>\beta</math>١)</i> .....	٧٣
<i>Patients and Methods</i> .....	٨٦
<i>Discussion</i> .....	١٣٩
<i>Summary and Conclusion</i> .....	١٥٩
<i>Recommendations</i> .....	١٦٣
References .....	١٦٤
Arabic summary .....	—

# List of Tables

Table No.	Title	Page No.
Table (١):	Potential causes of abdominal pain in SCA .....	٢٥
Table (٢):	Approaches of blood transfusion in patients with SCD .....	٤١
Table (٣):	Gender distribution in the study group .....	٩٧
Table (٤):	SCD subtypes distribution in the study group.....	٩٨
Table (٥):	The percentage of positive family history of hemolytic anemia in the study group.....	٩٩
Table (٦):	Frequency of splenectomy in the study group: .....	١٠٠
Table (٧):	Frequency of cholecystectomy in the study group .....	١٠١
Table (٨):	Frequency of stroke in the study group .....	١٠٢
Table (٩):	Frequency of ACS in the study group .....	١٠٣
Table (١٠):	Frequency of reduced hearing in the study group.....	١٠٤
Table (١١):	Frequency of hospital admission (due to sickling crisis) in patients with SCD during the study period .....	١٠٥
Table (١٢):	Frequency of blood transfusion per year in study group .....	١٠٦
Table (١٣):	HU usage in the study group .....	١٠٧
Table (١٤):	The use of iron chelators in the study group .....	١٠٨
Table (١٥):	Frequency of hepatomegaly in the study group.....	١٠٩
Table (١٦):	Descriptive data of the study group (Anthropometric measures).....	١١٠

# List of Tables (Cont..)

Table No.	Title	Page No.
<b>Table (١٧):</b>	Descriptive data of the study group (laboratory measurements) .....	١١٠
<b>Table (١٨):</b>	Comparison between study group and control.....	١١١
<b>Table (١٩):</b>	Comparison between group I (SS&Sβ <sup>-</sup> ) and group II (Sβ <sup>+</sup> ).....	١١٣
<b>Table (٢٠):</b>	Comparison between group I and group II as regard prevalence of microalbuminuria (MA).....	١١٦
<b>Table (٢١):</b>	Comparison between group I and group II as regard frequency of blood transfusion/ year. ....	١١٧
<b>Table (٢٢):</b>	Comparison between group I and group II as regard frequency of hospital admission (due to sickling crisis) during the study period .....	١١٩
<b>Table (٢٣):</b>	Comparison between group I and group II as regard percentage of positive family history of hemolytic anemia .....	١٢٠
<b>Table (٢٤):</b>	Comparison between group I and group II as regard use of HU .....	١٢١
<b>Table (٢٥):</b>	Comparison between group I and group II as regard iron chelators usage .....	١٢١
<b>Table (٢٦):</b>	Correlation between eGFR and (Age and Hb % ) of all patients with SCD.....	١٢٣
<b>Table (٢٧):</b>	Prevalence of microalbuminuria among male and female patients with SCD .....	١٢٤
<b>Table (٢٨):</b>	Comparison between microalbuminuric SCD patients and normoalbuminuric SCD patients.....	١٢٥

# List of Tables (Cont..)

Table No.	Title	Page No.
<b>Table (٢٩):</b>	Comparison between microalbuminuric and normoalbuminuric SCD patients as regard frequency of blood transfusion .....	١٢٦
<b>Table (٣٠):</b>	Comparison between microalbuminuric and normo-albuminuric SCD patients as regard frequency of hospitalization (due to sickling crisis) during study period .....	١٢٧
<b>Table (٣١):</b>	Comparison between microalbuminuric and normoalbuminuric SCD patients as regard presence of family history of anemia. ....	١٢٨
<b>Table (٣٢):</b>	Comparison between SCD patients receiving HU and those didn't receive HU as regard prevalence of MA. ....	١٢٨
<b>Table (٣٣):</b>	The correlation between HU usage and MA level, (urinary ACR), of micro-albuminuric patients.....	١٢٩
<b>Table (٣٤):</b>	Comparison between microalbuminuric and normoalbuminuric SCD patients as regard iron chelators usage. ....	١٢٩
<b>Table (٣٥):</b>	Correlation between MA level (ACR) and (age, Hb and GFR) of micro-albuminuric patients .....	١٣١
<b>Table (٣٦):</b>	The effect of HU usage on urinary TGF $\beta$ (pg/mg Cr) in SCD patients .....	١٣٤
<b>Table (٣٧):</b>	The effect of iron chelators usage on urinary TGF- $\beta$ (pg/mg Cr) in patients with SCD.....	١٣٥
<b>Table (٣٨):</b>	Correlation between urinary TGF- $\beta$ and (Hb, HbS and HbF) in SCD patients. ....	١٣٥



## List of Tables (Cont..)

Table No.	Title	Page No.
<b>Table (۳۹):</b>	The effect of gender of SCD patients on urinary TGF- $\beta$ (pg/mg Cr).....	۱۳۷
<b>Table (۴۰):</b>	Correlation between urinary TGF $\beta$ (pg/mg Cr) and (age, weight, BMI, e GFR, MA level, serum ferritin and serum creatinine) in patients with SCD.....	۱۳۸

# List of Figures

Fig. No.	Title	Page No.
<b>Figure (١):</b>	The arrowed cell is a sickle cell .....	١٤
<b>Figure (٢):</b>	An example of sickle cell dactylitis (hand-foot syndrome).....	٢٠
<b>Figure (٣):</b>	Dactylitis in the hands of an infant .....	٢٠
<b>Figure (٤):</b>	Chronic osteomyelitis. ....	٢٣
<b>Figure (٥):</b>	Abdominal U/S showing multiple gall stones in patients with SCD .....	٢٨
<b>Figure (٦):</b>	ERCP showing bile duct stones pre and post laparoscopic cholecystectomy .....	٣٠
<b>Figure (٧):</b>	TGF- $\beta$ 1 protein structure. Mature TGF- $\beta$ 1 is a ٢٥ kDa peptide .....	٧٤
<b>Figure (٨):</b>	Pathogenesis of TGF- $\beta$ 1-induced renal injury .....	٨٤
<b>Figure (٩):</b>	Gender distribution in the study group. ....	٩٧
<b>Figure (١٠):</b>	SCD subtypes distribution in the study group. ....	٩٨
<b>Figure (١١):</b>	The percentage of positive family history of hemolytic anemia in the study group.....	٩٩
<b>Figure (١٢):</b>	Frequency of splenectomy in the study group. ....	١٠٠
<b>Figure (١٣):</b>	Frequency of cholecystectomy in the study group.....	١٠١
<b>Figure (١٤):</b>	Frequency of stroke in the study group.....	١٠٢
<b>Figure (١٥):</b>	Frequency of ACS in the study group.....	١٠٣
<b>Figure (١٦):</b>	Frequency of reduced hearing in the study group.....	١٠٤

# List of Figures (Cont...)

Fig. No.	Title	Page No.
<b>Figure (١٧):</b>	Frequency of hospital admission (due to sickling crisis) in patients with SCD during the study period. ....	١٠٥
<b>Figure (١٨):</b>	Frequency of blood transfusion per year in the study group.....	١٠٦
<b>Figure (١٩):</b>	HU usage in the study group.....	١٠٧
<b>Figure (٢٠):</b>	Iron chelators usage in the study group. ....	١٠٨
<b>Figure (٢١):</b>	Frequency of hepatomegaly in the study group. ....	١٠٩
<b>Figure (٢٢):</b>	Comparison between study group and control group as regard urinary TGF-β <sup>١</sup> (pg/mg Cr).....	١١٢
<b>Figure (٢٣):</b>	Urinary TGF-β <sup>١</sup> (pg/mg Cr) in group I and group II.....	١١٤
<b>Figure (٢٤):</b>	Hb (g/dl) in group I and group II. ....	١١٥
<b>Figure (٢٥):</b>	Serum ferritin in group I and group II.....	١١٥
<b>Figure (٢٦):</b>	Age of diagnosis in group I and group II. ....	١١٦
<b>Figure (٢٧):</b>	The frequency of blood transfusion in the study group (as regard severity).....	١١٨
<b>Figure (٢٨):</b>	Frequency of hospitalization (due to sickling crisis) in group I and group II.....	١٢٠
<b>Figure (٢٩):</b>	Negative correlation between age & eGFR of all patients with SCD. ....	١٢٣
<b>Figure (٣٠):</b>	The frequency of blood transfusion in microalbuminuric and normoalbuminuric groups.....	١٢٦

## List of Figures (Cont...)

Fig. No.	Title	Page No.
<b>Figure (٣١):</b>	Comparison between microalbuminuric and normo-albuminuric SCD patients as regard frequency of sickling crisis. ....	١٢٧
<b>Figure (٣٢):</b>	Positive correlation between urinary ACR and age of micro-albuminuric patients. ....	١٣٢
<b>Figure (٣٣):</b>	Negative correlation between urinary ACR and Hb of micro-albuminuric patients. ....	١٣٢
<b>Figure (٣٤):</b>	Positive correlation between urinary ACR and GFR of microalbuminuric patients. ....	١٣٣
<b>Figure (٣٥):</b>	The effect of HU usage on urinary TGF- $\beta$ (pg/mg Cr) in patients with SCD.....	١٣٤
<b>Figure (٣٦):</b>	Negative correlation between urinary TGF- $\beta$ and Hb of SCD patients .....	١٣٦
<b>Figure (٣٧):</b>	Negative correlation between urinary TGF- $\beta$ and HbF of SCD patients .....	١٣٦
<b>Figure (٣٨):</b>	Positive correlation between urinary TGF- $\beta$ and HbS of SCD patients. ....	١٣٧

# List of Abbreviations

Abb.	Full term
ACE	: Angiotensin converting enzyme.
ACR	: Albumin creatinine ratio.
ACS	: Acute chest syndrome.
AKI	: Acute kidney injury.
ALK	: Activin receptor- like kinase.
ALP	: Alkaline phosphatase.
Ang II	: Angiotensin II.
ARB	: Angiotensin II receptor blocker.
BMI	: Body mass index.
BMP	: Bone morphogenetic protein.
BMT	: Bone marrow transplantation.
C <sub>3</sub>	: Complement $\gamma$ .
CBD	: Common bile duct.
CKD	: Chronic kidney disease.
CKI	: Chronic kidney injury.
CMV	: Cytomegalo virus.
CO	: Carbon monoxide.
CT	: Computerized tomography.
CTGF	: Connective tissue growth factor.
DBP	: Diastolic blood pressure.
DCT	: Distal convoluted tubules.
DNA	: Deoxyribonucleic acid
DNMT	: Deoxyribonucleic acid methyltransferase.
ECHO	: Echocardiography.
ECM	: Extracellular matrix.
eGFR	: Estimated glomerular filtration rate.
EMT	: Epithelial mesangial transition.
EPO	: Erythropoietin.
ERCP	: Endoscopic retrograde cholangiopancreatography.
ET-1	: Endothelin-1.
FSGS	: Focal segmental glomerulosclerosis.

# List of Abbreviations (Cont...)

Abb.	Full term
G $\gamma$ PD	: Glucose $\gamma$ phosphate dehydrogenase.
GFR	: Glomerular filtration rate.
Hb	: Hemoglobin.
HbF	: Fetal hemoglobin.
HbS	: Sickle hemoglobin.
Hct	: Hematocrite.
HGF	: Hepatocytes growth factor.
HIF $\gamma$ a	: Hypoxia inducible factor $\gamma$ a.
HIV	: Human immunodefficient virus.
HLA	: Human leukocyte antigen.
HPLC	: High performance liquid chromatography.
HU	: Hydroxyurea.
HU	: Hydroxyurea.
IgA	: Immunoglobulin A
IgG	: Immunoglobulin G.
IgM	: Immunoglobulin M.
I $\kappa$ B $\alpha$	: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
IV	: Intravenous.
IVIG	: Intravenous immunoglobulin.
KDa	: Kilodalton.
KIM- $\gamma$	: Kidney injury molecule- $\gamma$ .
LAP	: Latency-associated peptide.
LDH	: Lactate dehydrogenase.
L-FABP	: Liver-type fatty acid binding protein .
LIC	: Liver iron concentration.
LLC	: Large latent complex.
LR	: Leucoreduction.
LTBP	: Latent transforming growth factor-beta $\gamma$ binding protein.
MA	: Microalbuminuria.

# List of Abbreviations (Cont...)

Abb.	Full term
MCH	: Mean corpuscular hemoglobin.
MCV	: Mean corpuscular volume.
MH	: Mad-Homology.
miRNA	: Micro Ribonucleic acid.
MRI	: Magnetic resonance imaging
Na	: Sodium.
NAG	: N-acetyl- $\beta$ -D-glucosaminidase.
NF- $\kappa$ B	: Nuclear factor kappa-light-chain-enhancer of activated B cells.
NGAL	: Neutrophil gelatinase-associated lipocalin.
NO	: Nitric oxide.
NSAID	: Non steroidal anti-inflammatory drugs.
PCT	: Proximal convoluted tubules.
PCV	: Packed cell volume.
PG	: Prostaglandin
Pg/mg Cr	: Picogram/ milligram creatinine.
PH	: Power of hydrogen.
PP <sup>v</sup>	: Protein phosphatase- <sup>v</sup> .
RAAS	: Renin angiotensin aldosterone system.
RBCs	: Red blood cells.
RF	: Renal blood flow.
ROS	: Reactive oxygen species.
RPLS	: Reversible posterior leukoencephalopathy syndrome.
R-Smads	: Receptor- associated Smads.
SARA	: Smad Anchor for Receptor Activation.
SBP	: Systolic blood pressure.
SCA	: Sickle cell anemia.
SCD	: Sickle cell disease.
SCN	: Sickle cell nephropathy.
SCT	: Sickle cell trait.
SLC	: Small latent complex.