Evaluation of Hepcidin in Pediatric Patients with Nephrotic Syndrome

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LIST OF ABBREVIATIONS

AA	Amino acid
ACEI	Angiotensin converting enzyme inhibitors
BMP	Bone morphogenetic proteins
C/EBP	Core element binding protein
CKD	Chronic kidney disease
CsA	Cyclosporine A
CYP	Cyclophosphamide
DBP	Diastolic blood pressure
EDTA	Ethylene diamine Tetra-acetic Acid
ELISA	Enzyme linked immunosorbent assay
ESA	Erythropoiesis stimulating agents
FRNS	Frequent relapses nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
GDF15	Growth differentiation factor-15
HAMP	Hepcidin antimicrobial peptide
HCT	Hematocrite

HD	Haemodialysis
HDL	High density lipoproteins
HFP	Hemochromatosis protein
HH	Hemochromatosis
HIF/vHL	Hypoxia inducible factor/von Hippel-Lindau
HTN	Hypertension
IL-6	Interleukin-6
INS	Idiopathic nephrotic syndrome
IRIDA	Iron-refractory iron deficiency anemia
LDL	Low density lipoproteins
LEAP	Liver-expressed antimicrobial peptide
LMW	Low molecular weight
LMWP	Low molecular weight protein
MCNS	Minimal change nephrotic syndrome
MCV	mean corpuscular volume
mHJV	Membrane isoform of Hemojuvelin

MMF	Mycophenolate mofetil
MPGN	Membranoproliferative glomerulonephritis
NMR	Nuclear Magnetic Resonance
NS	Nephrotic syndrome
PCR	Polymerase chain reaction
Pr/Cr ratio	Protein/creatinine ratio
RDW	Red cell distribution weadth
SBP	Systolic blood pressure
SDNS	Steroid dependent nephrotic syndrome
SLE	Systemic lupus erethromatosis
SMAD	Sons of against decapentaplegic mother
SNS	Secondary nephrotic syndrome
SRINS	Steroid resistant idiopathic nephrotic syndrome
SRNS	Steroid resistant nephrotic syndrome
SSNS	Steroid sensitive nephrotic syndrome
STAT-3	Signal transducer activator of transcription-3

TfR2 Transferrin receptor 2

TMPRSS6 Transmembrane serine protease 6

UTI Urinary tract infection

VLDL Very low density lipoproteins

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Introduction

Nephrotic syndrome (N.S.) is a clinical and biochemical state that may develop as a primary disease or during the course of several different renal diseases that damages the tiny blood-filtering units (glomeruli) in the kidneys ***(Karnovsky and Ainsworth, 1976)***. Characterized by protienurea (>1g/m^2/day), hypoalbuminemia (<2.5 g/dL) and edema ***(Frank et al., 2000)***.

NS is a primarily pediatric disorder and is 15 times more common in children than adults, the incidence is 2-3/100,000 children per year, and the majority of affected children will have steroid-sensitive minimal change disease ***(Vogt and Avner, 2007).*** In Egypt, the annual incidence of NS ranged between 0.03-0.05% of children presented to the general Pediatric Nephrology Clinic, Ain Shams University ***(Farid et al., 1997)***.

Patients with NS have tendency to lose different types of proteins in urine including binding proteins as iron binding protein "transferrin" ***(Keddis et al., 2007)***. Transferrin is the most important glycoprotein for iron transport between sites of absorption and storage and use in the body, so decrease in serum transferrin in nephrotic patients leads to low plasma iron concentration ***(Andrews, 1999).*** In addition erythropoietin which is lost in urine, resulting in low plasma levels of erythropoietin. These factors combine to create iron resistant microcytic hypochromic anemia ***(Keddis et al., 2007)***.

Hepcidin is a 25-amino acid cysteine-rich peptide, present in human serum and urine. It is synthesized predominantly by hepatocytes as an 84-amino acid precursor protein and its mature form is released in circulation. This seems to be the "master regulator" of iron metabolism ***(Kemna et al., 2008)***.

Hepcidin acts by binding to ferroportin, which is located on the basolateral surface of gut enterocytes and the plasma membrane of reticuloendothelial cells, the only known cell iron exporter, inducing its internalization and subsequent degradation in the cytoplasm ***(Ganz et al., 2008)***.

In systemic level, hepcidin upregulation results in inhibition of iron absorption from intestinal enterocytes and iron recycling from macrophages. Hepcidin expression is up-regulated by Iron overload and inflammation, which increase hepcidin release whereas anemia and hypoxia suppress it ***(Kemna et al., 2008)***.