Protein Z Levels in Pediatric Patients with Nephrotic Syndrome

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By

Mostafa Mohammad Abu Elfotoh
M.B.B.Ch
Faculty of Medicine, Ain Shams University

Under Supervision of

Prof. Dr. / Farida Ahmed Farid
Professor of Pediatrics and Pediatric Nephrology
Faculty of Medicine, Ain Shams University

Dr. /Ahmed Abdullah Mohammad
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. /Rania Salah Eldin Kamel Shahin
Lecturer of Clinical and chemical pathology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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LIST OF FIGURES

List Of Tables

List Of Tables

List Of Tables

List of

Abbreviations

ACEIs	angiotensin converting enzyme inhibitors
ACS	acute coronary syndromes
AIIRAs	angiotensin II receptor antagonists
APL	antiphospholipid
APL-IgGs	antiphospholipid immuno globulin G
aPTT	Activated partial thromboplastin time
ATE	arterial thromboembolism
AUC	Area under curve
CGN	Crescentic glomerulonephritis
CKD	Chronic kidney disease
CPH	Cyclophosphamide
CsA	Cyclosporine A
CSVT	Cerebral sinovenous thrombosis
DNA	Dioxy nucleic acid
DVT	Deep venous thrombosis

ELISA	Enzyme linked immunosorbent assay
EGF	Epidermal growth factor
FN	False Negative
FRNS	Frequently relapsing nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
HD	Haemodialysis
HIB	Haemophilus influenza type B
HNF	Hepatocyte nuclear factor
HRP	Horse radish peroxidase
H2O2	Hydrogen peroxide
INS	Idiopathic nephrotic syndrome
ISKDC	International Study of Kidney Disease in Children
KD	Kilo Dalton
LMW	Low molecular weight
LMWH	low molecular weight heparin
LMWP	low molecular weight protein
MCNS	Minimal change nephrotic syndrome

MMF	Mycophenolate mofetil
mRNA	Messenger ribo nucleic acid
MPGN	Membranoproliferative glomerulonephritis
NS	Nephrotic syndrome
P	Predictive
PAD	peripheral arterial disease
PC	Protein C
PCR	Polymerase chain reaction
PD	Peritoneal dialysis
Pr/Cr	protein/creatinine ratio
PS	Protein S
PT	Prothrombin time
PTL	preterm labor
PZ	Protein Z
RPL	recurrent pregnancy loss
ROC Curve	Receiver operating characteristic curve.
SDNS	Steroid dependent nephrotic syndrome
SLE	Systemic lupus erethromatosis

Sn	Sensitivity
SNS	Secondary nephrotic syndrome
SRINS	Steroid resistant idiopathic nephrotic syndrome
SRNS	Steroid resistant nephrotic syndrome
SP	Specificity
SSNS	steroid-sensitive nephrotic syndrome
TE	thromboembolism
TEC	Thromboembolic complication
TP	True positive
TMB	Tetramethylbenzidine
Va	active factor V
VIIIa	active factor VIII
VTE	venous thromboembolism
ZPI	protein Z-dependent protease inhibitor

Introduction

Thromboembolic disease is an important complication in childhood nephrotic syndrome affecting about 5 % of patients ***(Ozkaya et al., 2006).***

Thrombosis in nephrotic syndrome may arise from the loss of proteins involved in the inhibition of systemic hemostasis (low antithrombin III and protein S levels), the increased synthesis of factors promoting thrombosis (factors I, V, VIII and von Willebrand factor), or by the local activation of the glomerular hemostasis systems (intra-glomerular fibrin deposition) ***(Singhal and Brimble, 2005).***

Protein Z (PZ) is a glycoprotein with structural similarities to protein C and coagulation factors VII, IX, and X. A key role for this liver-synthesized protein seems to be the down regulation of coagulation by inhibition of activated coagulation factor X ***(Broze, 2001).***

Increased blood concentrations of protein Z therefore might be expected to result in greater inhibition of blood coagulation, predisposing to bleeding, whereas reduced blood concentrations of protein Z might be expected to cause

reduced inhibition of blood coagulation, predisposing to thrombosis ***(Staton et al., 2005).***

Disruption of protein Z gene in mice leads to a prothrombotic phenotype ***(Yin et al., 2000)***, while in humans, protein Z deficiency has been linked to an increased risk of ischemic stroke ***(Vasse et al., 2001)***, early unexplained fetal loss ***(Gris et al., 2002)***, and enhanced prothrombotic phenotype in factor V Leiden patients ***(Kemkes-Matthes et al., 2002).*** In addition, evidence of protein Z deposits in arterial lesions suggests that this protein may play a role in atherosclerosis ***(Greten et al., 1998).***

Aim of the Work

The aim of this study is to evaluate blood and urine protein Z levels in children with nephrotic syndrome, and its correlation with activity of the disease, response to therapy and the degree of hypoprotenemia & proteinuria.

Childhood nephrotic syndrome

Protein handling by the kidney in normal children

The normal rate of protein excretion in the urine is <4 mg/m2/hour or <100 mg/m^2/day throughout childhood in both boys and girls ***(Ronald et al., 2000).***

Approximately 50% of this small amount of protein consists of Tamm-Horsfall protein, a glycoprotein secreted by the ascending limb of the loop of Henle. The rest is comprised of small quantities of plasma proteins filtered by the glomeruli, e.g. albumin, immunoglobulin, transferrin, and beta 2 micro globulin, with albumin comprising <30% of the total urinary protein in normal individuals ***(Ronald et al., 2000).***

The low excretion rate of protein occurs because: 1) the glomeruli restrict filtration of large serum proteins such as albumin and immunoglobulins, and 2) the proximal tubules reabsorb most of the low molecular weight proteins (LMWP), such as insulin or beta 2 micro globulin, which are filtered across the glomeruli.The resultant modest proteinuria that is present in normal individuals is usually not detected on routine dipstick testing ***(Ronald et al., 2000).***

Protein handling by the kidney in children with renal disease

Excess urinary protein losses may be caused by either: 1) increased permeability of the glomeruli to the passage of serum proteins (glomerular proteinuria), or 2) decreased reabsorption of LMW proteins by the renal tubules (tubular proteinuria) ***(Kevin et al., 2001).***

The finding of proteinuria in single urine specimen in children and adolescents is relatively common ***(Kevin et al., 2001).***

The prevalence varies in different studies but is generally between 5% and 15%. However, the finding of persistent proteinuria on repeated testing is much less common ***(Ronald et al., 2000).***

When proteinuria is detected, it is important to determine whether it is transient, orthostatic, or persistent in type ***(Ronald et al., 2000).***

Transient proteinuria, which is most often associated with fever, stress, dehydration, or exercise, is not considered to be indicative of underlying renal disease ***(Kevin et al., 2001).***