Serum level of Receptor Activator of Nuclear Factor-Kappa B ligand in Children with Nephrotic Syndrome

Thesis

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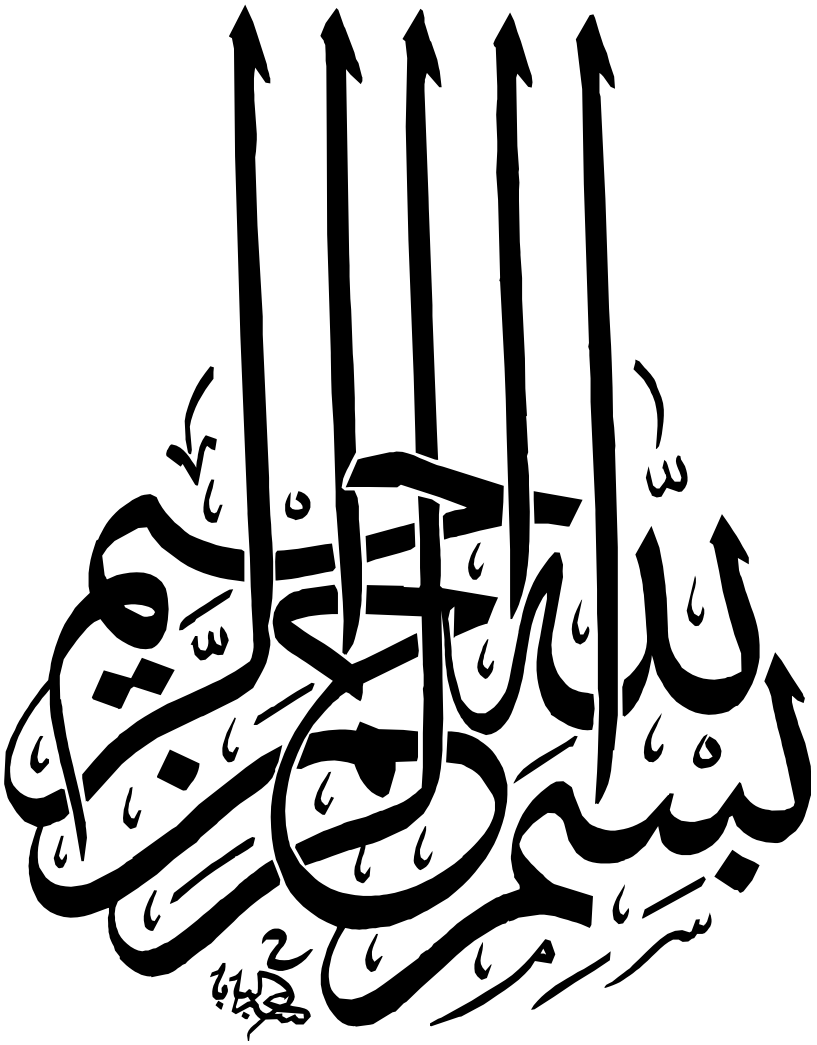
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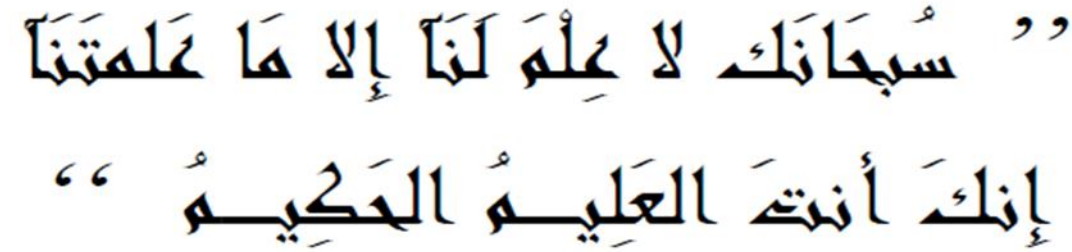

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Mohamed El_Sonbaty

Abstract

Nephrotic syndrome (NS) is considered as a common chronic disorder. Its prevalence in children is 15 times greater than adults. RANKL is one of proteins in the tumor necrosis factor (TNF)/TNF receptor families required for the control of bone remodeling. The aim of this study was to assess the serum level of RANKL in children with idiopathic nephrotic syndrome (INS) treated with glucocorticoids and its relation to the different stages of the disease (remission & relapse) all compared to normal children. The study comprised 40 children diagnosed as having INS. Twenty children were in relapse and the other 20 were in remission. Another 20 healthy children served as control group who were matching in age and sex involved in the study. They were screened for their anthropometric measurements (height, weight, Body mass index (BMI) for-age Z-score), clinical parameters and laboratory assessment (serum RANKL, Albumin, cholesterol, A/c ratio, calcium, phosphorus, ALP, urea, creatinine). Results of this work revealed that sRANKL concentration was significantly higher in relapse group as compared to control group (p=0.002). No similar difference was noted between remission and control. Also results showed a significant positive correlation between duration of glucocorticoids (GCS) treatment and concentration of sRANKL in both groups of NS patients. It was concluded from this study that treatment with GCS for long time results in bone affection so sRANKL can be used as a detector of bone affection and abnormality and accordingly early intervention and prevention of complications can take place.

Key Words: Nephrotic syndrome, Glucocorticoids, sRANKL, TNF

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ACEI	Angiotensin converting enzyme inhibitors
A/C Ratio	Albumin creatinine ratio
APCs	Antigen-presenting cells
ARB	Angiotensin receptor blockers
BMD	Bone mineral density
CKD	Chronic kidney disease
BUN	Blood urea nitrogen
Cbfa1	Core binding factor α 1
CMI	Cell mediated immunity
COPD	Chronic obstructive pulmonary disease
CS	Corticosteroids
CsA	Cyclosporine A
DMP	Diffuse Messangial proliferative glomerulonephritis
ELISA	Enzyme linked immune sorbent assay
ESRD	End stage renal disease
FSGS	Focal segmental glomerulosclerosis
GBM	Glomerular basement membrane
GC	Glucocorticoid
GCs	Glucocorticoids
GCW	Glomerular capillary wall
GFR	Glomerular filtration rate
GH	Growth hormone
GIO	Glucocorticoids-induced osteoporosis
GnRH	Gonadotropin releasing hormone
GR	Glucocorticoid receptor
GRE	Glucocorticoid response element
GWAS	Genome-wide association studies
hsp90	90-kda heat-shock protein
IGF-1	Insulin-like growth factor-1
IgM	Immunoglobulin M
IL	Interleukin
INS	Idiopathic nephrotic syndrome
ISKDC	International Study of Kidney Diseases in Children
JNK	Jun N-terminal kinase
MCD	Minimal change disease
MCNS	Minimal-change nephrotic syndrome
M-CSF	Macrophage colony-stimulating factor

MesPGN	Mesangioproliferative glomerulonephritis
MN	Membranous nephropathy
MPGN	Membranoproliferative glomerulonephritis
NF-κB	Nuclear factor- κB
NSAIDS	Non steroidal inflammatory drugs
NS	Nephrotic syndrome
OCIF	Osteoclast inhibitory factor
OB	Osteoblast
OPG	Osteoprotegerin
OPG-L	Osteoprotegerin ligand
PTH	Parathyroid hormone
PTHrP	PTH- related peptide
RANK	Receptor activator for nuclear factor kappa B
RANKL	Receptor activator for nuclear factor kappa B ligand
ROD	Renal osteodystrophy
SSNS	Steroid sensitive nephrotic syndrome
SDNS	Steroid dependant nephrotic syndrome
Teff	T cell effector
TH2	Type 2 helper T cells
TGF	Tumer growth factor
TNF	Tumor necrosis factor
TRAF	TNF receptor-associated family
TRANCE	TNF-related activation induced cytokine
TRAIL	TNF-related apoptosis-inducing ligand
Tregs	Regulatory T-cells

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INTRODUCTION

Nephrotic syndrome (NS) is considered as a common chronic disorder which is characterized by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of proteins **(Bagga and Mantan, 2005).** Important biological consequences such as reduced bone mineral density (BMD) and abnormal bone histology have been documented. The latter include osteomalacia of variable degrees as well as excessive bone resorption **(Bonilla-Felixm et al., 2009).**

Corticosteroids are the standard first-line of treatment in nephrotic children. Children are given high doses over a long period due to the chronic and recurrent nature of the disease **(Neuhaus et al., 2010)**. This increases the risk of osteoporosis (steroid induced osteoporosis) which in turn has long term complications **(Gulati et al., 2009)**.

Although it was reported that intermittent treatment with glucocorticoids in children does not significantly alter bone metabolism, still it seems reasonable to provide calcium supplements to patients with frequent relapses, steroid dependence or resistance who are likely to receive long term therapy with corticosteroids **(Leonard et al., 2007)**.

A set of proteins in the tumor necrosis factor (TNF)/TNF receptor families were reported to be required for the control of bone remodeling. These receptors, namely, receptor activator for nuclear factor kappa B (RANK), osteoprotegerin (OPG), and the RANK ligand (RANKL), were identified as forming a critical molecular triad that controlled bone remodeling (**Hofbauer et al., 2000).** The binding of RANKL to its receptor (RANK) induces differentiation, activation, and the prevention

of osteoclast apoptosis, leading to enhanced bone resorption and bone loss **(Khosla, 2001).**

Serum levels of RANKL in some pediatric disorders requiring therapy with glucocorticoids (GCS) were assessed. **Oelzner et al (2007)** demonstrated that high serum levels of RANKL were associated with osteoporosis in patients with rheumatoid arthritis. However, **Turk et al (2009)** found that free sRANKL and OPG showed a highly inverse relationship in patients with reduced bone density in the course of Crohn disease. Recently **Wasilewska et al (2010)** observed that INS children treated with GCS had an increased serum RANKL level, decreased serum osteoprotegerin (OPG) level, increased RANKL/OPG ratio. Their results also revealed a significant positive correlation between the cumulative dose of GCS and the serum RANKL. They also found that concurrent GCS treatment increased the serum RANKL level and the latter correlated negatively with the BMD Z-score.