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ORIGINAL ARTICLE

Assessment of Sclerostin as a Bone Metabolism Marker in Egyptian Children with Nephrotic Syndrome

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ABSTRACT

Background: Usingsteroids as a medical line of treatment for pediatric idiopathic nephrotic syndrome (INS) has a noxious aftereffect on the course of bone mineralization in the targeted children. Searching for new markers of bone mineralization seems to be an imperative issue. Sclerostin (Scl), a glycoprotein which is coded by the SOST gene, is noted as a pivotal controller of bone setup via its repressing outcome on Wnt signaling.

The aim of this study was to assess the concentration of Scl level in children with INS and to correlate Scl level with other existing markers of bone metabolism.

Method: A case control study achieved on 70 children including 35 patients with INS on corticosteroid therapy and 35apparently well age and sex alike children as a control group. Kidney function testing, bone markers, parathyroid hormone, and serum sclerostin, were assayed in both research groups.

Results: There was a statistically significant difference in serum Scl level between the studied groups, being higher in the nephrotic children than the control group (mean ± SD: 10.07 ± 3.650 vs. 5.29 ± 1.92, respectively with p<0.001). Among factors significantly correlated with serum sclerostin, only serum calcium was significantly independently associated with it (unstandardized β=-1.356). There was a statistically significant relation between serum Scl, steroid response and disease activity (p value= 0.001, 0.001 respectively).

Conclusion: The sclerostin serum level can serve as an indicator of bone mineralization in children with INS utilizing corticosteroids as a therapeutic agent.

Keywords: bonemineralization**,** idiopathic nephrotic syndrome, serum sclerostin.

INTRODUCTION

Nephrotic syndrome (NS) is considered as a clinical syndrome which can be identified by abundant proteinuria as well as hypoalbuminemia, with subsequent development of hyperlipidemia, edema, and various complications. Idiopathic nephrotic syndrome (INS) is the most usual kidney

disease in pediatrics.[1]Children with chronic kidney disease (CKD) are recorded to have bone aches, limb impairment, short stature, and more fracture probability than their healthy peer. Maintaining a good condition of bone health in pediatric patients with CKD is critical to avoid certain common complications, as bone fractures, to optimize bone growth and potentially even obstruct extra-osseous calcification, particularly vascular calcification.[2]A relapsing-remitting path is commonly observed in childhood NS, needing recurring courses of glucocorticoids (GC).[3] Prednisone is the drug of choice for INS to prompt remission, to prohibit relapses and to bypass the recurrent nature of the disease. Unluckily, steroid reliance implies a long therapy interval and subsequently increase the likelihood of bone metabolism problems.[4]GC is stated to inhibit osteoblastogenesis, this inhibition is mediated basically *via* down regulation of signaling pathways comprehended in influencing osteoblast differentiation, principally WNT and BMP pathways.[5]In the clinical judgment of children with CKD, observing bone health is considered to be an essential issue. However, the accessible appliances are deficiently investigated. An itemized evaluation of bone health state and bone mineralization demands a collection of laboratory studies, radiological work and even bone biopsy. Nevertheless, novel works claim that the estimation of ordinary bone markers does not confess an early appreciation of bone metabolism problems and radiological works have many restrictions. Bone biopsy is advised as a curious technique in children.[2] Therefore, searching for modern laboratory parameters is ongoing, with sclerostin (Scl) as an auspicious candidate.

Sclerostin which is a glycoprotein coded by the SOST gene, is chiefly generated by mature osteocytes and is a pivotal organizer of bone synthesis through its negative impact on Wnt signaling in osteoblasts.[6]Serum sclerostin value is swayed by both endogenous and exogenous glucocorticoids.[7]In a previous work conducted on an animal model of poor bone turnover, treatment with sclerostin antibody created an amelioration of trabecular mass and mineralization, suggesting that repression of sclerostin may help patients with adynamic bone disorders.[8] However, the role of serum sclerostin measurements is not yet clear in clinical care.Children with INS are at hazard of metabolic bone disease (MBD), abetted by crucial modifications of mineral metabolism and bone synthesis.[9] Early disclosure of bone metabolism disorders in children with INS using new biochemical markers as sclerostin which can provide a novel insight into the pathogenesis of the bone metabolism disorders. Therefore, the current study was held to inspect serum sclerostin level in children with INS and set to which magnitude glucocorticoid therapy has an aftereffect on serum sclerostin level.

PATIENTS AND METHODS

A case control study was implemented in the pediatricnephrology unit of our universityhospital from February 2022 to March 2023. The approval for the study was obtained from the Pediatrics Department of Zagazig University Hospitals after obtaining an approval from the Institutional Review Board (ZU-IRB# 6474) and the research was conducted in accordance with the Helsinki Declaration. Written consent was obtained from the guardians of patients and controls.

The study was performed on 70 children aged 1-16 years old who were registered in the study, 35 children with INS and 35 apparently well children, selected from the outpatient pediatric clinic, who shared the same age and sex as the patient group and complained of acute, temporary diseases. Kidney function tests for all patients were normal all through the research and none of the patients had any clinical proof of infection or showed positive results for any of the biomarkers of inflammation or sepsis.

Based on the International Study of Kidney Disease in Children (ISKDC) criteria, the diagnosis of INS was established when proteinuria (>40 mg/m2/h in 24 h urine collection or urine protein-to-creatinine ratio >2 mg/mg in a random urine sample), low serum albumin (below 2.5 g/dL), and edema were present. [10] The remission of proteinuria within 8 weeks of corticosteroid therapy is what is known as steroid responsive (SS) nephrotic syndrome. Failure to get full remission after 8 weeks of treatment is known as steroid resistance (SR).[11]We excluded patients with secondary NS, patients who had previous treatment for osteoporosis or vitamin

D as a therapeutic agent before or during the study were, and children having other states unrelated to NS that might impress bone health.

Every participant in the study underwent careful history evaluation along with the type of the preceding therapy, its interval and response. Detailed clinical examination with appropriate spotlight on anthropometric values was recorded.

Liver and kidney function test, lipid profile, Calcium, Phosphorus, and Alkaline phosphatase (ALP) were performed in Roche Cobas (8000) auto analyzer, c702 module by spectrophotometry; Parathormone (PTH) was analyzed on Roche Cobas (8000) auto analyzer, e 602 module by electrochemiluminescence; urinary protein creatinine ratio which was performed on Cobas 6000 auto analyzer, c 501module, by turbidimetry. All blood tests were assayed using dedicated reagent according to manufacturer recommendations (Roche diagnostics, Switzerland). Also, estimated GFR according to Schwartz formula was calculated.

Serum sclerostin assay: One milliliter of peripheral blood by vein puncture was collected in a sterile situation from each participant and placed in a plain vacutainer tube for serum separation. The sample was abandoned at room temperature for 20 minutes till complete coagulation, then centrifuged at 2000-3000 rpm for 20 minutes,and the consequent sera was kept at (-20c) for further analysis of sclerostin.

Test principle: The kit applies an enzyme-linked immunosorbent test with a double antibody sandwich (ELISA) to analyze the value of serum sclerostin in each specimen. Human sclerostin monoclonal antibody was used to pre-coat the monoclonal antibody enzyme well before adding sclerostin, which was followed by an incubation stage. Following the addition of biotin-labeled sclerostin antibodies and streptavidin-HRP to create an immunological complex, additional incubation and washing processes were carried out to remove the uncombined enzyme. Following the addition of Chromogen, Solutions A and B, the liquid's color changed to blue before quickly turning yellow under the action of acid. The concentration of the species' sclerostin and the color chroma were positively associated. The kit was supplied by Shanghai Sunred Biological Technology Co. Ltd., China (Catalog No. 201-12-5418).

Statistical Analysis:

The data was analyzed using SPSS (Statistical Program for the Social Sciences) version 26. For categorical data, percentages and numbers were used. The categorical variables were analyzed using the Chi-square test ($\chi 2$). The Kolmogorov-Smirnov test was used to determine the normality of quantitative data, supposing normality at $P > 0.05$. For quantitative data, variables like mean, standard deviations, and ranges were used. The student "t" test was used to assess normally distributed variables between two independent groups, while the Mann-Whitney U test was employed for nonparametric variables. To evaluate the correlation between nonparametric variables, Pearson correlation was used. $P < 0.05$ was considered significant and highly significant difference was present if $p \leq 0.001$.

RESULTS

35 cases of INS receiving corticosteroid treatment and 35 healthy children who were age and sex matched served as the study's control group. The age range of the children of NS investigated in the current study was 3 to 6 years; Median (IQR) was 4.21 years with male predominance (54.3%). There was a statistically significant difference regarding body mass index (BMI) between the tested groups. (Significantly higher in case group Mean ± SD [20.26 ± 6.29] versus control). **[table1]**

Table (1) Comparison between the studied groups regarding demographic data

	Nephrotic group	Control group	Test	p
	N=35(%)	N=35(%)		
Gender: **Female** **Male**	 16 (45.7%) 19 (54.3%)	 24 (68.6%) 11 (31.4%)	χ^2 = 3.733	0.053
Age (year) **Median (IQR)**	 4.21 (3 – 6)	 4 (2.75 - 6.5)	Z= -0.419	0.675
BMI (kg/m2) **Mean ± SD**	 20.26 ± 6.29	 17.0 ± 3.67	t = 2.645	0.01*

t independent sample t test Z Mann Whitney test χ^2chi square test *p<0.05 is statistically

Among 35 children with nephrotic syndrome, the median duration of corticosteroid use was 1 year (range from 0.7 to 5 years); there were 80% steroid-sensitive patients, 22.8% were in remission, 82.9% of patients took corticosteroids alone, while the rest patients received immunosuppressive medications in addition to steroids. [not tabulated]There was a statistically significant difference in the levels of serum sclerostin between the studied groups (mean ± SD was higher in INS group: 10.07 ± 3.650 vs. 5.29 ± 1.92, respectively) p<0.001. Regarding other laboratory parameters, a statistically significant difference was detected between both groups regarding urinaryprotein/creatinine ratio, parathyroid hormone, cholesterol, and serum phosphorus (significantly higher in the case group). While serum albumin and calcium were significantly lower in the case group. **[table2]**

Table (2) Comparison between studied groups regarding biochemical data.

	Nephrotic group	**Control group**	**test**	**p**
Serum sclerostin (ng/mL) Mean ± SD	10.07 ±3.65	5.29 ± 1.92	t 6.861	<0.001**
Serum albumin (g/dL) Mean ± SD	2.34 ± 1.2	4.43 ± 0.33	t -9.956	<0.001**
Serum cholesterol (mg/dL) Mean ± SD	358.77 ±149.12	107.89 ±7.44	t 9.941	<0.001**
Serum creatinine (mg/dL) Mean ± SD	0.46 ± 0.25	0.45 ± 0.1	t 0.247	0.806
eGFR Mean ± SD	114.18 ± 42.78	101.78 ± 19.19	t 1.564	0.124
Urine protein/creatinine ratio Median (IQR)	11.3 (6.2 – 18.1)	0.45 (0.38 – 0.48)	Z -7.148	<0.001**
Serum calcium (mg/dL) Mean ± SD	8.25 ± 0.77	10.33 ± 0.59	**t=** -12.723	<0.001**
Serum phosphorus (mg/dL) Mean ± SD	4.92 ± 1.14	4.01 ± 0.35	**t =** 4.476	<0.001**
ALP(U/L) Mean ± SD	103.43 ± 28.45	101.46 ± 25.78	**t =** 0.304	0.762
PTH (pg/mL) Median (IQR)	26 (20 – 30.9)	20 (16 – 26)	Z = -2.474	0.009*

t independent sample t test Z Mann Whitney test IQR interquartile range *p<0.05 is statistically significant **p≤0.001 is statistically highly significant PTH: Parathyroid hormone ALP: Alkaline phosphatase

There was a statistically significant positive correlation between serum sclerostin level and all of blood urea nitrogen, urine protein/creatinine ratio, total cholesterol, PTH, serum phosphorus level and duration of corticosteroid use. While serum sclerostin levels and both serum calcium and albumin levels had a statistically significant negative correlation. **[table 3]**

Table (3) Correlation between serum sclerostin level and the studied parameters

	r	**P**
Age	**-0.017**	**0.89**
Weight	**0.09**	**0.461**
Height	**-0.178**	**0.141**
BMI	**0.064**	**0.596**

	r	P
Albumin	-0.468	<0.001**
Cholesterol	0.402	0.001**
Creatinine	0.051	0.676
BUN	0.49	<0.001**
Urine protein/creatinine ratio	0.601	<0.001**
eGFR	-0.06	0.624
Serum calcium	-0.509	<0.001**
Serum phosphorus	0.242	0.044*
Parathormone	0.268	0.025*
Alkaline phosphatase	0.168	0.163
Duration of corticosteroid use	0.788	<0.001**

r Pearson correlation coefficient Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Among factors significantly correlated with serum sclerostin, only serum calcium was significantly independently associated with it (unstandardized β=-1.356). **[table 4]**

Table (4) Linear stepwise regression analysis of factors significantly associated with serum Sclerostin:

	Unstandardized Coefficients		Standardized Coefficients	t	P	95.0% Confidence Interval	
	B	Std. Error	Beta			Lower	Upper
(Constant)	21.945	3.041		7.215	<0.001**	15.874	28.015
Serum calcium	-1.536	.324	-.502	-4.745	<0.001**	-2.182	-.890

p≤0.001 is statistically highly significant

The relationship between serum sclerostin, steroid response, and disease activity was statistically significant (sclerostin was significantly higher in resistant and active groups). There was a statistically insignificant relation between the use of corticosteroid sparing agent and serum Sclerostin. **[table 5]**

Table (5) Relation between steroid response and serum sclerostin level:

	Sclerostin Mean ± SD	t test	p-value
Steroid response Responsive (n=28) Resistant (n=7)	 8.83 ± 2.52 15.06 ± 3.26	-5.51	<0.001**
Disease activity Active (n=27) Remission (n=8)	 11.09 ± 3.51 6.64 ± 1.23	3.659	0.001**
Corticosteroid sparing agent. No (n=29) yes (n=6)	 10.28 ± 3.95 9.07 ± 1.37	1.318	0.2

p≤0.001 is statistically highly significant

DISCUSSION

Long-term steroid medication may have particularly damaging effects on the human skeleton throughout the growing phase. GCs, in conjunction with INS, are the base of the care of several immunological diseases, and their toxic impact is one of the most frequent causes of iatrogenic illness when combined with their prolonged use. A significant risk of bone deficit during early months of use, along with a high risk of fractures, is one of these iatrogenic side effects. According to research conducted on children with INS, there was a negative link between bone density and the total dose of GCs prescribed. [12] As a result, it was essential to evaluate recent indicators

of bone and mineral metabolism in children with INS receiving GCs.

In the present study, the Ca level in patients decreased statistically significantly compared to controls. Throughout the course of this trial, patients' serum levels of phosphorus, ALP, and PTH were considerably higher than those of controls. This was in agreement with other studies that found that the majority of those with nephrotic syndrome who received corticosteroids developed hypocalcemia. [12, 13] This may be made clearer by the fact that corticosteroids cause hypocalcemia by lowering intestinal absorption of calcium and increasing renal tubular excretion of calcium.[14] The most likely cause of the hyperparathyroidism seen in the research was hypocalcemia that was induced by corticosteroid. Ca reabsorption from the bones was known to be induced by high PTH levels.[15] Increased bone turnover with corticosteroid therapy may explain why ALP levels increased.[13]

In the present study, serum scl levels were statistically significant different in between the analyzed groups ($p<0.001$), which was considerably greater in the case group than the control group. This finding is consistent with another study that included 70 children, 50 of whom had INS and 20 of whom did not, with all patients with INS having significantly more concentrations of Scl than the control group. [4] another study found that Scl serum concentrations in patients receiving hemodialysis were significantly higher than those seen in healthy controls who were age and sex matched. [16] Being raised from the early stages of CKD, sclerostin was thought to be a promising marker for detecting an early CKD and its related bone and mineral disease. [17]

In concordance with Pukajo et al. [4] who found that serum levels of Scl in INS patients increases along with the duration of GCS therapy, our results showed a statistically significant positive correlation between serum sclerostin level and duration of steroid therapy ($p<0.001$). This finding was in line with those of a study conducted in mice by Yao et al., who found a favorable correlation between the length of the steroid treatment and the expression of the gene SOST that encodes for Scl and the suppression of osteoblast activation and maturation [18]. NS children with higher cumulative doses and longer duration of the disease used steroids more frequently, which led to increased bone breakdown. There is currently a lack of information regarding the relationship between Scl and steroid therapy. [19]

We evidenced that there was a statistically significant negative correlation between serum sclerostin level and serum calcium ($p <0.001$) while, we investigated that there was a statistically significant positive correlation between serum sclerostin level and with PTH ($p =0.025$). Pukajło et al., found that sclerostin was positively correlated with PTH but no correlation was found between the sclerostin level and levels of phosphorus and calcium. [4] In opposition to our opinion, the concentration of Scl was correlated negatively with intact PTH concentrations but positively correlated calcium.[16] The significance of Scl in bone and mineral metabolism is still unknown based on the previously indicated conflicting data.

On applying linear stepwise regression analysis in the current work and among factors significantly correlated with serum sclerostin, only serum calcium was significantly independently associated with it ($p <0.001$). In harmony with our study, a preceding study conducted on 42 children with NS treated with glucocorticoids who underwent 24-hour urine calcium estimation and quantitative ultrasound bone mineral density (BMD) assessment discovered that just 0.5% of those in the normal BMD group and 47.4% of those in the osteopenia group had hypercalcemia, whereas all patients in the osteoporosis group experienced hypercalciuria.[20]

On assessing the concentration of serum sclerostin to evaluate the relationship between sclerotin level and disease activity, we ascertained that the level of sclerostin was significantly higher during the active phase of the disease than in remission. This analysis came in unison with Pukajło et al. who monitored higher values of sclerotin during relapse than sclerotin values during remission. [4] The earlier reported abnormalities might

be a result of the high dose GCs re-initialization, which led to worsening of the bone breakdown. Patients with steroid sensitive nephrotic syndrome (SSNS) receiving GCs therapy experience bone status modification that could be associated with the dosage and duration of the therapy. [15] These observations suggest that Scl is a major player in bone metabolic abnormalities caused by steroid treatment in INS.

We displayed that the concentrations of sclerostin were significantly higher in steroid resistant nephrotic syndrome (SRNS) group than SSNS group ($p<0.001$). Children with SRNS are at a higher risk of metabolic bone disorder that could be attributed to corticosteroid and immunosuppressant treatment-induced biochemical imbalances. [21]

Conclusion:

The sclerostin serum level can serve as an indicator of bone mineralization in children with INS receiving corticosteroids therapy. Early identification of the NS related disease may alert clinical physician about the possible susceptible osteoporosis.

There are a few limitations to our research. The study's small size. For a more thorough definition of this issue, longitudinal studies with a bigger sample size and a longer follow-up period are needed. It is necessary to conduct research on the impact of calcium and vitamin D supplements on the prevention and management of this issue. It would also be a good idea to compare the utility of the investigated parameters to alternative bone evaluation techniques, like as densitometry and ultrasound, in patients receiving long-term GCS.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

List of abbreviations:

CKD: chronic kidney disease
ALP: Alkaline phosphatase
GC: glucocorticoids
INS: Idiopathic nephrotic syndrome
ISKDC: International Study of Kidney Disease in Children
MBD: metabolic bone disease
PTH: Parathormone
SCL: sclerostin
SSNS: steroid sensitive nephrotic syndrome
SR: steroid resistance

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