Type of the Paper (Systematic Review)

Osteocalcin Level in Children with Nephrotic Syndrome: A Systematic Review

Sherin K. Hussein[1], Ghada A.O. Mohamed[2*], Doaa Y. Ali[3], Ashraf S. Kamel[1]

[1] Pediatrics Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

[2] Pediatrics Department, Pediatrics, Fayoum General Hospital, Fayoum, 63514 Egypt.

[3] Clinical Pathology Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

*Correspondence: Ghada A.O. Mohamed, futuredodo2@gmail.com, Tel: (002) 01067420603.

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Abstract:

Introduction: Osteocalcin (OC) is an important protein hormone in bone metabolism. OC levels have been impacted in children who exhibit nephrotic syndrome (NS), which is defined by inflammation and protein loss in urine.

Aim of the study: To assess the serum osteocalcin (S-OC) level in children diagnosed with NS.

Methods: I conducted a systematic examination of 975 children.

Results: A review of 10 studies, which included 975 children, determined remission as the lack of albumin in three early morning repeated samples of urine (or proteinuria <4 mg/m2/h). Regular recurrence was defined as experiencing two or more relapses within the initial half-year or encountering over three in a full year. Occasional recurrence was described as having less than 2 recurrences in 6 months after initial improvement or < 4 relapses in each following year. A tolerance on steroids was detected by two consecutive relapses throughout alternate-day steroid utilization or during 14 days of steroids. Steroid-Resistant NS is the inability to achieve recovery after 28 days of 2 mg/kg/day of prednisolone.

Conclusions: The increase in OC levels depends solely on the dosage of glucocorticoids GC given, not on the particular kind of GC prescribed. This could have importance in a clinical setting and could help reduce bone-related side effects. When vitamin D supplementation is provided, the utilization of multiple courses of steroid therapy usually has no impact on height as a growth parameter. It is not recommended to utilize OC as a screening tool in children on steroids, as the rise in serum levels might occur due to either bone turnover or formation.

Keywords: Nephrotic Syndrome; Children; Osteocalcin.

1. Introduction

Nephrotic syndrome (NS) is identified by high protein in urine, low albumin levels, increased cholesterol levels, and overall swelling [1].

The biochemical changes induced by kidney disease and therapy with steroids may increase the likelihood of turnover of bone in diseased children [2].

In prior research, steroid therapy can impact bone mineral density (BMD) on certain markers, specifically within the initial three months of starting treatment. The markers show a notable decrease in ca levels in comparison to the levels at the start of treatment [3].

Following the initiation of treatment, the urine calcium/creatinine ratio (Ca/Cr) and serum alkaline phosphatase ALP mean values show a notable increase compared to baseline levels [4].

Osteocalcin (OC) is a peptide found in the bone matrix that is non-collagenous and has a high amount of glutamate. It consists of 49 amino acids and weighs approximately 5800 kDa [5].

OC functions to impede the bones' mineralization. It prevents the calcium salt deposits in completely saturated solutions. Bone-specific ALP and OC serum levels indicate osteoblast cell activity [6].

Increasing turnover of bone and decreased levels of OC occur in those receiving anti-resorptive treatments like bisphosphonates or HRT, typically within 3 to 6 months of starting the therapy. Lower-level phases show positive reaction to therapy [7].

2. Methods

2.1. Literature search

Following the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines, this systematic review was carried out. A literature search for potential studies published was conducted utilizing PubMed, Web of Science, Cochrane, and Scopus.

The analyzed publications were sourced from research performed on the Web of Science database in August 2024. Throughout the initial search, the requirements included selecting the

document type as 'article', with 'Osteocalcin' in the topic and 'Childhood NS ' in the title. More research was carried out utilizing the criteria of document type 'article' and the search terms 'Osteocalcin' and 'bone turnover,' or 'nephrosis' and 'steroids' in the topic. The searches were conducted to collect articles on OC in diseased children having NS, resulting in the adoption of broader search terms.

2.2. Bias risk assessment, quality, and credibility of involved studies

The author evaluated the involved studies for quality and bias risk, including utilizing the Newcastle-Ottawa Scale.

3. Results

3.1. Search results and study selection

A PRISMA diagram is demonstrated in **Figure 1**. A 312 records were determined. After the removal of duplication, 287 records were kept out of the total of 312 records based on title and abstract. The eligibility of ten full-text articles was evaluated. The remaining papers from ten studies were eligible, while three did not match our research criteria (n=2: ineligible outcome; n=1 animal study).

3.2. *Included papers Characteristics*

The included papers are reported in **Table 1.** Most (2/7) were based on Egypt samples. One paper each from the US, Canada, Poland, the UK, and Indonesia comprised the remaining papers. The seven studies reported 370 subjects, all had been diagnosed with NS.

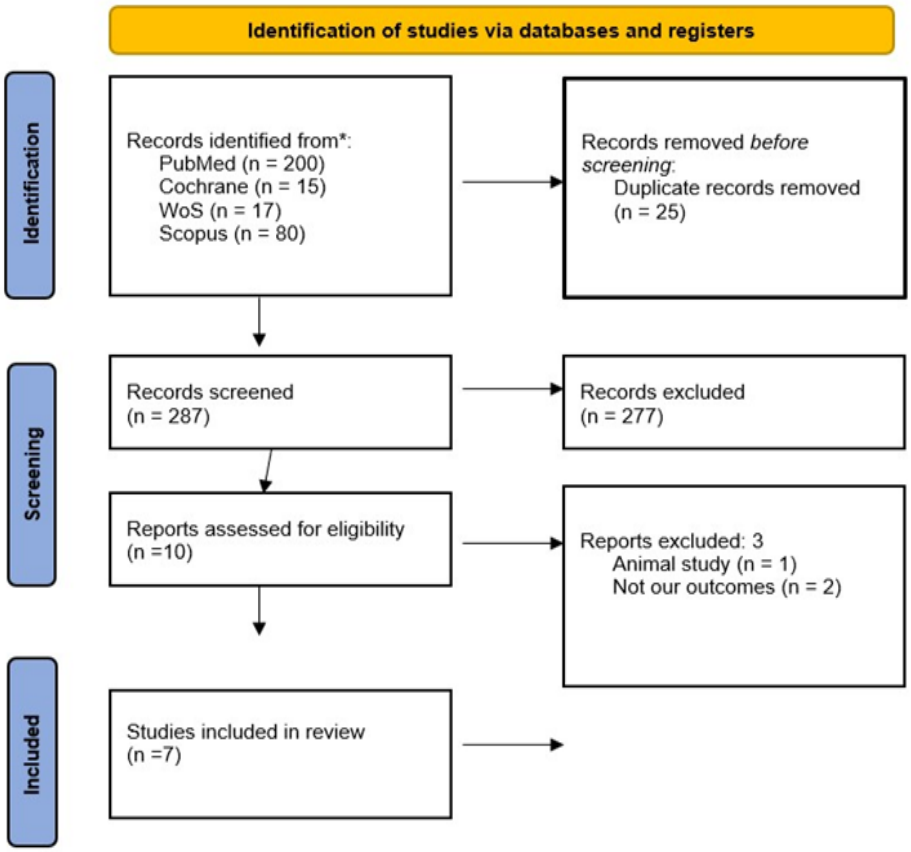

Figure 1: A PRISMA flow chart.

Table 1: Summary of involved studies.

Study ID	Location	Study Design	Study Population	Inclusion criteria	Exclusion criteria	Conclusion
Ghobrial et al., 2017 [8].	Egypt	Cross-sectional	• Steroid-dependent/ frequently relapsing (SDNS/FRNS). • Steroid-resistant nephrotic syndrome (SRNS) in children.	• Children ages 2-15 years. • The disease's duration ≥ 6 months.	• Patients with renal impairment, steroid-sensitive NS, congenital NS, and a disease duration <6 months. • Those with other reasons of low bone density (such	• NS cases who are on long-term steroid usage (SDNS/FRNS and SRNS) are at an increased bone metabolism. • The cases treated with high steroid concentrations show that growth and height may be influenced by a higher rate of bone turnover. • Height is particularly susceptible to the effects of recurrent relapses that arise throughout multiple courses of

					as thyroid, parathyroid hormone irregularities .	medication with steroids. • Thorough BMD assessment and early having ca and vitamin D as a prophylactic supplementation, OC utilization as a screening measure for bone turnover is advised for cases who are taking steroids.
Hammad et al., 2013 [9].	Egypt	Cross-sectional	• Children with steroid-sensitive and SRNS.	• Children who experienced their initial episode of idiopathic NS before receiving any immunosuppressive medications.	• Cases with a history of current steroid intake in the last 6 months have a higher serum Cr level, extensive hematuria, or a low serum C3.	• Before commencing therapy, cases with initial SRNS exhibit diminished glucocorticoid (GC) receptor production in peripheral blood mononuclear cells (PBMC). • This low expression may be one of the steroid resistance pathophysiological mechanisms.
Moon et al., 2014 [10]	UK	Case–control	• Diseased Children having NS.	• Five-year-old individuals . • They had no other significant medical conditions.		• NS children exhibit an increase in the cross-sectional area of their tibial bones. • It is a compensatory response to rising body weight. These patients did not reveal any abnormalities in trabecular BMD.
Phan et al., 2014 [11]	Canada	Prospective	• Diseased Children having NS.	• Children aged 1 month to 17 years. • Within 37 days of initiating GC therapy. • Underwent a baseline bone health assessment .	• Patients who received steroids for more than 14 days in one year to manage any other medical issue (e.g., asthma). • Individuals who had taken any medications for osteoporosis. • Individuals	• The rate of fractures in vertebra at one year was minimal, and most of diseased children experienced a 12-month improvement in their LS BMD Z-scores. • At twelve months, 25% of children had lumbar spine (LS) BMD Z-scores that were less than or equal to 1.0. • In these children, LS BMD Z-scores were inversely related to initial GC exposure, even though they had similar GC experience to the rest of the cohort.

					who had calcium or vitamin D supplements.	
Ribeiro et al., 2015 [12]	USA	Retrospective	• Diseased Children having NS.		• Cases were either lost to follow-up or exhibited inadequate therapeutic observance.	• Lower height and BMD Z-scores were significantly associated with increasing concentrations of GCs. • Significant growth effects were observed at cutoff concentrations exceeding 0.2 mg/kg/day.
Permatasari et al., 2017 [13]	Indonesia	Prospective longitudinal	• Diseased Children having NS.	• Minors with ages < 18 years who had a primary episode of NS, uncommon NS relapses, frequently relapsing NS, and steroid-dependent NS.	• SRNS cases.	• The OC levels suppression was reversible following the alternating phase. • It demonstrates the importance of a tapering off regimen. The clinical indicator of pain, bone/cramps, was almost nonexistent in all of these cases.
Panczyk-Tomaszewska et al., 2015 [14]	Poland		• Diseased Children having NS.	• Children aged 5–17 years.		• Bone mass loss is a result of corticosteroid therapy for diseased children having NS. • To prevent osteopenia, it is recommended that these children take vitamin D, which may exceed 800 IU/24 hours. • This is because serum Bone alkaline phosphatase BAP concentration is a spongy bone metabolism reliable indicator.

3.3. Publication bias and study quality

The small number of involved studies made it impossible to assess publication bias. However, the quality was good.

Table 2: Bias risk assessment utilizing Newcastle-Ottawa scale.

Study ID	Location	Journal	Newcastle–Ottawa Scale
Ghobrial et al., 2017 [8].	Egypt	Iranian Journal of Pediatrics	Good quality
Hammad et al., 2013 [9].	Egypt	Pediatr Nephrol Journal	Good quality
Moon et al., 2014 [10]	UK	Bone Journal	Good quality
Phan et al., 2014 [11]	Canada	International Osteoporosis Foundation	Good quality
Ribeiro et al., 2015 [12]	USA	Springer-Verlag Berlin Heidelberg	Good quality
Permatasari et al., 2017 [13]	Indonesia	Innovare Academic Sciences	Good quality
Panczyk-Tomaszewska et al., 2015 [14]	Poland	Springer International Publishing Switzerland	Good quality

4. Discussion

A total of 10 articles were chosen to assess levels of serum osteocalcin (S-OC) in 975 children diagnosed with NS.

In their initial research, Ghobrial et al. (2017) discovered that height is notably affected by repeated rounds of steroid treatment during recurrent relapses [8]. It is recommended to employ OC as a screening measure for bone turnover in cases of steroid therapy.

In a subsequent study, Hammad and colleagues found that kids suffering from primary SRNS had decreased levels of GR in PBMC before treatment, suggesting a potential link to their resistance to steroids [9].

The most frequently observed histological pattern in children with idiopathic SRNS at our center is mesangioproliferative glomerulonephritis, followed by FSGS and MCD [15].

In the fourth study, Moon and his team (2014) utilized pQCT scans to measure volumetric BMD and bone cross-sectional geometry at 4% and 66% metaphyseal and

diaphyseal sites in the tibia [10]. Total amount of GC exposure over one's lifetime.

Phan et al. (2014) stated in the fifth study that there were only a few vertebral fractures after one year, and most people experienced improvements in Z-scores for LS BMD by the 12-month mark [11]. 25% of children had LS BMD Z-scores that were -1.0 or lower at the age of 12 months.

In the sixth article, Ribeiro et al. (2015) discovered a link between elevated doses of GCs and decreased height and BMD Z-scores [12]. When doses > 0.2 mg/kg/day were administered, a notable impact on growth was noted.

The study by Clemens and Karsenty (2007) found that insulin regulates glucose levels by affecting osteoblasts and also uncovered that OC activation is triggered by bone resorption [16].

Karsenty and Ferron (2012) demonstrate in their study that organs often possess additional functions not typically anticipated, with the mouse genetic revolution serving as proof [17]. This recognition has led to a necessity to examine physiology on a holistic organismal level, instead of solely concentrating on molecular and cellular components.

Permatasari and colleagues (2017) demonstrated in their study that the decline in OC levels can be reversed following the alternating phase [13]. It demonstrates the importance of gradually reducing the dose timetable. Most of these patients did not exhibit clear clinical signs of bone pain or muscle spasms.

In the 10^{th} article, Panczyk-Tomaszewska et al. (2015) found that corticosteroid treatment for diseased children having NS can lead to decreased bone density. Serum BAP reveal a reliable trabecular bone turnover marker among these kids, who may require vitamin D supplementation in different doses, potentially exceeding 800 IU/24 h to avoid osteopenia [14].

In our article, statistically significant decreases in ionized and total Ca were observed with *p*-values of 0.01 and 0.001, respectively, whereas S-OC levels were significantly increased with a *p*-value of 0.03 in cases in comparison to the control group. A significant correlation was recorded between the steroid therapy period and the patient's weight, with a p-value of

less than 0.05. Both sets of patients who took vitamin D supplements for an extended duration saw a rise in their Body Mass Index. Research teams showed elevated OC levels in comparison to the control group, with individuals receiving high doses of steroids displaying the highest levels. In every patient, there was an inverse relationship between Ca levels and OC levels.

5. Conclusion

In conclusion, OC levels increase only depending on the GC dosage given, regardless of its particular form. This may have significant clinical implications and aid in decreasing bone-related side effects. OC utilization as a screening tool is not recommended in children on steroid therapy because the increase in S-OC level may be due to bone turnover or bone formation.

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References

1. Burgstein JM. Nephrotic syndrome. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders; 2008. p. 2340–2.
2. Mohamed GB, Abdel-Latif EA. Serum osteoprotegerin (OPG) in children with primary nephrotic syndrome. Saudi J Kidney Dis Transpl. 2011;22(5):955–62.
3. Kosan C, Ayar G, Orbak Z. Effects of steroid treatment on bone mineral metabolism in children with glucocorticoid-sensitive nephrotic syndrome. West Indian Med J. 2012;61(6):627–30.
4. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, et al. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007;130(3):456–69. doi:10.1016/j.cell.2007.05.047
5. Willems BA, Vermeer C, Reutelingsperger CP, Schurgers LJ. The realm of vitamin K dependent proteins: shifting from coagulation toward calcification. Mol Nutr Food Res. 2014;58(8):1620–35. doi:10.1002/mnfr.201300743
6. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. Int J Clin Pract. 2009;63(1):19–26. doi:10.1111/j.1742-1241.2008.01908.x
7. Harris SS, Soteriades E, Dawson-Hughes B. Secondary hyperparathyroidism and bone turnover in

elderly blacks and whites. J Clin Endocrinol Metab. 2001;86(8):3801–4. doi:10.1210/jcem.86.8.7741

8. Ghobrial EE, Abdel-Aziz H, El Sayed RH, Abdel-Aliem AM. Osteocalcin level in children with steroid dependent/frequently relapsing and steroid resistant nephrotic syndrome. Iran J Pediatr. 2017;27(6):e8095. doi:10.5812/ijp.8095
9. Hammad A, Yahia S, Gouida MS, Bakr A, El-Farahaty RM. Low expression of glucocorticoid receptors in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2013;28(5):759–63. doi:10.1007/s00467-012-2331-5
10. Moon RJ, Gilbert RD, Page A, Murphy L, Taylor P, Cooper C, et al. Children with nephrotic syndrome have greater bone area but similar volumetric bone mineral density to healthy controls. Bone. 2014;58:108–13. doi:10.1016/j.bone.2013.09.024
11. Phan V, Blydt-Hansen T, Feber J, Alos N, Arora S, Atkinson S, et al. Skeletal findings in the first 12 months following initiation of glucocorticoid therapy for pediatric nephrotic syndrome. Osteoporos Int. 2014;25(2):627–37. doi:10.1007/s00198-013-2466-7
12. Ribeiro D, Zawadynski S, Pittet LF, Chevalley T, Girardin E, Parvex P. Effect of glucocorticoids on growth and bone mineral density in children with nephrotic syndrome. Eur J Pediatr. 2015;174(7):911–7. doi:10.1007/s00431-015-2491-3
13. Permatasari FP, Asmaningsih N, Qibtiyah M, Yulistiani YU. Analysis of high dose and long-term prednisone therapy on osteocalcin levels in children with nephrotic syndrome. Asian J Pharm Clin Res. 2017;10(6):250–4.
14. Pańczyk-Tomaszewska M, Adamczuk D, Kisiel A, Skrzypczyk P, Przedlacki J, Górska E, et al. Markers of bone metabolism in children with nephrotic syndrome treated with corticosteroids. In: Pokorski M, editor. Body Metab Exerc. Adv Exp Med Biol. 2015;840:21–8. doi:10.1007/5584_2014_87
15. Shah SS, Akhtar N, Sunbleen F, ur Rehman MF, Ahmed T. Histopathological patterns in paediatric idiopathic steroid resistant nephrotic syndrome. J Ayub Med Coll Abbottabad. 2015;27(3):633–6.
16. Clemens TL, Karsenty G. The osteoblast: an insulin target cell controlling glucose homeostasis. J Bone Miner Res. 2011;26(4):677–80. doi:10.1002/jbmr.279
17. Karsenty G, Ferron M. The contribution of bone to whole-organism physiology. Nature. 2012;481(7381):314–20. doi:10.1038/nature10863