ISSN 0975-2366
DOI:https://doi.org/10.31838/ijpr/2020.12.04.347

**Research Article**

# The response of hypoalbuminemia, hypocalcemia and hypercholesterolemia to regular treatment in a group of pediatric patients with nephrotic syndrome

RAID DHIA HASHIM[1*], ISRAA NATHIR[2], NADIA MOHAMMED KHALIL[3]
[1]FICMS clinical chemistry, Al-Rasheed University College - Department of Dentistry
[2] MSc cinical pharmacy, Al-Rasheed University College - Department of Pharmacy
[3] DSc biochemistry, AlKarama Teaching Hospital - Laboratory Department
*Corresponding author
Email:vsdasd9@alrasheedcol.edu.iq
Received: 22.04.20, Revised: 14.05.20, Accepted: 02.06.20

## ABSTRACT

**Background:** Nephrotic syndrome represents a relatively common renal disorder in pediatric age group. It is commonly presented with a triad of edema, proteinuria and hypoalbuminemia. It has many histopathological types, with the minimal change disease being the most common type in children. This study aimed to evaluate the serum level of albumin, ionized calcium and cholesterol in patients already on treatment.

**methods**: 58 pediatric patients with nephrotic syndrome have been enrolled in the current study. All participants were investigated for serum albumin, ionized calcium and cholesterol, in addition to the basic laboratory tests. The results were statistically compared to the reference range using GraphPad prism software. Statistical correlation between the studied parameters has been evaluated as well.

**Results**: Mean serum albumin was significantly low (22.4 g/L ± 9.4), with 89% of participants had hypoalbuminemia. Mean serum cholesterol was significantly high (8.4 mmol/L ± 2.99), with 87% of participants had hypercholesterolemia, which has shown a strong negative correlation with serum albumin. Ionized calcium was normal in 97% of participants, where its mean was 1.13 mmol/L ± 0.2.

**Conclusion**: Correction of hypoalbuminemia and hypercholesterolemia seems to be much more difficult in pediatric patients with nephrotic syndrome compared to hypocalcemia.

**Keywords**: nephrotic syndrome, hypercholesterolemia, hypocalcemia, hypoalbuminemia, pediatric

## INTRODUCTION

Nephrotic syndrome is considered as one of the most common renal diseases in pediatric age group all over the world that is characterized by an extensive loss of plasma proteins in urin (Shatat et al., 2019) mainly due to disrupted glomerular filtration barrier which might be primary with no apparent cause (idiopathic) or secondary to various causes including drugs, toxins, infections, and diabetes mellitus (Bierzynska and Saleem, 2017).The estimated incidence of nephrotic syndrome in children is 2-7/100000, with a total prevalence of 16/100000. However, a wide range of variation has been revealed by researchers based on racial and environmental factors (Andolino and Reid-Adam, 2015). Minimal change nephrotic syndrome represents the major histopathological type in children (70% to 90%), where renal biopsy seems to be normal during a light microscopical examination. In contrast, membranous glomerulonephritis represents the primary type in adults (Vivarelli et al., 2017). It is relatively more common in males than females in the younger age group, but this gender difference disappears in adolescence (Alhassan et al., 2013).Nephrotic syndrome is conventionally classified into two major groups according to the patient's response to treatment, which are the steroid-sensitive type and the steroid-resistant type where a significant histopathological difference is present between these two groups (Nourbakhsh and Mak, 2017). Facial puffiness, especially in the morning, is the classical earliest presenting feature of nephrotic syndrome, which is usually followed by generalized edema. Other clinical features include recurrent infections, including peritonitis, hypertension, hypovolemia and thromboembolic attacks (Bitzan, 2014). Diagnosis depends mainly on the presence of proteinuria above the nephrotic range (3.5 g/24 hours) in addition to the other laboratory findings, including hypoalbuminemia, hypocalcemia and hypercholesterolemia. However, the measurement of protein creatinine ratio in a random urine sample is more convenient and sufficient for

making the diagnosis (Crew et al., 2004). Surprisingly, despite the inevitable increase in serum levels of cholesterol in patients with nephrotic syndrome, clear guidelines for treatment for this condition are absent. Furthermore, data about the consequences of persistent hypercholesterolemia in pediatric patients with nephrotic syndrome are very deficient, making this condition generally under-treated (Muso et al., 2015). What makes the situation worse is that HDL-cholesterol to total cholesterol ratio is persistently low in addition to the abnormalities in the structure of HDL-cholesterol, leading to impairment in its beneficial actions (Vaziri, 2016). Hypocalcemia is a well-known associated finding in patients with nephrotic syndrome, possibly due to the low level of all vitamin D metabolites secondary to urinary loss of their binding protein, which will, in turn, lead to impaired absorption of calcium in the small intestine (Esmaeeili et al.,2015). Unfortunately, vitamin supplements might have no significant impact on mineral density or mineral content of the bone even when serum vitamin D level is normalized (Banerjee et al., 2017). These metabolic disturbances were followed by many researchers for their possible use as indicators of response to treatment.

### Aim of the study

To estimate serum level of albumin, calcium and cholesterol in a group of pediatric patients with nephrotic syndrome as indicators of response to treatment.

## MATERIALS AND METHODS

The current study was performed at the pediatric nephrology department in an official hospital in Baghdad from January to March 2019. It involved estimating the serum levels of cholesterol, calcium and albumin for patients attending the mentioned department. A total number of 58 patients were enrolled in the current study, already diagnosed with nephrotic syndrome, receiving their different modalities of treatment, and attending the nephrology department for following up.

Exclusion criteria:

- Newly diagnosed patients.
- Patients poorly complied with treatment.
- Co-existence of other disorders that might interfere with the laboratory findings including:

-Diabetes mellitus
-established chronic kidney disease.

Accordingly, all participant in the current study were investigated for:

-serum cholesterol (non-fasting)
-serum albumin
- serum total calcium
-serum ionized calcium
-serum creatinine
-blood urea
-random blood glucose

Depending on the results of the above tests, the history of the patients and information collected from the physicians, the exclusion criteria were applied.

These laboratory tests were measured using Roche Cobas C311, daily quality control program was applied before considering the results as dependable. For serum ionized calcium, Roche 9180 electrolyte analyzer was used.

The obtained data were analyzed using GraphPad prism software version 8.

## Results

Fifty-eight patients were enrolled in the current study with a mean age of 6.4 years, 32 were males, and the remaining 26 were females; their results regarding the major investigated parameters were shown in table 1.

The results of the current study have shown that 50 patients of the total 58 investigated patients (87 %) had hypercholesterolemia of variable severity. Likewise, the results have shown that 51 patients of the total 58 (89%) had hypoalbuminemia of variable severity, mostly of a severe form.

In respect to serum calcium estimation, most patients had a variable degree of hypocalcemia when directly measuring the total serum calcium. Still, with the measurement of ionized calcium, which excludes the effect of low albumin, only two patients (3%) remained to have hypocalcemia.

When collectively taking the whole parameters, there were only four patients (7%) with no disturbance of any of the three parameters. At the same time, the results have shown that only two patients (3%) had hypoalbuminemia alone, while there was no patient with isolated hypocalcemia nor hypercholesterolemia. The main combination of abnormalities was between hypercholesterolemia and hypoalbuminemia as 49 patients (85%) had both of these abnormalities at the same time. As the analyzed data were not normally distributed, Spearman's rank-order correlation was applied to assess the correlation among the studied parameters and the most significant correlation has been detected between serum cholesterol and serum albumin concentration where a significant negative correlation has been observed between the two variables ($r_s$= - 0.731, P = 0.001).

**Table 1: Baseline characteristics of the patients**

| Variable | Mean | SD | Reference range |
|---|---|---|---|
| Albumin g/L | 22.5 | 9.4 | 35-55 |
| Total cholesterol mmo/L | 8.4 | 2.99 | 3.5- 5 |
| Ionized calcium mmol/L | 1.13 | 0.2 | 1.1-1.3 |
| Random blood glucose mmol/L | 10.9 | 2.2 | 7.8-11.1 |
| Blood urea mmol/L | 3.2 | 0.5 | 2.5-6 |
| Serum creatinine $\mu$mol/L | 68 | 18 | 60-110 |
| ALT IU/L | 28 | 7 | <40 |

## Discussion

Nephrotic syndrome is a chronic medical condition most prevalent in the pediatric age group. It is associated with various metabolic abnormalities, the most important of which include hypocalcemia, hypoalbuminemia and hypercholesterolemia.

Many medical studies have focused on these abnormalities to estimate the severity, extent and ability of medical therapy to correct these abnormalities.

In respect to serum cholesterol, it is obvious that hypercholesterolemia represents an extremely prevalent problem. Nearly 87% of the participating patient suffered from this condition, a significant number of whom was discovered to have a severe form of hypercholesterolemia with mean serum cholesterol of 8.4 mmol/L despite statin therapy. The difficulty in controlling hypercholesterolemia in patients with nephrotic syndrome reflected by high serum cholesterol concentration has been observed by Dnyanesh DK and his colleagues where the mean was 10.91mmol/L (SD 5.1) (Dnyanesh et al., 2014) which is nearly an identical mean serum cholesterol level observed by Jyotish Chandra Pandey and Chandra Kishore Prasad (10.59 mmol/L, SD 3.1) (Pandey and Prasad, 2016). In addition to the severe hypercholesterolemia shown as mean serum cholesterol of 11.29 mmol/L (SD 3.5), nephrotic syndrome has associated with a significant increase in serum concentration of apoB (Biswas et al., 2017) which is the main factor contributing to the development of hypercholesterolemia in nephrotic syndrome in addition to the impaired removal of lipoproteins from the circulation (Agrawal et al., 2018). Despite the use of statins by all patients who participated in the current study, the mean cholesterol level remained significantly high, despite that the initial cholesterol level was not obtained for those patients. This finding reflects the difficulty in treating this condition.

Regarding serum ionized calcium, it was expected to find a significant degree of hypocalcemia in patients with nephrotic syndrome. Total serum calcium was significantly low in patients who participated in the current study (mean 1.9 mmol/L), with around 83% of the participant suffered from hypocalcemia. Despite this disappointing finding, when serum ionized calcium was measured, most patients have shown normal serum calcium (97%of the participants), and the mean was greatly improved to be within the reference range (1.13 mmol/L). This finding reflects the ability of calcium and vitamin D supplements already received by the participants in addition to the specific therapy of nephrotic syndrome to correct the problem of hypocalcemia. A similar finding was observed by Azizul Hossain and his colleagues, where serum concentration of ionized calcium was identical to that of the current study (1.13 mmol/L) ( Hossain et al., 2015). Mahmoud M.E. El Kersh et al. have also detected a normal mean serum ionized calcium pediatric patients with nephrotic syndrome (1.07 mmol/L), although it was significantly lower than the control group (El Kersh et al.,2018). Such an interesting finding has been observed by Vaya Dasitania and her colleagues where hypocalcemia was corrected in two groups of pediatric patients eight weeks after initiating specific treatment of nephrotic syndrome in those who had received calcium and vitamin D supplements and those who had not with no significant difference in mean serum calcium between the two groups (Dasitania et al., 2104). Patients with nephrotic syndrome, during the remission phase, have shown no significant difference in mean serum ionized calcium

concentration compared to the control group in contrast to those who were in the relapse phase where ionized calcium was significantly lower as observed by Poonam Mehta and Sanjiv Nanda's study (Mehta and Nanda, 2016) . These findings collected from various studies, in addition to many others, indicate the great improvement in serum ionized calcium after ensuing treatment despite the initial hypocalcemia at the time of diagnosis or during the relapse phase. The main laboratory finding in patients with nephrotic syndrome is the hypoalbuminemia due to severe loss of albumin in the urine. So, hypoalbuminemia is directly related to the severity of albuminuria and regarded as an essential sign of response to treatment. Response to treatment, indicated by both clinical and laboratory improvement, varies significantly according to the histopathological type of nephrotic syndrome (Arif et al., 2016). The current study has not classified patients according to their specific type of nephrotic syndrome, in contrast, we have collectively assessed serum albumin level of the participants regardless of their specific type of nephrotic syndrome, and the result was surprising as 89% of the participants appeared to have hypoalbuminemia, and the mean serum albumin was 22.5 g/L (SD 9.4). Similar studies have shown a variable severity of hypoalbuminemia. C. Krishanamurthy et al. have detected a mean serum albumin concentration of 22.1 g/dl in patients with different types of nephrotic syndrome (Krishanamurthy et al., 2018). In comparison, it was only 18 g/dl in another study (Pandey and Prasad, 2016). In addition, 86% of the fifty patients with nephrotic syndrome were discovered to have hypoalbuminemia, as shown by P. Anil Kiran (Kiran and Kumar, 2017). These results and many others reflect the relative difficulty in controlling hypoalbuminemia in patients with nephrotic syndrome.

The severity and prevalence of both hypoalbuminemia and hypercholesterolemia represent a great challenge during the course of treatment of patients with nephrotic syndrome. In fact, hypercholesterolemia was negatively correlated to hypoalbuminemia in the current study and many other similar studies, as confirmed by Sadhana Kumari where serum cholesterol level was positively correlated with severity proteinuria (Kumari and Kumar,2018), while other studies have detected a strong negative correlation between serum cholesterol and serum albumin concentrations (Hossain et al., 2015, Reddy et al.,2017, Som and Roy,2018). .

## CONCLUSION

1. Both hypoalbuminemia and hypercholesterolemia are difficult to be controlled in pediatric patients with nephrotic syndrome which necessitate more attention by the physicians.
2. There is a strong negative correlation between hypoalbuminemia and hypercholesterolemia.

## REFERENCES


1. Agrawal, S., Zaritsky, J. J., Fornoni, A., & Smoyer, W. E. (2018). Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. Nature Reviews Nephrology, 14(1), 57.
2. Alhassan, A., Mohamed, W. Z., & Alhaymed, M. (2013). Patterns of childhood nephrotic syndrome in Aljouf region, Saudi Arabia. Saudi Journal of Kidney Diseases and Transplantation, 24(5), 1050.
3. Andolino, T. P., & Reid-Adam, J. (2015). Nephrotic syndrome. Pediatrics in review, 36(3), 117.
4. Arif, M. K., Arif, M., & Amjad, N. (2016). A histopathological outlook on nephrotic syndrome: A pediatric perspective. Indian journal of nephrology, 26(3), 188.
5. Banerjee, S., Basu, S., Sen, A., & Sengupta, J. (2017). The effect of vitamin D and calcium supplementation in pediatric steroid-sensitive nephrotic syndrome. Pediatric Nephrology, 32(11), 2063-2070.
6. Bierzynska, A., & Saleem, M. (2017). Recent advances in understanding and treating nephrotic syndrome. F1000Research, 6.121.
7. Biswas, A., Basu, R., & Basu, K. (2017). Nephrotic Syndrome Induced Dyslipidemia in Children and Need for Early Assessment. Journal of Medical and Dental Science Research, 3(12), 35-38.
8. Bitzan, M. (2014). Glomerular diseases. In Manual of Pediatric Nephrology,141-229.
9. Crew, R. J., Radhakrishnan, J., & Appel, G. (2004). Complications of the nephrotic syndrome and their treatment. Clinical nephrology, 62(4), 245-259.
10. Dasitania, V., Chairulfatah, A., & Rachmadi, D. (2014). Effect of calcium and vitamin D supplementation on serum calcium level in children with idiopathic nephrotic syndrome. Paediatrica Indonesiana, 54(3), 162-7.
11. Dnyanesh, D. K., Dnyanesh, S., & Shenoy, V. (2014). A study of serum lipids in nephrotic syndrome in children. IOSR-JDMS, 13(3), 01-06.
12. El Kersh, M. M., Sharaki, O. A., Omar, O. M., & Galal, Y. A. (2018). Ionized calcium, 25-hydroxyvitamin D, and parathyroid hormone in children with steroid-sensitive nephrotic syndrome. Alexandria Journal of Pediatrics, 31(3), 132.
13. Esmaeeili, M., Azarfar, A., & Hoseinalizadeh, S.

(2015). Calcium and vitamin D metabolism in pediatric nephrotic syndrome; an update on the existing literature. International Journal of Pediatrics, 3(2.1), 103-109.
14. Hossain, A., Mostafa, G., Mannan, K. A., Prosad Deb, K., & Hossain, M. M. (2015). Correlation Between Serum Albumin Level and Ionized Calcium in Idiopathic Nephrotic Syndrome in Children. Urol Nephrol Open Access J, 3, 70-71.
15. Kiran, P. A., & Kumar, B. D. (2017). Clinic-biochemical evaluation of nephrotic syndrome in children. Int J Contemp Med Res, 4, 2214-7.
16. Krishanamurthy, C., Rukmani, J., & Clarin, D. (2018). Evaluation of serum lipid profile in children with nephrotic syndrome admitted in emergency ward of Government Tirunelveli Medical College and Hospital, India. International Journal of Contemporary Pediatrics, 5(6), 2244.
17. Kumari, S., Kumar, R. (2018). Assessment of lipid profile and serum proteins in children with nephrotic syndrome. International Journal of Medical and Health Research, 4(12)190-192.
18. Mehta, P., & Nanda, S. (2016). Comparison of calcium metabolism in different subgroups of nephrotic syndrome in children. Indian Journal of Child Health, 216-219.
19. Muso, E., Mune, M., Hirano, T., Hattori, M., Kimura, K., Watanabe, T., ... & Shoji, T. (2015). A prospective observational survey on the long-term effect of LDL apheresis on drug-resistant nephrotic syndrome. Nephron Extra, 5(2), 58-66.
20. Nourbakhsh, N., & Mak, R. H. (2017). Steroid-resistant nephrotic syndrome: past and current perspectives. Pediatric Health, Medicine and Therapeutics, 8, 29.
21. Pandey, JC., Prasad, CK. (2016). Lipid profile abnormalities in nephrotic syndrome. Asian Journal of Biomedical and Pharmaceutical Sciences, 6(54), 17-19.
22. Reddy, B., Reddy, V., & Soren, C. (2017). Serum cholesterol levels in relation to the serum albumin in first episode of idiopathic nephrotic syndrome of childhood. IOSR Journal of Dental and Medical Sciences, 16(2), 22-25
23. Shatat, I. F., Becton, L. J., & Woroniecki, R. P. (2019). Hypertension in Childhood Nephrotic Syndrome. Frontiers in pediatrics, 7:287.
24. Som, S., & Roy, A. (2018). Correlation between Serum Cholesterol and Serum Albumin Levels in Idiopathic Nephrotic Syndrome in Children. Annals of International Medical and Dental Research, 4(4), 1.
25. Vaziri, N. D. (2016). HDL abnormalities in nephrotic syndrome and chronic kidney disease. Nature Reviews Nephrology, 12(1), 37.
26. Vivarelli, M., Massella, L., Ruggiero, B., & Emma, F. (2017). Minimal change disease. Clinical Journal of the American Society of Nephrology, 12(2), 332-345.