

## DISEASE-ASSOCIATED SYSTEMIC COMPLICATIONS IN CHILDHOOD NEPHROTIC SYNDROME: A SYSTEMATIC REVIEW

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### Abstract

**Background:** Nephrotic syndrome (NS) is characterized by massive proteinuria (more than 40 mg/m<sup>2</sup> per hour) which causes hypoalbuminemia (less than 30 g/L), hyperlipidemia, edema, and various other complications. This is caused by increased permeability due to damage to the basement membrane of the glomerulus of the kidney.

**The aim:** This study aims to show about Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 74 articles, whereas the results of our search on SagePub brought up 351 articles. The results of the search conducted for the last year of 2013 yielded a total 71 articles for PubMed and 202 articles for SagePub. The result from title screening, a total 22 articles for PubMed and 38 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

**Conclusion:** Nephrotic syndrome is one of the most common kidney diseases in children. Patients with nephrotic syndrome experience protein loss that has a negative impact on various biological functions and can result in disease-related complications.

**Keyword:** Nephrotic syndrome, Children, systemic complication

## INTRODUCTION

Kidney disease in children causes high levels of morbidity and mortality.<sup>1</sup> Globally, there is an increase in the prevalence of chronic kidney disease (CKD) with an incidence rate of 8% every year. Kidney disease in children in various regions is influenced by genetic, racial and environmental differences. Acute kidney injury (AKI) and nephrotic syndrome are the most commonly reported childhood kidney diseases in Africa. In contrast, the prevalence of chronic kidney disease and congenital abnormalities of the kidneys and urinary tract is still low due to the unavailability of screening or antenatal ultrasound examinations, resulting in an underestimate.<sup>2</sup>

Nephrotic syndrome (NS) is a major glomerular disease in children that occurs in 16 per 100,000 children. The initial features of the various subtypes of NS are similar and include the presence of proteinuria, edema, hypoalbuminemia, and hypercholesterolemia. Despite their initial similarities, NS subtypes have different disease courses and outcomes. Invasive biopsy remains the only method for positive diagnosis and the 2 most frequent histopathological findings are focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD). The prognosis of this disease depends on the underlying pathophysiology and response to steroid treatment. Approximately 95% of children with MCD achieve remission after 8 weeks of prednisone administration (steroid sensitive nephrotic syndrome [SSNS]) compared with 80% of patients with FSGS who fail to achieve remission in response to steroids (steroid resistant nephrotic syndrome) [SRNS]. Focal segmental glomerulosclerosis is a common cause of end-stage kidney disease in children and causes further complications of around 30% of post-transplant recurrences.<sup>3,4</sup>

Nephrotic syndrome (NS) is a relatively common chronic kidney disease in children, with an annual incidence of 2 to 7 per 100,000 children. An epidemiological study of pediatric NS (JP-SHINE study) found an incidence of 6.49 per 100,000, which is 3 to 4 times that reported in Caucasians. The male-to-female ratio was 1.9%, and 32.7% of patients had frequent relapses during the 1 to 4 year observation period. NS is classified into idiopathic (INS), secondary, and congenital, depending on the cause and timing of the proteinuria. INS accounts for 90% of NS in children. Furthermore, because more than 80% of INS in children are minimal change NS (MCNS), more than 70% of NS in childhood are MCNS. This epidemiology is very different from the epidemiology in adults.<sup>5,6</sup>

Focal segmental glomerulosclerosis (FSGS) is the second most common disease in pediatric INS after MCNS. However, the differences between MCNS and FSGS have been debated for years, but no conclusions have been reached. It is still unclear whether the two differ due to different etiology or stage/severity (early/mild for MCNS and advanced/severe for FSGS). So far, the etiology of MCNS and FSGS cannot be concluded.<sup>5,7</sup>

The four symptoms of specific nephrotic syndrome are severe proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Patients with nephrotic syndrome may have nephritic features, such as hypertension, hematuria, and decreased renal function. Likewise, patients with nephritic disease may have nephrotic features. Nephrotic syndrome patients may experience general physical changes and injury to the glomerular filtration barrier resulting in massive leakage of serum proteins into the urine causing proteinuria.<sup>8,9</sup>

Loss of protein negatively affects various biological functions and can lead to complications. Complications of nephrotic syndrome in childhood fall into two categories: disease-related complications and drug-related complications. Drug-related complications include sensitivity to steroids, which are used to treat NS. Steroid treatment is associated with severe side effects, such as growth retardation, hypertension, osteoporosis, and bone fractures, and is associated with psychological stress. The duration of treatment also affects the psychosocial and developmental phases in the form of internal problems, somatic complaints, and anxiety/depression which can reduce the quality of life.<sup>8,10</sup>

Complications of nephrotic syndrome were defined based on the magnitude of proteinuria, hypoalbuminemia or both, and their frequency and severity increased as proteinuria was higher than 8 g/day serum or as albumin decreased below 2 g/dL. Although proteinuria is an early event, the relationship between serum albumin levels and proteinuria is not constant, because some patients do not experience hypoalbuminemia despite the presence of massive proteinuria. Thus, the exact mechanism of hypoalbuminemia is still being explored and discussed. Hepatic synthesis does not appear to be defeated by albuminuria, in the absence of inflammation. Since inflammation is common in nephrotic syndrome, this may be a possible explanation. Other possible explanations are high catabolic levels of filtered albumin, reabsorption by the proximal tubule, gastrointestinal losses or capillary hyperpermeability but none of these have been proven so far. Nephrotic patients may have low levels of ion-binding proteins (iron, copper, zinc), vitamins (vitamin D), and hormones (steroid or thyroid hormones). In addition, lipoproteins, coagulation factors, or other drugs (such as coumarin anticoagulants or diuretics) are lost in the urine with different clinical consequences. The liver is stimulated to compensate for the loss and the synthesis of all types of non-selective proteins is increased, also with clinical consequences.<sup>11</sup>

## METHODS

### Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome. It is possible to accomplish this by researching or investigating the Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome. As the primary purpose of this piece of writing, demonstrating the relevance of the program that have been identified will take place throughout its entirety.

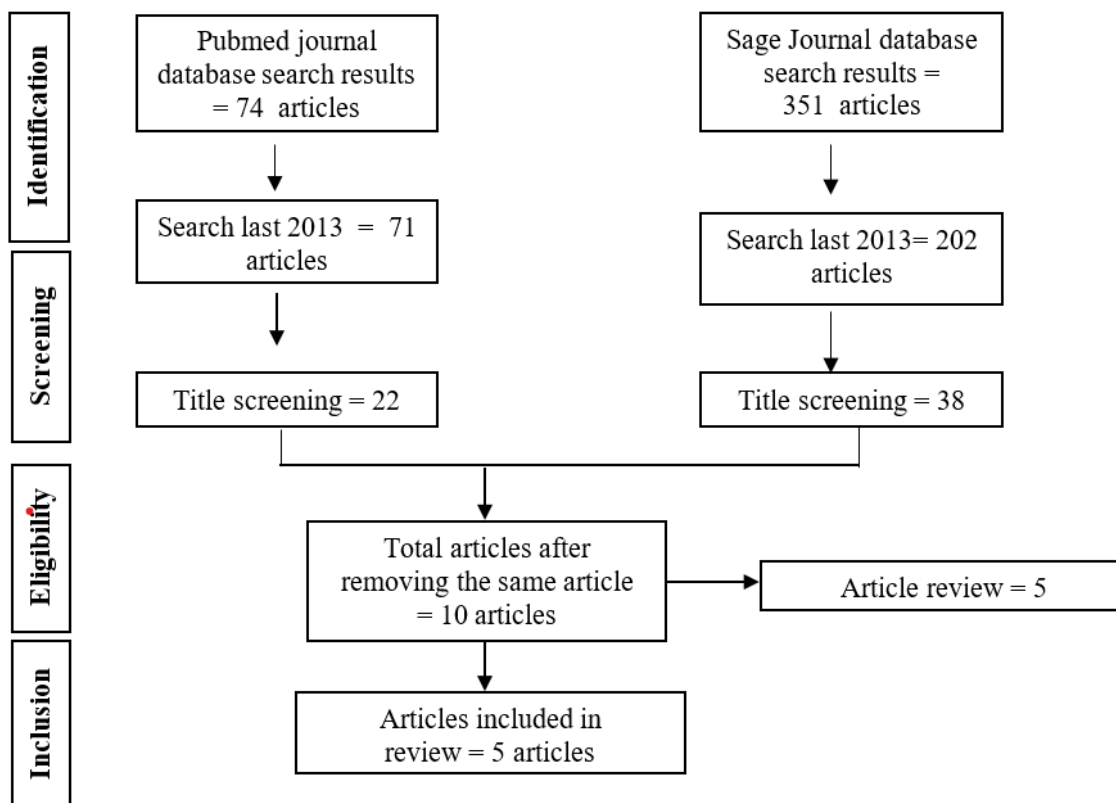
In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine the efficacy of dengue vaccine. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

**Search Strategy**

We used "Dengue vaccine efficacy"; "Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"Nephrotic Syndrome"[MeSH Subheading] OR "Nephrotic"[All Fields] OR "Nephrotic syndrome in children"[All Fields]*) AND (*"Childhood nephrotic syndrome"[All Fields] OR "complications of nephrotic syndrome"[All Fields]*) AND (*"complications in childhood nephrotic syndrome"[MeSH Terms] OR "nephrotic syndrome complications"[All Fields]*) OR (*"systemic disease in childhood nephrotic syndrome"[All Fields]*) AND (*"childhood nephrotic syndrome complications"[All Fields]*) OR (*"childhood nephrotic syndrome systemic disease"[All Fields]*) used in searching the literature.

**Data Retrieval**

After reading the abstracts and titles of each study, the authors conducted an examination to determine whether the study met the inclusion criteria or not. The author then selects and chooses previous research that will be used as a source for the articles to be made. After looking at a number of different studies, all of which seemed to show the same trend, the following conclusions were drawn. All submissions must be written in English and cannot be viewed anywhere else.



**Figure 1. Article search flowchart**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting

papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 74 articles, whereas the results of our search on SagePub brought up 351 articles. The results of the search conducted for the last year of 2013 yielded a total 71 articles for PubMed and 202 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria. Charambira *et al* (2023)<sup>2</sup> showed that the 2264 children admitted during the study period, 50 had kidney disorders giving an incidence of 2.2% (22 per 1000 admitted children). Majority were male (n = 30, 60.0%). Age ranged from 2 weeks to 13 years (mean 5.5 ± 3.5 years) with 58.0% being under 5 years. Overall, 123 children admitted in the paediatric unit died during the study period with 16 (13.0%) of these having kidney disease (case fatality rate of 32% (16/50). Of the 16 children with kidney who died 8 had ESKD, 5 had AKI, 2 with nephrotic syndrome and normal kidney function and 1 with Fanconi syndrome. The commonest diagnoses in the 50 children with kidney diseases in the unit were AKI (n = 16, 32%) nephrotic syndrome (n = 16, 32%), hypertension (n = 12, 24%) and ESKD (n = 11, 22%). Hypertension was diagnosed in 1 child with neuroblastoma, 3 with nephrotic syndrome, 3 with ESKD and 5 with glomerulonephritis. Of the 5 cases of glomerulonephritis 2 had rapidly progressive disease. One 7-year-old boy had pyelonephritis with posterior urethral valves and ESKD while a 12 years old girl who presented with seizures, bi-cytopenia, skin rash and severe joint pains that had rendered her bed ridden for 2 months, had systemic lupus erythematosus (SLE) that was managed successfully with steroids and cycles of cyclophosphamide.

Bennet *et al* (2016)<sup>12</sup> showed Fifty pediatric patients were enrolled over a 2-year period. Out of the 50 subjects, 20 presented with SRNS and 16 with FSGS on biopsy. Seventeen subjects had active disease and 3 were in remission. Thirty patients demonstrated response to corticosteroid therapy and were labeled SSNS at the time of sample collection, 14 SSNS patients had active proteinuria, and 16 presented without protein in their urine. Seventeen SRNS patients and the active SSNS patients had high-grade proteinuria as diagnosed by urine dipstick at the time of collection. The high-grade test result indicates protein levels greater than 2000 mg/dL. Steroid-resistant nephrotic syndrome patients differed from SSNS in age (12.3 vs 7.5 years, P < .001), ±hypertension (75% vs 30%, respectively, P = .003), pathologic diagnosis (FSGS vs no biopsy, P < .001), and current steroid therapy (SRNS 45% vs SSNS 87%, P = .001).

**Table 1. The literature include in this study**

Author	Origin	Method	Sample Size	Result
Charambira <i>et al.</i> , 2023 <sup>2</sup>	Zimbabwe	Retrospective observational study	2264 children	Kidney disease accounted for 2.2% (n = 50) of all 2264 admissions in the paediatric unit, with males constituting 60% (n = 30). Age ranged from 2 weeks to 13 years (mean 5.5 ± 3.5 years) with 58.0% being under 5 years. The commonest diagnoses in the unit were acute kidney injury (AKI) (n = 16, 32%) nephrotic syndrome (n = 16, 32%), hypertension (n = 12, 24%) and end stage kidney disease (ESKD) (n = 11, 22%) with some children presenting with more than 1 diagnosis. Only 3 out of 11 children with ESKD and 3 out of 8 children with AKI who required dialysis could be offered dialysis due to limited resources. Overall mortality rate was 32% (16/50): 5 children with AKI, 2 with nephrotic syndrome and normal kidney function, 8 with ESKD and 1 with Fanconi syndrome.
Bennett <i>et al.</i> , 2016 <sup>12</sup>	United State of America (USA)	Cross-sectional study	57 respondents	Concentrations of uVDBP were significantly higher (P < 0.001) in patients with SRNS (13,659 ng/mL, interquartile range [IQR] 477–22,979) than in patients with SSNS (94 ng/mL, IQR 53–202) and normal controls (23 ng/mL, IQR 22–99, P = 0.002). Significance did not change when the results were corrected for urine creatinine. uVDBP was significantly negatively correlated with estimated glomerular filtration rate (eGFR; R = -0.76, P = 0.03). However, uVDBP was still markedly elevated in patients with SRNS with eGFR >100 mL/minute/1.73 m <sup>2</sup> . There was a positive correlation between microalbuminuria (MALB/Cr) and uVDBP (R = 0.67, P < 0.001). However, uVDBP displayed a much higher discriminatory ability for distinguishing SRNS than MALB/Cr (area under the curve = 0.92 vs 0.67, respectively). An uVDBP cutoff of 362 ng/mL yielded the optimal sensitivity (80%) and specificity (83%) to distinguish SRNS from SSNS.
Ali <i>et al.</i> , 2021 <sup>13</sup>	Iraq	Case control study	80 participants	Statistical analysis of student's t-test showed that the mean levels of TotalCholesterol, Triglycerides, LDL were significantly increased in Group 1 when compared to Group 2 (p <0.001). PON1 and Lecithin Cholesterol acyltransferase levels were significantly lower in Group

				1 compared to Group 2, and there is no significant difference among nephrotic groups.
<b>Ghannam et al., 2019<sup>14</sup></b>	Egypt	Case control	40 respondents	Our study showed very high significant increase in P-C, both in activity and concentration in relapse but in remission its level decreased towards the normal level but still slightly increased and this increase is statistically nonsignificant. As regard serum albumin and serum total protein, the both were very highly significantly increased in relapse and remission as compared to the control. As regard PT and PTT were found to be highly significant decreased in relapse as compared to the control group.
<b>Alfakkeh et al., 2019<sup>15</sup></b>	Saudi Arabia	Cross sectional study	111 patients	: Out of 111 patients admitted with PCNS, 84 (76%) had both minor and major types of infection. Upper respiratory tract infection (URTI) was the most predominant type (n = 44, 52%). Among the major types of infection, urinary tract infection (UTI) was the most common infection (n = 21, 25%) followed by pneumonia (n = 17, 20%) then cellulitis (n = 6, 6%). Infection in children who received a higher annual cumulative dose of steroids (CDS) strikingly had a higher rate of infection in comparison to those who received lower CDS (p < 0.01). Moreover, those who received primary and secondary immunosuppressant's had 100% infection rate.

Ali et al (2021)<sup>13</sup> showed that the mean levels of S. Albumin significantly lowered in N.S. patients compared to control (1.330.12 vs. 4.120.06) respectively at p <0.001 whereas S.Ch, TG,LDL, were significantly increased in Group1 (Patients) when compared to Group 2(control)at (p <0.001). The levels of PON1enzyme activity and LCAT activity levels are significantly lower in Group 1 compared to Group 2 (p<0.001).

Ghannam et al (2019)<sup>14</sup> showed the hemoglobin in gm/dL was found to be decreased in cases of relapse & remission compared to the control & the mean value of Hb in remission was increased than that seen in relapse. RBCs count/cmm was found to be significantly decreased in case of patients in relapse in contrast to non-significant decreased in case of remission. The MCV was found to be very highly significant decreased in cases of relapse & highly significantly decreased in cases of remission. MCH was found to be significantly decreased in cases of relapse & remission while MCHC was found to be very highly significant decreased in cases of remission. Regarding serum Triglyceride (gm/dL) & serum Cholesterol (gm/dL), the both were very highly significant increase (P<0,001) in relaps and remission as compared to the control.

Alfakkeh et al (2019)<sup>15</sup> showed that the main clinical symptoms were edema (n = 101, 91%), followed by ascites (n = 29, 26%). Of the 31 nephrotic patients who underwent renal biopsy, minimal change disease was the predominant histopathological finding 16 (55%), followed by focal segmental glomerulosclerosis in 10 (35%) patients. All patients were treated with corticosteroids, in which 95 (86%) were steroid sensitive. Over 10 years, only two patients were admitted to paediatric Intensive Care Unit with complicated pneumonia. The patient who died with pneumonia was diagnosed with nephrotic syndrome since 2 years and was resistant to immunosuppressants including rituximab. During that period, 84 (76.4%) had both minor and major types of infection. The overall incidence of infection among genders was equal, boys = 59 (76%) and girls = 25 (76%). Children < 10 years of age had a slightly higher rate of infection (76%) compared to those who are older (71%). Other major determinants of the infections is those who received primary and secondary immunosuppressants.

**DISCUSSION**

Nephrotic syndrome (NS) is characterized by massive proteinuria associated with hypoalbuminemia, which can result in hyperlipidemia, edema, and various complications. This is caused by increased permeability through damage to the basement membrane in the renal glomerulus, especially due to infection or thromboembolism. This disease is triggered by glomerular permeability abnormalities caused primarily by intrinsic kidney disease in the kidney or secondary to congenital infections, diabetes, systemic lupus erythematosus, neoplasia, or the use of certain drugs. Nephrotic range proteinuria is defined as the loss of 3 grams or more of protein in the urine in 24 hours or in one urine sample there is 2 g of protein per gram of urine creatinine. Proteinuria can also be caused by other systemic diseases, such as amyloidosis.<sup>9</sup> The main cause of nephrotic syndrome is intrinsic kidney disease, such as membranous nephropathy, focal glomerulosclerosis, and minimal change nephropathy. Secondary causes may include systemic diseases, such as lupus erythematosus, diabetes mellitus, and amyloidosis. Congenital/hereditary focal glomerulosclerosis can result from genetic mutations in podocyte proteins, such as podocin, nephrin, or cation channel protein 6. An episode of infectious disease, particularly the upper respiratory tract, is the trigger in nearly half of cases, an allergic reaction in one third, and less commonly, insect bites or vaccinations. Nephrotic syndrome can also be caused by drug abuse, including heroin abuse.<sup>9</sup> Nephrotic syndrome is caused due to severe changes in the glomerular filtration barrier, so that large amounts of protein, mostly albumin, can be excreted freely in the urine. Various glomerular lesions are associated with nephrotic syndrome. Their types vary by age, gender and ethnicity. Given the high prevalence of diabetes mellitus, diabetic nephropathy is the



most common, followed by minimal change disease in children, focal and segmental glomerulosclerosis in adults of African descent, and membranous glomerulopathy in Caucasian adults. In young women, systemic lupus erythematosus should be suspected and, in patients over 65 years of age, solid cancer, lymphoma, or clonal B-cell proliferation is increasingly seen. Because many of these conditions can benefit from the use of specific therapy, a histopathological diagnosis is warranted. Currently, genetic abnormalities in several components of the glomerular filtration barrier have been identified. Although nephrotic syndrome is a rare condition, with an incidence of 2-7 cases/100,000 children per year and three new cases/100,000 adults per year, in many cases it requires special therapy; also, complications are common and must be recognized and treated properly.<sup>11</sup>

Cardiovascular complications in nephrotic syndrome include increased risk of atherosclerosis and thromboembolism, due to dysregulation of lipid metabolism and dyslipidemia. Thromboembolism is one of the most serious complications in patients with nephrotic syndrome. In addition, complications of atherosclerosis are a major cause of death and increase the need for dialysis and the risk of kidney transplantation. A study using blood samples from pediatric patients with nephrotic syndrome found lipid profile abnormalities. Total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and ET1 were significantly higher in the NS group than in the control group, while high-density lipoprotein (HDL) cholesterol, albumin, PON1, and lecithin:cholesterol acyltransferase activity were significantly different. PON1 and lecithin:cholesterol acyltransferase activity decreased significantly resulting in increased LDL oxidation, causing accelerated atherosclerosis.<sup>8</sup>

NS infection in childhood carries a high risk of complications, including infection. The pathogenesis of increased infection frequency is related to damage to cellular immunity, loss of immunoglobulins in the urine, factor B bands, and complement factors. Thyroid Hormone Complications Metabolic disorders, such as coagulation disorders, immune deficiency due to immunoglobulin and complement loss, and anemia due to deficiency of erythropoietin and transferrin, are associated with low molecular weight proteins, including some binding proteins, that are excreted in patients with NS. Thyroid hormone and binding globulin are also excreted excessively in the urine, and NS patients may exhibit hypothyroidism. Thyroid hormones have important roles in growth and development, the functioning of the central nervous system, cardiovascular function, and homeostasis. Subclinical hypothyroidism has been associated with hypertension, dyslipidemia, and cardiovascular morbidity through endothelial dysfunction.<sup>8,15</sup>

One of the important and worrying complications of idiopathic NS is acute kidney injury (AKI). Oral Health Complications Impaired calcium homeostasis in NS is associated with hypocalcemia, decreased vitamin D metabolites in serum, weakened intestinal calcium absorption, and increased parathyroid hormone levels, leading to bone histology abnormalities. Enamel development defects are caused by impaired calcium and phosphorus absorption and poor vitamin D metabolism that occurs during enamel formation in developing teeth. Irregular dental cleanings and examinations result in neglect of oral hygiene, and are a major concern in NS patients. Removal of dental biofilm can cause patients to experience gingival tissue inflammation and caries, and gingival hyperplasia is associated with medication use and an increased risk of devastating periodontal disease.<sup>8</sup>

## CONCLUSION

Nephrotic syndrome is one of the most common kidney diseases in children. Patients with nephrotic syndrome experience protein loss that has a negative impact on various biological functions and can result in disease-related complications. Complications often caused by nephrotic syndrome are complications to the cardiovascular system, infections, thyroid hormone complications, complications to kidney function, and complications to oral health.

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