

Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome: A Systematic Review

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Introduction: Nephrotic syndrome (NS) is one of the most common childhood kidney diseases. During the active phase, the disease pathogenesis affects various biological functions linked to loss of proteins negatively, which can result in systemic complications. Complications of childhood NS are divided into two categories: disease-associated complications and drug-associated complications. However, complications in pediatric patients with NS, especially disease-associated complications are still limited. Although reported in the literature, information is not comprehensive and needs to be updated. This study aimed to systematically assess systemic complications in children with NS, especially disease-associated complications, to better understand how they impact outcomes.

Methods: We conducted a systematic search of several databases: BioMed Central Pediatrics, PubMed, Google Scholar, the National Library of Medicine, Cochrane Library, CINAHL/EBSCO, *British Medical Journal*, Science Direct, Scopus, and Elsevier's ClinicalKey. We followed the PRISMA guidelines to plan, conduct, and report this review. We used the Joanna Briggs Institute's critical appraisal tools for assuring the quality of the journal articles that were chosen.

Results: Eleven articles concerning complications in childhood NS were analyzed. Systemic disease-associated complications in covered were cardiovascular complications, infections, thyroid-hormone complication, kidney complications, and oral health complications.

Conclusion: NS is marked by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia, which can result in systemic disease-associated complications. Cardiovascular complications, infections, thyroid-hormone complications, kidney complications, and oral health complications are the main systemic complications in childhood NS. It is essential that health-care providers prevent these complications for proper maintenance of patients' health.

Keywords: disease complications, nephrotic syndrome, pediatric, systemic complications

Introduction

One of the most common childhood kidney diseases is nephrotic syndrome (NS).¹ The prevalence of childhood NS worldwide is approximately 16 cases per 100,000 children, with an incidence of two to seven per 100,000 children. Primary causes of NS include minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, genetic disorders, and secondary diseases associated with infections, drugs, and neoplasia; however, it can also be idiopathic. NS can affect children of any age from infancy to adolescence and predominantly occurs in those aged 1–6 years.²

Four specific symptoms of NS are heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia.³ Patients with NS may have nephritic characteristics, such as hypertension, hematuria, and decreased kidney function. Similarly, patients with a nephritic disease may have nephrotic features.⁴ NS may have common physical changes and injury in the glomerular filtration barrier, resulting in a massive leak of serum proteins into the urine causing proteinuria.¹

NS has become one of the most common primary kidney diseases, and progressive forms can result in chronic kidney disease. Most patients with NS have a good response to steroid therapy and consequently a good prognosis. The treatment recommendation from the International Study of Kidney Disease in Children (ISKDC) is steroids, and initial remission >9 days and first relapse within 6 months are associated with frequent relapses.^{1,5} Based on the prospective and multicenter study conducted by ISKDC, a vast majority of patients with minimal change NS had responded to steroid therapy by 4 weeks.^{6,7} However, approximately 10% of children suffer steroid resistance and show no response to steroid therapy and have a poor prognosis.⁸

The loss of proteins negatively affects various biological functions during active disease, which can result in complications.⁴ Complications of childhood NS are divided into two categories: disease-associated complications and drug-associated complications.⁹ Drug-associated complications include sensitivity to steroids, which are used for the treatment of NS. Steroid treatment is associated with severe side effects, such as growth retardation, hypertension, osteoporosis, and bone fractures, and is also linked with psychological stress.¹⁰ Treatment duration also affects psychosocial and developmental phase in the form of internal problems, somatic complaints, and anxiety/depression, which can decrease the quality of life.¹¹

However, complications — especially disease-associated ones — in pediatric patients with NS are still limited. Although reported in the literature, information is not comprehensive and needs to be updated. Parents and caregivers are often worried about the long-term health outcomes for their children with NS, due to a lack of knowledge about these complications.¹² Most of the data related to complications in childhood NS are based on case reports, and there is a scarcity of systematic reviews. The aim of the study was to systematically assess disease-associated complications in children with NS to better understand how they impact outcomes. By understanding these complications, among health-care providers will be able to better manage children with NS to prevent the complications and aid decision-making on proper treatment programs.

Methods

We conducted a systematic review to analyze NS complications in children from Asia, Europe, the US, and Africa (Table 1). We followed the PRISMA guidelines for planning, conducting, and reporting.

Eligibility Criteria

Eligibility for inclusion was original research in English containing primary data on disease-associated complications in children with NS aged 0–18 years published in the last 5 years. We excluded case reports and reviews, where the study population comprised both children and adults, diagnosis was not NS, or only systemic diseases associated with NS were reported.

Search Strategy

We searched BioMed Central Pediatric, PubMed, Google Scholar, the National Library of Medicine, Cochrane Library, *British Medical Journal*, Science Direct, Scopus, and Elsevier's ClinicalKey. Initially, we identified all potentially relevant articles without date restrictions. Next, we restricted the search to include only publications in the last five years (2016–2021). Search terms used were “NS” AND “pediatric” OR “child” OR “children” OR “childhood” AND “complication” OR “complications.” Sources cited in any review articles were cross-referenced for additional relevant articles. Two reviewers (FM and ASL) screened the titles based on relevance, followed by selection of abstracts from potentially relevant titles based on the eligibility criteria. Lastly, we analyzed the full-text articles. Mendeley software was used to manage references, and any duplicates were removed.

Data Extraction

We used data-extraction forms to assess each population, setting, and focus. The aim, study design, subject, and main results were used for data extraction. Data were extracted by two reviewers (FM and ASL) and checked by two other reviewers (DH and AW). The main findings were assessed for relevance related to complications in childhood NS. We then compared the main findings to identify and address the objectives of this review.

Table 1 Description of included studies

Study	Country	Aim	Sample	Methods	Findings
Youssef et al ³³	Egypt	To investigate the correlation between carotid intima-media thickness (CIMT) and brachial artery flow-mediated dilatation with cardiovascular risk factors in patients with nephrotic syndrome	Patients (n=31) with nephrotic syndrome aged 3–10 years	• Case-control observational study to compare patients with nephrotic syndrome and controls. • All children were subjected to full history taking thorough clinical examination and laboratory investigations in the form of fasting lipid profile, serum urea and creatinine, total protein and serum albumin, CRP, ferritin, and urine protein:creatinine ratio. • All children were also subjected to imaging techniques.	• Serum cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were significantly higher in the case group than the control group. • High-density lipoprotein cholesterol and albumin levels were significantly lower in the case group. • Absolute change in brachial artery diameter was significantly lower in the case group. • Proportional change in brachial artery diameter was significantly lower in the case group. • CIMT in the case group was significantly higher. • Patients with NS were more prone to atherosclerosis and vascular changes.
Ali et al ³⁴	Iraq	To study serum lipids, PON1, and LCAT activity in children with nephrotic syndrome and correlations of lipid parameters with PON1 and LCAT activity	Two groups: group 1 (patients) consisted of 40 children with confirmed cases of nephrotic syndrome in an active phase with aged 2–14 years of both sexes. Group 2 (controls) consisted of 40 (age- and sex-matched) healthy controls.	• Case-control study: • lipid profile and PON1 and, lecithin: cholesterol, acyltransferase activity measured in both groups' serum samples.	• Albumin significantly lowered in patients. • Ch, TGs, LDL, significantly increased in patients. • PON1- and LCAT-activity levels were significantly lower in patients. • Significantly decreased PON1 I and lecithin:cholesterol acyltransferase activity resulted in increased oxidation of LDL, thus accelerating atherosclerosis.
Patnaik et al ³⁵	India	To define the extent of endothelial dysfunction by noninvasive evaluation for impairment of macrovascular and microvascular endothelial function in children with NS versus healthy controls by assessment of brachial artery, flow-mediated dilation, and cutaneous postocclusive reactive hyperemia	Total of 70 steroid-resistant NS (SRNS) 70 steroid-sensitive (SSNS) patients, and 70 healthy controls aged 1–18 years	• Prospective cohort study with • two phases: recruitment and baseline assessment of biomarkers of endothelial dysfunction (phase 1) and prospective follow-up and cardiovascular outcome assessment (phase 2). • After baseline assessment of functional and structural status of the heart, arteries, patients were investigated for endothelial dysfunction. • Venous blood samples (15 mL) were collected for routine investigations and assays of biochemical endothelial markers. • Patients were followed up at 12 and 24 months after recruitment to look for any change from baseline.	• This study may be able to delineate progression of endothelial dysfunction in relation to - disease activity (extent and duration of proteinuria) and structural markers of subclinical atherosclerosis • It may also provide correlation of cardiovascular risk factors with endothelial dysfunction and subclinical atherosclerosis for pediatric cardiovascular risk stratification in nephrotic syndrome.

(Continued)

Table I (Continued).

Study	Country	Aim	Sample	Methods	Findings
Biswas et al ¹⁶	India	To investigate changes in fractions of lipid and lipoprotein levels, as well as apolipoprotein concentrations so that (if necessary) early treatment can be started to prevent complications of atherosclerosis	Two groups of were selected: group A had 30 children with nephrotic syndrome and group B 26 age- and sex-matched healthy controls.	• Cross-sectional study. • Blood samples were drawn from all subjects following a fast of 12 hours. Serum triglycerides, cholesterol, HDL cholesterol (direct) and LDL cholesterol (direct) were estimated. • Serum apolipoprotein A1 and B were also estimated.	• Group A children had significant hyperlipidemia in the form of increased serum total cholesterol, triglycerides, LDL cholesterol, and apolipoprotein B compared to group B children. • HDL:LDL cholesterol, HDL cholesterol:triglyceride, HDL cholesterol were all significantly increased in group A children compared to group B children. • Apolipoprotein A1:B was significantly decreased in group A children compared to group B children.
Arumugam et al ³⁶	India	To evaluate ETI status in children with first-episode idiopathic nephrotic syndrome	Fifty children (25 cases and 25 controls) aged 1–15 years	• Analytical study with longitudinal follow-up. ETI was measured • at onset of disease and after 12 weeks of drug-induced remission, and sampling was done longitudinally. • Blood samples (3 mL) were collected by venepuncture.	• Children with nephrotic syndrome had high serum cholesterol, serum LDL, serum VLDL, serum triglycerides, and nephrotic range proteinuria, as expected. • ETI was significantly higher in children with first-episode of nephrotic syndrome than controls. • In SSNS at onset, ETI was significantly lower after 12 weeks of drug-induced remission than controls. • SRNS children had higher levels of ETI than SSNS ones at onset, but this was not statistically significant.
El Ghannam et al ¹⁵	Egypt	To estimate protein C quantity and quality in the blood of nephrotic patients for possible roles that it might play in the pathogenesis of thromboembolic complications in these patients and try to find correlations between protein C and some hemostatic parameters	Forty children diagnosed with nephrotic syndrome and 20 healthy children as controls	• Morning urine samples were taken for albumin:creatinine ratio and blood samples for • complete blood count, serum creatinine, serum albumin, serum total protein, ACR in urine, serum cholesterol, serum triglycerides, coagulation profile (PT-APTT), and quantitative determination of protein C	• There was a highly significant increase in protein C in both activity and concentration in relapse, but in remission levels decreased toward normal levels. • Serum albumin and serum total protein were very significantly increased in relapse and remission compared to controls. • PT and PTT were highly significantly decreased in relapse compared to the control group. • Increased levels of protein C in nephrotic syndrome denoted that it had no role in thromboembolic complications, and increased levels of protein C in nephrotic syndrome may afford some protection against thrombotic diathesis by counteracting hypercoagulability.
Sugimoto et al ³⁷	Japan	To examine cholesterol composition, including sdLDL-C level, in NS, referring to the “alternative LDL window” to provide better understanding of the lipid profiles of childhood-onset NS	A total of 87 patients were included, of whom 39 were enrolled for the final analysis after applying the exclusion criteria.	• Retrospective study: • laboratory data for serum creatinine, estimated GFR, serum concentrations of total protein, albumin, total cholesterol, triglycerides, LDL-C, HDL-C, uric acid, and creatinine levels were examined. • Non-HDL-C concentrations of urinary protein and creatinine were also measured.	• Lipid abnormalities, ie, TC, TGs, LDL-C, and non-HDL-C levels, were significantly higher than baseline. • A total of 32 (82%) exhibited hyper-TGs/non-HDL levels • There were markedly increased lipid profiles during the acute phase of nephrotic syndrome.

Jagadeeswari ²¹	India	To examine thyroid status in children with nephrotic syndrome in comparison to children without nephrotic syndrome	Sixty children aged 1–8 years	• Comparative study: 30 children • were admitted for reasons other than nephrotic syndrome and 30 were suffering from nephrotic syndrome. • Serum FT₃, FT₄, and TSH were measured.	• FT₄ and FT₃ levels in the nephrotic syndrome patients were significantly lower than the control group. • TSH levels were high in the nephrotic syndrome group. • Hypothyroidism was found more in children aged <6 years than those aged >6 years, which was statistically significant. • Nephrotic syndrome commonly has a state of mind or subclinical hypothyroidism during proteinuria.
Kaczmarek et al ²⁸	Poland	This study investigated oral health parameters in young participants suffering from nephrotic syndrome and compared them to healthy ones.	Male and female participants (n=110) aged 4–17 years	• Observational study comparing oral health in NS patients with healthy outpatients attending the dental clinic. • Dental examinations were performed using artificial light, a plane mirror, and a ball-ended dental probe.	• The prevalence of enamel hypoplasia in the NS group was over sevenfold that of the control group. • Group had double the incidence of severe gingivitis of controls. • Significantly worse oral hygiene in the NS group caused gingival inflammation due to dental plaque accumulation.
Alfakheekh et al ¹⁸	Saudi Arabia	To estimate the immunosuppressive burden and identify clinical risk factors in patients with primary childhood nephrotic syndrome (PCNS)	Patients aged ≤14 years with PCNS (n=111) admitted to the Department of Paediatrics	• Cross-sectional study of hospitalized children. • Infection was classified into major and minor types. The major types were urinary tract infection (UTI), pneumonia, and peritonitis.	• In sum, 84 (76.4%) had both minor and major types of infection. • About half the infections encountered by PCNS patients were upper respiratory tract infection (URTI), followed by UTI and pneumonia. • URTI was the predominant infection noted in our study. Among the major infections, UTI was the main type (n=21, 25%), followed by pneumonia (n=17, 20%) then cellulitis (n=6, 6%).
Yaseen et al ³⁸	Pakistan	To determine the clinical profile of children with INS who developed AKI and its short-term outcomes	A total of 119 children aged 2–18 years with INS	• Prospective observational study. • The primary end point was normalization of renal functions. Patients were followed for 3 months after an episode of AKI to observe outcomes (CKD/death/ recovered).	• Most respondents had steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis on histopathology. • Infections were the major predisposing factor for AKI cases, followed by drug toxicity. • A total of 54.6% of children recovered from AKI, while 45.4% did not. • CKD developed in 41.2% of non-recovered cases.

Study Quality

We used the Joanna Briggs Institute's critical appraisal tools for assuring the quality of the journal articles that were chosen for systematic review. These consist of several checklists based on research methods, and were used to assist in assessing the trustworthiness, relevance, and results of published papers.

Results

Publication Characteristics and Quality

A total of 11,717 articles were retrieved from the nine databases after removal of duplicates and one study in Arabic. We exclude 11,612: 8,942 did not report complications in childhood NS, 1,021 involved adults as subjects, 759 did not discuss NS only, 687 were case reports, and 203 were reviews. This resulted in 93 articles for full-text review. Finally, eleven articles were analyzed. A PRISMA flowchart¹³ of the search is shown in [Figure 1](#).

Disease-Associated Systemic Complications of Childhood NS

Cardiovascular Complications

Cardiovascular complications of NS include increased risk of atherosclerosis and thromboembolism, due to dysregulated lipid metabolism and dyslipidemia.¹⁴ Thromboembolic causes are among the most serious complications in patients with NS.¹⁵ Also, complications of atherosclerosis are a major cause of death and increase the need for dialysis and risk of renal transplantation.¹⁶ One study that used blood samples of pediatric patients with NS found lipid-profile abnormalities. Total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and ET1 levels were significantly higher in the NS group than the control group, while high-density lipoprotein (HDL) cholesterol, albumin, PON1, and lecithin:cholesterol acyltransferase activity levels were significantly lower. The change of brachial artery diameter was significantly lower in the NS group than the control group. The significantly decreased PON1 and lecithin:cholesterol acyltransferase activity resulted in increased oxidation of LDL, causing accelerated atherosclerosis. This study's results may represent the pathogenesis in the progression of endothelial dysfunction related to disease activity (extent and duration of proteinuria) and structural markers of subclinical atherosclerosis. They may also delineate the correlation of cardiovascular risk factors with endothelial dysfunction and subclinical atherosclerosis in childhood NS. The long-term survival of patients with NS is increasingly dependent on controlling the risk factors of atherosclerosis. Therefore, there is a need to evaluate lipid and lipoprotein levels early so that appropriate treatment can start quickly.¹⁶

Infections

Childhood NS carries a high risk of complications, including infection. The pathogenesis of the increased infection frequency is linked to defects in cell-mediated immunity, urinary loss of immunoglobulins, properdin factor band B, and complement factors.¹⁷ Alfakeekh et al showed that 76.4% of patients with childhood NS had both minor and major types of infection. Over half the infections encountered by patients with childhood NS were upper respiratory tract infection, followed by urinary tract infection, pneumonia, and cellulitis.¹⁸

Thyroid-Hormone Complications

Metabolic abnormalities, such as deranged coagulation, immunodeficiency from immunoglobulin and complement loss, and anemia from erythropoietin and transferrin deficiency, are linked with low molecular-weight proteins, including some binding proteins, that are excreted in patients with NS. Thyroid hormones and binding globulins are also excreted in urine in excess, and NS patients may show hypothyroidism.¹⁹ Thyroid hormones have prominent roles in growth and development, proper functioning of the central nervous system, cardiovascular function, and homeostasis. Subclinical hypothyroidism has been associated with hypertension, dyslipidemia, and cardiovascular morbidities through endothelial dysfunction.²⁰ Jagadeeswari showed that hypothyroidism was more common in children with NS. FT₄ and FT₃ levels in patients with NS were significantly lower than the control group, while TSH level was high. Hypothyroidism was found significantly more in children aged <6 years than those aged >6 years. NS commonly presents with subclinical hypothyroidism during proteinuria.²¹

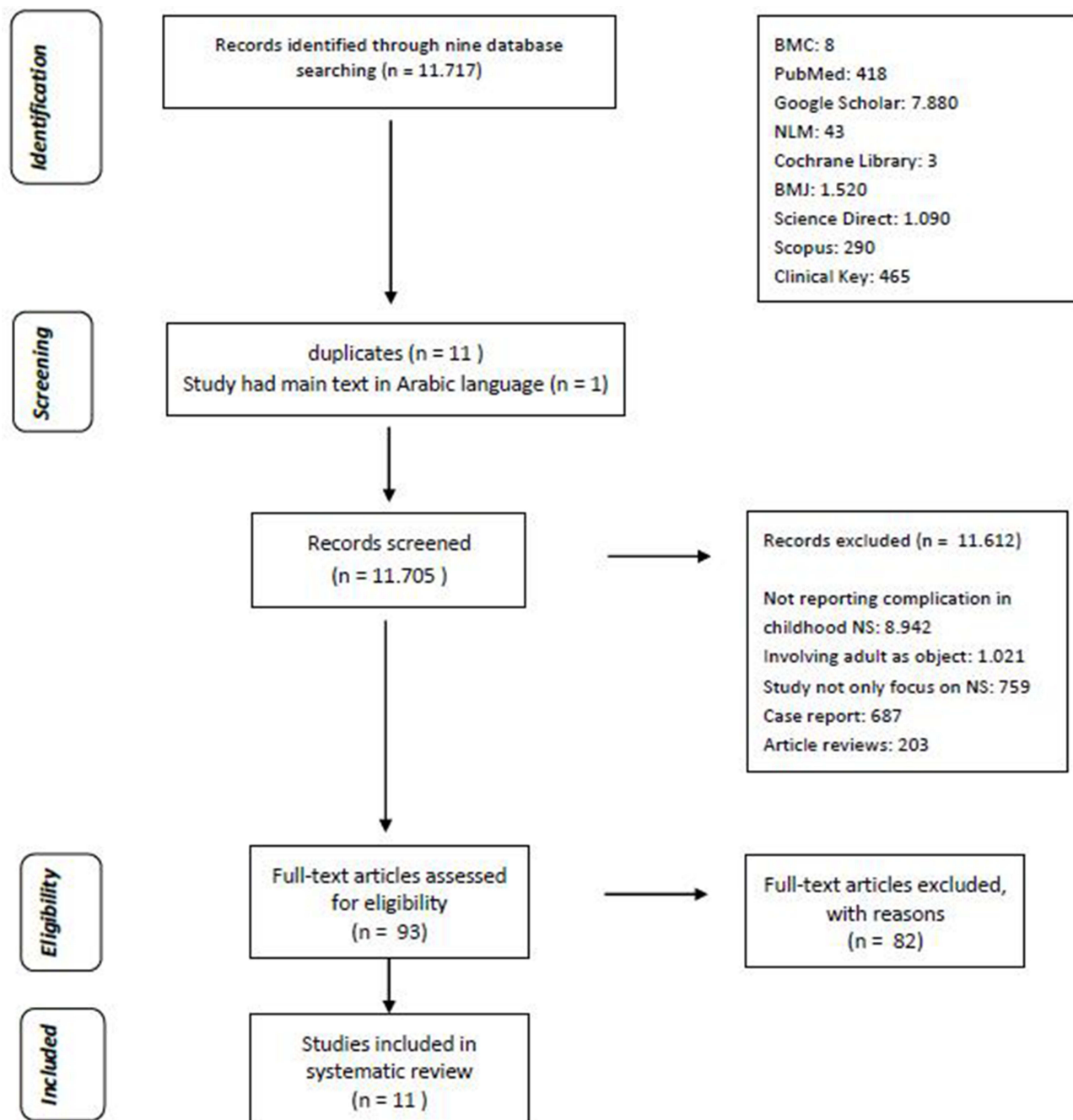


Figure 1 Flowchart of study search and selection. Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD. PRISMA 2020 flow diagram. *Bmj*. 2020;372(n71). <http://www.prisma-statement.org/PRISMAStatement/FlowDiagram>.¹³

Kidney Complications

One of the important and alarming complications of idiopathic NS is acute kidney injury (AKI).²² The etiology of AKI with NS includes acute renal tubular necrosis, toxicity of drugs, such as calcineurin inhibitors, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers, sepsis, renal vein thrombosis, peritonitis, and interstitial nephritis.²³ Yaseen et al showed that most subjects had focal segmental glomerulosclerosis on histopathology. Infections were a major predisposing factor for AKI. A total of 54.6% recovered from AKI, 45.4% did not, and chronic kidney disease developed in 41.2% of the non-recovered cases.²⁴

Oral Health Complications

Disturbance of calcium homeostasis in NS is linked with hypocalcemia, reduced vitamin D metabolites in serum, weakened intestinal absorption of calcium, and raised levels of parathyroid hormone, which lead to abnormal bone histology.²⁵ Developmental defects of enamel result from disruption in calcium and phosphorus absorption and poor metabolism of vitamin D occurring during the formation of enamel in developing teeth.²⁶ Irregular tooth cleaning and dental checkups result in the neglect of oral hygiene, and are major concerns in patients with NS. The removal of dental biofilm can predispose patients to inflammation of gingival tissue and caries, and gingival hyperplasia is associated with drug use and increased risk of destructive periodontal diseases.²⁷ Kaczmarek et al found that the prevalence of enamel hypoplasia in NS patients was over sevenfold that of controls, and patients with NS had double the incidence of severe gingivitis of controls. The significantly worse oral hygiene in the NS group caused gingival inflammation due to dental plaque accumulation.²⁸

Discussion

NS is one of the most common glomerular diseases in the spectrum of childhood renal diseases. These children have lesions of focal segmental glomerulosclerosis and suffer from severe and prolonged proteinuria that has been linked to a higher risk of systemic complications. The main pathomechanism of disease-associated complications in children with NS originates from the large loss of plasma protein via urine. This systematic review shows that the disease-associated systemic complications in childhood NS include cardiovascular complications, infections, thyroid complications, kidney complications, and poor oral health condition, ie, caries and enamel hypoplasia.

Arterial and venous thromboembolic complications are relatively common and bring serious consequences for pediatric patients with NS. Multiple abnormalities in the coagulation pathways are observed in NS that are linked to thromboembolism. This was supported by a review conducted by Zaffanello and Franchini in 2007 that indicated that the risk of thromboembolism in childhood NS should not be underestimated and had become the most-serious life-threatening complication. The most commonly involved vessels in vascular thrombosis are the deep veins of the legs, inferior vena cava, renal veins, superior vena cava, mesenteric artery, hepatic veins, and middle cerebral arteries. Iatrogenic thrombotic risk factors (diuretics, dehydration, and infections) should be avoided. The therapeutic approach to childhood thrombosis is anticoagulants (low molecular-weight heparin and/or fibrinolytic agents, such as streptokinase, urokinase, or tissue plasminogen activators).²⁹

Smoyer et al found that 7.4% of thromboses occurred during NS remission, of which renal vein thrombosis and pulmonary embolism were the most common — 33.3% and 25.9%, respectively. Most of the NS children with thromboembolisms (70.4%) resolved completely.^{30,31} Patients with childhood NS show lipid-profile abnormalities due to changes in the metabolism of lipoprotein, which then changes lipids' nature, both quantitatively and qualitatively. This was supported by a study conducted by Al-Bahrani in 2017 that showed that hyperlipidemia was one of the most common features of NS. Any abnormalities in lipid levels can lead to atherosclerotic, cardiovascular, and thromboembolic complications and lipid accumulation in glomeruli and proximal tubular epithelial cells. It is essential to maintain lipid levels in the body for good health.³²

Various medical conditions can affect oral health. Patients with childhood NS have such oral complications as removal of dental biofilm, gingival inflammation, defects in enamel, and enamel hypoplasia. This is supported by a review conducted by Gupta et al in 2014 indicating that in pediatric patients, renal disease, including NS, can affect oral condition, both hard and soft tissue. Oral manifestations in soft tissue include stomatitis (mucositis), can cause inflammation of the tongue and oral mucosa. Altered taste sensation, dysgeusia, gingival inflammation, and candidiasis infection can develop due to underlying renal disease. In hard tissue, enamel hypoplasia in the form of white or brown discoloration of primary teeth occurs and is correlated with the metabolic disturbance of renal disorders, including NS.²⁷

This was a novel systematic review of disease-associated complications in childhood NS that drew on data from seven countries. The number of studies included was limited due to the low number of studies available on disease-associated complications in childhood NS. Further studies should explore psychological and developmental complications in children with NS.

Conclusion

NS is one of the most common childhood kidney diseases. Patients with childhood NS suffer a loss of proteins that negatively affects various biological functions during active disease and can result in disease-associated complications. These children also have lesions of focal segmental glomerulosclerosis and suffer from severe and prolonged proteinuria, which has been linked to a higher risk of systemic complications. Complications in pediatric patients with NS include cardiovascular complications linked to atherosclerosis and thromboembolism, infections (both minor and major), thyroid-hormone complications, especially hypothyroidism, kidney complications involving AKI, oral health complications due to defects in enamel, and periodontal disease. These complications need the attention of health-care providers to prevent any worsening of patients' condition. Further research should also explore complications related to psychological and developmental problems that might decrease the quality of life in children with NS.

Disclosure

The authors report no conflicts of interest in this work.

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