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VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND NEOPTERIN LEVELS IN CHILDREN WITH STEROID-SENSITIVE AND STEROID-RESISTANT NEPHROTIC SYNDROME

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Abstract

Nephrotic syndrome is one of the most common glomerular disorders in children, with a global incidence ranging from 1.15 to 16.9 cases per 100,000. In Bukhara, the prevalence is approximately 6 per 100,000 population, with a male predominance (1.5–2:1). The condition is clinically characterized by massive proteinuria, hypoalbuminemia, and a relapsing course.

Histopathologically, nephrotic syndrome includes minimal change disease and focal segmental glomerulosclerosis as the principal subtypes. These entities differ significantly in their response to corticosteroid therapy: minimal change disease is typically steroid-sensitive, whereas focal segmental glomerulosclerosis is often steroid-resistant. Steroid-sensitive nephrotic syndrome is defined by complete remission within four weeks of standard corticosteroid therapy, while failure to achieve remission within this period indicates steroid resistance.

Steroid-resistant nephrotic syndrome is associated with a more severe clinical trajectory, including a higher risk of progression to chronic kidney disease and end-stage renal failure, significantly impairing the physical and psychosocial well-being of affected children. Recurrent relapses and hospitalizations further contribute to a substantial economic burden.

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Early differentiation between steroid-sensitive and steroid-resistant forms is essential for optimizing therapeutic strategies and improving patient outcomes. Although renal biopsy remains the gold standard for diagnosis, its invasive nature limits widespread application. Recently, non-invasive biomarkers such as vascular endothelial growth factor (VEGF) and neopterin have gained attention. VEGF plays a key role in increasing vascular permeability and proteinuria, while neopterin reflects immune activation and inflammatory processes. Elevated levels of these biomarkers may serve as valuable indicators for disease severity and progression, as well as potential tools for clinical differentiation.

Keywords: Child, neopterin, nephrotic syndrome, vascular endothelial growth factors.

Introduction

Nephrotic syndrome represents a major clinical entity in pediatric nephrology and remains one of the most frequently encountered glomerular diseases in childhood. It is characterized by a triad of heavy proteinuria, hypoalbuminemia, and edema, often accompanied by hyperlipidemia. Despite advances in understanding its pathophysiology and management, nephrotic syndrome continues to pose significant diagnostic and therapeutic challenges.

The incidence of nephrotic syndrome varies globally, with reported rates ranging from 1.15 to 16.9 per 100,000 children. Regional epidemiological data, including those from Bukhara, demonstrate a prevalence of approximately 6 per 100,000 population, with a higher occurrence in males compared to females. The disease typically follows a chronic relapsing course, requiring prolonged monitoring and repeated treatment interventions.

From a histopathological standpoint, minimal change disease and focal segmental glomerulosclerosis are the most common subtypes observed in children. These forms differ not only in their morphological features but also in

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their response to corticosteroid therapy, which remains the cornerstone of treatment. Minimal change disease is generally associated with a favorable response to steroids, whereas focal segmental glomerulosclerosis is frequently linked to steroid resistance and a less favorable prognosis.

Steroid resistance is a critical determinant of disease outcome. Children with steroid-resistant nephrotic syndrome are at a significantly increased risk of developing chronic kidney disease and progressing to end-stage renal failure. In addition to medical complications, the disease adversely affects growth, development, and quality of life, imposing psychological stress on both patients and their families. Furthermore, the economic burden associated with repeated hospitalizations and long-term treatment is considerable.

Currently, renal biopsy with histopathological examination remains the gold standard for differentiating between subtypes of nephrotic syndrome. However, due to its invasive nature and potential complications, there is an increasing need for reliable non-invasive diagnostic alternatives. In this regard, biomarkers detectable in serum and urine have emerged as promising tools.

Among these, vascular endothelial growth factor (VEGF) and neopterin have attracted particular interest. VEGF is a key mediator of angiogenesis and vascular permeability, playing an important role in the development of proteinuria. Neopterin, produced by activated monocytes and macrophages, serves as a marker of cellular immune activation and inflammation. Elevated levels of these biomarkers have been associated with disease activity, severity, and progression.

Therefore, investigating the diagnostic and prognostic value of VEGF and neopterin may contribute to improved differentiation between steroid-sensitive and steroid-resistant nephrotic syndrome, ultimately enhancing patient management and clinical outcomes.

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Materials and Methods

This cross-sectional study was conducted at the Children's Multifunctional Medical Hospital in Bukhara, Uzbekistan, over a one-year period from January to December 2025.

The diagnosis of nephrotic syndrome was established based on standard clinical criteria, including massive proteinuria (>40 mg/m²/hour, or a urinary protein-to-creatinine ratio [PrU/CrU] >2 mg/mg, or ≥2+ protein on urine dipstick), hypoalbuminemia (≤2.5 g/dL), and the presence of edema. Patients in complete remission were defined as those demonstrating negative or trace proteinuria for three consecutive days.

Eligible participants were further stratified into two groups: steroid-sensitive nephrotic syndrome (SSNS), defined as achieving complete remission within the initial four weeks of corticosteroid therapy, and steroid-resistant nephrotic syndrome (SRNS), defined as failure to achieve complete remission after eight weeks of standard corticosteroid treatment.

Renal biopsy was not performed in patients with idiopathic nephrotic syndrome in this study, as their clinical presentation was consistent with minimal change disease according to established clinical guidelines.

Exclusion criteria included children with end-stage renal disease (glomerular filtration rate ≤60 mL/min/1.73 m²), as well as those with concomitant systemic conditions such as malignancy, pulmonary tuberculosis, severe malnutrition, obesity, cardiovascular disease, hepatic disorders, systemic lupus erythematosus, and Henoch–Schönlein purpura.

A total of 120 children aged between 1 and 8 years were enrolled. The study cohort consisted of 60 patients diagnosed with nephrotic syndrome (subdivided into SSNS and SRNS groups) and 60 age-matched healthy controls.

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Data Collection

Demographic and clinical data, including age, sex, urine albumin-to-creatinine ratio (UACR), serum albumin concentration, total cholesterol level, blood urea level, serum creatinine level, vascular endothelial growth factor (VEGF), and neopterin levels, were obtained from each participant's medical records.

Spot urine samples were collected for urinary analysis, and approximately 15 mL of peripheral venous blood was drawn from each subject under aseptic conditions. Blood samples were processed to obtain serum for subsequent biomarker analysis.

Serum VEGF levels were quantified using a commercially available Quantikine ELISA kit for human VEGF (R&D Systems, Inc., Minneapolis, USA), following the manufacturer's instructions. Briefly, 50 µL of standards and 10 µL of serum samples were added to microplate wells containing 100 µL of assay diluent. The plate was sealed and incubated for 2 hours at room temperature on a microplate shaker. After incubation, the wells were washed four times, and 200 µL of conjugate solution was added. The plate was resealed and incubated for an additional 2 hours, followed by repeated washing. Subsequently, 200 µL of substrate solution was added to each well and incubated for 30 minutes at room temperature in the dark. The reaction was terminated by adding 50 µL of stop solution, and optical density was measured at a wavelength of 450 nm using a microplate reader.

Serum neopterin levels were determined using a neopterin enzyme immunoassay kit (IBL GmbH, Hamburg, Germany). In this assay, 20 µL of standards and serum samples were added to the wells, followed by the addition of 100 µL of enzyme conjugate and 50 µL of neopterin antiserum. The plate was covered with adhesive foil and incubated for 90 minutes at room temperature on an orbital shaker in the dark. After incubation, the wells were washed four times and residual liquid was removed. A mixture of 150 µL of TMB substrate solution and 150 µL of stop

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solution was then added, and optical density was measured to determine serum neopterin concentrations.

All laboratory investigations were performed at the time of hospital admission to ensure consistency and minimize variability.

Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (IBM Corporation, New York, USA). Categorical variables were analyzed using the Chi-square test, while Fisher's exact test was applied when the assumptions for the Chi-square test were not satisfied. Continuous variables were assessed for normality of distribution. For normally distributed data, comparisons among the three groups (control, steroid-sensitive nephrotic syndrome [SSNS], and steroid-resistant nephrotic syndrome [SRNS]) were conducted using one-way analysis of variance (ANOVA), followed by Bonferroni post hoc testing. For non-normally distributed data, the Kruskal–Wallis test was applied, followed by pairwise comparisons using the Mann–Whitney U test.

Correlations between serum VEGF and neopterin levels and clinical parameters, including UACR, serum albumin, total cholesterol, urea, and creatinine, were evaluated using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation for non-parametric data. A p-value of <0.05 was considered statistically significant**.**

Results

A total of 120 children were included in the study, comprising 36 patients with SRNS, 24 with SSNS, and 60 healthy controls. No statistically significant differences were observed between the groups in terms of age ($p = 0.375$) or gender distribution ($p = 0.269$), indicating comparability across study populations.Significant differences were identified between the nephrotic syndrome groups (SSNS and SRNS) and the control group with respect to UACR,

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serum albumin, total cholesterol, VEGF, and neopterin levels ($p < 0.05$). Specifically, children with nephrotic syndrome demonstrated higher UACR, total cholesterol, VEGF, and neopterin levels, along with lower serum albumin levels compared to healthy controls.However, no statistically significant differences were found between the SSNS and SRNS groups in terms of serum VEGF and neopterin concentrations.

Discussion

Nephrotic syndrome is a common chronic renal disorder in children, most frequently affecting those between 2 and 6 years of age, which is consistent with the demographic characteristics observed in this study. Although the majority of pediatric patients respond favorably to corticosteroid therapy, a subset develops steroid resistance, which is associated with a significantly increased risk of progression to end-stage renal disease.The present study demonstrated that children with nephrotic syndrome exhibited significantly lower serum albumin levels and elevated total cholesterol levels compared to healthy controls. These findings are consistent with the well-established pathophysiological mechanisms of nephrotic syndrome, including increased glomerular permeability and subsequent protein loss. Emerging evidence suggests the involvement of circulating permeability factors in the pathogenesis of nephrotic syndrome. In this context, VEGF has been identified as a key mediator due to its role in enhancing vascular permeability. Consistent with previous studies, our findings demonstrated elevated serum VEGF levels in children with nephrotic syndrome compared to controls. Experimental studies have further shown that overexpression of VEGF can induce albuminuria and structural glomerular changes resembling nephrotic syndrome, potentially contributing to steroid resistance. Despite these observations, no significant difference in VEGF levels was detected between SSNS and SRNS groups in this study, aligning with some previous reports. A weak-to-moderate positive correlation was observed between

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VEGF levels and UACR, suggesting a potential association between VEGF activity and the degree of proteinuria. However, conflicting evidence exists in the literature, with some studies reporting no association or even negative correlations, highlighting the complexity of VEGF's role in nephrotic syndrome. Neopterin, a biomarker of cellular immune activation, was also found to be significantly elevated in children with nephrotic syndrome compared to healthy controls. Furthermore, a positive correlation between neopterin levels and proteinuria was observed, supporting its role as an indicator of disease activity. However, similar to VEGF, neopterin levels did not significantly differ between SSNS and SRNS groups, suggesting limited utility in distinguishing steroid responsiveness. Additionally, a negative correlation between serum neopterin and albumin levels was identified. This finding may reflect the inverse relationship between inflammatory activity and serum protein levels, as albumin is known to decrease during systemic inflammation.

This study has several limitations. Potential confounding factors influencing VEGF and neopterin levels, such as genetic polymorphisms, were not assessed. Furthermore, the relatively small sample size and single-center design may limit the generalizability of the findings. Future multicenter studies with larger cohorts are recommended to validate these results.

Conclusion

Serum VEGF and neopterin levels are significantly elevated in children with nephrotic syndrome compared to healthy controls, indicating their association with disease activity. However, neither biomarker demonstrated the ability to differentiate between steroid-sensitive and steroid-resistant forms of nephrotic syndrome.

A positive correlation was observed between serum VEGF levels and UACR, while serum neopterin levels showed a negative correlation with serum albumin.

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These findings suggest that although VEGF and neopterin may serve as indicators of disease severity, their role in predicting steroid responsiveness remains limited.

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