

# Follow-up of linear growth of body height in children with nephrotic syndrome

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**Background and Purpose:** Steroid treatment is a mainstay in the management of nephrotic syndrome, but has the potential to impair growth and development of children. This study evaluated the effects of steroid regimens on linear growth of body height in children with nephrotic syndrome.

**Methods:** Hospital records of height measurements were reviewed for a selected cohort of 50 children with nephrotic syndrome. Patient data were obtained from disease onset until follow-up of at least 32 months. Information on dosage of prednisolone and immunosuppressive agents was also analyzed.

**Results:** The mean age at presentation was 6.8 years, and the mean age at final consultation was 10 years. Around one-half and one-third of children received the immunosuppressive agents cyclophosphamide and chlorambucil, respectively, in combination with prednisolone. Prednisolone treatment was associated with progressive reduction in height standard deviation score, which became statistically significant after 3 years ( $p < 0.05$ ). At year 3, patients receiving immunosuppressive agents in combination with prednisolone had significantly higher mean height standard deviation score values compared with prednisolone-only patients. There was a significant ( $p < 0.05$ ) inverse correlation between total prednisolone dose and percentile of body length during year 3 of treatment.

**Conclusions:** Prednisolone was associated with impairment of growth in body height, in a dose-dependent fashion. Combined administration of immunosuppressive agents significantly reduced this effect and appears to have a therapeutic role in this setting, particularly when long-term treatment is required.

**Key words:** Body height, follow-up studies, immunosuppressive agents, nephrotic syndrome, prednisolone

## Introduction

Growth in patients with idiopathic nephrotic syndrome is influenced by several factors [1-5]. Prior to the onset of the disease, growth in children who later develop nephrotic syndrome and that in other healthy children is influenced by the same factors. On onset of the disorder, the children suffer from proteinuria caused by the increase in glomerular permeability, leading to hypoproteinemia associated with urinary loss of several substances important for homeostasis. In most cases, after the start of steroid therapy, proteinuria subsides quickly [6,7]; however, the side effects of

glucocorticoid treatment persist; glucocorticoids alter growth by directly acting on the growth cartilage or via altering the levels of growth factors [8].

Chronic steroid treatment has long been recognized as a major risk factor for growth retardation in children [9]. Therefore, immunosuppressive agents have been advocated for use in children with nephrotic syndrome. Although prednisolone has been used as the first line of treatment for nephrotic children, only a limited number of studies have investigated the effects of steroid treatment on linear growth. Early administration of an immunosuppressive agent could reduce the side effects of steroids on growth [4,5]. A high correlation was found between growth retardation and cumulative steroid dose [1,2]. The purpose of this study was to determine whether the early administration of immunosuppressive agents could reduce growth retardation and to evaluate

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the association between the steroid cumulative dose and linear growth in children with nephrotic syndrome.

## Methods

We reviewed the medical records of patients with nephrotic syndrome followed in our renal nephrology division since 1979. Patients who met the criteria outlined in the patient demographics section below were enrolled in the study.

### Patient demographics

Fifty children (39 males and 11 females) were enrolled in the study; 20 children with nephrotic syndrome were steroid-dependent, and 30 children were found to have frequently relapsing nephrotic syndrome. The age of the children enrolled was <19 years and the minimum follow-up period was 3 years. The number of relapses and treatment modalities were carefully recorded during the follow-up period.

### Treatment regimens

Patients were initially treated with prednisolone. After the first one or two relapses, treatment was individualized based on clinical evolution, previous response to steroids, and side effects. When clinical signs of steroid toxicity were observed (e.g., hypertension, severe hirsutism, severe obesity, diabetes, and marked growth stunting) or if patients continued to experience frequent relapses on prednisolone therapy, immunosuppressive agents, including cyclophosphamide and chlorambucil, were used.

The children were divided into 3 groups based on the treatment regimens: group 1 included 9 children receiving prednisolone alone, group 2 included 25 children receiving prednisolone and cyclophosphamide, and group 3 included 16 children receiving prednisolone and chlorambucil.

Patients were instructed to perform regular urine dipstick tests for proteinuria at home. For each patient, the number of relapses, dosage of prednisolone (mg/m<sup>2</sup>), and other non-steroid treatments were recorded.

### Growth evaluation

Height measurements were expressed as height standard deviation score (HtSDS) and percentile at the end of every year.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 10.0; SPSS Chicago, IL, USA) software. Comparisons between data were performed with chi-squared test and *t* test. All *p* values are two-sided and considered statistically significant for *p* values <0.05.

## Results

The hospital records of 50 patients were analyzed. Of these, 39 (78%) were male and 11 (22%) were female. The patients' mean age at first consultation was 6.8 years (range, 8 months to 16 years 2 months). The mean age at final consultation was 10 years (range, 3 years 4 months to 19 years 5 months).

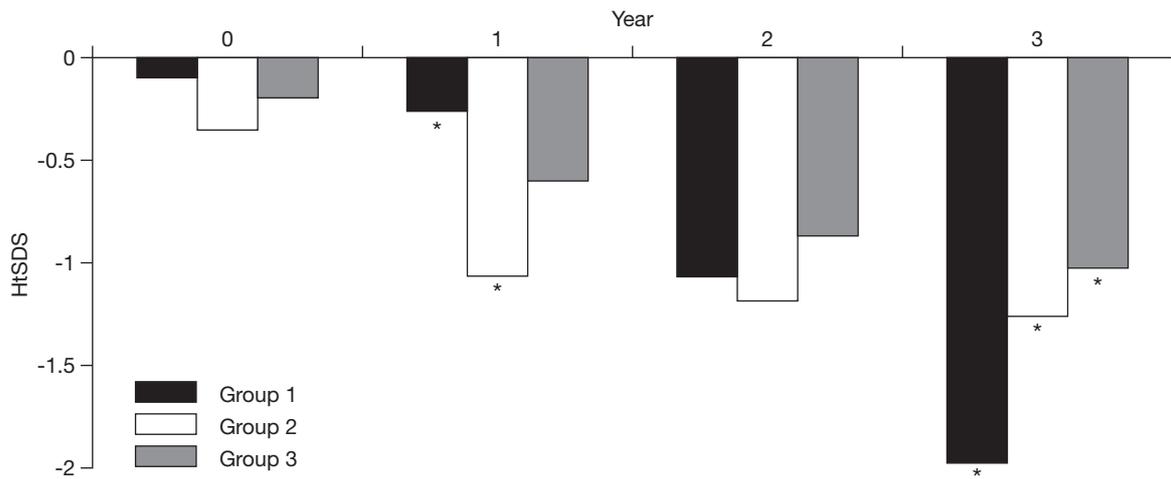
Percutaneous renal biopsy was performed in 29 of 50 (58%) patients with the following results: minimal change glomerular lesions in 9 (18%) patients, immunoglobulin M nephropathy in 9 (18%) patients, focal and segmental glomerulosclerosis in 4 (8%) patients, membranoproliferative glomerulonephritis in 2 (4%) patients, post-infectious glomerulonephritis in 2 (4%) patients, lupus nephritis in 2 (4%) patients, and immunoglobulin A nephropathy in 1 (2%) patient (Table 1).

The mean total cumulative dose of prednisolone for 3 years was 17,188.84 mg/m<sup>2</sup>. The mean duration of prednisolone use was 45 months. The immunosuppressive agents cyclophosphamide and chlorambucil were used with prednisolone in 25 (50%) children and 16 (32%) children, respectively. Statistically significant differences (*p*<0.05) were found between the first and third year HtSDS of group 1 and between the first year HtSDS of group 1 and group 2, between the third year HtSDS of group 1 and group 2, and between the third year HtSDS of group 1 and group 3 (Fig. 1). With regard

**Table 1.** Outcome of percutaneous renal biopsy in 29 patients

	Minimal change nephropathy	FSGS	IgM nephropathy	MPGN	Postinfectious GN	Lupus nephritis	IgA nephropathy
PDN			3	2		2	1
PDN + CPH	5	4	3		1		
PDN + CMB	4		3		1		

Abbreviations: FSGS = focal and segmental glomerulosclerosis; IgM = immunoglobulin M; MPGN = membranoproliferative glomerulonephritis; GN = glomerulonephritis; IgA = immunoglobulin A; PDN = prednisolone; CPH = cyclophosphamide; CMB = chlorambucil

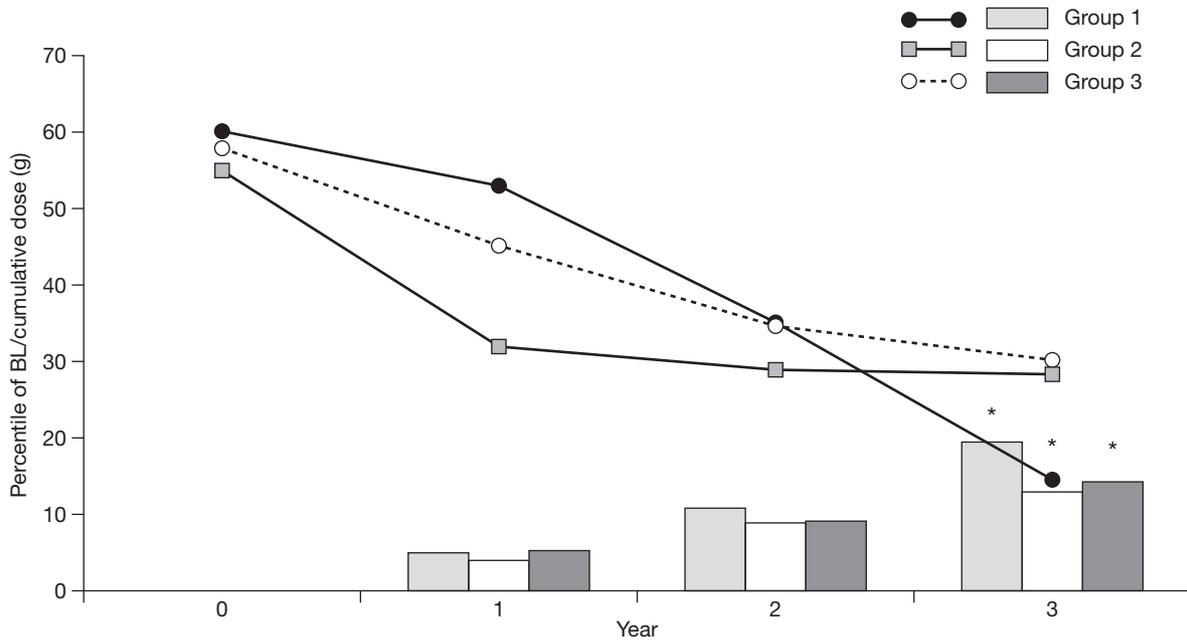


**Fig. 1.** Height standard deviation score (HtSDS) of groups 1, 2, and 3 from year 0 to year 3. Group 1 = prednisolone; group 2 = prednisolone + cyclophosphamide; group 3 = prednisolone + chlorambucil. \* $p < 0.05$ .

to the cumulative prednisolone dose and loss of linear growth, there was no statistically significant difference between the groups in the first and second years; however, statistically significant differences were found between groups 1 and 2 and between groups 1 and 3 in the third year (Fig. 2). There was a significant and positive correlation between cumulative dose and loss of linear growth in the third year.

### Discussion

Prednisolone treatment was found to be the primary risk factor for growth retardation [10]. According to the International Study of Kidney Disease in Children data, nearly 40% of children with minimal lesion nephrotic syndrome frequently relapse or become steroid-dependent. The chronic high-dose steroid administration



**Fig. 2.** Correlation between cumulative dose of prednisolone and percentile of body length (BL). Cumulative dose is indicated by bars. Linear curves indicate the percentile of BL. Group 1 = prednisolone; group 2 = prednisolone + cyclophosphamide; group 3 = prednisolone + chlorambucil. \* $p < 0.05$ .

resulting from this frequent relapsing or steroid-dependent course is often associated with significant side effects in children, most notably growth retardation [3, 11]. In many cases, growth stunting can also be attributed to the severity of the underlying disease. In children with steroid-resistant nephrotic syndrome, the progressive loss of HtSDS has been related to chronic urinary protein losses [10]. However, in children with steroid-sensitive nephrotic syndrome, there is limited proteinuria, and the decreased growth velocity is more likely to be related to the long-term effects of corticosteroid treatment.

The inclusion of children with a benign course of nephrotic syndrome may severely underestimate the side effects of prolonged steroid treatment and may explain the variability of the results that have been reported in several studies [10,12,13]. Our study included children with steroid-dependent nephrotic syndrome and children with frequently relapsing nephrotic syndrome. In clinical practice, patients with greater disease severity are more likely to experience toxicity related to prolonged and repeated courses of prednisolone [10]. No statistical significance was observed in the steroid-sparing treatment regimens by logistic regression analysis, indicating that the primary beneficial effect of these treatments on linear growth was related to their steroid-sparing effect, as previously reported. Longer steroid treatment with higher cumulative doses of prednisolone was also the main cause for the greater HtSDS losses in children with early-onset nephrotic syndrome [3]. Thus, children with early-onset nephrotic syndrome also appear to be at higher risk of growth retardation because they experience longer disease courses [1,14].

The results of our study help identify those patients who are at increased risk of impaired linear growth. The loss of growth percentile in nephrotic children on steroid treatment alone is related to the cumulative dose [10]. Steroid-sparing treatment regimens have been shown to have a beneficial effect on linear growth [14]. The effect is particularly evident in the third year.

In conclusion, our results show that children with steroid-dependent nephrotic syndrome or frequently relapsing nephrotic syndrome who are on steroid treatment are at risk of growth retardation. The addition of an immunosuppressive agent in combined prednisolone therapy decreases the risk of permanent loss of linear growth potential. Therefore, the use of steroid-sparing agents should be considered, particularly during periods of long-term steroid usage.

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