

## The Effect of Long-term Steroid Therapy on Linear Growth of Nephrotic Children

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### Abstract

**Objective:** Steroids are still the mainstay of management of nephrotic syndrome (NS). It was shown that steroids could impair growth and development of children. However, other clinical studies have shown conflicting results.

**Methods:** Hospital records of 147 children with diagnosis of NS who were followed during 1988-2008 are reviewed relating to height measurements. All patients were treated with prednisolone and had been followed for at least five years. Height measures were transformed into standard deviation score (SDS). Information on dose and duration of prednisolone therapy, histological findings of biopsy as well as concomitant use of steroid-sparing agents (SSA) were also analyzed.

**Findings:** Mean age at onset of NS was 5.94 years and at last follow-up visit 15.08 years. All patients had normal renal function during entire duration of the study. Analysis of the whole population did not show any significant alterations in the height SDS ( $Ht_{SDS}$ ) between the first and the last follow-up visit ( $P=0.5$ ;  $-0.76\pm 2.0$  vs.  $-0.89\pm 2.05$  respectively). The patients were divided into two subgroups. Subgroup A, which achieved growth improvement, was composed of 62 children (initial  $Ht_{SDS}$  -1.63; final  $Ht_{SDS}$  -0.08;  $P<0.001$ ) and subgroup B, that showed growth retardation, included 85 children (initial  $Ht_{SDS}$  -0.13; final  $Ht_{SDS}$  -1.59;  $P<0.001$ ).

**Conclusion:** No statistically significant retardation of linear growth was observed in the study population as a group following treatment with prednisolone according to the guidelines of ISKDC. Although about 62 subjects had growth retardation, children treated with prednisolone were not different from those who had increased growth.

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**Key Words:** Nephrotic Syndrome; Body Height; Growth; Corticosteroids; Prednisolone

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## Introduction

Nephrotic syndrome (NS) is usually presented with sudden onset of edema associated with proteinuria, hyperlipidemia, and hypoalbuminemia.

Usually the course of NS in children is chronic with periods of recurrence and if untreated, it will lead to end-stage renal disease (ESRD) and death. Steroids had been used to treat nephrotic children since 1950. Now oral corticosteroids are the first line treatment of NS and the majority of these children respond to steroids.

About 12-22% of the children with NS are steroid resistant and 70% will experience an episode of relapse. However, steroids reduced the mortality rate to about 3%<sup>[1,2]</sup>.

Long-term corticosteroid therapy has several known adverse effects like obesity, diabetes mellitus, poor growth, adrenal suppression, and hypertension. Despite the fact that both NS and its therapeutic protocols (steroids, and steroid sparing agents) can affect growth, clinical studies have shown conflicting results<sup>[3-5]</sup>. This study intends to assess the effect of corticosteroid on linear body growth of children.

## Subjects and Methods

### Setting and design:

The study was conducted in Children's Medical Center, the largest university affiliated pediatric hospital in Tehran. In a hospital-based retrospective approach the effect of steroid therapy on linear growth of nephrotic children in a 5-year follow up was evaluated. Hospital records of 147 patients with diagnosis of NS within 1988-2008 who met the following criteria were reviewed and data extracted; age within 1 to 15 years, admission to the Center on the first episode of NS, steroid therapy for at least four months, minimum follow-up of five years, accurate and careful data registry of height measurements and treatment modalities.

Patients had been instructed to perform regular urine dipstick tests for proteinuria at home. All patients had normal renal function with serum

creatinine level of <0.8 mg/dl and creatinine clearance of  $\geq 100$  ml/min per  $1.73 \text{ m}^2$  at the last visit.

### Diagnosis of nephrotic syndrome:

Nephrotic syndrome was considered in patients who had proteinuria ( $>40 \text{ mg/m}^2/\text{h}$ ), and hypoalbuminemia (serum albumin  $<2.5 \text{ g/dl}$ ) according to the criteria of International Study of Kidney Disease in Children (ISKDC)<sup>[6,7]</sup>.

The 'Remission' of the disease was characterized by disappearance of albuminuria (dipstick testing 0 to trace), whereas 'Relapse' was defined as reappearance of proteinuria (dipstick testing  $\geq 2+$  for at least 3 consecutive days).

Kidney Biopsy had been done in children with early ( $<1$  year old) or late ( $>10$  years) disease onset, presence of gross hematuria, persistent hypertension with or without microscopic hematuria, low GFR unresponsive to correction of intravascular volume depletion, steroid resistance or dependence, frequent relapses, family history of glomerulopathies, and low C3 level.

### Treatment regimen:

Patients were initially treated with  $60 \text{ mg/m}^2/\text{d}$  ( $2 \text{ mg/kg/d}$ ) of oral steroids [prednisolone (PSL)] for at least 4 weeks. The therapy was followed by another 4 weeks with  $40 \text{ mg/m}^2/\text{d}$  ( $1.5 \text{ mg/kg/d}$ ) on alternate days and then it was tapered and stopped over the next 8-12 weeks.

The above therapeutic protocol had been prescribed for the first episode of the disease, while an individualized treatment had been considered for the next episodes. Steroid-sparing agents (including levamisole, cyclophosphamide, cyclosporine A, and azathioprine) had been given if indicated. The period of PSL administration, total dosage of PSL in terms of milligram per kilogram, and prescription of steroid-sparing agent treatments were recorded for each patient.

### Growth measurement:

Data on subjects' height at admission and in the last follow-up visit were gathered. In order to compare their linear growth with normal population and adjustment of age and sex, standard deviation score (SDS) of the height was calculated by plotting figures on Centers for Disease Control of USA (CDC) growth chart for the

respective age and sex. The height SDS ( $Ht_{SDS}$ ) was then calculated for each subject according to the following equation:

$$\text{Height SDS } (Ht_{SDS}) = (\text{patient's height} - \text{height at } 50^{\text{th}} \text{ percentile}) / (\frac{1}{2} \text{ height at } 50^{\text{th}} \text{ percentile} - \text{height at } 5^{\text{th}} \text{ percentile})$$

Changes in  $Ht_{SDS}$  ( $\delta Ht_{SDS}$ ) throughout follow-up visits were also calculated.

In order to evaluate the effect of pre-pubertal steroid therapy of NS on patients' linear growth, age of 10 years for female and 12 years for male patients was considered as the age of puberty.

### Statistical analysis:

Analysis used SPSS version 15 (SPSS, Inc, Chicago, IL, USA). All  $P$ -values were two-sided and considered statistically significant if  $P < 0.05$ . Chi-square test and student's  $t$ -test were used to compare losses and gains in percentiles with nominal variables such as histological type of NS, sex, and steroid-sparing medications. The Pearson's correlation was used to compare gains and losses in percentiles ( $\delta Ht_{SDS}$ ) in the patient population as a whole and in selected subgroups, considering continuous variables including onset age, age at last follow up, duration of PSL medication, and cumulative received PSL.

## Findings

Hospital records of 147 patients consisting of 99 (67.3%) males and 48 (32.7%) females were reviewed. Mean age of the subjects at first visit was 5.14 (range 1 to 15 years) and the mean follow-up time was 9.3 years (range 4 to 20 years). NS had a significantly earlier onset in the male

patients compared to the female group ( $P=0.024$ ). By the last follow-up visit, 6 (12.5%) female patients were  $\leq 10$  years and 42 (87.5%)  $> 10$  years old, while 34 (34.35%) male patients were  $\leq 12$  years and 65 (65.7%)  $> 12$  years old. Percutaneous renal biopsy was performed in 34.7% of the subjects, in 26 of whom histo-pathological findings were compatible with minimal change NS.

Mean total dose of prednisolone was 2205.90 mg/kg ( $\pm 1265.40$ ) with a mean duration of 7.05 years steroid therapy. Steroids were given to 69 subjects before puberty (54 males and 15 females), while 78 patients (45 males and 33 females) received PSL before and after puberty.

One, two, or three SSA were given in conjunction with prednisolone in 88 (59.9%) children (53, 21, or 14 patients respectively).

The mean  $Ht_{SDS}$  of the 147 patients' initial height was  $-0.76 \pm 1.96$ , and the final  $Ht_{SDS}$   $-0.89 \pm 2.05$  ( $P=0.49$ ). The height of 39 (21.1%) patients measured  $< 5\%$  CDC (less than 2 SD of normal population) at the first visit. However, 13 of these patients had reached the 5<sup>th</sup> percentile for height or higher (Table 1).

Sixty-two children (group A) had linear growth improvement during the follow-up time, whereas 85 (group B) were found to have growth retardation. Those who had improved linear growth included 40 males and 22 females with the mean initial and final  $Ht_{SDS}$  of  $-1.63 \pm 1.87$  and  $-0.08 \pm 2.13$  respectively ( $P < 0.001$ ).

First height of 22 (15.0%) of these children was below the 5<sup>th</sup> percentile. However, by the last follow-up visit, 13 of them had heights above 5<sup>th</sup> percentile. On the contrary, group B comprised 85 (59 male and 26 female) patients, whose average  $Ht_{SDS}$  for initial and final height records were  $-0.13 \pm 1.78$  and  $-1.59 \pm 1.68$  respectively (Table 2). From the first till the last follow up visit, 22

**Table 1:** Cross-tabulation between  $Ht_{SDS}$  of the first and last follow-up visit

Height SDS at initial visit	Height SDS at final follow-up			Total
	$< -2$	$\geq -2 < +2$	$> +2$	
$< -2$	18 (12.2%)	12 (8.2%)	1 (0.7%)	31 (21.1%)
$-2 \leq \text{and} < +2$	23 (15.6%)	76 (51.7%)	7 (4.8%)	106 (72.1%)
$+2 \leq$	1 (0.7%)	7 (4.8%)	2 (1.4%)	10 (6.8%)
<b>Total</b>	40 (27.2%)	97 (66.0%)	10 (6.8%)	147 (100.0%)

SDS: standard deviation score /  $\delta Ht$ : gains and losses in percentiles of height (growth change)

**Table 2:** Comparison of growth determinants between children according to their growth status, improvement (group A) or retardation (group B)

Category	Group A Mean ± SD	Group B Mean ± SD	P-value
Age at onset (Years)	5.0±3.7	5.2±3.2	>0.05
Age last follow-up (Years)	14.2±3.6	14.6±3.2	>0.05
Duration of steroid therapy (Years)	6.9±4.0	7.2±4.0	>0.05
Cumulative dose of Prednisolone (mg/kg)	2163.2±1257.6	2237.0±1277.4	>0.05
SDS for height at first visit	-1.6±1.9	-0.1±1.7	<0.001
SDS for height at last visit	0.8±2.0	-1.6±1.7	<0.001

SDS: standard deviation score

patients suffered negative growth below the 5<sup>th</sup> percentile while the rest, though showing negative growth, remained above the 5<sup>th</sup> percentile. As it is shown in Table 3, patients that had received SSA were younger and had received significantly higher doses of PSL.

Linear growth was not related to age at onset, age at final follow-up, duration of the disease, or cumulative dosage of PSL (Table 4).

We also compared the various histological types of NS for differences in the growth indicators. Significant differences were noticed in the age at onset ( $P=0.008$ ), duration ( $P=0.006$ ) and dose ( $P=0.006$ ) of steroid therapy, but not the age at the last follow-up visit.

## Discussion

In the past when steroids were not prescribed for NS, a major cause of growth retardation was

protein calorie malnutrition secondary to poor appetite, malabsorption due to GI tract edema, and proteinuria. Today, corticosteroids are believed to be the major cause, though emotional deprivation and chronic anxiety may also play a role. In NS, the dosage and duration of steroid therapy and renal function are principal factors associated with patients' linear growth. Prolonged high-dose corticosteroid administration suppresses growth. However, previous studies on NS raised controversies, whereas some reported loss of growth velocity in long-term steroid therapy<sup>[8-12]</sup>, others failed to show significant growth impairment<sup>[2,13-17]</sup>.

In the current study, we found no difference between subjects' first and final height. This is consistent with findings of other studies<sup>[5]</sup>. This favorable outcome might be due to long-term maintenance steroid therapy administered on alternate days. However, inclusion of children with a benign course of NS might also underestimate the side effects of prolonged steroid treatment. Linear growth was not related

**Table 3:** Comparison of growth indicators between patients who used prednisolone alone and those who used additional steroid-sparin

Category	Prednisolone	Prednisolone and SSA	P. value
Age at onset (Year)	5.6 ± 3.5	4.5 ± 3.5	0.039
Age at last follow-up (Year)	14.9 ± 4.5	14.1 ± 3.6	0.19
Duration of steroid therapy (Year)	5.7 ± 4.1	8.0 ± 3.8	0.001
Cumulative dose of Prednisolone (mg/kg)	1785.16 ± 1287.0	2488.0 ± 1175	0.001
ΔHt <sub>SDS</sub>	-0.1 ± 2.1	-0.1 ± 2.3	0.32

SSA: steroid sparing agent / ΔHt: gains and losses in percentiles of height (growth change)

**Table 4:** Pearson correlation coefficients and significance (*P*. values) between growth change ( $\delta Ht_{SDS}$ ) and growth determinants

Variable	Pearson's correlation	<i>P</i> . value
Age at onset (Year)	0.007	0.935
Age at last visit (Year)	-0.054	0.516
Duration of Prednisolone use (Year)	-0.027	0.740
Cumulative dose of Prednisolone (mg/kg)	-0.027	0.744

to gender, age at onset, age at final follow-up, duration of the disease, cumulative dosage of PSL, and NS histology.

There was no difference in mean  $Ht_{SDS}$  change between patients treated with and without steroid-sparing agents ( $-0.14 \pm 2.30$  vs.  $-0.11 \pm 2.13$ ;  $P=0.93$ ), which is in accordance with the findings of the study by Matsukura et al<sup>[5]</sup>, in which they found no association between height SDS change and SSA use in NS patients. As previously reported in a study by Padilla et al<sup>[18]</sup>, these agents are beneficial for linear growth through steroid sparing effect. Total PSL dose and duration of steroid therapy were significantly higher in the group who received additional steroid-sparing agents. This is in agreement with an earlier study by Kitamura<sup>[19]</sup>, which showed no significant reduction in the dose or duration of prednisolone treatment by concomitant SSA administration as it is more probable that these patients were steroid resistant.

We also compared various histological types of NS for differences in the potential growth determinants. Age at onset of the disease, as well as duration and dose of steroid therapy were significantly different. Though a larger population of renal biopsy is required to better elucidate these differences, our data is in agreement with those of the ISKDC which shows that MCNS is more frequent in younger ages<sup>[6,7]</sup>. MCNS could, due to its higher relapse rate, more likely cause longer duration and higher cumulative dose of steroid medication.

It is hard to explain the difference between the two groups (group A and B) as they were both comparable for potential determinants of  $Ht_{SDS}$ . Even the patients' clinical history did not reveal any data suggestive of chronic disease before

onset of the NS. One of the three patients with  $Ht_{SDS} < -2$  (below the 5<sup>th</sup> percentile) at first visit, achieved a  $Ht_{SDS}$  of  $\geq 5^{\text{th}}$  percentile for height by the end of follow up time. Loke et al<sup>[20]</sup> suggest that catch-up growth compensates for pubertal growth retardation.

In subgroup A, the gain of growth percentiles could possibly be attributed to several factors that acted in isolation or in concert: catch-up growth could have affected 34 of 99 male and 6 of 48 female children who received steroids intermittently and have gained growth percentiles before adolescence in accordance with a study by Loke et al<sup>[20]</sup>. A pubertal growth spurt might have occurred in 45 male and 33 female patients during the follow-up period.

Both effects (pubertal growth spurt and catch-up growth) might have been operating in 20 male and 9 female patients who were able to discontinue steroids before puberty and afterwards, still off steroids, entered puberty during the study period.

Considering the similarities of group B patients with those of group A, the cause of loss of growth percentiles in group B could be attributed to more sensitivity to side effects of PSL or a more severe disease. Corticosteroids are believed to be associated with elevation of serum IGF-1 levels that can result in IGF resistance and growth retardation<sup>[21]</sup>. However, this finding is in agreement with several other studies<sup>[22-25]</sup>.

It is noteworthy that the net effect of corticosteroids is highly variable. This could be due to differences in pharmacokinetics, steroid sensitivity, and severity of the underlying disease. Identifying these factors will be of great value in clinical practice, but until then, steroids side effects have to be monitored individually.

## Conclusion

Though height SDS was not significantly decreased in the studied subjects following prednisolone therapy according to the guidelines of ISKDC, mild retardation was observed in a group of children. In order to further elucidate this issue, additional research is required with regard to the period of active proteinuria, other causes of growth retardation such as hypothyroidism and vitamin D deficiency as well as accurate consideration of number of relapses.

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**Conflict of Interest:** None

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