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Systematic Review

Correlation between Corticosteroid Therapy and Height in Childhood Nephrotic Syndrome: A Systematic Review

Dian Anggraini P. Musalim [1*], Risky Vitria Prasetyo [2], Danti Nur Indiastuti [3], Mia Ratwita Andarsini [4]

[1] School of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2] Division of Nephrology, Department of Child Health, Dr. Soetomo General Hospital Surabaya, Indonesia
[3] Departement of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4] Division of Hematology Oncology, Department of Child Health, Dr. Soetomo General Hospital Surabaya, Indonesia

*** Corresponding Author:** Dian Anggraini P. Musalim, MD, Ph.D, School of Medicine, Universitas Airlangga, Surabaya, Indonesia. Fax: +62-83845455400, E-mail: dian.anggraini.permatasari-2017@fk.unair.ac.id

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Abstract

Introduction: Nephrotic syndrome is a clinical manifestation of glomerular disease characterized by severe or nephrotic-range proteinuria >3.5 g/24 hours. The treatment of nephrotic syndrome using corticosteroid especially prednisone, belongs to a class of glucocorticoid. Glucocorticoids are proven to be able to inhibit growth through several mechanisms. The objective of this study was to analyze the characteristic of height in childhood nephrotic syndrome and analyze the correlation between corticosteroid therapy and height in childhood nephrotic syndrome.

Methods: This systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline. The literature search was conducted in November 2020 in four databases: PubMed, Science Direct, Scopus, and DOAJ. Quality assessment was carried out using a quality assessment tool for quantitative studies from EPHPP.

Results: Six studies met the inclusion criteria for final analysis. The mean final height z-scores were -0.66 ± 3.04. The height z-scores of Steroid-Dependent Nephrotic Syndrome (SDNS) (-0.33 ± 0.87) and Steroid-Resistant Nephrotic Syndrome (SRNS) (-0.97 ± 1.34) patients were lower than Steroid-Sensitive Nephrotic Syndrome (SSNS) (-0.20 ± 3.14) patients. The height z-scores of nephrotic syndrome children were significantly lower than a normal population. Five studies suggested that there is a correlation between corticosteroid therapy and height on childhood nephrotic syndrome and one study did not find a correlation between them.

Conclusion: According to findings, there is a negative correlation between corticosteroid therapy and height in childhood nephrotic syndrome. Nephrotic syndrome children had significantly lower height z-scores than a normal population. The SDNS and SRNS patients are more susceptible to have a lower height than SNSS patients as they have a higher cumulative corticosteroid dose.

Keywords: Corticosteroid, Prednisone, Growth, Height, Nephrotic Syndrome

Introduction

Nephrotic syndrome is a clinical manifestation of glomerular disease characterized by severe (nephrotic-range) proteinuria >3.5 g/24 hours or a urine protein: creatinine ratio exceed 2. Proteinuria occurs due to an increase in permeability of the glomerular capillary walls. The triad of nephrotic syndromes that can be found is hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).[1] The incidence of nephrotic syndrome is increasing and has been reported to be the second most common disease found in pediatric nephrology.[2] The incidence of nephrotic syndrome in East Asia/Southeast Asia is 1.81/100000. This number is higher than the number in Europe and it is reported that the incidence is higher in developing countries.[3] In Indonesia, the incidence is reported to be 6 per 100 000 per year in children under 14 years.[4]

Treatment of nephrotic syndrome is based on guidelines from Kidney Disease: Improving Global Outcome (KDIGO) using corticosteroid especially prednisone or prednisolone, which belongs to a class of glucocorticoid. Oral prednisone is given once a day as a single daily dose starting at 60 mg/m^2/day or 2 mg/kg/day to a maximum 60 mg/day for 4-6 weeks and followed by alternate dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) for 2-5

months while gradually decreasing it or tapering off the dose.[5] If the patients experience a relapse, this therapy can last for 6-12 months.[4] Glucocorticoids have an immunomodulating effect that will remove circulating Vascular Permeability Factor (VPF) and have a direct effect on podocytes and/or on slit diaphragm to accelerate the glomerular filtration barrier back to normal. Glucocorticoids also have a pro-survival effect on podocytes and even glucocorticoids have a protective effect on the glomerular basement membrane and podocytes. It also reduces Vascular Endothelial Growth Factor (VEGF) levels while higher VEGF levels cause vascular leak in nephrotic syndrome. Furthermore, glucocorticoids will inhibit the production of cytokines at the genetic level by binding with nuclear transcription factors, especially NF-kB. Glucocorticoids will inhibit NF-kB activity by binding to DNA and will stimulate IkBα transcription to decrease NF-kB activity. Research on mice has indicated that glucocorticoids can reduce the expression of excess angioprotein-like-4, which causes massive proteinuria.[6]

Glucocorticoids have adverse side effects on growth. The side effect of glucocorticoids is to suppress osteoblastogenesis in the bone marrow and prolong the life span of osteoclasts so that it harms bone mass and growth, especially in the first six months of treatment. Glucocorticoids cause the body to lose calcium through renal excretion and inadequate absorption from the intestine, thus inducing osteoclast activity which will damage the bones.[7] In addition to causing impaired bone growth, glucocorticoids also cause physical growth retardation. Physical growth retardation that occur are caused by suppression of Growth Hormone (GH) secretion and other growth-supporting factors. Research shows that 77% of children have decreased height z-scores.[8] The results of other studies also showed permanent growth retardation in children with long-term exposure to corticosteroids.[9] Studies in India suggest that there is a positive correlation between decreased growth rate and cumulative dose of steroids in children with SDNS, infrequently relapsing nephrotic syndrome, and frequently relapsing nephrotic syndrome. This growth retardation is very likely to occur considering the prevalence of nephrotic syndrome sufferers, most of whom are children who are in their growth phases.[10] Therefore, this systematic review aims to analyze the characteristics of height in childhood nephrotic syndrome and to prove the correlation between corticosteroid therapy and height in childhood nephrotic syndrome.

Materials and Methods

Literature Search Strategy

This systematic review was carried out according to the PRISMA[11] guidelines. The PICO question of this study was: P = childhood nephrotic syndrome; I = corticosteroid or prednisone or prednisolone; C = without being compared; O = the height in childhood nephrotic syndrome. The literature search was carried out on four electronic databases, namely PubMed, Science Direct, DOAJ (Directory of Open Access Journals), and Scopus with keywords (corticosteroid OR prednisone OR prednisolone) AND (height) AND (nephrotic syndrome) AND (children). The literature search was carried out in November 2020.

Inclusion and Exclusion Criteria

The inclusion criteria of this systematic review included studies that had discussed the correlation between height and corticosteroid therapy in terms of the cumulative corticosteroid dose of nephrotic syndrome in children aged 1-18 years, literature published in the last 16 years (January 2004-November 2020), and only literature written in English. Literature that came from non-research studies such as review articles, conference papers, and book chapters were excluded from the systematic reviews. Duplicated literature and the results of quality assessment using the quality assessment tool for quantitative studies from EPHPP[12] which are classified as weak scales were alsoexcluded.

Data Extraction and Synthesis

The extracted data consisted of the author's name, year of publication, publication title, final height z-scores, main findings, and country of study (Table 1). The final height z-scores data will be processed into a new mean ± standard deviation using the formula found in the Cochrane Handbook for Systematic Review.[13] The used formula can be seen in Figure 1. If the data is obtained in the form of median and interquartile range, the data will be converted into mean ± standard deviation using the website http://vassarstats/net/median_range.html.

Table 1. Characteristics of Included Research Studies in this Systematic Review (N=6)

No	Author (Year)	Title	Final height z-scores	Main findings	Country
1	Freundlich et al. (2004)	Bone Histology in Steroid-Treated Children with Non-azotemic Nephrotic Syndrome	SSNS= -0.28±0.82	The height z-scores at the time of bone biopsy correlated inversely with the dose of administered prednisone (r = -0.71; p < 0.05).	Florida
2	Leonard et al. (2004)	Long-Term, High-Dose Glucocorticoids and Bone Mineral Content in Childhood Glucocorticoid-Sensitive Nephrotic Syndrome	SSNS= -0.10±1.00	As compared with the healthy control subjects, the SSNS patients had significantly lower height z-scores (0.35 ± 1.07 *vs* -0.10 ± 1.00; p = 0.008). The height z-scores was significantly and inversely correlated with the lifetime cumulative dose of glucocorticoids in milligrams (r = -0.28; p = 0.03) and milligrams per kilogram (r = -0.38; p = 0.003)	Philadelphia
3	Mohan et al. (2009)	Growth in Children with Steroid Sensitive Nephrotic Syndrome	-	The cumulative dose of steroids (as mg/kg/year) increase the ΔHt.Zs (Δ Height z-scores) decreases, it means that growth retardation worsens and this was statistically significant (p = 0.045) and the Pearson's correlation was -0.341 indicating fair correlation.	India
4	Madani et al. (2011)	The Effect of Long-term Steroid Therapy on Linear Growth of Nephrotic Children	All subjects= -0.89±2.05	There are 22 children whose initial height is below the 5th percentile but 13 children at the last visit had a height above the 5th percentile. Linear growth does not correlate with the accumulated dose of prednisolone (r = -0.03; p = 0.74).	Iran
5	Ribeiro et al. (2015)	Effect of Glucocorticoids on Growth and Bone Mineral Density in Children with Nephrotic Syndrome	All subjects= -0.1±0.45 SSNS= 0.38±0.48 SDNS= 0±0.40 SRNS= 0±0.56	Change in height z-scores is negatively correlated with the cumulative glucocorticoids dose (p = 0.04; R^2=15%). The higher the glucocorticoid dose received, the lower the z-scores will be. SDNS or SRNS patients had lower final height than SSNS patients (p <0.01). The final height z-scores are lower in the moderate and high-dose groups receiving glucocorticoids >0.2 mg/kg/day (p = 0.001).	Swiss
6	Valavi et al. (2020)	Effect of Prednisolone on Linear Growth in Children with Nephrotic Syndrome	All subjects= -0.5±1.07 SSNS= -0.42±0.99 SDNS= -0.44±0.96 SRNS= -1.59±1.34	The cumulative prednisolone dose is significantly correlated with worsening ΔHt.Zs (p = 0.001). The higher the cumulative dosage of prednisolone, the greater the decrease height z-scores. The correlation between cumulative dosage of prednisolone and ΔHt.Zs is higher in girls than boys (0.002 vs. 0.088). The correlation between cumulative dosage of prednisolone and Δheight predictions is higher in boys (0.003 vs. 0.111).	Iran

	Group 1	Group 2	Combined groups
Sample size	N_1	N_2	N_1+N_2
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SB_1	SB_2	$\sqrt{\frac{(N_1-1)SD_1^2 + (N_2-1)SD_2^2 + \frac{N_1N_2}{N_1+N_2}(M_1^2 + M_2^2 - 2M_1M_2}{N_1+N_2-1}}$

Figure 1. Formulae for Combining Groups.

Quality Appraisal

The quality appraisal uses the quality assessment tool for quantitative studies from the Effective Public Health Practice Project (EPHPP). There are six general assessment components (selection bias, study design, confounders, blinding, data collection

methods, and withdrawals and dropouts) as well as two additional research components (intervention integrity and analyses). The final score of each literature is grouped into three quality scales, namely strong, moderate, and weak according to the criteria determined by EPHPP.

Results

The search of the three databases resulted in 1238 literatures and the literature was screened based on the criteria of the year and type of article, which resulted in 232 literatures. The researchers excluded 194 literatures that did not fit the topic or which could not be fully accessed in full-text, hence there was 38 full-text literatures according to the topic. After analyzing 38 literatures, six studies were analyzed in this systematic review Figure 2). The section of studies was done in Florida (1 study), Philadelphia (1 study), India (1 study), Iran (2 studies), and Switzerland (1 study). Quality appraisal using the quality assessment tool for quantitative studies from EPHPP resulted in five literatures classified as strong and one literature classified as moderate so that no literature was excluded based on quality assessments. The results of data processing of the mean of final height z-scores can be seen in Table 2.

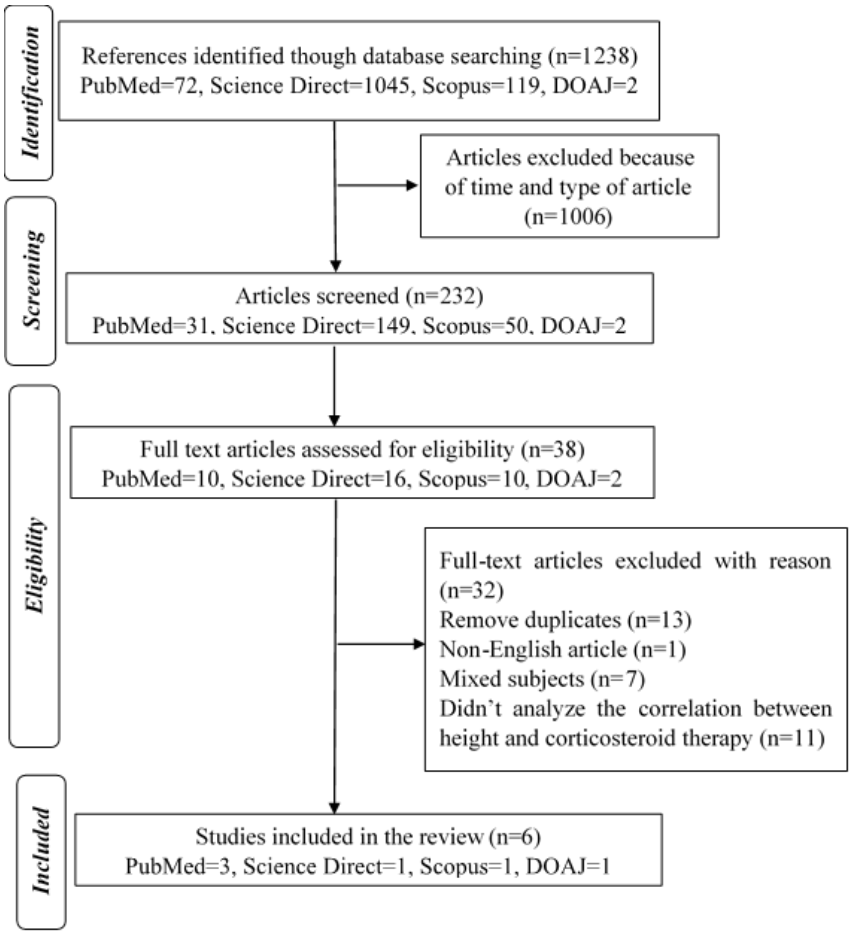

Figure 2. PRISMA Flow Chart Showing Literature Search Strategy.

Table 2. Results of Combined Mean±SD of Final Height Z-scores

No	Group	Combined mean±SD
1	All subjects	-0.66 ± 3.04
2	SSNS (steroid-sensitive nephrotic syndrome)	-0.20 ± 3.14
3	SDNS (steroid-dependent nephrotic syndrome)	-0.33 ± 0.87
4	SRNS (steroid-resistant nephrotic syndrome)	-0.97 ± 1.34

Discussion

Characteristics of Height in Childhood Nephrotic Syndrome

Research conducted by Madani et al.[14] reported 22 children (15%) whose initial height was below the 5th percentile but at the last visit 13 children had a height above the 5th percentile. Improvements in growth percentiles were also reported in another study, as many as 15 children (17%) were below the 5th percentile at the beginning of the study, and 8 of them were above the 5th percentile at the end of the study.[15]

At the end of the observation, 26 children (17.69%) in the study conducted by Madani et al.[14] were classified as short (<5th percentile). In some studies, short stature has been considered as a side effect of corticosteroid therapy in childhood nephrotic syndrome. Research in Turkey found 2 (6%) of 33 subjects who were classified as short and there were no pathological conditions that could cause short stature.[16] A study in Saudi Arabia found that 69.7% of subjects were of short stature and short stature was considered a complication of nephrotic syndrome after 10 years of treatment.[17]

A study by Leonard et al.[18] stated that the height z-scores of children with nephrotic syndrome is reported to be lower than normal children and this is statistically significant (-0.1 ± 1.00 *vs* 0.35 ± 1.07; $P = 0.008$). The height z-score of children with SSNS was also lower than normal children (-0.27 ± 0.89 *vs* 0.27 ± 0.92; $P<0.0001$).[19] Research in Nepal found that the final height of SSNS children aged 2-12 years had a mean of 114.30±18.60 cm, while as a comparison, using the normal height of children, the mean was 124.88 ± 104.42 cm.[20]

Research conducted by Freudlich[21] reported that the rate of growth velocity ranged from 1.5 to 10.6 cm/year, corresponding to a z-scores range from -1.6 to 3.2 and the mean of growth velocity z-scores was 1.0 ± 1.45. A study in Sri Lanka found the median height velocity of SDNS patients was 3.45 cm/year which was significantly lower than the height velocity of 6.15 cm/year for the nephrotic syndrome patients who were off corticosteroid in the past three months. Height velocity of SDNS patients was also significantly lower than that in the normal population.[22] It can actually be stated that children with SSNS are more likely to experience decreased growth velocity due to the long-term effects of corticosteroid treatment.[23]

Based on the study of Ribeiro et al.,[24] SDNS and SRNS patients had lower final height when compared to SSNS patients and this is statistically significant ($P<0.01$). Research by Valavi et al.[7] also reported the same results. The height z-scores of SDNS patients was -0.44 ± 0.96 and SRNS patients was -1.59 ± 1.34 while the height z-scores of SSNS was -0.42 ± 0.99.[7] Another study found that the mean height of SDNS patients was lower than nephrotic syndrome patients who had infrequent relapses and nephrotic syndrome patients who had frequent relapses.[25]

Correlation between Corticosteroid Therapy and Height in Childhood Nephrotic Syndrome

There are differences in the results of the six literatures used in this systematic review. Research by Valavi et al.,[7] Mohan et al.,[10] Leonard,[18] Freundlich,[21] and Ribeiro et al.[24] revealed that there is a correlation between corticosteroid therapy and height in childhood nephrotic syndrome, while the study by Madani et al.[14] found no specific correlation between them.

The insignificant correlation in the study of Madani et al.[14] was due to maintenance therapy given at alternate dose and the inclusion criteria of this study which only included subjects with a mild nephrotic syndrome without a prior chronic disease. Maintenance therapy given at alternate dose which has been reported in several studies can reduce growth restriction. Glucocorticoids increase the synthesis and secretion of GH from pituitary cells in vitro, activate transcription genes of GH, and increase Growth Hormone-Releasing Hormone (GHRH) receptors. However, it will inhibit the secretion of GH if given continuously.[26] This mechanism can explain that corticosteroid therapy at alternate dose can reduce growth restriction, while daily use of corticosteroids causes growth restriction. Pharmacokinetic variability and/or individual susceptibility to steroids, as well as the severity of the nephrotic syndrome, may also influence the effect of corticosteroid therapy itself.[14,27]

Some subjects also experienced an improvement in the height percentile from below the 5th percentile and improved to above the 5th percentile at the last visit. This can occur due to catch-up growth which compensates for the loss of height during corticosteroid therapy.[14] Catch-up growth was also reported in 31 of 47 children who received intermittent steroid therapy and they were able to return to normal curves before adolescence.

This growth acceleration or growth spurt started two years after discontinuation of steroid therapy and this catch-up process is almost equivalent to a loss of the height z-score during prednisolone therapy.[26] Other researchers stated that the growth rate decreased significantly in the first month during which the child was given the full dose of prednisolone therapy and returned to normal within one year.[6] When growth restriction occurs, it will decrease chondrocytes proliferation. But when the causes for growth restriction are solved, these cells show increased proliferative potential.[25]

Previous research[7,10,18,21,24] have reported that a correlation exists between corticosteroid therapy and height in childhood nephrotic syndrome. The negative effects of steroids on short-term growth depend on the dose and type of steroid. In general, this effect occurs in the first six months of treatment.[7] Corticosteroid therapy in large doses can interfere with the secretion of GH by increasing somatostatin and causing decreased response and activity of GH. Corticosteroid will stimulate the production of Insulin-Like Growth Factor-Binding Protein-3 (IGFBP-3), a growth inhibitor. Corticosteroids can also enter the growth plate, interfering with the growth rate and vascularity. Besides, corticosteroids can also modulate the action of thyroid hormones on the growth plate.[28,29] It is known that daily, supraphysiologic dose of glucocorticoids inhibit growth by decreasing the activity of Insulin-like Growth Factor-1 (IGF-1) in growing bones with the loss of IGFBP-3 in nephrotic children which may directly prompt growth defect and retardation.[10]

The decrease of height z-scores per year is higher in the medium dose (0.2-0.4 mg/kg/day) and high dose groups (>0.4 mg/kg/day). The low dose group (<0.2 mg/kg/day) tend to have increased height z-scores per year. Other studies have suggested a greater cutoff above 0.75 mg/kg/day.[24]

There is a negative correlation between growth and cumulative steroid dose in nephrotic syndrome. The higher the cumulative steroid dose, the lower the height z-scores will be.[10,15,18,21,24] Prednisone therapy was the only variable that correlated with worsening ΔHt.Zs in patients with nephrotic syndrome (P = 0.003; X^2 = 8.7). This study followed by 11.7 ± 3.5 years states that prednisolone therapy had a negative correlation with ΔHt.Zs (P = 0.003).[26] The group which had four or more relapses showed more decrease in mean height z-scores than the group with less than four relapses.[7]

The long-term effect of corticosteroid therapy is more significant in boy than girl subjects (P = 0.003 vs. P = 0.111).[7] Previous studies have revealed the same result and concluded that decreased height z-scores in boys is correlated with the delayed secondary sexual growth.[30] Delayed puberty in boys was also reported in another study in which 27 out of 30 boy subjects had delayed puberty (P = 0.012).[31] Furthermore, the peak growth of puberty is more inhibited in boys than in the population (+0.7 ± 0.8 years) with a significance value of <0.03. Boys also reached the final height longer than the population (P <0.01) but this did not happen to girl subjects.[26]

Studies on the effects of the cumulative prednisone dose for height are better observed in longitudinal studies.[7] The predicted values for height were lower after long-term prednisolone therapy. The study that was followed by 6.75 ± 3.75 years received significantly higher baseline height z-scores than post-therapy z-scores (-0.69 ± 0.80 *vs* -2.07 ± 1.61; P = 0.003) with a mean reduction of -1.37 ± 1.55.[8] This decrease occurred in the group that had a higher corticosteroid dose. There was a loss of height z-scores of 0.49 ± 0.6 in growth before puberty with a significance value of <0.001. This is while patients who had achieved final height lost their z-scores of 0.92 ± 0.8 from the onset of nephrotic syndrome (P <0.001).[26] Furthermore, there was also a loss of target z-scores of 0.68 ± 0.7 (P <0.001). In other studies, a significance value of 0.04 was reported.[24,26]

On 11-year-old boys and 9-year-old girls who were still receiving prednisone therapy had a greater risk of losing height z-scores. Linear growth retardation due to prednisolone therapy was reported to be more visible in the puberty group than in the pre-pubertal group.[26] The decrease height z-scores every year was more prevalent at the age after 12 years than before 12 years (-0.18 *vs* -0.09) with a significance value of 0.03.[27] Patients who exclusively received prednisone during the pre-pubertal period showed an increase of initial to final height z-scores (+0.73 ± 0.83) but patients who exclusively received prednisone during the puberty period had a loss of -0.37 ± 0.41 height z-scores with a significance value of <0.006.[31] This is because growth during puberty is sensitive to steroids (glucocorticoids also disturb the pituitary function to release gonadotropins hormone) or due to the larger accumulated doses during puberty. When children receive prednisolone

for more than six months per year so that the accumulated dose of prednisone increases, the child is 7.2 times more likely to lose height z-scores.[26,29]

The best way to prevent growth impairment in nephrotic children is avoiding an unnecessary prolonged corticosteroid with large doses, providing adequate intake of calories and proteins, and always monitoring their growth.[10]

Limitation

In a systematic review, there is a possibility of bias because the research from the obtained literature comes from various countries, and thereby the effect of corticosteroid therapy will vary. Moreover, there are also differences in the division of research groups from the obtained literature.

Conclusion

The incidence of nephrotic syndrome in children is increasing every year. Treatment of nephrotic syndrome using corticosteroids can last for 6-12 months. The side effect of corticosteroids is that they can interfere with the growth of children. There is a negative correlation between the cumulative corticosteroids dose and height in childhood nephrotic syndrome. This means that the higher the cumulative corticosteroids dose, the lower the height z-scores will be. The height z-scores of children with nephrotic syndrome is reported to be lower than normal children and this is statistically significant. Also, the SDNS and SRNS patients had lower height z-scores (-0.33 ± 0.87 and -0.97 ± 1.34) than SSNS patients (-0.20 ± 3.14) because the SDNS and SRNS patients received more doses and longer corticosteroid therapy than SSNS patients. Therefore, it is necessary to always monitor the growth of children with a nephrotic syndrome so that growth delays can be detected and treated immediately.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

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