Original Article

Linear growth and systemic glucocorticoid therapy in children with systemic lupus erythematosus

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Abstract

Background The use of long-term oral glucocorticoid therapy, specifically in the treatment of systemic lupus erythematosus (SLE), has increased in the past two decades. Chronic glucocorticoid use may lead to a linear growth disturbances.

Objective To determine the association between linear growth and systemic glucocorticoid therapy in pediatric SLE patients.

Methods This retrospective cohort study used medical record data of pediatric SLE patients. All subjects received systemic glucocorticoids. The linear growth parameters recorded in this study were height-for-age z-score (HAZ) and height velocity at 0, 6, and 12 months of treatment. We recorded potential risk factors of linear growth disturbance, such as pubertal status, sex, SLE severity, pulse methylprednisolone use, daily glucocorticoid dose, and nutritional status.

Results Of 42 patients with SLE, 83.3% were female, with a mean age of 13 years at diagnosis. Eighteen subjects (42.9%) experienced abnormal height velocity. There was a significant reduction in HAZ between 0, 6, and 12 months of treatment (P=0.016). Between 0 and 6 months of treatment, there was a mean HAZ decrease of 0.11 (P=0.015). There was a trend towards a risk for decreased HAZ at 6 and 12 months of treatment with pulse methylprednisolone (RR 1.25 and 1.27, respectively), as well as for abnormal height velocity (RR 1.73), but they did not reach statistical significance.

Conclusion There is a reduction in linear growth in the first 12 months of systemic glucocorticoid therapy in children with SLE. Administration of systemic glucocorticoid significantly reduces HAZ in the first six months of therapy. **[Paediatr Indones. 2022;62:37-43 ; DOI: 10.14238/pi62.1.2022.37-43].**

Corticosteroids are synthetic analogues of the steroid hormones produced and released by the adrenal cortex. Corticosteroids consist of two types, glucocorticoids and mineralocorticoids.[1] Long-term oral glucocorticoid therapy has increased 34% in the past 20 years.[2]

Systemic lupus erythematosus (SLE) is one of the diseases commonly treated with glucocorticoid therapy. The annual incidence of SLE in the United States is approximately 5.1 cases per 100,000. The reported prevalence of SLE is 52 cases per 100,000, with a female-to-male ratio of 9-14:1. National epidemiological data on SLE in Indonesia are limited. In 2002, SLE accounted for 1.4% of outpatient visits to the Internal Medicine Rheumatology Clinic at Cipto Mangunkusumo Hospital, Jakarta. In 2010, this proportion was 10.5% at the Rheumatology Polyclinic, Hasan Sadikin Hospital, Bandung.[3] At Sardjito Hospital, Yogyakarta, the incidence of new SLE cases from 2015 to 2017 was 10.6%.[4]

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Glucocorticoids are the mainstay of therapy in pediatric SLE patients with or without major organ involvement.[5] One of the long-term side effects of glucocorticoids is growth disorders. Growth retardation occurs in children using hydrocortisone at a dose of ≥ 45 mg/m²/day or its equivalent.[1] Growth disturbance is dose-dependent and mostly occurs after six months of treatment.[6]

Glucocorticoids have a direct inhibitory effect on growth plates. Glucocorticoids slow longitudinal bone growth by inhibiting chondrocyte proliferation, hypertrophy, and cartilage matrix synthesis. Glucocorticoids also inhibit cross-sectional bone growth in the periosteum.[7] The side effects of methylprednisolone on muscles and bones include osteoporosis, osteonecrosis, and myopathy.[8]

Several studies, as reported in a systematic review, have shown a 0.7% decrease in the annual growth rate of children who used inhaled corticosteroids.[9] However, to our knowledge, there have been no worldwide prevalence studies for pediatric patients receiving systemic corticosteroid therapy and no prevalence studies on systemic corticosteroid therapy associated with height-for-age. Glucocorticoids cause muscle wasting and decreased bone formation. Osteoporosis induced by steroids increases if the duration of treatment is >3 months or consists of 3 courses of treatment per year with at least a 5 mg oral dose of prednisone per day. Glucocorticoids produce oxidative stress in many tissues including bone, nerves, and muscle.[10]

Steroids play an important role in cartilage synthesis, but at high doses and long duration, they may affect growth and secretion of growth hormone by increasing hypothalamic tone, which then suppresses the mRNA from IGF-1 (insulin-like growth factor-1) in the liver. If the levels of growth hormone and IGF-1 remain normal, side effects may occur through a tissue-level mechanism, causing loss of growth plate sensitivity.[11]

A review showed that the use of low or moderate daily dose of inhaled corticosteroids in children with mild to moderate persistent asthma was associated with a decrease in mean height of 0.48 cm per year and a linear change in height growth of 0.61 cm over one year. The growth-suppressing effect of inhaled corticosteroids appears to be maximal during the first year of treatment.[12] A study showed that steroids induced a decrease of height in patients that received steroid therapy at the age of 12-16 years, with patients' height having a mean height -2SD and 10 cm below the expected height.[13] In contrast, another study in Denpasar, Bali, showed that height and bone age had no relationship with the cumulative steroid dose, duration of therapy, or number of relapses in nephrotic syndrome patients who received long-term steroid therapy.[14] Because of the lack of agreement among studies, we aimed to assess for a possible association between linear growth in pediatric SLE patients who received systemic glucocorticoid therapy.

Methods

This was a retrospective cohort study in children aged 5 to 18 years who were diagnosed with SLE based on the *1997 American College of Rheumatology* (ARC) criteria at Sardjito General Hospital from August 2018 to July 2020 and were followed up for at least 12 months following their SLE diagnosis. Patients had height data recorded over the period of systemic glucocorticoid administration. The exclusion criteria were incomplete medical records, a history of familial growth delay, chronic renal failure or primary malignancy or metastases in the kidney, or pituitary tumors.

Patients with SLE were identified in the medical record database system based by the ICD 10 code M32.9. Data collected from patient medical records were age, gender, date of diagnosis, nutritional status, and height. We also noted the type and dose of glucocorticoid therapy that patients received during follow-up, as well as the use of pulse methylprednisolone.

Linear growth was defined as growth due to increased bone mass, observed as increase in height.[15] The linear growth parameters used in this study were height-for-age z-score (HAZ) and height velocity. Determination of HAZ was based on the *WHO* growth charts and classified as short, normal, or tall.[16] Height velocity was defined based on the AAP curve and categorized as normal when it was on or above the 50th percentile or abnormal when it was less than the 50th percentile.[17]

The diagnosis of SLE was classified as either mild-to-moderate or severe. A patient was considered to have mild-to-moderate SLE when there were cutaneous manifestations, and non-life-threatening arthritis; they may also have mild-to-moderate nephritis (class I and

II lupus nephritis), and/or thrombocytopenia (platelets 20,000-50,000/mm³). Severe SLE was characterized by serositis disorders (pleuritis and pericarditis), blood disorders (AIHA), and neurological disorders.[17]

Nutritional status was determined according to *2000 Waterlow CDC* criteria using weight-for-height (percentage of actual weight over ideal weight for height). Weight-for-height of >120%, 110% to 120%, 90% to <110%, 70% to 90%, and <70% were classified as obese, overweight, normal, undernourished, and severely malnourished, respectively.[18] Subjects who had received methylprednisolone at a dose of 1,000 mg/day for 1-3 days were grouped as pulse methylprednisolone users. Glucocorticoid regimens were administered in various doses, from low (prednisone 0.1-0.2 mg/kg/day), moderate (0.2-0.5 mg/kg/day), to high (0.5-1 mg/kg/day). Patients receiving low and moderate doses were grouped together.[19]

We used *SPSS version 22* (*IBM*, Armonk, New York) to aid in data analysis. Repeated measure ANOVA with pairwise comparison and Fisher's exact test were used in bivariate analysis to determine the association between height status at different observation points, as well as risk factors that affect linear growth. Results with P values <0.05 were considered to be statistically significant.

The study protocol had been approved by the Ethics Committee of the Faculty of Medicine, Gadjah Mada University. Patient identity data were kept confidential.

Results

There were 118 patients diagnosed with SLE from August 1, 2018 - July 31, 2020. We excluded 66 patients due to incomplete medical records and 10 with chronic kidney disease. The remaining 42 patients were included in the analysis.

The baseline characteristics of subjects are presented in **Table 1**. Of 42 subjects, 35 (83.3%) were female. The median age at diagnosis was 13 (range 9-17) years, with the majority of patients having started puberty (85.7%). There were slightly fewer subjects with severe SLE (47.6%) than mild-moderate SLE (52.4%). Most patients had good nutritional status at diagnosis (52.3%). Subjects' height-for-age status at the start of glucocorticoid therapy were mostly normal

(59.5%), followed by short stature (40.5%). Subjects' mean height velocity was 2.28 cm per year; height velocity was abnormal in 42.9% of subjects. Most patients (69.1%) received methylprednisolone therapy; 47.5% received pulse methylprednisolone. Based on the cumulative doses received, 76.2% of patients had high-dose glucocorticoid therapy.

Comparison of HAZ at 0, 6, and 12 months of glucocorticoid therapy is presented in **Tables 2** and **3**. Repeated measure ANOVA test revealed a significant difference in HAZ between 0 to 12 months after diagnosis (P=0.016) (**Table 2**). Continued analysis with pairwise comparison between 0 and 6 months, 0 and 12 months, and 6 and 12 months of glucocorticoid therapy revealed a statistically significant decrease in mean

Table 1. Baseline characteristics of subjects

Characteristics	N=42
Sex, n (%)	
Female	35 (83.3)
Male	7 (16.7)
Disease severity, n (%)	
Severe	20 (47.6)
Mild-moderate	22 (52.4)
Pubertal status at diagnosis, n (%)	
Pre-pubertal	6 (14.3)
Pubertal	36 (85.7)
Therapy received, n (%)	
Methylprednisolone	29 (69.1)
Prednisone	9 (26.2)
Combination	4 (4.7)
Pulse methylprednisolone use, n (%)	
Yes	20 (47.6)
No	22 (52.4)
Cumulative dose, n (%)	
High	32 (76.2)
Low-moderate	10 (23.8)
Nutritional status at diagnosis, n (%)	
Severely malnourished	0
Undernourished	11 (26.2)
Normal	22 (52.3)
Overweight	7 (16.7)
Obese	2 (4.8)
Height for age, n (%)	
Short	7 (40.5)
Normal	25 (59.5)
Tall	0
Height velocity, cm/year	
Mean (SD)	2.28 (1.89)
Median (range)	2 (0-10.00)
Height velocity category, n (%)	
Abnormal	18 (42.9)
Normal	24 (57.1)

HAZ of 0.11 between 0 to 6 months of glucocorticoid therapy (P=0.015) compared to other periods (**Table 3**). There was a mean increase in HAZ of 0.03 from 6 to 12 months of glucocorticoid therapy (P=1.000) and a mean decrease of 0.08 from 0 to 12 months (P=0.446), but neither were statistically significant. Thus, glucocorticoid administration significantly reduced HAZ in the first 6 months.

Table 4 shows the results of bivariate analysis to evaluate possible risk factors that affect changes in HAZ at 6 months of glucocorticoid treatment. At 6 months, 32 (76.2%) subjects had decreased HAZ. Pulse methylprednisolone treatment had the highest risk ratio (RR) for decrease in HAZ at 6 months, but the association did not reach statistical significance (RR 1.125; p=0.284; 95%CI 0.89 to 1.75). Similarly, none of the other potential risk factors analyzed were statistically significant.

Bivariate analysis of potential risk factors for HAZ reduction at 12 months is shown in **Table 5**. At 12 months, 28 (66.7%) subjects had decreased HAZ. There was a trend towards increased risk of decreased HAZ at 12 months in the presence of malnutrition, pre-pubertal age, and pulse methylprednisolone use, but none were statistically significant.

Table 6 shows the bivariate analysis of potential risk factors for abnormal height velocity. Pulse methylprednisolone use, pre-pubertal age at diagnosis, and severe SLE were associated with higher proportions of abnormal height velocity, but none were found to be statistically significant.

Overall, our analyses revealed that MP pulse use was more risk factor for decreased HAZ at 6 and 12 months, and more risk factor for abnormal height velocity. Pre-pubertal age was more risk factor for decreased HAZ at 12 months and for abnormal height velocity. In addition, malnutrition was more risk factor for decreased HAZ at 12 months. But not statistical significant.

Table 2. Comparison of HAZ at 0, 6, and 12 months of glucocorticoid treatment (repeated measures ANOVA)

Months of treatment	Mean HAZ (SD)	P value
0	-1.59 (1.26)	0.016
6	-1.70 (1.29)	
12	-1.67 (1.16)	

Table 3. Comparison of HAZ at 0, 6, and 12 months of glucocorticoid treatment (ANOVA with pairwise comparison)

Comparison	Difference in mean HAZ	P value
0 *vs.* 6 months of treatment	-0.29	0.015
0 *vs.* 12 months of treatment	-0.08	0.446
6 *vs.* 12 months of treatment	0.03	1.000

Table 4. Potential risk factors for deteriorating height status at 6 months of treatment

Risk factor	HAZ change		RR	95%CI	P value
	Decreased (n=32)	Not decreased (n=10)			
Age			1.11	0.74 to 1.66	1.000
Pre-puberty	5	1			
Puberty (ref.)	27	9			
Sex			1.08	0.65 to 1.78	1.000
Female	27	8			
Male (ref.)	5	2			
Severity of SLE			1.10	0.78 to 1.54	0.723
Severe	16	4			
Mild-moderate (ref.)	16	6			
Pulse methylprednisolone			1.25	0.89 to 1.75	0.284
Yes	17	3			
No (ref.)	15	7			
Daily dose			1.12	0.72 to 1.74	0.678
High	25	7			
Low-moderate (ref.)	7	3			
Nutritional status at diagnosis			1.10	0.78 to 1.56	1.000
Undernourished	9	2			
Normal (ref.)	23	8			

Table 5. Potential risk factors for deteriorating height status at 12 months of treatment

Risk factor	HAZ change		RR	95%CI	P value
	Decreased (n=28)	Not decreased (n=14)			
Age			1.30	0.85 to 2.01	0.645
Pre-puberty	5	1			
Puberty (ref.)	23	13			
Sex			0.92	0.54 to 1.56	1.000
Female	23	12			
Male (ref.)	5	2			
Severity of SLE			0.95	0.62 TO 1.47	0.827
Severe	13	7			
Mild-moderate (ref.)	15	7			
Pulse methylprednisolone			1.27	0.83 to 1.950.275	0.275
Yes	15	5			
No (ref.)	13	9			
Daily dose			0.94	0.58 to 1.521	1.000
High	21	11			
Low-moderate (ref.)	7	3			
Nutritional status at diagnosis			1.34	0.89 to 1.98	0.283
Undernourished	9	2			
Normal (ref.)	19	12			

Table 6. Potential risk factors for abnormal height velocity

Risk factor	Height velocity		RR	95%CI	P value
	Abnormal (n=18)	Normal (n=24))			
Age			1.71	0.85 to 3.45	0.375
Pre-puberty	4	2			
Puberty (ref.)	14	22			
Sex			0.52	0.28 to 1.98	0.118
Female	13	22			
Male (ref.)	5	2			
Severity of SLE			1.10	0.55 to 2.21	0.789
Severe	9	11			
Mild-moderate (ref.)	9	13			
Pulse methylprednisolone			1.73	0.83 to 3.58	0.129
Yes	11	9			
No (ref.)	7	15			
Daily dose			0.81	0.38 to 1.72	0.720
High	13	19			
Low-moderate (ref.)	5	5			
Nutritional status at diagnosis			1.08	0.50 to 2.34	1.000
Undernourished	5	6			
Normal (ref.)	13	18			

Discussion

This study was conducted at a major national referral hospital accepting patients with level 3 severity, who have multiple diagnoses as well as chronic diseases.[20] We had more female than male subjects, which was in agreement with an epidemiological study reporting a female predominance in SLE.[21] The ratio of girls to boys changes with age: before puberty, the ratio is 3:1; after puberty, the ratio increases to 9:1.[22] In our study, 83.3% of subjects were female and 16.7% were male. Most SLE is diagnosed in adolescence, which is consistent with our findings, as 85.6% of subjects were diagnosed with SLE at pubertal age, while only 14.3% were pre-

pubertal. Our subjects' mean age was 13 years.

Most subjects' nutritional status at diagnosis was normal (52.3%), followed by overweight (16.7%) and obese (4.8%). A previous study reported that 1.2% of SLE patients were malnourished, 35.9% overweight, and 25.8% obese. However, the association between obesity, sociodemographic and clinical characteristics, drug use, and physical activity in SLE patients has not been widely studied.[23]

Glucocorticoids are the main treatment of SLE for induction therapy, treating acute flares, and improving the prognosis of severe SLE.[19] In our study, all patients with severe SLE were given pulse methylprednisolone. A daily dose of prednisone >6 mg has been shown to increase the risk of organ damage by 50%. Rapid bone loss of up to 12% may occur during the first 6 to 12 months of glucocorticoid therapy; glucocorticoid-induced osteoporosis is the most common cause of iatrogenic osteoporosis.[21] Bone loss is often exacerbated by chronic glucocorticoid use, which increases osteoclast activity. The most commonly used method of assessing bone mineral density and bone mass is absorptiometric X-ray examination, although computed tomography is more accurate. Children with SLE on chronic glucocorticoid therapy who receive prednisone at doses of >0.15 mg/kg/day for three months or more should undergo bone density evaluation.[24]

At high concentrations, glucocorticoids dramatically decrease bone growth rate, osteoblast count, as well as osteocyte count and activity. Evidence for a direct effect independent of an inflammatory effect was found in a study in which healthy subjects given 5 mg of prednisone daily experienced a rapid and significant decrease in osteoclastin, a specific marker of bone formation. The changes did not continue after discontinuation of prednisone.[25]

Bone damage and short-term bone growth impairment are dependent on the type and dose of glucocorticoids and occur most prominently during the first six months of therapy. Glucocorticoids have the effect of suppressing osteoblastogenesis in bone marrow and promoting osteoblast and osteocyte apoptosis, thereby leading to decreased bone formation.[6] This observation was consistent with our findings of significant reductions in HAZ at 6 months of therapy.

In 42 SLE patients who received high-dose or low-to-moderate glucocorticoid therapy, 42.9% had abnormal height velocity. There was also a significant change in HAZ associated with long-term (>6 months) glucocorticoid therapy. According to a previous study, an earlier effect of glucocorticoids on bone varies between 1.5 and 20% loss of BMD in the first 6 months after starting therapy, followed by a slower rate of 1-3% per year thereafter.[26]

The strength of this study was that we were able to determine the incidence of subjects experiencing linear growth retardation. Our analysis demonstrated the changes of linear growth parameters over time, as well as trends in linear growth changes in the presence of potential risk factors. However, there were subjects who did not visit the hospital every month for follow-ups, such that it was difficult to regularly record the dosage of glucocorticoids.

In conclusion, there was a significant association between reduced linear growth and systemic glucocorticoid therapy in pediatric SLE patients. Administration of systemic glucocorticoids significantly reduced HAZ in the first 6 months of therapy. Further research using a prospective cohort method with closer monitoring of height and glucocorticoid doses is needed to further elucidate the association between potential risk factors with linear growth.

Conflict of interest

None declared.

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