Paediatrica Indonesiana

VOLUME 55 July• 2015 NUMBER 4

Original Article

Corticosteroids and obesity in steroid-sensitive and steroid-resistant nephrotic syndrome

Nina Lestari, Neti Nurani, Madarina Julia

Abstract

Background Children with nephrotic syndrome need high-dose corticosteroids to achieve remission. Studies have estimated a 35-43% risk of obesity in these patients after corticosteroid treatment.

Objective To determine the prevalence of obesity in children who received corticosteroids for nephrotic syndrome, and to compare the risk of obesity in children with steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS).

Methods We performed a retrospective cohort study in 50 children with SSNS or SRNS who received corticosteroid treatment. Obesity was defined to be a BMI-for-age Z-score above +2.0 SD, according to the *WHO Growth Reference 2007*. Central obesity was defined to be a waist-to-height ratio > 0.50.

Results The overall prevalence of obesity was 22%, with 29% and 14% in the SSNS and SRNS groups, respectively. The overall prevalence of central obesity was 50%, with 54% and 46% in the SSNS and SRNS groups, respectively. The cumulative steroid doses in this study were not significantly different between the SSNS and SRNS groups. There were also no significant differences between groups for risk of obesity (RR 2.53; 95%CI 0.58 to 10.99) or central obesity (RR 1.39; 95%CI 0.45 to 4.25).

Conclusion In children with nephrotic syndrome who received corticosteroids, the prevalence of obesity is 22% and of central obesity is 50%. In a comparison of SSNS and SRNS groups, cumulative steroid dose as well as risks of obesity and central obesity do not significantly differ between groups. **[Paediatr Indones. 2015;55:194-8]**.

Keywords*: nephrotic syndrome, obesity, central obesity, body mass index, waist-to-height ratio*

Nephrotic syndrome (NS) is a chronic glomerular disease that mostly occurs in children. The incidence of nephrotic syndrome is 2-7 per 100,000 children per year. Indonesia was reported to have 6 cases per 100,000 children per year. Children with nephrotic syndrome receive a corticosteroid regimen to achieve and maintain remission. Of the potential side effects of corticosteroid, obesity is one of the most common. Previous studies estimated a 35-43% risk of obesity after treatment with corticosteroids.[1-5]

A significantly increased risk of obesity in children with steroid sensitive nephrotic syndrome (SSNS) has been reported.[5-6] However, previous studies did not consider the effect of the regimen of steroids, cumulative corticosteroid dose, cumulative steroid-free period, physical activity or calorie intake.[5] In addition, there have been few studies on the association between nephrotic syndrome (NS) and the incidence of central obesity in children.[6]

From the Department of Child Health, Gadjah Mada University Medical School/Sardjito Hospital Yogyakarta, Indonesia.

Reprint requests to: Madarina Julia, Department of Child Health, Universitas Gadjah Mada Medical School/Dr. Sardjito Hospital, Jln. Kesehatan no.1, Sekip Utara, Yogyakarta 55284, Indonesia. Tel. +62-815-78505740, Fax. +62-274-583745. E-mail: madarinajulia@yahoo.com, madarinajulia@ugm.ac.id.

Steroid sensitive nephrotic syndrome (SSNS) patients receive frequent steroid treatment because of recurrent relapses, while steroid resistant nephrotic syndrome (SRNS) patients receive fewer repeated doses, due to the use of steroid-sparing agents. We aimed to evaluate the risks for obesity and central obesity in SSNS and SRNS children.

Methods

We conducted a retrospective study involving a cohort of children with NS who visited the Outpatient Clinic of the Pediatric Nephrology Department of Dr. Sardjito Hospital from September 1, 2012 to October 31, 2013. The cohort comprised of 50 children with NS who were born between 1995 and 2010.

We reviewed medical records to determine the type of NS, based on the corticosteroid regimen, i.e., SSNS or SRNS. The following information was also obtained: age at diagnosis of NS, response to steroid treatment, type of corticosteroid used, number of full initial dose, cumulative corticosteroid dose, cumulative steroid-free period, and the time lapsed between the last steroid use and the day of measurement. We did not assess subjects' obesity status before the start of steroid treatment, because all of them had anasarca.

Inclusion criteria were children with NS, aged 3-18 years, in remission with negative or minimal proteinuria, who were either undergoing low-dose prednisone therapy (≤ 0.5 mg /kg/day) or had stopped using steroids. Exclusion criteria were patients with edema or other chronic diseases that affected growth or body composition.

Outcome data, i.e., anthropometric measurements, were obtained when the subjects visited the clinic. Weights were measured with an electronic digital scale to the nearest 0.1 kg, while height were measured with a stadiometer to the nearest 0.1 cm. Data on weight and height were converted into body mass index (BMI) by dividing weight in kg by height in meters-squared (kg/m^2). Obesity was defined as a BMI-for-age Z-score above +2.0 SD, according to the *WHO Growth Reference 2007*. Waist circumferences were measured with a non-stretchable measuring tape passing the umbilicus, to the nearest 0.1 cm. Central obesity was defined as a waist-to-height ratio > 0.50.

Data taken from medical records were age at NS diagnosis, response to steroid treatment, type of corticosteroid used, number of full initial dose, cumulative corticosteroid dose, cumulative steroid-free period, and the time lapsed between the last steroid use and the day of measurement.

Diet was assessed using a 24-hour dietary recall method. Subjects, parents, or caregivers were interviewed to recall foods that were consumed by the subjects in the 24 hours prior to the interview. This information was completed by the following: how the food was cooked and served, food brand, number, and portion size of the food.[7]

Physical activity was measured using the *Physical Activity Questionnaire for Older Children* (PAQ-C) and *Physical Activity Questionnaire for Adolescents* (PAQ-A).[8] These questionnaires were used to assess the subjects' physical activity during the seven days prior.

Data were analyzed using Chi-square and Fisher's test with a 95% confidence level (CI), α of 5%, and power of 80% with 20% β, at a significance level of $P < 0.05$. The risk for obesity and central obesity was calculated using relative risk (RR) with 95%CI. Pearson's correlation was used to assess for associations between cumulative corticosteroid dose, cumulative steroid-free period, and time lapsed between last steroid use and the day of measurement, and BMI Z-scores and waist-to-height ratios. This study was approved by the Ethics Committee for Research at Gadjah Mada University.

Results

Fifty children were included as subjects of the study. The subjects' characteristics are presented in **Table 1**. The overall prevalence of obesity was 22%, 8/28 in SSNS group and 3/23 in SRSS group. The overall prevalence of central obesity was 50%, 15/28 in SSNS group and 10/22 in SRNS group. There were no significant differences between the SSNS and the SRNS groups in terms of risks of obesity (RR 2.53; 95%CI 0.58 to 10.99) or central obesity (RR 1.39; 95%CI 0.45 to 4.25) (**Table 2** and **Table 3**).

The three patients who had stopped receiving steroids for more than six months had neither obesity nor central obesity. Although not statistically significant, receiving more than one full initial dose

increased the risk of central obesity (RR 1.76; 95%CI 0.99 to 3.13). The prevalence of central obesity was 17/27 in those who received more than one full initial dose, but only 8/23 in those who received one initial dose. Similar findings were observed for cumulative doses, with patients who received a higher total cumulative dose (>7,200 mg) tending to have more central obesity; but this result was not statistically significant (RR 1.76; 95%CI 0.99 to 3.13).

There were no significant correlations between cumulative corticosteroid dose, cumulative steroid-free period, or the time lapsed between last steroid use and the day of measurement, and BMI Z-scores or waist-to-height ratio (**Table 3**).

Table 1. Baseline characteristics of subjects

Characteristics	SNSS group (n= 28)	SRNS group (n = 22)	P value
Gender, n			0.03
Male	24	13	
Female	4	9	
Mean age at diagnosis (SD), years	7.07 (4.11)	7.29 (4.63)	0.96[b]
Type of corticosteroid, n			0.16[a]
Prednisone	25	16	
Methylprednisolone	3	6	
Full initial dose, [c] n			0.01
1 time	8	15	
>1 times	20	7	
Mean cumulative corticosteroid dose (SD), mg/kg BW	219.58 (127.31)	298.91 (219.99)	0.12[b]
Mean steroid-free duration (SD), months	18.64 (30.99)	12.09 (21.56)	0.02[b]
Mean time lapsed between last dose of steroid until the study visit (SD), months	3.22 (9.17)	1.0 (2.20)	0.01[b]
Physical activity,[d] n			1.00[a]
Low (score 1-3)	27	22	
High (score 4-5)	1	0	
Mean daily energy intake (SD),[e] % RDA	70.18 (22.39)	74.51 (23.28)	0.51
Mean waist circumference (SD), cm	66.98 (10.71)	64.36 (12.87)	0.29[b]
Mean hip circumference (SD), cm	72.21 (12.43)	71.41 (12.56)	0.82
Mean arm circumference (SD), cm	21.25 (3.93)	20.77 (5.07)	0.44[b]
Mean waist-to-height ratio (SD)	0.52 (0.08)	0.51 (0.08)	0.82[b]
Mean BMI Z-score (SD)	0.70 (1.58)	0.44 (1.25)	0.53

SSNS: steroid-sensitive nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome, BMI: body mass index.
[a] Fisher's Exact Test
[b] Mann-Whitney Test
[c] standard full corticosteroid treatment for initial episode of NS
[d] measured with physical activity questionnaire for older children and adolescents
[e] measured with a 24-hour-recall diet

Table 2. Association between SSNS or SRNS and obesity or central obesity

Type of obesity	SSNS group (n=28)	SRNS group (n=22)	RR (95%CI)	P value
Obesity,[a] n				
Yes	8	3	2.53 (0.58 to 10.99)	0.31[c]
No	20	19		
Central obesity,[b] n				
Yes	15	10	1.39 (0.45 to 4.25)	0.57
No	13	12		

[a] BMI-for-age z-scores above +2.0 according to the WHO Growth Reference 2007
[b] waist-to-height ratio > 0.50
[c] Fisher's exact test

Table 3. Pearson's correlation between cumulative corticosteroid dose, cumulative steroid-free period, and the time lapsed between last steroid use and the day of measurement and BMI Z-scores and waist-to-height ratio

	BMI-z-score		Waist-to-height ratio	
	R	P value	R	P value
Cumulative corticosteroid dose	0.06	0.68	-0.17	0.23
Cumulative steroid-free period	-0.01	0.93	-0.06	0.69
Last time steroid*	0.01	0.95	-0.22	0.13

* Time lapsed between last steroid use and the day of measurement

Discussion

Because of differences in clinical response, SSNS patients were more likely to receive only one initial dose. They also had longer cumulative steroid-free periods and longer time lapsed between last steroid use and the day of measurement. Of the three patients who had stopped using steroids for more than six months, all were from the SSNS group. Because of partial responses and frequent relapses, it is more difficult to stop treatment in SRNS patients.[9-12]

The average ratio of waist circumference to height was 0.52 in SSNS patients and 0.51 in SRNS patients. Children with ratios>0.50 are considered to have central obesity. Using this parameter, half of our subjects had central obesity. However, using a BMI-for-age Z-score cut off >+2.0 SD, less than one-fourth of our subjects had obesity.

Central or abdominal obesity is a better predictor of cardiovascular risk than BMI. One of the limitations of BMI in diagnosing obesity, is that it does not take into account the presence of abdominal obesity, which is strongly related to cardiovascular disease and diabetes mellitus. Therefore, the ratio of waist circumference to height is the best proxy for central obesity in children.[6,13-15]

The prevalence of obesity was 29% in the SSNS group. Compared to SRNS, SSNS was not a risk factor for childhood obesity. A study in Cipto Mangunkusumo Hospital, Jakarta, Indonesia observed a 23% prevalence of obesity in SSNS patients.[9] Both studies in Indonesia showed lower prevalence of obesity in SSNS patients than in the US.[4,6,9] The use of high-dose and long-term steroids leads to increased food intake and inhibited energy expenditure through stimulation of neuropeptide-Y and inhibited release of corticotrophin hormone. The process triggers an anabolic process and leads to obesity. Excessive glucocorticoids also increase the activity of 11β - HSD1 isozyme and glucocorticoid receptor in omental adipose tissue, resulting in central and visceral obesity.[6,16-18]

A previous study showed an association between higher cumulative dose and risk of obesity. Liu *et al*. observed a 4 to 8% weight gain with 5 to 10 mg/day prednisone for more than 2 years, with an average cumulative dose of 7,200 mg.[19] Although not statistically significant, we observed a higher risk of central obesity in those who received more than 7,200 mg of prednisone.

In conclusion, we find no significant association between steroid regimen and the risk of obesity or central obesity in children with nephrotic syndrome.

Conflict of interest

None declared.

References

1. Behrman RE, Kliegman RM, Jenson HB. Nephrotic syndrome. In: Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders; 2004. p. 1753-8.
2. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, *et al*. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124:747-57.
3. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003;362:629-39.
4. Wirya IW. Penelitian beberapa aspek klinis dan patologi anatomis sindrom nefrotik primer pada anak di Indonesia [dissertation]. [Jakarta]: FKUI; 1992.
5. Merritt RJ, Hack SL, Kalsch M, Olson D. Corticosteroid therapy-induced obesity in children. Clin Pediatr. 1986;25:149–52.
6. Foster BJ, Shults J, Zemel BS, Leonard MB. Risk factors for glucocorticoid-induced obesity in children with steroid-

sensitive nephrotic syndrome. Pediatr Nephrol. 2006;21: 973–80.
7. Thompson FE, Byers T. Dietary assessment resource manual. J Nutr. 1994;124:2245S-317S.
8. Kowalski KC, Crocker PRE, Donen RM. The physical activity questionnaire for older children (PAQ-C) and adolescents (PAQ-A) manual. Canada: University of Saskatchewan; 2004.
9. Vidianty J, Pardede SO, Hendarto A and Akib AAP. Obesity in children with frequent relapse and steroid dependent nephrotic syndrome. Paediatr Indones. 2010;50:139-43.
10. Olowu WA, Adelusola KA, and Adefehinti O. Childhood idiopathic steroid resistant nephrotic syndrome in Southwestern Nigeria. Saudi J Kidney Dis Transpl. 2010;21:979-90.
11. Hoyer PF, Brodehl J. Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. J Am Soc Nephrol. 2006;17:1151–7.
12. Kim JS, Bellew CA, Silverstein DM, Aviles DH, Boineau FG, Vehaskari VM. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. Kidney Int. 2005;68:1275–81.
13. Ashwell M. Charts based on body mass index and waist-to-height ratio to assess the health risks of obesity: a review. Open Obes J. 2011;3:78-84.
14. Panjikkaran ST. Waist to height ratio for recording the risks of overweight in schoolchildren in Kerala. Indian Pediatr. 2013;50:493-5.
15. Lee KK, Park HS and Yum KS. Cut-off values of visceral fat area and waist-to-height ratio: diagnostic criteria for obesity-related disorders in Korean children and adolescents. Yonsei Med J. 2012;53:99-105.
16. Niaudet P. Long-term outcome of children with steroid-sensitive idiopathic nephrotic syndrome. Clin J Am Soc Nephrol. 2009;4:1547–8.
17. Cavagnini F, Croci M, Putignano P, Petroni ML, Invitti C. Glucocorticoids and neuroendocrine function. Int J Obes Relat Metab Disord. 2000;24:S77-9.
18. Stewart PM. The adrenal cortex. In: Larson PR, Kronenberg H, Melmed S, editors. William's textbook of endocrinology. 10th edition. Philadelphia: Saunders; 2003. p. 491-551.
19. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, *et al.* A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30.