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Original article

The Long-term (five years) Effects of Prednisone Therapy in Children with Frequently Relapsing Nephrotic Syndrome: A Controlled Study of Anthropometric Parameters and Metabolic Abnormalities

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Abstract. *Background:* Steroids are the main drugs used for the treatment of nephrotic syndrome (NS) in children. *Aim of study:* We investigated the steroid effect on linear growth and weight gain as well as the prevalence of different metabolic components and dysglycemia in children with NS with multiple relapses for 5 years in relation to the cumulative dose of steroids. *Study population and sample size:* Data of 30 children with NS were analyzed retrospectively. They received prednisolone treatment as advised by international guidelines. The cumulative dose of prednisolone (CDP) over the 5 years was calculated for each child. Their growth and different metabolic criteria, including impaired fasting glucose (IFG), high LDL and cholesterol, lower HDL, and high blood pressure studied over this period and compared with the data for 66 age-matched obese non-nephrotic children. *Results:* The mean CDP was 100 ± 63 mg /kg/yr given over an average duration of 5 years. The height-SDS was not affected after 3 years but decreased by -0.4 SD after 5years. The body mass index-SDS increased from 0.65 to 0.97 and 1.1 after 3 and 5 years, respectively. Obesity and overweight increased from 25% pre-treatment to 59.2% after 5 years of treatment. After 5 years of treatment, IFG was detected in 35 %, hypertension in 40%, high LDL in 77%, and high cholesterol in 80%. *Conclusion:* In children with frequently relapsing NS, long-term steroid therapy was associated with a higher rate of obesity, short stature as well as the occurrence of different metabolic syndrome (MetS) abnormalities. (www. actabiomedica it)

Key words: Nephrotic syndrome, prednisone therapy, obesity, metabolic syndrome, hypertension, growth

Introduction

Nephrotic syndrome (NS) is a rare disease with an incidence of around 2–7 cases per 100,000 children per year and a prevalence of nearly 16 cases per 100,000 (1). Although NS can affect people of any age, it's usually first diagnosed in children aged between 2 and 7 years old. It affects more boys than girls (2,3). The main treatment for NS is steroids, but additional treatments may also be used if a child develops significant side effects. Most children have relapses until their late teens and need to take steroids when these occur. In most children, treatment with corticosteroids will make NS improve—also called "remission." If symptoms return, called a "relapse," the health care professional may prescribe a shorter course of corticosteroids (CS) until the disease goes into remission again. Subjects with minimal change disease (MCD) accounts for 76% of idiopathic NS (4,5). These patients have a 95% response rate to steroids, however,

75% will relapse and 50% (frequent relapses or steroid dependent subjects) require higher and prolonged doses of steroids thus increasing the risk of side effects (4). Various CS (deflazacort, dexamethasone, methylprednisolone), in association with immunosuppressive drugs, are used in place of prednisolone (PDN) in steroid resistant subjects. In most cases, relapses happen less often as children get older (3,4).

Systemic CS increase the risk for developing obesity and adverse cardio-metabolic (hypertension and dyslipidemia) and dysglycemic abnormalities leading to metabolic syndrome (MetS) (6-8).

Nevertheless, there is scarcity of studies that focused on the long-term effect of CS on the development of the various components of MetS in children. Hence, we assessed the associations between overall CS use and the different components of MetS as well as anthropometric data in children with NS in relation to their cumulative dose of prednisone.

Patients and Methods

1. Study Design and Setting

A retrospective study was conducted at the Department of Pediatrics, Dietetics and Nutrition of Hamad General Hospital, Doha (Qatar). Data were collected from 2012 to 2020. Ethical approval was obtained from the Institutional Review Board (IRB) of Hamad Medical Centre before the beginning of the study (MRC-01-19-053).

2. Study Population and Sample Size

We evaluated the anthropometric and biochemical profiles of 30 children with NS and 66 obese non-nephrotic children. The nephrotic children received prednisolone treatment according to the International Pediatric Nephrology Association (IPNA) guidelines for initial treatment and relapse (9). The cumulative dose of CS over the period of 5 years was calculated for each child. Data recorded included: age, gender, weight and height, body mass index (BMI), systolic and diastolic blood pressures, lipid profile, glycated hemoglobin (A1C), and alanine transferase level (ALT).

The data of NS were compared to normal lab data for the same age group of subjects as well as to obese non-nephrotic age matched children (BMI-SDS > 2). Growth data were correlated with the cumulative dose of steroid.

3. Definition of Metabolic Syndrome (MetS)

The International Diabetes Federation (IDF) consensus (10) for the definition of MetS in children and adolescents was based on waist circumference (WC) /Age-SDS ≥ +2 (11), triglyceride level (≥ 1.7 mmol/L= ≥150 mg/dl), HDL-C level < 1.03 mmol/L (<40 mg/dl), systolic blood pressure > 130 and diastolic blood pressure > 85 mmHg (12), and fasting glucose > 5.6 mmol/L (100 mg/dl).

4. Statistical Analysis

Data were presented as mean ± SD. Non-paired t test was used to compare anthropometric and biochemical data of children of the two groups when data were normally distributed, and Wilcoxon test was used when the data were not normally distributed. Paired t test was used to compare anthropometric and biochemical changes in the same group before versus after CS therapy. The prevalence of each component of MetS is presented in percent. Linear regression equation was used to find correlations between variables. Significance was accepted when P value was <0.05.

Results

The mean cumulative prednisone was 100 ± 63 mg/kg/yr given over an average duration of 5 years. The height (Ht)-SDS was not affected after 3 years of CS treatment (from -0.38 to -0.35, respectively) but decreased to -0.79 after 5 years (-0.4 SD loss) of CS treatment. The BMI-SDS increased from 0.65 to 0.97 and 1.1 after 3 and 5 years, respectively. The cumulative obesity (OB) and overweight (OW) increased from 25% pre-treatment to 59.2% after 5 years of treatment. Hypertension was detected in 14% and

40% of patients after 3 and 5 years of CS treatment (Table 1 and Figure 1).

After 3 and 5 years of treatment, impaired fasting glucose (IFG) was found in 24 and 36 % respectively, high LDL in 89% and 80% respectively, and high cholesterol in 85% and 100% respectively. Hypertension (BP > 95th percentile) was detected in 14% and 40% of patients after 3 and 5 years of treatment. The mean serum cholesterol and LDL levels were significantly higher than normal in treated children after 3 and 5 years of CS treatment (Table 2).

Comparison between the NS group treated for an average of 5 years with long-term prednisone therapy (LTPT: cumulative dose = 100 ± 63 mg/kg/yr) and the obese non-nephrotic group showed that the prevalence of short stature (Ht-SDS < -2), impaired fasting glucose (IFG), high cholesterol, triglycerides (TG) and LDL levels were significantly more frequent in the NS group. 40% of the NS group had hypertension (BP>95th percentile) versus 12.5% of the obese group (Table 3).

Children with NS who developed obesity during CS therapy (n =16) were significantly shorter than their age-matched non-nephrotic obese group. The nephrotic obese group had a greater prevalence of high cholesterol, TG and LDL levels compared to the non-nephrotic obese group (Table 4).

Table 1. Anthropometric data of children with nephrotic syndrome during prednisone therapy.

	Age	WT	WT-SD	HT	HT- SD	BMI	BMI-SD
At presentation	years	kg		cm		kg/m^2	
Mean	3.99	17.66	0.19	102.17	-0.38	16.67	0.65
SD	2.19	6.40	0.77	16.35	1.09	1.34	0.90
After 3 years							
Mean	6.72	26.97	0.70	118.98	-0.35	18.29	0.97
SD	2.50	11.77	1.37	15.16	1.02	4.22	1.51
After 5 years							
Mean	8.93	34.88	0.42	126.91	-0.79	19.98	1.10
SD	3.85	21.30	1.28	21.44	1.21	5.68	1.28

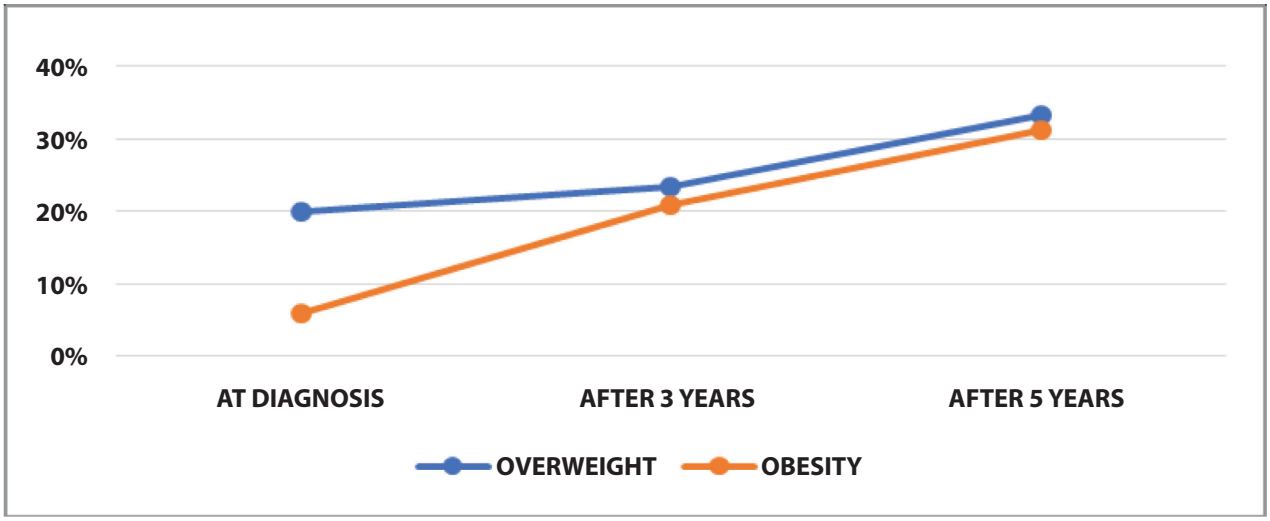

Figure 1. Percentages of obesity and overweight in children with nephrotic syndrome during prednisone therapy (after 3 and 5 years).

Table 2. Anthropometric and biochemical data of children with nephrotic syndrome on long-term prednisone therapy.

Variables	At diagnosis	3 yr.	5 yr.	P-value
Number	30	30	30	
IFG (FBG >5.6 mmol/L	15.9%	24.1%	35.71%	0.08
LDL > 2.7 mmol/L	88.8%	88.8%	80.0%	0.35
HDL < 1.03 mmol/L	10.5%	10.0%	0.0%	0.07
TG >1.7 mmol/L	77.2%	33.3%	60.0%	0.23
Cholesterol > 4.5 mmol/L	100.0%	85.7%	100.0%	1
BP > 95th centile for age and sex	13%	14.3%	40.0%	0.019

Table 3. Anthropometric and biochemical data of children with nephrotic syndrome (NS) on long-term prednisone (Pred) therapy versus obese non-nephrotic children.

Variables	NS on Pred >5 yr.	Obese 6-12 yr.	P value
Number	30	66	
Mean Age	8.9 ± 3.8	9.8 ± 2.5	
Number of relapsers	26/30	--	
Number of steroid resistant subjects	11	--	
Number of relapses during the F/U	3.4 ± 0.7	--	
Overweight and obese	50%	100%	<0.005
Short stature HtSDS <-2	22%	6%	0.02
IFG >5.6 mmol/L	35%	17.8%	0.06
LDL > 2.7 mmol/L	77.7%	8.0%	<0.005
HDL < 1.03 mmol/L	10%	20.8%	0.19
TG >1.7 mmol/L	33.3%	8.0%	0.002
Cholesterol > 4.5 mmol/L	100%	20.8%	<0.005
Hypertension BP >95th centile for age and sex	40%	12.5%	0.002

A significant positive correlation was observed between the cumulative dose and duration of prednisone therapy and BMI, and a significant negative correlation was found between the cumulative dose of prednisone and Ht-SDS at the last follow-up.

Discussion

In the present study, long-term prednisone therapy (LTPT; for 5 years), with a mean cumulative dose of prednisone equal to 100 ± 63 mg/kg/yr, was associated with increased prevalence of overweight and obesity as well as with a higher risk of developing hypertension, dysglycemia, and dyslipidemia. These changes can be partially explained by the different effects of excess corticosteroid (prednisone) both on a short-term and long-term basis (13).

Glucocorticoids induce insulin resistance by directly interfering with signaling cascades, mainly the GLUT4 transporter, within muscle cells, with the subsequent significant decrease in insulin-stimulated glucose uptake and insulin-stimulated glycogen synthesis (14-16). On the other hand, excess CS stimulates catabolism of proteins leading to increased serum amino acids, which also interfere with insulin signaling in the muscle cell. In addition, CS increases lipolysis, resulting in an increase in serum-free fatty acids and triglycerides (14,17).

Table 4. Metabolic risk factors among obese children nephrotic syndrome (NS) on long-term prednisone therapy (LTPT) for > 5 years vs. age-matched obese children.

Variables	Obese NS on LTPT	Obese 6-12 yr.	P-value
Number	16	66	
Age	8.5 ± 3.7	9.1 ± 2.5	NS
Short stature Ht-SDS <-2	12.5%	6%	NS
HtSDS	-0.44 ± 1	1 ± 0.8	<0.001
IFG>5.6 mmol/L	25%	17.8%	0.61
LDL > 2.7 mmol/L	81.2%	8.0%	<0.001
HDL < 1.03 mmol/L	0%	20.8%	0.027
TG >1.7 mmol/L	68.7%	8.0%	<0.001
Cholesterol > 4.5 mmol/L	100%	20.8%	0.008
Hypertension BP > 95th centile for age and sex	37.5%	12.5%	0.009

Table 5. Correlations between anthropometric data and duration and cumulative dose of prednisone.

	HT-SD	Delta Ht-SDS	BMI	BMI-SD	Cumulative CD dose	Years of CS therapy
HT-SD	1.000					
Delta Ht-SDS	0.672	1.000				
BMI	0.084	-0.097	1.000			
BMI-SD	0.211	-0.132	0.755	1.000		
Cumulative CS dose	-0.33*	-0.270	0.524*	0.321*	1.000	
Years of therapy	-0.257	-0.270	0.615*	0.265	0.880*	1.000

Legend: *p<0.05; CS: corticosteroid (prednisone)

This metabolic swing is beneficial on a short-term basis, but prolonged glucocorticoid exposure has been related to the increased occurrence of many undesirable anthropometric and metabolic consequences. A link has been found between the metabolic effects of long-term/prolonged CS treatment and development of Metabolic Syndrome. The pathophysiology of those changes is often explained by the effects of CS in several tissues. In skeletal muscle, chronic CS exposure leads to insulin resistance, decreases GLUT4 translocation, and increases ectopic fat accumulation. In the pancreas, CS excess leads to hyperinsulinemia. In the liver, chronic CS effects lead to insulin resistance, decreased insulin clearance, increases gluconeogenesis, increased glucose output, and hyperglycemia. Increased lipogenesis leads to fatty liver, and increased VLDL synthesis and release. In the adipose tissue, CS induces HSD11B1 activity leading to hypertrophy/hyperplasia and producing insulin resistance in the mature adipocytes. Moreover, long-term prednisone therapy (LTPT) can significantly increase appetite and the risk of obesity (18). Collectively, these changes can cause obesity, hyperglycemia, dyslipidemia, muscle wasting, and osteoporosis (19-22).

Our children with steroid-sensitive nephrotic syndrome who developed obesity while on LTPT had significantly shorter stature and a higher prevalence of hyperlipidemia and hypertension compared to age-matched non-nephrotic obese children. The BMI was correlated significantly with the cumulative dose of prednisone. These data confirmed the higher risk of developing impaired linear growth, obesity, and metabolic abnormalities related to the metabolic syndrome in children with NS on LTPT, especially those who developed obesity during prednisone therapy.

In support of our findings, an epidemiological study conducted by Horton et al. (23) calculated the associations of glucocorticoid dose per age- and sex-imputed weight with incident-treated diabetes, hypertension, and venous thromboembolism (VTE) in a large retrospective cohort that included more than 930,000 children diagnosed with autoimmune and nonimmune diseases. Crude rates for glucocorticoid-exposed children were highest for hypertension. Strong dose-dependent relationships were found between current glucocorticoid exposure and all outcomes These results suggest strong relative risks of diabetes and hypertension in children taking high-dose oral glucocorticoids.

Our nephrotic children had a high prevalence of hypertension after 5 years of LTPT. In addition, obese nephrotic children on LTPT had a higher prevalence of hypertension compared to age-matched obese non-nephrotic children.

Glucocorticoids can induce hypertension through several mechanisms. They are agonists of mineralocorticoid receptor (MR), which upon activation leads to renal salt retention and elevated blood pressure. They activate the renin-angiotensin system; by enhancement of vasoactive substances, and by causing suppression of the vasodilatory systems. In addition, glucocorticoids may exert some hypertensive effects on cardiovascular regulation through the CNS via both glucocorticoid and mineralocorticoid receptors (24-27).

In our study, nephrotic children lost around 0.4 SD of their Ht-SDS after 5 years of LTPT. In addition, obese nephrotic children on LTPT were significantly shorter compared to age-matched non-nephrotic obese children. The cumulative dose of prednisone was correlated negatively and significantly with the Ht-SDS of children on LTPT. In support of our findings, Emma et al. (28) evaluated the risk of permanent linear growth impairment in a selected group of 42 children with steroid-dependent nephrotic syndrome and 14 children with frequently relapsing nephrotic syndrome for a mean follow-up of 11.7 ± 3.5 years. During the prepubertal period, patients lost 0.49 ± 0.6 Ht-SDS. Those who reached their final height had an average loss of 0.92 ± 0.8 Ht- SDS from the onset of their disease (P: <0.001) and 0.68 ± 0.7 from their target Ht-SDS (P:<0.001). Valavi et al. (29), studied 97 prepubertal children with NS who received prednisone > 6 months, and with a minimum prednisolone cumulative dose of 152 mg/kg. They observed a significantly negative effect of cumulative dosages of prednisolone on linear growth, which was greater in children with four or more relapses. Hung et al. (30), studied 50 prepubertal children with NS and confirmed that prednisolone was associated with impairment of height growth in a dose-dependent fashion.

Ribeiro et al. (31), analyzed data from 30 children with NS followed for 10 years. They reported that Ht-SDS and bone mineral density were both negatively associated with the cumulative dose of CS. The ultimate Ht-SDS were significantly decreased in patients receiving >0.2 mg/kg/day CS (P: 0.001). Simmonds et al. (32), found some delay in HT-SDS in 41 children during periods of higher intake of CS (over 0.75 mg/kg/day) but a catch-up growth occurred during the intake of lower doses of CS.

These data confirm the negative effect of prolonged use of prednisone therapy, especially with higher cumulative doses, on linear growth and final adult height.

Prolonged use of CS can markedly impair linear growth through many mechanisms. CS has a suppressive effect on osteoblastogenesis within the bone marrow and promotes the apoptosis of osteoblasts and osteocytes, thus resulting in decreased bone formation. High-dose CS therapy can attenuate physiological growth hormone (GH) secretion via an increase in somatostatin tone, and the GH response to GH stimulation tests may be reversibly impaired in some cases of steroid exposure. CS may have a direct inhibitory effect on the growth plate. Infusion of CS into the growth plate leads to a temporary reduction in the growth rate and may disrupt the growth plate vasculature. In addition, CS can suppress IGF-1 production within the growth plate chondrocytes (32- 36).

An important question regards “the risk to develop growth and metabolic complications in some children on LTPT compared to others”. This can be partially explained by the difference in their sensitivity versus resistance to CS. Savas et al. (37) genotyped 10,621 adult participants for glucocorticoid receptor (GR) hypersensitive (1/2 copies BclI and/or N363S) and GR resistant (1/2 copies ER22/23EK and/or 9β) variants. They assessed the relationship between

functional GR polymorphisms with BMI, waist circumference (WC), and MetS in users of CS. They found that polymorphisms associated with increased GR sensitivity are related to increased BMI, waist circumference, and an increased MetS presence in corticosteroid users. Molnar et al. (38) found that patients with adrenal insufficiency treated with glucocorticoids had different weight gain. Moreover, homozygous carriers of BcII had significantly higher BMI compared to the heterozygous carriers (P: 0.007). The rs4844880 polymorphism of the HSD11B1 gene exerted a significant impact on BMI and weight gain compared to the non-carriers.

In support of this view, in mice models with transgenic HSD11B1 overexpressing, different features of metabolic syndrome and obesity have been replicated. HSD11B1 gene deficiency or HSD11B2 gene overexpression were associated with improvements in the metabolic profile (39).

In conclusion, children with frequently relapsing nephrotic syndrome who required LTPT had an increased risk to develop obesity, slow linear growth, and higher occurrence of the different components of the metabolic syndrome including hypertension, dysglycemia, and dyslipidemias compared to age-matched obese children. Regular monitoring of linear growth, blood pressure as well as glucose and lipid abnormalities are highly required in these patients. Lowering the dose of prednisone to the minimum required and applying dietary and lifestyle modifications may reduce these risks.

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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