Pediatr Nephrol (2006) 21: 973–980
DOI 10.1007/s00467-006-0100-z

ORIGINAL ARTICLE

Bethany J. Foster · Justine Shults · Babette S. Zemel · Mary B. Leonard

Risk factors for glucocorticoid-induced obesity in children with steroid-sensitive nephrotic syndrome

Received: 3 October 2005 / Revised: 13 January 2006 / Accepted: 17 January 2006 / Published online: 30 May 2006

Abstract The objective of this work was to determine the prevalence of obesity, defined as BMI >95th percentile, in children treated with glucocorticoids for steroid-sensitive nephrotic syndrome (SSNS), and to identify risk factors for the development for glucocorticoid-induced obesity. The experimental design involved a cross-sectional study of 96 individuals (4 to 21 yrs) treated with glucocorticoids for SSNS and 186 healthy reference subjects. Logistic regression was used to generate odds ratios for obesity. Glucocorticoid exposure was classified as recent in the 54 subjects treated with glucocorticoids in the prior six months, and remote in the remaining 42 subjects. Recent exposure was associated with significantly increased odds of obesity [odds ratio (95% CI): 26.14 (7.54, 90.66)] in non-blacks only. Each one-unit increase in maternal BMI was associated with a 35% increase in the odds of obesity in recent SSNS subjects (p=0.003). The effect of maternal BMI on the odds of obesity was significantly greater in recent SSNS subjects than in reference subjects (test for interaction p=0.038). The odds of obesity were also significantly increased [odds ratio 5.22 (1.77, 15.41), p=0.003] in all subjects with remote glucocorticoid exposure (black and non-black). These results indicate that non-black race and increased maternal BMI are risk factors for glucocorticoid-induced obesity in subjects with recent exposure.

Keywords Obesity · Body composition · Steroids · Nephrotic syndrome · Corticosteroids

Dr. Foster was supported by a National Research Service Award F32DK62637–01 and by a Duncan L. Gordon Fellowship from the Hospital for Sick Children Foundation, Toronto, Canada. The protocol was supported by NIH grants K08-DK02523 (MBL) and the General Clinical Research Center (M01RR00240) at the Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine.

B. J. Foster
Department of Pediatrics, Division of Nephrology,
Montreal Children's Hospital,
McGill University School of Medicine,
Montreal, Quebec, Canada

M. B. Leonard
Department of Pediatrics, Division of Nephrology,
The Children's Hospital of Philadelphia,
Philadelphia, PA, USA

B. S. Zemel
Department of Pediatrics,
Division of Gastroenterology and Nutrition,
The Children's Hospital of Philadelphia,
University of Pennsylvania School of Medicine,
Philadelphia, PA, USA

M. B. Leonard · J. Shults
Department of Biostatistics and Epidemiology,
University of Pennsylvania School of Medicine,
Philadelphia, PA, USA

B. J. Foster (✉)
Montreal Children's Hospital,
2300 Tupper Ave.,
Montreal, Quebec, H3H 1P3, Canada
e-mail: beth.foster@muhc.mcgill.ca
Tel.: +1-514-4124400
Fax: +1-514-4124359

Introduction

Steroid-sensitive nephrotic syndrome (SSNS) often requires repeated and prolonged courses of glucocorticoid therapy to maintain remission. Of the many potential adverse effects of glucocorticoid therapy, obesity is perhaps the most common, and may be one of the major reasons for nonadherence to therapy. In addition, obesity is one of the most common complications of glucocorticoid therapy, prompting the use of adjunctive, steroid-sparing agents such as cyclophosphamide and cyclosporine in frequent relapsers or steroid-dependent patients.

Previous studies of SSNS have estimated the prevalence of obesity at 35–43% during treatment with glucocorticoids [1–3]. Decreases in relative body weight were noted when glucocorticoid doses were reduced [1, 3] or discontinued [2]. However, it is not clear if body weight returns to normal after cessation of glucocorticoid therapy. Because prior

studies of obesity in glucocorticoid-exposed children and adolescents did not include healthy reference subjects, they were unable to quantify the excess risk of obesity associated with glucocorticoids, or to address potential risk factors for obesity among children treated with glucocorticoids. For example, maternal obesity and black race are known risk factors for obesity in healthy children [4–6]; however, the impact of these risk factors on glucocorticoid-induced weight gain and retention of excess weight after cessation of glucocorticoid therapy is not known. Identification of risk factors for glucocorticoid-induced obesity would help clinicians target strategies for prevention of obesity to those at highest risk, and may prompt earlier introduction of steroid-sparing agents in these high-risk patients.

The objective of this cross-sectional study of stature and body composition in children and adolescents treated with chronic, high-dose glucocorticoids for SSNS was to identify risk factors for obesity among two groups of glucocorticoid-exposed children: one with current or recent exposure, and another with remote exposure to glucocorticoids. In order to achieve this, we estimated the prevalence of obesity, relative to a healthy reference group, in these two groups of children.

Methods

The protocol was approved by the Institutional Review Board, and written informed consent was obtained.

Study subjects-SSNS group Children and adolescents with SSNS, ages 4 to 21 years, were identified through medical record review at The Children's Hospital of Philadelphia (CHOP) and St. Christopher's Hospital for Children. Eligible subjects fulfilled the International Study of Kidney Disease in Children criteria for SSNS [7], had normal renal function as estimated by the Schwartz formula [8] (glomerular filtration rate >90 ml/min/1.73 m^2), and had been treated with glucocorticoids within the previous ten years. Subjects were excluded for other chronic medical conditions potentially affecting growth or body composition. Study visits in the CHOP Nutrition and Growth Laboratory were scheduled after greater than 14 days of urinary remission (negative or trace proteinuria by dipstick) in SSNS subjects in order to allow complete resolution of edema. Negative or trace proteinuria and absence of edema were documented at the study visit.

Study subjects-Reference group Healthy children and adolescents, ages 4 to 21 years, were recruited prospectively from pediatric clinics and the surrounding community as controls for ongoing studies of bone health and body composition [9, 10]. Subjects with chronic medical conditions potentially affecting growth, pubertal development or body composition were excluded.

Anthropometry and Tanner staging Measures of height (Holtain wall-mounted stadiometer, Crosswell, Wales) and weight (Scaletronix digital scale, White Plains, NJ, USA) were obtained in triplicate and the mean used for analysis. Tanner stage was determined for all subjects by physical exam by the same pediatrician. Parental height and weight were obtained by report.

Body composition A detailed evaluation of body composition was performed by dual energy X-ray absorptiometry (DXA, Hologic QDR 2000, Waltham, MA, USA). A prior report describes the total and regional body composition of these subjects [11].

SSNS disease characteristics Medical charts were reviewed for date of diagnosis of SSNS and subsequent relapses. All doses of prednisone and methylprednisolone were documented and converted to prednisone equivalents. The total cumulative glucocorticoid doses were summarized as mg, mg/kg, and mg/kg/day. Insufficient data on height over the SSNS treatment interval were available to generate cumulative measures of glucocorticoid per body surface area. In the event that glucocorticoid exposure data were not available in greater than 25% of the SSNS treatment interval within a given subject, the glucocorticoid exposure status was categorized as incomplete for that subject. Cumulative glucocorticoid dose was calculated from the available data, even if it was known to be incomplete.

SSNS subjects were divided into two groups: (1) those who had received glucocorticoid therapy within six months of the study visit, called the "recent" exposure group, and (2) those who had received no glucocorticoids for at least six months, called the "remote" exposure group. The six month cut-off was chosen as it was hypothesized that most subjects would have lost glucocorticoid-related excess fat within this six-month time frame [2].

Statistical analyses

Analyses were conducted using STATA 8.2 (Stata Corporation, College Station, TX, USA). Two-sided tests of hypotheses were used and a p value ≤ 0.05 was considered statistically significant. Mean differences between SSNS and reference subjects were assessed using the t-test. Cross-classified data were compared using the chi-square test.

Height and BMI percentiles

Subjects' sex and age-specific height- and body mass index (BMI) percentiles were determined using National Center for Health Statistics (NCHS) data [12]. The NCHS BMI for age centile curves were created using the LMS method [13], and allow determination of a child's BMI percentile (interchangeable with standard deviation score, or z-score) [13] for age and sex. BMI percentiles, or z-scores, are the accepted way of expressing BMI relative to sex and age in children; this method has been used in many recent studies [14–16]. Obesity was defined as BMI >95th percentile for age and sex [17].

Fat mass for height percentiles

Total fat-mass-for-height percentiles were calculated using data from the healthy reference group as previously described [11]. This provided a more direct measure of adiposity than BMI percentile. By definition the mean fat-mass-for-height of the reference group was at the 50th percentile.

Risk of obesity and risk factors for obesity

The odds ratios for obesity in the recent and remote SSNS groups, relative to the reference group, were determined by logistic regression, including sex, race (black vs. non-black), age, pubertal status (Tanner 1–2 vs. Tanner 3–5), and maternal BMI as covariates. Odds ratios indicate the magnitude of the difference in the odds (analogous to risk) of an outcome between groups. For example, an odds ratio of 2.0 means that the odds of the outcome are twice as high in one group compared to another group. An indicator variable was used for group (reference, recent SSNS or remote SSNS) such that each of the SSNS groups was compared to the reference group. Interactions between SSNS status and race, sex, and maternal BMI were also considered.

In order to assess potential risk factors for obesity specific to glucocorticoid-exposed subjects, a second model, limited to subjects with recent glucocorticoid exposure, was used. Although obesity in the remote group may have been partially attributable to persistence of glucocorticoid-induced weight gain, risk factors for persistence of glucocorticoid-induced obesity may not be the same as risk factors for the initial development of glucocorticoid-induced obesity. Potential risk factors for obesity included age at initiation of glucocorticoids, total duration of glucocorticoid exposure, cumulative mg/kg glucocorticoid exposure, race, sex, and maternal BMI. Pubertal status at initiation of glucocorticoids was not known, so was not included. The bivariate relations between obesity and each of these potential risk factors were evaluated. Then, backwards stepwise logistic regression (alpha=0.20) was used to identify independent risk factors for obesity among glucocorticoid-exposed subjects in the recent exposure group. Receiver-operating characteristic (ROC) curves were constructed to evaluate the performance of the model and to compare the importance of the individual risk factors identified by the model. Risk factors for persistent obesity in subjects with remote glucocorticoid exposure were not sought due to the wide variability in the time interval since the last dose of glucocorticoids. In order to reliably identify risk factors for persistent obesity, a group of subjects with the same interval since the last dose of glucocorticoids (i.e. two or three years) would need to be evaluated.

Results

A total of 96 children with SSNS were enrolled, 54 in the recent, and 42 in the remote exposure group. The reference group consisted of 186 subjects. The characteristics of the two SSNS groups and the reference group are presented in Table 1. Overall, a greater proportion of SSNS subjects were male, reflecting the known male-predominance of this disorder. Significantly fewer remote SSNS subjects than reference subjects were black. Maternal BMI was comparable among the groups. Paternal BMI was available in an insufficient number of subjects to be included in the analyses.

Details of the SSNS course and exposure to glucocorticoids are presented in Table 2. Among the subjects with recent glucocorticoid exposure, 44 (81%) were taking glucocorticoids at the time of the study visit.

Height, BMI and adiposity

The mean (95% CI) height percentiles for recent SSNS, remote SSNS and reference subjects were 47th (39, 56), 48th (39, 56), and 61st (56, 65) respectively. Both recent and remote SSNS subjects were significantly shorter than reference subjects ($p \leq 0.01$). The mean (95% CI) BMI percentiles for recent SSNS, remote SSNS and

Table 1 Subject characteristics: characteristics of reference subjects and of SSNS subjects with recent and remote glucocorticoid exposure are presented, along with a comparison of subject characteristics between each SSNS group and the reference group

	SSNS		Reference	Recent vs. Reference	Remote vs. Reference
	Recent (n=54)	Remote (n=42)	(n=186)	P-values	P-values
Age (yrs) at evaluation[a]	9.2±3.9	11.6±4.2	10.3±4.3	0.08	0.08
Males (%)	38 (70)	27 (64)	78 (42)	<0.01	<0.01
Black (%)	14 (26)	6 (14)	72 (39)	0.09	<0.01
Pubertal (%) (Tanner 3–5)	9 (17)	16 (38)	54 (29)	0.07	0.25
Maternal BMI (kg/m^2) [a]	26.7±6.1	26.5±4.5	27.3±7.7	0.6	0.5
Height percentile [a]	47±31	48±28	61±29	0.004	0.009
BMI percentile [a]	82±23	65±30	59±31	<0.00001	0.29

[a](mean±sd)

Table 2 Steroid-sensitive nephrotic syndrome (SSNS) course and exposure to glucocorticoids: disease characteristics and glucocorticoid exposure data in recent and remote SSNS subjects

	Recent		Remote	
	Median	Range	Median	Range
Age at glucocorticoid initiation (y)	3.1	0.8–12.1	3.1	1.5–12.6
Number of relapses	10.5	0–50	3.5	0–17
Duration of glucocorticoid therapy (mo)	45.5	6.7–208.1	33.2	1.9–168.4
Cumulative mg glucocorticoid[a]	18,633	1,733–87,556	10,150	1,020–39,495
Cumulative mg/kg glucocorticoid[a]	801	25–3,054	458	85–1,797
Average mg/kg/day glucocorticoid[a]	0.60	0.01–2.3	0.54	0.29–1.72
Months since last dose	0	0–4.1	42.9	6.3–118.2
Months since last remission	3.7	0.46–30.6	[b]	[b]
Subjects with incomplete glucocorticoid exposure data (%)	7 (13)	–	10 (24)	–

[a]Between date of first dose and date of last dose
[b]Exceeds interval since last dose
Although it appears that subjects with remote exposure were exposed to substantially lower doses of glucocorticoids than recent exposure subjects, almost twice as many remote as recent subjects had incomplete glucocorticoid exposure data. Glucocorticoid exposure was calculated with available data, recognizing that the large amount of missing data in some subjects would lead to a significant underestimation of actual glucocorticoid exposure

reference subjects were 82nd (76, 88), 65th (55, 74), and 59th (55, 64) respectively. The mean BMI percentile was significantly higher in recent SSNS subjects compared with reference subjects. The distributions of BMI percentiles (with corresponding z-scores) for SSNS and reference subjects are shown in Fig. 1.

Fat-mass-for-height percentiles approximately paralleled BMI percentiles, as demonstrated in Fig. 2. Fat-mass-for-height percentiles were lower than BMI percentiles in all groups. This was expected, and reflects the fact that the contemporary reference group which provided the data used to generate fat-mass-for-height percentiles had a greater level of adiposity than the NCHS reference group which provided the data used to generate BMI percentiles.

Height-for-age percentile was significantly inversely correlated with cumulative glucocorticoid exposure in the recent (r=−0.42, p=0.002), but not in the remote (r=−0.18, p=0.3) group. BMI-for-age percentile, in contrast, was not significantly correlated with any of the glucocorticoid exposure measures in either the recent or remote groups. For example, the correlation between cumulative glucocorticoid exposure and BMI percentile was −0.21 (p=0.14) in subjects with recent glucocorticoid exposure. Similarly, none of the glucocorticoid exposure measures were associated with fat-mass-for-height percentile either [11]. Whether the correlations were done expressing height, BMI and fat-mass-for-height as percentiles, or as z-scores, the results were the same.

Obesity in the reference group

The prevalence of obesity in the reference subjects was 16%, consistent with the national average of 15.5% [18]. In addition, the distribution of reference subjects into obese or normal weight categories by race was comparable to that reported in a national sample [18].

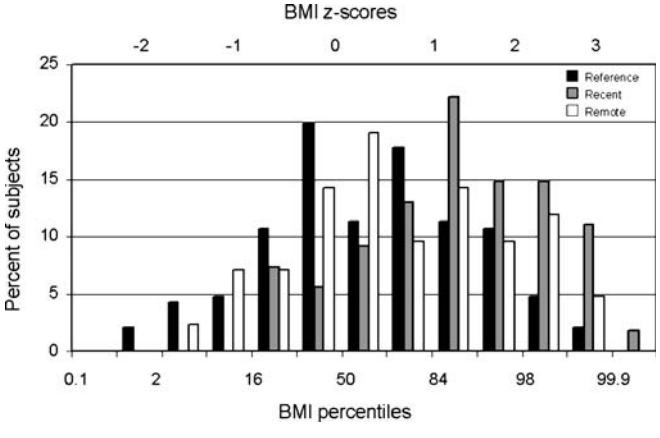

Fig. 1 Distribution of BMI percentile by group: the distribution of BMI-for-age percentiles, and corresponding z-scores, for reference, recent SSNS and remote SSNS subjects are shown

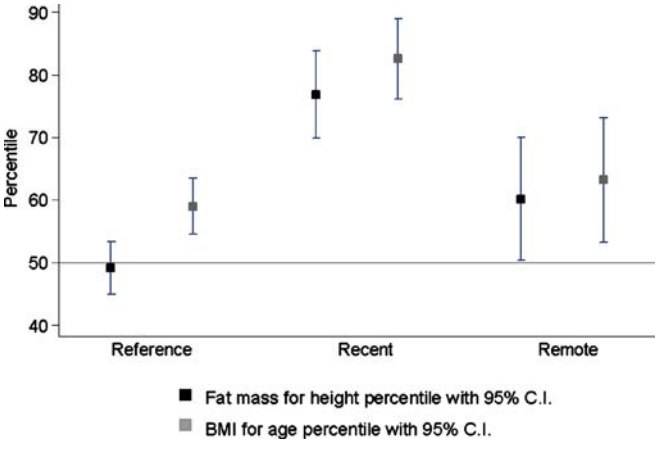

Fig. 2 Mean BMI for age and fat-mass-for-height percentiles by group: mean BMI for age and fat mass for height percentiles with 95% confidence intervals are shown for the recent SSNS, remote SSNS, and reference groups

Obesity in recent and remote SSNS

The prevalence of obesity among SSNS subjects with recent glucocorticoid exposure was 41%, markedly increased compared with the reference group ($p<0.0001$). The unadjusted odds ratio for obesity among recent SSNS subjects, relative to reference subjects, was 3.57 (95% C.I. 1.83, 6.98, $p<0.0001$). Twenty percent of remote SSNS subjects were obese; this was not significantly greater than the prevalence in the reference group. The unadjusted odds ratio for obesity in remote SSNS subjects compared with the reference group was 1.42 (0.62, 3.27), $p=0.40$. However, unadjusted odds ratios do not account for differences in the sex, age, race, pubertal status, and maternal BMI distributions between SSNS and reference subjects. Since differences in these factors may have an important influence on the risk for obesity, independent of the effect of glucocorticoids, adjusted odds ratios are also presented. Adjustment for these covariates effectively estimates the odds ratio that would be obtained if the groups were indistinguishable with respect to sex, age, race, pubertal status, and maternal BMI distributions. Unadjusted odds ratios, together with adjusted odds ratios, are summarized in Table 3.

Risk factors for glucocorticoid-induced obesity

Increased maternal BMI was a significant risk factor for obesity in all groups (reference, remote and recent SSNS). However, the influence of increased maternal BMI differed significantly across the subject groups. The effect of maternal BMI was more pronounced among recent SSNS subjects than among reference subjects (test for interaction $p=0.038$): a 1 kg/m^2 increment in maternal BMI was associated with an odds ratio of 1.35 (1.10, 1.64) for obesity in recent SSNS subjects ($p=0.003$), compared to an odds ratio of 1.08 (1.03, 1.13) in reference subjects ($p=0.001$). The influence of maternal BMI did not differ significantly between remote SSNS and reference subjects (test for interaction $p=0.80$).

Female sex was a significant risk factor for obesity with equivalent influence in all three groups [odds ratio 2.14 (1.00, 4.56), $p=0.049$]. Neither age [odds ratio 0.94 per one year increment (0.82, 1.08), $p=0.37$] nor pubertal status [odds ratio 0.96 for pubertal (0.29, 3.25), $p=0.95$] were significant risk factors for obesity.

Black race was an important risk factor for obesity in reference subjects [odds ratio 4.42 (1.76, 11.13), $p=0.002$]. However, the influence of race was reversed in recent SSNS subjects. There was a significant interaction between SSNS group and race (test for interaction $p=0.003$). Therefore, the adjusted odds ratios for obesity in recent SSNS subjects were calculated separately for blacks and non-blacks, as shown in Table 3. Among non-blacks, the odds of obesity for recent SSNS subjects were 26.14 (7.54, 90.66) times higher than in reference subjects ($p<0.0001$) after adjustment for sex, pubertal status and maternal BMI. In contrast, among black subjects, there was no significant increase in the odds of obesity in the recent SSNS group (odds ratio 0.32 (0.032, 3.29), $p=0.34$) compared with reference subjects. In the comparison of remote SSNS subjects with the reference group, there were no significant interactions between group and race. That is, the influence of race on the odds of obesity was the same for remote SSNS subjects as for reference subjects. However, there was inadequate power to test this interaction: there were only six black subjects with remote glucocorticoid exposure. After adjustment for age, race, sex, pubertal status and maternal BMI, the odds of obesity in remote SSNS subjects were 5.22 [(1.77, 15.4), $p=0.003$] times higher than in reference subjects.

Table 4 summarizes the results of the model evaluating potential risk factors for obesity specific to subjects recently exposed to glucocorticoids. Only maternal BMI and race were independent predictors of obesity. Evaluation of ROC curves indicated that only maternal BMI had a substantial influence on the performance of the model (Fig. 3). The area under an ROC curve for a model that perfectly predicts obesity would be 1.0. For a model that correctly predicts obesity only 50% of the time, the area under the ROC curve would be 0.5. The area under the ROC curve for the model including all three covariates was

Table 3 Odds of obesity in SSNS subjects compared with the reference group: results are presented as odds ratios for recent and remote SSNS subjects, relative to reference subjects

Group		Subgroup	Odds ratio	95% CI	*p* value
Recent SSNS	Unadjusted	–	3.57	1.83, 6.98	<0.0001
	Adjusted	Black	0.32	0.032, 3.29	0.34
		Non-black	26.14	7.54, 90.66	<0.0001
Remote SSNS	Unadjusted	–	1.42	0.62, 3.27	0.40
	Adjusted	–	5.22	1.77, 15.4	0.003

The logistic regression models were adjusted for sex, age, race, pubertal status and maternal BMI. Within the model comparing recent SSNS subjects to the reference group, the test for interaction between SSNS and race was significant. That is, the impact of recent glucocorticoid exposure on the odds of obesity was significantly different in blacks and non-blacks. Therefore, the odds ratios are presented for non-black and black recent SSNS subjects separately. There were no significant interactions between remote glucocorticoid exposure and other covariates, including black race; therefore the results for remote SSNS are not stratified on race. Since the odds for obesity in recent SSNS relative to reference subjects varied depending on maternal BMI, these odds ratios were calculated setting the maternal BMI at 27.1 (the mean maternal BMI for all subjects) for all subjects

Table 4 Risk factors for obesity in recent SSNS subjects: sex, race, age at GC initiation, duration of GC therapy, cumulative mg/kg GC, and maternal BMI were entered into this model

Variable	Number of observations	Odds ratio	95% CI	*p* value
Age at glucocorticoid initiation (per 1 year increment)	48	0.80	0.63, 1.02	0.077
Race (black)	48	0.054	0.0037, 0.81	0.035
Maternal BMI (per unit increment)	48	1.41	1.14, 1.74	0.002

The final model was arrived at using backwards stepwise logistic regression, setting alpha at 0.20

0.84. When only maternal BMI was included, the area under the curve dropped only slightly, to 0.79. This indicates that maternal BMI contributed most to the predictive power of the model. None of the glucocorticoids exposure measures listed in Table 2 were related to the odds for obesity.

Discussion

This examination of 54 children and adolescents recently treated for SSNS with a median of 18,000 mg of cumulative glucocorticoids demonstrated severe obesity. The mean BMI was at the 82nd percentile for age and sex. Unlike previous studies [1–3], we included a concurrent, healthy reference group with a BMI distribution comparable to the national distribution, allowing us to compare the odds of obesity with contemporary reference subjects, and to identify risk factors for obesity in children treated with glucocorticoids for SSNS. These analyses demonstrated unexpected interactions of glucocorticoid exposure status with race and maternal BMI. Consistent with studies of healthy children, female sex and increased maternal BMI were significant risk factors for obesity among reference and SSNS subjects alike [5, 6]. However, increased maternal BMI had a much more pronounced influence on the odds of glucocorticoid-induced obesity than on the odds of obesity in healthy children.

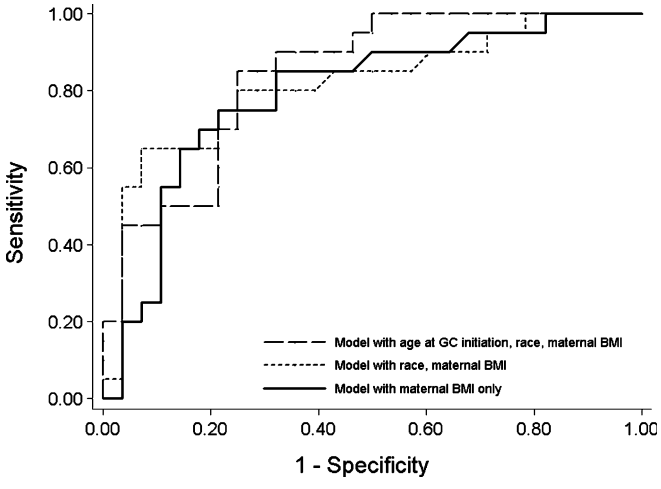

Fig. 3 Receiver-operator characteristic curves: these ROC curves evaluate the performance of the logistic regression model used to assess potential risk factors for obesity among recent SSNS subjects. Maternal BMI was the most important predictor of obesity

Surprisingly, black race, a known risk factor for obesity among otherwise healthy subjects [5, 6], appeared to protect against glucocorticoid-induced obesity. This result should be interpreted with caution; there were only 14 black SSNS subjects with recent glucocorticoid exposure. In addition, the possibility that race-based differences in socioeconomic status between SSNS and reference subjects account for this finding cannot be excluded. Socioeconomic status was not measured. Although our data suggest that black subjects exposed to glucocorticoids were no more likely to be obese than black reference subjects, the upper 95% confidence limit indicates that odds of obesity may be three times higher in black glucocorticoid-exposed subjects compared to black reference subjects. However, even three-fold higher odds are markedly and significantly lower than the 26-fold higher odds of obesity found among non-black glucocorticoid-exposed subjects compared with non-black reference subjects. There may be genetic factors leading to differences in the metabolism of glucocorticoids between blacks and non-blacks that account for this finding.

Some readers may be surprised by the lack of correlation between glucocorticoid exposure and BMI. However, it must be borne in mind that these children were evaluated at varied time points in the course of their disease; in some cases the greatest glucocorticoid exposure was years before the study visit. Therefore, a child with a high total lifetime glucocorticoid exposure may have lost weight while being maintained on small doses of glucocorticoids for several years. Alternatively, a child with a lower total lifetime glucocorticoid exposure may have gained weight during therapy for a recent relapse. Since BMI, unlike height, can change in either direction relatively rapidly, it is not surprising that body composition correlates poorly with lifetime glucocorticoid exposure. Recent longitudinal studies in the pediatric renal transplant population—another group treated initially with relatively high doses of glucocorticoids—suggest that glucocorticoid-related weight gain occurs rapidly after initiation of glucocorticoid therapy, but that weight may be subsequently lost after dose reduction [19, 20].

Although cross-sectional, our study is strengthened by the inclusion of subjects who had discontinued glucocorticoids up to ten years prior to evaluation. Only one other study of children with glucocorticoid-related obesity (n=23) evaluated children after discontinuation of glucocorticoids [2]. The authors stated that all participants were evaluated after at least six months of remission, and concluded that most glucocorticoid-induced obesity re-

solves after discontinuation of glucocorticoids. However, they did not quantify "most". Our data suggest that return to normal weight after cessation of glucocorticoid therapy may be incomplete.

The 42 children and adolescents with remote exposure to glucocorticoids had a mean BMI at the 65th percentile, compared with the 59th percentile in the reference group. Although the prevalence of obesity in the remote SSNS group was not significantly different from that in the reference group, and the impact of risk factors for obesity in this group did not differ from the reference group, subjects with remote exposure were over five times as likely as healthy subjects to be obese, after sex, race and pubertal status distribution in the group was taken into account.

Although it appears that subjects with remote exposure were exposed to substantially lower doses of glucocorticoids than recent exposure subjects, almost twice as many remote as recent subjects had incomplete glucocorticoid exposure data. Glucocorticoid exposure was calculated with available data, recognizing that the large amount of missing data in some subjects would lead to a significant underestimation of actual glucocorticoid exposure. Of particular note is the fact that some of the most severe, steroid-dependent subjects in the remote group had long periods of missing glucocorticoid exposure data. Treatment regimens for SSNS have not changed over the last twenty years. Therefore, subjects with remote glucocorticoid exposure likely received doses of glucocorticoids similar to the recent exposure group; however we cannot exclude the possibility that steroid exposure was lower in the remote group. Importantly, even if the remote glucocorticoid exposure group did receive lower doses of glucocorticoids than the recent exposure group, the conclusions would be unchanged.

The most important limitation of this study is the absence of height and weight data prior to starting glucocorticoid therapy. Reliable weights at initiation of glucocorticoid therapy are particularly difficult to obtain, since individuals with SSNS uniformly present with substantial edema. Previous studies have estimated pre-glucocorticoid weight with the weight obtained during the first remission, once edema had resolved [2]. However, this likely overestimates true pre-glucocorticoid weight because weight gain may be rapid upon initiation of high-dose daily glucocorticoids. Given the abrupt onset of SSNS in previously healthy children, it is reasonable to assume that the BMI distribution in SSNS subjects prior to initiation of glucocorticoids was similar to the reference population.

In considering risk factors specific to glucocorticoid-exposed subjects, increased maternal BMI was the most important predictor of obesity among subjects recently treated with glucocorticoids. It is possible that maternal BMI is a proxy for pretreatment obesity, and that much of the effect of maternal BMI simply reflects the power of past obesity to predict future obesity. The importance of maternal BMI may not have been as great had we been able to control for subjects' BMI prior to glucocorticoid exposure. However, it is also possible that maternal BMI is a marker for genetic and environmental factors predisposing children to weight gain during glucocorticoid therapy. Glucocorticoid-induced obesity is likely mediated in large part by the appetite stimulating effect of glucocorticoids. Elevated maternal BMI may be a marker for the availability of high-calorie snack foods in the home.

Prospective studies are required to further examine the impact of race, to characterize the pattern of weight loss following termination of glucocorticoid therapy, and to identify risk factors for persistent obesity. Children and adolescents with an obese mother should be considered at very high risk for glucocorticoid-induced obesity.

References

1. Tanaka R, Yoshikawa N, Kitano Y, Ito H, Nakamura H (1993) Long-term ciclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 7:249–252
2. Merritt RJ, Hack SL, Kalsch M, Olson D (1986) Corticosteroid therapy-induced obesity in children. Clin Pediatr 25:149–152
3. Elzouki AY, Jaiswal OP (1988) Long-term, small dose prednisone therapy in frequently relapsing nephrotic syndrome of childhood. Effect on remission, statural growth, obesity, and infection rate. Clin Pediatr 27:387–392
4. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH (1997) Predicting obesity in young adulthood from childhood and parental obesity (comment). N Engl J Med 337:869–873
5. Stettler N, Tershakovec AM, Zemel BS, Leonard MB, Boston RC, Katz SH, Stallings VA (2000) Early risk factors for increased adiposity: a cohort study of African American subjects followed from birth to young adulthood (comment). Am J Clin Nutr 72:378–383
6. Dowda M, Ainsworth BE, Addy CL, Saunders R, Riner W (2001) Environmental influences, physical activity, and weight status in 8- to 16-year-olds. Arch Pediatr Adolesc Med 155:711–717
7. International Study of Kidney Disease in Children (1979) Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early (Report of the International Study of Kidney Disease in Children). J Pediatr 95:239–243
8. Schwartz GJ, Gauthier B (1985) A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr 106:522–526
9. Burnham J, Shults J, Semeao E, Foster B, Zemel B, Stallings V, Leonard M (2004) Whole body bone mineral content in pediatric crohn disease: independent effects of altered growth, maturation, and body composition. J Bone Miner Res 19:1961–1968
10. Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA (2004) Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. N Engl J Med 351:868–875
11. Foster BJ, Shults J, Zemel BS, Leonard MB (2004) Interactions between growth and body composition in children treated with high-dose chronic glucocorticoids. Am J Clin Nutr 80:1334–1341
12. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL (2000) CDC growth charts: United States. Advance data. National Center for Health Statistics, Hyattsville, MD, pp 1–27
13. Cole TJ (1990) The LMS method for constructing normalized growth standards. Eur J Clin Nutr 44:45–60
14. Robinson RF, Batisky DL, Hayes JR, Nahata MC, Mahan JD (2004) Body mass index in primary and secondary pediatric hypertension. Pediatr Nephrol 19:1379–1384

15. Norman LJ, Macdonald IA, Watson AR (2004) Optimising nutrition in chronic renal insufficiency-growth. Pediatr Nephrol 19:1245–1252
16. Filler G, Payne RP, Orrbine E, Clifford T, Drukker A, McLaine PN (2005) Changing trends in the referral patterns of pediatric nephrology patients. Pediatr Nephrol 20:603–608
17. Krebs NF, Jacobson MS, American Academy of Pediatrics Committee on Nutrition (2003) Prevention of pediatric overweight and obesity. Pediatrics 112:424–430
18. Ogden CL, Flegal KM, Carroll MD, Johnson CL (2002) Prevalence and trends in overweight among US children and adolescents, 1999–2000 (comment). JAMA 288:1728–1732
19. Foster BJ, Shults J, Foerster D, Zemel BS, Leonard MB (2005) Changes in body composition following pediatric renal transplantation. J Am Soc Nephrol 16:707A
20. Pradhan M, Shults J, Baluarte HJ, Jones A, Leonard MB (2005) Obesity and hypertension in pediatric kidney transplant recipients. J Am Soc Nephrol 16:706A