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ORIGINAL ARTICLE

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Bone histology in steroid-treated children with non-azotemic nephrotic syndrome

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Abstract Patients with nephrotic syndrome (NS) and normal glomerular filtration rate (GFR) frequently exhibit abnormalities of calcium and vitamin D homeostasis, mainly hypocalcemia and reduced circulating vitamin D metabolites. These abnormalities have been linked to alterations of bone histology in adults with non-azotemic NS, particularly osteomalacia and excessive bone resorption. Whether similar abnormalities of bone histology occur in children and adolescents with NS, particularly in those requiring prolonged treatment with corticosteroids, remains largely unknown. Thus, bone histomorphometry and selected bone-modulating hormones were studied in eight children (aged 2–16 years) with normal GFR (range 85–169 ml/min per 1.73 m^2) and NS. All patients received corticosteroids for at least 12 months prior to bone biopsy. At the time of bone biopsy, the urine protein/creatinine ratio was elevated (2.1±3.6), while the average concentrations of parathyroid hormone (36±13 pg/ml), 25-hydroxyvitamin D [25(OH) D] (22±14 ng/ml), and $1,25(OH)_2D$ (59±22 pg/ml) were normal. Bone histomorphometry displayed focal osteomalacia (OM) and mild increased bone resorption in most patients. The mineralization lag time, an indicator of the degree of osteomalacia, correlated with the time elapsed since the original diagnosis of NS (r=0.93, P<0.0005). Overt hyperparathyroidism was not evident, but increased eroded perimeter and elevated bone formation rate (BFR) were evident in two patients, suggesting high-turnover bone disease. The BFR was inversely correlated with the administered dose of prednisone at the time of biopsy (r=–0.78, P<0.05) and one patient exhibited low bone turnover changes. The growth velocity standard deviation score (SDS) at time of biopsy ranged from –1.6 to 3.2, resulting in a height SDS range of –1.9 to 0.6. The height SDS at time of bone biopsy correlated inversely with the dose of administered glucocorticoid (r=–0.71, P<0.05) and with the duration of the disease (r=–0.7, P=0.05). These data, albeit preliminary, demonstrate that children with NS treated with prolonged corticosteroid therapy exhibit bone histopathological changes without a concomitant impairment in GFR. While the OM appears to be related to the disease process, the alterations of bone formation and the adynamic changes are likely the result of the corticosteroid therapy. The potential consequences of these findings on adult bone mass and ultimate height deserve further studies.

Keywords Nephrotic syndrome · Bone histology · Adynamic bone · Glucocorticoids

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Introduction

Derangements of mineral metabolism can occur in patients with nephrotic syndrome (NS) even with preserved glomerular filtration rate (GFR) [1, 2, 3, 4, 5]. These abnormalities include hypocalcemia [1, 2], secondary hyperparathyroidism [6], and reduced levels of circulating vitamin D metabolites [3, 4, 5]. As a consequence, osteomalacia (OM) and excessive bone resorption have both been detected in adult patients with protracted NS

undergoing bone biopsy [6, 7]. In pediatric patients, the onset and subsequent relapses of the NS [8] frequently coincide with periods of maximal bone mineral accretion [9], and a substantial proportion require steroid treatment for several years prior to and throughout adolescence to control their disease activity [10, 11]. High-dose corticosteroid treatment protocols have been recommended in children with NS unresponsive to traditional therapeutic schemes, attempting to halt the progression to renal failure [12, 13]. Diminished bone mineralization has been reported in NS children by conventional radiography [14], and more recently utilizing densitometric methods [5, 11, 15, 16]. However, neither method can clearly differentiate whether the mineralization defects are the result of disturbances of the hormonal homeostasis of vitamin D and parathyroid hormone (PTH), or of the corticosteroid therapy [17]. Furthermore, corticosteroids can affect bone formation and turnover and may result in bone loss and osteoporosis [18]. A proportion of patients with idiopathic NS may eventually develop renal insufficiency and end-stage renal disease (ESRD) [19] and thus the typical bone changes of azotemic renal osteodystrophy [20, 21]. Reports of the biological consequences of the disturbances of mineral metabolism in adults with NS prior to any decline of GFR are not consistent, and range from clearly abnormal [6] to basically normal bone histology [22]. Furthermore, the potential effects of continuous and prolonged corticosteroid therapy on bone histology in NS are unknown and have not been reported. The present study was designed to evaluate the bone histology in children with NS and normal renal function, to analyze and quantitate the bone mineralization, and to assess the consequences of prolonged corticosteroid therapy on bone formation rates (BFR) in the absence of the usual confounding factors present with renal insufficiency.

Materials and methods

All patients were South Florida residents and attended the pediatric renal center located in Hollywood, Florida. All patients with primary NS followed at our center with a steroid- dependent or partially responsive clinical course to oral glucocorticoids at the time of the study were screened. Twelve qualified and eight of those, following informed consent, were enrolled. The additional study inclusion criteria were: age <16 years; typical primary idiopathic NS characterized by gross proteinuria, hypoalbuminemia, hypercholesterolemia, and edema [8]; continuous administration of oral corticosteroid therapy, with or without additional doses of parenteral glucocorticoids, for at least 12 months; and GFR >85 ml/min per 1.73 m^2. Exclusion criteria were secondary NS (systemic lupus, mesangioproliferative nephritis, membranous nephropathy, HIV nephropathy); administration of vitamin D compounds, supplemental calcium, or other drugs affecting bone metabolism within 6 months prior to enrollment in the study; prior episodes of acute renal failure or transient periods during which the GFR was <75 ml/min per 1.73 m^2. The study group includes six boys and two girls with ages ranging from 2 to 16 years and an estimated GFR [23] ranging from 85 to 169 ml/min per 1.73 m^2. The GFR was estimated on multiple occasions throughout the study period, including during periods of minimal or absent proteinuria. The onset of the NS preceded the bone biopsy by periods ranging from 2 to 14 years, during which all patients had either persistent proteinuria (patients 3 and 7) or multiple relapses (all other patients) of varying degree. Initial therapy of the NS consisted of 60 mg/m^2 oral prednisone (maximum 80 mg) per day in three divided doses for 4–6 weeks followed by 40 mg/m^2 (maximum 60 mg) in one single morning dose on alternate days for an additional 4–6 weeks. Subsequent relapses were treated with prednisone 60 mg/m^2 (maximum 80 mg) per day in three doses until 3 consecutive days without proteinuria, followed by 40 mg/m^2 (maximum 60 mg) in one single morning dose every other day for 4 additional weeks [24]. Cyclophosphamide, 2 mg/kg body weight per day for 8–12 weeks, was required by all patients at some point earlier in their clinical course prior to enrollment in the present study, and one patient had received cyclosporine for 1 year until 15 months prior to enrollment. In addition to oral prednisone (daily and/or alternate days), four patients also received 1-monthly parenteral doses of 1 g IV methylprednisolone, throughout 12 (patient 2) or 18 months (patients 5, 6, and 8) preceding the bone biopsy, following published protocols [12, 13]. The dose of prednisone at the time of biopsy and at 6 and12 months prior to biopsy was calculated from the average oral daily dose (in mg/m^2 surface area administered during the 4 preceding weeks) and did not include the dose of parenteral methylprednisolone. Since some patients were treated at other locations earlier in their clinical course, the precise total cumulative dose of corticosteroids administered since the initial onset of the NS could not be estimated. Most patients had undergone kidney biopsies prior to enrollment as part of their clinical management at the time, usually preceding the administration of cyclophosphamide. Height (H) measurements, obtained with a stadiometer and growth velocity (cm/year) are reported as age and sex-adjusted standard deviation scores (SDS).

Bone biopsy and bone histomorphometry

All bone biopsies were obtained from the anterior iliac crest with a Bordier needle following double tetracycline labeling, as previously described [20], and were performed at the time of a kidney biopsy. The terminology for quantitative histomorphometry used for the presentation of results is that established by the Nomenclature Committee of the American Society for Bone and Mineral Research [25], and the skeletal lesions were classified by histomorphometric criteria with reference to values previously established in children with normal renal function [20, 21]. This protocol was approved by the Human Subjects Protection Committee of Memorial Regional Hospital (Hollywood, Florida), where all bone and kidney biopsies were performed following parental consent.

Biochemical determinations

Creatinine, calcium, phosphorus, and albumin levels in blood were measured by standard automated methods [5]. Serum PTH was measured using a two-site immunoradiometric assay that detects full-length PTH (1–84) and the amino-truncated PTH (7–84) fragments [26, 27], and its reference range for subjects with normal renal function is 10–65 pg/ml. Serum 25 hydroxyvitamin D [25(OH)D, calcidiol] (normal range 9–52 ng/ml) was measured by radioimmunoassay [28], and 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol], (normal range 15–60 pg/ml) was determined by a radioreceptor assay [29]. The degree of proteinuria [estimated from random urinary protein/creatinine ratios (UP/C) in mg/mg] was considered moderate (UP/C 0.2–1.0) or nephrotic (UP/C >1.0) [30]. All kidney biopsy specimens were analyzed for light and electron microscopy, and immunofluorescent staining.

Statistical analysis

Results are expressed as mean ± one standard deviation. Statistical analysis was performed by Student′s *t*-test and the linear regression was calculated by the method of least squares. A P value of <0.05 was considered significant.

Results

Individual biochemical data for each of the patients at time of the bone biopsy are presented in Table 1. Renal histopathology disclosed minimal change disease in two patients and focal segmental glomerulosclerosis in the remaining six patients. The estimated GFR was normal in all patients, ranging from 85 to 169 ml/min per 1.73 m^2. The mean GFR values at the time of biopsy (138±32 ml/min per 1.73 m^2) were not statistically different from the GFR estimations at 6 and 12 months prior to biopsy (130±24 and 137±40 ml/min per 1.73 m^2, respectively). At the time of biopsy, the degree of proteinuria ranged from modest to nephrotic (UP/C 0.2–11) and the serum albumin concentration ranged from 1.0 to 4.5 g/dl. The serum concentrations of total calcium, phosphorus, and PTH were normal in all patients. The concentrations of 25(OH)D were normal in all patients except in one who had markedly diminished levels. The serum levels of $1,25(OH)_2D$ were normal in most patients and elevated in two patients. Serum albumin concentrations and the degree of proteinuria at 6, 12, and 18 months prior to the bone biopsy ranged from mild to overt NS and the corresponding values are depicted in Table 2. Overall serum albumin levels were slightly decreased and the UP/C ratios were persistently elevated for up to 18 months prior to the bone biopsy. The doses of administered oral prednisone at the time of biopsy ranged from 3.5 to 57 mg/m^2 per day. These were not statistically different from those administered at 6 and 12 months prior to biopsy and are summarized in Table 3. The mean H-SDS 12 months prior to bone biopsy was similar to that at the time of biopsy (−0.35±1.0 vs. −0.28±0.8, *P*=NS) and the rate of growth velocity ranged from 1.5 to 10.6 cm/year, corresponding to a SDS range from –1.6 to 3.2 (Table 3). The H-SDS at the time of biopsy correlated with the dose of administered prednisone (r=−0.71, P<0.05) and with the time elapsed since the original diagnosis of NS (r=−0.70, P=0.05). The H-SDS and the growth velocity SDS at the time of biopsy did not correlate with the prevailing serum albumin concentration.

Bone histomorphometry

Results of the bone histomorphometric parameters are depicted in Table 4. Focal signs of OM with spotty accumulation of osteoid and moderately elevated osteoid area (<12%) were observed in more than one-half of the patients. The mostly normal mineralization lag time, the normal osteoid thickness, and an osteoid area not exceeding 12% in any of the patients also indicated a lack of more overt and generalized OM. The osteoid perimeter was elevated in four of eight patients, the majority of patients displayed normal values for eroded perimeter, and none exhibited overt hyperparathyroidism with fibrous tissue deposition or excessive osteoclastic activity. However, bone area and trabecular thickness were low or at the lower limit of the normal range in nearly one-half of

Table 1 Patient characteristics and biochemical determinations at the time of bone biopsy (*MCD* minimal change disease, *FSGS* focal segmental glomerulosclerosis, *GFR* glomerular filtration rate, *P/C* protein/creatinine ratio on random urinary specimens, *Ca* calcium, PO_4 phosphate, *PTH* parathyroid hormone)

Patient no.	Age	Sex	Renal Biopsy	Duration of nephrosis	GFR	Urine P/C	Serum albumin	Serum Ca	Serum PO_4	PTH	25(OH)D	$1,25(OH)_2D_3$
	(years)			(years)	(ml/min per 1.73 m^2)	(mg/mg)	(g/dl)	(mg/dl)	(mg/dl)	(pg/ml)	(ng/ml)	(pg/ml)
1	3	M	MCD	2	169	1.5	1	8.5	4.7	42	14	75
2	4	M	FSGS	2	113	1.6	4.3	9.7	4.7	29	19	92
3	5	M	MCD	2.5	85	11	2	8.1	5.6	20	4	22
4	7	F	FSGS	6	165	1	3.7	9.1	5.4	32	10	71
5	10	M	FSGS	3	158	0.7	4.2	9.5	4	32	32	38
6	9	M	FSGS	5	169	0.2	4.5	9.7	4.8	57	43	49
7	15	F	FSGS	14	117	0.2	4.1	9.2	3.5	50	17	68
8	16	M	FSGS	2	126	0.8	3.9	9.4	4.9	45	40	55
Mean±SD	8.6±4.9			5.6±4.1	138±32	2.1±3.6	3.5±1.3	9.2±0.6	4.7±0.9	38±12	22±14	59±22
Reference values					80–120	<0.1	>3.5	8.5–10.3	2.5–4.5	10–65	9–52	15–60

Table 2 Serum albumin concentration and degree of proteinuria at 6, 12, and 18 months prior to bone biopsy

Patient no.	Serum albumin (g/dl)			Urinary P/C ratio (mg/mg)		
	-6 months	-12 months	-18 months	-6 months	-12 months	-18 months
1	2.3	0.6		4+	4+	
2	3.4	1.2		2.7	10	
3	2.8	4.2	2.2	6.5	0	4
4	1.6	3.8	3.7	10.6	0	0.5
5	4	3.7	3.7	0.7	0.4	1.2
6	4.6	3.4	2.6	0.4	4.4	7
7	2	1.6	3.9	5.3	7.3	0
8	3.4	3	2.5	0.9	1.7	4.5
Mean±SD	3.0±1.0	2.7±1.4	3.1±0.7	3.9±3.8	3.4±3.9	2.9±2.7

Proteinuria in patient 1 (4+) estimated by dipstick sampling

Table 3 Z-Scores for height at time of bone biopsy and 12 months earlier, growth velocity at time of biopsy, and dose of prednisone (mg/m^2 per day) at biopsy and at 6 and 12 months earlier

Patient	Height Z-score		Growth velocity Z-score	Dose of prednisone		
	At biopsy	-12 months	At biopsy	At biopsy	-6 months	-12 months
1	-1.1	-1.5	0.6	46	42	52
2	-0.2	0.3	2.3	3.5	15	38
3	0	-0.9	3.2	43	14	15
4	-0.1	-0.3	1.1	44	33	0
5	0.3	0.6	-1.6	16	16	16
6	0.2	0.4	0	19	20	29
7	-1.9	-2.0	1.6	57	43	22
8	0.6	0.6	1.3	16	16	17
Mean±SD	-0.28±0.82	-0.35±1.0*	1.0±1.45	30.6±9.1	25±12.5*	27±38*

* Not significant compared to values at biopsy

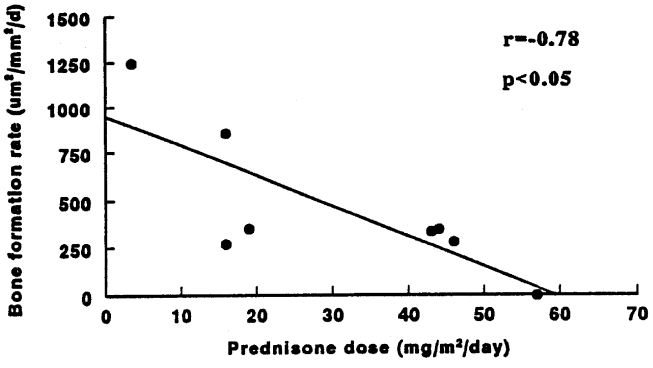

Fig. 1 Correlation of the dose of prednisone (mg/m^2 per day) at the time of biopsy with the bone formation rate

the patients. BFR, an indicator of bone turnover, was normal in most patients, elevated in two, and undetectable in one patient. The BFR did not correlate with the serum calcitriol concentrations, with the time elapsed since the original diagnosis of NS, with the H-SDS at the time of biopsy, or with the growth velocity SDS. However, the two lowest H-SDS (−1.1 and –1.9) at the time of biopsy corresponded to the patients with the lowest BFR values (patients 1 and 7). The BFR, however, correlated with the daily dose of prednisone administered at 6 months prior to the biopsy (r=–0.6, P=0.06) and at the time of biopsy (r=–0.78, P=0.02) (Fig. 1). The dose of prednisone at the time of biopsy also correlated with the adjusted apposition rate (r=–0.7, P<0.05). The mineralization lag time correlated strongly with the time elapsed since the original diagnosis (r=0.93, P<0.0005) and less strongly with the osteoid perimeter (r=–0.51, P=0.09), but did not correlate with the degree of proteinuria at the time of biopsy or at 6 months prior to biopsy. There was an almost significant correlation between the serum albumin concentration and the osteoid width (r=0.6, P=0.07). Histochemical staining for aluminum was negative in all biopsies.

Discussion

The present study demonstrates the existence of bone histological alterations in patients with NS who required prolonged therapy with glucocorticoids, prior to any decline in GFR and without abnormalities in the serum concentrations of the main calciotropic hormones. These findings, previously unavailable in children, are less pronounced but similar to those described in adults [6, 7, 31]. A major finding of the present study is the diminished BFR in relation to the administered dose of corticosteroid. These observations may have important consequences for the long-term management of pediatric patients with long-standing NS requiring high doses of glucocorticoid therapy.

Indeed, glucocorticoids have important effects on the skeleton, as they enhance bone resorption and decrease bone formation, resulting in decreased bone mass [18],

Table 4 Bone histomorphometry in patients with nephrotic syndrome

Patient	Bone area	Osteoid area	Osteoid perimeter	Osteoid thickness	Eroded perimeter	Trabecular thickness	Trabecular spacing	Double-labeled tetracycline perimeter	Bone formation rate	Mineralization lag time	Adjusted apposition rate
	(%)	(%)	(%)	(μm)	(%)	(μm)	(μm)	(%)	($\mu m^2/mm^2$ per day	(days)	(μm/day)
1	23.4	6.4	32.1	8.6	1.19	87	283	5	281	53	0.16
2	21.5	11	45.6	11.1	5.4	91	334	15.1	1246	19	0.58
3	19	6.7	39.3	10	2.3	117	498	7.9	336	38	0.26
4	9.4	6.9	29.1	9.8	1.8	82	792	6.6	349	19	0.52
5	19	7.4	31	12.3	1.2	104	442	15.7	856	16	0.75
6	13.7	3.3	17.2	9.4	1.2	97	611	10.7	355	13	0.73
7	20.3	5.4	26.3	12	2.5	117	462	0	0	5000	0
8	21.6	5.5	39.1	9.6	0.4	137	497	8	270	44	0.21
Mean±SD	18.5±4.6	6.6±2.2	32.5±8.8	10.3±1.3	2±1.6	104±19	490±158	8.6±5.2	462±395	650±1,758	0.4±0.28
Reference range	14.6–27.0	0.2–5.8	4.3–31.7	4.1–13.1	0.4–3.4	90–175	351–737	1.6–15.8	93–613	5–104	0.14–0.81

and by affecting growth plate chondrocyte cell replication [32] steroids may profoundly affect longitudinal growth. The impairment of bone formation results from direct effects of glucocorticoids on osteoblastic activity [33] and to inhibitory actions on bone matrix formation [18]. The most significant effect of glucocorticoids in bone is an inhibition of bone formation due to a decrease in the number of osteoblasts and their function [33]. The decrease in cell number is secondary to a decrease in osteoblastogenesis and an increase in the apoptosis of mature osteoblasts [33, 34]. The impact of corticosteroid therapy on diminishing BFR and on the eventual development of adynamic changes is suggested by the inverse correlation between the administered dose of prednisone and the BFR. As a result of the reduction in BFR and adjusted apposition rate, patients can develop decreased skeletal mass with reduced bone mineral density (BMD) [11, 16] and may be prone to bone fractures. Although BMD was not studied in this group of patients, low BMD values have been associated with increased risk of fractures in children [35].

Glucocorticoids may decrease intestinal calcium absorption and thus stimulate PTH secretion [36]. However, serum concentrations of PTH are frequently in the normal range, as in the present study, and enhanced bone resorption can be demonstrated without elevated serum PTH concentrations [37]. Shortly after the administration of glucocorticoids, there is an initial and accelerated bone resorption [33], which is probably responsible for the rapid bone loss observed when measured by BMD [38]. These earlier changes probably result from glucocorticoid-induced osteoclastogenesis mediated through enhanced signaling from the osteoblast receptor activator of the nuclear factor k-B ligand (RANK-L) independent of PTH [39]. The present observations of bone histomorphometry provide a better understanding of the role of corticosteroids as a main cause for the reduced BMD in children with prolonged NS [11]. These findings are consistent with those reported by Monier-Faugere et al. [40] in post renal transplant recipients. Normal mineral accretion rates, especially high during adolescence, are main determinants of adult peak bone mass [9, 41]. The potential interference by corticosteroid therapy with BMD and with attaining optimal bone mass in children with NS [16], could constitute risk factors for osteoporosis later in life.

The potential adverse effects of glucocorticoid therapy on growth are well recognized [11, 42]. The persistently negative height Z-scores in some of the patients during the 12 months prior to biopsy support these observations. The negative correlations between the administered dose of prednisone and the length of the disease with the height Z-score at time of biopsy suggest an adverse influence of the corticosteroid therapy on linear growth. A significant negative impact of the duration of corticosteroid treatment on height Z-scores in nephrotic children [43] and the deleterious effects of prolonged prednisone therapy on height velocity in glomerular diseases [11] have been noted by other investigators. Additional inhibitory effects of glucocorticoids on skeletal growth involve interference with os-

teoblastic insulin-like growth factor (IGF-I) mRNA expression and IGF-I transcription, and inhibition of IGFBP-5 expression [44], and suppression of IGF-I induced chondrocyte cell replication [32]. The combined effects on osteoblastic and chondrocytic activities constitute the central mechanisms responsible for the inhibitory actions of glucocorticoids on bone formation and skeletal growth.

While disturbances of mineral metabolism potentially affecting bone integrity are recognized in patients with NS [1, 2, 3, 4, 5, 6, 31], controversy prevails about the presence of altered bone histology in adults with NS. While Lim et al. [2] and Korkor et al. [22] observed normal bone histology in a combined total number of 13 patients, Malluche et al. [6] reported defective mineralization and hyperparathyroidism in 6 patients. More recently, Mittal et al. [7] reported OM as the most prevalent finding in 30 patients with NS and normal GFR.

In the present study, most patients displayed one or more indices of osteoid accumulation, as judged by the increased osteoid area and osteoid perimeter. These findings, together with the normal mineralization lag time, the normal double tetracycline labeling uptake in most patients, and an osteoid area not >12%, denote focal signs of OM. Although osteoid thickness was not elevated, its positive correlation with the prevailing serum albumin concentrations suggests a potential relationship between clinical disease activity and eventual OM. Furthermore, the relationship between the duration of NS and the mineralization lag time suggests that patients with a more prolonged clinical course are at risk of developing OM, consistent with the findings reported in adults [7, 31]. Persistent clinically active NS may eventually result in more intense and generalized OM [6, 7] even without a decline in GFR. None of the patients studied by Korkor et al. [22] exhibited evidence of OM, but their concentrations of 25(OH)D were not as reduced as reported by other investigators [6, 7, 45]. In the present study, normal levels of vitamin D metabolites in most patients at the time of biopsy may in part explain the lack of more prominent OM. Children living in more northern latitudes may be at greater risk for OM due to reduced sun exposure and lower circulating vitamin D concentrations [46]. Overt OM with normal circulating levels of vitamin D metabolites has also been described in patients following kidney transplantation, suggesting a possible state of vitamin D resistance at the receptor level [40].

Bone histological evidence of hyperparathyroidism [6, 7] is not a consistent finding in NS [22]. In the present study, signs of overt hyperparathyroidism, including excessive osteoclastic activity, markedly elevated trabecular bone area, and peritrabecular or marrow fibrosis deposition were conspicuously absent. Nevertheless, the majority of patients displayed one or more signs of less prominent excessive bone resorption, including increased eroded perimeter, high-normal bone area, and elevated osteoid perimeter, and two patients had elevated BFR, indicating high bone turnover. As in previous reports, serum PTH concentrations were normal even in patients with hypocalcemia [5, 22, 31, 47]. This is possibly related to changes in the pattern of PTH secretion following glucocorticoid administration [48].

Adynamic osteodystrophy, well recognized in patients with chronic renal failure [49], is characterized histopathologically by an overall reduction in cellular activity in bone [50]. Originally described as a manifestation of bone aluminum toxicity, adynamic bone changes can arise from a variety of causes, including calcitriol therapy, exogenous calcium loading, prolonged immobilization, and glucocorticoid therapy [50]. All patients were active and ambulatory, none had diminished GFR or received treatment with calcitriol, and staining for aluminum was consistently negative in all bone biopsies. The absent BFR in one of our patients, a defining feature of a prominent adynamic bone lesion, has not been previously reported in children with non-azotemic glomerular disease and probably represents an inhibitory effect of glucocorticoids on osteoblastic activity [33].

Since the onset and subsequent relapses of the NS usually occur during periods of active somatic growth and maximal bone mineral accretion, attempts to ameliorate the potentially deleterious effects of long-term therapy with high doses of glucocorticoids on bone integrity and linear growth are justified. This seems particularly pertinent to corticosteroid-dependent NS, since a proportion of these patients may eventually develop renal insufficiency and ESRD [19, 30], with consequent renal osteodystrophy [20], and eventually may require renal transplantation with further exposure to corticosteroid therapy and risk of fractures [51]. Reports on the use of growth hormone [52], bone-sparing corticosteroids like deflazacort [53], calcitonin, and vitamin D [54], and more recently bisphosphonates [55] are encouraging. However, long-term longitudinal studies evaluating peak bone mass and possibly bone histomorphometry in patients with prolonged NS are needed.

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