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Children with nephrotic syndrome have greater bone area but similar volumetric bone mineral density to healthy controls

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ABSTRACT

Background: Glucocorticoid use has been associated with an increased fracture risk and reduced bone mineral density (BMD), particularly in the trabecular compartment. However the contribution of the underlying inflammatory disease process to these outcomes is poorly understood. Childhood nephrotic syndrome (NS) typically follows a relapsing–remitting course often requiring recurrent courses of glucocorticoids, but with low systemic inflammation during remission. NS therefore represents a useful clinical model to investigate the effects of glucocorticoids on BMD and bone geometry in childhood.

Methods: Children with NS were compared to age and sex matched healthy controls. Body composition and areal BMD (whole body, lumbar spine and hip) were assessed by DXA. Peripheral quantitative computed tomography (pQCT) scans were obtained at metaphyseal (4%) and diaphyseal (66%) sites of the tibia to determine volumetric BMD and bone cross-sectional geometry. Lifetime cumulative glucocorticoid exposure was calculated from medical records.

Results: 29 children with NS (55% male, age 10.7 ± 3.1 years) were compared to 29 healthy controls (55% male, age 11.0 ± 3.0 years). The children with NS were of similar height SDS to controls ($p = 0.28$), but were heavier (0.65 ± 1.28SDS vs −0.04 ± 0.89SDS, $p = 0.022$) and had greater body fat percentage SDS (0.31 ± 1.01 vs −0.52 ± 1.10, $p = 0.008$). Tibial trabecular and cortical vBMD were similar between the two groups but bone cross-sectional area (CSA) was significantly greater in children with NS at both the metaphysis (954 ± 234 mm^2 vs 817 ± 197 mm^2, $p = 0.002$) and diaphysis (534.9 ± 162.7 mm^2 vs 463.2 ± 155.5 mm^2, $p = 0.014$). Endosteal and periosteal circumferences were greater in children with NS than controls (both $p < 0.01$), resulting in reduced cortical thickness (2.4 ± 0.7 mm vs 2.8 ± 0.7 mm, $p = 0.018$), but similar cortical CSA ($p = 0.22$). The differences in cortical geometry were not statistically significant when weight was included as a confounding factor. There were no associations between cumulative steroid exposure, duration of NS or number of relapses and any bone parameter.

Conclusions: Tibial bone CSA is increased in children with NS. We speculate that this is a compensatory response to increased body weight. Defects in trabecular BMD were not identified in this cohort of children with NS.

Introduction

Glucocorticoids cause dose-dependent bone loss in adults which occurs rapidly on drug introduction, and is associated with increased fracture risk and secondary osteoporosis [1]. An increased fracture risk has also been reported in children requiring recurrent courses of glucocorticoids [2] and reduced bone mineral density (BMD) has been demonstrated in a number of paediatric conditions treated with glucocorticoids, including inflammatory bowel disease, systemic lupus erythematosus, inflammatory arthritides and nephrotic syndrome [3–5]. Bone strength is determined by both BMD and geometric properties of bone, yet fewer studies have attempted to elucidate the effects of glucocorticoids on bone geometry. Children treated with glucocorticoids for juvenile rheumatoid arthritis and inflammatory bowel disease have reduced bone cross-sectional area (CSA), cortical CSA and cortical thickness, as determined by peripheral quantitative computed tomography (pQCT), which result in reduced bone strength [3,6,7].

Importantly, the underlying inflammatory disease process may also contribute to the detrimental bone outcomes. It is recognised that pro-inflammatory cytokines may adversely affect bone formation and

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remodelling in children [8], and vertebral fractures have been identified at diagnosis in children with some systemic inflammatory conditions [9]. Furthermore, improvements in trabecular volumetric BMD (vBMD) following anti-inflammatory treatment for childhood Crohn's disease have been observed [3], thus highlighting the difficulties in determining the differential effects of glucocorticoids and the inflammatory processes on the growing skeleton in these clinical models.

This study aimed to examine vBMD and bone geometry using pQCT in a cohort of children with childhood nephrotic syndrome (NS). In contrast to other inflammatory conditions, NS responds rapidly to glucocorticoids with little evidence of systemic inflammation during periods of remission [10,11]. However, the majority of children with NS will follow a relapsing–remitting course requiring multiple courses of glucocorticoids throughout childhood. Recent evidence suggests around 80% of children diagnosed with NS will have at least one relapse after initial remission, and a median of four relapses will occur [12,13]. Studies in children using DXA have reported conflicting effects of NS treatment on bone mineral content (BMC) [14,15] and areal BMD (aBMD) [5,16,17]. In one case-controlled study using pQCT, reduced trabecular vBMD, with preservation of cortical vBMD, was reported [18]. Alterations in vBMD and geometry have also been reported in healthy overweight children [19,20], and it is recognised that children with NS are often heavier than healthy controls. We therefore undertook this study to investigate vBMD and bone geometry in relation to body composition, disease characteristics and glucocorticoid exposure in children with NS and healthy controls.

Methods

Study subjects

Children with NS were recruited from the regional tertiary nephrology clinic at University Hospitals Southampton NHS Foundation Trust, UK. Exclusion criteria included age ≤ 5 years at time of recruitment and other significant medical co-morbidity. Steroid exposure and disease characteristics were determined from medical and parent held records. A healthy control group who had never received steroid treatment and had no other chronic medical conditions was recruited by asking subjects to invite a friend of similar age to participate. Fracture history was determined in both groups by direct questioning. All fracture types (appendicular and axial) were considered.

The study was approved by the Southampton Research Ethics Committee and written informed consent was obtained from all participants and/or their parent or guardian.

Anthropometric assessment

Height was measured using a wall mounted stadiometer (Marsden HM-200) and weight to the nearest 0.1 kg using electronic scales (Marsden MPPS-250). Standard deviation scores (SDS) were calculated for height, weight and body mass index (BMI) from the 1990 British reference data [21,22]. Pubertal status was assessed by participant self-assessment using standard photographs and a Prader orchidometer, and classified according to the method of Tanner.

Dual-energy X-ray Absorptiometry Scans (DXA)

Measures of BMC, aBMD and bone area were obtained using a Hologic Discovery W Dual-energy X-ray absorptiometer (Hologic, Inc., Bedford, MA, USA) with fan beam technology (software version 12.5) for whole body (WB), left hip and lumbar spine (L1–L4) (LS). aBMD SDS were provided for age and gender from the manufacturer's software. Two methods were used to minimise the effect of body size on areal BMD. Firstly, height specific SDS were calculated using published North American reference data as a method of adjusting for body size [23], and secondly, bone mineral apparent density (BMAD), a validated transformation to calculate a volumetric density from DXA data, was used. This uses the assumption that the measured site is a cylinder with a volume proportional to the second power of the projected anteroposterior area obtained from DXA measurement of areal BMD. SDS for participant age were calculated using published British reference data [24]. Body composition (fat mass and lean mass) was also determined from the whole body DXA scan. Fat-free mass (FFM) was calculated as lean mass + BMC, and fat-free mass index (FFMI) as FFM/Height^2. Fat percentage and FFMI SDS for age were calculated using North American reference data for children over 8 years of age [25]. The local experimental coefficient of variation for the DXA instrument using a spine phantom was 0.68%.

Peripheral quantitative computed tomography (pQCT)

pQCT scanning was performed using a Stratec XCT-2000 scanner (Stratec Inc., Pforzhein, Germany). The non-dominant leg was scanned at two sites; a metaphyseal site (largely trabecular bone) and a diaphyseal site (largely cortical bone) which corresponded to 4% and 66% of the distance from the medial malleolus to the tibial tuberosity, respectively. At each site a single 2 mm thick tomographic slice was sampled at a voxel size of 0.5 mm.

At the metaphyseal site, BMC, total vBMD (the mean mineral density of the total cross-section), trabecular vBMD and total bone cross-sectional area (CSA) were calculated using the manufacturer's software version 5.4. At the diaphyseal site, BMC, total vBMD, cortical vBMD, total bone cross-sectional area (CSA), cortical CSA and muscle CSA were obtained. Periosteal and endosteal circumferences and cortical thickness were calculated using the circular ring model in which bone was assumed to be a cylinder [26]. The BMC:muscle ratio was calculated as an indicator of bone mineralization relative to muscle strength [27].

Bone strength measurements were derived from the pQCT data. Torsional resistance was estimated by strength strain index (SSI) measured at the diaphyseal site [28], and bone strength index (BSI), an indicator of ability to withstand compressive forces, at the metaphyseal site [29].

The coefficient of variation for this pQCT instrument has previously been demonstrated to range from 0.88% (tibial total metaphyseal density) to 8.8% (total radial diaphyseal area), but typically 1–3% [30].

Biochemical analysis

Blood and urine samples were obtained and analysed for serum calcium, albumin and alkaline phosphatase (ALP) and urinary protein: creatinine ratio by standard laboratory analysis (Beckman UniCel DxC Synchron, Beckman Coulter (UK) Ltd., High Wycombe, UK). Serum total 25-hydroxy-vitamin D [25(OH)D] was determined using liquid chromatography mass spectrometry (Waters Acquity UPLC, Waters Corporation, Milford, MA, USA) with 26,27-hexadeuterium-25-OH-Vitamin D3 as an internal standard. Serum parathyroid hormone (PTH) was measured using a two-site immunoenzymatic assay (Beckman Unicel DXi 800, Beckman Coulter (UK) Ltd., High Wycombe, UK).

Statistical analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS) v19. Data are presented as mean ± SD unless otherwise stated. Data were checked for normality, and where necessary log-transformed. The independent *t*-test and Mann–Whitney *U* test were used to determine statistical significance between groups for normal and non-normally distributed samples, respectively. Linear regression was subsequently used to adjust for age, gender, pubertal status and height. Correlations were assessed using Pearson coefficient and Spearman's rank. $p \leq 0.05$ was considered significant.