SHORT REPORT

Cortical bone geometry in asthmatic children

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At the mid-radius, pre-pubertal asthmatic children had smaller periosteal and endosteal circumferences and thicker cortical shells compared to controls, when assessed by peripheral quantitative computed tomography. Asthmatics had diminished periosteal expansion for muscle size, suggesting that asthma, its treatment, or its effects on physical activity had resulted in impaired adaptation of bone to muscle loading. Alterations in cortical bone geometry might explain the increased fracture risk in asthmatic children.

We previously reported that pre-pubertal asthmatic patients treated with moderate to high doses of inhaled corticosteroids (ICS) had normal spinal and distal radial volumetric trabecular bone mineral density.¹ Using the large UK General Practice Research Database, van Staa *et al* found an increase in the risk of non-vertebral fractures in 7–14 year old asthmatic children treated with ICS compared to asthmatics treated with inhaled bronchodilators only and controls who did not suffer from asthma. The authors attributed the excess risk of fractures in ICS users to their asthma and its severity rather than to use of ICS.² Melton *et al* also reported an increased rate of peripheral fractures in asthmatics diagnosed before 35 years (mean age of diagnosis 6 years).³ This epidemiological evidence of increased peripheral fractures in asthmatic children prompted us to study the mid-radial parameters of bone strength. Peripheral quantitative computed tomography (pQCT) allows measurement of volumetric bone mineral density (vBMD) of cortical and trabecular bone separately. It also allows measurement of cross-sectional muscle area (CSMA) and geometric properties of cortical bone (endosteal circumference, periosteal circumference, cortical thickness, cortical bone cross-sectional area (CbCSA), axial moment of inertia, stress-strain index), which are related to bending and torsional strength of long bones.⁴ For this study we used the data collected in our original cohort of asthmatic children.¹

METHODS

The characteristics of the asthmatic subjects studied and methods have been previously described.¹ The study was approved by the Central Manchester Local Research Ethics Committee.¹ From the original dataset, 13 (6 males) of 20 children with chronic asthma had satisfactory pQCT (Stratec, Pforzheim, Germany) at 50% of the non-dominant forearm length. A 1.2 mm thick single tomographic slice was sampled using the scan speed of 25 mm/s and voxel size of 0.4 mm, and analysed using the software version 5.50 d. At the mid-radius the cortical bone cross-sectional area (mm²), cortical thickness (mm), muscle cross-sectional area (mm²), and outer and inner cortical bone contours (periosteal and endosteal circumferences in mm) were determined. The axial moment of inertia (mm⁴), which is a measure of the distribution of cortical bone mass about the centre of the cross-section of a tubular bone

and is related to bending strength of bone, and the stress-strain index (mm³), which is related to torsional strength, were also measured. The control group consisted of 88 (36 males) age matched healthy Manchester schoolchildren who had all been recruited to obtain normative data on bone mineral density, bone geometry, and body composition; age matching was by group and not case-control. Of the initial 108 age matched subjects, 20 children with a history of mild asthma were excluded from the analysis.

Statistical analysis was performed using SPSS (version 11.5) for Windows. Population parameters were summarised by their standard deviation score medians and interquartile ranges. Analysis of covariance was used to compare muscle and bone parameters in the asthmatic and control groups after controlling for the linear variables of age, gender, and height. A muscle-group interaction was tested to determine the relation between periosteal circumference (reflecting periosteal apposition), CSMA (surrogate for muscle strength), and groups (asthmatics and controls). Significance was based on two tailed tests; $p < 0.05$ was considered to be significant.

RESULTS

There were no significant differences in anthropometric data (table 1). Asthmatics had smaller periosteal and endosteal circumferences and thicker cortices compared to controls. There were no significant differences in bone mineral content, CbCSA, axial moment of inertia, or the strength-strain index between the two groups. A significant interaction was found

Figure 1 The relation between cross-sectional muscle area and periosteal circumference in the asthmatic and control group; a significant interaction was found between periosteal circumference and disease group ($R^2=0.56$, $p<0.001$).

Table 1 Age, height standard deviation score (SDS), weight SDS, and cortical bone data of asthmatic and control subjects

Variable	Asthmatics (n = 13; 6 males)	Controls (n = 88; 36 males)	p value
Age	7.66 (6.89–8.40)	8.18 (7.04–8.99)	0.31
Weight SDS	−0.19 (−0.56–0.90)	0.22 (0.09–0.50)	0.68
Height SDS	−0.34 (−0.86–0.49)	0.24 (0.04–0.42)	0.14
Cortical BMC (mg)	41.56 (37.48–45.41)	43.59 (36.82–49.84)	0.25
CbCSA (mm ²)	38.88 (37.20–43.44)	42.08 (36.68–48.24)	0.39
Cortical thickness (mm)	1.89 (1.62–2.25)	1.77 (1.58–1.97)	0.001
Periosteal circ (mm)	27.86 (25.82–29.11)	29.54 (27.82–31.51)	0.04
Endosteal circ (mm)	14.87 (12.86–18.59)	18.24 (16.29–20.51)	0.001
CSMA (mm ²)	1286.72 (1165.84–1685.44)	1618.96 (1158.96–1455.56)	0.10
Axial moment of inertia (mm ⁴)	259.00 (208.00–289.50)	323.50 (251.25–407.75)	0.15
Stress-strain index (mm ³)	79.90 (69.75–92.72)	87.52 (73.53–100.37)	0.53

The bone and muscle variables in the two groups were compared using the analysis of covariance after controlling for age, height, and weight.

between periosteal circumference and study groups (fig 1; $R^2 = 0.56$, $p < 0.001$), thus indicating that changes in periosteal circumference with CSMA differed between healthy controls and asthmatics.

DISCUSSION

Bone strength depends both on the amount of bone mass contained within the periosteal envelope and bone geometry. According to Frost, bones adapt their strength to the mechanical forces that they are subjected to, which primarily arise from muscles.⁵ In tubular bones, this adaptation results in deposition of bone on outer periosteal surfaces, thus increasing their external bone circumference. This deposition of bone mass further away from the centre of the marrow cavity serves to increase their resistance to fracture arising from bending and torsional loads.⁴ The use of pQCT to measure the geometric properties of the mid-radius has allowed us to study how peripheral long bones adapt to asthma and/or its treatment. We found that after adjustment for age, gender, and height, asthmatic children had smaller periosteal and endosteal circumferences and thicker cortical shells compared to controls (fig 2). The distribution of bone mass closer to the central axis of the bone in asthmatics suggests either deposition of extra bone mass endosteally, or less endosteal resorption in comparison to controls; changes on the endosteal surface of bones confer little or no extra bone strength which is in contrast to periosteal apposition which would increase bone strength. Although not statistically significant, the reduced axial moment of inertia and the stress-strain index are consistent with diminished torsional and bending bone strength in asthmatic children.

There was a difference in the relation between periosteal circumference and CSMA between the groups, showing that in comparison to controls, asthmatics have diminished

Figure 2 Hypothetical diagram showing smaller periosteal and endosteal circumferences and thicker cortical shells at the mid-radius in asthmatics compared to controls.

What is already known on this topic

- Asthmatic children have a higher incidence of non-vertebral fractures
- Asthmatic children treated with inhaled corticosteroids have normal spinal and distal radial volumetric trabecular bone mineral density

What this study adds

- Asthmatic children have slender long bones with thicker cortices
- Alterations in cortical bone geometry might explain the increased fracture risk in asthmatic children

periosteal circumference for muscle size. Possible explanations for the observed impairment in periosteal apposition to muscle loading in asthmatics include reduced physical activity, treatment (bronchodilators and ICS), or disease related alterations in cytokine and cellular factors. Further studies are needed to investigate the basis of these geometrical changes, and their impact on increased fracture risk in asthmatic children.^{2 3}

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Working with the tooth fairy

Posthumous molecular genetic analyses of tissue such as teeth are common in forensic investigation but their use in clinical genetic counselling has rarely been reported. In Perth, Australia (Helen Leonard and colleagues. *Lancet* 2005;**366**:1584) DNA analysis of tissue from a saved deciduous tooth established a diagnosis of Rett syndrome 13 years after the death of a child.

The child died of pneumonia at the age of 7 years in 1991. Her early development had been normal but she had deteriorated neurologically from the age of 16 months, with seizures from the age of 3 years. Extensive investigations between the ages of 2 and 4 years had not produced a diagnosis. In 2002 her mother read a magazine article about Rett syndrome and in 2004, after an internet search, she contacted the Australian Rett Syndrome project. The parents attended a clinic and the mother asked whether the putative diagnosis of Rett syndrome might be confirmed by analysis of a saved baby tooth. Subsequent DNA analysis of the pulp of the tooth showed a nonsense mutation (c.502C>T; pR168X) in the *MECP2* gene on the X chromosome, confirming the diagnosis. The parents gained relief and comfort in several ways. They finally had a diagnosis that enabled them to understand their daughter's illness. It also assuaged their feelings that they may have been, in some way, to blame; feelings that centred on the child's having been vaccinated a month before the onset of symptoms and on the circumstances surrounding a fall when she was 17 months old. They had also been worried about the genetic implications for future grandchildren and were reassured that their son, now in his mid-twenties and healthy, could not be a carrier of the causative mutation.