Osteoporosis and the Marfan syndrome

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Summary: Fourteen patients with Marfan syndrome, defined according to present criteria, had bone mineral content of the distal forearm measured by single photon absorptiometry. Patients were matched for age and sex with a large local group of healthy volunteers. While further work is needed with other methods of densitometry with measurements at other sites, our results provide no evidence that there is an increased incidence of osteoporosis in Marfan syndrome. Previous reports of an association were probably due to incorrect clinical diagnosis or confusion with clinically similar syndromes known to cause osteoporosis.

Introduction

Marfan syndrome is a disorder of connective tissue showing autosomal dominant inheritance and wide clinical variability. The estimated prevalence is about 4–6 per 100,000 persons.¹ Classically abnormalities occur in the cardiovascular and musculoskeletal systems, and the eyes. With the advent of stricter diagnostic criteria² it has become possible to evaluate patients with Marfan syndrome more critically. Because Marfan syndrome is a disorder of connective tissue it has long been thought to predispose to osteoporosis. Authoritative texts list Marfan syndrome as a cause of osteoporosis^{3–5} and clinician guidelines from the National Osteoporosis Foundation² imply that it is a cause. The aim of our study was to evaluate, by measurement of forearm bone mass, the presence of osteoporosis in volunteer patients known to suffer from Marfan syndrome as diagnosed by strict criteria.² The only earlier study, by Brenton *et al.*,⁶ lacked the clear clinical diagnostic criteria now available and used only the relatively crude technique of spinal radiography for the assessment of osteoporosis.

Methods

The patients met the criteria of the Berlin Nosology (Table I), which requires classical skeletal involvement plus features in two other systems, including at least one major feature, if there is no definite family history. The subjects comprised 10 male patients aged between 21 and 68 years of age and

four female patients aged between 22 and 51 years of age. Patients were interviewed to obtain information on the number of past fractures (if any), smoking history, medication and alcohol intake. Patients were matched for age and sex with control subjects from a large local group of healthy volunteers.

Bone mineral content (BMC), corrected for fat, was measured in the non-dominant distal forearm using a Molsgaard ND1100A single photon absorptiometer with a ¹²⁵I source (150 mCi).⁷ The

Table I Marfan syndrome criteria according to the Berlin Nosology 1986²

In the absence of a definitely affected relative there should be skeletal involvement plus involvement of two other systems, at least one of which shows a cardinal feature (*)

Systems

1. **Cardiovascular**
Aortic aneurysm*
Mitral regurgitation*
'Floppy' mitral valve
2. **Ophthalmological**
Ectopic lentis*
Severe myopia
Retinal detachment
3. **Neurological**
Dural ectasia*
4. **Respiratory**
Pneumothorax
5. **Skeletal**
Abnormal long lower segment
Span exceeds height by >7 cm
Kyphosis
Chest wall deformity

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'distal' (DBMC) measurements are at a site comprising approximately 50% trabecular bone and the 'proximal' (PBMC) site comprises approximately 90% cortical bone.⁸ BMC values were divided by bone width at the measurement site to provide an index of bone density (DBMC/BW and PBMC/BW). The precision of the bone mineral content estimations was assessed by two operators carrying out the procedure on one healthy female volunteer (age 23) on 10 occasions at approximately weekly intervals. The coefficients of variation were 1.3% for distal BMC (mean 28.5) and 1.2% for proximal BMC (mean 32.2). There were no significant differences between the two operators.

Baseline BMC measurements were expressed as 'z' scores: the number of standard deviations (s.d.) of the patient's value from the age and sex-adjusted mean of a local reference population. The reference interval (± 2 s.d. from the mean) was calculated for each sex from BMC measurements on normal subjects aged between 20 and 80 (91 men in 10 year age groups and 286 women in 5 year age groups). Differences between the Marfan syndrome patients and the control subjects were analysed by Student's *t*-test.

Results

Figure 1 illustrates the distribution of sample results as the number of standard deviations from the mean for an age- and sex-matched population. The female results marked with an asterisk came from one individual who had been immobilized by vertebral crush-fractures due to long-term oral steroid therapy. The other three female patients had a DBMC/BW measurement within the reference interval for age and sex. All the DBMC/BW measurements for the males were within the reference interval and 60% were within one standard deviation (Figure 1).

Discussion

In 1972 Brenton *et al.* compared a series of 22 cases of homocystinuria with 16 cases of Marfan syndrome.⁶ The diagnostic criteria were much less precise than those currently accepted and used in this present study. The age range in Brenton's 'Marfan' patients was from 5 years 7 months to 31 years 11 months; we felt that our study should be limited to adults for whom a well-documented local reference population was available.

Figure 1 Bone mineral content expressed as standard deviations (z scores) from the mean for an age- and sex-matched local population. NS = not significant ($P > 0.05$); *the single individual mentioned in the text; # P value $0.02 < 0.05$ ($n = 4$); P value not significant if patient indicated by asterisk excluded. DBMC = distal forearm bone mineral content; DBMC/BW = distal forearm bone mineral content standardized for bone width; PBMC = proximal forearm bone mineral content; PBMC/BW = proximal forearm bone mineral content standardized for bone width.

Using the relatively crude technique of spine radiology, Brenton concluded that none of the 'Marfan' patients had osteoporosis, whilst half of the homocystinuria patients showed 'moderate' or 'severe' osteoporotic changes.

Despite the conclusion of this earlier paper we found several examples of authoritative current literature referring to Marfan syndrome as a cause of osteoporosis. Using more precise techniques, an age range for whom good control data was available, and the current stricter diagnostic guidelines, we present data that suggest that osteoporosis is not a significant problem in the patients we studied. The male patients showed no evidence of reduction in bone mass. The number of females studied to date was small, and results were influenced by the low bone mineral content of one patient who had received long-term oral steroid therapy and suffered long periods of immobility.

Our results imply that there is no evidence that osteoporosis is a feature of Marfan syndrome patients. However, we recognize that our study was

carried out with measurements only at the radius. Several studies have shown that measurement at this site is as good as measurement of spinal bone mass for prediction for future fractures.^{9,10} It is hoped that further study using dual energy X-ray densitometry of the spine and hips which is planned, will clarify the question of osteoporosis.

The findings were not artefacts resulting from the long slender bones of the Marfan patient's since the results were comfortably normal whether or not divided by bone width (BW). It is likely that earlier confusion arose because of the difficulties in diagnosing Marfan syndrome and in distinguishing it from clinically similar syndromes such as homocystinuria.

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