Bone Mineral Density Determinations by Dual-Energy x-ray Absorptiometry in the Management of Patients with Marfan Syndrome—Some Factors Which Affect the Measurement

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Abstract Reduced bone mineral density (BMD) was sporadically reported in patients with Marfan syndrome. This may or may not place the Marfan patient at increased risk for bone fracture. In comparing the BMDs of our patients with those reported in the literature, it seemed that agreement between values, and hence the degree of osteoporosis or osteopenia reported, was dependent on the instrumentation used. The objective of this study was to statistically assess this impression. Bone mineral density measurements from our previously published study of 30 adults with Marfan syndrome performed on a Lunar DPXL machine were compared with studies published between 1993–2000 measured using either Lunar or Hologic bone densitometry instruments. The differences of our measurements compared with those made on other Lunar machines were not statistically significant, but did differ significantly with published results from Hologic machines ($P < 0.001$). Before progress can be made in the assessment of BMD and fracture risk in Marfan patients and in the evidence-based orthopedic management of these patients, standardization of instrumental bone density determinations will be required along with considerations of height, obesity, age, and sex.

Key words BMD · bone mineral density · dual-energy x-ray absorptiometry · Marfan syndrome · study comparisons

Introduction

Marfan syndrome is an autosomal dominant disorder of connective tissue caused by mutations of the fibrillin-1 gene on the long arm of chromosome 15 (15q21.1) [1]. The estimated incidence in the general population is 1 of 10,000 [2]. With improved cardiac treatment [3], the prolonged survival of patients with Marfan syndrome has revealed a number of noncardiac health issues, including musculoskeletal concerns that may affect quality of life [4].

Questions have arisen regarding the existence of decreased bone mineral density (BMD) in patients with Marfan syndrome. Conflicting reports have described generalized or localized decreased BMD in Marfan syndrome [5–10]. Information is lacking regarding the management and prevention of osseous complications in patients with Marfan syndrome. The need to orthopedically assess and reduce fracture risk in the face of low BMD could be an important issue in the management of these patients. Thus, it has become increasingly important to accurately determine the BMD and orthopedic status of these patients.

In a previously published study where BMD was assessed with a Lunar DPXL instrument [11], BMD measurements corresponding to osteopenia in the femoral neck of adult men with Marfan syndrome ($P < 0.001$) were reported. Carter et al. [10], using Hologic QDR1000 to assess BMD, also reported lower values for femoral neck BMD ($P < 0.05$) in men whose average age was much younger compared to men in the study of Giampietro et al. [11], although differences observed by this group were more pronounced. Conflicting results were obtained regarding BMD status in adult women with Marfan syndrome [6, 7, 9–11]. We speculated whether these differences could be related to the instrumentation used. To address

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Table 1 Summary of previously reported BMD results in males with Marfan syndrome (units of BMD)

Authors	Mean age (year)	Spine				Femoral Neck			
		N	Mean	SD	P value ^a	N	Mean	SD	P value ^a
Giampietro et al. [11] (Lunar)	41.1	11	1.21	0.18	–	11	0.88	0.09	–
LeParc [9] (Hologic)		–	–	–	–	19	0.804	0.138	.1
LeParc [9] (Controls-Hologic)		–	–	–	–	45	0.895	0.146	–
Carter et al. [10] (Hologic)	33	12	1.02	0.11	.006	12	0.83	0.12	.3

^aDenotes comparison between the study and the study of Giampietro et al.
SD=standard deviation

this possibility, we compared the results of the study of Giampietro et al. [11] to other published studies, which employed either the Lunar DPX or Hologic QDR 1000W dual-energy x-ray absorptiometry (DXA) bone densitometers to assess BMD in patients with Marfan syndrome [7–10].

Methods

Analytical studies of BMD reported in the literature on adult patients with Marfan syndrome [7–11] were retrospectively reviewed. The following definitions for categories established by the World Health Organization for clinical characterization of BMD will be operative for this report.

- *Normal bone density*: BMD within 1 standard deviation (SD) of peak bone mass;
- *Osteopenia*: BMD that is between 1–2.5 SD below peak bone mass; and
- *Osteoporosis*: BMD ≥ 2.5 SD below peak bone mass.

Further definitions include:

- Anatomic site T scores: the number of SD above or below the average normal peak bone density; and
- z-scores: the number of SD above or below an age- and gender-matched control.

One-way ANOVA with Student–Newman–Keuls pairwise comparisons was used to compare BMD values obtained from the study of Giampietro et al. [11] to other published studies [7–10].

Results

Whereas our study reported T-scores, those by Kohlmeier et al. [6, 8], LeParc et al. [9], and Carter et al. [10] utilized z-scores for reporting BMD variation. Tobias et al. [7] reported BMD but did not provide z- or T-scores.

The results of comparisons of the study of Giampietro et al. [11] and the other published studies that reported actual BMD values [7–10] in male and female subjects with Marfan syndrome are summarized in Tables 1 and 2. Reduced BMD was previously reported in the femoral neck of adult men in two studies [9, 10]. Decreased axial (L2–L4) BMD in women was also reported in these studies [9, 10], but this was not observed in the study of Giampietro et al. [11]. Our BMD values for L2–L4, femoral neck, and total body in women with Marfan syndrome were significantly higher than some reported values [8, 10], but were similar to the values of L2–L4 and femoral neck reported by Tobias et al. [7]. A Lunar DXPL machine with presumably the same reference pool was used in that study. LeParc et al. [9] had reported decreased BMD z-scores in adult women with Marfan syndrome. Because the adult female subjects were predominately Caucasian [7, 8, 10], it is unlikely that the observed difference in BMD values is because of variation attributable to race within the different study populations.

In addition, we observed significantly higher differences in spine BMD in both men and women compared to Carter et al. [10]. Our BMD values of the femoral neck in

Table 2 Summary of previously reported BMD results in females with Marfan syndrome (units of BMD)

Authors	Average Age (year)	Spine				Femoral Neck				Total Body			
		N	Mean	SD	P value ^a	N	Mean	SD	P value ^a	N	Mean	SD	P value ^a
Giampietro et al. [11] (Lunar)	40.8	17	1.22	0.23	–	19	0.9	0.21	–	13	1.11	0.1	–
Kohlmeier et al. [8] (Hologic)	37.0	14	1.008	0.12	.003	17	0.713	0.104	.002	15	0.784	0.15	<.001
Tobias et al. [7] (Lunar)		14	1.182	0.166	>.05	14	0.929	0.121	>.05	–	–	–	–
Carter et al. [10] (Hologic)	43.0	13	0.9	0.15	<.001	13	0.69	0.18	<.001	–	–	–	–

^aDenotes comparison between the study and the study of Giampietro et al.
SD=standard deviation

men were higher than those reported by both LeParc et al. [9] and Carter et al. [10], but are closer to the control values reported by LeParc et al. [9].

Discussion

The present study demonstrated that variability in BMD measures obtained using various DXA instruments and different versions of software used for data interpretation confounded interstudy comparisons. However, from a clinical perspective, use of DXA scanners to obtain accurate, sensitive, and specific BMD measures on Marfan patients to inform long-term health management planning would be highly desirable. The ability to discern true osteoporosis in patients with Marfan syndrome is important from a treatment perspective for a variety of reasons. Whereas pharmacological treatment of osteoporosis in these patients is important to support maintenance or improvement of bone density, treatment of patients who do not have true osteoporosis is inadvisable because of newly emerging evidence of maxillary osteonecrosis associated with bisphosphonate use [12]. In addition, cost of treatment with these drugs may be a substantial burden to the patient. We therefore recommend that all patients have longitudinal BMD studies performed on the same scanner to provide a valid basis for comparison for patient care planning, and further, facilitating standardization for possible future larger multicenter study comparisons.

Lack of standardization in reporting BMD values is partly attributable to their conversion into *T*- or *z*-scores. These scores are calculated by referencing the manufacturer's database for spine bone density. There is no direct mathematical relationship between *T*- and *z*-scores. Therefore, accurate cross-study comparison of a reported *T*- vs *z*-score BMD is not possible. In addition, DXA instruments require extensive calibration [13], and instrumental BMD determinations are far from straightforward [14] and may contribute to variability in measurement outcome. Equations were derived to convert *T*-scores for femoral neck [15] or hip [16] readings between different instruments, but these equations only offset the differences and did not correlate them [15]. Moreover, comparisons in BMD readings between instruments showed greater deviation at higher BMD values both in postmenopausal women [17] and when utilizing phantoms [18]. Furthermore, different control populations were used as references for different instruments, and these differences were considered a source of discrepancy [15, 19]. In short, none of the methods have provided a perfect conversion between machines. Further calibration and standardization considerations are required as instrumentation evolves.

Should the inherent instrumental configuration and database software differences ultimately be resolved, a number of considerations remain when applying DXA to Marfan patients. In normal populations, biological covariates are known to affect BMD readings, including exercise levels (especially during development), body fat, sex, age, and height [20]. LeParc et al. [9] reviewed the effect of many

biological variables on measured BMD results in patients with Marfan syndrome and postulated that increased height, decreased weight, and adipose tissue observed in their Marfan patient sample contributed to a lower body mass index and decreased BMD. The same parameters contribute to differences in BMD measures obtained by different scanners and may accentuate the differences noted across study groups measured on different machines.

Very tall individuals have an artifact, which confounds meaningful interpretation of BMD results. The DXA is an areal determination correcting for height and width of the vertebra, but not the depth. Quantitative computed tomography (QCT) provides true three-dimensional images and reports BMD as true volume density measurements [21]. The ability of QCT to address volume and density of bone in the axial and appendicular skeletons, without influence from body or skeletal size, provides a major advantage over other methodologies for bone measurements in children and adults. It is possible that morphologic characteristics of bone, such as vertebral height and cross-sectional area, are altered in patients with Marfan syndrome compared to control patients matched for age, sex, race, height, and weight. If indeed these characteristics are increased in Marfan syndrome, they could act to decrease the fracture risk.

Future studies could be aimed at comparisons between adult patients with Marfan syndrome and height-matched control patients with respect to QCT measurement.

Results are mixed with regard to the reported risk for bone fracture in Marfan patients [6–9, 11, 22]. In the study of Giampietro et al. [11], while they identified some difference in bone density among Marfan patients, they did not demonstrate increased risk of bone fracture above that of normally active populations. More longitudinal studies are needed.

Although we cannot eliminate the possibility that differences in BMD among the different studies may reflect differences in factors such as height, age, weight, physical activity, and calcium intake that would impact on skeletal health, the conflicting reports regarding the BMD status of patients with Marfan syndrome leaves a management quandary. Are instrumental determinations of BMD in Marfan patients inaccurate and misleading? Is decreased bone density a feature that is associated with Marfan syndrome? If so, why are fractures not more frequently reported in patients with Marfan syndrome? Could this possibly be because of restriction of activities [23]? Should aggressive bone mineralization therapy be pursued to avoid future fractures, especially as more individuals enter the geriatric age group? Because the life expectancy for patients with Marfan syndrome has increased dramatically, practitioners need to be aware of the issues regarding interpretation of BMD determinations based on instrumentation in their patient management.

Although these analyses were limited to reviews of DXA BMD measurements in patients with Marfan syndrome, we propose that the findings reported in this study related to scanner-associated measurement variability have much broader implications and are not likely limited only to the

subset of patients with Marfan syndrome diagnosis. As technological capabilities continue to evolve, comparison and standardization of measurement outcomes across different technologies is a formidable problem for which there was no definitive approach or solution. An example is encountered in the challenges that continue to plague standardization of digital mammography across disparate digital mammography screening systems and approaches. The American College of Radiology has attempted to standardize mammography reporting by development of the Breast Imaging Reporting and Data Systems lexicon and the mammography quality standards act [24]. Whereas standardization was met with some degree of success, it was not possible to definitively address whether digital mammography demonstrates improved performance over screen film approaches. The Digital Mammographic Imaging Screening Trial, a ~2-year large multicenter trial involving mammography screening of 49,528 asymptomatic women at 33 participating sites, was undertaken to examine as its primary aim, the diagnostic accuracy of digital and screen film mammography during breast screening using five different types of mammography equipment and screen films [25]. Study outcomes are currently pending. Such an approach may merit consideration to address technology-related BMD measurement discrepancies.

Finally, we wish to acknowledge limitations of the present study. Because data compared in this study were drawn from multiple studies, it should be recognized that the study populations were different. As a result, it was not possible to adjust for factors that may impact bone health. Therefore, we cannot conclusively state that the BMD measurement differences observed among the studies are exclusively associated with the model of scanner used to perform the measurements. To verify the preliminary observations and conclusions reported in this study, the same population will need to be examined using multiple scanners at a given time point to validate that variability in BMD measures is largely attributable to the scanner employed.

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