Original Research

Osteoporosis Is Associated With Increased Marrow Fat Content and Decreased Marrow Fat Unsaturation: A Proton MR Spectroscopy Study

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Purpose: To use proton magnetic resonance spectroscopy (^{1}H-MRS) to evaluate vertebral marrow fat, and to determine whether bone density correlates with fat content and fat unsaturation levels in postmenopausal women.

Materials and Methods: Fifty-three women (mean age = 70 years) underwent dual energy x-ray absorptiometry and ^{1}H-MRS, and 12 young female controls (mean age = 28 years) underwent ^{1}H-MRS of the lumber spine. Water and lipid peak amplitudes were measured to calculate fat content and fat unsaturation index. Spearman's correlation tests and a t-test comparison of means were applied.

Results: ^{1}H-MRS was successful in 15 normal, 15 osteopenic, and 20 osteoporotic subjects, and in all controls. Marrow fat content was significantly elevated in osteoporotic (65.5% ± 10%) and osteopenic (63.5% ± 9.3%) subjects compared to normal subjects (56.3% ± 11.2%) and young controls (29% ± 9.6%). The fat unsaturation index was significantly decreased in osteoporotic (0.091 ± 0.013) and osteopenic (0.097 ± 0.014) subjects compared to normal subjects (0.114 ± 0.016) and young controls (0.127 ± 0.031). A good inverse correlation was observed between the fat content and the unsaturation index ($r_s = -0.53$, $P < 0.0001$).

Conclusion: Osteoporosis is associated with increased marrow fat. As marrow fat increases, saturated lipids appear to increase preferentially to unsaturated lipids.

Key Words: magnetic resonance (MR); spectroscopy; bone marrow; osteoporosis; unsaturation; fatty acids; lipids
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OSTEOPOROSIS IS A BONE DISEASE characterized by low bone mass and a structural deterioration of bone tissue that leads to bone fragility and an increased susceptibility to fracture (1). This disease affects about 40% of women and 20% of men over the age 50 years (2,3). As the world's population ages, the magnitude of health problems associated with osteoporosis is expected to increase (3). Dual-energy x-ray absorptiometry (DXA) and quantitative CT (QCT) are commonly accepted methods of assessing osteoporosis (4). However, magnetic resonance (MR) can potentially provide additional information that is not obtainable by means of DXA or QCT.

Recent in vivo proton MR spectroscopy (^{1}H-MRS) studies have shown both a linear increase in vertebral marrow fat content with aging and a higher fat concentration in males than females of similar age groups (5–7). However, since those studies did not specifically measure bone density, it has not been determined whether a relationship exists between increased marrow fat and bone density.

Histomorphometric studies on bone biopsy samples have shown that marrow fat is increased in osteoporosis (8). Bone marrow fat is known to consist primarily of saturated, monounsaturated, and polyunsaturated triglycerides (9). It is not known whether (or how) the composition of marrow fat changes with osteoporosis. Alterations in the arterial wall, platelet, and bone fatty acid unsaturation have been observed in animal models of hypertension (10), and patients with coronary heart disease (11) and osteoarthritis (12), respectively. ^{1}H-MRS is a useful technique for studying the triglyceride chemical composition of bone marrow in vivo (13). Since lipid peaks in marrow are usually incompletely resolved on ^{1}H-MRS, the application of prior knowledge in spectral analysis can enable the reliable assessment of overlapping lipid peaks (14). Provided that signal contributions from individual lipid peaks can be identified and measured, ^{1}H-MRS can also allow the lipid composition change that accompanies osteoporosis to be assessed.

The aim of this study was to use ^{1}H-MRS to evaluate vertebral marrow fat in postmenopausal women to determine whether bone density correlates with marrow fat content, and whether a change in the composition of marrow fat occurs with a change in bone density.

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MATERIALS AND METHODS

Subject Population

Fifty-three females above the age of 60 years who attended our institution's Center for Osteoporosis Care and Control between June 2002 and August 2004 were invited to participate in this study. The inclusion criteria were 1) no known preexisting bone disease (such as tumor, metastases, or metabolic disorder), 2) absence of documented vertebral abnormality (such as vertebral fracture), 3) absence of drug therapy known to affect bone density, and 4) absence of implants contraindicated for MR examination. Twelve premenopausal females were also recruited as young control subjects for ^{1}H-MRS. The ethics committee of our institution approved the study and written consent was obtained from all subjects prior to examination.

Radiographic and DXA Examinations

Lateral radiographic imaging of the lumbar spine was performed on all subjects upon enrollment in this study to assess the presence of vertebral fracture and aid in the detection of any other bony abnormality that could affect DXA or ^{1}H-MRS. A DXA examination of the lumbar region (L1–L4) was performed on all of the postmenopausal subjects (Hologic QDR-4500W; Hologic, Inc., Waltham, MA, USA) within 1 month of the MR examination. Based on the DXA results, the subjects were grouped into three categories according to the t-scores and World Health Organization criteria (15). Normal bone density was defined as a t-score ≥ -1.0, osteopenia as a t-score between -1.0 and -2.5, and osteoporosis as a t-score ≤ -2.5.

MR Examination

All subjects were examined in the supine position on a 1.5-T whole-body MRI system (Gyroscan ACS-NT; Philips, Best, The Netherlands) with a 30 mT/m maximum gradient capability. A 20-cm-diameter circular surface coil, centered at the third lumbar vertebra (L3), was used to optimize signal sensitivity for ^{1}H-MRS. After scout images were acquired in the axial, coronal, and sagittal planes, a volume of interest (VOI) was positioned in the central portion of the L3 vertebral body for spectroscopy. The width (w), length (l), and height (h) of the L3 vertebral body were first measured on MR images, and the VOI dimensions for each subject were given by $w/2 \times l/2 \times h/2$ cm^3. After local shimming and gradient adjustments were performed, data were acquired at a spectral bandwidth of 1000 Hz with 512 data points, and 64 non-water-suppressed signals were obtained using a point-resolved spectroscopy (PRESS) sequence (TR/TE = 3000/25 msec).

Spectral Fitting and Data Analysis

Spectra acquired from the L3 vertebral body of each subject were exported and analyzed on an offline computer using a time-domain fitting routine known as AMARES, a method implemented in the MRUI software package (16). Starting values used in the nonlinear least-squares fitting algorithm consisted of a manually selected resonance frequency and the linewidth of each peak of interest. Spectral assignments were based on previous studies (10,11,13), and only peaks that were clearly identifiable were measured. These included olefinic protons (–CH=CH–) around 5.35 ppm, water around 4.65 ppm, methylene protons (–CH=CHCH$_2$–) around 2.06 ppm, bulk methylene protons (–(CH$_2$)$_n$–) around 1.3 ppm, and terminal methyl protons (–CH$_3$) around 0.9 ppm. The rules applied in the fitting procedure were as follows: the linewidth of the water and methylene (1.3 ppm) peaks was unconstrained, all lipid peaks had a linewidth equal to that of the peak at 1.3 ppm, zero- and first-order phase correction was estimated by AMARES, resonance frequencies were constrained to lie within ± 0.05 ppm of the peaks' known resonance frequencies, and a Gaussian model function was assumed for all peaks. The linewidth of water and lipid (1.3 ppm) as determined by MRUI was measured to show overall spectral quality and to assess changes in magnetic field inhomogeneity caused by changes in bone density.

The vertebral body marrow fat content, defined as the relative fat signal amplitude in percentage of total signal amplitude (water and fat), was calculated according to the equation:

$$\text{Fat content} = (I_{fat}/(I_{fat} + I_{water})) \times 100[\%], \quad (1)$$

where I_{fat} and I_{water} are the peak amplitudes of fat (1.3 ppm) and water, respectively. Fat and water signal amplitudes, determined by spectral fitting, were not corrected for T2 decay. No T1-dependent saturation correction was judged necessary, given that only a marginal effect of T1 saturation of water resonance exists at TR $\geq$ 2 seconds (17). Marrow lipid unsaturation index was calculated according to

$$\text{Unsaturation index} = I_{olefinic}/(I_{olefinic} + I_{methylene} + I_{methyl}), \quad (2)$$

where $I_{olefinic}$, $I_{methylene}$ and I_{methyl} are the signal amplitudes of the olefinic peak (5.35 ppm), methylene peaks (2.06 ppm and 1.3 ppm), and terminal methyl peak (0.9 ppm), respectively.

Phantom Test

To verify assignment of fatty acid peaks in the bone marrow spectra, we performed measurements on a plastic phantom filled with pure corn oil (Mazola, ACH Food Companies, Cordova, USA) using a similar ^{1}H-MRS protocol with 256 signal averages. All clearly visible peaks in the corn oil spectrum were fitted with a linewidth equal to the linewidth of the dominant peak at 1.3 ppm, with other spectral fitting rules similar to those employed for marrow spectra. The unsaturation index for corn oil was determined as the relative contribution of olefinic proton (5.35 ppm) to the total proton signal arising from lipids. We compared our results with published values (18).

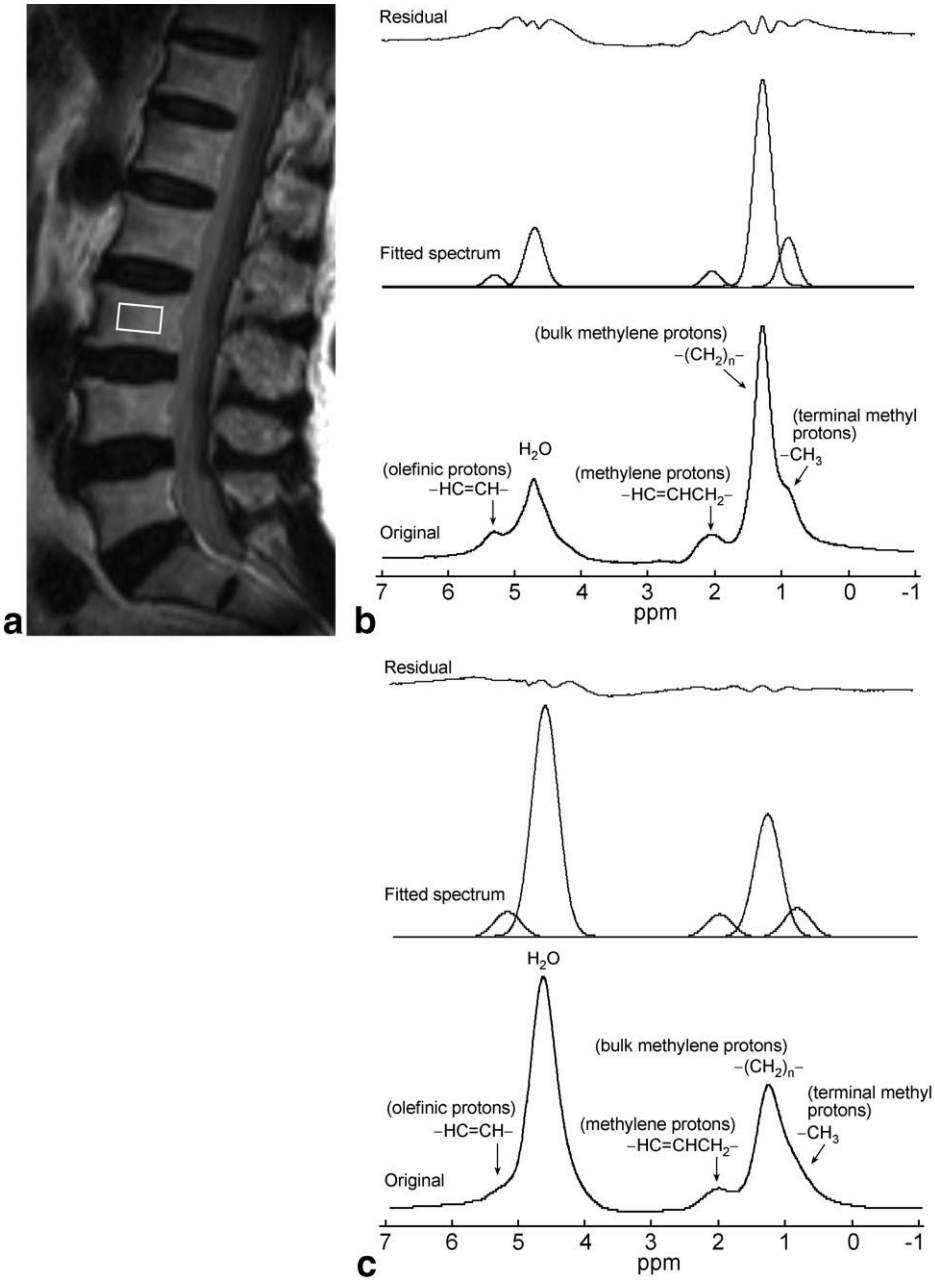

Figure 1. ^{1}H-MRS performed on the L3 vertebral body of a 72-year-old woman with osteoporosis (t-score = –2.8) and a 40-year-old premenopausal woman. **a:** Sagittal MR scout image (900/150) of the lumbar spine shows the position of a VOI (white rectangle) in the central portion of L3. **b:** Spectrum (bottom trace) acquired from a woman with osteoporosis shows a relatively intense lipid peak from bulk methylene protons compared to the water peak (4.65 ppm), indicating increased marrow fat content. The lipids that were identifiable in vivo were olefinic protons (–CH=CH–) at 5.35 ppm, methylene protons (–CH=CHCH$_2$–) at 2.06 ppm, bulk methylene protons (–(CH$_2$)$_n$–) at 1.3 ppm, and terminal methyl protons (–CH$_3$) at 0.9 ppm. The middle trace shows the fitted spectrum using prior knowledge, and the top trace is the residual spectrum. **c:** Spectrum acquired from a premenopausal woman shows a relatively intense water peak compared to bulk methylene protons.

Statistical Analysis

The mean values for vertebral marrow fat content, unsaturation index, water, and lipid linewidths were calculated for postmenopausal subjects above 60 years irrespective of bone density, and for premenopausal control females. Data for the postmenopausal women were then grouped according to bone density (normal bone density, osteopenia, and osteoporosis). The mean values for marrow fat content, unsaturation index, water and lipid linewidths for each bone density group were calculated and compared using Student's t-test. To rule out age differences as a possible confounding factor in this study, a t-test was performed comparing the mean age of each bone density group. A low probability for an age difference could be assumed if high *P*-values (> 0.05) were obtained. To test for the correlation between bone density (t-score) and marrow fat content, between unsaturation index and marrow fat content, and between bone density and unsaturation index, Spearman's correlation test was employed.

RESULTS

Spectral Fitting and Phantom Tests

Figure 1 shows the location of a VOI placed within the central portion of the L3 vertebral body, together with examples of marrow spectra acquired from a subject with osteoporosis and a premenopausal control subject, respectively. By incorporating prior knowledge in the fitting process, water and overlapping lipid peaks were analyzed to yield signal amplitude values for the determination of fat content using Eq. [1], and the un-

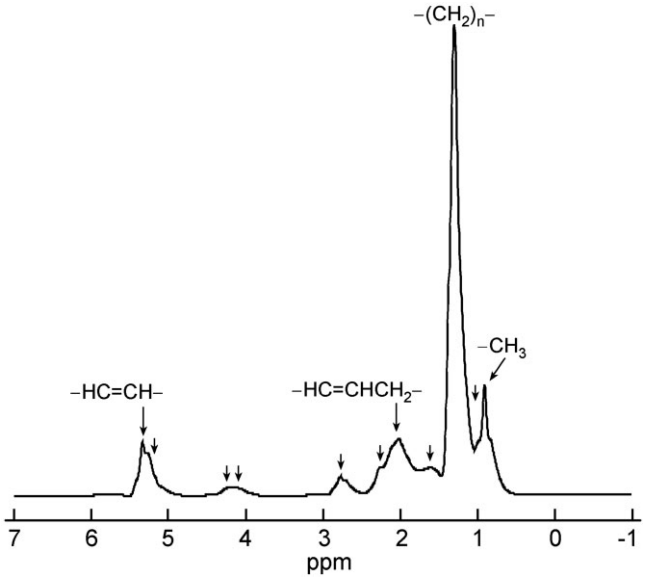

Figure 2. Spectrum acquired from corn oil shows seven more peaks (short arrows) in addition to those seen in vivo: 5.25 ppm (c_2, glycerol backbone), 4.29 ppm and 4.14 ppm (c_1 and c_3, glycerol backbone), 2.79 ppm (=$CHCH_2CH$=), 2.27 ppm (–CH_2CH_2CO–); 1.6 ppm (–CH_2CH_2CO–), and 0.97 (–CH=$CHCH_2CH_3$).

saturation index using Eq. [2]. Figure 2 presents a spectrum acquired from corn oil that shows not only the same four prominent lipid peaks at 5.35 ppm, 2.06 ppm, 1.3 ppm, and 0.9 ppm, as in vivo spectra, but also seven additional peaks of low signal amplitudes. The unsaturation index for corn oil was 0.077, based on the relative contribution of the olefinic peak to the total fatty acid signals in the spectrum.

Postmenopausal and Control Subjects

Fifty-three spectra were acquired using VOIs ranging from 2.7–5.5 cm^3 (mean = 3.7 cm^3). Three spectra from postmenopausal subjects were excluded because they were not interpretable, and the remaining spectra had a mean unsuppressed water peak linewidth of 29.8 ± 3.3 Hz. The results from the 50 postmenopausal subjects were grouped into three categories (normal, osteopenia, and osteoporosis) according to the t-scores. The calculated mean fat content, mean unsaturation index, mean water linewidth, and mean lipid linewidth for each group are shown in Table 1. Age differences between the three groups were not statistically significant (osteoporosis vs. normal, $P = 0.805$; osteoporosis vs. osteopenia, $P = 0.419$; osteopenia vs. normal, $P = 0.258$). Young premenopausal control subjects had a lower mean marrow fat content and a higher unsaturation index compared to the overall values for the 50 postmenopausal subjects (Table 1). When analyzed according to bone density, osteoporotic and osteopenic subjects had a significantly higher vertebral marrow fat content than subjects with normal bone density (Table 2, Fig. 3). The opposite trend was observed for the unsaturation index (Table 2, Fig. 3). Subjects with normal bone density had a significantly higher unsaturation index than osteopenic and osteoporotic subjects (Table 2, Fig. 3). In other words, there was a general trend of increasing marrow fat with decreasing bone density. This increase in marrow fat appears to be preferentially due to saturated triglycerides rather than to unsaturated triglycerides.

Table 2
Statistical Test Results for Postmenopausal Women

	P values	
	Fat content	Unsaturation index
Normal bone density vs. osteopenia	0.0489[b]	0.0066[b]
Normal bone density vs. osteoporosis	0.0137[b]	< 0.0001[b]
Normal bone density vs. reduced bone density[a]	0.0098[b]	< 0.0001[b]
Osteopenia vs. osteoporosis	0.7769	0.2432

[a]Reduced bone density group comprises both osteopenic and osteoporotic subjects.
[b]Statistically significant differences between the groups compared.

Spectral Linewidth and Bone Density

The mean water and lipid linewidths showed no clear trend between subjects with different bone densities (Table 1). No statistically significant differences in the

Table 1
MR Spectroscopy Results for All Subjects

Subject group	Number	Mean age (years)	T-score	Water linewidth (Hz)	Lipid linewidth (Hz)[c]	Fat content (%)	Unsaturation index
Young control females	12	28 (18–43)[a]	ND[b]	30 ± 4.3	26.5 ± 2.5	29.0 ± 9.6[c]	0.127 ± 0.031
All subjects above 60 years[d]	50	70 (66–81)	–1.8 ± 1.2	29.8 ± 3.3	24.7 ± 3.9	62.1 ± 10.7	0.099 ± 0.017
Normal bone density	15	70 (66–74)	–0.3 ± 0.7	30.4 ± 2.6	24.9 ± 2.8	56.3 ± 11.2	0.114 ± 0.016
Osteopenia	15	71 (66–75)	–1.8 ± 0.4	30.9 ± 2.7	26.4 ± 4.2	63.5 ± 9.3	0.097 ± 0.014
Osteoporosis	20	70 (66–81)	–3.0 ± 0.5	28.3 ± 3.7	23.1 ± 3.9	65.5 ± 10.0	0.091 ± 0.013

[a]Numbers in parentheses are age ranges in years.
[b]No data (ND) were available for control females as they did not undergo DXA examination.
[c]Figures shown as mean ± SD.
[d]Subject group "All subjects above 60 years" is a combination of all subjects above 60 years irrespective of bone density.
[e]Lipid peak at 1.3 ppm.

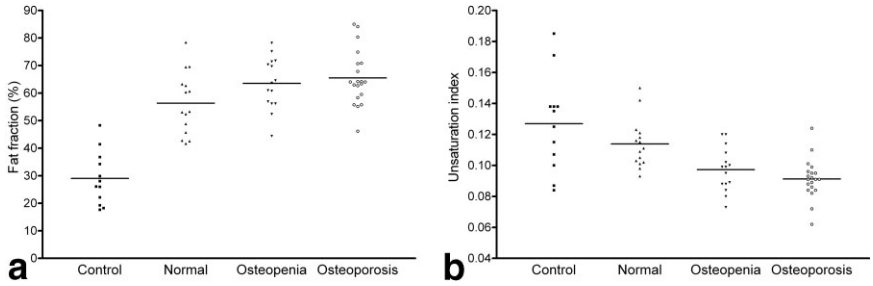

Figure 3. Bone marrow fat content and unsaturation index grouped according to bone density status to show differences between groups (young controls, postmenopausal normal bone density, osteopenia, and osteoporosis). **a:** Marrow fat content. **b:** Marrow fat unsaturation index. The mean value for each group is represented by the horizontal bar.

mean water ($P = 0.066$) or lipid ($P = 0.121$) linewidths were measured between postmenopausal subjects with normal bone density and subjects with osteoporosis.

Correlation Between Marrow Fat and Bone Density

With the use of Spearman's correlation analysis, a weak negative correlation was found between bone density and marrow fat content ($r_s = -0.32$, $P = 0.0211$; Fig. 4). There was a good negative correlation between the unsaturation index and marrow fat content ($r_s = -0.53$, $P < 0.0001$; Fig. 4), and a moderate positive correlation between bone density and the unsaturation index ($r_s = 0.48$, $P = 0.0004$; Fig. 4). In other words, a reduction in bone density was associated with an increase in marrow fat and a decline in fat unsaturation index.

DISCUSSION

MR-detectable bone marrow signal is composed mainly of water and lipids, and these two key components may be measured accurately by ^{1}H-MRS (19–21). Recent studies have documented age- and sex-specific differences in the ^{1}H MR spectrum of vertebral bone marrow (5,6); however, whether a relationship exists between bone density and marrow fat is not known. Our results for vertebral marrow fat content in young females in the age range of 18–43 years (29% ± 9.6%) are in good agreement with uncorrected values reported by Schellinger et al (5) (22–28%), and corrected values published by Kugel et al (6) (27.5–29.7%). When we compared our results for postmenopausal females irrespective of bone density status with reported values, we found a slightly higher marrow fat content of 62.1% ± 10.7% for subjects in the age range of 66–81 years compared to that reported by Kugel et al (6) (53.8% ± 5.6% (corrected), or about 60% (uncorrected), which was based on 14 women). Our data also confirmed that there was no clear relationship between spectral linewidth and bone density (7).

When the results were grouped according to bone density, we found a significantly higher level of marrow fat in females with osteoporosis (65.5% ± 10%) compared to age-matched females with normal bone density. Our results are in accord with earlier findings of Schellinger et al (7), who reported that patients with imaging evidence of bone weakness (i.e., Schmorl's nodes, endplate depression, or compression fractures) had a significantly higher relative fat content than control subjects. A report from the same authors based on data from 26 subjects was inconclusive as to whether a relationship existed between bone density and bone

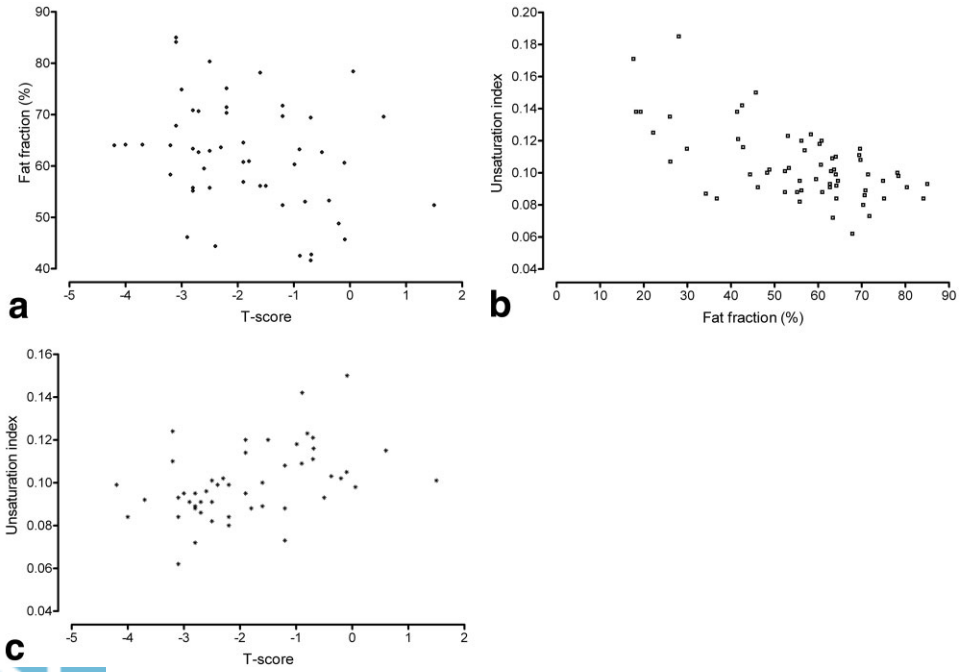

Figure 4. Scatter plots showing the relationships among the marrow fat content, unsaturation index, and t-score. There was (**a**) a weak negative correlation between the t-score and marrow fat content ($r_s = -0.32$), (**b**) a good negative correlation between the unsaturation index and marrow fat content ($r_s = -0.53$), and (**c**) a moderate positive correlation between the t-score and unsaturation index ($r_s = 0.48$).

marrow fat content (22). Our study shows that there is an inverse relationship between bone density and marrow fat content, indicating that as cortical and trabecular bone is reduced there is a corresponding increase in the degree of marrow fat. Accumulation of lipids in the bone marrow of patients with osteoporosis has been demonstrated in histomorphometric studies (23–25). A recent study suggested that the close packing of fat cells within the confines of the marrow cavity may be responsible for the reduction in water diffusion observed in subjects with reduced bone density (26).

Proton MR spectra of marrow are dominated by water (4.65 ppm) and by an intense lipid peak (1.3 ppm) arising from bulk methylene protons (–$(CH_2)_n$–). All previous in vivo studies of vertebral body marrow, except a study by Mulkern et al (13), ignored the presence of other lipids, such as olefinic protons (–CH=CH–), methylene protons (–CH=$CHCH_2$–), and terminal methyl protons (–CH_3), because these peaks are generally weak or incompletely resolved and therefore are more difficult to measure. It has been shown that applying prior knowledge in spectral fitting is an effective way to quantify overlapping peaks (14), and our results show that in vivo assessment of marrow fatty acid composition is feasible using this spectral fitting technique. Our result for the unsaturation index of corn oil (0.077) is in good agreement with reported results, which range from 0.079–0.084 (18), indicating that ^{1}H-MRS may be a reliable technique for assessing bone marrow fatty acid composition in vivo.

There was a decreasing trend in the level of lipid unsaturation from normal subjects to osteopenic subjects to osteoporotic subjects. To the best of our knowledge, no previous in vivo study has examined whether the composition of marrow fat changes in relation to osteoporosis. This study shows that there was a significant reduction in the degree of fatty acid unsaturation of marrow lipids in osteopenic and osteoporotic subjects compared to age-match subjects with normal bone density. Our results also showed a good correlation between marrow fat content and the unsaturation index, implying that as fat content increases with reducing bone density, saturated fats tend to increase preferentially relative to unsaturated fats.

Lipids are increasingly believed to play an important role in the pathogenesis of osteoporosis (27) and other conditions, such as hypertension and coronary artery disease (10,11). Epidemiologically, osteoporotic postmenopausal women are at significantly greater risk for cardiovascular disease than age-matched controls (28), with higher serum lipid levels having been identified in both diseases (29). Recent studies have shown that adipose tissue is more than just a storage tissue and may well have an important physiological role in regulating hormones involved in obesity, diabetes, and inflammation (30). In adult bone marrow, adipocytes are the most abundant stromal cell phenotype and are believed to influence both hematopoiesis and osteogenesis (31).

Adipocytes and osteoblasts share a common progenitor (mesenchymal stem cells) in the bone marrow, such that increased adipogenesis may be associated with decreased osteoblastogenesis. Accumulating evidence suggests that a reciprocal relationship may exist between these two processes (8). However, the molecular mechanism underlying this reciprocal relationship is not yet fully understood. While some reports have suggested that mature adipocytes may impair osteoblastic proliferation (32) through the release of polyunsaturated fatty acids (33), others have focused on transcriptional mechanisms regulating adipogenesis and osteogenesis that rely, in part, on nuclear hormone receptors and their ligands (34). One of these nuclear hormone receptors is peroxisome proliferator activated receptor (PPAR)γ, whose ligands include long-chain fatty acids and oxidized derivatives of fatty acids. The ligands for PPARγ are known to promote bone marrow stromal cell adipogenesis and inhibit osteogenesis (35). Our results confirm that osteoporosis is associated with an elevated marrow fat content and that this fat is relatively higher in saturated than unsaturated lipids. Further studies are required to elucidate whether a change in marrow fatty acid composition actually impairs osteoblastic activity.

We recognize that there are limitations involved in the use of ^{1}H-MRS to assess marrow lipids. Using a single-voxel acquisition protocol, we could only study one vertebral body during each examination, and were therefore unable to verify whether similar changes occurred in neighboring vertebral bodies. Chemical shift imaging techniques (36) may overcome this limitation by facilitating the sampling of either multiple vertebral bodies or various locations within a single vertebral body simultaneously. However, marrow fat is not evenly distributed within and between vertebral bodies (20), and to avoid introducing these confounding factors we chose to examine only a single vertebral body (L3) in every subject and to sample only the central portion of this vertebral body with a VOI size adjusted according to the vertebral body size.

Although using a surface coil does improve the signal-to-noise ratio (SNR) of in vivo ^{1}H-MRS, and therefore the detection of low-intensity marrow fatty acids, the sensitivity is still dependent on the inherent sensitivity of the MR system operating at 1.5 T. Lipids with low signal intensities, such as those resonating at 5.25 ppm, 4.29 ppm, 4.14 ppm, 2.79 ppm, 2.27 ppm, 1.6 ppm, and 0.97 ppm, were too weak to be measured accurately, and as such their contributions were not accounted for in our assessment of the unsaturation index in vivo. We may also have overestimated the peak amplitudes of methylene protons at 1.3 ppm and methyl protons at 0.9 ppm because these peaks were broadened by the presence of lipids at 1.6 ppm and 0.97 ppm, respectively. In addition, we may also have underestimated the olefinic protons at 5.35 ppm due to strong J-coupling interactions (37). In consideration of these technical errors, we believe that the unsaturation index obtained from our measurements should not be regarded as an absolute measure of marrow fatty acid unsaturation, but could be used as a relative index for assessing lipid composition changes associated with osteoporosis.

In conclusion, ^{1}H-MRS potentially may be applied to the noninvasive assessment of marrow lipids and help establish the role of such lipids in the pathogenesis of

osteoporosis. There is a clear relationship between marrow fat and bone density as measured by DXA, in that subjects with osteoporosis or osteopenia have significantly higher marrow fat content compared to age-matched subjects with normal bone density. The increase in marrow fat seen in subjects with osteoporosis or osteopenia appears to be the result of a preferential increase in saturated lipids compared to unsaturated lipids.

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