**Title page**

Spinal Multiparametric MRI and DEXA changes over time in men with prostate cancer treated with Androgen Deprivation Therapy: A potential imaging biomarker of treatment toxicity.

**Abstract**

*Objectives*

To explore changes in Bone Mineral Density (BMD) measured by DEXA and MRS Fat Fraction (FF), Dixon FF and ADC in lower spinal vertebral bodies in men with prostate cancer treated with Androgen Deprivation Therapy (ADT).

*Methods*

28 men were enrolled onto a clinical trial. All received ADT. DEXA imaging was performed at baseline and 12 months. L-spine MRI done at baseline and six months.

*Results*

The number of patients who underwent DEXA, Dixon, ADC and MRS at baseline/follow-up were 28/27, 28/26, 28/26 and 22/20. An increase in FF was observed from T11 to S2 (average 1%/vertebra). There was a positive correlation between baseline MRS FF and Dixon FF ($r=0.85$, $p<0.0001$) and a negative correlation between MRS FF and ADC ($r= -0.56$, $p= 0.036$). Over six months, MRS FF increased by a median of 25% in relative values ($p=0.0003$), Dixon FF increased ($p<0.0001$) and ADC values decreased ($p=0.0014$). Men with >5% BMD loss after one year had triple the percentage increase in MRS FF at six months (61.1% v 20.9%, $p=0.19$).

*Conclusions*

Changes are observed on L-spine MRI after six months of ADT. Further investigation is warranted of MRS change as a potential predictive biomarker for later BMD loss.

**Keywords**:

Magnetic Resonance Imagining
Bone Density
Prostate Neoplasms
Biomarkers
Toxicity

**Key points**:

- Spinal marrow fat fraction increases after 6 months of Androgen Deprivation Therapy.
- More inferior vertebral bodies tend to have higher fat fractions
- MRS Fat Fraction changes were associated with later changes in DEXA BMD.

**Acronyms**

ADT = Androgen Depravation Therapy
BMD = Bone Mineral Density
DEXA = Dual-Energy X-Ray Absorptiometry
DWI = Diffusion Weighted Imaging
FF = Fat Fraction
HRPC = High Risk Prostate Cancer
PRESS = Point Resolved Spectroscopy
PROCITT = PROstate Cancer Imaging, Treatment and Toxicity
SVS = Single voxel spectroscopic

## Introduction

Some men with apparently non-metastatic prostate cancer at diagnosis have a high probability of developing widespread disease following local therapy.[1] This entity of high risk prostate cancer (HRPC) has been extensively studied, and multimodality treatment with pelvic radiotherapy and androgen deprivation therapy (ADT) has been shown in multiple randomized controlled trials to have a survival advantage compared to either treatment alone.[2,3]

ADT reduces testosterone levels and leads to lower amounts of peripherally converted estrogens, which has a direct effect on bone mineral density (BMD). Numerous studies have demonstrated that this leads not only to changes on DEXA imaging, but also osteoporotic fracture rates and even overall survival.[4-6] Current consensus guidelines recommend annual DEXA monitoring of BMD for men on ADT and intervention with anti-resorptive agents for those found to have osteopaenia or osteoporosis.[7] Population based data suggests that less than 20% of men on ADT have a DEXA performed, suggesting a low awareness of the importance of managing bone health for such patients.[8]

There is a wide variety in the rate of BMD change for men on ADT, quoted between 0 and 8% in the first year of treatment.[6,9] It is therefore plausible that a risk adapted approach is better targeted not only to men with osteopaenia or osteoporosis at baseline, but also the subgroup with more rapid loss in BMD. Concurrently, literature has begun to emerge suggesting MRI Fat Fraction (FF) has a correlation with DEXA measured BMD.[10] There is a biological rationale for this given the common stem cell progenitors for both bone forming osteoblasts and fat containing adipocytes and the effect of estrogen on driving the relative proportions of cellular differentiation.[11] MRI also has the advantages of being a fully 3-dimensional approach better suited to understanding changes within a multifunctioning organ such as bone which is not susceptible to artefacts which can confound the interpretation of DEXA imaging.[12]

We hypothesize that early changes on serial MRI of the spine may correlate with the rate of change in DEXA measured BMD for men on ADT. If this is the case, further investigation of early selective intervention with anti-resorptive therapy for such higher risk men would be warranted.

## Materials and Methods

*Patient Recruitment*

A prospective clinical trial (PROCITT: PROstate Cancer Imaging, Treatment and Toxicity) was offered to men with HRPC between January 2013 and July 2014. Eligible men needed to have non-metastatic HRPC features (any one of: PSA>20, Gleason score of 8-10 or Stage of T3-T4 or N1), and be appropriate for an 18 month course of ADT and definitive prostate radiotherapy. The Hunter New England Human Research Ethics committee provided ethical approval (12/08/15/4.02). The project was funded by an unrestricted investigator initiated study grant by Abbvie Pharmaceuticals. 28 men with high risk prostate cancer were recruited to the study over an 18 month period. The median age was 70 years (range 54-78), median PSA was 12.4, and 23 of the men had Gleason score 8 or 9 disease.

*Management*

After providing informed consent, all men had baseline imaging including a MRI, plain films of the thoracic-lumbar spine and DEXA imaging. They then commenced an 18 month course of ADT. As per national bone health consensus guidelines, they were all recommended to commence oral Vitamin D and Calcium supplementation as well as moderate physical activity.[7] At the six month time point, men had a repeat MRI just prior to commencing a course of prostate+/-pelvic radiotherapy, the technical details of which have been reported.[13] Men continued to be followed after radiotherapy including receiving annual DEXA imaging for three years. An MRI at 6 months was selected as a compromise between sufficient time to assess any changes whilst still providing an opportunity for possible bone health interventions, while a DEXA at 12 months complies with consensus guidelines as well as the period of most rapid loss in BMD.[7, 14]

*Imaging Protocols*

*MRI Dixon Method*

All patients underwent morphological imaging of the lumbar spine in supine and feet first orientation on a 3 Tesla whole body scanner (Magnetom Skyra, Siemens AG, Erlangen, Germany) with the combination of a dedicated 18 Channel body matrix and 32 channel phase array spine receiver coils. After localiser scans, a 3-point Dixon Turbo Spin Echo T1 weighted scan was performed in sagittal plane to assess fat fraction. Four series of images (in/opposed phases, fat/water only) generated by the system were used for FF analysis. The sequence parameters were TR/TE=600/9.5ms, Slice thickness/gap=3mm/10%, FOV=340mm, Matrix=384x384 with 0.9x0.9 in-plane resolution, iPAT=2, Number of slices=28 and Average=1.

Regions of interest (ROIs) were manually applied in 2-dimensions on the mid-sagittal slice for all vertebral bodies within the field of view. Each ROI would typically require a polygon with 6-10 points of at least 3 $cm^2$, with the same ROI copied onto the corresponding Fat and Water images. Mean readings from the Fat and Water Dixon images were recorded, and Dixon FF calculated for individual vertebral bodies as Mean Fat/(Mean Fat+Mean Water).

*Diffusion Weighted Imaging (DWI)*

After six patients had been accrued, a protocol amendment was made to allow more routine acquisition of DWI and MR Spectroscopy. Following T1 weighted scan, Echo planar spin echo based (Single shot EPI) DWI sequences with a pair of rectangular motion probing gradient pulses along three orthogonal directions (phase, frequency and slice) were obtained with b-values equal to 0, 250, 500 and 750 $s/mm^2$.[15] Six sagittal slices were acquired. The sequence parameters include TR/TE=1400/87ms, Slice thickness/Gap=10mm/10%, FOV=260mm, Matrix=156x156mm with 1.7mmx1.7mm in-plane resolution, iPAT=2.

The quantitative analysis of diffusion was performed by calculating the Apparent Diffusion Coefficient (ADC) values. The ADC value was derived from the equation ADC = -1/b ln (S(b)/S(0)) where Sb and S0 are signal intensities from each voxel with and without diffusion gradients and b is the sensitizing parameter. The three directional diffusion images were used to generate an average ADC map using Syngo (Siemens Healthcare, Erlangen, Germany). The ADC values were measured for each patient at all four b-values from 0 to 750 $s/mm^2$ by drawing a ROI similar to the Dixon ROI within each vertebral body from T12 to S1 on all the DWI images.

*$^1$H-Magnetic Resonance Spectroscopy (MRS)*

Single voxel spectroscopic (SVS) technique was employed in the transverse plane to generate non-water suppressed 1H spectra, and the voxel was placed within the marrow of the L3 vertebral body seen on T1 weighted images. The spectroscopic data was acquired using a double echo, slice selective technique based on Point Resolved Spectroscopy (PRESS) with an echo time of 30ms, TR of 2000ms, 64 signal averages, 1024 complex data points, and bandwidth of 2000Hz and automatic image based shimming. A voxel size of $8cm^3$ was used.

Spectra were reconstructed using Syngo which involved water referencing for frequency shift correction, a Gaussian filter of 125ms was applied to the time domain data. Following the fourier Transform, phase correction and baseline correction was applied to the spectrum. A series of peaks, including water at 4.7 ppm and five fat peaks at 1.1, 1.39, 1.9, 2.5 and 5.36 ppm was used to model the spectrum using the Syngo curve fitting routine (see Figure 1). The lipid peak area (LPA) was the sum of the dominant fat peaks at 1.1 (-CH3) and 1.39 (-CH2) ppm and quantified relative to the sum of the water peak area (WPA) to give a MRS FF using LPA/(LPA+WPA).

One male subject not managed with ADT was scanned twice within one week to assess reproducibility. This showed an average coefficient of variation of 3.5% for Dixon FF, 4.0% for ADC and a 3% variation in MRS FF.

*DEXA*

A DEXA scan was performed on all subjects within one week of their baseline MRI. Readings of BMD in $g/cm^2$ were obtained individually for L1-L4 vertebral bodies as well as both necks of femurs (NOFs). These were translated into age and gender

matched T-Scores as per WHO recommendations. Serial imaging was performed 12 months later on the same DEXA scanner that the baseline imaging occurred on.

*Statistical Analysis*

DEXA Lumbar spine T-score scan values were averaged across L1-L4. For Dixon and ADC, all fully visualized vertebrae were used, usually from T10 or T11 down to S1 or S2. Due to evidence of a statistical interaction both over time and between vertebral body level and various scan parameters, it was not appropriate for all data to be pooled together for analysis, and hence the various analyses are presented separately.

Correlations between scans/parameters were examined using Pearson correlation. Changes between baseline and follow-up scan values for each vertebra were examined using linear mixed modelling with robust standard errors. Mean changes with 95% confidence intervals from baseline and p-value are presented. All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, North Carolina, USA).

## Results

*Baseline DEXA Results*

All men had baseline DEXA imaging. Baseline DEXA T-Scores averaged from L1-L4 spanned a range of -2.63 to 4.05, with a mean of 0.07. Baseline DEXA showed a correlation between raw BMD measured at the NOF and L-Spine averaged from L1-L4 (r= 0.62, p=0.0004). An inverse correlation was noted between increasing age and raw BMD at the NOF (r= -0.41, p=0.03 – see Figure 2), with a weaker correlation between age and raw BMD at the L-Spine (r= 0.26, p=0.19). The latter may be due to some confounding from degenerative changes in the L-Spine on DEXA imaging.[12]

Two men, aged 76 and 77, had a new diagnosis of osteoporosis on their baseline DEXA imaging with NOF T-scores of -2.8 and -2.7 respectively. As per national consensus guidelines, they were commenced on oral bisphosphonate therapy.[7] All 28 men had no insufficiency fractures on thoraco-lumber spinal plain film imaging. No metastases were observed, but two men had evidence of haemangiomas of the vertebral bodies which were excluded from ROI delineation.

*Baseline MRI Results*

The number of patients who underwent DEXA, Dixon, ADC and MRS at baseline/follow-up were 28/27, 28/26, 28/26 and 22/20, respectively. Examining individual Dixon FF measures from T11 to S2, there was evidence of increasing values with more inferior vertebral bodies by 1%/vertebral body on average (Figure 3). The only exception was the L5-S1 vertebral bodies where a slight decrease was noted, possibly due to the different mechanical stress at this level. For ADC, no strong trend was noted between the individual vertebral measurements from T11 to S2.

*MRI Correlations*

There was evidence of a correlation between baseline MRS FF and Dixon FF (r=0.85, p<0.0001). For the 14 men who had both an MRS FF and ADC at L3 performed at baseline, there was a negative correlation between these parameters (r= -0.56, p= 0.036).

Some correlation was noted between Age and increased MRS FF (r=0.37, p=0.09). Exploring a relationship between age and individual vertebral body Dixon FF and ADC values showed only weak positive correlations without any strong evidence of statistical association. There was no evidence of a relationship between baseline MRS FF, Dixon FF or ADC values per vertebral body verses baseline DEXA BMD at the L-spine or NOF.

*DEXA and MRI Changes over time*

On serial DEXA 12 months apart, similar relative median changes in raw BMD were observed both for the L-Spine (-3.2%, IQR -1.7 – -5.7, p<0.0001) and NOF (-3.4%, IQR -0.4 – -6.4, p=0.0003). Due to our series focussing on the L-spine changes on MRI, and the potential for spurious relationships if excessive correlations were attempted, further analysis of BMD focussed on the L-Spine rather than NOF. Out of

the 26 patients who had 2 DEXAs performed, four had an increase in L-Spine DEXA raw BMD ranging from 0.1% to 7.4%, and ten had large decreases of greater than 5% ranging from -5.2% to -11.7%.

Men managed with ADT had MRS FF increase by an absolute median value of 0.092 over six months. This corresponded to a median 25% relative increase (IQR 17% - 89%, p=0.0003). Dixon FF also showed median increases over six months from a minimum of 6.3% at S2 to a maximum of 10.4% at T11 ($p<0.0001$ – table 1 and figure 4). Conversely, ADC values tended to decrease over six months (p=0.0014 – table 2).

*Predictors of DEXA Changes*

We wished to investigate whether there were any parameters at baseline or within the first six months of treatment which predicted for larger changes in BMD at one year. We defined a larger change in DEXA L-spine raw score as a loss of BMD of at least 5% over 12 months, which is double the mean change in this parameter reported in the literature for men with prostate cancer on ADT.[16] The univariate analysis of potential predictive factors is presented in table 3. Note that the patients with >5% loss in BMD at one year had nearly triple the percentage increase in their MRS FF at L3 (61.1% v 20.9%). Exploring DEXA BMD change and MRS FF change as continuous variables amongst the 17 patients who had all four relevant scans performed show that only three patients had a reduction in MRS FF, and these were the only three to exhibit an eventual increase in DEXA BMD of between 3.2 and 7.4%. The correlation between these variables is negative (r= -0.44, p=0.076), and is shown in figure 5).

## Discussion

Our work shows correlations between various baseline MRI sequences, changes in FF between adjacent vertebral bodies and over time, and a correlation between changes in MRI FF at six months verses DEXA BMD changes after 12 months. Some of these replicate earlier work, particularly the correlations between MRS FF with both Dixon FF and ADC[17] as well as changes in FF between adjacent vertebral bodies on MRS and using In-Out Phase techniques.[18] The increased FF is plausible given the known effects of ADT on lipogenesis, with the increased adipocyte volume also potentially causing restricted diffusion. The changes in MRI sequences over time under the influence of various oncological interventions and their correlation with DEXA BMD changes is a more emergent area which our work helps lay a stronger foundation for.

Previous studies looking at changes in serial MRI FF have tended to be small and have heterogeneous interventions. One series used a 9 patient cohort with gynaecological cancers managed with either chemotherapy or various pelvic radiotherapy regimens and showed over 6 months increases in In-Out Phase FF in L4 by an absolute average of 16.1%.[19] A second series used a 19 patient cohort with a range of pelvic malignancies managed with several chemotherapy regimens in concert with various types and doses of pelvic radiotherapy.[20] They observed using an In-Out FF measure that increases were more marked in the L4-S2 region than at other spinal levels, and also influenced by the myelotoxicity of the chemotherapy regimen. Given the treatment variations, it can be challenging to be confident of the specific effect of the dose-volume response effect of either radiotherapy or a particular chemotherapy agent in this setting, as well as their interaction. Our work shows that in the face of a standardised intervention, there is approximately a 25% relative increase in MRI FF over six months of ADT, but with a wide range, and there are some patients demonstrating much larger changes of 50% or more. As this appears to have some correlation with later DEXA BMD changes, such patients may represent a subgroup where more aggressive early intervention with antiresorptive agents such as denosumab or bisphosphonates might be investigated.

There is now a growing body of work showing a correlation between MRI FF measured using either MRS or In-Out Phase, as well as ADC with DEXA BMD in various populations.[10] This is not a relationship which we were able to confirm in our cohort. Possible reasons for this include that some of the positive series were relatively small and included both men and women with a wide age range. An early report examined 16 volunteers with an age range of 8-57, of whom only 2 males and 4 females had both a DEXA and MRI performed.[21] This series showed an inverse correlation between the two scans with a p-value of 0.076, but considered each vertebral body as a separate entity despite evidence of a strong within patient relationship across adjacent vertebrae. Despite this, these initial findings have been largely confirmed in several subsequent series, including a 560 subject cohort spanning a wide age range and including both males and females.[22] As outlined in the Introduction, here is also a biological rationale for this.[11] We hypothesize that our inability to detect such a relationship in our cohort was a function of the relatively low number of patients, who were all male with a limited range of largely normal baseline BMDs.

Several small studies have reported on the use of serial multiparametric MRI and changes in various imaging parameters as correlating with treatment response in several malignancies including rectal, prostate and head and neck cancers.[23-25] Many studies are ongoing exploring multiparametric MRI and other functional imaging such as PET as an early biomarker of later tumour response.[26] Such concepts have the appeal of potentially allowing treatment adaptation, either intensification or de-escalation, while it is still being delivered. Care is needed in the interpretation of such studies however, given the often large number of parameters explored in multiple physical locations over serial scans increasing the chance of a type I statistical error ie finding a statistical relationship when no real relationship exists.

To our knowledge, the use of MRI as an early biomarker of treatment toxicity is a much less investigated entity. Given that ADT can cause mild anaemia and fatigue, both of which could plausibly be mediated via effects at the level of bone marrow, there is potential for imaging to predict a suite of ADT related toxicity. The PROCITT study prospectively collected serial data on fatigue and blood counts, and once this data collection is complete we intend to explore whether such relationships exist.

Our series has the advantages of being prospective and hence relatively standardised in patient population, treatment delivered and imaging protocols. There are clear limitations. It is a relatively small series, although larger than others looking at serial imaging of patients undergoing cancer treatment. Although a comparison between Dixon and DEXA changes were the main aim of the study, the ADC and MRS sequences were not uniformly applied for all patients, reducing our power to detect a meaningful impact from these sequences. Given the highly targeted patient cohort, further work will be required to assess whether similar observations occur in the broader population. Although gross lesions seen on MRI were excluded from ROIs, degenerative changes may have affected the DEXA outputs; the lack of any major disc loss on plain films and MRI make this less likely to be a major confounder. The use of manual techniques to define ROIs is common, but does introduce additional variability into assessments. We also used several DEXA platforms in the community, although our concentration on relative changes over time would be considered to be platform independent.

There are several other potential future directions. The utilisation rates of DEXA imaging for men on ADT is suboptimal, and a multifaceted Implementation science approach is being explored to try to use patients and their local medical officer to try to correct this. It is possible that the inclusion of additional clinical factors such as serum and urine markers of bone turnover, and anthropomorphic parameters such as height, weight and BMI may lead to greater predictive power regarding men at risk of more rapid loss in BMD. Some very preliminary work in this area is promising.[16] We have collected such data, and hope to analyse this as our BMD data matures with further serial DEXA imaging.

**Acknowledgements**

The authors wish to acknowledge the assistance of Katie Baker and Hannah Woodford who assisted in MRI data extraction. Mary-Clare Hanlon assisted with manuscript submission. Peter Stanwell assisted with MRI sequence programming. Abbvie pharmaceuticals provided an unrestricted investigator initiated grant which funded the scans, trial management and statistical analysis. All analysis and manuscript preparation was performed without any input from Abbvie Pharmaceuticals.

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**Figure Captions**

Figure 1: Example of curve fitting for a L3 MRS showing the water (left) and fat (right) peaks along with the area under the curve for each of the six respective positions.

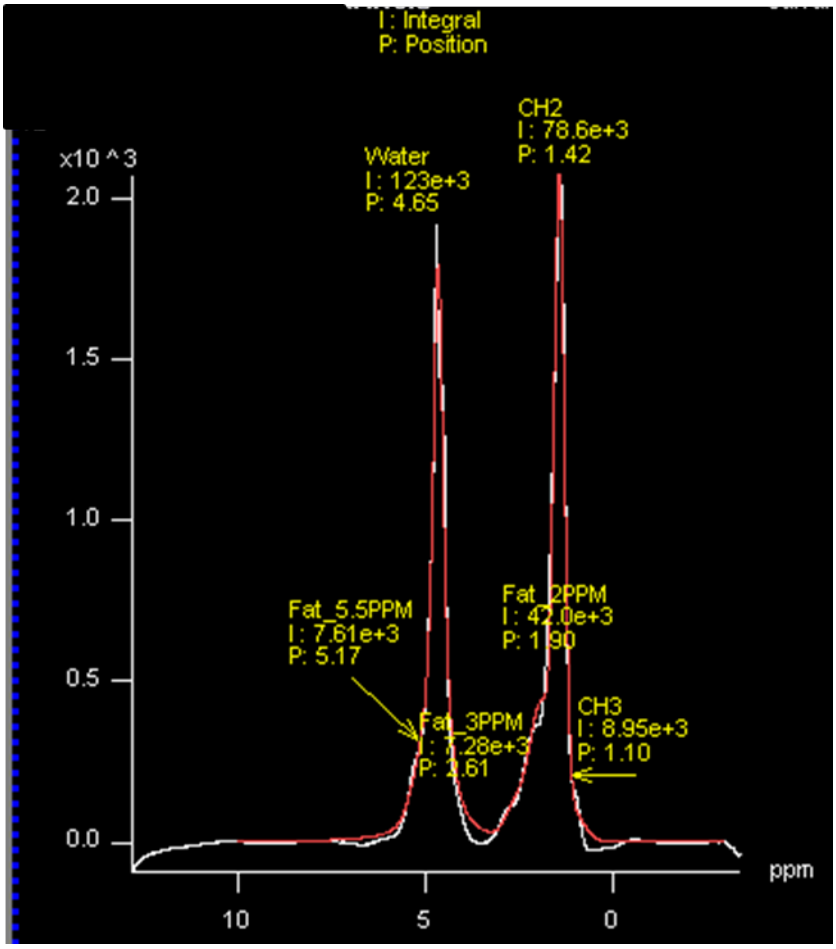
Figure 2: Association between age and DEXA BMD at the neck of femur (r= -0.41, p=0.03, 95% CI limits shown).

Figure 3: Trend for Dixon FF to increase by approximately 0.01/vertebral body moving inferiorly. Note that most of the results are clustered around the fitted lines and that the slopes for the individual lines are generally similar to the fitted lines, both suggesting relatively small variations between individuals in this population.

Figure 4: Line graph showing Dixon FF at baseline and six months per vertebral body. Note again the trend for higher FF with more inferior vertebral body and the consistent increase in mean FF for every vertebral body over time.

Figure 5: Percentage change in MRS FF over six months plotted against percentage change in DEXA L-Spine raw score over 12 months. Note the small number of men exhibiting a positive change in both factors, and the moderate inverse relationship between the two variables (r= -0.44, p=0.076).

Figure 1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P: Position
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1.5
1.0
0.5
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Water
I : 123e+3
P: 4.65
CH2
I : 78.6e+3
P: 1.42
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I : 7.61e+3
P: 5.17
Fat_2PPM
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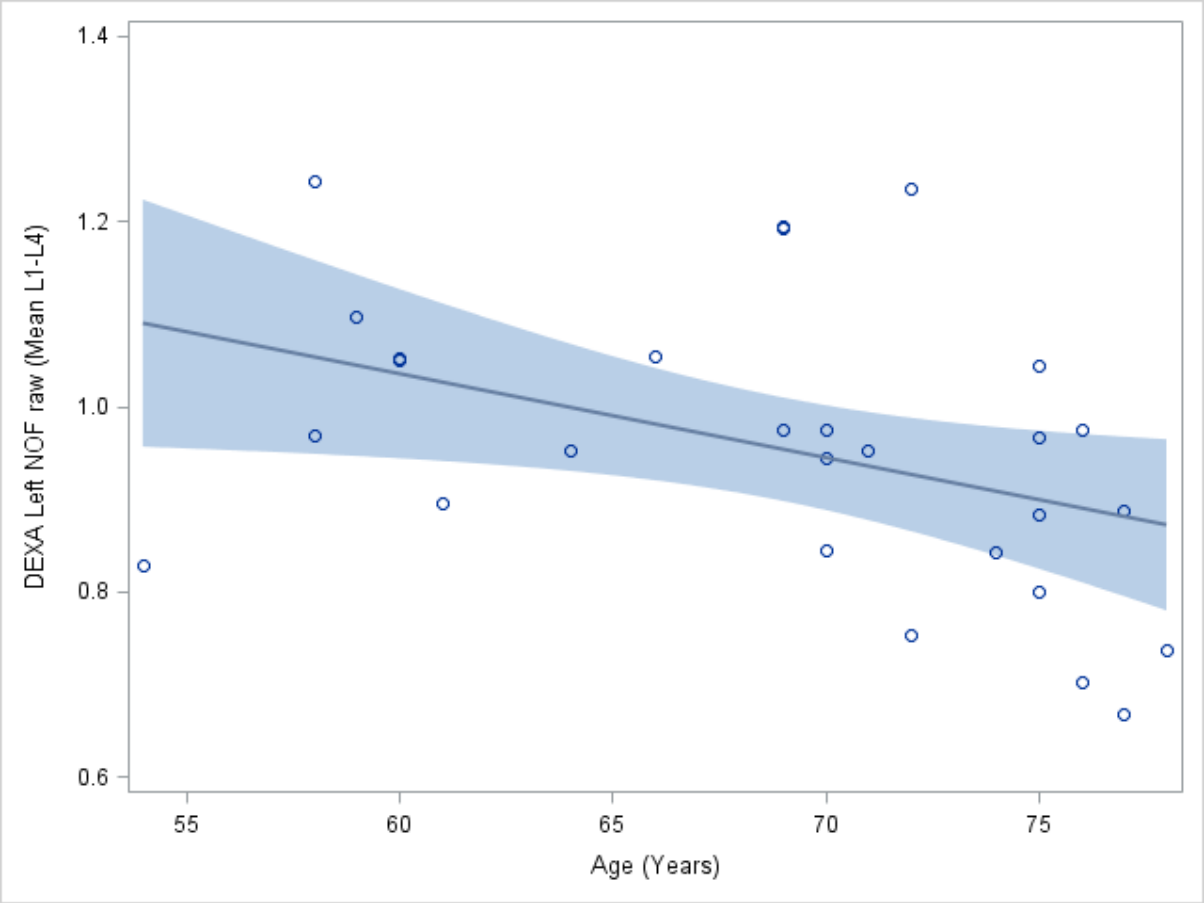
Figure 2


DEXA Left NOF raw (Mean L1-L4)
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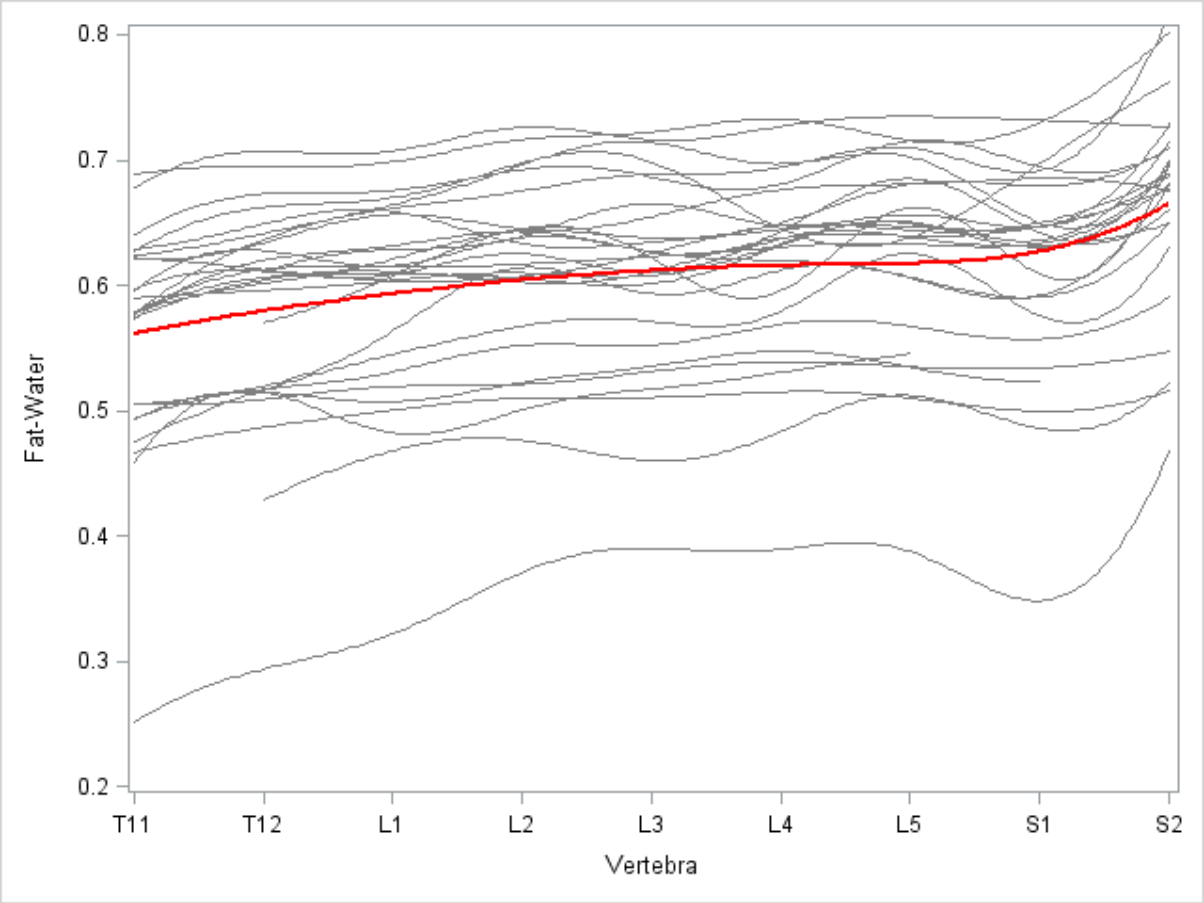
1.0
0.8
0.6
55
60
65
70
75
Age (Years)

Figure 3


0.8
0.7
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0.3
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Fat-Water
T11
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L1
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L4
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S1
S2
Vertebra

Figure 4

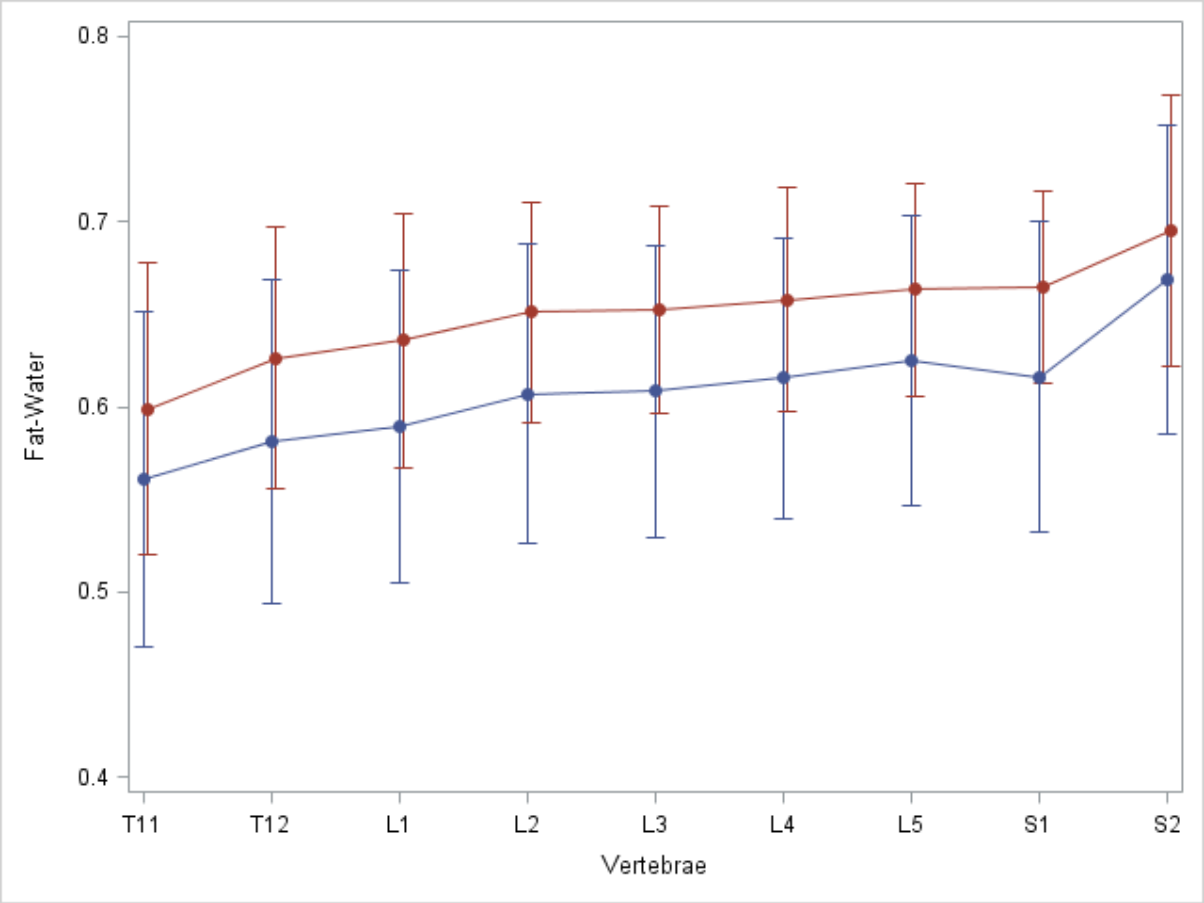

Figure 5

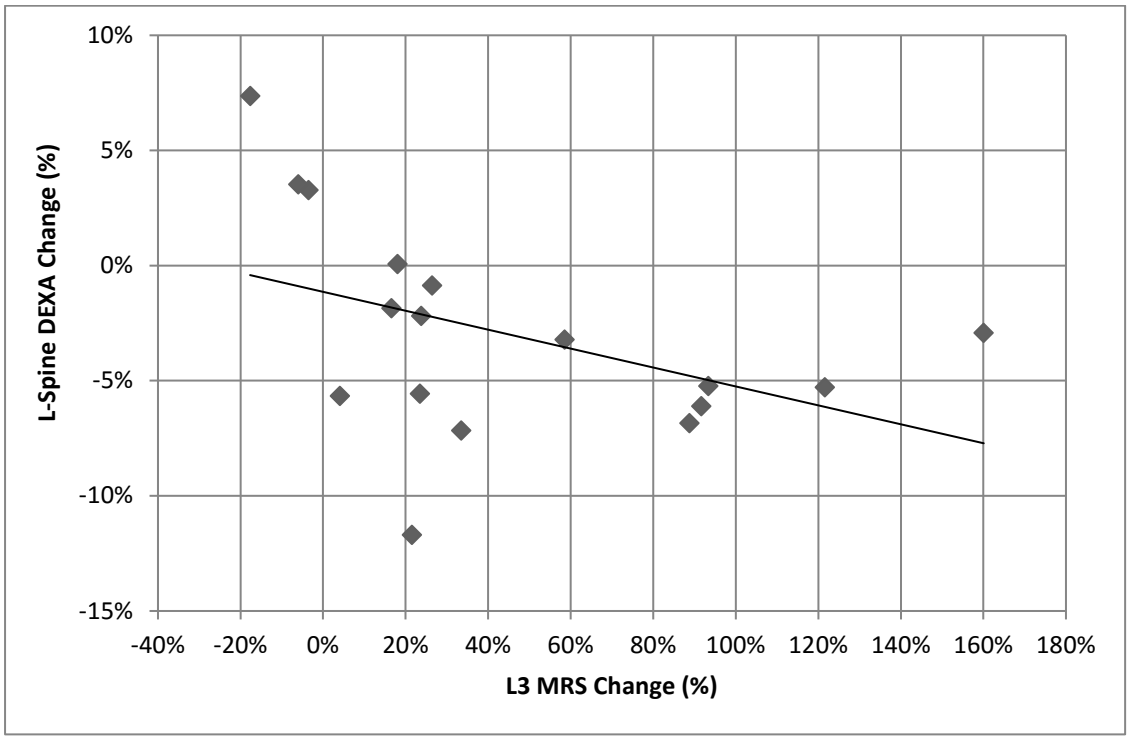
10%
5%
0%
-5%
-10%
-15%
L-Spine DEXA Change (%)
-40%
-20%
0%
20%
40%
60%
80%
100%
120%
140%
160%
180%
L3 MRS Change (%)

**Table Legends**

Table 1. Change in MRI Dixon Fat Fraction between baseline and after six months of ADT. P-values are adjusted for bisphosphonate use and age at baseline.

Table 2. Change in MRI ADC between baseline and after six months of ADT. P-values are adjusted for bisphosphonate use and age at baseline.

Table 3. Univariate associations between various factors and DEXA percent decrease >5%. Age, bisphosphonate use and DEXA T-Score are all from baseline, the MRS FF, Dixon FF and ADC percentage changes were all between baseline and the six month scans, and the average Dixon FF vertebra change looked at the gradient in FF across vertebral bodies at baseline.

Table 1. Change in MRI Dixon Fat Fraction between baseline and after six months of ADT. P-values are adjusted for bisphosphonate use and age at baseline.

| Vertebral Level | Dixon change | | p-value |
|---|---|---|---|
| | Percentage | Absolute (95% CI) | Overall <0.001 |
| T11 | 10.40 (3.8, 14.6) | 0.045 (0.027, 0.062) | <.0001 |
| T12 | 7.25 (2.6, 15.0) | 0.048 (0.031, 0.064) | <.0001 |
| L1 | 9.50 (1.8, 15.7) | 0.049 (0.035, 0.064) | <.0001 |
| L2 | 8.80 (0.8, 14.4) | 0.046 (0.030, 0.061) | <.0001 |
| L3 | 8.80 (2.7, 16.3) | 0.046 (0.028, 0.063) | <.0001 |
| L4 | 7.95 (1.7, 13.7) | 0.044 (0.027, 0.060) | <.0001 |
| L5 | 6.82 (1.2, 11.6) | 0.040 (0.022, 0.058) | <.0001 |
| S1 | 8.61 (-0.1, 13.5) | 0.051 (0.029, 0.073) | <.0001 |
| S2 | 6.33 (3.8, 9.8) | 0.035 (0.015, 0.054) | 0.0005 |

Table 2. Change in MRI ADC between baseline and after six months of ADT. P-values are adjusted for bisphosphonate use and age at baseline.

| Vertebral Level | ADC Change | | p-value |
|---|---|---|---|
| | Percentage | Absolute (95% CI) | Overall 0.0014 |
| T12 | -50.42 (-63.6, -33.3) | -0.00012 (-0.00019, -0.00005) | 0.0012 |
| L1 | -29.63 (-46.9, 19.2) | -0.00007 (-0.00012, -0.00001) | 0.0120 |
| L2 | -58.57 (-78.2, -18.5) | -0.00011 (-0.00017, -0.00005) | 0.0002 |
| L3 | -17.09 (-61.5, 65.0) | -0.00004 (-0.00009, 0.00001 ) | 0.0952 |
| L4 | -28.41 (-62.5, 14.3) | -0.00005 (-0.00010, -0.00001) | 0.0284 |
| L5 | 23.05 (-34.5, 90.9) | -0.00003 (-0.00009, 0.00004 ) | 0.4436 |
| S1 | -50.00 (-73.1, 4.5) | -0.00011 (-0.00018, -0.00004) | 0.0026 |

Table 3. Univariate associations between various factors and DEXA percent decrease >5%. Age, bisphosphonate use and DEXA T-Score are all from baseline, the MRS FF, Dixon FF and ADC percentage changes were all between baseline and the six month scans, and the average Dixon FF vertebra change looked at the gradient in FF across vertebral bodies at baseline.

| **Factor** | | **Large decrease (>5%) of DEXA raw score** | | |
|---|---|---|---|---|
| | | **No (n=18)** | **Yes (n=10)** | **p-value** |
| Age at baseline [mean (SD)] | | 69 (8) | 69 (6) | 0.84 |
| Bisphosphonate Use | No | 16 (62%) | 10 (38%) | 0.27 |
| | Yes | 2 (100%) | 0 | |
| DEXA T-score at Baseline [mean (SD)] | | 1.216 (0.197) | 1.260 (0.158) | 0.55 |
| MRS FF percent change [median (IQR)] | | 20.89 (-3.5, 39.01) | 61.10 (22.48, 92.51) | 0.19 |
| Dixon FF percent change [median (IQR)] | | 8.12 (1.41, 15.11) | 9.22 (1.39, 12.23) | 0.90 |
| ADC percent change [median (IQR)] | | -24.21 (-50.8, 10) | -58.89 (-62.65, 5.57) | 0.44 |
| Average Dixon FF vertebra change [median (IQR)] | | 0.01 (0.007, 0.012) | 0.009 (0.005, 0.012) | 0.41 |