Original Article

Assessment of bone marrow fat by 3-Tesla magnetic resonance spectroscopy in patients with chronic kidney disease

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Background: Proton magnetic resonance spectroscopy (^{1}H MRS) is an imaging method for quantification of bone marrow fat. It has been used for evaluation of bone marrow changes in patients with chronic disorders, such as chronic kidney disease (CKD). In these patients, there is a high turnover state, with an excessive amount of non-mineralized component of bone, leading to skeletal fragility and subsequent increased fracture risk.

Methods: Thirty CKD patients underwent magnetic resonance spectroscopy (MRS) and quantitative computed tomography (QCT), and eight healthy controls underwent MRS at lumbar spine. Proton density fat fraction (PDFF) and volumetric bone mineral density (vBMD) of L1–L3 were determined from MRS and QCT respectively. CKD patients were divided into three groups according to glomerular filtration rate (GFR); for each patient, blood levels of parathyroid hormone (PTH) were also reported. Paired *t*-tests, Pearson's correlation coefficients and analysis of variance were applied.

Results: The mean age of patients was 59.6±11.5 years, mean GFR value was 21.5±8.8 mL/min and mean PTH value was 149.2±53.1 pg/mL. PDFF at L1–L3 levels was significantly higher in CKD patients compared to controls (71.4±8.7 *vs.* 55.5±7.6; P<0.001) and showed an inverse correlation with vBMD (r=–0.71; P<0.001). PDFF significantly increased from CKD group 1 to CKD group 3 (P=0.002) and was inversely correlated with GFR (r=–0.53; P=0.003). There was no significant association between PDFF and PTH values (P>0.05).

Conclusions: In CKD patients, PDFF assessed by MRS at lumbar spine is higher than in healthy population, correlates with bone loss assessed by QCT and significantly increases with the worsening of renal function. MRS is a reliable and highly repeatable tool for PDFF quantification in CKD patients.

Keywords: Bone marrow; chronic renal insufficiency; magnetic resonance spectroscopy (MRS)

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Introduction

Bone marrow fat is the main tissue filling porous trabecular bone in adults and represents the third largest adipose depot after subcutaneous and visceral fat. For many years its exact role in the regulation and development of bone environment has been ignored. Several studies have recently revealed that bone marrow fat has important endocrine and paracrine functions, and influences hematopoiesis, osteogenesis and whole-body-energy metabolism (1-3). Adipogenesis in bone marrow cavities has been shown to be associated with aging, estrogen deficiency and various metabolic diseases (4-7). Moreover, it has been found that high bone marrow fat correlates with low bone volume and with vertebral fractures risk independently of bone volume, suggesting a possible role of marrow adipose tissue in the pathogenesis of bone deterioration (8,9). Consequently, quantification of bone marrow fat has recently gained an increasing interest. Proton magnetic resonance spectroscopy (^{1}H MRS) is a commonly used imaging method for non-invasive quantification of bone marrow fat. It uses the signal of hydrogen atoms derived from different tissues to differentiate lipids from water peak, providing quantitative assessment of proton density fat fraction (PDFF) with a high accuracy and a strong correlation with fat content values from biopsy (8,10-13).

Comparing to other quantitative magnetic resonance (MR) techniques applied in bone marrow (e.g., Dixon imaging), MRS provides more detailed information on chemical shift dimension, enabling the measurement not only of PDFF but also of the distinct lipids contained in bone marrow. However, a robust MRS extraction of small components of lipids in bone marrow can be challenging due to the presence of broad water peaks. Other technical aspects of MRS, such as a relatively long acquisition time and the presence of potential chemical shift displacements and T2 decay effects, should be considered and adequately balanced (13,14).

MRS quantification of PDFF has been compared between 1.5 and 3.0 Tesla, demonstrating an improvement of spectral resolution and signal-to-noise ratio at the higher field strength (15,16).

Recently, chemical shift encoding-based water-fat imaging, also known as Dixon imaging, has been proposed for measuring PDFF in bone marrow (17,18). In contrast to MRS, it allows a spatially resolved quantification of PDFF, that is advantageous in presence of a heterogeneous distribution of bone marrow (e.g., proximal femur, spine), and has a short scanning time. However, the accuracy of PDFF assessment by Dixon imaging is limited by several confounding factors (e.g., multiple peaks in the fat spectrum, T1-bias effects, phase errors, T2 decay effects) that make necessary further technical improvements, especially concerning the signal model (13,14,19).

Hence, despite of its limitations, MRS is currently the preferable quantitative MR technique for bone marrow fat evaluation at various skeletal sites, with vertebral bone marrow representing the region most extensively investigated in MRS studies (8,12,15).

So far, researchers have focused on MRS evaluation of bone marrow changes in patients with chronic disorders such as osteoporosis or type 2 diabetes mellitus (8,16,20).

Few investigations exist regarding the assessment of bone marrow fat by MRS in patients with renal osteodystrophy (21,22).

Renal osteodystrophy is an abnormal bone histomorphometry associated with chronic kidney disease (CKD) and represents one component of the systemic symptoms of CKD-mineral bone disorder (23-25).

Patients with CKD have a wide spectrum of findings on bone biopsy from high-turnover forms associated with hyperparathyroidism to adynamic bone disorders or osteomalacia related to mineralization defects. Various paracrine and endocrine signals participate in bone remodeling, with parathyroid hormone (PTH) playing a central role. In CKD patients PTH metabolism is altered and secondary hyperparathyroidism is an almost universal complication of advanced stages of disease due to many factors such as hypocalcemia, retention of phosphorus, decreases in the levels of calcitriol, intrinsic alterations within the parathyroid gland and skeletal resistance to the actions of PTH (26).

Sustained high PTH levels in CKD cause a high turnover state in bone, where bone resorption and, in a lesser degree, bone formation are stimulated. The disturbed osteoblast activity results in disorganized bone formation,

with an excessive amount of non-mineralized component of bone, leading to skeletal fragility and subsequent increased fracture risk, particularly at the peripheral skeleton (27).

In fact, fractures are two to four times more prevalent in patients with CKD compared to the general population (24,28).

Fracture risk is determined by bone strength, that depends on bone mass and bone quality. Bone mass is traditionally measured by bone mineral density using dual energy X-ray absorptiometry (DXA) but in the last years other bone indices such as volumetric bone mineral density (vBMD) using quantitative computed tomography (QCT) have been shown to be more accurate than DXA bone measurements for prediction of future fracture in CKD patients as well as in general population (29-31). Bone quality is determined by some bone tissue properties such as bone turnover, mineralization, microarchitecture, matrix composition. In renal osteodystrophy bone abnormalities imply defects of both bone mass and bone quality, that are mainly related to PTH excess. However, the evidence of an increased fracture risk in CKD patients even at low levels of PTH suggests that there are others factors dependent on kidney function that impair bone health (32,33). Since the characteristics of CKD are similar to those of aging process, but with an accelerated deterioration of tissues and cellular functions (34), it is possible to hypothesize that, as observed in aging population (4,9), also in patients with impaired kidney function bone marrow adipogenesis may play an important role in bone metabolism.

Only two previous studies investigated vertebral bone marrow fat content in CKD, demonstrating an increased bone marrow fat deposition in patients with CKD compared to healthy controls (21,22). However, neither of them evaluated the association between bone marrow fat and severity of CKD.

In the present study, we used MRS to assess PDFF at lumbar spine in patients with CKD. In this population, we correlated PDFF measurements with vBMD obtained by QCT and investigated if PDFF is associated with severity of renal function impairment.

Methods

Study population

CKD subjects were recruited consecutively for participation in the study, and the inclusion criteria were age ≥45 years old, estimated GFR ≤45 mL/min/1.732 m^2 (MDRD formula) in the last 6 months, elevated PTH above the normal range (65 pg/mL) in the past year and QCT examination as part of diagnostic workup. Females who were pregnant or nursing, a prior history of lumbar fracture, general contraindications to MRI/MRS exam (e.g., IUD, pacemaker), history of haematological malignancy, chemotherapy or radiation therapy, and participants who were unable to consent were also excluded.

The healthy control volunteers were asymptomatic, had no history of spinal or other disease, and had not received any medicine that could have affected their bone marrow. They were matched to CKD patients based on race, gender, and age by 10 years. Between January 2019 and February 2020, 42 people (34 CKD patients and 8 healthy controls) were enrolled. Four CKD patients were removed due to technical issues with MRS scans, leaving 38 people in the analysis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of IRCCS "Casa Sollievo della Sofferenza" Hospital (No. 12/CE). Written informed consent was obtained from all participants.

Study procedures

To evaluate the repeatability of the MRS analysis, eight subjects (all healthy controls) were scanned twice at lumbar vertebrae on the same day with repositioning between the two scans. The repositioning of the subjects was done by the same technologist. Each lumbar vertebral level L1, L2 and L3 were selected for MRS analysis.

In CKD subjects, QCT and MR examinations of the lumbar spine were performed on the same day. For each patient, a blood sample for PTH measurement was collected at the time of MRS scan. GFR values were taken from the last clinically available assessment, within the last 6 months. CKD patients were stratified in three groups according to GFR levels in order to examine the influence of increasing impairment of renal function on bone marrow fat content. The group 1 included patients with moderate chronic renal insufficiency (GFR from 45 to 30 mL/min), the group 2 patients with severe chronic renal insufficiency (GFR from 29 to 15 mL/min) and the group 3 patients with the most advanced stage of renal failure (GFR <15 mL/min).

QCT examination

vBMD of the lumbar spine was assessed by QCT, a three-dimensional method which measures trabecular BMD

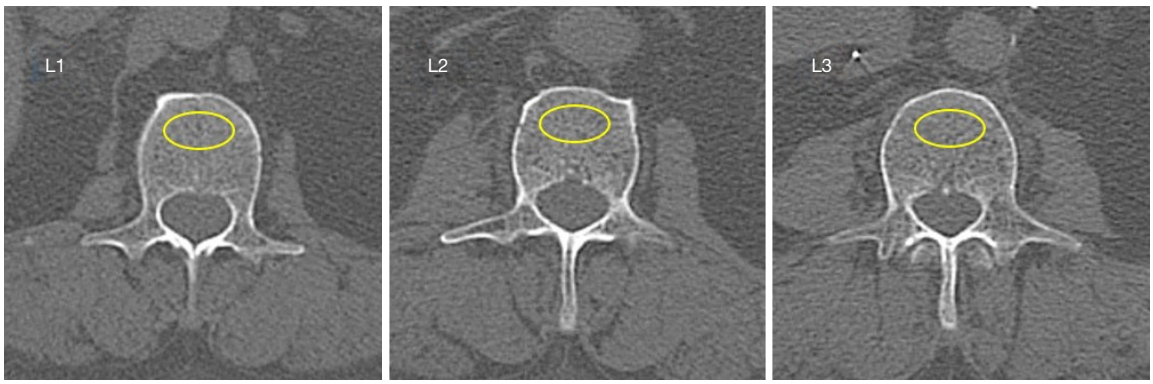

Figure 1 QCT based vBMD measurements of L1 (on the left), L2 (in the middle) and L3 (on the right) vertebrae. Measurements were assessed by a dedicated software, with semi-automatic placement of regions of interest (yellow marked) in the trabecular part of the lumbar vertebrae. QCT, quantitative computed tomography; vBMD, volumetric bone mineral density.

in milligrams per cubic centimeter by indirectly quantifying hydroxyapatite in comparison to a reference phantom.

All examinations were performed by using a 16-row multidetector CT scanner (Aquilion, Toshiba Medical System, Tokyo, Japan). A non-simultaneous calibration system was used (Lumbar Reference Simulator, CIRS, Norfolk, VA, USA). The scan protocol was standardized and consisted of a tube voltage of 120 kVp and a tube current of 200 mAs. Slice thickness was 3 mm. QCT scans were analyzed on a workstation using the dedicated software (Mindways QCT Pro, Austin, USA). Elliptical regions of interest (ROIs) were manually placed by an experienced operator in the trabecular part of vertebral bodies from L1 to L3, avoiding cortical bone, basivertebral veins and sclerotic foci (*Figure 1*). The ROIs size was kept the same for all QCT analyses.

For each patient, vBMD values derived from the three lumbar vertebrae were annotated and the mean lumbar vBMD was computed by averaging vBMD measurements.

The precision error of vBMD measurements by QCT was previously reported (CV =1.8%) (35).

MR spectroscopy

All MR examinations were performed on a 3T MRI scanner (Philips Ingenia 3.0) using a phased array spine coil.

Subjects were in supine position with knees supported by a form wedge to reduce spine curvature and motion by improving patient comfort. The imaging protocol included T1-weighted TSE sequence [sagittal plane, repetition time (TR) 450–700 ms, echo time (TE) 9 ms, turbo factor 5, field of view (FOV) 32 cm, slice thickness 3 mm, spacing 0.3 mm, acquisition time 3 min and 21 s] and T2-weighted mDIXON TSE sequences (sagittal and coronal planes, TR 2,500–4,000 ms, TE 80 ms, turbo factor 19, FOV 32 cm, slice thickness 3 mm, spacing 0.3 mm, acquisition time 3 min and 5 s).

Proton MR spectroscopy was performed using a single voxel spectroscopy technique (voxel size 15×15×15 mm^3). The T2-weighted sequences were used to guide the optimal positioning of volumes of interest (VOI) within the selected lumbar vertebrae (L1–L3). Unless spine fractures, degenerative alterations or focal lesions (e.g., hemangiomas) were identified, the VOI was placed in the center of the vertebral bodies, avoiding the posterior venous plexuses. The voxel size was maintained the same for each vertebral level and for each subject.

The Point Resolved Spectroscopy (PRESS) method was used, and the spectroscopy sequence parameters were: TR 2,000 ms, TE 40 ms, spectral bandwidth 2,000 Hz, samples 1,024, voxel volume 3.4 cm^3, acquisition time 5 min and 24 s).

Neither pre-saturation bands nor water suppression was used.

A second order shimming method was applied to optimize tissue homogeneity in MRS voxel. A mean FWHM <30 Hz was obtained.

MR image analysis

All spectroscopy data were transferred to a research workstation and analyzed with Spectroview software (Philips Medical Systems, Best, The Netherlands) using Gaussian line shapes and frequency-based methods. After

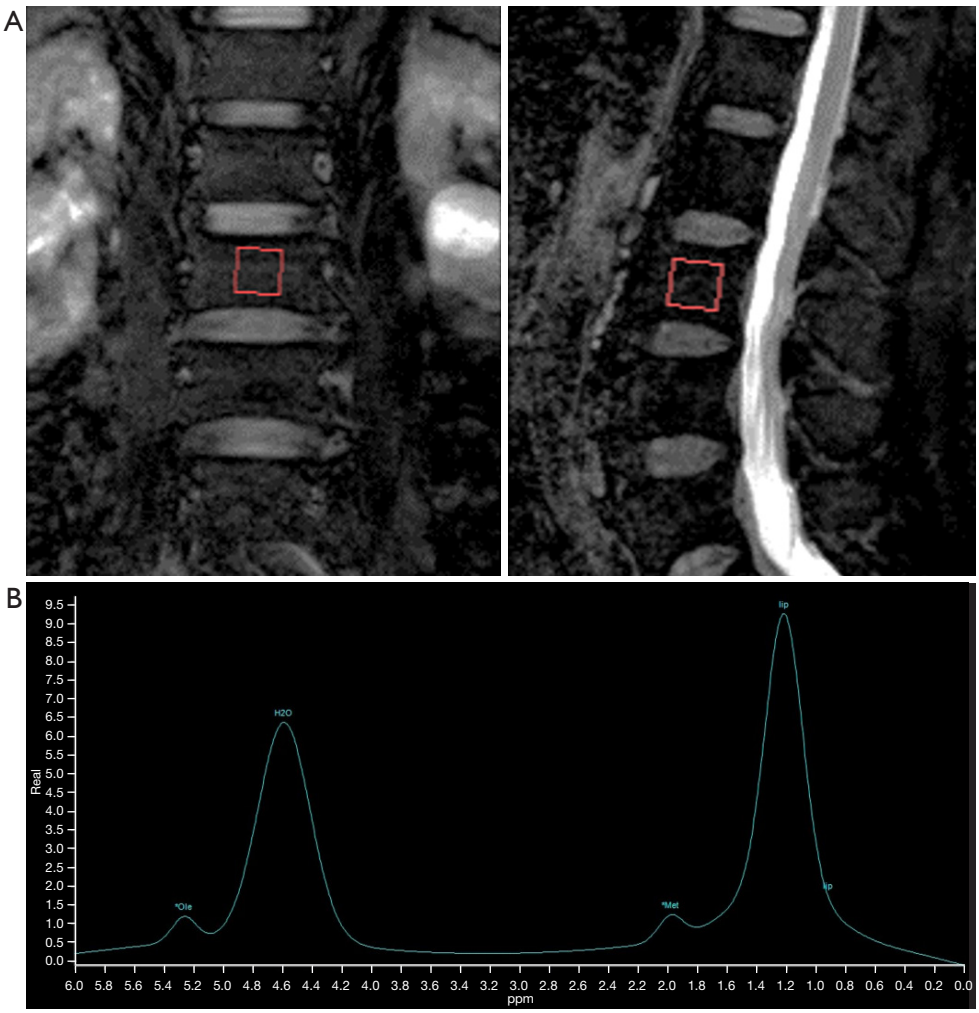

Figure 2 ^{1}H-MRS performed at lumbar spine in a 69-year-old woman with CKD (GFR =29.7 mL/min). (A) Sagittal T2-weighted MR images show the position of spectroscopy measurement box in the middle of the vertebral body (L3 in this example). (B) Bone marrow spectrum identifies a water peak (4.77 ppm) and four lipid peaks, including olefinic (5.35 ppm), methylene (2.06 ppm), bulk methylene (1.3 ppm) and terminal methyl (0.9 ppm) protons. The typical spectrum had two dominant peaks: water and bulk methylene. ^{1}H-MRS, proton magnetic resonance spectroscopy; CKD, chronic kidney disease; GFR, glomerular filtration rate; MR, magnetic resonance.

reconstruction, corrections for phase, frequency shift, and baseline distortion were performed on spectral data. The spectrum acquired included a water peak at 4.77 ppm and four lipid peaks, consisting of 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 (*Figure 2*).

All the peaks were fitted to obtain their line widths and areas.

After fitting, PDFF was calculated as the ratio of all the fat peak areas to the sum of all the fat peak and water peak areas and expressed as percentage. The measurement of PDFF was obtained at each vertebral level. Moreover, for each participant, the average PDFF value derived from all three vertebral levels was calculated.

Statistical analysis

The repeatability of MRS for PDFF measurements in healthy controls was evaluated using coefficients of variation (CV) and Bland-Altman plots; the variability or precision of PDFF measurements was expressed as coefficient of repeatability (CR).

Paired *t*-tests were used to compare PDFF values at each

Table 1 Demographics characteristics of study population

Values	Controls	CKD patients
Sample size (n)	8	30
Age (years)	56.3±12.4	59.6±11.5
Males (%)	75	70
Caucasian (%)	100	100
BMI (kg/m^2)	26.9±4.5	27.1±5.1

Data are expressed as mean ± standard deviation. CKD, chronic kidney disease; BMI, body mass index.

Table 2 Marrow fat % at different vertebral levels and coefficients of variation (n=8)

Vertebral level	Mean ± SD (%)	CV (%)
L1	53.1±8.6	2.1
L2	56.3±7	4.6
L3	57.1±7.3	4.3

SD, standard deviation; CV, coefficient of variation.

lumbar site between CKD patients and healthy controls matched according to race, gender and age ±10 years.

Spectroscopic measurements of PDFF were correlated with vBMD values using Pearson's correlation coefficients and multiple linear regression analysis was applied to estimate the effects of age on vBMD and PDFF measurements. Pearson's correlation was also calculated to determine the association of PDFF and vBMD with GFR and PTH values.

One-way analysis of variation (ANOVA) was used to identify significant differences in PDFF and vBMD among the three groups of patients formed according to the severity of CKD. If a statistical significance was present, Tukey *post hoc* test was applied in order to find out which groups differed. Results were expressed as mean ± standard deviation. All statistical analysis was performed using SPSS software (version 29.0) and MedCalc software (version 22.005). Statistical significance was defined as P<0.05.

Results

Study population

Demographics characteristics of study population are presented in *Table 1*. In CKD patients, mean GFR value was 21.5±8.8 mL/min and mean PTH value was 149.2±53.1 pg/mL. When stratified by GFR, 23.3% (7/30) of patients had a GFR from 45 to 30 mL/min (group 1), 56.7% (17/30) had a GFR from 29 to 15 mL/min (group 2) and 20% (6/30) had a GFR <15 mL/min (group 3).

Repeatability of PDFF spectroscopic measurements

Bone marrow spectrum was dominated by water peak (4.7 ppm) and an intense lipid peak (1.3 ppm) deriving from bulk-methylene protons. Olefinic (5.35 ppm) and methylenic (2.06 ppm) protons peaks were also well identified, though with smaller tips compared to the two main peaks. Terminal methyl protons peak (0.9 ppm) was more difficult to resolve due to the overlapping with the broad lipid peak from bulk-methylene protons.

The mean bone marrow fat, measured in the eight subjects was 53.1%±8.6% at L1, 56.3%±7% at L2 and 57.1%±7.3% at L3.

MRS measurements of PDFF at all vertebral levels were highly repeatable, with CV values ranging from 2.1% to 4.6% (*Table 2*). The Bland-Altman plots, used to visually assess the differences between repeated MRS measurements at each vertebral level, showed a low variability with CR values of 0.041 for L1, 0.090 for L2 and 0.079 for L3 (*Figure 3*).

Differences in PDFF between CKD patients and controls

At each lumbar spine site, the mean marrow fat content was significantly elevated in patients compared to controls (*Table 3*). The mean fat content at L1 was 70.5%±8.3% in subjects with CKD versus 53.1%±8.6% in controls (P<0.001). At L2, the bone marrow fat was 71.5%±11.9% in CKD versus 56.3%±7% in controls (P<0.001). Similarly, at L3, the bone marrow fat was 72.4%±9.5% versus 57.1%±7.3% (P=0.02).

Correlation between PDFF and vBMD

The average values of vBMD, measured in all CKD patients, were 104.1±32.6 mg/cm^3 at L1, 97.1±26.4 mg/cm^3 at L2 and 93.0±34.7 mg/cm^3 at L3. The mean value of vBMD at all lumbar sites was 98.1±27.9 mg/cm^3.

Mean PDFF showed a strong negative correlation with vBMD (r=–0.71; P<0.001) as represented on *Figure 4*. In multiple linear regression analysis, age was a significant predictor of vBMD (P=0.001; R^2=0.33); conversely, no significant interaction was found between age and PDFF.

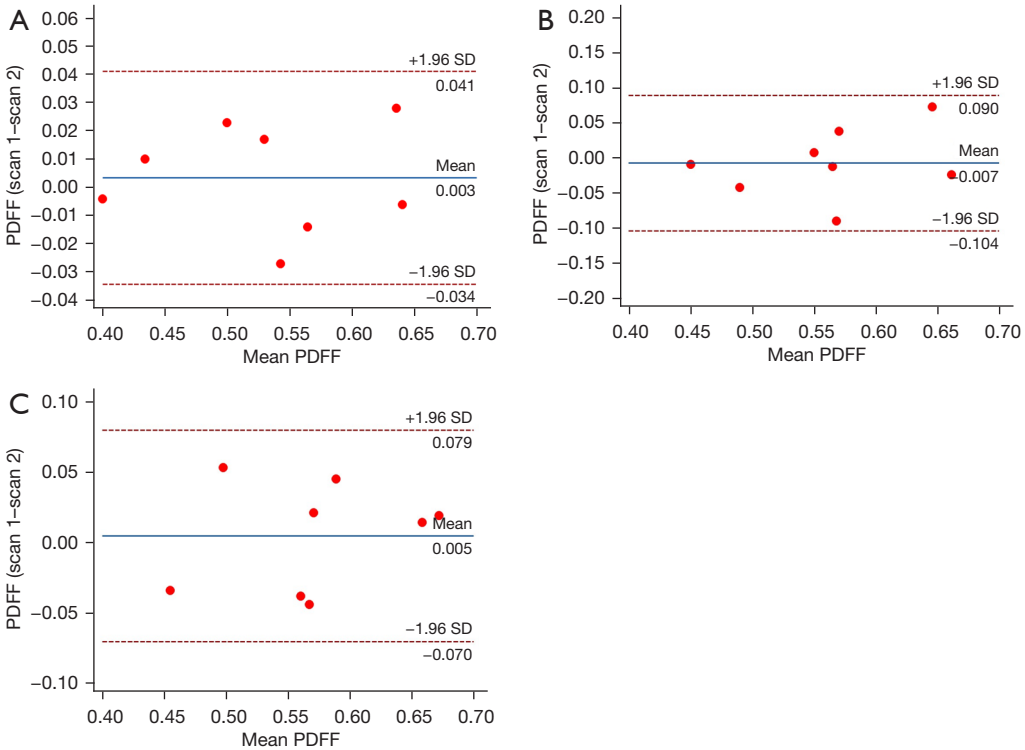

Figure 3 Bland-Altman plots obtained to assess the differences between PDFF derived from repeated MRS scans at L1 (A), L2 (B) and L3 (C) levels. The average difference (expressed as bias ±1.96 SDs) was equal to 0.003±0.02% for L1, –0.007±0.05% for L2 and 0.005±0.04% for L3. Moreover, the variability or precision of MRS measurements was expressed as CR equal to 0.041 for L1, 0.090 for L2 and 0.079 for L3. PDFF, proton density fat fraction; SD, standard deviation; MRS, magnetic resonance spectroscopy; CR, coefficient of repeatability.

Table 3 Marrow fat % at L1, L2 and L3 in CKD patients and controls

Vertebral level	CKD patients (n=30)	Controls (n=8)	P value
L1	70.5±8.3	53.1±8.6	<0.001
L2	71.5±11.9	56.3±7	<0.001
L3	72.4±9.5	57.1±7.3	0.02
All levels (L1–L3)	71.4±8.7	55.5±7.6	<0.001

Data are expressed as mean ± standard deviation. CKD, chronic kidney disease.

Association of PDFF and vBMD with CKD severity and PTH values

Results of Pearson's correlation test revealed a good negative correlation between PDFF and GFR (r=–0.53; P=0.003). Moreover, one-way ANOVA showed statistically significant

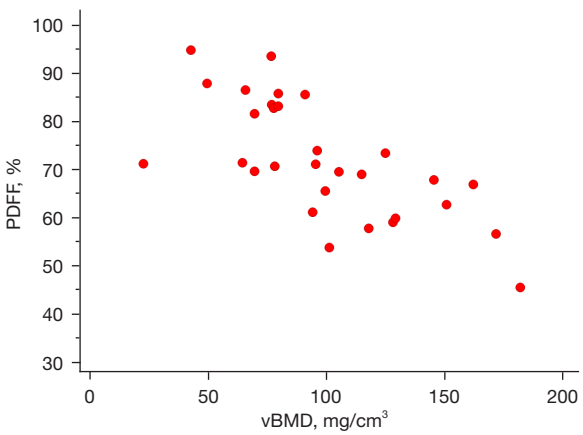

Figure 4 Scatter plot showing a strong negative correlation between PDFF and vBMD at lumbar spine in CKD patients (r=–0.71; P<0.001). PDFF, proton density fat fraction; vBMD, volumetric bone mineral density; CKD, chronic kidney disease.

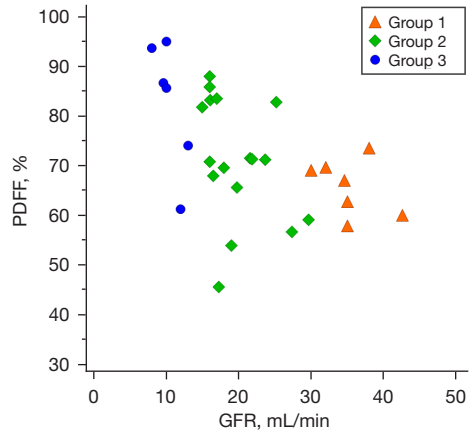

Figure 5 Scatter plot representing the association between PDFF and GFR values in CKD patients. Different colours and markers are used to identify the three GFR subgroups (group 1 with GFR values from 45 to 30 mL/min, group 2 with GFR values from 29 to 15 mL/min, group 3 with GFR values inferior to 15 mL/min). As shown, PDFF significantly increased with the worsening of renal function (r=–0.53; P=0.003). PDFF, proton density fat fraction; GFR, glomerular filtration rate; CKD, chronic kidney disease.

differences of fat fraction in the three groups of CKD patients stratified by GFR (P=0.002). Specifically, PDFF was lower in group 1 (65.4%±0.8%) compared to group 2 (69.2%±1.2%) and higher in group 3 (82.1%±1.9%) compared to the other two groups (Tukey: P<0.05) (*Figure 5*).

There was no significant correlation between mean PDFF and PTH values (P>0.05). The mean vBMD was 105±37.9 mg/cm^3 in group 1, 96.1±47.8 mg/cm^3 in group 2 and 93.2±28.4 mg/cm^3 in group 3, however its values were no significantly different among the three CKD groups and no significantly correlated with GFR and PTH (P>0.05).

Discussion

In this study, we used MRS at 3T for evaluating bone marrow fat at lumbar spine. The repeatability of bone marrow fat measurements by MRS was optimal at all lumbar vertebral levels. Recent studies have documented the reliability of MRS in marrow fat quantification and the advantages of acquiring spectral data with a high field strength (13,15,16,18). In particular, 3T MR technique has a high signal-to-noise ratio that allows the acquisition of higher quality and more easily quantifiable spectra in smaller voxels and/or in shorter times. Moreover, the high spectral resolution at 3T helps to better detect even lipid peaks with low signal intensity. As known, MRS quantification of PDFF may be challenging for the presence of broad water and bulk-methylene lipid peaks due to susceptibility differences between bone and marrow. This results in a poor identification of the remaining lipid peaks that, although small, contribute to the total lipid signal (13,14,17). The use of MRS at high field strength allows to accurately measure signals derived from olefinic protons (5.31 ppm), even if partially overlapped with the water peak, and from methylene protons (2.06 ppm), that have a weak intensity. Fitting MRS spectra in either frequency-domain or time-domain may also improve the differentiation between adjacent peaks in the spectrum, and the accuracy of PDFF quantification (13,17). In our study, we obtained a good spectral quality, as shown in *Figure 2*; olefinic and methylene protons peaks were definitely or partially resolved in all spectra. However, MRS measurements of the individual lipid components were less repeatable than measurements of the total fat fraction, with CV values ranged between 13.1% and 15.4% (data not shown). Despite the great advantages of the high field MR spectroscopy, further developments in both acquisition and post processing methods are needed to better overcome potential limitations of 1H-MRS and facilitate its application in the clinical routine. In our research, we focused on bone marrow fat quantification by MRS in patients with CKD and compared them with healthy subjects. Our results demonstrated that MRS measurements of PDFF were significantly elevated in patients with chronic renal impairment. So far, few studies have investigated bone marrow composition by MR imaging in patient with CKD (21,22). Moorthi *et al.* found that bone marrow fat by MRS was significantly higher in CKD patients compared to controls (21). Woods *et al.* also observed an association between CKD and spectroscopic measurements of bone marrow fat, with higher values of in subjects with GFR <45 mL/min compared to those with GFR >60 mL/min (22). Our data are consistent with these findings.

The novel finding of our study was that bone marrow fat and vBMD were inversely related in patients with CKD. In this population, we found elevated values of PDFF and low levels of vBMD, with a significant negative correlation between the two parameters, both measured at lumbar spine respectively by MRS and QCT. We chose QCT instead of DXA because this three-dimensional technique allows obtaining volumetric BMD measurements, that are more consistent with those of MR spectroscopy than bi-dimensional BMD measurements of DXA.

In addition, we explored the possible connection between bone marrow fat and severity of CKD. To our knowledge, this investigation has not been performed so far.

In aging population, MRS measurements of bone marrow fat correlate with osteopenia and osteoporosis assessed on the basis of BMD and vertebral fractures, as demonstrated in several reports (8,9,36).

The similarities among these studies and our results suggest that in both CKD and aging there is an increased marrow fat deposition, whose cause is still unknown. CKD represents a model of premature aging, characterized by an accelerated deterioration of physiological cellular and tissue functions. In this condition, the common cellular precursors of adipocytes and osteoblasts (i.e., mesenchymal stem cells) are functionally altered due to the accumulation of oxidative stress, leading to a preferential differentiation towards adipocyte lineage in bone marrow (34,37). This observation suggests that an impaired kidney function affects bone marrow environment. Accordingly, the evidence of a reciprocal relationship between marrow fat and bone mineral density supports the observation that bone weakening depends not only on trabecular bone loss but also on increased adipogenesis. In fact, excessive amounts of marrow fat determine the reduction of bone mass, and consequently of bone strength. In addition, a disproportionate adipogenesis may inhibit normal osteoblast activity, resulting in bone loss and alteration of bone quality. These mechanisms could be responsible for the higher fracture rates in CKD patients compared to general population (24,28).

Bone abnormalities affect almost all patients with CKD requiring dialysis and the majority of patients with CKD stages 3–5 (27,38). So, we hypothesized an increased marrow fat in patients with late stages of chronic renal insufficiency. In effect, our results demonstrated that PDFF increased significantly with the decline of GFR, suggesting that the normal mineral and endocrine functions disrupted in CKD patients play an important role in modulation of marrow adipogenesis. In our study, changes in bone marrow fat related to CKD were not affected by age. This finding, though unexpected, was consistent with the results of Woods *et al.* (22). A possible explanation may be the relatively young age of our cohort of patients (mean age 59.6±11.5 years).

We also investigated the relationship between marrow fat content and blood levels of PTH, that is considered a valuable biomarker of bone remodeling in CKD. Our results did not show a significant association between these two parameters. A small portion of CKD patients received treatment for secondary hyperparathyroidism and the effects of drugs may have influenced blood levels of PTH. In the future, we will correlate bone marrow fat with biochemical markers of bone turnover in patients with chronic renal insufficiency, at baseline and after specific treatment to correct secondary hyperparathyroidism. These observations may help to understand if bone marrow fat composition is a "reversible" condition that changes with clinical improvement of mineral disorder related to CKD.

An interesting finding of our analysis was the evidence of no association between vBMD and severity of CKD. Moreover, vBMD did not show a significant correlation with PTH values. In accordance with our results, previous reports conducted on CKD patients demonstrated that while at hip hyperparathyroidism was associated with low vBMD, resulting in high fracture risk, at spine this association was less strong (39,40). Whether in CKD patients the increased marrow fat adipogenesis may explain the high bone fragility and fracture risk at lumbar spine, independently of PTH, it deserves further studies.

The current study has some limitations. The population size is relatively small, in particular healthy controls, and measurements of vBMD by QCT were not available in healthy subjects. It should be emphasized that several studies have already examined association between marrow fat and bone density in healthy population (8,9,36,41). However, further investigations are needed to recruit a larger sample of subjects for comparing their bone composition with those of CKD patients.

In our research, we did not have histological data derived from bone biopsy to confirm MRS marrow fat measurements in CKD patients. Nevertheless, a recent study of Cohen *et al.* performed in osteoporotic and control subjects demonstrated a correlation between marrow fat content in trans-iliac crest biopsy and lumbar spine marrow fat content by MRS (42). Although related to a different study population, these results contribute to better validate MRS in bone marrow fat assessment.

Lastly, in a small number of our study population eventual drug therapies affecting bone and mineral metabolism may have had effects on blood PTH values measured in those patients, influencing our results in terms of correlation with marrow fat content. Regardless of that, there is a need to understand if CKD-induced disturbances of PTH metabolism may have a role in changes of bone marrow composition.

Conclusions

This study demonstrates that a decrease in bone density within lumbar vertebrae is associated with a significant increase of bone marrow fat in CKD patients. Moreover, bone marrow fat modifications correlate with the severity of renal function impairment.

Based on our results, we believe that 3T MRS quantification of bone marrow fat is reliable and highly repeatable, indicating its possible role as quantitative imaging biomarker for bone marrow changes in CKD patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-530/coif). GG serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of IRCCS "Casa Sollievo della Sofferenza" Hospital (No. 12/CE). Written informed consent was obtained from all patients in this study.

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