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Research Article

Structural alterations during fracture healing lead to void spaces developing in surrounding bone microarchitecture

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Abstract

Distal radius fractures are among the most common fracture sites, with a high incidence across all age groups. High-resolution peripheral quantitative computed tomography (HR-pQCT) has enabled assessment of bone microarchitecture in vivo at the distal radius, providing new insights into the healing process. However, we have observed structural bone loss that is not captured by standard analysis. This study uses void space analysis to quantify the development of localized structural bone loss during fracture healing. Twenty-six participants (21 female, 5 male; aged 18-79 yr) with conservatively-treated distal radius fractures were scanned using HR-pQCT at 6 study visits post-fracture (wk 1, 3, 5, 12, 26, and 52). Total BMD (Tt.BMD), bone volume fraction (BV/TV), and void space volume fraction (VS/TV) were measured. Grip strength relative to the non-fractured wrist and patient rated wrist evaluation (PRWE) were measured at all study visits after cast removal. The cumulative expansion of VS/TV across sequential study visits was quantified to differentiate voids that developed during healing from pre-existing void space. A 5-fold increase in median VS/TV was observed during the follow-up period, from 1.0% (0.6%-9.0%) to 5.5% (2.5%-12.4%). Tt.BMD and BV/TV did not significantly change in this same time interval. Relative grip strength after cast removal was significantly inversely correlated with final VS/TV ($\rho = -0.63$, $p = .02$) and cumulative expansion of new void space during healing ($R = -0.67$, $p < .01$), whereas no significant associations were found with age or PRWE. This study suggests that there are adverse changes in bone microarchitecture during fracture healing, despite the preservation of overall Tt.BMD and BV/TV in the same region. Reduced grip strength is correlated with more severe void space formation, but the mechanistic relationship requires further exploration. The formation of void spaces may have long-term implications on bone strength and could provide insight into risk of re-fracture.

Keywords: high-resolution peripheral quantitative computed tomography, bone microarchitecture, fracture healing, void space; distal radius fracture

Lay Summary

Distal radius fractures, or wrist fractures, are common across all ages. Advanced imaging (HR-pQCT) has helped researchers study how these fractures heal, revealing changes not seen in standard tests. This study examined 26 patients over a year and found that localized regions of structural bone loss, or void spaces, formed in the bone outside the immediate fracture zone, even though overall bone density appeared stable. Patients with weaker grip strength after healing had more of these voids. These findings suggest that fracture healing changes bone structure in a way that may weaken the surrounding bone and increase risk of re-fracture.

Introduction

Distal radius fractures are among the most common skeletal injuries, with a high incidence across all age groups, from children to the elderly.[1] Although distal radius fracture outcomes are often less severe than fractures at axial sites, such as the hip and spine,[2] they still have important clinical implications and can be indicative of osteoporosis in adults over 50 yr. Radius fractures result in loss of function, pain, and, if complications arise, can require extensive rehabilitation.[3] Moreover, distal radius fractures serve as an important predictor of future fracture risk, particularly in older individuals with osteopenia or osteoporosis.[4,5] The standard treatment for most radial fractures is cast immobilization, typically for a period of 4–6 weeks. However, the optimal timing for cast removal remains uncertain and can significantly influence patient outcomes.[6] Factors such as age and bone quality further contribute to the variability observed in the healing process,[7,8] underscoring the need for a better understanding of the mechanisms underlying bone healing and post-fracture function to guide clinical decision-making and improve patient care.

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In recent years, high-resolution peripheral quantitative computed tomography (HR-pQCT) has enabled assessment of bone microarchitecture *in vivo* at the distal radius, providing new insights into the healing process.[9–13] Despite substantial progress in high-resolution imaging of peripheral fractures, the variability in patient outcomes regarding bone mineral density (BMD) and microarchitecture underscores the complex nature of fracture healing and the necessity for further investigation of structural changes during this process. Traditional density and morphological measures often fall short in fully capturing the dynamics of fracture healing,[14] indicating a critical gap in our understanding of the mechanisms underpinning successful bone recovery. In previous work, we performed longitudinal HR-pQCT analyses to quantify formation and resorption rates throughout the first year of fracture healing.[15] Interestingly, we observed that elevated bone remodeling extended beyond the immediate fracture zone, resulting in rapid structural bone loss of seemingly intact microarchitecture. Although these observations have been noted in HR-pQCT studies[9,15] and in clinical practice,[16] the extent to which structural bone loss occurs in the region surrounding fracture, and why severity across individuals varies, remains underexplored and unquantified. A recently developed morphological metric, termed void space, can quantify such structural deterioration beyond typical morphological measures quantified by HR-pQCT.[17] Void space is a measure of atypical structural bone deterioration, quantified as a volume in trabecular bone compartment that lacks a well-connected mineralized network, presumably filled with bone marrow. Void spaces are potentially permanent bone loss, found to be more prevalent and severe with aging,[17] and in hip fracture patients.[18]

In this exploratory study we aimed to investigate structural bone loss during fracture healing based on our previous observations. This is accomplished by quantifying changes in void space volume, and determining whether an association exists between bone loss during fracture healing and measured functional outcomes.

Materials and methods

Participants and study design

Patients with stable distal radius fractures were recruited from the Inselspital Bern, Switzerland, at their initial trauma appointment. Patients were eligible if they were at least 18 years of age and sustained a unilateral distal radius fracture that was treated conservatively by cast immobilization. Patients were considered ineligible if they were pregnant or breastfeeding, sustained a previous fracture at the same distal radius site, had polytrauma injuries, were currently on steroid or osteoporosis treatment (eg, bisphosphonate), had a disease impairing wrist function (eg, stroke, paresis), metabolic, or inflammatory disorders impacting bone metabolism (eg, rheumatoid arthritis), underwent radio- or chemotherapy in the last year, or were currently participating in a pharmaceutical study. All participants provided written informed consent prior to participation, and the study protocol was approved by the local ethics committee (Swiss Ethics, Project 320030L_170205).

This study was designed as a prospective cohort study, where participants were invited to attend 6 follow-up study visits at the Department of Osteoporosis at the University Hospital of Bern, scheduled at 1-, 3-, 5-, 12-, 26-, and 52-wk post-fracture. During this period, all participants were provided standard-of-care treatment, where the fractures were diagnosed with anterior–posterior and lateral view radiographs, followed by immobilization in a fiberglass cast for 5 weeks, after which fracture stability was confirmed by radiographs.

Participant demographics, including age at time of fracture, sex, height, weight, and handedness, were collected at the baseline visit (1-week visit post fracture) alongside health history questionnaires. At all study visits HR-pQCT scans were acquired of the fractured radius, following the protocol described in the following section. At the 3-week study visit, dual-energy X-ray absorptiometry (DXA) scans of the non-dominant proximal femur were obtained, and the femoral neck T-score was measured. Finally, functional outcomes were measured at the study visits after cast removal, occurring at 12-, 26-, and 52-weeks post-fracture. These included the German version of the patient rated wrist evaluation (PRWE) questionnaire and hand grip strength. The PRWE questionnaire is a validated patient-rated scoring tool to assess pain and function outcomes after a distal radius fracture and provides an aggregated score ranging from 0 (no pain/disability) to 200 (very severe pain/disability).[19,20] Hand grip strength was measured using a hydraulic hand dynamometer (Biometrics, Ltd.), taken in a seated position with the elbow bent 90° in flexion and forearm in neutral position. The average of 3 repeated measurements on each side was taken, and the measure reported as the percent difference between the grip strength of the fractured side relative to the non-fractured side.

Image acquisition and processing

HR-pQCT scans (XtremeCT II, Scanco Medical AG) of the fractured distal radius were collected using a custom image acquisition protocol to capture an extended scan region. First, an anterior–posterior scout view was taken, and the reference line was placed at the inflection point of the distal endplate. The scan region began at a fixed offset of 1.2 mm distal to the reference line, extending proximally 30.6 mm (504 slices with a 60.7 μm isotropic voxel size). This acquisition protocol was performed to ensure the complete fractured region was captured, while also aligning the middle position of the scan region with the standard acquisition protocol.[21] All scans were scored for motion on a scale of 1 (no motion artifacts) to 5 (severe discontinuities), and scans with a motion score of 4 or greater were excluded from analysis.[22] Participants were excluded from analysis if they had fewer than 4 study visits with complete HR-pQCT image data or did not complete the follow-up period to at least 26 weeks.

Gray-scale density values of HR-pQCT images obtained at the week 1 and 3 visits were scaled using established calibration equations to correct for minor beam hardening effects caused by the overlying fiberglass cast.[23] Periosteal contours were automatically generated using an automated 3D geodesic active contouring technique,[24] and longitudinal scans were registered using a previously established multi-stack rigid registration protocol that corrects for stack-shift artifacts that can arise with the extended scan length protocol.[25] Images were transformed to a common reference space for morphological analysis, and the mineralized bone structure was segmented by applying a Gaussian filter (sigma 0.8, support 1.0) and a fixed threshold of 320 mg HA/cm^3. Total

bone mineral density (Tt.BMD, mg HA/cm^3), total cross-sectional area (Tt.Ar, mm^2), and total bone volume fraction (BV/TV, %) were quantified using standard protocols (Image Processing Language, v5.42, Scanco Medical AG).[21]

Regions of structural bone loss at each study visit were measured by segmenting void spaces in the mineralized bone structure and quantified as void space to total volume fraction (VS/TV, %) following the previously established protocol.[17] Further, void space expansion and contraction over time were assessed by superimposing the segmented void space volumes across sequential scans and performing voxel-wise subtraction of the segmented void space volume. Any void space that was only present in the earlier measurement was labeled as contracted void space over that duration, whereas void space present only in the latter measurement corresponded to newly expanded void space. Expansion and contraction volumes were reported as volume fractions and normalized as a weekly rate of expansion and contraction (%/wk) to account for the variable duration between study visits. Finally, the cumulative void space expansion and contraction over the 1-year follow-up period was quantified as the summation of total void space expansion and contraction across all study visits. This was performed to distinguish between voids that developed during fracture healing versus those that arose due to the fracture incident or were pre-existing.

Statistical analysis

Normally distributed variables, as determined by the Shapiro–Wilk test, were reported as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range (IQR). Changes in bone properties (Tt.BMD, Tt.Ar, BV/TV, and VS/TV) between the first and last available study visits for each participant were compared using paired t-tests or Wilcoxon signed rank test, depending on data distribution. Void space expansion and contraction over the 1-year follow-up period were fitted using a locally estimated scatterplot smoothing regression curve with 95% confidence intervals to explore the temporal progression of structural change over time. Finally, the association between cumulative void space expansion and contraction with age and functional outcome measures (grip strength and PRWE) were assessed using Pearson or Spearman's correlation coefficients, depending on data distribution. All statistical analysis was performed in R (R Project, version 4.1.1), and the significance level was set as $p < .05$, adjusted using the Benjamini–Hochberg method,[26] when multiple comparisons of related measures were performed.

Results

In total, 26 participants were recruited (19 female, 7 male) with an age range between 18 and 79 years. Five participants were excluded due to insufficient study visits (<4) or follow-up time (<26 weeks) with complete clinical and image data. Baseline descriptive characteristics are summarized in Table 1 for the remaining 21 participants included in the analysis. The median times of the first and last study visits were 1.1 weeks (IQR = 0.9-1.1) and 52.3 weeks (IQR = 42.9-54.1) post-fracture, respectively. Two participants (9.5%) were considered osteoporotic according to their femoral neck T-score, while 6 (28.6%) had low bone mass, and 12 (57.1%) had normal areal bone density.

Table 1. Descriptive characteristics of the participants who completed at least 4 visits and were followed for at least 26 wk post-fracture over the follow-up period.

	Mean ± SD (n = 21)
Age at time of fracture (yr)	47.5 ± 19.2
Height (cm)	167.2 ± 8.5
Weight (kg)	65.7 ± 15.6
Femoral neck T-score[a]	−1.04 ± 1.04
	N (%)
Sex (female)	16 (76)
Dominant hand fractured	8 (38)
Menopause[b]	8 (50)

[a] n = 1 participant missing DXA information. [b] Percentage considers female participants only.

Median void space volume fraction significantly increased by more than 5-fold in size during the 1-year follow-up of fracture healing (550%, p =.01), in contrast to Tt.BMD and BV/TV did not significantly change over the same period, and Tt.Ar decreased marginally (−3.3%, p <.02) (Figure 1A and Table 2). Bone microarchitecture properties across all study visits are reported in the supplemental materials (Figure S1 and Table S1).

Spatial–temporal assessment of void space contraction and expansion during fracture healing indicated that contraction preceded expansion, where void space contraction occurred most rapidly immediately following the fracture incident (weeks 1 to 5 post-fracture) while void space expansion occurred over a longer duration, peaking between week 5 and 12 post-fracture on average (Figure 1B and C). Further, void space expansion typically occurred in the region outside the immediate fracture zone (proximal bone) that did not have initial void spaces present, and appeared structurally intact on radiograph and HR-pQCT (Figure 1C and Figure 2). To confirm this spatial distribution, we performed a sub-analysis quantifying void space parameters separately in the proximal and distal bone regions (Figure S2 and Table S2). This analysis confirmed that VS/TV significantly increased only in the proximal region (further from the fracture), from a median VS/TV 1.6% to 23.0% between the first and last study visits (p =.001). In contrast, VS/TV in the distal region, which included the fracture, remained unchanged between first and last study visits (median VS/TV of 0.9% to 2.4% at first and last study visits, respectively, p =.19).

The relative grip strength of the fractured wrist measured at 12 weeks post-fracture was significantly correlated with final VS/TV ($\rho = -0.63$, p =.02) and with the cumulative expansion of new void space during healing (R = -0.67, p <.01), whereas no significant associations were found for age or PRWE with void space outcomes (Figure 3, Table 3). Further, no associations were found between assessed clinical measures (age, PRWE, and grip strength) and cumulative void space contraction over the 1-year follow-up period (Table 3).

Discussion

This study demonstrated that fracture healing at the distal radius led to the development of void spaces in bone microarchitecture among most participants. Void space expansion appeared to be predominantly driven by structural bone loss outside the immediate fracture zone and occurred most rapidly between 5 and 12 weeks after fracture. In

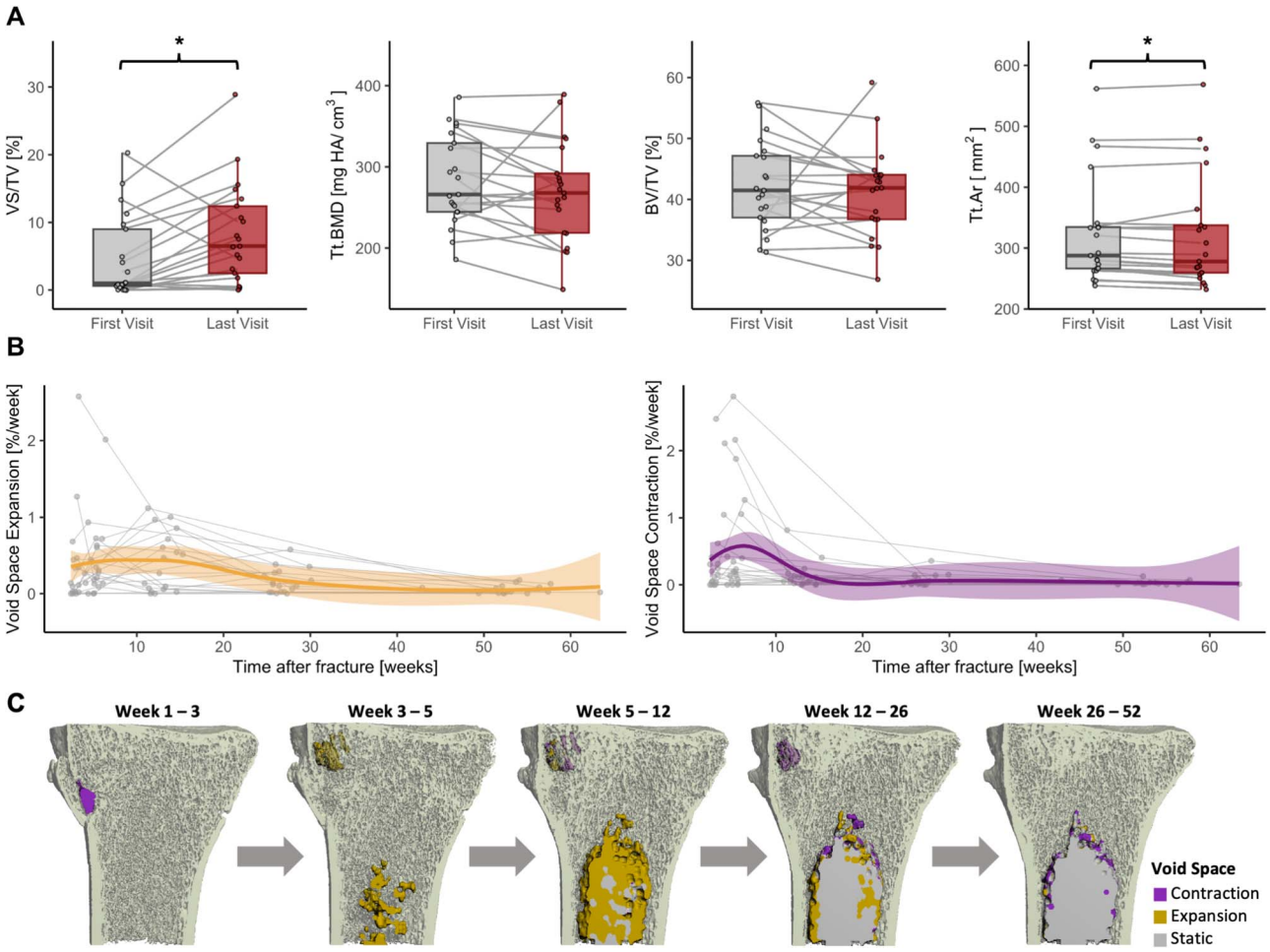

Figure 1. (A) Change in bone properties measured by HR-pQCT between first and last measured study visit, where ∗ indicates differences are statistically significant ($p < .05$). (B) Time series line plots of void space expansion and contraction during fracture healing. Individual participant trajectories are shown in light gray, and a locally estimated scatterplot smoothing (LOESS) regression curve with 95% confidence intervals is fit to illustrate the groupwise trend over time for expansion (yellow) and contraction (purple). (C) Representative time-series visualizations of void space contraction and expansion over time in a distal radius fracture of a 29-yr-old female whose VS/TV was 7.5% by the end of the 1-year follow-up period.

Table 2. Change in bone properties between the first and last available study visit over the 1-year follow-up period ($n = 21$). Normally distributed variables are reported as mean ± SD and non-normally distributed variables are reported as median (interquartile range). Significant differences are denoted with an Asterix (*).

	First study visit	Last study visit	Difference (%)	*p*-value
VS/TV (%)	1.0 (0.6 – 9.0)	6.5 (2.5 – 12.4)	**550**	**0.01***
Tt.BMD (mg HA/cm^3)	283.5 ± 55.1	268.7 ± 61.5	−5.2	0.16
BV/TV (%)	42.3 ± 7.2	41.2 ± 7.2	−2.7	0.48
Tt.Ar (mm^2)	287.8 (266.5 – 334.7)	278.2 (259.6 – 337.5)	**−3.3**	**0.02***

Abbreviations: BV/TV, bone volume to total volume ratio; Tt.Ar, total cross-sectional area; Tt.BMD, total BMD; VS/TV, void space to total volume ratio.

contrast, void space contraction typically occurred early in fracture healing (between week 1 and 5). The size of void spaces that persisted 1 year after fracture was notably larger on average than what has been observed in a non-fractured normative adult population. Specifically, the median VS/TV observed in adults between 18 and 79 yr ranges between 0.8% and 4.0%,[17] while in the present study, the fractured cohort had a final median VS/TV of 6.5%. Concerningly, the void spaces that developed during fracture healing are comparable to what has been observed in elderly patients who have suffered a recent hip fragility fracture (mean VS/TV = 6.8%).[18] The persistence of large void spaces during healing signifies potentially permanently compromised structural integrity of the bone. Given that void spaces and trabecular heterogeneity have been associated with major osteoporotic fractures,[18,27] these alterations could indicate elevated susceptibility to subsequent fractures in the future; however, further investigation is required.

The inverse correlation between void space expansion and grip strength indicates that mechanical stimuli likely play an important role, as grip strength has been shown to be an effective surrogate measure of patient-specific physiological loading at the distal radius.[28] In the present study, lower levels of mechanical loading (measured by grip strength) during fracture healing are associated with greater void space expansion in the 1 year following fracture. The findings are in line with pre-clinical models where subject-specific loading was found to be beneficial in promoting bone remodeling

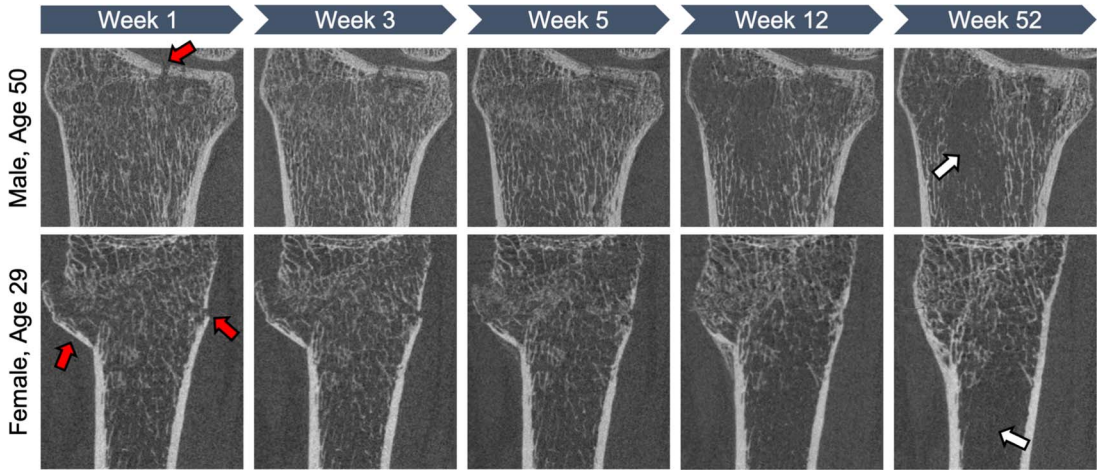

Figure 2. Sequential greyscale HR-pQCT scans of the fracture radius in 2 participants with void space expansion occurring during healing. Red arrows in the first study visit indicate the fracture location and white arrows in the last study visit indicate the formed void space. The top example (male, age 50) shows an anterior–posterior cut plane, and the bottom example (female, age 29) shows a lateral cut plane along the mid radius. Accelerated loss of bone microarchitecture is most evident at 12 weeks post-fracture and did not recover over the 1-year follow-up period.

Table 3. Associations between clinical measures during early fracture healing and final void space outcomes over the 1-year follow-up period. Correlations are linear unless indicated, and significant correlations are denoted with an Asterix (*).

	Correlation coefficient	Adjusted *p*-value
Final void space volume fraction		
Relative grip strength	**−0.63**[a]	**.02***
PRWE score	0.19[a]	.40
Age at time of fracture	0.41[a]	.07
Cumulative void space expansion		
Relative grip strength	**−0.67**	**<.01***
PRWE score	0.27	.23
Age at time of fracture	0.40	.08
Cumulative void space contraction		
Relative grip strength	−0.30[a]	.21
PRWE score	0.41[a]	.06
Age at time of fracture	0.33[a]	.15

[a] Spearman's ρ. Abbreviation: PRWE, patient rated wrist evaluation.

during fracture healing.[29] Recent clinical studies support these findings, indicating that early weight bearing may improve functional outcomes.[30] Our findings strengthen this notion that modest levels of mechanical stimuli during the healing process may mitigate adverse structural bone loss. However, we acknowledge the absence of a control group or specific intervention to increase mechanical loading constrains our ability to draw definitive conclusions about the direct impact of mechanical stimuli on void space formation, along with what magnitude, frequency, and timing is safe or appropriate. Future controlled studies with interventions targeting mechanical loading are needed to elucidate the precise relationship between mechanical stimuli and structural bone alterations during fracture healing.

The average Tt.BMD and BV/TV of participants did not significantly change over the 1-year follow-up period after fracture, although outcomes were highly variable at the participant-specific level. These findings are in line with previous studies that have investigated fracture healing over a 6-month to 2-year period.[9,10,31] However, previous studies have consistently shown that bone stiffness increases during healing, indicating that bone may be rapidly remodeling to restore mechanical integrity, resulting in variable structural reorganization.[9,10] Although the outcome may appear counter-intuitive to the current findings, it is possible that rapid void space expansion is a result of mechanical adaptation in the bone, where the bone structure is resorbed in regions experiencing lower mechanical strains to facilitate repair of the unstable fracture region that is under higher local strains, as observed in murine defect models.[29] A recent study by Bevers et al. has also demonstrated how the newly formed under-mineralized tissue significantly contributes to overall bone stiffness at 12 weeks post-fracture,[9] the same period where maximum void space expansion is observed in the present study. However, in the present study, we did not perform microFE analysis due to the complexity in defining suitable boundary conditions that account for our scan region intersecting the distal endplate. Thus, future investigation would be required to accurately map the local mechanical environment experienced during healing to regions of bone resorption and formation to test this hypothesis.

Overall, this study presents novel and intriguing insights into fracture healing, but some limitations exist. Notably, this study has a limited sample size, and although in line with prior studies investigating fracture healing with HR-pQCT, it is not possible to perform sub-analyses on specific cohorts. For instance, stratification based on sex or osteoporosis status by DXA T-score was not possible. Further, the 3D image

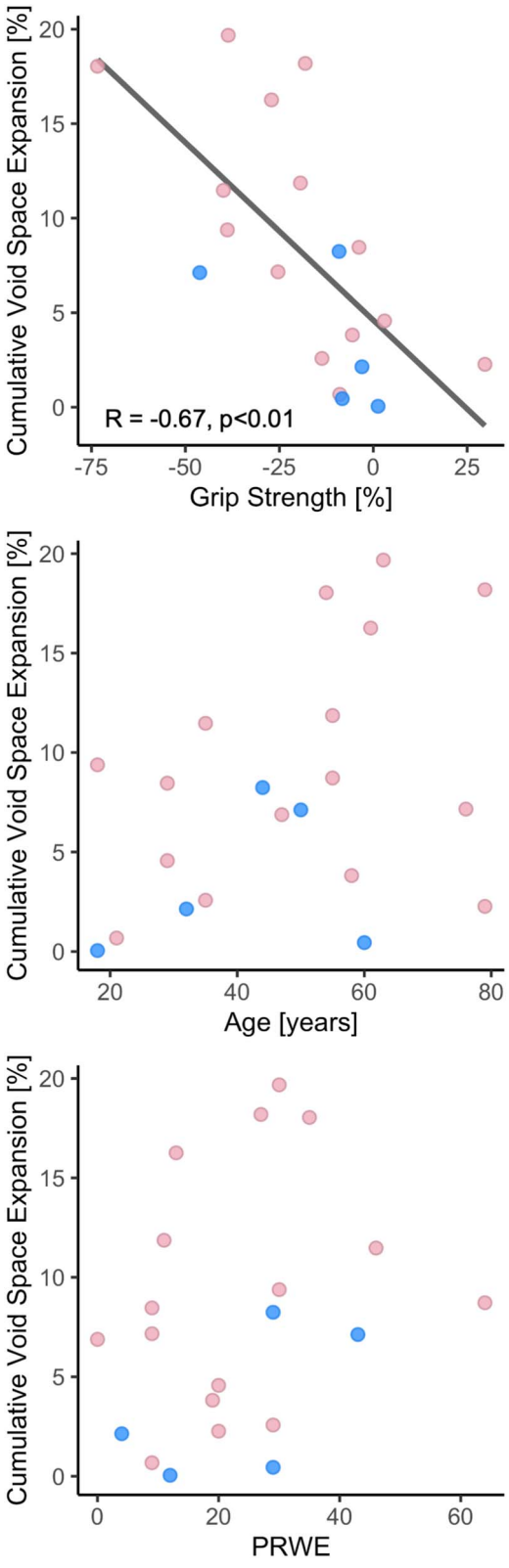

Figure 3. Scatter plots between early measures of relative grip strength, age, and patient rated wrist evaluation (PRWE) with cumulative void space expansion over the 1-year follow-up of fracture healing. Data points are colored to indicate participant sex (male = blue, female = pink).

registration approach implemented assumes a rigid structure and cannot account for fracture fragments moving relative to one another in the scan region. These slight shifts may induce measurement errors. To mitigate this issue, all images were visually inspected to ensure large fragment shifts were not present, and it is expected that the impact on void space measures is minimal.

In conclusion, this study provides novel insight into the dynamic behavior of bone adaptation during fracture healing. We extended a prior void space segmentation method to enable longitudinal tracking of the dynamic contraction and expansion of these spaces within the bone structure during fracture healing. With this approach, we demonstrated in conservatively treated distal radius fractures that void spaces often develop in bone microarchitecture, reaching a maximum rate of expansion between 5 and 12 weeks post-fracture. The severity of void space expansion is inversely correlated with relative grip strength at this same time interval. These findings suggest a potential relationship between mechanical loading, as indicated by grip strength, and structural changes in bone during fracture healing. However, the mechanistic cause of void space expansion, its implications, and potential prevention require further investigation.

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Author contributions

Danielle Whittier Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing—original draft; Matthias Walle—Conceptualization, Software, Validation, Writing—original draft, Writing—review & editing; Penny Atkins—Project administration, Writing—review & editing; Caitlyn Collins—Project administration, Writing—review & editing; Matthias Zumstein—Conceptualization, Methodology, Resources, Writing—review & editing; Patrik Christen—Conceptualization, Funding acquisition, Project administration, Writing—review & editing; Kurt Lippuner—Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—review & editing; Ralph Mueller—Funding acquisition, Resources, Supervision, Writing—review & editing.

Supplementary material

Supplementary material is available at *Journal of Bone and Mineral Research* online.

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Conflicts of interest

DW: none, MW: none, PRA: none, CJC: none, PC, none; KL: none, RM: none.

Data availability

The analysis scripts developed and used in this study will be made available through an open access GitHub repository (https://github.com/PaediatricMSKImaging/Open_IPL). The image datasets analyzed during the current study are not publicly available to protect confidentiality and privacy of participants, but may be made available with reasonable justification.

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