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Tomography-based in vivo quantification of bone turnover
– Age associated 3D dynamics of cortical bone during adaptation –

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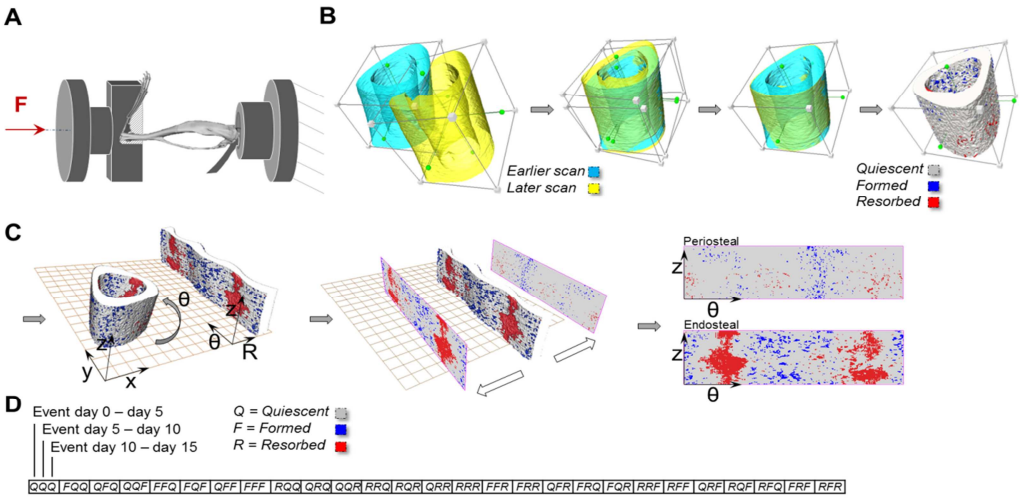
With aging populations, therapies minimizing fragility are essential to avoid bone fractures in healthy but especially in osteoporotic individuals. Bone turnover, i.e. bone volume resorbed or formed over a certain period of time, has been identified as a predictor of fracture risk and is independent of areal BMD [1,2]. Since bone turnover cannot be clinically assessed directly, serum markers are frequently used as surrogates to assess fracture risk. However, an undeviating assessment of bone turnover would be appreciated to quantify directly the restructuring processes in bone. Turnover during skeletal growth and renewal is performed by two processes occurring on discrete locations of the bone surface: resorption and formation of bone packets. During remodeling, formation follows resorption at the same site. In contrast during modeling, formation and resorption are not spatially correlated; bone is selectively added or removed from existing surfaces to optimize geometry. Adaptation is a key process by which the skeleton adjusts to changes in the loading environment. It is assumed that both processes – modeling and remodelling – are sensitive to the surrounding mechanical environment. However, it is unknown to what extent modeling, remodeling, or both occur during adaptation. The overall goal of this investigation was to improve the assessment of bone turnover and differentiation between modeling and remodeling by introducing a new microCT based method. We hypothesized that with ageing overall bone turnover would increase and remodeling would dominate modeling. Mechanical loading would further increase turnover and shift (re)modeling towards increased modeling, independent of age.
Twenty-nine mice underwent two weeks of in vivo cyclic tibial compression (216 cycles/day; f = 4 Hz; ε_{max} = 1200 microstrain, right tibia as internal control, Fig A, [3]). In vivo microCT (vivaCT 40, Scanco Medical; isotropic resolution 10.5µm, 55kVp, 145µA, 600ms integration time, no frame averaging) was performed (day 0, 5, 10, 15). The scan region was centered at the midshaft (5% of tibia). Images were rigidly registered using normalized mutual information and segmented using an automatic algorithm. Two consecutive images in a common coordinate system were compared to identify occurring changes (day t – day t+1); these changes were classified into formation, resorption and quiescence (Fig B). Voxels existing only at the first time point are defined as resorbed, voxels existing only at the later time point are defined as formed, and voxels existing at both time points are defined as quiescent regions. To track surface changes over time, we created an artificial fixed geometry. Therefore, the bone surfaces were projected onto a cylinder with the two coordinates: angle Θ and height z. The resulting three matrices (day 0 – day 5, day 5 – day 10 and day 10 – day 15)

were then again compared to identify (re)modeling sequences (Fig C). Therefore surface changes were followed between the four time points in order to track how (re)modeling occurred site-specifically over time. Twenty-seven (re)modeling sequences representing the possible combination of formation (F), resorption (R) and quiescence (Q), at the three time intervals were defined and the occurring spatially correlated temporal changes were assigned to them (Fig D). Active surface area (AS/BS), meaning surfaces that were mineralizing and/or resorbing, were quantified and divided into subgroups: (1) short term formation, (2) long term formation, (3) short term resorption, (4) long term resorption, (5) mixed sequences in which resorption followes formation, (6) mixed sequences in which resorption precedes formation, which is defined as remodelling and (7) fast remodeling, which represents 1.5 remodeling cycles. ANOVA was used to assess within-subject and between-subject effects and interactions. T-tests were used to determine differences between loaded and control bones.
In the nonloaded control tibia, 18.82±4.83% of the bone surface was forming or resorbing bone (AS/BS), with aging this increased to 21.28±7.97% and and 24.7±11.52% in adult and elderly mice, respectively. In the loaded tibia, AS/BS was increased to 44.06±8.39%, 28.55±5.25% and 29.57±9.98% of the bone surface in the young, adult and elderly mice. From the 27 (re)modeling sequences only few could be observed with a detectable frequency. Bone adaptation occurred predominately by short term modeling (i.e by the sequences FQQ, QFQ, QQF) or short term resorption (i.e. RQQ, QRQ, QQR). In addition, young and adult bones could temporally extend formation processes (i.e. FFQ, QFF, FQF, FFF, where FQF could be an FFF sequence, where the resolution of the µCT was not high enough), whereas the elderly lost this ability. Additionally, aging was characterized by a reduction in adaptive modeling and a corresponding increase in remodeling (i.e. RRF, RFF, QRF, RQF, RQF).
The number of remodeling events may have been underestimated in our study, if the remodeling period in these mice is longer than 15 days, as our results strongly depend on the time period of observation. Therefore, future studies should investigate longer time periods.
The new computational approach provides a powerful new tool to identify changes in bone turnover in animal models and may possibly improve the determination of bone turnover parameters in human patients in the future.



REFERENCES

[1] Cummings et al. 2002, Am J Med112 (4):281-289.
[2] Garnero et al., 1999, JBMR 14(9):1614-1621.
[3] Willie et al., 2013, Bone 55 (2):335–346.