Bone3D

2D and 3D Quantification of Bone Structure and its Changes in Microgravity Condition by Measures of Complexity

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Abstract

The objective of the research program is to establish a precise diagnostic method for the quantification of changes in bone structural composition. The project develops the tools to evaluate structural loss in bone architecture and gains new quantitative information about the bone metabolism in microgravity condition. This evaluation is mostly based on symbolic dynamics and measures of complexity derived from the field of nonlinear dynamics.

The most precise procedure for diagnosing structural alterations will be developed and scientifically proven through the research project. The outcome of such comprehensive diagnostic program will provide the fundamental basis for monitoring, prevention, and treatment of structural changes of the bone in microgravity condition. The results of this project will have an impact on health care for astronauts and other space-flying personnel working on the ISS in the future, and for patients with metabolic bone diseases on Earth.

The first phase of the project, which lasted two years until the end of December 2002, has solved the following tasks:

- development of a method for non-invasive evaluation of the bone structure using 2D quantitative computed tomography (CT) images based on human specimens acquired at different skeletal sites,
- the new measures were tested on paradigmatic mathematical and physical models,
- development of a procedure for the precise quantification of a 3D bone architectural composition by analyzing human bone biopsy data sets obtained by micro-CT,
- validation of the findings by comparison of the micro-CT-outcome with static histomorphometric examinations.

After the successful completion of the entire research program (5-year program) the prospects will be:

- Microgravity effects on bone can be precisely quantified and monitored with the proposed technique.
- Crew persons may be selected by model-based predictions of their potential bone structure loss.
- The outcome of this research program will provide new information about bone metabolism and will lead to a better and quantified diagnosis for patients with bone diseases in general.
- The expansion of the technique of symbolic dynamics and measures of complexity to analyze 3D data will have a significant impact on nonlinear dynamics. It opens new prospects to analyze, quantify, and compare numerically different aspects of a structural organization when the information of the underlying model is not available.
- An integrated 3D working environment will be available offering new powerful methods for analyzing and visualizing complex 3D image data for quantitative bone assessment.

Beside the effects on space medicine and musculoskeletal diseases the project will give impulses to diverse fields of research such as theoretical physics, signal and image analysis, biomedical science, material science, scientific visualization, image data analysis, and management of large data sets.

The project was conducted as a close team work between the Center of Muscle and Bone Research, Dept. of Radiology and Nuclear Medicine, University Hospital Benjamin Franklin, Free University Berlin (Germany); the Dept. of Scientific Visualization, Zuse Institute Berlin (Germany); Dept. of Nonlinear Dynamics, Institute of Physics, University of Potsdam (Germany); the Dept. of Cell Biology, Institute of Anatomy, University of Aarhus (Denmark); Scanco Medical AG (Switzerland); and the Div. Medical Equipment of Siemens AG (Germany). The coordinator has been Wolfgang Gowin, MD, PhD from the Center of Muscle and Bone Research.

Non-destructive and non-invasive examinations of the human bones can only be performed with the application of radiological procedures. Pathological alterations of the bone appear as changes in radiological density and as changes of the structure. Changes of density can be quantified by several osteodensitometric methods.

The two methods to evaluate the structure of the bone are the histomorphometric approach to examine bone biopsies, and biopsy examinations by recently developed micro-CT devices. All parameters derived from microscopic examination of thin bone sections are limited as they are localized expressions of the structural arrangement within a two-dimensional plane. The structural elements of the bone are arranged in three dimensions and the architectural composition is based on the direction of the applied load. This can result in dramatic differences of the spatial arrangement of these structural elements within very short distances. To overcome the inherent difficulties of histomorphometry, the radiological method of micro-CT has been applied to examine bone samples. Biopsies can be examined without destruction of the sample. Slices with the same thickness as histological sections can be produced and analyzed by conventional histomorphometry parameters. A 3D reconstruction of the data resembles the biopsy itself. True assessments of the 3D architecture are possible only with 3D data sets acquired by micro-CT. Current trends in the field of radiological assessment of bone structure and microarchitecture are the refinement and further development of the micro-CT technique which is being improved by cone beam technology, variation of sample size up to 5 cm in diameter, refinement of the resolution down to 10 μm, and multi-slice techniques.

The architectural composition of a complex porous material such as bone may be assessed with different measures which evaluate its homogeneity, the regularity, the degree of order or disorder, and its complexity. Such assessments would result in a quantification of the architecture as a whole (3D) still including the single parts it is built from. This is a new innovative approach to quantify architecture opposed to traditional measures that evaluate only single attributes of the structural composition. A set of 6 parameters (measures of complexity) has been developed that quantifies the architecture of bones from different skeletal regions, distinguish these skeletal regions from each other, quantify changes in the structure very sensitively, detect changes before a trained radiologist is able to detect them visually (performed on mathematical models only), demonstrate that structural changes are more pronounced than changes in bone mineral density, identify structure even in images with an unfavorable signal/noise ratio, differentiate general structural bone loss from other localized causes.

2D simulations were performed as numerical experiments. These utilized a regular lattice to simulate trabecular bone tissue, and later CT-images of human vertebral trabecular bone

tissue. The results were important for further development of the measures of complexity. We came to the following conclusions:

- Measures of complexity are very sensitive in the detection of local defects and local elements which appear invisible to the eye.
- Measures of complexity are very sensitive to the appearance of disorder, and are equally good in the detection of order or disorder.
- Measures of complexity can differentiate between regular or random changes.
- Measures of complexity are more efficient than bone mineral density-measurements concerning the description of changes in a given bone slice.

Through experimental research, we were able to demonstrate a clear distinction of the architecture of normal, osteopenic, and osteoporotic bones and quantify their differences. Normal trabecular bone has a complex and ordered structure. Osteopenic bone is disordered and has a significantly lower complexity, whereas osteoporotic bone exhibits a simple and ordered structure. The effects of exposure to microgravity without any countermeasures are similar as the development from normal to osteoporotic bones. The loss of architectural complexity and density leads to a steep increase of fragility, a condition that is highly undesirably for space-flying personnel.

It has been shown that different skeletal regions have different bone mineral densities. It is assumed that the structural composition differs from region to region as well. This research project evaluated 9 different skeletal regions: distal radius, proximal tibia, lumbar vertebral body, femoral neck, border between femoral neck and femoral head, femoral head, 2 regions within the calcaneus, and the humerus.

Our findings are (see Fig. 1):

- Each region is different in its structural composition and in its bone mineral density.
- The tibia has the lowest bone mineral density range from all bone locations.
- The steepest slope is found at the femoral head.
- Structural changes appear more rapidly than changes in bone mineral density, except for the humerus.
- The humerus, a predominantly cortical bone, changes its bone mineral density faster than its structural composition.
- The femoral neck and the radius as bones with a thick cortical shell behave in-between. A decrease in bone mineral density causes less structural changes than in predominant trabecular bones.
- The highest structural complexity is found in the femoral head, the lowest in the vertebra.

The reference bones for bone density measurements have been lumbar vertebral bodies. We found that the proximal tibia is similar in its bone mineral density value and in its architectural composition. Since the proximal tibia is easier to reach, has less soft tissue around it and, therefore, has a higher signal/noise ratio in radiological imaging. Its smaller volume produces images with much higher resolutions in patient examinations. It might be the better location for quantitative assessment of the bone status than the lumbar vertebrae.
The sensitivity of architectural changes is the highest in the trabecular bone of the tibia and, similar, in the lumbar vertebral body. If the cortical bone is included in the calculation of the bone status, the tibia is slightly the better bone for the quantification procedure.
Bones with large amounts of cortical bone surrounding the trabecular part of the bone, such as the radius and the femoral neck, have a much lesser sensitivity to changes in their composition. Therefore, the radius as well as the femoral neck is not an ideal location for a bone status evaluation.

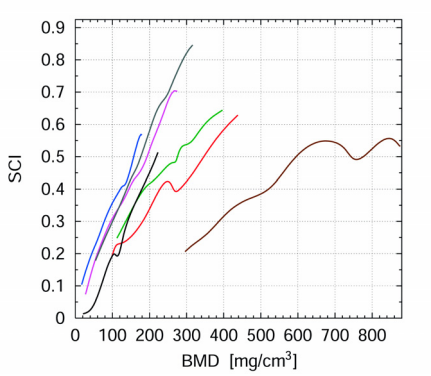

Fig. 1: Complexity measure Structure Complexity Index (SCI) versus calculated bone mineral density (BMD). The data are approximated by Bézier curves for visualization purpose.
The curves have different slopes characterizing different rates of change of the structural complexity for a given amount of bone loss. When evaluating a particular BMD-level, for instance 200 mg/cm³, the respective complexity of the bone architecture differs considerably from one location to another.

Color codes: Tibia Femoral head Calcaneus L3 Femoral neck Radius Humerus

After the establishment of procedures to acquire bone biopsies with the least damage to the bone structure, preparation of biopsies for micro-CT scanning, and artifact reduction methods; we were able to develop 3D measures of complexity based on 3D datasets of human bone biopsies. The 3D research is essential to prove that the newly developed 2D measures of complexity represent reliable parameters for the assessment of a bone status. We have to keep in mind that 2D measures can be obtained in vivo and are non-invasive, whereas 3D measures are always based on ex vivo invasive evaluations.

The results acquired by evaluating 3D data sets obtained by micro-CT were compared with traditional histomorphometry parameters derived from the very same bone biopsies.

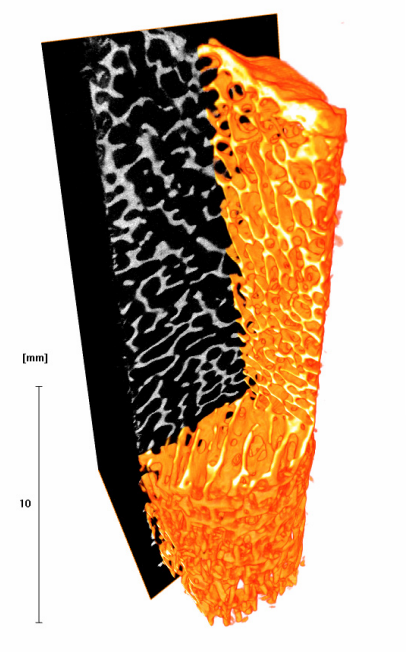

Fig. 2: Example of a visualization of parts of a 3D bone biopsy data set obtained by micro-CT. The visualization is realized by Amira, a 3D visualization and quantification platform developed by one of the partners of this team (ZIB). The bone biopsy was taken from the medial side of the proximal tibia. The background shows a frontal 2D view in black and white. The orange colored trabecular network is cut in the lower part to demonstrate an axial view, and cut at the right to show a sagittal view of the trabecular bone.
The thicker layer at the top represents the medial cortical shell. The anatomical location is turned up, 90° counter clockwise.

The anatomical directions are mentioned according to the bone tissue direction within the proximal tibia.

The comparison between the 2D and 3D data results in excellent correlations. The two most important histomorphometric measures bone volume/tissue volume (BV/TV) and connectivity density (CD) show the strongest correlations (0.96 and 0.95). We are now able to compare directly histomorphometric measures (gold standard) with new 3D measures of complexity derived from micro-CT data sets.

The development of 3D measures of complexity required the establishment of a standardized volume of examination. Acquired results are still confidential at this point in time, however, the achievements are extremely promising and provide already new insights to the structural composition of human bones.