Medical Image Analysis 40 (2017) 30–43

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

Detection and characterisation of bone destruction in murine rheumatoid arthritis using statistical shape models

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ARTICLE INFO

Article history:
Received 27 September 2016
Revised 7 April 2017
Accepted 22 May 2017
Available online 23 May 2017

Keywords:
Statistical shape models
Quantification of bone destruction
Rheumatoid arthritis
Murine models

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease in which chronic inflammation of the synovial joints can lead to destruction of cartilage and bone. Pre-clinical studies attempt to uncover the underlying causes by emulating the disease in genetically different mouse strains and characterising the nature and severity of bone shape changes as indicators of pathology. This paper presents a fully automated method for obtaining quantitative measurements of bone destruction from volumetric micro-CT images of a mouse hind paw. A statistical model of normal bone morphology derived from a training set of healthy examples serves as a template against which a given pathological sample is compared. Abnormalities in bone shapes are identified as deviations from the model statistics, characterised in terms of type (erosion / formation) and quantified in terms of severity (percentage affected bone area). The colour-coded magnitudes of the deviations superimposed on a three-dimensional rendering of the paw show at a glance the severity of malformations for the individual bones and joints. With quantitative data it is possible to derive population statistics characterising differences in bone malformations for different mouse strains and in different anatomical regions. The method was applied to data acquired from three different mouse strains. The derived quantitative indicators of bone destruction have shown agreement both with the subjective visual scores and with the previous biological findings. This suggests that pathological bone shape changes can be usefully and objectively identified as deviations from the model statistics.

1. Introduction

1.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory disease of autoimmune origin. It is most common in the elderly population, but it can affect people of all ages. It is a chronic disease, and being one of the most common causes of disability, it constitutes a public health problem.

The autoimmune response mounted by the body affected by RA gives rise to chronic inflammation of the synovial joints between the bones, which are the most common type of movable joints in the body. A proportion of sufferers will develop persistent inflammation of the synovial membrane (synovium) leading to the destruction of both cartilage and bone. Damage to the bone is thought to occur through imbalance of two processes: bone erosion (the breakdown of bone through secretion of enzymes that demineralise the bone matrix) and bone formation (deposition of new bone mineral into the underlying bone matrix). In healthy patients the two mechanisms are tightly regulated to ensure that on average, bone integrity remains constant. In patients with RA bone erosion dominates and over time the destruction of the bone surface can impair normal joint function and lead to structural deformities. In approximately 90% of cases where inflammation is persistent, patients will be clinically disabled within 20 years (Buckley, 1997).

1.2. Mouse models of the disease

The exact cause of rheumatoid arthritis is unknown, which limits the number of available treatment options. Pre-clinical studies attempt to uncover the underlying causes by emulating the disease in animals. Animal models of disease allow biomedical researchers to investigate medical conditions through experimentation that would otherwise be infeasible or unethical to perform on human subjects. Mice are particularly well-suited due to their high

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http://dx.doi.org/10.1016/j.media.2017.05.006
1361-8415/

genetic homology with humans, speed of breeding and inexpensive housing costs. A number of laboratory mouse strains have been developed and bred to be near genetically identical to one another. This allows for the roles of different genes to be investigated in a way that eliminates genetic variation as a factor and helps to gain better understanding of disease mechanisms and of the efficacy of new treatments. Characterisation of bone destruction is one of the key factors in understanding RA pathogenesis.

In longitudinal studies mice may be examined for traits associated with inflammatory arthritis. These could be based either on measurements (e.g. paw and ankle thickness, body weight, grip strength) or on subjective qualitative scoring (e.g. limb deformity, colouration, gait). Typically a hind paw is examined. Based on such observations and measurements individual animals are assigned a physiological disease index score according to disease severity. Assessment of disease in this way is an effective method for determining the gross differences between individual animals, but it does not provide explicit information about how the disease affects bones and joints.

1.3. Objective characterisation of RA

The nature and severity of bone shape changes are important indicators of pathology in mouse models of rheumatoid arthritis. Researchers that rely on the assessments of the external signs of the disease, as described above, cannot characterise a specific nature of bone destruction in different models of RA. Observation of the pattern of joint involvement and the bias towards bone formation compared to bone destruction allows characterisation of the nature of the arthritis, for example spondyloarthropathy is characterised by bone formation at the sites of tendon insertion whilst rheumatoid arthritis shows predominantly bone erosion at sites close to the articular joints. The spatial pattern of malformations can help to uncover cellular mechanisms of bone destruction by, for example, identifying the sites where activated osteoclasts proliferate causing bone erosion, or studying regulatory factors that control osteoclast differentiation and activity at specific bone junctions (Goldring, 2003; Romas et al., 2000).

In order to assess the degree of damage to bone, x-ray based techniques such as micro-CT are employed to reveal changes in bone structure. The technique has been demonstrated early on in animal studies of RA as a suitable means for evaluating bone loss and osteophytosis (formation of bone spurs) through visual examination of a sequence of two-dimensional micro-CT slices (Pettit et al., 2001; Pine et al., 2007). The process of identifying bone abnormalities is carried out manually and relies on the experimenter's own experience of how such bones appear under normal (non-pathological) circumstances.

A number of methods have been proposed to automate the analysis of bone destruction in RA, both in animal models and in humans. Of particular interest to this paper are volumetric methods that consider three-dimensional bone surface data. Quantification of bone volume is one possible approach, where gross differences can be determined automatically from image data. This approach has been used to assess mice with collagen induced arthritis (CIA), which were shown to have significantly lower bone volume and density than wild-type (normal) controls (Yang et al., 2013). One of the main limitations of this approach is that it provides no data about bone morphology, or the nature of the bone destruction that has occurred. This problem has since been tackled using surface-based registration of bones (Joshi et al., 2013).

In a longitudinal study of treatment efficacy, three-dimensional CT images were acquired from patients with established RA. Individual bones were manually segmented, and surface representations generated as triangulated meshes. Surface registration of bones at different stages of treatment was followed by calculation of point-wise distances between them, and used to determine local differences in bone volume. These differences were visualised as colourised surface renderings, highlighting the presence of abnormalities. This approach is effective in assessing bone changes over time in individual patients, but is not well-suited to detecting abnormalities in multiple subjects imaged at a single time point. Subsequently this work was extended to analyse statistical shape differences in wrist bone shapes of different populations (Joshi et al., 2015). This involved constructing an atlas of bone shapes where each surface point is characterised by the mean and variance and the p-value of the locations in individual samples. Shape differences were then visualised on colour-coded surface maps of p-values. A similar approach was used to identify erosive changes of carpal bones in longitudinal patient studies. The detected erosions were quantified by measuring changes in their depth.

The osteoarthritic changes affecting the mandibular joint were analysed in a study aiming to correlate the nature of morphological changes of the bone shape and the amount of pain experienced by a patient (Cevidanes et al., 2010). Individual bone instances were segmented, meshed and registered via spherical mapping using Procrustes alignment, followed by building a statistical shape model (SSM). Variations in the three aspects of morphological changes (flattening, erosions and osteophytes) for mild, moderate and severe conditions were visualised by generating the meshes from the SSM.

1.4. Objectives and contributions of this work

This paper presents an automated method for obtaining quantitative measurements of bone destruction in mouse models of RA from micro-CT images. A statistical model of normal bone morphology derived from a training set of healthy examples serves as a "template" against which a given sample is compared. Abnormalities in bone shapes for a given RA model are identified as deviations from the model statistics and are then characterised in terms of type (erosion / formation) and quantified in terms of severity (affected bone area). The colour-coded magnitudes of the deviations superimposed on a three-dimensional rendering of the paw show at a glance the spatial distribution and severity of the bone erosions and formations and their association with specific joints. The method has been applied to investigate the nature of bone destruction in three different mouse models of inflammatory arthritis, providing an insight into the different ways that joints are affected by the disease.

1.5. Outline of the paper

The hypothesis underpinning this work is that shapes of bones affected by pathology depart from statistically normal bone shape variations. This suggests the three-step procedure: first, the development of a statistical shape model of a normal limb; second, the detection of bone regions that lie outside the statistically predicted boundaries; and third, qualitative and quantitative characterisation of the detected abnormal regions both globally and locally. Step 1 was the subject of an earlier paper (Brown et al., 2014). This paper focuses on the detection and quantification of the bone destruction.

The mouse models used in the experiments are discussed in Section 2.1. Section 2.2 briefly describes data acquisition and sample preparation. The construction of the articulated statistical shape model (ASSM) of a normal mouse hind paw is outlined in Section 2.3. Shape model fitting and abnormality detection are described in Sections 2.4 and 2.5 respectively. Validation of the abnormality detection methods is presented in Section 2.6 followed by results (Section 3), discussion (Section 4) and conclusions (Section 5).