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● *Original Contribution*

ULTRASOUND PARAMETERS FOR HUMAN OSTEOARTHRITIC SUBCHONDRAL BONE *EX VIVO*: COMPARISON WITH MICRO-COMPUTED TOMOGRAPHY PARAMETERS

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Abstract—The aim of this study was to identify ultrasound parameters reflecting subchondral porosity (P_o), subchondral plate thickness (T_{pl}) and bone volume fraction at the trabecular bone region (BV/TV_{Tb}). Sixteen osteoarthritic human lateral femoral condyles were evaluated *ex vivo* using a 15-MHz pulsed-echo ultrasound 3-D scanning system. The cartilage–subchondral bone (C-B) surface region (layer 1) and inner subchondral bone region (layer 2) were analyzed; we newly introduced entropy (ENT) and correlation (COR) of ultrasound texture parameters of the parallel (x) or perpendicular (z) direction to the C-B interface for this analysis. P_o, T_{pl} and BV/TV_{Tb} were evaluated as reference measurements using micro-computed tomography. ENT_{L1x} (ENT of layer 1, x-direction) and ENT_{L1z} were significantly correlated with P_o (both r values = 0.58), COR_{L2x} with T_{pl} ($r = -0.73$) and COR_{L2z} with BV/TV_{Tb} ($r = -0.66$). These are efficient indicators of the characteristics of osteoarthritis-related subchondral bone; the other texture parameters were not significant. (E-mail: kuroki.hiroshi.6s@kyoto-u.ac.jp) © **2018 World Federation for Ultrasound in Medicine and Biology. Published by Elsevier Inc. All rights reserved.**

Key Words: **Osteoarthritis, Subchondral bone, Micro-computed tomography, Ultrasound, Texture parameter, Porosity, Thickness, Bone volume fraction, Cartilage.**

INTRODUCTION

Osteoarthritis (OA) of the knee, one of the most common locomotive diseases (Felson et al. 1987; Hart and Spector 1993; Yoshimura 2009), considerably decreases the quality of life (Norman-Taylor et al. 1996). The early stages of OA have been characterized by cartilage degeneration, such as damage to the collagen meshwork in the superficial zone of cartilage (Han et al. 2002; Poole et al. 2002) and fibrillation of the cartilage surface (Minns et al. 1977). However, changes in subchondral bone have received increasing attention in recent years despite an early OA stage. Elevated bone remodeling and subchondral bone losses have been seen in the early stages of OA in humans (Bettica et al. 2002). Thinning and increased porosity of the subchondral bone plate were reported in a canine early OA model (Intema et al. 2010). After temporal thinning, subsequent thickening of the subchondral bone plate was revealed with OA progression in an animal OA model (Batiste et al. 2004; Intema et al. 2010). Normal to severely degenerated samples were included; subchondral plate thickness and bone volume fraction (BV/TV) in trabecular bone were strongly correlated with OA histopathological grade (Finnilä et al. 2017). For such OA-related osteochondral changes, ultrasound parameters have been investigated. Amplitude-based ultrasound parameters,

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such as the reflection coefficient (R) and integrated reflection coefficient (IRC) from the cartilage surface, were sensitive to surface roughness (Chérin et al. 1998; Kaleva et al. 2009; Kiyan et al. 2017; Saarakkala et al. 2004, 2006), collagen orientation in the superficial layer of cartilage (Kiyan et al. 2017) and enzymatic digestion of collagen (Saarakkala et al. 2004). The wavefront is disturbed by the fibrillated cartilage surface, and the acoustic impedance approaches the surrounding medium by disrupting the collagen meshwork. These are assumed to lower the echo amplitude from the cartilage surface.

For subchondral bone, comparison of the histological evaluation and quantitative ultrasound findings revealed that IRC at the cartilage−subchondral bone (C-B) interface significantly increased in the degenerated osteochondral samples (Saarakkala et al. 2006). The apparent integrated backscatter (AIB) from the bone was negatively correlated with bone mineral density (BMD) of the subchondral plate (Aula et al. 2010). The AIB from the subchondral bone was also correlated with surface/volume ratio and trabecular thickness (Liukkonen et al. 2013). Thus, several studies have reported the sensitivity of IRC or AIB in determining the BMD of the subchondral bone plate or histological score. However, no report has investigated the relationships between ultrasound parameters and porosity at the surface of the subchondral bone plate, subchondral plate thickness or BV/TV in the trabecular region as microstructural characteristics. Ultrasound of lower frequency (<5 MHz) has been used to detect osteoporosis from a macroscopic point of view such (Hoffmeister et al. 2006; Karjalainen et al. 2009). However, focused ultrasound with high and broadband frequency, leading to high resolutions, might be efficient when the aim is limited to the detection of pores on the subchondral plate surface, subchondral plate thickness (Finnilä et al. 2017; Li et al. 1999; Milz et al. 1995) or BV/TV just beneath the subchondral plate with sub-millimeter measurements. Furthermore, pores at subchondral plate surface are expected to lower the echo intensity from the C-B interface locally. Internal microstructural characteristics of subchondral bone are also expected to disturb the scattered intensity from the subchondral plate−bone marrow interface because the subchondral plate is not a simple plane plate, but is complex with areas of the junction to trabecular bone. Therefore, parameters that reflect the spatial distribution of echo intensity might efficiently detect such microstructural changes in the subchondral bone. However, parameters of the distribution of the echo intensity for microstructural changes in the subchondral bone have not yet been investigated. In addition, AIB or IRC from bone is affected by attenuation of ultrasound in cartilage (Joiner et al. 2001). Parameters that are not affected by attenuation in cartilage or thickness of cartilage are needed to determine the microstructural characteristics of subchondral bone.

In this study, we sought to determine ultrasound parameters that reflect the microstructural changes in subchondral bone porosity (P_o), subchondral plate thickness (T_{pl}) and BV/TV at the trabecular area (BV/TV_{Tb}). We focused on detecting subchondral bone changes, not cartilage degeneration, especially in the early to mild stages of OA. For the ultrasound parameters, the IRC at the C-B interface and the AIB from the subchondral bone were evaluated. IRC at the C-B interface and AIB from the subchondral bone are expected to be influenced by the effect of attenuation through the cartilage. The degree of attenuation in the cartilage layer was considered equal for both IRC and AIB because they were attenuated from the same sound pathway in the overlying cartilage. Therefore, we also evaluated the difference between AIB and IRC, expecting tolerability of attenuation of ultrasound in cartilage. As indicators reflecting spatial distribution, we introduced texture parameters (Haralick et al. 1973) for detecting microstructural characteristics in subchondral bone. As reference measurements, P_o, T_{pl} and BV/TV_{Tb} were evaluated using micro-computed tomography (CT).

METHODS

Samples

The protocol used in the present study was approved by the National Hospital Organization, Kyoto Medical Center Review Board (Approval No. 09-31). Sixteen human knee osteochondral samples were obtained from 16 OA patients (age 76 ± 5 y: 12 females and 4 males) who underwent total knee arthroplasty. Samples were kept in the freezer at −80°C. Before the ultrasound measurements were taken, samples from the load-bearing region of lateral femoral condyles were cut to approximately 14×7 mm^2 (Fig. 1a) sections, left out to thaw and prepared for ultrasound measurements. Here, we focused on detecting the characteristics in normal to mild OA subchondral bone samples, excluding severely degenerated samples. Sixteen samples were visually judged as International Cartilage Repair Society (ICRS) grades 0−2 (Brittberg and Peterson 1998) by Y.N., who has been an orthopedic surgeon for more than 30 years. Five samples were graded as 0, nine as 1 and two as 2.

Ultrasound measurement system

The 3-D ultrasound scanning system consisted of a computer (NI PXIe-8133, National Instruments, Austin, TX, USA), a digitizer with 14-bit resolution and sampling frequency of 100 MHz (NI PXIe-5122, National Instruments), an X-Y stage, a stage controller (SHOT-202AM, Sigma Koki, Japan), a pulser-receiver