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The SPECTRA Collaboration OMERACT Working Group: Construct Validity of Joint Space Outcomes with High Resolution peripheral Quantitative Computed Tomography (HR-pQCT)

Running Title: JSW Construct Validity

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ABSTRACT

Objective: We assessed construct validity of high-resolution peripheral quantitative computed tomography (HR-pQCT) joint space outcomes by comparison with x-rays in rheumatoid arthritis patients.

Methods: In 43 patients, quantitative, volumetric, HR-pQCT measurements were compared with ordinal van der Heijde-Sharp scoring (vdH-S) in the 2nd and 3rd metacarpophalangeal joints.

Results: Ordinal logistic regression showed that joint space minimum, standard deviation and asymmetry by HR-pQCT were associated with vdH-S scores ($p < 0.05$). There was a considerable range in HR-pQCT measurements at vdH-S equal to 0.

Conclusions: HR-pQCT demonstrated construct validity outcomes and provides improved 3D visualization of joint space.

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INTRODUCTION

Patients with Rheumatoid Arthritis (RA) develop joint damage as a result of an immune process involving synovium and periarticular bone, which manifest radiographically as joint space loss (1,2). The importance of joint space narrowing on function has been demonstrated (3). Conventional radiographs (CR) remain a feasible standard in clinical practice and research, but have known limitations in resolution, sensitivity and responsiveness (4). X-ray scoring systems may be predisposed to floor and ceiling effects as significant progression is required for changes in ordinal scores, and scoring systems cannot demonstrate ongoing damage once the highest ordinal score has been achieved (5-7).

State-of-the-art high-resolution peripheral quantitative computed tomography (HR-pQCT) is a sensitive tool used in the assessment of metacarpophalangeal (MCP) joints to describe joint space width (JSW), erosion number and size as well as bone density and microarchitecture with high precision (8-11). JSW outcomes are calculated volumetrically using an operator-independent algorithm (12) and are minimally sensitive to positioning (13). However, to date no comparisons have been made between HR-pQCT and x-ray across the full range of joint damage scored on x-ray. To establish the construct validity of HR-pQCT-derived 3-dimensional volumetric JSW outcomes, according to the OMERACT 2.0 filter (14,15), a comparison with outcomes from CR is required. The purpose of this study was to compare HR-pQCT-derived outcomes of JSW with the radiographs evaluated using the joint space domain of the vdH-S scoring system.

METHODS

Study Design

43 patients who met the 2010 ACR/EULAR Classification for RA (16) were recruited for a larger study on the effects of biologic therapy on HR-pQCT outcomes. HR-pQCT scans were performed at the University of Calgary between 2014 and 2016 and conventional x-rays performed as standard of care were obtained from medical records. For this analysis, we paired an individual's HR-pQCT scan and x-ray, conducted within 2 months of each other. Therapy was maintained for 3 months prior to HR-pQCT scans and did not change between x-ray and HR-pQCT scans. All participants provided written informed consent prior to participation. Approval for all procedures was obtained by the Conjoint Health Research Ethics Board at the University of Calgary (REB 13-0743).

Conventional Radiography

CRs of the hands were scored using the van der Heijde-modified total Sharp score (vdH-S) score by a single experienced reader from Imaging Rheumatology International (Meersen, Netherlands) (17). Only the joint space domain from the 2nd and 3rd MCPs of the dominant hand was used for this analysis, to match the joints scanned by HR-pQCT. Joint space narrowing was scored as 0 = normal, 1 = focal, 2 = generalized (> 50% of original joint space left), 3 = generalized (< 50% of the original joint space left or subluxation) and 4 = bony ankylosis or complete luxation.

HR-pQCT Image Acquisition

HR-pQCT scans of 2nd and 3rd MCP joints of the participant's dominant hand were acquired. The hand was secured in a custom positioning device (XtremeCTII, Scanco Medical,

Brüttisellen, Switzerland) using an established protocol (18). We obtained a reference x-ray in the coronal plane, and a reference line was placed at the distal cortical surface of the 2nd metacarpal head. Beginning 3 mm distal to the reference line, a total of 30.6 mm was acquired in three 10.2 mm sections or "stacks" with a nominal isotropic resolution of 60.7 μm using manufacturer standard settings (68 kVp, 1470 μA, 43 ms integration time).

HR-pQCT Image Processing and Analysis

All image processing was conducted using Image Processing Language (IPL, Scanco Medical). The outer, periosteal surface of the 2nd and 3rd metacarpal and phalangeal bones were identified using an automated method (9,19). To segment bone from soft tissue, a Gaussian filter (sigma = 0.5, support = 1) and fixed global threshold (12% of maximum grey scale value) were applied. Each scan was evaluated for motion in each stack using the manufacturer's standard scoring system from 1-5. Scans that included a motion score of 4 or 5 were excluded.

Volumetric joint space was quantified using an algorithm developed by consensus from the Study grouP for eXtreme Computed Tomography in Rheumatoid Arthritis (SPECTRA) (12). 3D JSW including mean (JSW.Mean, mm), maximum (JSW.Max, mm), minimum (JSW.Min, mm), standard deviation (JSW.SD, mm), asymmetry (defined as JSW.Asymm = ratio of JSW.Max/JSW.Min, [1]) as well as volume (JSV, mm^3) were calculated. 2D cuts through the sagittal and coronal planes were automatically generated for visualization. A rheumatologist with HR-pQCT expertise reviewed all joints and scored for degree of luxation (none, subluxation, luxation) and bone-on-bone contact (yes, no).

Statistical Analyses

Data was visualized using strip charts to compare x-ray and HR-pQCT outcomes. Generalized estimating equations were used to obtain an estimate of the ability of HR-pQCT outcomes to predict CR scoring, and account for the correlation between joints within a participant. All statistical analyses were performed using R (v3.3) and RStudio (v1.0.136).

RESULTS

Demographics

Five joints were excluded due to motion artifact in the HR-pQCT scans. One joint was excluded due to inability of the algorithm to correctly define the joint space. The final dataset included 80 joints (40 2nd MCP and 40 3rd MCP) from 43 participants (34 female, 9 male). The participants had a mean age of 56 years (range 22 to 82 years, SD 13 years), and a mean disease duration of 12 years (range 0.5 to 39.1 years, SD 8.5 years). The mean time interval between x-ray and HR-pQCT acquisition was 1.5 weeks (range 0 to 9.1 weeks, SD 1.5 weeks).

Joint Space Width Results

Distribution of vdH-S scores for the 2nd and 3rd MCPs is shown in Table 1. Figure 1 shows the distribution of HR-pQCT measurements by vdH-S scores. More sub(luxations) were identified by HR-pQCT than x-ray. Bone-on-bone contact was observed in 5 joints on HR-pQCT, despite an absence of ankylosis observed on x-ray. Generalized estimating equation results indicate decreased JSW.Min, increased JSW.SD, and increased JSW.Asymm were

associated with increasing vdH-S ($p < 0.05$). However, no significant relationship was observed for JSW.Max, JSW.Mean or JSV ($p > 0.05$). Visual examples of congruent and incongruent HR-pQCT and vdH-S are shown in Figure 2.

DISCUSSION

Minimum joint space width, standard deviation and asymmetry assessed by HR-pQCT were correlated with the joint space domain of an x-ray scoring system. However, large variability for vdH-S scores across all quantitative outcomes confirms that the radiographic score is indeed an ordinal scale, and consequently progression would not be linear. The considerable number of subluxations, luxations and bone-on-bone contact observed with HR-pQCT, as well in previous studies using the current gold standard clinical computed tomography (20), suggests there may be a degree of subluxation and ankylosis that precedes detection of this damage on x-ray. Finally, it is difficult to interpret disease progression based on a single quantitative HR-pQCT outcome such as volume as there is a non-linear association with x-ray score. The relationship between these pathological manifestations and clinical and patient-reported outcomes needs to be further explored to understand how they relate to disease outcome.

HR-pQCT may provide advantages over x-ray for monitoring disease progression particularly in the context of clinical trials. HR-pQCT quantitative measurements appear less susceptible to floor and ceiling effects as there is a wide range of measurements in JSW.Min and JSW.SD when the ordinal score is assigned 0, and there is no maximum limit to SD and asymmetry outcomes. The quantitative nature of the analysis and sensitivity of the technique will allow observation of increases or decreases in joint space. Further,

automated image processing makes HR-pQCT outcomes less susceptible to reader interpretation.

A key limitation of HR-pQCT might be that fewer joints are accessible than in x-ray; however, focusing on the 2nd and 3rd MCP of the dominant hand somewhat comes by that limitation since these are the most commonly affected joints in RA. Although this cohort comprised participants with severe disease activity, the most common vdH-S score was 0. This is likely reflective of the general RA population where there is a need for more sensitive measures relevant to earlier stages of joint damage. Further, interpretation of volumetric joint space outcomes in sub(luxed) joints is a challenge, and whether progression in these highly damaged joints a) can be observed, and b) follow a similar quantitative pattern to less damaged joints needs to be determined in a longitudinal analysis. While our study used second generation HR-pQCT, the results should be directly applicable to first generation HR-pQCT, as the algorithm accounts for changes in spatial resolution and we have previously observed minimal difference between measurements of the same joints on both scanner generations. Finally, as the algorithm captures thickness of the joint space, joints with bone-on-bone contact typically correspond to a minimum width of one or two voxels rather than zero. There are plans to capture this bone-on-bone contact in the future, however, as the discrepancy between the current algorithm and the absolute minimum is smaller than our reproducibility error, this small discrepancy does not impact the results.

In summary, we have demonstrated aspects of construct validity for HR-pQCT against a well-established x-ray scoring system. As HR-pQCT provides 3D visualization of the joint that is not available using CR, its utility for assessing disease prior to evidence of radiographic joint space damage and with levels of significant joint space damage is

promising. Further longitudinal studies are planned to understand the sensitivity of HR-pQCT outcomes to change over a wide range of joint damage and repair.

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FIGURE LEGENDS

Figure 1. Comparison between volumetric joint space outcomes derived from HR-pQCT with van der Heijde modified Sharp joint space scores (vdH-S) from conventional x-rays for the 2nd and 3rd MCP (n = 80 joints from 43 participants).

Figure 2. Examples of 3D volumetric renderings of HR-pQCT scans and corresponding HR-pQCT outcomes across the range of van der Heijde modified Sharp joint space scores (vdH-S).

TABLE LEGEND

Table 1. Frequency of joint space narrowing scored using the van der Heijde modified Sharp (vdH-S) scoring system on conventional radiographs (n = 80 joints from 43 participants).