TITLE PAGE

Title: Understanding the use of thermography and its ability to predict ultrasound-detected joint inflammation at the metacarpophalangeal joint in patients with rheumatoid arthritis.

Authors

York Kiat Tan[1,2,3] , Philip G. Conaghan [4]

Author affiliation(s)

[1] Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

[2] Duke-NUS Medical School, Singapore

[3] Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[4] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK

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Thermal and US imaging of MCPJs in RA

Correspondence:

York Kiat Tan. Department of Rheumatology and Immunology, Singapore General Hospital, Outram Road, Singapore 169608. Email: tan.york.kiat@singhealth.com.sg.

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ABSTRACT

Objectives

To study the correlation of thermography with ultrasonography and whether thermography can help predict ultrasound-detected joint inflammation at the metacarpophalangeal joints (MCPJs) in patients with rheumatoid arthritis (RA).

Methods

Thermography recorded maximum (Tmax), average (Tavg) and minimum (Tmin) temperatures which were summed for the MCPJs of each hand, and their relationship with the summed power Doppler (PD) and grey-scale (GS) scores explored using correlation analysis and simple linear regression. The ability of the summed thermographic temperatures to predict summed PD score≥1 and summed GS score≥18 (median score) were studied using receiver operating characteristic (ROC) analysis. Intra-observer reliability (single observer) was analyzed using intra-class correlation coefficient (ICC).

Results

This cross-sectional study examined 810 joints from 81 RA patients. At both right and left MCPJs, all the summed thermographic temperatures correlated significantly ($P<0.05$) and had significant relationship ($P<0.05$) with the summed ultrasound scores (for PD and GS: correlation coefficients ranged from 0.45 to 0.52 and 0.26 to 0.29, respectively, while regression coefficients ranged from 0.094 to 0.137 and 0.058 to 0.086, respectively). At the bilateral MCPJs, the area under the ROC curves (AUCs) for the summed thermographic temperatures in predicting summed PD score≥1 and summed GS score≥18 ranged from 0.80 to 0.82 and 0.65 to 0.66, respectively. The ICC values (for 45 baseline MCPJs whose thermographic temperatures were re-segmented >2 weeks apart) were excellent (all >0.90).

Conclusions

Thermographic temperatures are reflective of ultrasound-detected joint inflammation, and appear useful in predicting PD vascularity at the MCPJs of patients with RA.

INTRODUCTION

Infrared thermography objectively quantify joint inflammation by detecting joint surface temperatures in patients with rheumatoid arthritis (RA) [1]. Thermography detects heat signatures overlying inflamed joints, although, unlike ultrasound, it does not directly visualize the inflamed synovium [1, 2] and bone erosions, nor does it differentiates the morphological substrate of the inflammatory process (synovitis, tenosynovitis, enthesitis, etc). Nonetheless, thermography has its own strengths/attributes making it a promising imaging modality for RA joint inflammation assessment. Firstly, thermography is non-invasive, requiring less training than ultrasonography for its operators [1, 3]. Image acquisition although simple, requires standardization (e.g ambient conditions) and subsequent timely image processing for consistent results. Moreover, there is a need to establish validated cut-off values for data interpretation. Secondly, modern handheld thermal cameras are compact and highly portable with quick image acquisition and digital readout which are easy/convenient to use in the rheumatologist office, and cost less than magnetic resonance imaging (MRI) and ultrasound machines [1, 3-5]. Finally, being contactless, thermography can potentially be used in remote telemedicine consultation whereby physical examination of patients is not possible [6]. These reasons provide a good rationale to explore thermography in assessing RA joint inflammation. In this study, the metacarpophalangeal joints (MCPJs) were chosen as these are commonly affected in patients with RA and hence representing a good model to study synovial inflammation. We aim to (1) study the correlation of thermography with ultrasonography and (2) whether thermography can help predict ultrasound-detected joint inflammation at the MCPJs of patients with RA.

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MATERIALS AND METHODS

This cross-sectional study conducted at the Singapore General Hospital was approved by the local institutional review board and conforms to the relevant research ethical guidelines. Patients fulfilling the

2010 RA classification criteria [7] and other recruitment criteria (Supplementary Table S1) were consecutively recruited from the hospital's rheumatology outpatient clinic. All patients provided written informed consent before enrolment.

Baseline patient characteristics

Patient characteristics obtained from their medical records were: 28-joint disease activity score (DAS28), age, ethnicity, sex, disease duration, medications use.

Imaging assessment

Ultrasonography and thermography were performed independently during the same patient study visit. Dorsal recesses of bilateral MCPJs 1-5 were scanned by a rheumatologist (>10 years of experience in musculoskeletal ultrasound) blinded to the findings from thermography. A Mindray M9 ultrasound machine (settings at Doppler frequency, 5.7 MHz and pulse repetition frequency, 700 Hz) and a L14-6Ns linear probe (frequency ranging from 6-14 MHz) set at 12 MHz was utilized for scanning. Ultrasonography followed the EULAR guidelines [8], while PD vascularity and GS synovial hypertrophy were scored separately and each graded semi-quantitatively (0-3) using validated scoring methods [9]. In our study which focuses on synovitis assessment, other structures (such as tendons, erosions or features of osteoarthritis like osteophytosis, etc) were not evaluated.

Thermography was performed by a trained study team personnel (blinded to ultrasonography's findings) in a standardized manner following established methods [1, 10, 11] using a high performance thermal camera (FLIR T865) with pixel resolution, 640 x 480, thermal sensitivity of <30 milli-Kelvin at 30°C and predefined emissivity value of 0.98 for skin [1]. Thermography was performed in a windowless draft-free room in a facility with central cooling system (with measured ambient temperature of around 23°C [10]).

Patients were acclimatized by being rested for 15 minutes before starting thermography [1, 10]. Physical objects blocking the thermal camera's view were removed. The dorsal aspect of each hand was imaged by placing the thermal camera 50cm directly above the hand which was placed on a flat tabletop. Following the commonly utilized region of interest (ROI) manual segmentation approach [1, 11] (Supplementary Figure S1), the maximum (Tmax) average (Tavg) and minimum (Tmin) temperatures were obtained from the ROIs of the MCPJs per hand thermogram.

Statistical analysis

The maximum (Tmax), average (Tavg) and minimum (Tmin) temperatures were respectively summed at the MCPJs per hand and compared with the summed PD and GS scores. Correlation analysis was performed using the Spearman's correlation coefficient while relationship between variables were analysed using simple linear regression. At the bilateral MCPJs 1-5, the ability of the summed thermographic temperatures to predict summed PD score≥1 and summed GS score≥18 (median score) were studied using receiver operating characteristic (ROC) analysis. Without general consensus on what constitutes a higher or lower GS inflammatory burden at the bilateral MCPJs 1-5, the median (50^{th} percentile) summed GS score was arbitrarily used as a cut-off to categorize them into two groups: those with a higher summed GS score versus those with lower summed GS scores. For the ROC analysis, the 'Closest to Top Left' method was applied to determine the optimal cut-off which was used to obtain the corresponding sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV). Forty-five MCPJ ROIs were manually re-segmented (>2 weeks apart) from a subset of baseline thermograms and the intra-observer reliability (single observer) tested using the intra-class correlation coefficient (ICC). ICC results interpretation are [12]: low (<0.40), moderate (0.40-0.74), substantial (0.75-0.90) and excellent (>0.90). Statistical analyses were performed using SPSS version 26 statistical software.

RESULTS

Baseline patient characteristics

Eighty-one patients had 810 joints examined. 53 patients were Chinese (65.4%) and 59 patients were female (72.8%). The mean (SD) age, disease duration and DAS28 were 54.9 (14.4) years, 7.3 (6.3) months and 3.7 (1.3), respectively. See supplementary Table S2 (baseline DAS28 subcomponents and medications use).

Correlation analysis

At the right and left MCPJs, all summed thermographic temperatures correlated significantly ($P<0.05$) with the summed ultrasound scores (Table 1) although the correlation appears stronger for the summed PD score (correlation coefficients ranged from 0.45-0.52) when compared to the summed GS score (correlation coefficients ranged from 0.24-0.29).

Regression analysis

At the right and left MCPJs, a significant relationship ($P<0.05$) was demonstrated between all summed thermographic temperatures (Table 2) and the summed ultrasound scores. For the summed PD score, the regression coefficients ranged from 0.094-0.137. For the summed GS score, the regression coefficients ranged from 0.058-0.086.

ROC analysis

For the bilateral MCPJs, the area under the ROC curves (AUCs) values were higher for the summed thermographic temperatures when used in predicting summed PD score≥1 (AUC ranged from 0.80-0.82)

than when used in predicting summed GS score≥18 (AUC ranged from 0.65-0.66). The cut-off values, SN, SP, PPV and NPV results are summarized in Table 3.

Intra-observer reliability

The ICC values (single observer) for 45 manually re-segmented MCPJ ROIs were high: ICC (95% CI) of Tmax, Tavg and Tmin were 0.9994 (0.9990-0.9997), 0.9996 (0.9993-0.9998) and 0.9990 (0.9980-0.9993), respectively.

DISCUSSION

In this study, we have shown that thermographic temperatures were reflective of ultrasound-detected joint inflammation, demonstrating stronger association with PD versus GS joint inflammation. The summed thermographic temperatures at the MCPJs perform well (with AUC≥0.8) in identifying PD vascularity, a key component of ultrasound-detected joint inflammation [4, 13].

There have been limited studies evaluating the performance of thermography in discriminating RA joint inflammation severity/disease activity [1]. A small scale RA hands/wrists study demonstrated higher thermographic temperatures in PD positive joints and GS positive joints, although discriminating ultrasound-detected joint inflammation severity using thermography were not assessed [11]. Morales-Ivorra et al [14] demonstrated that a joint inflammation score based on computational analysis of hand thermal images can help identify patients (31 RA patients at baseline) who transited (over 3 months) from 28-swollen joint count (28-SJC) >1 to 28-SJC ≤1 (with AUC result of 0.71). Triantafyllias et al [15] evaluated a high-resolution thermography marker (utilizing the Hotspot/ROI-Ratio (HRR)-values) and demonstrated an AUC of 0.72 in discriminating between 267 finger joints (from 30 patients with mixed

inflammatory arthritis) with and without PD score≥1 and GS score>0. The above three studies [11, 14-15] and our study suggest that thermography is promising in assessing RA hand joint inflammation.

Our study has limitations. It has a cross-sectional design, hence future longitudinal study with thermography performed at multiple time-point will be necessary to explore its responsiveness. The focus on MCPJs in our study limits the generalizability of our findings (e.g. to other joint types). Future studies will be needed to explore the use of thermography at various other joint sites especially given thermography's ability to assess multiple joints simultaneously. We analysed the intra-observer reliability of thermography for a single observer. Subsequent RA studies with >1 observers will be necessary to assess inter-observer reliability. We utilized an ROI manual segmentation approach for thermography. We envisage research innovation enabling computer-assisted automated detection to help advance this technology for remote RA telemedicine consultation. We did not split our data into smaller subgroups to compare thermography with ultrasonography based on clinical joint status (e.g. in patients with ≥1 swollen joint). This is an important topic for future research and subsequent larger scale RA studies will be required to evaluate this aspect. In our study, we did not include a control group. Future studies should ideally incorporate a control group (e.g. healthy subjects) for comparative analysis.

In conclusion, we have demonstrated that thermographic temperatures at the MCPJs were reflective of ultrasound-detected joint inflammation (with stronger association with PD versus GS joint inflammation), and appear useful in predicting PD vascularity in RA patients.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

Data are available from the corresponding author upon reasonable request.

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Table 1. Correlation analysis of thermography versus ultrasound variables

Thermographic parameter	Summed PD score		Summed GS score	
	Correlation coefficient	P-value	Correlation coefficient	P-value
Right first to fifth MCPJs				
Summed Tmax	0.52	<0.001	0.26	0.020
Summed Tavg	0.52	<0.001	0.26	0.019
Summed Tmin	0.50	<0.001	0.24	0.031
Left first to fifth MCPJs				
Summed Tmax	0.51	<0.001	0.29	0.008
Summed Tavg	0.50	<0.001	0.27	0.015
Summed Tmin	0.45	<0.001	0.24	0.032

Abbreviations: PD, power Doppler; GS, grey-scale; Tmax, maximum temperature; MCPJs, metacarpophalangeal joint; Tavg, average temperature; Tmin, minimum temperature.

Table 2. Comparing relationship between thermography and ultrasound variables

Thermographic parameter	Summed PD score		Summed GS score	
	β Coefficient (95% CI)	P-value	β Coefficient (95% CI)	P-value
	Right first to fifth MCPJs			
Summed Tmax	0.100 (0.050, 0.150)	<0.001	0.062 (0.010, 0.114)	0.021
Summed Tavg	0.103 (0.053, 0.153)	<0.001	0.063 (0.011,0.115)	0.019
Summed Tmin	0.094 (0.044, 0.143)	<0.001	0.058 (0.006, 0.109)	0.029
	Left first to fifth MCPJs			
Summed Tmax	0.135 (0.080-0.190)	<0.001	0.086 (0.032, 0.139)	0.002
Summed Tavg	0.137 (0.083, 0.192)	<0.001	0.081 (0.027, 0.134)	0.004
Summed Tmin	0.120 (0.067, 0.173)	<0.001	0.072 (0.021, 0.123)	0.007

Abbreviations: PD, power Doppler; GS, grey-scale; Tmax, maximum temperature; MCPJs, metacarpophalangeal joint; Tavg, average temperature; Tmin, minimum temperature.

Table 3. Use of thermographic parameters in identifying ultrasound joint-inflammation severity/activity

Thermo-graphic parameter	AUC (95% CI)	Cut-off[a]	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative Predictive value (%)
Bilateral first to fifth MCPJs (in identifying summed PD score≥1)						
Summed Tmax	0.82 (0.72, 0.92)	316.8	84.7	68.2	87.7	62.5
Summed Tavg	0.81 (0.70, 0.92)	306.7	79.7	68.2	87.0	55.6
Summed Tmin	0.80 (0.69, 0.92)	299.5	78.0	72.7	88.5	55.2
Bilateral first to fifth MCPJs (in identifying summed GS score≥18)						
Summed Tmax	0.65 (0.53, 0.77)	318.7	76.7	44.7	61.1	63.0
Summed Tavg	0.66 (0.54, 0.78)	310.5	69.8	52.6	62.5	60.6
Summed Tmin	0.66 (0.54, 0.78)	302.2	69.8	52.6	62.5	60.6

Abbreviations: AUC, area under the receiver operating characteristic curve; MCPJs, metacarpophalangeal joint, PD, power Doppler; GS, grey-scale; Tmax, maximum temperature; Tavg, average temperature; Tmin, minimum temperature. [a]Cut-off determined using the 'Closest to Top Left' method.