

Usefulness of cortical thickness ratio of the third metacarpal bone for prediction of major osteoporotic fractures

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ABSTRACT

Objective: Patients with rheumatoid arthritis (RA) are at high risk for osteoporotic fractures. We developed an index called the third metacarpal cortical thickness ratio (CTR), which reflects bone mineral density (BMD) in RA patients. A longitudinal study was conducted to verify the usefulness of CTR during the follow-up period.

Methods: Patients with RA who underwent dual energy X-ray absorptiometry (DXA) and hand X-ray simultaneously were monitored for disease activity and activities of daily living at 3-month intervals, and BMD and CTR were measured at 1-year intervals. Mean CTR during follow-up was tested for correlation with mean BMD at both the lumbar spine (LS) and femoral neck (FN) during follow-up. Correlations were examined, including other variants potentially correlated with BMD. The risk ratio of accidental major osteoporotic fractures (MOF) in the variance including CTR and BMD was evaluated.

Results: A total of 300 patients, 40 men and 260 women, were enrolled. Mean follow-up length was 49.6 months. CTR was significantly associated with BMD in FN using a multivariate model of linear regression analysis ($p < 0.0001$), whereas CTR was significantly associated with BMD in LS using only a univariate model ($p < 0.01$). The only variant with a significantly higher risk ratio for incident MOF was the presence of prevalent MOF. CTR and BMD did not show a significantly higher risk ratio using Cox regression analysis.

Conclusion: CTR correlated significantly with BMD even during follow-up, especially in FN. However, CTR and BMD were not risk factors for major MOF.

1. Introduction

Patients with rheumatoid arthritis (RA) are at high risk for osteoporotic fractures (Hooymans et al., 1984; Hall et al., 1993; Haugeberg et al., 2000; Huusko et al., 2001; Lodder et al., 2004; van Staa et al., 2006; Güler-Yüksel et al., 2009; Kim et al., 2010; Brennan et al., 2014; Heidari and Roushan, 2012; Sung, 2017). These risks include chronic persistent inflammation (Cortet et al., 2000), joint contractures (Haugeberg et al., 2000; Furuya et al., 2013), undernutrition (Gosch et al., 2012), glucocorticoid steroids administration (Cortet et al., 2000; Furuya et al., 2013; Kanis et al., 2004), and the presence of anti-citrullinated polypeptide antibodies (ACPA) (Amkreutz et al., 2021). All these risks cause bone fragility and increased ability to fall. Thus, having RA is an independent and strong risk of osteoporotic fractures.

One of the recently proposed X-ray markers is the cortical thickness ratio (CTR) of the third metacarpal bone (Yoshii and Akita, 2020). This index strongly correlates with bone mineral density (BMD) at both the lumbar spine (LS) and femoral neck (FN), and CTR may serve as an alternative index for measuring BMD by dual-energy X-ray absorptiometry (DXA). However, the CTR has not examined the association with the development of significant major osteoporotic fractures (MOF), including vertebral, hip, humeral, and wrist fractures. Using single-center retrospective cohort data, we sought to evaluate the relationship between CTR and incident MOF.

2. Materials and methods

RA patients with bilateral hand radiographs and simultaneous BMD

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with DXA measurements from April 2013 to September 2017 were selected. The diagnosis of RA is based on the clinical record of whether clinical features met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA (Aletaha et al., 2010). Patients were treated for RA according to a treatment-target (T2T) strategy and were followed until termination, loss of follow-up, or end of study at the time of the first fracture or death. A T2T treatment strategy means treating the patient as a potential target for clinical remission using the Brief Disease Activity Index (SDAI) within 6 months of initiation (Smolen et al., 2010). During follow-up, patients' SDAI and Health Assessment Questionnaire Disability Index (HAQ) were monitored at least 3 months apart. Sharp/van der Heijde Score (SHS) and CTR were calculated from radiographs at annual intervals, and BMD of LS and FN was also measured by DXA at annual intervals. Baseline was set as the first calculation date for CTR and the study's primary outcome was set as the appearance of incident MOF collected from medical record.

2.1. Republished: measurement and calculation of CTR

Measurement and calculation of CTR are as follows; Cortical thickness was calculated from the mid-portion of the 3rd metacarpal bone in the dominant hand from X-ray pictures taken for the calculation of SHS, with the bone diameter of the third metacarpal bone from the transverse diameter taken at the same point. We set the CTR as the cortical diameter relative to the transverse diameter (Fig. 1). These procedures were performed manually by one physician and double-checked by another physician.

2.2. Preliminary study: CTR, SHS, and BMD distribution and its change in follow-up period calculation

Calculation of CTR was repeated when X-ray picture of the hand was taken. Mean value, range of the CTR at follow-up divided by the CTR at baseline and mean standard deviation of CTR at follow-up for each patient were also calculated. Same calculations were performed in regard with SHS and BMD in both parts as well.

2.3. Independent variant selection

Independent variables in regard with potential osteoporotic likelihood risk such as female gender, older age, longer disease duration, ACPA positivity, rheumatoid factor (RF) positivity, higher SHS, higher SDAI score, higher HAQ score, lower BMD in LS, lower BMD in FN, lower CTR, presence of lifestyle-related diseases (LSD) (Sugimoto et al., 2016), presence of hyper fall-ability (Kersch-Schindl, 2016), chronic kidney diseases (CKD) \geq Stage3a (Kim et al., 2016), presence of cognitive impairment (Ebrahimpur et al., 2020), administration of anti-osteoporotic drug, administration of glucocorticoid steroid, and rehabilitation interventions including strength training, were selected in the study. Diagnosis of LSDs including type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, chronic heart failure, and insomnia, were made by the authors, who are specialists certified by the Japanese Society of Internal Medicine, and diagnosis of hyper fall-ability inducing diseases such as musculoskeletal ambulation disability complex, osteoarthritis of the lower extremities, joint contractures of the trunk or lower extremities, disuse syndrome, parkinsonism, and neuromuscular disorders, were made by the authors, who are specialists certified by the Japanese Orthopaedic Association. Cognitive impairment was diagnosed by the specialists who are certified by the Japanese Society of Psychiatry and Neurology.

2.4. Association between BMD and CTR study

Association between CTR and mean values of independent variables including BMS in LS and FN at follow-up was evaluated statistically using linear regression analysis. Association between BMD and independent variants including CTR was also evaluated with a same manner. BMDs were evaluated for both LS and FN.

2.5. Association between incident osteoporotic fracture and risk factors study

Risk ratios of incident osteoporotic fracture occurrence for the independent variables including CTR and BMDs in LS and FN were evaluated using Cox regression analysis.

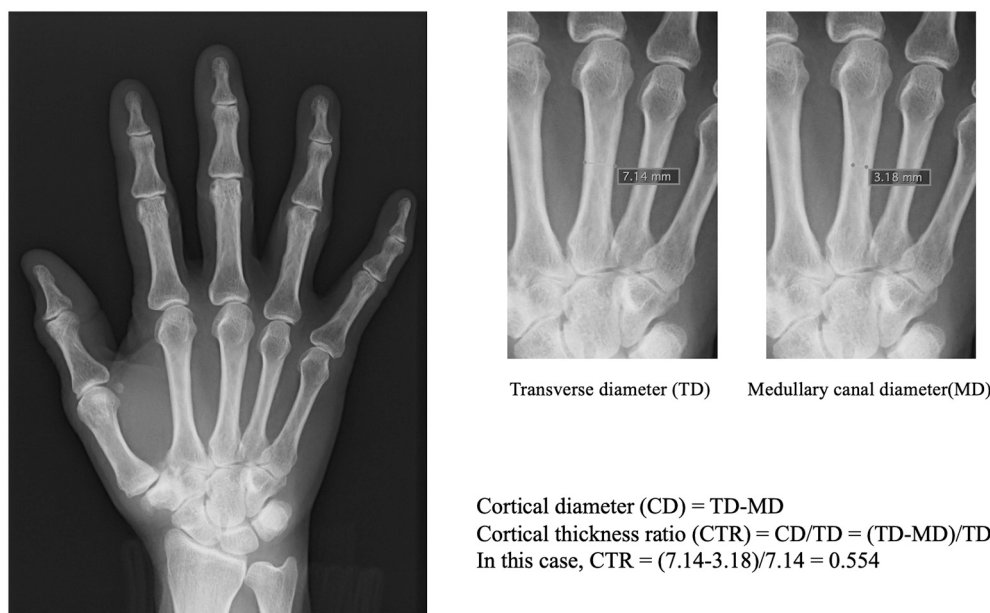


Fig. 1. Calculation of CTR.

The calculation procedure for CTR is shown. The transverse diameter (TD) of the third metacarpal bone in the mid-portion was calculated. In addition, the medullary canal diameter of the bone (MD) was calculated from the same place. Then the diameter of the cortical bone (CD) was calculated as TD-MD. The CTR is the CD divided by TD, which equals (TD-MD)/TD.

$$\begin{aligned} \text{Cortical diameter (CD)} &= \text{TD} - \text{MD} \\ \text{Cortical thickness ratio (CTR)} &= \text{CD} / \text{TD} = (\text{TD} - \text{MD}) / \text{TD} \\ \text{In this case, CTR} &= (7.14 - 3.18) / 7.14 = 0.554 \end{aligned}$$

2.6. Statistical procedures

We identified significant correlated factors within 5% in univariate models and evaluated multivariate model of these factors in both statistical analyses. All statistical analyses were performed using StatPlus: mac® (AnalystSoft, Inc., Walnut, CA, USA).

3. Results

A total of 300 patients, in these 40 male and 260 female included, were picked up in the study. Average age at first X-ray of the hand was 74.0 (SD: 10.8) year-old, disease duration at baseline was 7.4 (8.7) years, mean length of follow-up period was 49.6 (23.7) months. Mean SDAI score and HAQ score at baseline were 6.42 (8.29) and 0.561 (0.653), respectively. Background demographic characteristics of the subjects were shown in Table 1.

3.1. Preliminary study

CTR, SHS, and BMD in LS and FN at baseline were 0.275 (0.118), 59.7 (73.1), 0.871 (0.206) g/cm², and 0.695 (0.146) g/cm², respectively. Mean values of CTR, SHS, and BMD in LS and FN at follow-up were 0.275 (0.117), 58.1 (68.2), 0.853 (0.184), and 0.666 (0.126),

Table 1
Patients background and demographic characteristics.

Cases	300
Female (%)	260 (86.7)
Age at baseline	74.0 (10.8)
Disease duration at baseline, years	7.4 (8.7)
ACPA positivity (%)	211 (73.2)
Follow-up length, months	49.6 (23.7)
At baseline	
RF, IU/mL	96.8 (213.5)
SHS	59.7 (73.1)
SDAI	6.42 (8.29)
SDAI remission rate	51.8%
HAQ	0.561 (0.653)
Presence of LSD (%)	223 (74.0)
Presence of fall-ability (%)	182 (60.7)
CKD ≥ Stage3a (%)	73 (24.3)
Presence of cognitive impairment (%)	26 (87.1)
BMD in LS, g/cm ²	0.871 (0.206)
BMD in FN, g/cm ²	0.695 (0.146)
CTR	0.275 (0.118)
Prevalent osteoporotic fracture (%)	151 (50.3)
At follow-up	
RF, IU/mL	102.1 (228.6)
SHS	58.1 (68.2)
SDAI	4.11 (3.86)
SDAI remission rate	53.4%
HAQ	0.517 (0.593)
BMD in LS, g/cm ²	0.853 (0.184)
BMD in FN, g/cm ²	0.666 (0.126)
CTR	0.275 (0.117)
Incident osteoporotic fracture (%)	47 (15.7)
Anti-osteoporotic drug administration, ever ^a	239 (79.7)
Romozumab administration during follow-up (%)	11 (3.7)
Teriparatide administration during follow-up (%)	21 (7.0)
Denosumab administration during follow-up (%)	155 (51.7)
Glucocorticoid steroid administration, ever (%)	164 (54.7)
Glucocorticoid steroid administration during follow-up (%)	139 (46.3)
Mean glucocorticoid steroid dosage during follow-up, mg/day	4.4 (5.6)
Biologic or targeted synthetic DMARD administration, ever (%)	116 (38.7)
Rehabilitation interventions, ever (%)	134 (44.7)

The values are presented as mean (SD) unless indicated otherwise.

In the other, number of cases and percentage are presented.

Abbreviations: ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; SHS, Sharp/van der Heijde score; SDAI, simplified disease activity index; HAQ, Health Assessment Questionnaire Disability Index; LSD, lifestyle-related diseases; CKD, chronic kidney diseases; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; CTR, cortical thickness ratio.

^a Anti-osteoporotic drugs included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romozumab.

respectively, whereas difference between maximum and minimum values of CTR, SHS, and BMD in LS and FN at follow-up divided by each value at baseline were 3.0%, 7.0%, 7.8%, and 7.8%, respectively. Mean standard deviation of CTR, SHS, and BMD in LS and FN divided by each parameter value at baseline were 2.1%, 5.5%, 4.3%, and 4.1%, respectively (Table 2).

3.2. Association between BMD and CTR study

CTR correlated significantly with BMD in LS and FN using univariate models, however BMD in FN only significantly correlated using multivariate model. For the other variables, CTR significantly correlated negatively with older age, longer disease duration, higher SHS, and higher HAQ score, whereas significantly correlated negatively with older age and higher SHS using multivariate model. BMD in LS significantly correlated negatively with female gender, prevalent osteoporotic fracture, and anti-osteoporotic drug administration using multivariate model, whereas BMD in FN significantly correlated negatively with older age and anti-osteoporotic drug administration except of CTR. p-Values in detail are shown in Table 3.

3.3. Association between incident osteoporotic fracture and risk factors study

Using a Cox regression analysis, significantly higher risk ratio of incident osteoporotic fracture demonstrated significantly for older age, presence of LSD, presence of CKD ≥ Stage3a, presence of cognitive impairment, lower BMD in FN at follow-up, presence of prevalent osteoporotic fracture at baseline, and rehabilitation interventions including strength using univariate models, whereas prevalent osteoporotic fracture at baseline was the only variant that had significant higher risk ratio using multivariate model (Table 4).

4. Discussion

CTR was developed in order to indirectly estimate the BMD even in the clinic without the BMD measuring device such as DXA, if there was an index which reflects the BMD by the roentgenogram without depending on the DXA measurement. In the paper in the development, CTR recognized the strong correlation with the BMD especially in FN, and it was verified even in present study.

In the present study, we measured the time course of CTR and found the least change among CTR, BMD, and SHS. Though CTR is a manual measurement method and its consistency is feared, the result with the least change seems to be evidence that CTR is an index with high reproducibility. CTR was measured by one physician and verified by another physician. This method can reduce the intra-observer variation. This suggests the possibility of estimating the degree of bone density to some extent by measuring CTR. In the future, when it becomes possible to measure CTR using AI, it is expected that the index which shows no difference by manual measurement will become an index reflecting BMD.

CTR was measured in 300 of 576 RA patients, but not in the remaining 276 patients because BMD was not measured. The CTR can be calculated by hand radiography, because even if the patient has flexion contracture, the morphologic ratio does not change depending on the angle difference.

The result of multivariate linear regression analysis showed that CTR had a strong inverse correlation with SHS. There was a strong correlation between CTR and femoral neck, and also a significant correlation with age. It was indicated that the possibility in which CTR also reflected the degree of the joint deformation was high on this fact.

However, neither CTR nor BMD in LS showed a significantly higher risk ratio for the development of incident osteoporotic fracture even using univariate model Cox regression analysis. Significant higher risk ratio was found in older age, presence of LSD, CKD ≥ Stage3a, presence

Table 2

Mean value at baseline and at follow-up, range from maximum to minimum value per baseline value, and standard deviation in values at follow-up of CTR, SHS, and BMD in LS and FN.

Variables	At baseline		At follow-up			
	Mean value	Mean value	Mean maximum value	Mean minimum value	Mean value range per value at baseline	Mean SD at follow-up per value at baseline
CTR	0.275 (0.118)	0.275 (0.117)	0.278 (0.117)	0.271 (0.117)	3.0%	2.1%
SHS	59.7 (73.1)	58.1 (68.2)	59.7 (69.0)	56.3 (66.7)	7.0%	5.5%
BMD in LS	0.871 (0.206)	0.853 (0.184)	0.893 (0.189)	0.807 (0.183)	7.8%	4.3%
BMD in FN	0.695 (0.146)	0.666 (0.126)	0.701 (0.133)	0.634 (0.129)	7.8%	4.1%

Abbreviations: CTR, cortical thickness ratio; SHS, Sharp/van der Heijde score; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck.

Table 3

p-Value of variables in correlation with CTR and BMDs.

Independent variables	CTR		BMD in LS		BMD in FN	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Female gender	0.16		2.6×10^{-4}	2.2×10^{-3}	0.16	
Age	2.4×10^{-7}	9.0×10^{-5}	0.96		2.4×10^{-7}	7.9×10^{-3}
Disease duration	3.6×10^{-4}	0.88	0.60		0.17	
ACPA positivity	0.11		1.1×10^{-4}	0.45	2.0×10^{-5}	0.44
RF	0.29		0.96		0.46	
SHS	2.8×10^{-4}	2.2×10^{-2}	0.95		1.8×10^{-2}	0.20
SDAI	6.7×10^{-2}		0.17		3.1×10^{-2}	0.61
HAQ	6.9×10^{-3}	0.31	0.92		2.2×10^{-4}	0.55
Presence of LSD	0.16		3.8×10^{-4}	0.63	3.0×10^{-5}	0.27
Presence of fall-ability	0.16		4.1×10^{-4}	0.14	3.0×10^{-5}	0.14
CKD \geq Stage3a	0.14		4.8×10^{-4}	0.51	3.0×10^{-5}	0.18
Presence of cognitive impairment	8.0×10^{-2}		7.9×10^{-4}	0.76	1.0×10^{-5}	0.42
CTR	–	–	2.9×10^{-3}	0.29	1.2×10^{-11}	6.0×10^{-5}
BMD in LS	2.9×10^{-3}	0.98	–	–	–	–
BMD in FN	1.2×10^{-11}	3.6×10^{-4}	–	–	–	–
Prevalent osteoporotic fracture	0.12		2.0×10^{-4}	3.7×10^{-2}	8.7×10^{-6}	7.1×10^{-2}
Incident osteoporotic fracture	0.17		2.9×10^{-4}	0.58	9.2×10^{-6}	0.21
Anti-osteoporotic drug administration, ever ^a	0.15		2.7×10^{-4}	2.4×10^{-2}	2.0×10^{-5}	9.3×10^{-3}
Glucocorticoid steroid administration, ever	0.11		3.5×10^{-4}	0.29	2.0×10^{-5}	0.85
Rehabilitation interventions, ever	0.33		0.27		0.69	
R	0.53		0.35		0.58	
p-Value	1.6×10^{-10}		6.0×10^{-3}		3.4×10^{-10}	

Abbreviations: CTR, cortical thickness ratio; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; SHS, Sharp/van der Heijde score; SDAI, simplified disease activity index; HAQ, Health Assessment Questionnaire Disability Index; LSD, lifestyle-related diseases; CKD, chronic kidney diseases.

R and p-value are presented correlation coefficients and statistical significance of equation.

Bold styles are presented significant correlation.

Italic styles are presented negative correlation.

^a Anti-osteoporotic drugs included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab.

of cognitive impairment, lower BMD in FN, presence of prevalent osteoporotic fracture, and rehabilitation interventions using univariate models, and prevalent osteoporotic fracture remained as a only factor with significantly higher risk ratio using multivariate model. Because CTR correlated with older age and BMD in FN significantly, the significance was absorbed in these variables, and it seemed to be weak as an independent risk factor.

Although there was no direct correlation for the subjects of this study, it was surprising that rehabilitation intervention showed a significantly higher risk ratio for the development of osteoporotic fractures. Rehabilitation interventions have been used in patients whose mobility has decreased to the required level of rehabilitation, and are presumed to be ineffective. Since there was a significant negative correlation between the administration of anti-osteoporotic drugs and BMD, it was considered that anti-osteoporotic drugs were administered to patients with a history of osteoporotic fracture and relatively low BMD in both LS and FN.

The study was limited to a single-center study, no asymptomatic/morphometric fractures inclusion, and the possibility of other

confounding factors could not be ruled out, with an average observation period of less than 4 years and relatively short. However, it is undoubtedly true that the CTR is strongly correlated with BMD, and the fact that the same findings were obtained at follow-up demonstrates the high reliability and reproducibility of the CTR.

In conclusion, CTR significantly correlates with BMD in FN, and negatively correlates with older age and higher SHS. However, CTR is not suitable as a predictive marker for incident osteoporotic fracture. Even BMD does not function as a predictive marker for incident osteoporotic fracture. The presence of prevalent osteoporotic fracture is the only predictive risk factor for the development of osteoporotic fracture.

Ethics approval

This study was approved by Yoshii Hospital ethics committee (approval number: Y-RA-2021-1) in accordance with the ethical standards laid down in 1964 Declaration of Helsinki and its later amendments. In addition, anonymity was ensured for all patients and their families who participated in this study, and no names, and/or addresses

Table 4
Results of Cox regression analysis.

Variables	Univariate	Multivariate	
	p-Value	p-Value	Risk ratio (95% CI)
Female gender	0.48		
Older age	1.2×10^{-3}	0.77	1.01 (0.97–1.05)
Disease duration	0.48		
ACPA positivity	0.35		
RF	0.16		
SHS	0.26		
SDAI	0.15		
HAQ	5.7×10^{-2}		
Presence of LSD	2.0×10^{-3}	0.42	4.04 (0.53–30.84)
Presence of fall-ability	5.3×10^{-2}		
CKD \geq Stage3a	2.0×10^{-2}	0.28	1.44 (0.75–2.75)
Presence of cognitive impairment	4.4×10^{-3}	0.29	1.64 (0.65–4.17)
CTR	0.71		
BMD in LS	0.28		
BMD in FN	1.0×10^{-3}	9.2×10^{-2}	0.13 (0.01–1.39)
Prevalent major osteoporotic fracture	2.0×10^{-5}	1.8×10^{-3}	4.96 (1.81–13.58)
Anti-osteoporotic drug administration, ever ^a	0.11		
Glucocorticoid steroid administration, ever	0.12		
Rehabilitation interventions, ever	1.1×10^{-3}	0.12	1.62 (0.88–3.00)

Abbreviations: ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; SHS, Sharp/van der Heijde score; SDAI, simplified disease activity index; HAQ, Health Assessment Questionnaire Disability Index; LSD, lifestyle-related diseases; CKD, chronic kidney diseases; CTR, cortical thickness ratio; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck.

^a Anti-osteoporotic drugs included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab.

were issued that could help identify these individuals.

Declaration of competing interest

Ichiro Yoshii, Naoya Sawada, Tatsumi Chijiwa and Shohei Kokei declare that they have no conflict of interest. And their families have nothing to declare for this study.

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