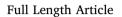
Contents lists available at ScienceDirect

Human Movement Science

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



Sex differences in three-dimensional talocrural and subtalar joint kinematics during stance phase in healthy young adults



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ARTICLE INFO

Keywords: Joint kinematics Talocrural joint Subtalar joint Walking Sex difference

ABSTRACT

The ankle joint, including the talocrural and subtalar joints, plays an important role in human locomotion. Sex differences in walking patterns among young and old adults have been studied; however, little information exists on sex-based variations in talocrural and subtalar joint kinematics during walking. Thus, the purpose of this study was to investigate sex-based differences in the talocrural and subtalar joint kinematics during walking.

We obtained lateral fluoroscopic images from 10 male and 7 female healthy volunteers during stance phase, and determined the three-dimensional bone orientations using 3D-2D model-image registration techniques to compare sex-specific differences.

The orientation of the tibia, talus, and calcaneus were comparable in the static reference position. Sex-based differences in the range of motion were observed in talocrural dorsi/plantar flexion, subtalar eversion/inversion and subtalar external/internal rotation while walking. The ranges of motion in talocrural dorsi/plantar flexion (male, $13 \pm 4^{\circ}$; female, $17 \pm 3^{\circ}$), subtalar eversion/inversion (male, $8 \pm 3^{\circ}$; female, $11 \pm 3^{\circ}$) and subtalar external/internal rotation (male, $5 \pm 2^{\circ}$; female, $7 \pm 2^{\circ}$) were significantly larger in females than in males.

Differences in rearfoot kinematics between males and females may reflect anatomic, physiologic and locomotor differences. Greater bone rotations in the female hindfoot may predispose women to different pathologies, or merit different treatments, than men based upon subtalar and talocrural kinematics during gait.

1. Introduction

The synergistic movement of the ankle joint, including the talocrural and subtalar joints, is crucial for human locomotion. Walking is an essential daily activity that habitually loads the joints of the lower extremities and likely contributes to the development and progression of joint degeneration such as osteoarthritis. Therefore, accurate knowledge of the kinematics during walking can contribute to understanding of the etiology of lower extremity joint degeneration.

Sex differences in walking patterns and ankle motion among young and old adults have been reported. Young healthy females tended to have shorter stride length, slower gait speed (Cho, Park, & Kwon, 2004), and greater ankle flexion/extension range of motion (ROM) (Bruening, Frimenko, Goodyear, Bowden, & Fullenkamp, 2015) compared to healthy young men while walking at self-

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https://doi.org/10.1016/j.humov.2018.06.003

Received 5 September 2017; Received in revised form 19 April 2018; Accepted 1 June 2018

Available online 04 August 2018

Abbreviations: ROM, Range of motion; BMI, Body mass index; ANOVA, Analysis of variance; CT, Computed tomography; ICC, Interclass correlation coefficient

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selected speeds; additionally, elderly women walked with less hip ROM and greater ankle ROM than elderly men (Boyer, Beaupre, & Andriacchi, 2008; Ko, Tolea, Hausdorff, & Ferrucci, 2011), and adult females ranging from 23 to 62 years old had more plantar flexion at toe-off and early swing than males (Roislien et al., 2009). Despite this knowledge of sex-based kinematic differences in gross motion while walking, it is unknown whether sex-based differences exist specifically in talocrural and subtalar joint kinematics during walking. Sex-based differences in walking mechanics could lead to differences in the occurrence of certain diseases and/or degeneration related to aging (Boyer et al., 2008). For example, ankle osteoarthritis is more frequent in males than in females (Cushnaghan & Dieppe, 1991; Koepp et al., 1999). Deeper understanding of such sex differences might offer insight into the design of interventions to maintain normal gait or prevent mobility limitations (Ko et al., 2011). Thus, we hypothesized that sex-based variations in talocrural and subtalar joint kinematics exist during walking.

3D-2D model image registration techniques have been used to evaluate *in vivo* ankle kinematics in recent years (Campbell, Wilson, LaPrade, & Clanton, 2014; de Asla, Wan, Rubash, & Li, 2006; Fukano, Kuroyanagi, Fukubayashi, & Banks, 2014; Yamaguchi, Sasho, Kato, Kuroyanagi, & Banks, 2009), and an advantage of this method is its ability to describe talocrural and subtalar joint kinematics separately without artifacts produced by skin movement. Current motion analysis techniques using reflective skin markers on selected anatomical landmarks are unable to provide precise talocrural and subtalar joint kinematics due to artifacts produced by skin movement and the absence of palpable landmarks of the talus (Nester et al., 2007; Westblad, Hashimoto, Winson, Lundberg, & Arndt, 2002). Although the 3D-2D model image registration technique can provide good spatial accuracy, to the best of our knowledge, a detailed comparison between sexes of talocrural and subtalar joint movement during stance phase has not been reported.

Thus, the purpose of the present study was to investigate sex-based differences in the talocrural and subtalar joint kinematics during walking.

2. Methods

This study was approved by the Ethics Committees on Human Research of Waseda University, Tokyo, Japan. Written informed consent regarding the purposes and procedures of this study was obtained from each participant prior to their involvement.

Seventeen healthy volunteers, 10 males (age 21.2 ± 1.2 years; height 171.0 ± 5.6 cm; weight, 65.6 ± 5.8 kg) and 7 females (age 24.1 ± 3.0 years; height 160.3 ± 4.5 cm; weight, 55.7 ± 7.8 kg) participated in this study. Regarding the subjects' physical characteristics, the height and weight of the males were significantly greater than that of the females (F = 3.09 and 0.42 respectively, p < .05). Body mass index (BMI) (male, 22.4 ± 1.2 ; females, 21.7 ± 2.5) was comparable between sexes. All subjects were free of lower extremity and lower back pain and had no history of serious injuries or any operative treatment, and no subjective symptoms interfering with sport activities. When we conducted this experiment, each individual was participating in various recreational sports activities two or three times per week. We planned this study using repeated measures ANOVA to test between-within interactions. A sample size calculation based on prior normally distributed data indicated that a total of 16 participants were required to reject the null hypothesis (effect size = 0.25, p < 0.05, power = 0.9, number of groups = 2).

The participants were required to perform one gait cycle task (pace, 60 steps/min; stride, self-defined) on their right foot on a raised walkway with a fluoroscopic C-arm (Fig. 1). Participants prepared themselves by standing upright on the walkway and striding forward on their right foot. Each participant was instructed in the proper walking technique and required to practice beforehand. The static reference position, standing on the right leg, was obtained before the trial for each subject. The participants wore radiation shielding coats (Magical light, Maeda & Co., Ltd., Tokyo, Japan; lead equivalent: 0.25 mmPb) during trial and computed tomography scanning.

Each trial was recorded using flat-panel lateral fluoroscopy (Infinix CeleveTM-i INFX-8000C; Toshiba Medical Systems Corporation, Tochigi, Japan). Ankle images during one gait cycle were obtained at a rate of 60 Hz, with 1 ms X-ray pulses (200 mA, 50 kV, 512 \times 512 pixel images, 0.004 mGy/frame).

Participants underwent computed tomography (CT) scanning from 15 cm proximal to the lateral malleolus to the plantar surface, with overlapping slices with a thickness of 0.4 mm (200 mA/slice, 120 kV, 512 \times 512 pixel images, CTDI 15.5 mGy) (IDT 16; Philips,

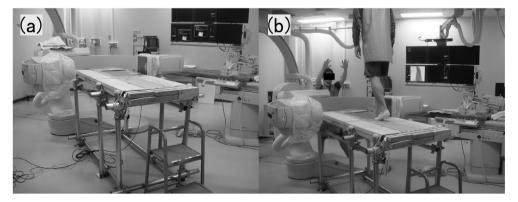


Fig. 1. Experimental set-up of the fluoroscopy system and walkway (a) and the participants walking (b).

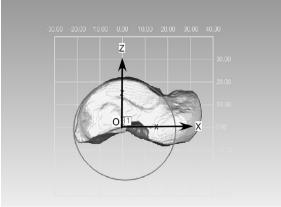


Fig. 2. The origin of the talus was placed at the center of a circle that circumscribed the trochlea tali; the circle included the midpoint of the anteromedial and anterolateral edges and the midpoint of posteromedial and posterolateral edges of the trochlea.

Amsterdam, Netherlands).

Three-dimensional bone surface models of the tibia, talus, and calcaneus were created from CT scans by segmenting exterior boundaries of the bony cortex using open source software (ITK-SNAP (Yushkevich et al., 2006)). Anatomical coordinate systems were embedded in each model according to published definitions (Fukano et al., 2014; Yamaguchi et al., 2009) (Geomagic Studio; Geomagic, NC, USA). The tibial origin was placed at the centroid of the tibial plafond; the Y-axis was parallel to the tibial shaft; and the X-axis was the line perpendicular to the line connecting the anteromedial and anterolateral edges of the tibial plafond. The talar origin was placed at the center of a circle that circumscribed the trochlea tali; the circle included the midpoint of the anteromedial and anterolateral edges and the midpoint of posteromedial and posterolateral edges of the trochlea (Fig. 2). The Z-axis was defined as the line perpendicular to the circle, with the X-axis parallel to the line linking the anterior and posterior edges of the trochlea. The calcaneal origin was placed at the center of the line that linked the most lateral point of the posterior articular surface with the most medial point of the middle articular surface. The X-axis was parallel to the inferior surface of the calcaneus, and the Y-axis was parallel to the lateral surface. Dorsi/plantar flexion was defined as rotation around the medial/lateral axis. Eversion/inversion was defined as rotation about the anterior/posterior axis and external/internal rotation was defined as rotation around the superior/ inferior axis (Fig. 3).

The *in vivo* three-dimensional position and orientation of each bone model was determined from the lateral fluoroscopic images and bone models using 3D-2D model-based registration technique (Banks & Hodge, 2004) (JointTrack, sourceforge.net/projects/ jointtrack). The bone models were projected onto the fluoroscopic images and precisely matched, frame-by-frame, until the silhouette of the projected bone models matched the osseous contours in the fluoroscopic images (Fig. 4). The joint kinematics data were calculated using custom-written programs (MATLAB, Math Works, MA, USA) referencing standard conventions (Wu et al., 2002). Talocrural joint motion was defined as the motion of the talus relative to the tibia. Subtalar joint motion was defined as motion of the calcaneus relative to the talus. One investigator repeated this measurement procedure 3 times on all study series of images. The intraclass correlation coefficient for the three repeated measures was > 0.95, with average differences from the mean of 0.60 mm for in-plane translations, 1.8 mm for out-of-plane translations, and 0.59° for rotations (Fukano & Fukubayashi, 2014). Interclass correlation coefficients (ICCs) for the kinematics data were > 0.98 for dorsi/plantar flexion, > 0.78 for eversion/inversion, and > 0.91 for external/internal rotation (Fukano & Fukubayashi, 2014).

We analyzed the kinematic data for one stance phase for each subject, from heel strike to toe off, and normalized each stance phase time as a percentage. The average of three measured values was considered an individual's data. Each individual set of kinematic data was referenced to that subject's static reference position, standing on the right leg, so that all rotations in the reference position were zero and dynamic rotational excursions were expressed relative to the reference position. The data were processed in a single-blinded manner from immediately after data collection until kinematic calculation.

All statistical analyses were conducted using statistical analysis software (IBM SPSS Statistics ver. 20, IL, USA) A two-tailed unpaired *t*-test was used to compare the physical characteristics and the rotations of the tibia, talus, and calcaneus relative to the global coordinate system in the static reference pose and the total ROM of the talocrural and subtalar joints between sexes. Changes in kinematic data between sexes (male, female) by time (every 10% of stance phase) were tested using between-within two-way ANOVA. Bonferroni's post hoc analysis was conducted if the ANOVA showed statistically significant main effects and no interaction effects. The significance was set at p < 0.05. The effect sizes correlation (*r*) from Cohen's *d* was calculated from the *t* values and appropriate degrees of freedom. Data are described as mean \pm standard deviations.

3. Results

Table 1 shows the sex-based comparison of tibia, talus, and calcaneus orientations relative to the global coordinate system while participants maintained the reference position. We did not detect any differences between sexes in the reference position.

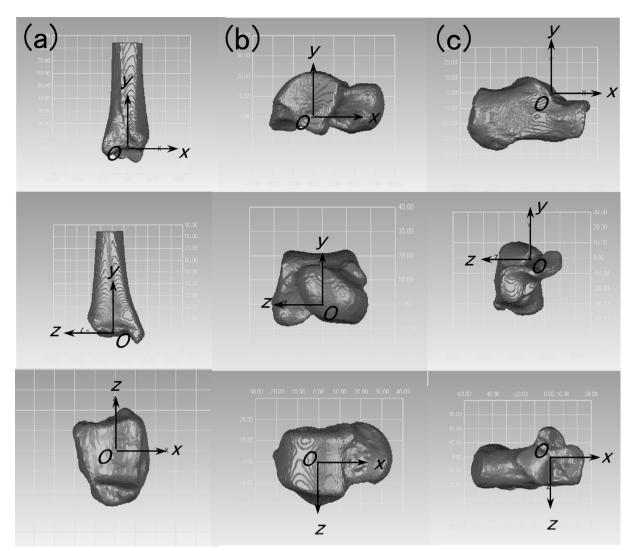


Fig. 3. Anatomical coordinate system of the tibia (a), talus (b), and calcaneus (c) from lateral (upper), frontal (middle), and top or bottom (lower) views. o, origin of anatomical coordinate systems in each bone model.

The talocrural and subtalar joint kinematics at every 10% of stance phase are shown in Fig. 5. Two-way ANOVA indicated a statistically significant main effect according to time of talocrural dorsi/plantar flexion (F = 18.32, p < .001), external/internal rotation (F = 8.65, p < .001), subtalar dorsi/plantar flexion (F = 19.88, p < .001), inversion/eversion (F = 35.50, p < .001), and external/internal rotation (F = 16.289, p < .001). No statistically significant interaction effects were observed. The talocrural joint was in dorsiflexion and slight external rotation at heel strike. In the sagittal plane, the talocrural joint plantarflexed during the first 20–30% of the stance phase and dorsiflexed subsequently. In the frontal plane, the talocrural eversion/inversion angle did not vary throughout the stance phase. In the coronal plane, the talocrural joint rotated internally from heel strike to approximately the first half of the stance phase, while the joint rotated externally during the last half of the stance phase. The subtalar joint demonstrated a slightly plantarflexed, inverted and internally rotated position at heel strike (Fig. 5). The joint tended to be dorsiflexed, everted, and externally rotated during approximately the first half of the stance phase and tended to be plantarflexed, inverted, and internally rotated later in the stance phase.

Two-way ANOVA indicated a statistically significant main effect of sex on talocrural dorsi/plantar flexion (F = 5.09, p = .037), eversion/inversion (F = 9.66, p = .007) and subtalar external/internal rotation (F = 5.09, p = .039). Talocrural dorsiflexion in females was significantly greater than that in males at heel strike (0%), 10%, and toe off (100%) of the stance phase (males: $5 \pm 6^{\circ}$ (0%), $2 \pm 10^{\circ}$ (10%), $7 \pm 8^{\circ}$ (100%); females: $7 \pm 9^{\circ}$ (0%), $4 \pm 10^{\circ}$ (10%), $11 \pm 7^{\circ}$ (100%), respectively); in contrast, talocrural dorsiflexion in males was significantly greater than that in females at 30% of the stance phase (males: $1 \pm 7^{\circ}$; females: $-1 \pm 8^{\circ}$). In the frontal plane, the talocrural joint of females was significantly inverted from 10% to 30% of the stance phase (males: $0 \pm 1^{\circ}$ (10%), $0 \pm 1^{\circ}$ (30%); females: $-2 \pm 2^{\circ}$ (10%), $-2 \pm 2^{\circ}$ (20%), $-2 \pm 1^{\circ}$ (30%), respectively). At the subtalar joint, the females demonstrated significant internal rotation from heel strike to 30% of the stance phase and at toe off (males: $0 \pm 1^{\circ}$ (0%),



Fig. 4. A single fluoroscopic image with 3D bone models superimposed on the radiographic image and registered to the osseous contours of the bones in the image.

Table 1

Sex comparison of rotational angles of the tibia, talus, and calcaneus relative to the global coordinate system in the static reference position.

Bone	Variable (deg)	Male	Female	Female	
		Mean ± SD	Mean ± SD	p value	r
Tibia	Dorsi(+)/plantar(-) flexion	4 ± 11	-6 ± 10	0.095	0.42
	Eversion(+)/inversion(-)	3 ± 5	3 ± 4	0.967	0.01
	External(+)/internal(-) rotation	-4 ± 10	0 ± 9	0.966	0.18
Talus	Dorsi(+)/plantar(-) flexion	-11 ± 4	-9 ± 5	0.393	0.22
	Eversion(+)/inversion(-)	1 ± 3	2 ± 6	0.191	0.33
	External(+)/internal(-) rotation	-3 ± 5	-4 ± 4	0.757	0.08
Calcaneus	Dorsi(+)/plantar(-) flexion	22 ± 8	23 ± 5	0.847	0.05
	Eversion(+)/inversion(-)	7 ± 6	8 ± 5	0.846	0.05
	<pre>External(+)/internal(-) rotation</pre>	5 ± 5	9 ± 5	0.149	0.37

*Significant difference; SD, standard deviation.

Values are mean \pm standard deviation.

 $1 \pm 2^{\circ}(10\%), 2 \pm 3^{\circ}(20\%), 3 \pm 3^{\circ}(30\%), 1 \pm 3^{\circ}(100\%);$ females: $-4 \pm 4^{\circ}(0\%), -2 \pm 4^{\circ}(10\%), -2 \pm 2^{\circ}(20\%), -1 \pm 3^{\circ}(30\%), -4 \pm 4^{\circ}(100\%),$ respectively).

Table 2 shows the comparison among sexes of the total ROM of the talocrural and subtalar joints for the stance phase. The ROM in females for talocrural dorsi/plantar flexion and subtalar eversion/inversion and external/internal rotation were significantly larger than those in males.

4. Discussion

In this study we investigated sex-based differences in talocrural and subtalar joint kinematics during stance phase using fluoroscopy. Our results showed that the movement pattern of each joint was not different between sexes, no statistically significant different interaction effects between sexes on movement patterns were observed; however, sex-based differences in ROM were found in talocrural dorsi/plantar flexion, subtalar eversion/inversion and subtalar external/internal rotation while walking. Comparable rotations of the tibia, talus, and calcaneus in the static reference position indicate that sex-based kinematic differences arise during walking, rather than differences in bony alignment between sexes. To the best of our knowledge, this study provides the first quantitative descriptions of sex-based kinematic differences in talocrural and subtalar joints during walking. Our results may be useful to better understand sex-specific etiologies and incidence of joint degeneration and thus allow for better treatment pre-scriptions.

The female ankle exhibited more talocrural dorsiflexion, inversion and subtalar internal rotation in the early stance phase. A previous study employing dual orthogonal fluoroscopic imaging and model image registration for quasi-static gait (de Asla et al.,

Effect size

r

0.338

0.278

0.191

0.027

0.040

0.05

0.25

0.28

0.33

0.54

0.50

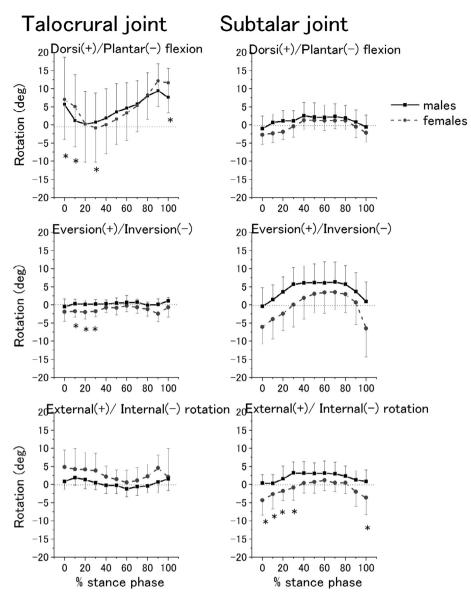


Fig. 5. Mean results of the talocrural and subtalar joint kinematics at every 10% of stance phase. Rotations are referenced to the static standing posture. Descriptive data are expressed as mean \pm standard deviation; *significant difference (males vs. females).

 5 ± 1

7

± 2

 6 ± 2

 11 ± 3

 7 ± 2

Sex comparison of t	he total range of motion (ROM)	in the talocrural and su	btalar joints.		
Joint	Variable (deg)	Male	Female		
		Mean ± SD	Mean ± SD		p value
Talocrural joint	Dorsi/plantar flexion	13 ± 4	17 ± 3	*	0.050

 4 ± 1

 6 ± 1

 4 ± 2

8 ± 3

 5 ± 2

Values are mean \pm standard deviation.

Table 2

Subtalar joint

* Significant difference; SD, standard deviation.

Eversion/inversion

Dorsi/plantar flexion

Eversion/inversion

External/internal rotation

External/internal rotation

2006) reported similar joint movement patterns, with the exception of talocrural movement for the duration of midstance to toe off. A possible reason for this discrepancy in talocrural joint movement from midstance to toe off might be attributed to static measurement; subjects simulated the positions of heel strike, midstance, and toe off in the previous study, whereas our data reflects joint motions throughout the walking stance phase. Most kinematic differences between sexes occurred in early stance phase. This result suggests that males and females have different impact attenuation and/or adaptation to surface strategies. Chiu, Wu, and Chang (2013) reported that the center of pressure of males moved laterally to that of females at approximately 10% of stance phase; the authors speculated that males had less rear-foot (calcaneus) eversion than females. Based on our results, the shift in center of pressure they observed could be interpreted as a more inverted position at the talocrural joint in females at this point in stance phase.

Talocrural dorsi/plantar flexion and subtalar eversion/inversion and external/internal rotation ROM was significantly larger in females than in males. Regarding talocrural dorsi/plantar flexion, this difference may arise from the difference in bone geometry at the distal tibia between sexes. The depth of fibular incisures of the tibia of females was shallower than that of males, and shallow fibular incisura of the tibia may cause displacement of the distal tibia (Yildirim, Mavi, Buyukbebeci, & Gumusburun, 2003); additionally, the distal tibiofibular syndesmosis in females is potentially looser than in males, since females tend to have more ligamentous laxity than males (Schwarz, Kovaleski, Heitman, Gurchiek, & Gubler-Hanna, 2011; Wilkerson & Mason, 2000). Thus, the less stiff articular mortise formed by the tibia and fibula may provide females with added mobility during walking. Regarding the subtalar joint, subtalar eversion/inversion and external/internal rotation ROM was larger in females than in males. The talus and calcaneus are tightly connected by the interosseous talocalcaneal ligament. The higher ligamentous laxity of females could also be a factor leading to this difference. The interosseous talocalcaneal ligament is disposed approximately 35° obliquely compared to the frontal plane, and this ligament can be considered the central pivot of rotatory stability (Bonnel, Toullec, Mabit, Tourne, & Sofcot., 2010). It is also considered a contributor to subtalar mediolateral stability, although the role of this ligament is still controversial. With respect to rotations of the tibia, talus, and calcaneus in the static reference position, there were some noticeable differences and variations with medium sized effects, however none were statistically significant. Moreover, there were no statistical correlations between referenced bone rotations and the ROMs for the stance phase, indicating that they do not significantly contribute to the ROM for this phase. The variability of bone rotations in static reference positions could come from individual differences in bone morphology, since the anatomical coordinate system was set based on the individual bone shape of each subject. Although statistical differences were not observed for reference bone rotations between the sexes, previous study has reported sex-related differences in clinically relevant 3D morphological parameters of the normal calcaneus (Qiang, Chen, Zhang, Li, & Dai, 2014). Given this, the relationship between bone morphological characteristics and joint movements needs to be taken into account in future studies. Although, the ROMs of the subtalar inversion/eversion and internal/external rotation obtained in this study were smaller than those previously observed (Chen Wang et al., 2016), this difference was attributed to the particular experimental conditions used in this study, such as walking speed and stride, which would result in distinct joint movements.

Regarding gross motion, the difference of walking strategy between sexes could also be a potential reason for the larger talocrural dorsi/plantar range of motion of females. In the sagittal plane, Ko et al. (2011) stated that females relied more on ankle angular motion, while males relied more on hip angular motion for forward progression. The results in the sagittal plane were consistent with those of previous studies (Bruening et al., 2015; Ko et al., 2011); however, our results in the frontal plane were different (Ko et al., 2011), and no comparable data are available in the coronal plane. The values in the previous studies were reported collectively as one joint. Our results demonstrate clear evidence of sex-based differences in both talocrural and subtalar joint kinematics while walking. This may prove beneficial for future research that examines sex-specific disorders such as degenerative arthritis and joint fusion of the talocrural and subtalar joints.

Another useful method to provide precise *in vivo* bone movement is intracortical pins. A previous study using intracortical pins in three subjects (Arndt, Westblad, Winson, Hashimoto, & Lundberg, 2004) reported comparable joint rotation of the talocrural and subtalar joints during the stance phase of walking. The intercortial pins method is useful to obtain the talocrural and subtalar joint kinematics during activities, however, this method is highly invasive and difficult to use for large numbers of subjects. The data obtained using the 3D-2D model-based registration technique, therefore, are considered valuable.

This study has several limitations. First, it examined only a single gait cycle motion of the talocrural and subtalar joints due to spatial limitations and in order to avoid increasing the number of redundant gait trials. Given that this study involves the risk of X-ray radiation exposure, it was important that the number of trials was kept to a minimum. Therefore, the walking speed measured was slower than the actual normal daily walking speed and can result in a different joint motion from midgait. Second, the use of the 3D-2D model-based registration technique using single-plane fluoroscopy has much greater uncertainty for out-of-plane (i.e., medio-lateral) translation, whereas the registration technique using biplane fluoroscopy has more uniform errors (Moro-oka et al., 2007). To our knowledge, there is no previous study regarding the relationship of out-of-plane errors with the magnitude of the kinematics. Third, the subjects were young and healthy. Sex-specific disorders such as degenerative arthritis and joint fusion develop and progress due to a habitual load in daily activities such as walking for an extended period. This contributes to the understanding of sex-based kinematic differences in young healthy ankles and can be used to compare data obtained from elderly subjects and/or injured ankles. Additionally, bone morphology may differ between sexes, leading naturally to different joint rotation ROM. Thus, morphological characteristics should be taken into account in future studies.

5. Conclusions

Sex-specific differences in talocrural and subtalar joint kinematics during walking were investigated using fluoroscopy and 3D-2D model-based registration techniques. We found that the orientations of the tibia, talus, and calcaneus were comparable in the static

reference position; however, sex-based differences in ROM were present in talocrural dorsi/plantar flexion, subtalar eversion/inversion, and subtalar external/internal rotation, with the ROM being significantly greater in females during the stance phase of walking.

6. Declarations

6.1. Ethics approval and consent to participate

Ethical approval was obtained by the Ethical Review Committee of Waseda University, Tokyo, Japan (2013-073). The purpose, procedures and risks of the study were informed, and obtained written informed consent from each subject for taking part in the study.

7. Consent for publication

Consent was obtained from participants for publishing the results of the study in scientific journals and presentation at academic conferences and meetings.

8. Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

9. Competing interests

The authors declare that they have no competing interest.

10. Funding

This work was supported by JSPS KAKENHI Grant No. 26870640 (Grant-in-Aid for Young Scientists (B).

11. Authors' contributions

MF wrote the study protocol, and carried out the acquisition, analysis and interpretation of data, performed the statistical analysis and drafted the manuscript. TF conceived of the study, participated in its design and coordination, and helped to draft the manuscript. SB performed data analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

12. Conflict of interest disclosure

No relevant financial conflict to disclose.

Acknowledgements

The authors acknowledge the technical support of the Graduate School of Human Sciences at Tsukuba University, Tsukuba, Japan.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.humov.2018.06.003.

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