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In vivo kinematics of functional ankle instability patients during the stance phase of walking

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ABSTRACT

Background: Previous studies showed functional ankle instability (FAI) patients have morphological ligamentous abnormality, despite having no apparent joint laxity.
Research question: Whether tibiotalar and subtalar joints hypermobility exists in FAI patients during stance phase of walking, remains controversial.
Methods: Ten unilateral FAI patients, ten unilateral lateral ankle sprain (LAS) copers and ten healthy controls were included. A dual fluoroscopy imaging system was utilized to capture the fluoroscopic images of tibiotalar and subtalar joint during the stance phase of walking. Kinematic data from six degrees of freedom were calculated utilizing a solid modeling software. The range of motion and joint excursions about six degrees of freedom were compared among the three groups. The correlations between range of motion and Cumberland Ankle Instability Tool (CAIT) scores were assessed utilizing the Spearman's correlation coefficient (r).
Results: During the stance phase, the FAI patients and LAS copers showed larger tibiotalar anterior/posterior translation than the healthy controls (FAI patients, $p = .013$; LAS copers, $p = .002$). The FAI patients also showed significantly larger lateral/medial translation ($p = .035$) and inversion/eversion rotation ($p = .003$) of subtalar joints than healthy controls. By contrast, the subtalar joints of the LAS copers were not different from those of the healthy controls in the lateral/medial translation ($p = .459$) and inversion/eversion rotation ($p = .091$). CAIT scores were negatively correlated with range of motion.
Significance: During the stance phase of walking, FAI patients showed significantly larger hypermobility of subtalar joints than healthy controls, contrary to the LAS copers. These findings justify the utilization of dual fluoroscopy imaging system to detect joint hypermobility in FAI patients. Treatment for FAI patients may require stabilization of the subtalar joint.

1. Introduction

After an initial lateral ankle sprain (LAS), residual symptoms such as pain, swelling, recurrent ankle sprains, giving way and feeling of instability, are known collectively as chronic ankle instability (CAI). On the contrary, individuals who had lateral ankle sprains but considered themselves to be fully recovered from their initial injury, and no longer have episodes of giving way or repetitive ankle sprains, are known as LAS copers [1]. CAI can be categorized as functional ankle instability (FAI) and mechanical ankle instability (MAI). FAI is a kind of CAI with subjectively perceived instability, but without mechanical laxity on the physical examination, stress radiography or ankle arthrometry. MAI is a kind of CAI with ankle joint laxity caused by structural changes of the ankle joint complex.

Traditionally, FAI is believed to be a disruption to afferent pathways without disruption of lateral ankle ligaments or joint laxity, but previous studies showed FAI patients have morphological ligamentous abnormality in arthroscopic assessment, despite having no radiographical joint laxity [2,3]. Also, joint kinematics differences between FAI patients and healthy subjects were reported in several studies [4–6]. Whether tibiotalar and subtalar joints hypermobility exist in FAI during dynamic activities remains controversial.

Operative treatment for ankle instability eliminates mechanical laxity and restores normal joints kinematics [7,8]. Operative treatment

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reduce symptoms both for MAI patients and FAI patients [2,9]. For MAI patients, mechanical laxity on physical examination, stress radiography or ankle arthrometry is an important operative indication. However, this criterion does not work for FAI patients, for lack of effective method to evaluate their joint hypermobility. New method is needed for clinicians to document abnormal joint movement of FAI patients. Dual fluoroscopy imaging system is a non-invasive technique to investigate in vivo six degrees of freedom skeletal kinematics. Previous studies utilized dual fluoroscopy imaging system to investigate the in vivo kinematics of MAI patients [10,11]. The in vivo kinematics of FAI patients during walking was reported but seldom compared with a group of LAS copers [6]. In the current study, we utilized dual fluoroscopy imaging system to investigate the in vivo kinematics of tibiotalar and subtalar joints of FAI patients and LAS copers during the stance phase of walking. We hypothesized that, compared to healthy subjects and LAS copers, FAI patients still have joint hypermobility, which is not captured using traditional methods.

2. Methods and materials

2.1. Subjects

This descriptive laboratory study was approved by the Institutional Review Board of our institution and informed consents from all subjects were collected. A total of 30 individuals, including 10 healthy subjects (6 males and 4 females), 10 unilateral LAS copers (5 males and 5 females), and 10 unilateral FAI patients (5 males and 5 females) participated in this study. The subjects in the current study were the same individuals as in a previous study [12]. Demographic features of recruited subjects are listed in Table 1.

The inclusion criteria for FAI patients were as follows: (1) initial ankle sprain for more than 12 months ago, and the sprain diagnosed at emergency room as grade II or III, resulting in either at least three days of immobilization and/or non-weight bearing and/or the use of a protective device; (2) recurrent ankle sprain (at least two sprains in the same ankle), giving way (more than twice in the recent 6 months), or feeling of instability in the previously injured ankle during activities of daily living; (3) negative talar tilt test and anterior drawer test; and (4) a Cumberland ankle instability tool (CAIT) score lower than 24 [12–14].

The inclusion criteria for LAS copers were as follows: (1) initial ankle sprain for more than 12 months ago, and the sprain diagnosed at emergency room as grade II or III, resulting in either at least three days of immobilization and/or non-weight bearing and/or the use of a protective device; (2) without recurrent ankle sprains, episodes of giving way, and/or feelings of instability for at least 12 months; (3) resumed to pre-injury levels of weight-bearing physical activity for at least 12 months; and (4) a CAIT score higher than 24 [1,12].

Healthy controls met the following inclusion criteria: (1) no history of the ankle sprain which led to at least one day of interruption in physical activities; and (2) a CAIT score higher than 24.

Subjects were excluded when they have Godin Leisure Time Physical Activity lower than 10, or the following histories: (1) fracture requiring realignment or musculoskeletal surgery in either lower extremity; (2) acute trauma in either lower extremity in the previous 3 months, or time since the last sprain of less than 3 months; (3) positive talar tilt test or anterior drawer test findings; (4) osteoarthritis in either lower extremity, or other conditions that could affect normal gait; and (5) general joint hypermobility (Beighton score equal or higher than 4).

Table 1
Demographic features of recruited subjects.

	FAI	LAS Copers	Control
Number of patients	10	10	10
Gender (M/F)	5M/5F	5M/5F	6M/4F
Age (years)	24.4 ± 5.4	25.5 ± 4.6	26.4 ± 2.5
Body mass index (kg/m2)	21.1 ± 1.9	21.4 ± 1.4	21.7 ± 1.6
Duration since first ankle sprain (months)	39.6 ± 16.2	37.9 ± 15.1	N/A
CAIT scores	16.5 ± 4.1*	27.0 ± 2.1	29.3 ± 1.3
AOFAS ankle hind-foot scale	83.2 ± 10.8*	96.3 ± 5.1	98.0 ± 4.2

* $p < .05$ compared to control group.

2.2. Motion imaging capture

A dual fluoroscopy imaging system was utilized to capture the walking motion of subjects [15]. This dual fluoroscopy imaging system was validated in a previous study [16]. The dual fluoroscopy imaging system comprised two approximately orthogonal fluoroscopies (BV Pulsera, Phillips Medical, USA) and a custom-made walking platform with a force plate embedded, which accommodated the height of the X-ray beam. Two fluoroscopies with resolution of 1024 × 1024 pixels and beam energy settings of 75 kV and 40 mA were utilized. The subjects were instructed to walk slowly at approximately 1 m/s for two continuous steps. During the second step, the subjects were instructed to step on a previously marked position above the force plate. During the stance, the foot did not move relative to the ground to facilitate the inclusion of the stance phase of the second step in the dual fluoroscopic views and capture via the dual fluoroscopy imaging system at a frame rate of 30 Hz. Thus, the following seven key poses were selected to analyze the tibiotalar and subtalar kinematics (Fig. 1): (1) heel strike of the tested side; (2) foot flat of the tested side; (3) mid-stance of the tested side and toe off of the contra-lateral side; (4) mid-stance of the tested side and swing phase of the contra-lateral side; (5) heel off of the tested side and preparation for heel strike of the contra-lateral side; (6) heel strike of the contra-lateral side; and (7) toe off of the tested side and mid-stance of the contra-lateral side [17]. The seven key poses were selected based on the embedded force plate during the stance phase. Three trials were performed and averaged for each subject.

2.3. CT scan and 3D bone model creation

All tested feet underwent CT scan (Light Speed, GE, USA) from 10 cm above the tibiotalar joints to the toe tips. The procedure was set to a thickness, in-plane resolution, voltage, current, and matrix of 0.67 mm, 0.35 mm, 120 kV, 200 mA, and 512 × 512 pixels, respectively. All CT images were imported to a 3D reconstruction software (Amira 5.3.2, Visage Imaging, Inc., Germany) to be segmented and create 3D bone models for the tibia, talus, and calcaneus. Cartesian coordinate systems were established in a solid modeling software (Rhinoceros 5.0, McNeel & Associates, USA) for the tibia, talus, and calcaneus of each tested foot based on the anatomic landmarks as Yamaguchi et al [18] described. The directions of anterior/posterior, lateral/medial, and distal/proximal were aligned with the *x*-, *y*-, and *z*-axes of the coordinate systems. The dorsi-flexion/plantar-flexion, external rotation/internal rotation, and inversion/eversion were determined as rotations around the lateral/medial, distal/proximal, and anterior/posterior axes, respectively. The six degrees of freedom (DOF) kinematics of the tibiotalar and subtalar joints were defined as the relative motions of the talus coordinate system with respect to the tibia coordinate system and calcaneus coordinate system with respect to the talus system.

2.4. Kinematic measurements

The author who contributed to the motion imaging capture and the author who processed the kinematic measurements were blind to the patient information. Seven key poses of the stance phase were selected as previously described for analysis. The first, the fourth, and the seventh key pose of the stance phase was the heel strike of the tested foot, the mid-stance of the tested foot, and the toe off of the tested foot,

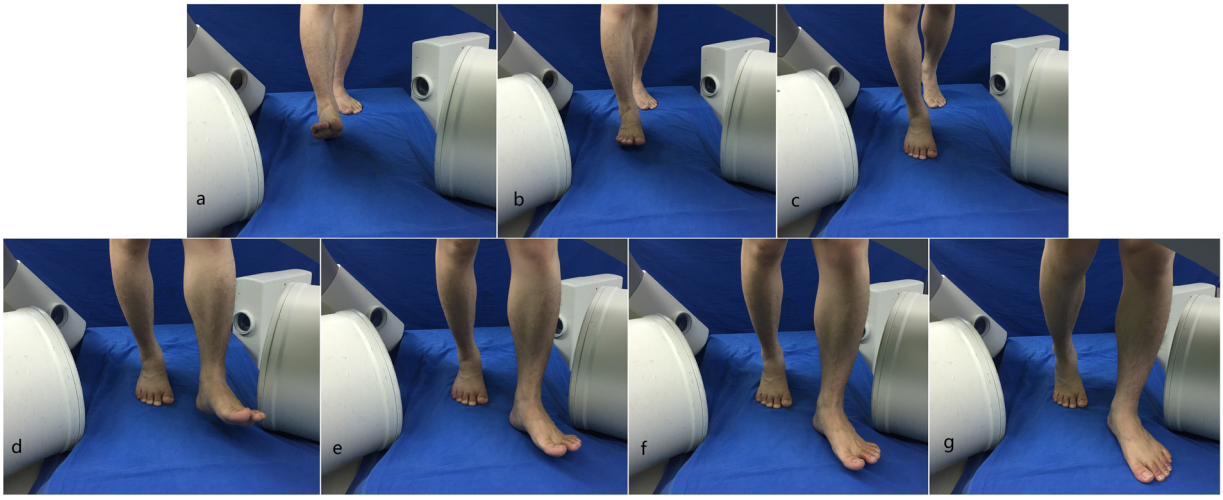

Fig. 1. Seven key poses selected in the stance phase of walking. The heel strike of the tested side (a), foot flat of the tested side (b), mid-stance of the tested side and toe off of the contra-lateral side (c), mid-stance of the tested side and swing phase of the contra-lateral side (d), heel off of the tested side and preparation for heel strike of the contra-lateral side (e), heel strike of the contra-lateral side (f), and toe off of the tested side (g) are shown.

respectively. Seven pairs of fluoroscopic images were imported into a solid modeling software (Rhinoceros 5.0, McNeel & Associates, USA). The 3D bone models were also imported into the same software in the virtual 3D environment, in which the models moved and rotated independently at increments of 0.01 mm and 0.01 degrees. The 3D–2D model-image registration was accomplished through semi-automatic matching [19]. The six DOF kinematics of the tibiotalar and subtalar joints were calculated as the relative motions of the coordinate systems, which were grouped with 3D bone models.

The range of motion (ROM) about each degree of freedom was defined as the maximum minus the minimum among all the seven key poses. The joint excursion from the heel strike to the mid-stance, and from the mid-stance to the toe off, about each degree of freedom was the difference between the first and fourth key poses, and the difference between the fourth and seventh key poses, respectively. The positive values of the joint excursion corresponding to anterior translation, lateral translation, proximal translation, external rotation, eversion, dorsiflexion and negative values corresponding to the opposites.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 19.0. GraphPad Prism 6 (GraphPad Software, San Diego, CA) was used to create the artwork. Data were statistically analyzed by one-way repeated measures multivariate analysis of variance and differences were regarded as statistically significant when $p < .05$. Significantly different data were further analyzed by Bonferroni test to determine the significant difference between each pair among the three groups. The correlations between the ROMs and CAIT scores among 30 subjects were assessed utilizing the Spearman's correlation coefficient (r). A p value $< .05$ indicated significant correlation.

3. Results

3.1. The in vivo kinematics of tibiotalar joints in the stance phase

The ROMs of the tibiotalar joints of FAI patients, LAS copers and healthy controls in the stance phase are presented in Table 2. In the stance phase, the anterior/posterior translation of tibiotalar joints were 1.6 ± 0.6, 1.8 ± 0.5, and 1.0 ± 0.3 mm for FAI patients, LAS copers, and healthy controls, respectively. The FAI patients ($p = .013$) and LAS copers ($p = .002$) showed significantly larger anterior/posterior translation of tibiotalar joints compared with healthy controls in the stance phase. The anterior/posterior translation ROM and the lateral/medial translation ROM of tibiotalar joint have moderate negative correlations with CAIT score (anterior/posterior, r = -0.487, p = .006; lateral/medial, r = -0.415, p = .023).

The joint excursions in the tibiotalar joints of the FAI patients, LAS copers, and healthy controls in the stance phase are presented in Fig. 2. From the mid-stance to the toe off, tibiotalar joints of the FAI patients anteriorly translated by 0.8 ± 0.8 mm. This result was significantly larger than the -0.1 ± 0.4 mm posterior translation in the tibiotalar joints of healthy controls ($p = .004$). From the mid-stance to the toe off, the tibiotalar joints of the LAS copers anteriorly translated by 0.5 ± 0.3 mm. This result was significantly larger than the -0.1 ± 0.4 mm posterior translation in the tibiotalar joints of healthy controls ($p = .049$).

3.2. The in vivo kinematics of the subtalar joints in the stance phase

The ROMs of the subtalar joints of the three groups in the stance phase are presented in Table 3. During the stance phase, the lateral/medial translation of subtalar joints were 4.1 ± 1.9 and 2.5 ± 0.9 mm for FAI patients and healthy controls, respectively. The FAI patients ($p = .035$) showed significantly larger lateral/medial translation of the subtalar joints than the healthy controls. During the stance phase, the inversion/eversion rotation of the subtalar joints were 13.0 ± 2.6 degrees and 8.8 ± 2.4 degrees for the FAI patients and healthy controls, respectively. The FAI patients showed a significantly larger inversion/eversion rotation of subtalar joints than the healthy controls ($p = .003$). The subtalar joints ROMs of LAS copers were not different from those of the healthy controls (lateral/medial translation, $p = .459$; inversion/eversion rotation, $p = .091$). The lateral/medial translation ROM and the eversion/inversion ROM of subtalar joint have moderate negative correlations with CAIT score (lateral/medial, r = −0.500, p = .005; eversion/inversion, r = −0.503, p = .005).

The joint excursions of the three groups during the stance phase are illustrated in Fig. 3. From the mid-stance to the toe off, the subtalar joints of FAI patients inverted by −12.0 ± 3.3 degrees, which was significantly larger than the −6.8 ± 3.9 degrees inversion in the subtalar joints of the healthy controls ($p = .013$). From the mid-stance to the toe off, the subtalar joints of FAI patients translated laterally by 2.2 ± 1.9 mm, which was significantly larger than the -0.4 ± 1.8 mm medial translation in the subtalar joints of the healthy controls ($p = .005$). The subtalar joint excursions of the LAS copers were not different from those of the healthy controls (lateral translation from the

Table 2
The ROMs of the tibiotalar joints and their correlation with CAIT scores.

DOF	FAI patients		LAS copers		Healthy controls		Spearman's correlation	
	mean	SD	mean	SD	mean	SD	r	p
Anterior/posterior translation*#	1.6	0.6	1.8	0.5	1.0	0.3	−0.487	.006
Proximal/distal translation	1.8	0.6	2.0	0.5	1.8	0.8	n.s.	
Lateral/medial translation	2.1	0.7	1.9	0.7	1.4	0.4	−0.415	023
Dorsiflexion/plantarflexion	20.1	7.2	20.0	4.4	15.4	6.7	n.s.	
Eversion/inversion	4.5	2.2	3.7	2.0	3.9	2.0	n.s.	
External/internal rotation	9.4	3.0	10.4	3.7	8.4	2.6	n.s.	

ROM, range of motion; CAIT, Cumberland Ankle Instability Tool; DOF, degree of freedom; SD, standard deviation. Group difference analyzed by one-way analysis of variance: +, significant difference between FAI patients and LAS copers; *, significant difference between FAI patients and healthy controls; #, significant difference between LAS copers and healthy controls.

mid-stance to the toe off, $p = .322$; inversion from the mid-stance to the toe off, $p = .054$).

4. Discussion

The current results indicated that FAI patients showed different in vivo kinematics of tibiotalar and subtalar joint. These findings justify the utilization of dual fluoroscopy imaging system to detect joint hypermobility in FAI patients.

4.1. Tibiotalar joints kinematics

In the current study, FAI patients and LAS copers were associated with larger tibiotalar joint anterior/posterior translation during the entire stance phase. From the mid-stance to the toe off, the tibiotalar joints of FAI patients and LAS copers showed significantly larger anterior translation than the tibiotalar joints of the healthy controls. CAIT scores were negatively correlated with anterior/posterior and lateral/medial translation ROM of tibiotalar joint.

Several previous studies utilized skin markers and gait analysis to study the tibiotalar joints kinematics of the FAI patients. Studies reported decreased vertical foot-floor clearance and increased rear-foot inversion of FAI ankles [4,5]. However, a marker-based approach typically does not get used to calculate individual bone translations [20,21]. None of these studies reported tibiotalar anterior translation of FAI patients and LAS copers [5,22].

In a comparable in-vivo kinematic study focusing on the dynamic activities of MAI patients, Roach et al [11] performed the first study that investigated the in vivo kinematics of MAI patients during walking motions with dual fluoroscopy imaging system and highlighted the necessity of investigating ankle instability kinematics during dynamic motions. By contrast, the current study reported less tibiotalar rotational hypermobility. The discrepancies may due to the small sample size (only 4 patients) in the study of Roach et al. Moreover, for technical reasons, the treadmill walking movements in the study of Roach et al [11,23] were combined from the separated trials rather than acquired through a complete gait cycle. This limitation might affect the calculation of kinematic data.

In the current study, larger anterior translation was observed as previous studies [8,10,24]. Anterior talofibular ligament rupture has been reported to be responsible for anterior dislocation of the talus [25]. The overstretch of anterior talofibular ligament and larger anterior translation of tibiotalar joints were consistent in different groups, i.e., the FAI, MAI patients, and LAS copers [26]. These results indicated

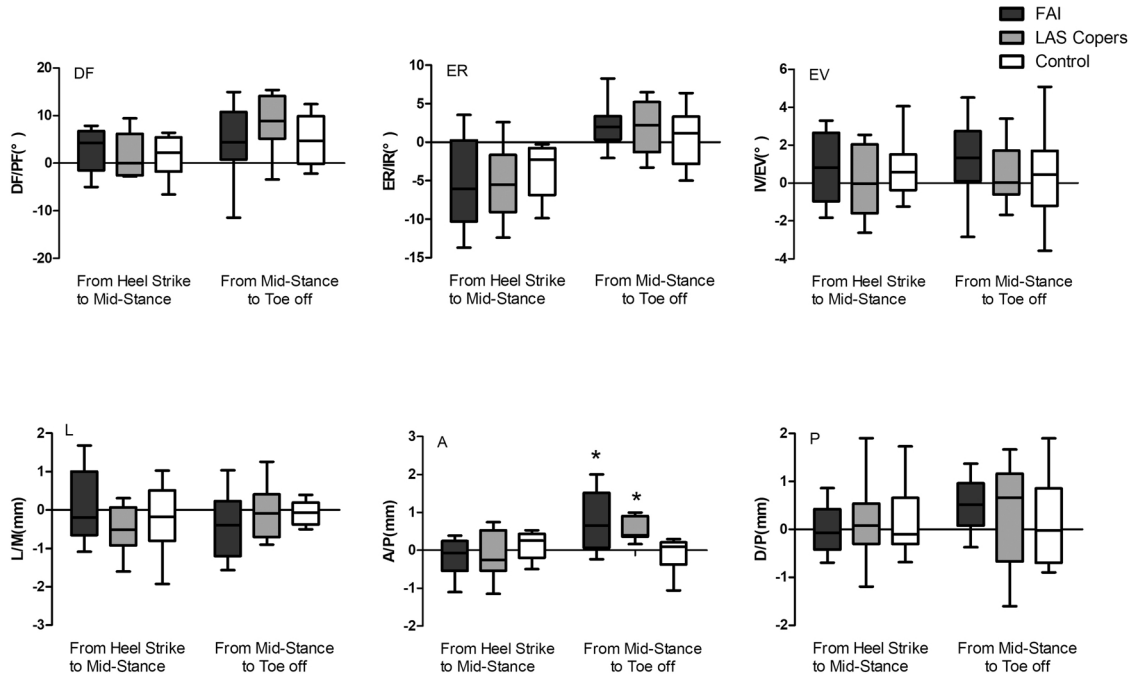

Fig. 2. Joint excursions in the tibiotalar joints of FAI patients, LAS copers and healthy controls in the stance phase. Box and whisker plot showed the lower limit, 1st quartile, median, 3rd quartile and upper limit of the joint excursion value about each degree of freedom. From the mid-stance to the toe off, tibiotalar joints of the FAI patients ($p = .004$) and LAS copers ($p = .049$) showed larger anterior translation than those of the healthy controls. * $p < .05$.

Table 3
The ROMs of the subtalar joints and their correlation with CAIT scores.

DOF	FAI patients		LAS copers		Healthy controls		Spearman's correlation	
	mean	SD	mean	SD	mean	SD	r	p
Anterior/posterior translation	2.6	0.5	2.6	1.2	2.6	0.9		
Proximal/distal translation	2.1	0.7	2.1	0.9	1.9	1.1		
Lateral/medial translation*	4.1	1.9	3.3	0.8	2.5	0.9	−0.500	.005
Dorsiflexion/plantarflexion	7.4	3.1	7.8	2.3	7.6	3.5		
Eversion/inversion*	13.0	2.6	11.4	2.7	8.8	2.4	−0.503	.005
External/internal rotation	7.5	2.6	6.9	3.3	7.4	2.4		

ROM, range of motion; CAIT, Cumberland Ankle Instability Tool; DOF, degree of freedom; SD, standard deviation. Group difference analyzed by one-way analysis of variance: +, significant difference between FAI patients and LAS copers; *, significant difference between FAI patients and healthy controls; #, significant difference between LAS copers and healthy controls.

that ligamentous injury may persist in both FAI patients and LAS copers. The FAI patients and LAS copers show excessive anterior translation of less than 1 mm in the current study. Although anterior translation of tibiotalar joint has statistically significant difference, a difference of less than 1 mm is unlikely to be clinically significant. Similarly, previous studies reported that, compared to healthy subjects, ankle instability patients had an anterior talar positional fault on static lateral radiograph, which could be a risk factor for ankle sprains [27,28].

4.2. Subtalar joints kinematics

FAI patients showed larger subtalar joints lateral/medial translation and inversion/eversion rotation during the whole stance phase. From the mid-stance to the toe off, the subtalar joints of FAI patients were more inverted and laterally translated than LAS copers and healthy controls. This finding confirmed the joint hypermobility during the stance phase of walking in FAI patients. Furthermore, CAIT scores were negatively correlated with lateral/medial translation and eversion/inversion ROM of subtalar joint.

Kobayashi et al [24] utilized single plane fluoroscopic imaging and noticed that increased internal rotation of MAI patients occurred in the subtalar joint. Another study indicated that the subtalar joints of MAI patients showed excessive rotation during the 1 m/s gait [11]. Previous studies of FAI patients also reported subtalar hypermobility during stance phase of walking [6]. The subtalar hypermobility has been reported to be highly prevalent in patients with initial LAS, and is associated with the injury of the calcaneofibular ligament and interosseous talocalcaneal ligament [29]. However, the subtalar joint motions of LAS copers were not significantly different from those of the healthy controls. Enhanced peroneal and anterior tibialis contraction may refrain the hypermobility of subtalar joints in LAS copers through co-contraction mechanism [30,31]. The results also showed that increased subtalar inversion/eversion rotation and lateral/medial translation mainly occurred from the mid-stance to the toe off. The plantarflexed position of the foot may be more susceptible to supination trauma [32].

Traditionally, FAI is believed to be a disruption to afferent pathways, and thus creating instability without the presence of mechanical disruption of lateral ankle ligaments. In the current study, compared to healthy subjects and LAS copers, FAI patients do still possess joint hypermobility, which could be derived from ligament laxity, but rather from the subtalar joint. An anterior drawer test or talar tilt test would not capture disruption of the subtalar ligaments. This provided additional evidence that both MAI and FAI might be derivatives of either

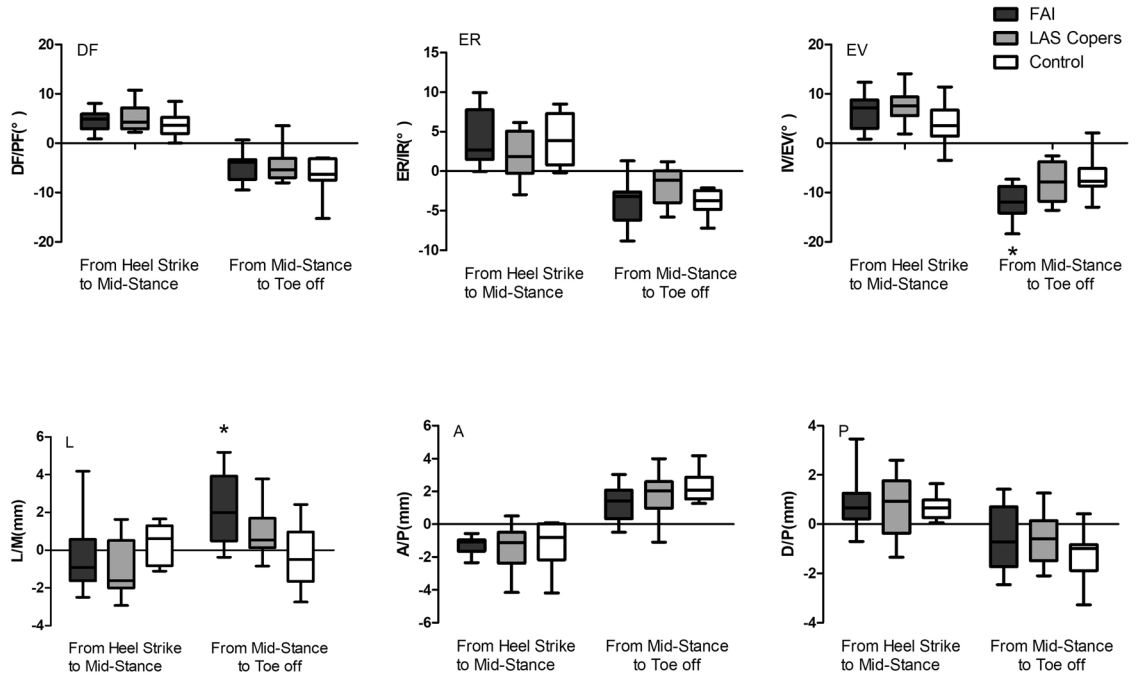

Fig. 3. Joint excursions in the subtalar joints of FAI patients, LAS copers and healthy controls in the stance phase. Box and whisker plot showed the lower limit, 1st quartile, median, 3rd quartile and upper limit of the joint excursion value about each degree of freedom. From the mid-stance to the toe off, subtalar joints of FAI patients showed larger inversion ($p = .013$) and lateral translation ($p = .005$) than those of the healthy controls. * $p < .05$.

mechanical disruption of the lateral ankle ligaments, the subtalar ligaments, or both.

For the FAI patients, neuromuscular training and ankle-foot orthosis are performed prior to operative procedure. The current study may provide new insights that could benefit the treatment of FAI. For FAI patients, ankle-foot orthosis with deep heel cup or utilizing rigid material around the subtalar joints might stabilize the subtalar joints and eliminate the instability symptoms of FAI patients. In particular, the operative treatment of FAI is beneficial for FAI patients who are refractory to nonoperative treatment, and may require stabilization of the subtalar joint. The modified Brostrom-Gould procedure, which helps restore the subtalar joints stability, may be the first choice [7].

Dynamic activities under dual fluoroscopic imaging system are helpful to discover the subtalar hypermobility in FAI patients who have stable ankle joint complexes on the physical examination. The negative correlation between CAIT score and ROM justify the utilization of this method to quantify self-reported ankle instability during diagnosis of FAI and evaluation of rehabilitation programs.

4.3. Limitations

The current study has several limitations. First, we did not analyze continuous dynamic motions, such as treadmill walking, because the narrow dual fluoroscopic views limited the capture of continuous dynamic motions. The treadmill would move the foot out of the dual fluoroscopic field of view prior to the completion of the gait cycle. To accommodate the narrow dual fluoroscopic views, the subjects were instructed to step on a previously marked position during the second step of two continuous steps. This method could show the whole picture of stance phase. Combined separated trials are not needed to demonstrate the kinematic characteristic during the stance phase of walking [11]. The chosen gait speed, 1 m/s, is similar to the gait speed in previous studies [5,11] to facilitate the motion imaging capture.

Second, considering the radiation exposure, we did not perform truly continuous analysis in the current study. The cumulative absorbed dose of dual fluoroscopy imaging system for each subject in the current study is no more than 4 mGy. Only seven key poses in the stance phase of walking were selected for analysis. Although this method did not alter the kinematic characteristic during the stance phase of walking, it may not reflect the true peaks and valleys of the kinematics curves.

Moreover, only 10 FAI patients, 10 LAS copers, and 10 healthy controls were included in the current study. The sample size was relatively small. The three groups compared were not strictly matched. This limitation will affect the generalization of the results.

5. Conclusion

FAI patients and LAS copers have hypermobility of the tibiotalar joints. Contrary to LAS copers, despite having no apparent joint laxity under static condition, FAI patients also showed a significantly larger hypermobility of subtalar joints than healthy controls. These findings justify the utilization of dual fluoroscopy imaging system to detect hypermobility in FAI patients.

Author contributions

Shengxuan Cao contributed to the data analysis and preparation of the manuscript. Chen Wang contributed to the methodology. Gonghao Zhang contributed to the model reconstruction. Xin Ma contributed to the study design. Xu Wang and Jiazhang Huang contributed to the recruitment of volunteers. Chao Zhang contributed to the statistical analysis. Kan Wang contributed to the imaging.

Declaration of Competing Interest

None.

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