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# Concomitant osteochondral lesion of the talus affects in vivo ankle kinetics in patients with chronic ankle instability

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### Aims

This cross-sectional study aimed to investigate the in vivo ankle kinetic alterations in patients with concomitant chronic ankle instability (CAI) and osteochondral lesion of the talus (OLT), which may offer opportunities for clinician intervention in treatment and rehabilitation.

#### Methods

A total of 16 subjects with CAI (eight without OLT and eight with OLT) and eight healthy subjects underwent gait analysis in a stair descent setting. Inverse dynamic analysis was applied to ground reaction forces and marker trajectories using the AnyBody Modeling System. One-dimensional statistical parametric mapping was performed to compare ankle joint reaction force and joint moment curve among groups.

#### Results

The patients with OLT showed significantly increased dorsiflexion moment in the ankle joint compared with healthy subjects during 38.2% to 40.9% of the gait cycle, and increased eversion moment in the ankle joint compared with patients without OLT during 25.5% to 27.6% of the gait cycle. Compared with healthy subjects, the patients with OLT showed increased anterior force during 42% to 43% of the gait cycle, and maximal medial force (p = 0.005,  $\eta p 2 = 0.399$ ).

# Conclusion

The patients with concomitant CAI and OLT exhibit increased dorsiflexion and eversion moment, as well as increased anterior and medial ankle joint reaction force during stair descent, compared with patients with CAI but without OLT and healthy subjects, respectively. Thus, a rehabilitative regimen targeting excessive ankle dorsiflexion and eversion moment may help to reduce ankle joint loading.

# **Article focus**

 The current study aimed to investigate the ankle kinetic alterations in patients with concomitant chronic ankle instability (CAI) and osteochondral lesion of the talus (OLT), which may offer opportunities for clinician intervention in treatment and rehabilitation.

#### **Key messages**

- Patients with concomitant CAI and OLT exhibit increased dorsiflexion and eversion moment compared with patients with CAI but without OLT and healthy subjects.
- Patients with concomitant CAI and OLT exhibit increased anterior and medial ankle joint reaction force compared with



patients with CAI but without OLT and healthy subjects.

 Joint mobilization targeting range of motion restriction and eccentric/concentric training targeting neuromuscular change of invertors and evertors may help to reduce ankle joint loading.

# **Strengths and limitations**

- The current study adds evidence for the simultaneous appearance of kinetic alterations and OLT in the ankle joint of some patients with CAI.
- As a limitation, in vivo ankle kinetics from a pressure sensor were not acquired for the validation of this method.

# Introduction

After an initial ankle sprain, mechanical and functional impairments contribute to symptoms such as pain, swelling, recurrent ankle sprain, giving way, and feeling of instability, collectively known as chronic ankle instability (CAI).<sup>1</sup> About one-third of patients with CAI have concomitant osteochondral lesion of the talus (OLT).<sup>2</sup> Concomitant OLT predisposes patients with CAI to inferior clinical outcomes, and remains a challenge in treating these patients.<sup>3-6</sup> Although several studies have focused on the biomechanics of patients with CAI, little is known about the biomechanics of patients with concomitant OLT and CAI.<sup>2,7</sup> The recommendations for the inclusion of patients with CAI failed to distinguish patients with CAI and OLT from those with CAI but without OLT, which is likely one of the reasons why studies on the biomechanics of patients of patients with CAI contradict one another.<sup>8,9</sup>

Patients with CAI show increased plantarflexion, internal rotation, and inversion in the ankle joint complex during walking, running, and other functional tasks.<sup>7,10</sup> Kinetic studies have shown that patients with CAI have delayed muscle response, which results in moment change in frontal and sagittal planes.<sup>7</sup> Modelling and simulation reveal the migration of peak stress toward the medial and anterior side of the talus and shear force toward the same directions.<sup>11,12</sup> In our previous study on the biomechanics of patients with CAI and OLT, we utilized skin-marker based motion capture and wireless electromyographic system, and indicated that these subjects have decreased maximal plantar flexion and internal rotation angle, accompanied by decreased peroneal activation in 0% to 6% of the stance phase during stair descent.<sup>13</sup> These variables can be utilized to monitor the function of patients with CAI and their possibility of developing OLT.

However, the OLT development is closely related to kinetic change (joint reaction force and moments) of ankle joint, which is not discussed in our previous study. Whether long-term biomechanical maladaptation plays an important role in the developing pathology of OLT remains unknown.<sup>9</sup> The rate of concomitant OLT presence in patients with acute ankle fracture could be as high as 60% at the time of initial trauma.<sup>14</sup> However, an arthroscopic evaluation of patients with ankle fracture history shows that the rate of concomitant OLT presence is lower at 30% after 34 months post-injury.<sup>15</sup> Patients with ankle fracture history may restore ankle stability through bony stability, and a biomechanically stable ankle allows healing of OLT to occur. The rate of concomitant OLT presence may be reduced in long-term follow-up post-injury, which may be one of the reasons for the disagreement in

OLT rate among studies. Healing occurs in patients with OLT under stable biomechanical conditions.<sup>16</sup> However, a postinjury duration of an initial ankle sprain of five years or longer is significantly associated with the presence of OLT in patients with CAI, indicating that ankle biomechanical alterations may serve as long-term effects in the development of OLT.<sup>17</sup> The current study aimed to use musculoskeletal modelling for investigating the in vivo ankle kinetic alterations that may perpetuate or develop OLT in patients with concomitant CAI and OLT, during a dynamic stair descent scenario, and to find biomechanical targets for rehabilitation interventions. We hypothesized that the presence of OLT and increase in ankle joint loading or alteration in the direction of shear force coexist in patients with CAI.

# Methods

This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University. Participants and settings of motion capture analysis were as described by Cao et al.<sup>13,18,19</sup> A priori power analysis was done, and a sample size of eight for each group was required to detect a group difference of 2° in the ankle joint, at the level of significance of 0.05, and the test power of 0.8.<sup>19</sup> A total of 25 individuals with CAI willing to participate in the current study underwent surgery in our institution from June 2019 to January 2020, and were screened for eligibility by two senior orthopaedic surgeons (XW, XM). Overall, 16 of them were eventually included in the current study based on the inclusion and exclusion criteria adapted from the recommendations of the International Ankle Consortium.<sup>8</sup> Patients with CAI were categorized into patients without OLT (four males and four females, with a mean age of 40.8 years (SD 12.0), a mean height of 167.3 cm (SD 8.8), a mean Beighton Score of 2.3 (SD 1.5), and a mean weight of 66.3 kg (SD 9.9)) and patients with concomitant OLT (four males and four females, with a mean age of 37.9 years (SD 8.5), a mean height of 169.6 cm (SD 6.8), a mean Beighton Score of 1.6 (SD 1.4), and a mean weight of 68.8 kg (SD 11.1)) based on MRI and subsequent arthroscopic evaluation (Figure 1). The criteria for OLT are based on MRI (as T2 high-signal in the cartilage or subchondral bone of the talus). One patient had OLT in zone 6, and seven patients had OLT in zone 4 in accordance with the anatomical grid scheme.<sup>13</sup> The Pritsch Grade system modified by Takao et al<sup>20</sup> of each patient with CAI and OLT was determined in subsequent arthroscopic evaluation. Two patients with OLT were grade I, two were grade II, three were grade III, and one was grade IV. Patients with OLT with a diameter of over 15 mm were excluded to ensure consistency inside this group. All included patients were treated with an arthroscopic modified Broström procedure, and those with OLT were treated with a microfracture procedure. Preoperative biomechanical analysis was performed for each patient. Eight healthy subjects (four males and four females, with a mean age of 37.6 years (SD 8.1), a mean height of 170.4 (SD 8.4), and a mean weight of 63.5 kg (SD 8.9) comprised volunteers without musculoskeletal disorders, and they were recruited via posters to match the patient group with regard to age, height, and weight.

All subjects completed six satisfactory three-step stair descent trials, and three randomly selected trials were used for analysis. In addition, the mean values of these three trials were calculated. A total of 26 10 mm reflective markers were placed



#### Fig. 1

Patient with chronic ankle instability (CAI) and osteochondral lesion of the talus (OLT) included in the current study based on MRI and subsequent arthroscopic evaluation. a) Coronal MRI image showing OLT on the medial shoulder of the talus. Red arrow: OLT. b) Sagittal MRI image showing OLT on the talus. Red arrow: OLT. c) Transverse MRI image showing anterior talofibular ligament thickening and slacking. Red arrow: anterior talofibular ligament. d) Arthroscopic assessment showing scar tissue on the anterior talofibular ligament fibre. Red arrow: anterior talofibular ligament. e) Arthroscopic assessment showing OLT on the medial shoulder of the talus. Red arrow: OLT.



#### Fig. 2

Prominent similarity found in the contradistinction between electromyography (EMG) results and AnyBody results in the same experiment, which validates the modelling method. a) EMG results of peroneus longus in contradistinction to AnyBody results. b) EMG results of anterior tibialis in contradistinction to AnyBody results. (c) EMG results of gastrocnemius in contradistinction to AnyBody results.

on the anatomical landmarks of each participant in accordance with the Helen–Hayes model.<sup>21</sup> During stair descent, trajectories of skin markers were sampled at 60 Hz using a motion capture system (Cortex-64; Motion Analysis, USA), and the ground reaction force was recorded using force plates (OR6-7; Advanced Mechanical Technology, Inc., USA). Ankle kinetics and ground reaction force were the basis for numerical simulations performed in AnyBody Modeling



#### Fig. 3

Ankle moments during a stair descent gait cycle from the initial contact of the injured leg on the second step to the initial contact of the injured leg on the ground level. a) and b) Mean ankle dorsiflexion/plantarflexion, internal/external rotational, and inversion/eversion moments with standard deviation clouds during a stair descent gait cycle. Positive values indicate moments in the dorsiflexion, external rotation, and inversion directions. d) to l) Statistical parametric mapping analysis results showing that the comparisons in Figures 3f and 3j reached statistical significance, as indicated by the dashed lines above and below 0. The boxed area represents the area of statistical significance between the two groups. BW, body weight; CAI, patient with chronic ankle instability without osteochondral lesion of the talus; CAI+OLT, patient with chronic ankle instability and osteochondral lesion of the talus; H, height.

System v.7.3 (AnyBody Technology, Denmark).<sup>22</sup> Surface electromyography signals of the peroneal longus, anterior tibialis, and medial gastrocnemius were sampled at 2,000 Hz by using a wireless electromyography system (m320RX; Myon, Switzerland) based on the SENIAM guidelines.<sup>23</sup> The electromyography value was used to validate the calculated muscle force results of the AnyBody Modeling System.

The motion capture model taken from a repository (AnyBody Managed Model Repository v2.3; AnyBody Technology, Denmark) was applied for gait analysis. The model of the lower part of the human body consisted of 17 rigid body segments, connected by 16 joints with 32° of freedom. The model of each lower limb comprised 55 muscles divided into 169 branches modelled using the simple-type model. The generic standard model was scaled in accordance with the length-mass-fat scaling law using the anthropometric data and the recorded position of markers for each participant. Models prepared for particular participants, together with ground reaction forces and marker trajectories, were imported into AnyBody, and such models served as the basis for inverse dynamic analysis to calculate external joint moments (ankle plantarflexion/dorsiflexion (+) moment, inversion (+)/eversion moment, and external (+)/internal rotational moment).<sup>24</sup> The muscle force was distributed using the second-order polynomial muscle recruitment criterion. Finally, the ankle joint reaction force was obtained as a result of muscle forces and the forces of gravity and inertia, and it was further split into three components: superior (+)/inferior, anterior (+)/ posterior, and medial/lateral (+).

The ankle coordinate system was based on the bony landmarks of the tibial plafond in the centre of the medial and lateral malleolus. The Z axis (medial/lateral) was passed through the lateral and medial malleolus pointing laterally. The X axis (anterior/posterior) of the ankle joint coordinate system was perpendicular to the Z axis and the long axis of the shank pointing anteriorly. The Y axis (superior/inferior) was perpendicular to the Z and X axes and was directed proximally. The moments were normalized relative to the body weight × Table I. Kinetic comparison of three groups. Data shown as mean (SD).

Kinetic variable	Patients with CAI without OLT	Patients with CAI and OLT	Healthy subjects	p-value‡	ηp2	Power
Maximal dorsiflexion moment	0.078 (0.017)	0.069 (0.016)	0.069 (0.017)	0.449	0.073	0.173
Maximal plantarflexion moment	-0.013 (0.004)	-0.013 (0.008)	-0.007 (0.004)	0.047	0.253	0.595
Maximal external rotational moment	0.034 (0.020)	0.037 (0.021)	0.019 (0.008)	0.104	0.194	0.449
Maximal internal rotational moment	-0.005 (0.004)	-0.008 (0.005)	-0.005 (0.003)	0.267	0.118	0.268
Maximal inversion moment	0.020 (0.010)	0.025 (0.012)	0.025 (0.005)	0.493	0.065	0.157
Maximal eversion moment	-0.016 (0.006)*	-0.011 (0.003)	-0.007 (0.005)	0.005	0.402	0.888
Maximal anterior force	3.183 (1.059)	3.544 (1.434)	2.160 (0.587)	0.048	0.251	0.590
Maximal posterior force	0.008 (0.014)	0.008 (0.012)	-0.002 (0.012)	0.211	0.138	0.313
Maximal lateral force	0.634 (0.147)	0.539 (0.161)	0.604 (0.150)	0.456	0.072	0.170
Maximal medial force	-0.567 (0.597)	-0.882 (0.236)†	-0.176 (0.137)	0.005	0.399	0.884
Maximal superior force	-0.009 (0.008)	-0.007 (0.008)	-0.006 (0.010)	0.701	0.033	0.100
Maximal inferior force	-4.765 (1.026)	-4.315 (0.839)	-5.243 (1.022)	0.183	0.149	0.340

Positive values indicate directions toward anterior, lateral, superior, dorsiflexion, external rotation, and inversion, and negative values indicate opposite directions. Force values were normalized relative to the body weight (newtons, N) of the subject. Moment values were normalized relative to the body weight (N) and height (m).

\*Statistically significant difference between patients with CAI without OLT and healthy subjects using the Benjamin–Hochberg correction (post hoc p = 0.004).

 $\pm$  the statistically significant difference between patients with CAI and OLT and healthy subjects using the Benjamin–Hochberg correction (post hoc p = 0.004).  $\pm$ Analysis of variance (ANOVA).

ANOVA, analysis of variance; CAI, chronic ankle instability; OLT, osteochondral lesion of the talus.

# height of each subject, and the forces were normalized relative to the body weight of each subject.

The raw electromyography results were bandpass filtered at a frequency range of 20 to 500 Hz. For each trial, electromyography data were full-wave rectified and filtered using a Butterworth filter with a cut-off frequency of 10 Hz, and then the non-reproducible part of the signal was minimized by applying digital smoothing algorithms. The electromyography data over each 1% of the gait cycle were averaged as a mean value, so the steep amplitude spikes were cut away and the signal received a 'linear envelope'. The electromyography value was calculated as the integral of the rectified, filtered, and smoothed electromyography data over time interval T divided by T. The peak values in the respective muscle tests were used for the normalization of the electromyography signal. The raw electromyography and integral electromyography data were real time recorded and displayed by the data process system; furthermore, the integral electromyography results were used to validate the muscle force calculated in the AnyBody Modeling System. Prominent similarity could be founded in the contradistinction between the electromyography results and AnyBody results in the same experiment (Figure 2).

Ankle joint reaction forces and external joint moments during a stair descent trial were standardized to a complete (100%) gait cycle from the initial contact of the index leg on the second step to the initial contact of the index leg on the ground level. Curve analysis, namely one-dimensional statistical parametric mapping (SPM), was performed to compare the ankle joint reaction force and joint moment curve over the entire normalized time series comprising the stance phase and non-weight-bearing swing phase of the gait cycle.<sup>25,26</sup> All SPM analyses were implemented in Python 3.7 (Python Software Foundation, USA). Random field theory was used to calculate the threshold of SPM[F] and post hoc SPM[t], above which only  $\alpha = 5\%$  of the data can reach the test statistical trajectory. Any cluster of SPM[t] that exceeded this threshold was considered significantly different. The maximal joint reaction force and joint moment during stair descent of the included subjects were analyzed through one-way, repeated-measure multivariate analysis of variance (ANOVA) using SPSS (version 19.0; IBM, USA). The differences were regarded as statistically significant when p < 0.05. Significantly different data were further analyzed using the Benjamin-Hochberg correction to determine the significant difference between each pair among the three groups, which may decrease the false discovery rate. Post hoc powers and effect sizes were calculated using G\*Power software (v3.1.8; Heinrich-Heine-Universität Düsseldorf, Germany). Partial eta-squared effect sizes (np2 values) were included and interpreted as small (0.01 to 0.059), moderate (0.06 to 0.139), and large (> 0.14).

# Results

The patients with OLT showed significantly more dorsiflexion moment in the ankle joint compared with healthy subjects during 38.2% to 40.9% of the stair decent gait cycle, and more eversion moment in the ankle joint compared with patients without OLT during 25.5% to 27.6% of the stair decent gait cycle (Figure 3). The maximal eversion moments in the ankle joints of the patients without OLT were larger than those of the healthy subjects (p = 0.005, ANOVA; pp2 = 0.402; Table I; ).

The patients with OLT showed significantly more anterior force in the ankle joint compared with healthy



#### Fig. 4

Ankle joint reaction forces during a stair descent gait cycle from the initial contact of the injured leg on the second step to the initial contact of the injured leg on the ground level. a) to c) Mean ankle anterior/posterior, lateral/medial, and superior/inferior forces with standard deviation clouds during a stair descent gait cycle. Positive values indicate forces in anterior, lateral, and superior directions. d) to l) Statistical parametric mapping analysis results showing that the comparisons in Figures 4e, 4j, and 4k reached statistical significance, as indicated by the dashed lines above and below 0. The boxed area represents the area of statistical significance between the two groups. BW, body weight; CAI, patient with chronic ankle instability without osteochondral lesion of the talus; CAI+OLT, patient with chronic ankle instability and osteochondral lesion of the talus.

subjects during 42% to 43% of the gait cycle, more medial force in the ankle joint compared with patients without OLT during 14.7% to 17.2% of the gait cycle, and more medial force in the ankle joint compared with healthy subjects during 11.3% to 19.1% of the gait cycle (Figure 4). Compared with healthy subjects, the patients with OLT showed increased maximal medial force (p = 0.005, ANOVA;  $\eta p 2 = 0.399$ ; Table I; ).

### Discussion

The current study demonstrated that altered kinematics and ground reaction force drive kinetic differences in the ankle joint, especially the increased dorsiflexion and eversion moments, and shear force toward the anterior and medial direction, using musculoskeletal modelling. The current study provides evidence supporting that the biomechanical maladaptation and OLT coexist in some patients with CAI.

The patients with OLT showed increased eversion moment in the ankle joint during 25.5% to 27.6% of the gait cycle compared with those without OLT. The patients with CAI but without OLT showed continuous activation deficit in the early stance phase.<sup>13</sup> Deficit in peroneal muscle volume and reaction time is a well-recognized mechanism in postsprain subjects.<sup>27-31</sup> The impairment of the eccentric contraction of the invertors is also present in patients with CAI.<sup>32</sup> Eccentric and concentric ankle power decreases during initial landing in patients with CAI.<sup>33</sup> Delayed anterior tibial and peroneal activation leads to decreased ankle stiffness in initial contact.<sup>33,34</sup> However, the patients with OLT showed more decreased peroneal muscle activation after initial contact during stair descent compared with those without OLT, and a postponed peroneal activation peak compared with healthy subjects,<sup>13</sup> which explains the decreased maximal eversion moment and delayed increase of eversion moment.<sup>31</sup>

The current study suggests an increased dorsiflexion moment of patients with OLT during 38.2% to 40.9% of the stair decent gait cycle. The restriction of the dynamic sagittal ankle movement is a biomechanical feature of patients with OLT.<sup>35</sup> Decreased dorsiflexion is related to inferior functional scores.<sup>13</sup> A previous study has indicated that patients with OLT have increased reliance on bony stability, and decreased reliance on injured lateral ligaments, compared with those with CAI.<sup>36</sup> Compared with patients with CAI but without OLT showing decreased ankle sagittal stiffness,<sup>33,34,37</sup> patients with concomitant CAI and OLT are featured with increased sagittal bony constraint compared with healthy subjects, thereby leading to decreased dorsiflexion motion and increased dorsiflexion moment.

The patients with OLT showed increased medial shear force compared with healthy subjects during 11.3% to 19.1% of the gait cycle. The increased medial shear force during the stance phase is consistent with the medial migration of the peak strain shown in a previous study.<sup>12</sup> A previous study on patients with CAI using a modelling method also suggested a mediolateral change of the shear force; however, during the first peak and impulse of level walking, the lateral shear force significantly increased.<sup>38</sup> The increased medial force may be attributed to the insufficiency of both ligamentous tissue quality and peroneal activation, as static and dynamic stabilizers of lateral ankle, respectively. The postponed peroneal activation peak compared with healthy subjects may produce increased eversion moment during 25.5% to 27.6% of the gait cycle, and restore mediolateral force back to the same level as the control group. Eccentric/concentric training targeted on neuromuscular changes of invertors and evertors, particularly eccentric, may decrease the excessive eversion moment of patients with OLT and excessive joint loading.<sup>39</sup> Surgical repair of lateral ankle ligaments and reinforcement of inferior extensor retinaculum may give patients static stabilization after initial contact. The improved dynamic stabilization may also be achieved after the increased static stability of the ankle, which prevents reinjury to the lateral ligaments and surrounding structures, and supports active rehabilitation.<sup>19</sup>

The current study also suggests an increase in ankle anterior shear force in patients with OLT, which is consistent with previous studies.<sup>11,38</sup> Decreased dorsiflexion motion and increased dorsiflexion moment may lead to increased anterior shear force caused by bony constraint. Surgical treatment of concomitant CAI and OLT results in increased dynamic dorsiflexion motion, presumably through the debridement of impingement tissue.<sup>19</sup> Joint mobilization targeting range of motion restriction may also help to reduce ankle joint loading.<sup>40</sup>

Finite element analysis indicated that OLT presence changed ankle joint stress.<sup>41,42</sup> The current study also suggests altered kinetics towards increased anterior and medial shear force in OLT presence. The SPM analyses in the current study allow discussion of temporal differences between patients and healthy subjects. Following decreased peroneal activation and decreased static stabilizing effect of ligamentous tissue during initial contact of patients with OLT, increased medial shear force during initial contact occurs. Increased eversion moment comes after, which suggests that coping mechanisms such as postponed peroneal activation during early stance phase of gait cycle may occur. During late stance phase, increased dorsiflexion moment and subsequent increased anterior shear force occur in patients with OLT, which suggests that higher demand of ankle dorsiflexion angle in late stance phase exacerbates increase in ankle anterior shear force in patients

with OLT. Surgical repair of static stabilizers of lateral ankle, and eccentric/concentric training targeted on neuromuscular changes of invertors and evertors, may help to reduce mediolateral ankle joint loading during initial contact and early stance phase. Surgical debridement of impingement tissue and joint mobilization targeting dorsiflexion range of motion restriction may also help to reduce anteroposterior ankle joint loading during late stance phase. Different rehabilitative methods may complement each other in a temporal manner. In contrast to attributing OLT to initial trauma, the current study and relevant studies support that OLT is developed from a long-term mechanical and functional joint loading imbalance.<sup>17</sup>

The current study has several limitations. First, the number of included subjects is small, which limits the generalization of the conclusions. There is a potential lack of statistical power when addressing sample size concerns. Thus, a larger sample size is needed to draw more specific conclusions. Second, the musculoskeletal modelling method is validated through the comparison of recorded muscle activation and calculation results of the model. A direct comparison of ankle force and data from a pressure sensor cannot be acquired because of ethical problems. Third, given the cross-sectional nature of the current study, the relationship between ankle loading and OLT development remains unknown. The rationale from ankle loading alteration to OLT development must be tested in prospective studies on the in vivo and in vitro cellular and molecular level.43-45 Joint biomechanics and cell molecular change responding to altered mechanical loading is worthy of further investigation. Fourth, the current study indicates that kinetic change occurs in certain phases of the gait cycle, which are relevant to each other, but the interactive mechanisms cannot be determined because of the cross-sectional nature of the study.

In conclusion, patients with concomitant CAI and OLT exhibit increased dorsiflexion and eversion moment, as well as anterior and medial ankle joint reaction force during stair descent compared with patients with CAI but without OLT and healthy subjects, respectively. A rehabilitative regimen targeting excessive ankle dorsiflexion and eversion moment may help to reduce ankle joint loading.

#### Supplementary material

Table showing the location and Pristsch grade of osteochondral lesion of the talus.

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- S. Cao: Writing original draft, Investigation.
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- S. Jiang: Software.
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- X. Wang: Writing review & editing.
- C. Wang: Methodology.
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# **Data sharing**

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

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