



The influence of footwear on functional outcome after total ankle replacement, ankle arthrodesis, and tibiototalcalcaneal arthrodesis

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ABSTRACT

Background: Gait analysis after total ankle replacement and ankle arthrodesis is usually measured barefoot. However, this does not reflect reality. The purpose of this study was to compare patients barefoot and with footwear. **Methods:** We compared 126 patients (total ankle replacement 28, ankle arthrodesis 57, and tibiototalcalcaneal arthrodesis 41) with 35 healthy controls in three conditions (barefoot, standardized running, and rocker bottom shoes). Minimum follow-up was 2 years. We used dynamic pedobarography and a light gate. Main outcome measures: relative midfoot index, forefoot maximal force, walking speed.

Findings: The relative midfoot index decreased in all groups from barefoot to running shoes and again to rocker bottom shoes ($p < 0.001$). The forefoot maximal force increased wearing shoes ($p < 0.001$), but there was no difference between running and rocker bottom shoes. Walking speed increased by 0.06 m/s with footwear ($p < 0.001$). Total ankle replacement and ankle arthrodesis were equal in running shoes but both deviated from healthy controls (total ankle replacement/ankle arthrodesis smaller RMI $p = 0.07/0.017$; increased forefoot maximal force $p = 0.757/0.862$; slower walking speed $p < 0.001$). In rocker bottom shoes, this ranking remained the same except the relative midfoot index merged to similar values. Tibiototalcalcaneal arthrodesis were inferior in both shoes.

Interpretation: Runners are beneficial and the benefit is greater for fusions and replacements. Rocker bottom shoes have little added benefit. Total ankle replacement and ankle arthrodesis were equal but inferior to healthy controls. Tibiototalcalcaneal arthrodesis has an inferior outcome.

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1. Introduction

There is an ongoing debate concerning the relative merits of total ankle replacement (TAR) and ankle arthrodesis (AA), and a burgeoning literature is dedicated to the study of their comparative advantages (Atkinson et al., 2010; Beyaert et al., 2004; Coester et al., 2001; Daniels et al., 2014; Doets et al., 2007; Hahn et al., 2012; Henricson et al., 2007; Hobson et al., 2009; Krause et al., 2011; Mittlmeier, 2013; Müller et al., 2006; Piriou et al., 2008; SooHoo et al., 2007; Thomas et al., 2006; Wood et al., 2009). A priori, one would expect the mobile TAR to fare better than the stiff AA. However, a review of the scientific literature comparing TAR and AA reveals the following: (1) similar post-operative clinical outcomes and both better than preoperatively with improvement of pain scores and functional scores (AOFAS) (Atkinson et al., 2010; Beyaert et al., 2004; Coester et al., 2001; Doets et al., 2007; Müller et al., 2006; Piriou et al., 2008; SooHoo et al., 2007; Thomas et al., 2006); (2) same walking speed but slower than healthy

subjects (Beyaert et al., 2004; Doets et al., 2007; Thomas et al., 2006); (3) development of subtalar osteoarthritis (3% in 5 years for AA, 1% in 5 years for TAR) (SooHoo et al., 2007); and (4) an increased motion of the knee joint as compensation for the rigid ankle and consequent development of arthritis both in AA and TAR, but controversially discussed (Doets et al., 2007; Hahn et al., 2012; Piriou et al., 2008). The only advantage of TAR over AA measured with gait analysis was a more symmetrical gait (Doets et al., 2007; Müller et al., 2006).

The picture changes when we focus on longevity. The revision rate in AA is 7–26% compared to 17–54% in TAR (Daniels et al., 2014; Krause et al., 2011; SooHoo et al., 2007). Furthermore, implant failure in TAR of 24–11% after 10 years has to be taken into account (Henricson et al., 2007; Hobson et al., 2009; Mittlmeier, 2013; Stengel et al., 2005; Wood et al., 2009) while AA last forever. There are only few studies of the treatment effects of TTC (Ajis et al., 2013; Jastifer et al., 2015; Tenenbaum et al., 2014). They report satisfaction scores of 91% for AA and 88% for TTC and good clinical and functional results for both AA and TTC (Ajis et al., 2013; Jastifer et al., 2015; Tenenbaum et al., 2014). These figures, however, conceal the clinically observed impairment after adding a subtalar fusion to an AA.

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The literature has two unclear spots. First, the treatment outcomes are always assessed in barefoot condition. However, it is unclear whether barefoot results are relevant in an everyday context. Humans typically wear shoes when walking, and shoes have a crucial influence on the foot's functionality. Therefore, the aim of this study is to compare healthy subjects and patients not only barefoot but also in running and rocker bottom shoes. Second, the focus in studies is on isolated ankle arthrodesis (AA) and the rare reporting of tibiototalcalcaneal arthrodesis (TTC) (Ajis et al., 2013; Jastifer et al., 2015; Tenenbaum et al., 2014). TTC, in essence an ankle fusion combined with a subtalar fusion, is a frequent medical treatment. Therefore, this study will include TTC patients.

We therefore measured four groups (TAR, AA, TTC, and healthy controls) in three conditions (barefoot, wearing standardized running, and rocker bottom shoes) to address the following issues:

1. What are the differences between the four groups barefoot?
2. What are the differences between the four groups in running and rocker bottom shoes?
3. What is the influence of footwear in each group?

2. Methods

We retrospectively reviewed all patients with ankle osteoarthritis who underwent TAR, AA, or TTC between 2003 and 2006 at the author's university (292 patients with 294 operations, including 2 conversion of TAR to AA). A three-component mobile bearing TAR (Hintegra, New Deal, Saint Priest France) was used. Indications for TAR were low-demand lifestyle, sufficient ligament stability, plantigrade hindfoot, and ankle alignment. Ankle fusions were performed taking a transfibular approach, using three 6.5 mm screws for tibiotalar fixation and two 3.5 mm screws for fixation of the fibula. TTC arthrodesis were performed using a transfibular approach and a straight retrograde intramedullary nail (Biomet, Warsaw, IN; Stryker, Kalamazoo, MI).

We included patients meeting the following criteria: (1) unilateral TAR, AA, or TTC with a minimal follow-up of 2 years and (2) complete preoperative and postoperative radiographs available on a DICOM/PACS system. We excluded patients who had persistent painful non-unions ($n = 5$), were bedridden ($n = 22$), deceased ($n = 6$), had amputations ($n = 9$), had comorbidities that precluded walking over the pedobarograph ($n = 7$), incomplete radiographs or data during follow-up ($n = 26$), refused to participate ($n = 39$), moved away to unknown addresses ($n = 17$), lived outside the city more than 1 hour away ($n = 28$), chronic pain syndrome ($n = 4$), conversion from TAR to AA ($n = 2$, included in the study as arthrodesis), or dorsiflexion $<5^\circ$ in TAR ($n = 3$).

These exclusions left 126 patients (Table 1): TAR ($n = 28$), ankle arthrodesis ($n = 57$), and TTC arthrodesis ($n = 41$). Minimum follow-up was 2 years (average 4 years; range 2–6 years). Thirty-five healthy volunteers were recruited from patients' companions. Inclusion criteria were no history of foot problems, no disorders seen on clinical examination, a Charlson score¹⁸ of 0, and an AOFAS score (Kitaoka et al., 1994) of 100 (Table 1). No radiographs of the healthy subjects were made. All subjects provided informed consent to participating in the study. The study was approved by the ethics board of the university and performed

in accordance with the World Medical Association Declaration of Helsinki.

The follow-up was carried out by two study nurses and a research fellow; all three were blinded for the type of surgery. All participants had their AOFAS score (Kitaoka et al., 1994) taken and underwent a radiographic follow-up (Saltzman and el-Khoury, 1995). The data for this study were collected using dynamic pedobarography on a 10 m runway (Novel emed m/E, St. Paul, MN). All participants were asked to walk at their own chosen speed and with normal strides. They made five steps before and after entering the platform (five step method) (Mazur et al., 1979). Patients walked at least eight times over the runway; the records of these footprints were then averaged. We equipped the runway with a light gate measuring the walking speed.

All patients were measured in three conditions: barefoot, in running, and in rocker bottom shoes. To avoid effects due to different footwear, all patients were wearing a standardized New Balance 926 orthopaedic running shoe, available in all sizes for both feet. This shoe could be converted into a rocker bottom shoe by attaching a rocker-shaped stiff plastic piece with velcro to the sole (Fig. 1).

All feet were analyzed in a four area mask: hindfoot, midfoot, forefoot, and toes. Boundaries between the areas were 45% and 73% of length (MacWilliams and Armstrong, 2000). The Novel software provided 18 primary parameters for each area as well as for the entire foot. This amounts to 90 parameters (5×18). Since the toes are not critical for the roll over process (and since single toes may exhibit high pressures) the toe mask was excluded from analysis, reducing the number of parameters to 72.

In an earlier study, this number was reduced to 27 parameters (9 each for hindfoot, midfoot, and forefoot) (Frigg et al., 2012). This reduction was crucial to make the data amenable to statistical analysis and for an interpretation of results. The remaining variables were aggregated into clusters, thus creating an *index of rollover* (representing all parameters of time) and an *index of load* (representing all parameters of load) for each area. The core result was that the index of load of the midfoot was the only cluster that showed a significant difference between healthy volunteers, AA, and TTC (Frigg et al., 2012).

This study builds on this result. Within the index of load for the midfoot the maximal force (MF) was the strongest contributor to the net effect. Furthermore, a force is in general the parameter that provides most insight into gait mechanics. We therefore chose the midfoot MF as one main parameter of this study. However, rather than working with the pure midfoot MF, we created a new parameter, the *relative midfoot index* (RMI). This parameter measures the depth of the midfoot valley in relation to the average of the hindfoot and forefoot MF (Fig. 2):

$$RMI = 1 - \frac{2MF_m}{MF_f + MF_h},$$

where MF_m , MF_f , and MF_h are the MF for the midfoot, forefoot, and hindfoot, respectively. In normal triphasic gait, the RMI is expected to assume values close to one, while in the pathologic biphasic gait, it is expected to be close to zero. Walking speed was the only parameter of time that showed significant results in a previous study (Frigg et al., 2012). We therefore considered a faster walking speed as an indicator of health and included it as another main parameter. The final main

Table 1

Characteristics of study participants: healthy volunteers, patients after total ankle replacement (TAR), ankle arthrodesis, or tibiototalcalcaneal (TTC) arthrodesis.

Characteristic	Healthy controls ($n = 35$)	TAR ($n = 28$)	AA ($n = 57$)	TTC ($n = 41$)
Female gender, n (%)	18 (51%)	9 (32%)	18 (32%)	15 (37%)
Median age (IQR), years	34 (30–41)	68 (61–78)	65 (56–73)	65 (54–67)
Median height (IQR), cm	176 (166–179)	170 (166–178)	171 (162–177)	172 (163–175)
Median weight (IQR), kg	72 (63–82)	84 (74–96)	88 (77–102)	87 (77–94)
Median AOFAS score (IQR)	100 (100–100)	75 (65–88)	72 (60–81)	58 (42–66)
Charlson score (average)	0	0.64 (0–3)	0.67 (0–4)	1.09 (0–4)

Abbreviations: TAR, total ankle replacement; AA, isolated ankle arthrodesis; TTC, tibiototalcalcaneal; IQR, interquartile range; AOFAS, American Orthopaedic Foot and Ankle Society.



Fig. 1. New Balance 926 orthopaedic modular shoe with removable stiff rocker bottom, which can be used either as a normal runner or rocker bottom shoe.

parameter is the MF in the forefoot because it is considered a possible trigger for adjacent joint osteoarthritis in the midfoot and subtalar joint. To allow for a complete comparison of all parameters, we also report other typical pedobarographic measurements, namely, the maximal force in the hind- and midfoot and relative contact times in the hind-, mid-, and forefoot (Table 3).

Because for each participant, three sets of pedobarography measurements were recorded, the set of outcomes formed a multivariate response. The statistician used correlated errors models with a general covariance structure for the repeated observations on a participant to estimate differences in outcome between healthy controls and patients after TAR, AA, or TTC arthrodesis, and between barefoot and running or rocker bottom shoes. In our models, we fitted the group (healthy controls, TAR, AA, or TTC), condition (barefoot, running, or rocker bottom shoes), and group–condition interaction effects as fixed effects. Models

for forefoot MF were adjusted for potential confounding variables: body weight and walking speed. We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for our analyses; and for graphics, we used R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). We report median and interquartile range for all parameters because the data were not normally distributed. Effects of footwear and participant group with the correspondent *p*-values are given in the Supplementary Website Material in Table A1–6. *p*-values <0.05 were considered significant.

3. Results

1. What are the differences between the four groups barefoot?

The RMI in barefoot condition was significantly lower than in TAR ($p = 0.005$) and AA ($p < 0.001$) relative to healthy controls, but not different between TAR and AA (median and interquartile ranges are reported in Table 2, line graphs in Fig. 3). The RMI of TTC patients was significantly lower than the other groups ($p = 0.001$). This indicates that both TAR and AA are inferior to healthy subjects while being on par with each other and TTC is inferior to both TAR and AA. For simplification and better understanding of the results, we call this the “HATT ranking” (healthy trumps AA and TAR, which in turn trump TTC). There was no significant difference in forefoot MF between TAR and AA in barefoot condition (Table 2, Fig. 4). Relative to healthy controls, TAR ($p = 0.076$) and AA ($p = 0.105$) had an increased forefoot MF; these differences were, however, not significant. TTC showed a similar MF forefoot as AA and TAR (Table 2, Fig. 3). There was no difference in walking speed between TAR and AA in barefoot condition, but both groups were walking 0.3 m/s slower than healthy controls ($p < 0.001$; Table 2, Fig. 5). TTC were significantly slower than all other groups ($p = 0.036$). We also find the HATT ranking for walking speed.

2. What are the differences between the four groups in running and rocker bottom shoes?

In running shoes, TAR and AA had the same RMI but smaller than healthy controls (TAR $p = 0.07$, AA $p = 0.017$). TTC had significantly lower RMI than the others ($p < 0.001$). Once again, we find the HATT

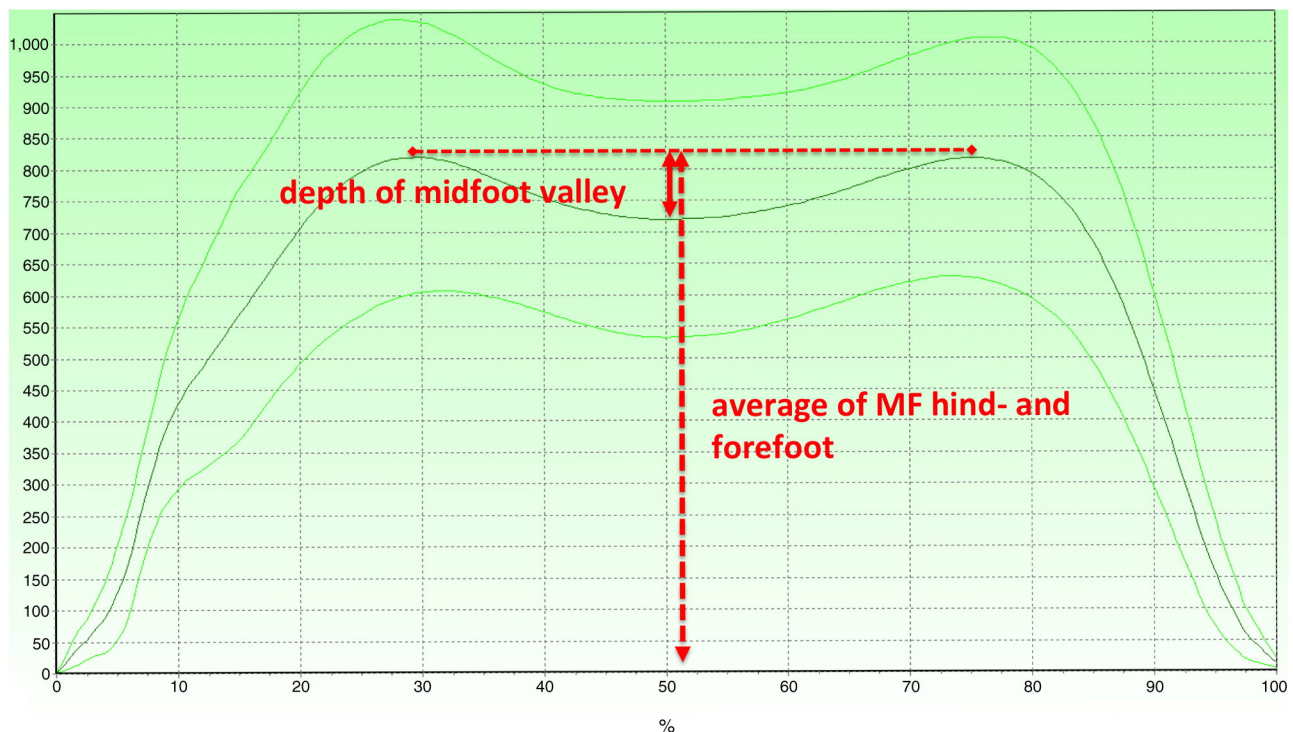


Fig. 2. Relative midfoot index (RMI): the RMI is calculated by setting the depth of the midfoot valley in relation to the average of the MF hind- and forefoot. The aim of the RMI is to facilitate the interpretation of a large amount of pedobarographic data, and it is independent of individual body weight and walking speed, both affecting absolute MF values.

Table 2

Median and Interquartile range of the main outcome parameters:.

Parameter	Healthy controls (n = 35)	TAR (n = 28)	AA (n = 57)	TTC (n = 41)
<i>rMI</i>				
- Barefoot	0.85 (0.79–0.89)	0.71 (0.62–0.79)	0.61 (0.52–0.77)	0.54 (0.42–0.71)
- Running shoes	0.61 (0.54–0.64)	0.52 (0.45–0.59)	0.49 (0.43–0.6)	0.42 (0.33–0.51)
- Rocker bottom shoes	0.43 (0.38–0.49)	0.42 (0.31–0.47)	0.41 (0.33–0.49)	0.36 (0.26–0.46)
<i>MF forefoot (N)</i>				
- Barefoot	576 (511–666)	730 (625–820)	709 (645–891)	704 (596–801)
- Running shoes	676 (590–813)	798 (711–875)	795 (717–959)	747 (629–872)
- Rocker bottom shoes	699 (597–807)	788 (703–911)	825 (709–978)	773 (596–801)
<i>Walking speed (m/sec)</i>				
- Barefoot	1.26 (1.08–1.4)	0.96 (0.79–1.2)	0.96 (0.79–1.17)	0.84 (0.68–1.03)
- Running shoes	1.32 (1.11–1.59)	1.01 (0.86–1.2)	1.06 (0.85–1.22)	0.91 (0.69–1.06)
- Rocker bottom shoes	1.28 (1.14–1.54)	1.03 (0.9–1.19)	1.08 (0.82–1.22)	0.93 (0.69–1.09)

Abbreviations: TAR, total ankle replacement; AA, isolated ankle arthrodesis, TTC, tibiototalcalcaneal arthrodesis.

ranking. In rocker bottom shoes, there were no significant differences anymore between TAR, AA, and healthy controls. TTC, however, still had a significantly smaller RMI than the other groups ($p = 0.002$, Table 2, Fig. 3). Wearing running shoes, both AA and TAR had increased forefoot MF compared to healthy controls, but this was not significant (TAR $p = 0.757$, AA $p = 0.862$). TTC had a similar forefoot MF as the healthy controls. In rocker bottom shoes, we found the same pattern: for both shoe types, the relative rankings remain the same as in barefoot condition (Table 2, Fig. 4). Also walking speed conformed to the HATT ranking: in both running and rocker bottom shoes, the walking speed of healthy controls was considerably higher than that of AA and TAR ($p < 0.001$), which were not significantly different from each other. TTC were noticeably slower than AA and TAR ($p = 0.16$, Fig. 5).

3. What is the influence of footwear to each group?

While the relative merits of treatment options remain unchanged when wearing shoes rather than walking barefoot, the merits in absolute terms change: The RMI decreased in all groups significantly from barefoot to running shoes and again to rocker bottom shoes ($p < 0.001$). The forefoot MF increased significantly wearing shoes ($p < 0.001$), but there was no significant difference between running and rocker bottom shoes, except for TTC where we found a small increase when using rocker bottom shoes ($p = 0.005$). Walking speed increased significantly by 0.06 m/s wearing either running or rocker

bottom shoes compared to barefoot ($p < 0.001$), but did not significantly differ between the two shoes.

4. Discussion

Comparing TAR, AA, TTC, and healthy subjects barefoot and shod, we found what we call the HATT ranking: healthy subjects do best, AA and TAR are equally good but inferior to healthy, and TCC is the worst option.

This study has certain limitations: First, comparing TAR or AA with a high evidence level, a randomization of patients would be necessary. However, this would be unfeasible in the clinical setting and present ethical problems as there are indications and contraindications for TAR. Second, a three-dimensional gait analysis would be preferable but was not possible due to limited financial capabilities (gait analysis is about 10 times more expensive and 10 times more time consuming than pedobarography). Third, healthy volunteers were not age- and weight-matched to the patient group, which has previously been encountered by other authors (Piriou et al., 2008). Fourth, the RMI is not yet a validated new parameter. It was the attempt of a clinical working orthopaedic surgeon to facilitate the interpretation of a large number of pedobarographic parameters.

In selected gait analysis studies, TAR appears to regain more natural joint function and a more symmetrical gait (Chopra et al., 2014; Flavin

Table 3

Median and interquartile range of the other pedobarographic parameters: maximal force (MF) and relative contact time (contact time of each area in relation to the total contact time).

Parameter	Healthy controls (n = 35)	TAR (n = 28)	AA (n = 57)	TTC (n = 41)
<i>MF hindfoot (N)</i>				
- Barefoot	513 (444–591)	478 (419–596)	576 (456–693)	530 (423–721)
- Running shoes	523 (471–604)	522 (461–604)	617 (461–751)	612 (431–721)
- Rocker bottom shoes	559 (483–639)	591 (484–653)	662 (524–783)	631 (515–716)
<i>MF midfoot (N)</i>				
- Barefoot	83 (54–108)	171 (126–267)	227 (155–318)	284 (185–362)
- Running shoes	229 (200–290)	313 (250–405)	344 (259–415)	391 (327–452)
- Rocker bottom shoes	341 (310–406)	404 (331–506)	424 (351–526)	441 (370–507)
<i>Contact time hindfoot (%)</i>				
- Barefoot	0.58 (0.52–0.62)	0.63 (0.57–0.72)	0.61 (0.5–0.66)	0.63 (0.54–0.74)
- Running shoes	0.6 (0.54–0.64)	0.68 (0.61–0.76)	0.69 (0.61–0.74)	0.76 (0.65–0.8)
- Rocker bottom shoes	0.53 (0.49–0.58)	0.64 (0.57–0.72)	0.66 (0.59–0.73)	0.7 (0.63–0.8)
<i>Contact time midfoot (%)</i>				
- Barefoot	0.62 (0.57–0.67)	0.7 (0.67–0.74)	0.7 (0.66–0.74)	0.73 (0.65–0.78)
- Running shoes	0.59 (0.51–0.61)	0.67 (0.63–0.69)	0.68 (0.65–0.71)	0.71 (0.76–0.81)
- Rocker bottom shoes	0.56 (0.49–0.6)	0.66 (0.62–0.69)	0.68 (0.61–0.7)	0.71 (0.66–0.74)
<i>Contact time forefoot (%)</i>				
- Barefoot	0.84 (0.82–0.86)	0.87 (0.84–0.89)	0.85 (0.81–0.87)	0.83 (0.8–0.87)
- Running shoes	0.77 (0.75–0.8)	0.8 (0.79–0.83)	0.79 (0.77–0.81)	0.79 (0.76–0.81)
- Rocker bottom shoes	0.74 (0.7–0.79)	0.78 (0.76–0.8)	0.76 (0.74–0.79)	0.78 (0.75–0.8)

Abbreviations: TAR, total ankle replacement; AA, isolated ankle arthrodesis, TTC, tibiototalcalcaneal arthrodesis.

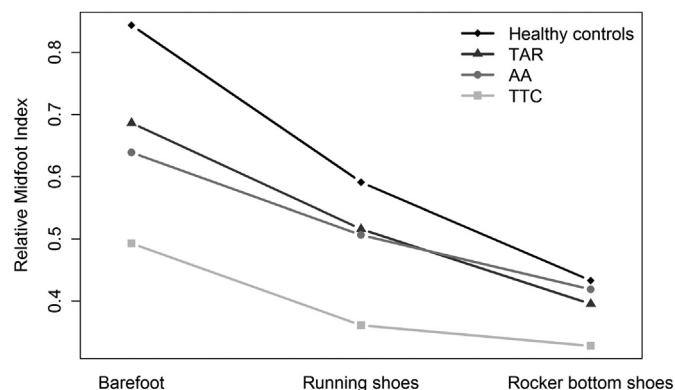


Fig. 3. The median of RMI for TTC (squares), AA (circles), TAR (triangle), and healthy controls (diamonds). For values of the mean and interquartile range, please see Table 2; for *p*-values, please see Supplementary Website Material.

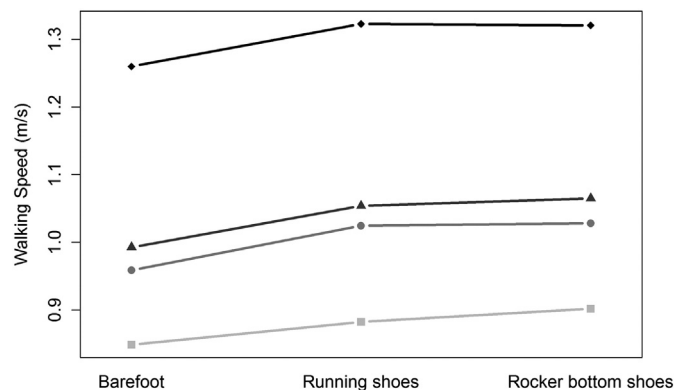


Fig. 5. The median of walking speed for TTC (squares), AA (circles), TAR (triangle), and healthy controls (diamonds). For values of the mean and Interquartile range, please see Table 2; for *p*-values, please see Supplementary Website Material.

et al., 2013; Hahn et al., 2012; Piriou et al., 2008; Singer et al., 2013). Singer described 4.4° more dorsiflexion in TAR than AA with impaired plantarflexion in both groups (Singer et al., 2013). Van Engelen found 7.6% increased metabolic cost in AA (van Engelen et al., 2010), and Doets found 28% in TAR compared to healthy subjects (Doets et al., 2007). These results raise questions: First, it is unclear whether these differences would still be measurable wearing shoes. Second, it is questionable whether a 4.4° larger dorsiflexion is clinically relevant. In the light of our results, summarized as “HATT” ranking, there is the question whether the subtle possible biomechanical advantages of TAR should be bought at the cost of a higher rate of revisions and implant failure (Daniels et al., 2014; Krause et al., 2011; SooHoo et al., 2007).

A possible biomechanical explanation of the increased midfoot and forefoot load after AA may be that the midfoot and forefoot have to compensate for the stiff ankle joint. Sealey et al. (2009) observed a compensatory increase in sagittal motion of the subtalar and medial column joints by 6° after ankle fusion. This could also explain why patients after TTC arthrodesis show even a greater increase in midfoot load: the subtalar joint, which has a compensatory hypermobility after ankle arthrodesis, is fused and therefore the midfoot is loaded even more and has to compensate alone for the motion in the sagittal plane (Sealey et al., 2009).

One would have expected the difference in RMI of healthy subjects and patients to become smaller when wearing shoes due to patients' values coming closer to healthy values. However, the RMI values of healthy subjects and patients converge to approximately 0.5. This is a pathological value, and so we are faced with the paradoxical fact that

shoes make the RMI of healthy subjects converge to an unhealthy value. The reasons for this are subject for future research.

There are only two studies assessing TAR and AA in shoes, which are in line with our findings: Jastifer et al. (2015) allowed patients to wear their own shoes. They observed also no difference between TAR and AA on flat surfaces but better results walking upstairs, downstairs, and downhill in TAR. Chopra et al. (2014) compared AA and TAR in sandals in 4 sizes and found a fully recovered bilateral gait mechanics in TAR but an altered mechanics in AA despite the differences in several parameters than compared to healthy controls.

The prescription of rocker bottom shoes with a stiff sole is a general practice after ankle arthrodesis and is expected to compensate for the loss of motion in the ankle (Hefti et al., 1980; King et al., 1980; Mazur et al., 1979; Sirveaux et al., 2006). We found no further beneficial effects of rocker bottom shoes compared to running shoes. Indeed, running shoes provided similar beneficial effects as rockers.

In conclusion, runners are beneficial for all patients including healthy controls. Rocker bottom shoes do not benefit much more and the benefit is greater for fusions and replacements. Because of this effect, future biomechanical studies should be done with shoe wear on. Furthermore, our results showed no difference between TAR and AA barefoot or shod. In all conditions, TAR and AA were inferior to healthy controls and TTC had the most inferior outcome barefoot or shod.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.clinbiomech.2015.12.013>.

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Fig. 4. The median of forefoot MF for TTC (squares), AA (circles), TAR (triangle), and healthy controls (diamonds). For values of the mean and Interquartile range, please see Table 2; for *p*-values, please see Supplementary Website Material.

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