The Journal of Foot & Ankle Surgery 58 (2019) 663–668

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

The Effect of Sagittal and Coronal Balance on Patient-Reported Outcomes Following Mobile-Bearing Total Ankle Replacement

Sarah Johnson-Lynn, PhD, FRCS (Tr & Orth)[1], Malik Siddique, MD, FRCS (Tr & Orth)[2]

[1] Orthopaedic Registrar, Department of Orthopaedics, Freeman Hospital, Newcastle upon Tyne, UK
[2] Consultant Orthopaedic Surgeon, Department of Orthopaedics, Freeman Hopsital, Newcastle upon Tyne, UK

ARTICLE INFO

Level of Clinical Evidence: 2

Keywords:
alignment
patient-reported outcome measures
total ankle arthroplasty

ABSTRACT

Total ankle replacement (TAR) is an established technique for the treatment of end-stage ankle arthritis. The aims of TAR include pain relief, preservation of tibiotalar movement, protection of adjacent joints, and restoration of anatomic alignment in the coronal and sagittal planes. The aims of this study were to determine the relative importance of pre- and post-TAR coronal and sagittal balance on postoperative patient-reported outcome measures (PROMs). A total of 101 ankles in 99 patients were included in this retrospective cohort study. Patients were scored preoperatively and at a minimum of 2 years by using the Foot and Ankle Outcome Score (FAOS), the American Orthopedic Foot and Ankle Society (AOFAS) hindfoot-ankle score, the Short Form-36 measures, and a set of radiographic measurements to define the sagittal and coronal alignment. There was no significant difference between the groups regarding the anterior or posterior translation of the talus preoperatively. There were no statistically significant correlations between any preoperative measure and any domain of the PROM data. Significant correlations were observed between postoperative medial distal tibial angle and the function domain of the FAOS and the AOFAS hindfoot-ankle score. Preoperative coronal and sagittal plane deformity are not markedly different, depending on the diagnosis. Preoperative deformity does not appear to correlate significantly with postoperative function, as measured by the PROM scores. Postoperative sagittal plane alignment does not correlate significantly with postoperative function, as measured by PROMs. Coronal plane alignment, as measured by the medial distal tibial angle, may be associated with postoperative function, as measured on the AOFAS hindfoot-ankle and FAOS function subscales.

Total ankle replacement (TAR) is an established technique for the treatment of end-stage ankle arthritis (1–3). The aims of TAR include pain relief, preservation of tibiotalar movement, protection of adjacent joints, and restoration of anatomic alignment in the coronal and sagittal planes (4). Most previous studies of ankle alignment before and after TAR have focused on the restoration of the coronal axis. A small number of previous studies have addressed sagittal alignment, but none have been addressed in the United Kingdom population, utilizing an uncemented, mobile-bearing TAR prosthesis (5). Cadaveric work has demonstrated that alterations in sagittal alignment affect the postoperative range of movement (6). However, previous studies have also demonstrated markedly varying degrees of restoration of sagittal alignment (7). They have mainly addressed the issue whether component malalignment and the geometry of bone cuts are associated with poor bony support and premature implant failure (8,9). They have not specifically addressed the relative importance of either pre- or postoperative sagittal and coronal alignment on patient-reported outcome measures (PROMs). Previous studies have also neither differentiated between patients on the basis of the reason for TAR nor attempted to determine whether any variation exists in the degree of preoperative deformity, depending on whether patients present because of osteoarthritis (OA), posttraumatic osteoarthritis (PTOA), or rheumatoid arthritis (RA).

The aims of this study were to determine the relative importance of the pre- and post-TAR coronal and sagittal balance on PROMs in the United Kingdom population, and to determine whether the cause of ankle arthritis is associated with the degree of pre- or postoperative deformity.

Patients and Methods

Patients

A total of 110 TARs in 108 consecutive patients were included in this retrospective cohort study. Ethical approval was not required, because clinical and PROM data were collected routinely and anonymized (by S.J.L.). Surgery of all patients was performed by a single surgeon (M.S.) with the Mobility (Depuy; Raynham, MA), uncemented, mobile-bearing TAR. All surgeries were performed between March 2006 and December 2009. All patients undergoing TAR during this period were included. However, 9 (8.2%) TARs were excluded, because they did not complete the minimum 2-year follow-up period, leaving

Financial Disclosure: None reported.
Conflict of Interest: None reported.

Address correspondence to: Sarah Johnson-Lynn, PhD, FRCS, Department of Orthopaedics, Freeman Hospital, Freeman Road, Newcastle upon Tyne, NE7 7DN, United Kingdom.

E-mail address: selynn@doctors.org.uk (S. Johnson-Lynn).

1067-2516/$ - see front matter © 2018 by the American College of Foot and Ankle Surgeons. All rights reserved.
https://doi.org/10.1053/j.jfas.2018.11.007

101 TARs in 99 patients. Patients were included in the RA group if they had a definitive diagnosis of seropositive rheumatoid disease from a consultant rheumatologist (10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] M05.8); those included in the PTOA group had a documented history of ankle, pilon, or talus fracture (ICD-10 M19.1); and those in the OA group presented with noninflammatory arthritis of the ankle, with no definite history of trauma (ICD-10 M19.0). The mean age of the patients was 61.5 (range 42 to 80) years, and 59 (60.0%) patients were male. Eighteen (18.2%) patients received a TAR for RA, 29 (29.3%) for PTOA, and 54 (54.5%) for primary OA. The mean follow-up period was 47 (range 36 to 73) months. There were 1 (0.99%) and 3 (2.97%) revisions in this cohort within 2 years and 5 years, respectively, of the day of the TAR surgery.

Patient-Reported Outcome Measures

The American Orthopedic Foot and Ankle Society (AOFAS) hindfoot-ankle score (10,11), the Foot and Ankle Outcome Score (FAOS) (12), and the Short Form-36 (SF-36) Health Survey (13) were completed by all patients preoperatively and at 1 year and 2 years postoperatively.

Radiographic Assessment of Outcome

The measurement of radiographic parameters was based on that of Cho et al (5) to provide some standardization with the existing literature. Radiographic parameters were assessed by 1 author (S.J.L.), using standard weightbearing anteroposterior and lateral radiographs, centered on the tibiotalar joint. Pre- and postoperative measurement comparisons were made between the immediate preoperative radiograph and the earliest postoperative radiograph taken weightbearing, with the angle between the tibia and the floor being within 5° of that in the preoperative radiograph. All reasonable attempts were made to standardize weightbearing radiographs, but small amounts of variation in rotation, particularly of the lateral radiograph, were encountered.

The preoperative parameters measured were tibial plafond height (TPH) (Fig. 1*A*), lateral malleolus–talar dome height (LM-T) (Fig. 1*B*), the ratio between TPH and LM-T (TPH/LM-T), the distance from the center of the talar body to the lateral process of the talus (T-L) (Fig. 1*C*), the tibiotalar ratio (TTR) (Fig. 1*D*), the anterior distal tibial angle (ADTA) (Fig. 1*E*), and the medial distal tibial angle (MDTA) (Fig. 1*F*).

TPH was measured on the anteroposterior radiographs as the distance from the center of Chaput tubercle to the tibial plafond; LM-T was measured on the same radiograph from the tip of the lateral malleolus to the talar dome; and T-L was measured on the lateral radiograph from the center of a circle of best fit, superimposed on the talar dome, giving the center of the talar body and a vertical line through the lateral process of the talus. The TTR was measured on the lateral radiograph as the ratio of the distance along a horizontal line bisecting the talus that is intersected by a line down the anatomic axis of the tibia and dividing this by the total talar length along the horizontal line. The ADTA was measured on the lateral radiograph as the anterior angle subtended by the anatomic axis of the tibia and a horizontal line along the inferior border of the tibial plafond. The MDTA was measured on the anteroposterior radiograph as the medial angle subtended by the anatomic axis of the tibia and the tibial plafond line.

Postoperative measurements consisted of repeating the MDTA, ADTA, TTR, TPH/LM-T, and T-L, but taking the center of the 2 components as the references for the measurements. In addition, the lateral talar bone-component angle (LTBCA) and the anteroposterior offset ratio (APOR) of the talar compared to the tibial component were also measured. The LTBCA was calculated on the lateral radiograph as the angle between the long axis of the talus and the long axis of the talar component. The APOR was calculated as the horizontal distal between the centers of the circles of best fit over the distal tibia and over the dome of the talar component.

To establish normal values for the measurements in the local United Kingdom population, measurements were performed on the radiographs of 50 patients who were treated for soft tissue injury of the ankle, with no evidence of arthritis. The summary values are presented in Table 1.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism 6 (GraphPad Software, San Diego, CA) (by S.J.L.). Normality of the data was assessed using the Shapiro-Wilk test, and nonparametric methods were employed for further analysis. Comparisons of the pre- and postoperative radiographic measures were performed using the Kruskal-Wallis test. A power calculation was performed with $\alpha = 0.05$ and $\beta = 80\%$, and based on the work of Cho et al (5), the minimum sample size estimated to identify a statistically significant difference in the main radiographic parameters, should one exist, was 16. The correlation of the PROM data with the radiographic measures was performed using Spearman's correlation. We defined statistical significance at $p \leq .5$.

Results

Figure 2 illustrates the preoperative radiographic measurements. The mean ± standard deviation (SD) preoperative TTR was 0.50 ± 0.079 in the control group, 0.56 ± 0.23 in the OA group, 0.61 ± 0.24 in the PTOA group, and 0.48 ± 0.16 in the RA group (Fig. 2). There was no significant difference between the groups with regard to the anterior or posterior translation of the talus preoperatively, as measured by the TTR. There was a tendency for a greater degree of anterior talar translation in the PTOA group than in the control group, but this did not reach significance. No statistically significant differences were detected in preoperative ADTA between the groups, but there was a trend for less posterior slope of the tibia in the PTOA group. The MDTA demonstrated a trend for lesser ankle varus in the RA than in the control group, but this did not reach significance. This is reflected in Fig. 3, which demonstrates that <30% of the OA and RA groups had measures of the ADTA and the MDTA outside 2 SDs from the mean measurement of the control group; however, >50% of the PTOA group had a TTR value outside 2 SDs from the mean measurement of the control group.

Very little difference was seen in MDTA or TTR between pre- and postoperative measures in any group; therefore, there was little evidence of correction toward the control group mean. The postoperative ADTA measures diverged further from the mean measurement of the control group, suggesting that the posterior tibial slope was not recreated (Fig. 4). No significant differences were seen between the diagnostic groups for any of the postoperative measures, likely owing to the high variability of the data (Fig. 5). Preoperative radiographic parameters were correlated with the separate domains of the SF-36, FAOS, and the total AOFAS hindfoot-ankle scores at 2 years. No statistically significant correlations were detected between any preoperative measure and any domain of the PROM data (Table 2). Correlations between the postoperative radiographic measures and the PROM scores are depicted in Table 3. Significant correlations were observed between postoperative MDTA and the mental component of the SF-36 score, the function domain of the FAOS, and the AOFAS hindfoot-ankle score. There was also a significant correlation between postoperative T-L and the function domain of the FAOS.

Discussion

Malalignment in the sagittal and coronal planes in the context of end-stage arthritis of the ankle is common, and 1 of the main goals of TAR is to restore normal alignment. It is perhaps surprising that no significant differences were found in the preoperative radiographic measures on any parameter between the diagnostic groups. As the PTOA was analyzed separately, a greater degree of deformity may be expected in these patients; however, this was not the case in the current cohort. The preoperative measures also confirm that the anterior displacement of the talus was the most common deformity in the sagittal plane in the osteoarthritic and PTOA groups. Preoperative varus alignment was more common in both the OA (31, 57.4%) and PTOA groups (18, 62.1%), whereas valgus alignment was more common in the RA group (10, 55.6%).

Although there was a significant correlation between postoperative MDTA and several domains on the PROM scores at 2 years, no significant difference was detected either in postoperative MDTA between the groups or in the PROM scores. There was no significant difference, within the sample available, between the groups on the other postoperative radiographic measures, demonstrating similar effectiveness with regard to deformity correction in all groups. Previous authors have also not found any significant difference in PROMs between diagnostic groups at 2 years following Mobility TAR (14). A previous study has found the preoperative anterior translation of the talus to be corrected postoperatively and not associated with postoperative poorer outcomes (15). This may be owing to the movement at the interfaces between the tibial and talar components and the polyethylene, allowing a degree of autocorrection of alignment during movement (16). However, other authors have found some correlation between the APOR and both the AOFAS hindfoot-ankle score and the range of movement (17).

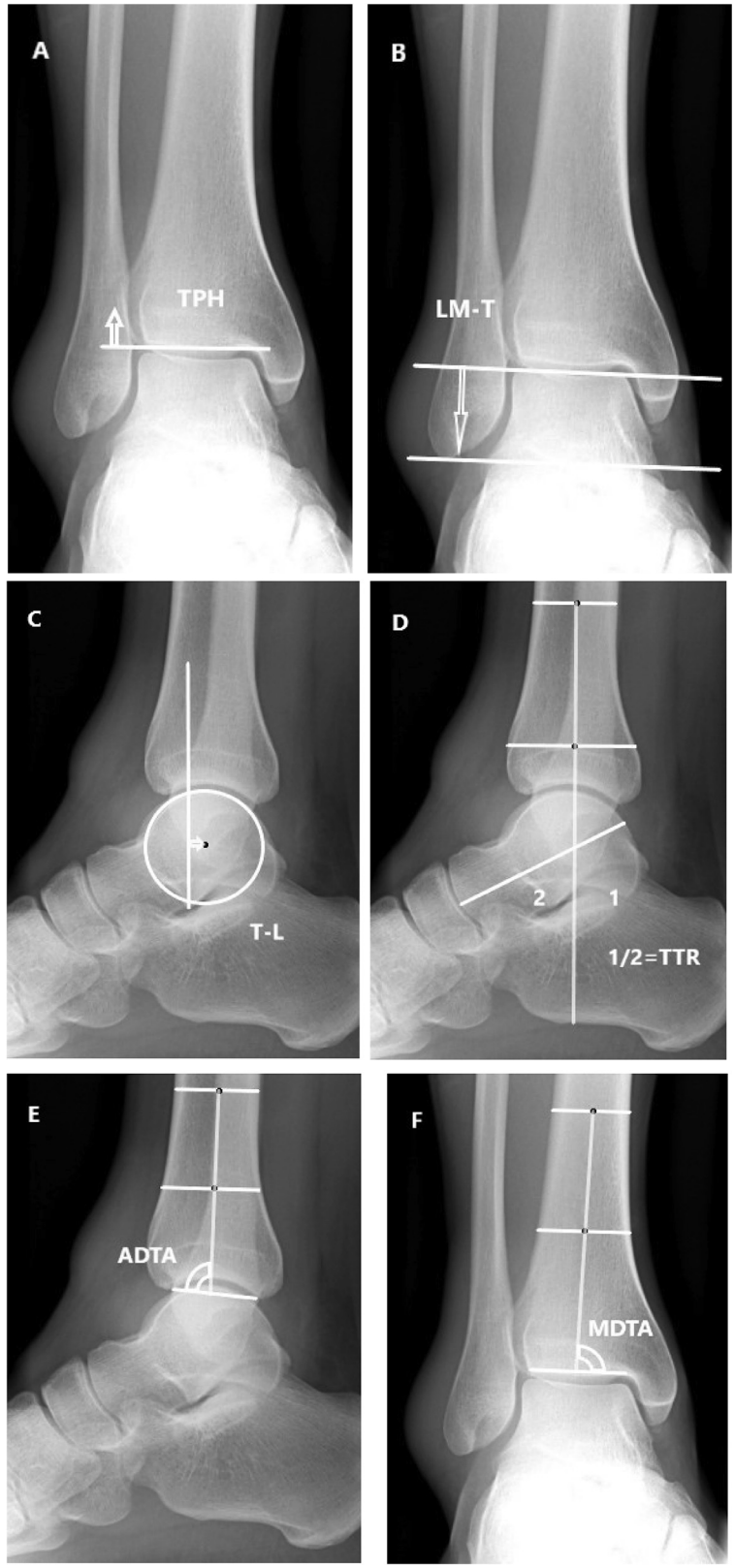

Fig. 1. (*A*) Tibial plafond height (TPH): Distance from the center of Chaput tubercle to the tibial plafond. (*B*) Lateral malleolus–talar dome height (LM-T): Tip of the lateral malleolus to the talar dome. (*C*) Distance from the center of the talar body to the lateral process of the talus (T-L): Center of a circle of best fit, superimposed on the talar dome, giving the center of the talar body and a vertical line through the lateral process of the talus. (*D*) Tibiotalar ratio (TTR): Ratio of the distance along a horizontal line bisecting the talus that is intersected by a line down the anatomic axis of the tibia and the total talar length along the horizontal line. (*E*) Anterior distal tibial angle (ADTA): Angle on the lateral radiograph subtended by the anatomic axis of the tibia and a horizontal line along the inferior border of the tibial plafond. (*F*) Medial distal tibial angle (MDTA): Medial angle subtended by the anatomic tibial axis and the tibial plafond line.

Table 1
Local population values for preoperative radiographic parameters (N = 50)

	Pre-TPH/LM-T	Pre-T-L (mm)	Pre-TTR	Pre-ADTA (°)	Pre-MDTA (°)
Control	0.276 ± 0.067	8.03 ± 1.00	0.495 ± 0.079	84.16 ± 2.68	88.65 ± 2.59

Abbreviations: ADTA, anterior distal tibial angle; LM-T, lateral malleolus–talar dome height; MDTA, medial distal tibial angle; T-L, distance from the center of the talar body to the lateral process of the talus; TPH, tibial plafond height; TTR, tibiotalar ratio.
Data presented as mean ± standard deviation.

As with the findings by Cho et al (5), the anterior translation of the talus was the most common sagittal plane deformity in this cohort and varus deformity was somewhat more common than valgus. This was reflected in the number of patients with a TTR outside 2 SDs from the mean measurement of the control cohort being higher than that for other measures (39% to 52%). Previous authors have found that anterior placement of the talar component in comparison with the tibial component results in an improved range of movement (7). However, there was only a weak correlation between the correction of preoperative deformity and

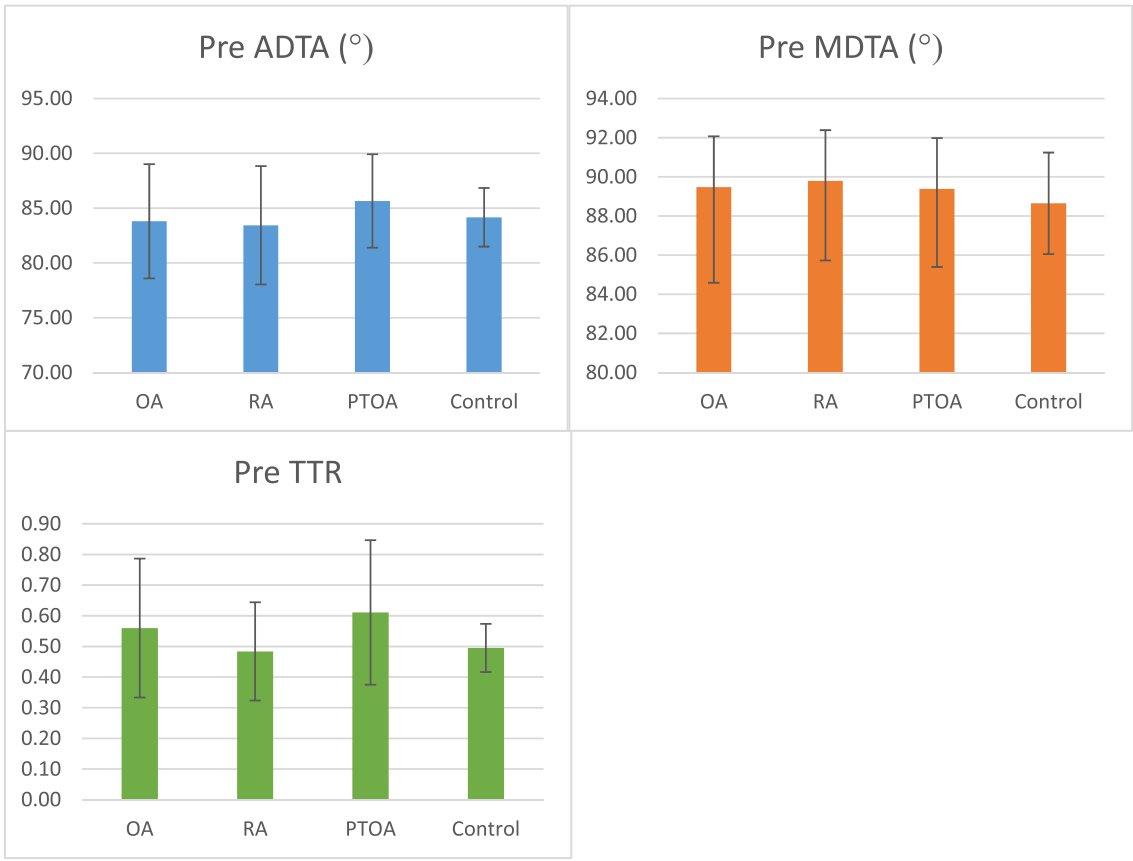

Fig. 2. Preoperative radiographic parameters by diagnostic group, illustrating anterior distal tibial angle (ADTA), medial distal tibial angle (MDTA), and tibiotalar ratio (TTR) for each of the diagnostic groups and the control group (osteoarthritis [OA], n = 54; posttraumatic arthritis [PTOA], n = 29; rheumatoid arthritis [RA], n = 18).

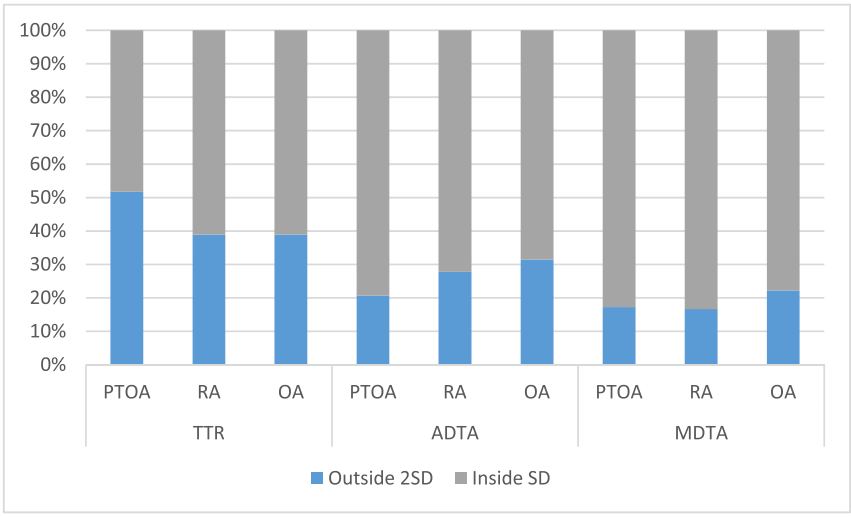

Fig. 3. Percentage of ankles inside and outside 2 standard deviations (SDs) from the mean of the control cohort for each preoperative radiographic measure (N = 101). ADTA, anterior distal tibial angle; MDTA, medial distal tibial angle; OA, osteoarthritis; PTOA, posttraumatic arthritis; RA, rheumatoid arthritis; TTR, tibiotalar ratio.

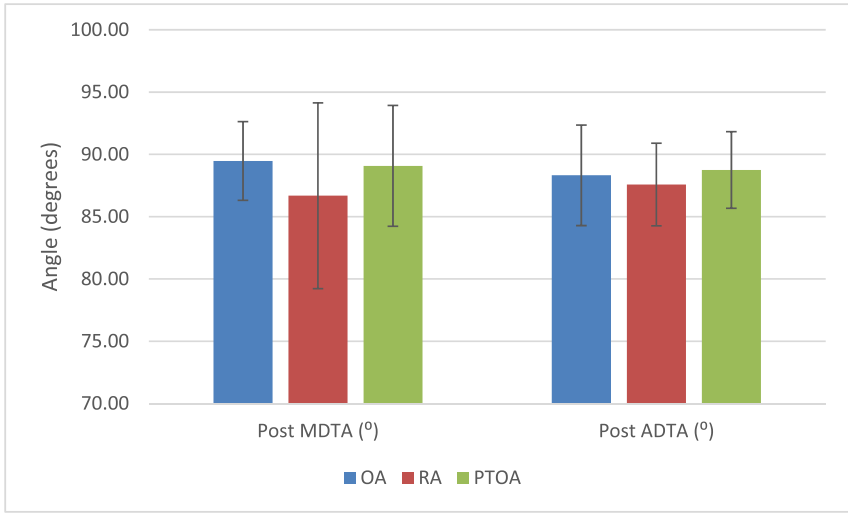

Fig. 4. Graph of postoperative medial distal tibial angle (MDTA) (°) and anterior distal tibial angle (ADTA) (°) grouped by diagnosis (osteoarthritis [OA], n = 54; posttraumatic arthritis [PTOA], n = 29; rheumatoid arthritis [RA], n = 18).

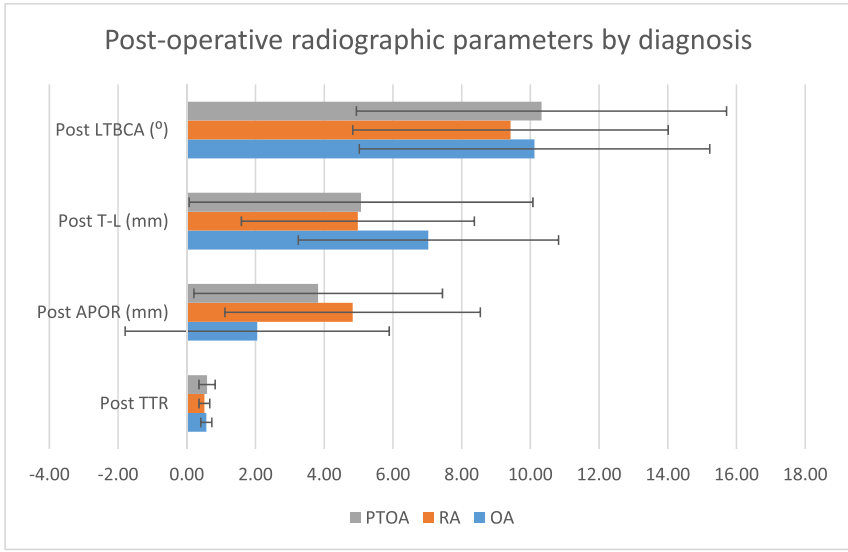

Fig. 5. Postoperative radiographic parameters, lateral talar bone-component angle (LTBCA), distance from the center of the talar body to the lateral process of the talus (T-L), anteroposterior offset ratio (APOR), and tibiotalar ratio (TTR), grouped by diagnosis. OA, osteoarthritis; PTOA, posttraumatic arthritis; RA, rheumatoid arthritis.

Table 2
Correlation of preoperative radiographic parameters with patient-reported outcome measures data (N = 101)

	SF-36 Physical	SF-36 Mental	FAOS Stiffness	FAOS Function	FAOS Pain	AOFAS
TTR	0.67	0.57	0.1	0.37	0.15	0.23
ADTA	0.21	0.5	0.13	0.17	0.26	0.43
MDTA	0.99	0.7	0.98	0.4	0.42	0.46

Abbreviations: ADTA, anterior distal tibial angle; AOFAS, American Orthopedic Foot and Ankle Society; FAOS, Foot and Ankle Outcome Score; MDTA, medial distal tibial angle; SF-36, Short Form-36; TTR, tibiotalar ratio.
Data presented as Spearman correlation coefficients.

postoperative function. A large degree of the range of movement following TAR can be attributed to the anteroposterior movement of the polyethylene bearing, which may explain the lack of convincing correlation between sagittal alignment and function (18). An important part of restoring coronal and sagittal alignment in TAR is the ligament tensioning and rebalancing, which may not be fully accounted for by the current radiographic measures (19).

With a mean follow-up period of 47 months and only 3 revisions in that time, the influence of alignment on failure in this cohort in the longer term cannot be determined. Previous studies have suggested a higher rate of revision in patients with more significant coronal plane deformity (8). However, other authors have found equivalent rates of revision in individuals with very significant preoperative coronal plane deformity and equivalent functional outcomes (20). Correlation of both

Table 3
Correlation of postoperative radiographic parameters with patient-reported outcome measures data (N = 101)

	SF-36 Physical	SF-36 Mental	FAOS Stiffness	FAOS Function	FAOS Pain	AOFAS
APOR	0.61	0.7	0.43	0.45	0.48	0.7
TTR	0.07	0.85	0.53	0.37	0.57	0.75
MDTA	0.24	0.05	0.24	0.04	0.07	0.001
ADTA	0.39	0.43	0.95	0.39	0.97	0.56
T-L	0.1	0.76	0.08	0.03	0.07	0.86
LTBCA	0.62	0.23	0.97	0.16	0.12	0.64

Abbreviations: ADTA, anterior distal tibial angle; AOFAS, American Orthopedic Foot and Ankle Society; FAOS, Foot and Ankle Outcome Score; APOR, anteroposterior offset ratio; LTBCA, lateral talar bone-component angle; MDTA, medial distal tibial angle; SF-36, Short Form-36; T-L, distance from the center of the talar body to the lateral process of the talus; TTR, tibiotalar ratio.
Data presented as Spearman correlation coefficients.

pre- and postoperative radiographic measures with the PROM data demonstrated no significant correlation for preoperative measures, perhaps unsurprising, because the aim of TAR is to restore more normal ankle kinematics. However, the correlation with postoperative measures demonstrates significant associations with the coronal plane (MDTA) rather than the sagittal plane alignment, suggesting a more important role for correct alignment in the coronal plane in terms of postoperative function. A recent article also demonstrated no clear link between the sagittal alignment or the translation of the talus and the short-term functional outcome (5).

There were several methodologic limitations of this study. These include the retrospective nature, relatively short follow-up period, and small subgroups, particularly the RA group, increasing the likelihood of a type II statistical error. The differences in the control group parameter measurements may make comparisons with other populations difficult. Furthermore, the fact that a single surgeon used only 1 type of total ankle implant in the cohort, means that the results may not generalize to a wider range of surgeons and devices. However, despite our appreciation of the limitations of this investigation, we believe that this study adds useful information to the currently available literature on the effect of deformity and its correction on the outcome of TAR.

In conclusion, although there were more patients with varus malalignment in the PTOA and OA groups and more valgus malalignment in the RA group, there was no significant difference in preoperative coronal and sagittal plane deformity between patients with RA, PTOA, and OA. Moreover, there was no statistically significant correlation between preoperative deformity and postoperative function, as measured by the AOFAS hindfoot-ankle score, FAOS, or SF-36 scores ($p > .05$ for TTR, ADTA, and MDTA). Furthermore, postoperative sagittal plane alignment did not correlate significantly with postoperative function, as measured by the AOFAS hindfoot-ankle score, FAOS, or SF-36 scores ($p > .05$ for T-L, ADTA, and TTR). Finally, coronal plane alignment, as measured by the MDTA, was significantly correlated with the postoperative AOFAS hindfoot-ankle score ($p = .001$) and the function subscale of the FAOS score ($p = .04$).

Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1053/j.jfas.2018.11.007.

References

1. Desai S, Glazebrook M, Penner M, Wing K, Young A, Pinsker E, Daniels T. Quality of life in bilateral vs. unilateral end-stage ankle arthritis and outcomes of bilateral vs. unilateral total ankle replacement. J Bone Joint Surg Am 2017;99:133–140.
2. Henricson A, Skoog A, Carlsson A. The Swedish ankle arthroplasty register: an analysis of 531 arthroplasties between 1993 and 2005. Acta Orthop 2007;78:569–574.
3. Stengel D, Bauwen K, Ekernkamp A, Cramer J. Efficacy of total ankle replacement with meniscal-bearing devices: a systematic review and meta-analysis. Arch Orthop Trauma Surg 2005;125:109–119.
4. Greisberg J, Hansen Jr ST, Digiovanni C. Alignment and technique in total ankle arthroplasty. Oper Tech Orthop 2004;14:21–30.
5. Cho J, Yi Y, Ahn TK, Choi HJ, Park CH, Chun DI, Lee JS, Lee WC. Failure to restore sagittal tibiotalar alignment in total ankle arthroplasty. Bone Joint J 2015;97:1525–1532.
6. Tochigi Y, Rudert MJ, Brown TD, McIff TE, Saltzman CL. The effect of accuracy of implantation on range of movement of the Scandinavian total ankle replacement. J Bone Joint Surg Br 2005;87:736–740.
7. Cenni F, Leardini A, Belvedere C, Buganè F, Cremonini K, Miscione MT, Giannini S. Kinematics of the three components of a total ankle replacement: in vivo fluoroscopic analysis. Foot Ankle Int 2012;33:290–300.
8. Wood PLR, Karski MT, Watmough P. Total ankle replacement: the results of 100 mobility total ankle replacements. J Bone Joint Surg Br 2010;92:958–962.
9. Bischoff JE, Schon L, Saltzman C. Influence of geometry and depth of resections on bone support for total ankle replacement. Foot Ankle Int 2017;38:1026–1034.
10. Kitoaka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux and lesser toes. Foot Ankle Int 1994;15:349–353.
11. Ibrahim T, Beri A, Azzabi M, Best AJ, Taylor GJ, Menon DK. Reliability and validity of the subjective component of the American Orthopaedic Foot and Ankle Society clinical rating scales. J Foot Ankle Surg 2007;46:65–74.
12. Roos EM, Brandsson S, Karlsson J. Validation of the Foot and Ankle Outcome Score for ankle ligament reconstruction. Foot Ankle Int 2001;22:788–794.
13. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993;2:217–227.
14. Ramaskandhan J, Kakwani R, Kometa S, Bettinson K, Siddique M. Two-year outcomes of MOBILITY total ankle replacement. J Bone Joint Surg Am 2014;96:e53.
15. Lee K, Kim M, Park K, Cho K, Primadhi A. Effect of anterior translation of the talus on outcomes of three-component total ankle arthroplasty. BMC Musculoskelet Disord 2013;14:260.
16. Barg A, Elsner A, Chuckpaiwong B, Hintermann B. Insert position in the three-component total ankle replacement. Foot Ankle Int 2010;31:754–759.
17. Barg A, Elsner A, Anderson AE, Hintermann B. The effect of three-component total ankle replacement malalignment on clinical outcome: pain relief and functional outcome in 317 consecutive patients. J Bone Joint Surg Am 2011;87:736–740.
18. Cenni F, Leardini A, Cheli A, Catani F, Belvedere C, Romagnoli M, Giannini S. Position of the prosthesis components in total ankle replacement and the effect on motion at the replaced joint. Int Orthop 2012;36:571–578.
19. Colin F, Bolliger L, Lang T, Knupp M, Hintermann B. Effect of supramalleolar osteotomy and total ankle replacement on talar position in the varus osteoarthritic ankle: a comparative study. Foot Ankle Int 2014;35:445–452.
20. Hobson SA, Karantana A, Dhar S. Total ankle replacement in patients with significant preoperative deformity of the hindfoot. J Bone Joint Surg Br 2009;91:481–487.