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ORIGINAL REPORT

VARUS KNEE LIMITS PAIN RELIEF EFFECTS OF LATERALLY WEDGED INSOLES AND ANKLE-FOOT ORTHOSES IN MEDIAL KNEE OSTEOARTHRITIS

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Objective: **To investigate the impact of varus malalignment of the knee on pain reduction achieved by an ankle-foot orthosis and a laterally wedged insole in patients with medial knee osteoarthritis.**
Design: **Secondary analysis of a randomized, clinically prospective cross-over study.**
Patients: **Twenty-eight participants with medial knee osteoarthritis.**
Methods: **All participants wore a 5-mm laterally wedged insole and an ankle-foot orthosis for a period of 6 weeks each in a randomized order. Pain was reported on a numerical rating scale and was correlated with limb alignment, as defined by the mechanical axis deviation in full-leg standing radiographs.**
Results: **Insole and orthosis use reduced pain compared with baseline (median knee pain change: insole −0.5 (−5 to +6), orthosis −1.5 (−7 to +5). A higher mechanical axis deviation (greater varus) correlated significantly with smaller pain reduction for both aids (insole $p = 0.003$, orthosis $p < 0.001$). A cut-off to predict pain response was found at a mechanical axis deviation of 14–15 mm for both aids, i.e. >3° knee varus.**
Conclusion: **There is a correlation between varus malalignment and pain reduction. There seems to be a mechanical axis deviation cut-off that predicts the response to treatment with the aids with good sensitivity.**

Key words: orthoses; foot orthoses; osteoarthritis of the knee; pain; arthralgia; conservative treatment.

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LAY ABSTRACT

Osteoarthritis of the knee can be treated using orthoses and insoles to unload the most damaged and painful inner (medial) part of the knee. However, patients do not benefit equally from these devices and there is not enough scientific data to predict which patients will benefit from an orthosis or insole. This study investigated whether the genu varum (degree of bow-leggedness) correlates with pain reduction when using an insole or an ankle-foot orthosis. A total of 28 patients with knee osteoarthritis received both aids, each for a period of 6 weeks, in random order. They documented knee pain before and after using the devices. Radiographs of the leg were analysed to determine the degree of genu varum. Statistical analysis showed that patients with straighter legs experienced better pain reduction with both aids than did bow-legged patients. In conclusion, ankle-foot orthoses and insoles are less effective in bow-legged patients.

Approximately 45% of women and 33% of men over the age of 60 years show radiological signs of osteoarthritis of the knee, but only one-third develop symptoms (1). The distribution of osteoarthritis in the knee joint is not symmetrical. It is assumed that the significantly higher biomechanical load of the medial joint compartment, which transfers 60–80% of the load, is a major contributor to the tenfold more frequent affection of this compartment (2, 3).

The conservative treatment of medial knee osteoarthritis aims to reduce pain, improve function and slow the progression of the disease (4, 5). Laterally wedged insoles (LWI) are an established therapy concept, described by Sasaki & Yasuda (6). Biomechanically, they act by shifting the centre of pressure below the foot laterally. This reduces the frontal lever arm of the ground reaction force and, subsequently, the external knee adduction moment (eKAM) (7). Although a number of clinical studies and meta-analyses have shown positive clinical and biomechanical effects (7–9), other authors did not find sufficient evidence for therapy recommendation (10, 11). A Cochrane review from 2015 was inconclusive (12).

Ankle-foot orthoses (AFO) represent a more recent approach in the treatment of medial knee osteoarthritis first described in 2006 by Schmalz et al. in healthy participants (13). More recent studies show positive clinical and biomechanical effects in patients

with knee osteoarthritis (14–17). Nevertheless, not all patients within these cohorts benefited from AFO treatment.

There is a need for predictors for the heterogeneous response to these conservative treatment approaches. While a relevant number of biomechanical non-responders to LWI (18) may explain why no consistent clinical benefit can be shown, the lack of correlation between pain and eKAM reduction shows that other mediators must be considered (19). In forward musculoskeletal modelling, next to muscle activation, frontal and sagittal plane moments, the knee varus angle seems to have a greater influence on medial contact forces (20). It is not only predictive of disease progression (21). A varus deformity above 5° (mechanical tibiofemoral angle) has also been shown to reduce the effect of quadriceps muscle strengthening on pain (22). The authors assumed that soft tissue stretching in the malaligned knee might play a role in maintaining the pain, underlining that varus deformity should be considered in conservative treatment approaches (22).

Limb alignment can be quantified clinically, or in full-leg standing radiographs. The mechanical axis (MA) is defined as the line joining the hip joint centre and the centre of the dome of the talus; the mechanical axis deviation (MAD) represents the distance of the MA from the knee joint centre in the frontal plane, as shown in Fig. 1 (23).

The aim of this study was to investigate whether the MAD is a predictor for the clinical response to LWI and AFO in the treatment of medial osteoarthritis of the knee. Since pain is a major cause of disability, and thus a main target in disease treatment (24), the influence of the MAD on the symptom "pain" was investigated.

MATERIAL AND METHODS

Study design

This is a secondary analysis carried out on participants of a study comparing AFO and LWI in patients with medial osteoarthritis of the knee (25), hypothesizing that the MAD has an influence on the clinical response to LWI and AFO.

Randomized, monocentric, clinically prospective cross-over study conducted at Heidelberg University Hospital, Clinic for Orthopaedics and Trauma Surgery. Data acquisition and analysis were performed in compliance with protocols approved by the ethics committee of the medical faculty of Ruprecht Karl University of Heidelberg (S–021/2018). The study was registered in the German Register of Clinical Studies (DRKS00016783) and was conducted in accordance with the Declaration of Helsinki.

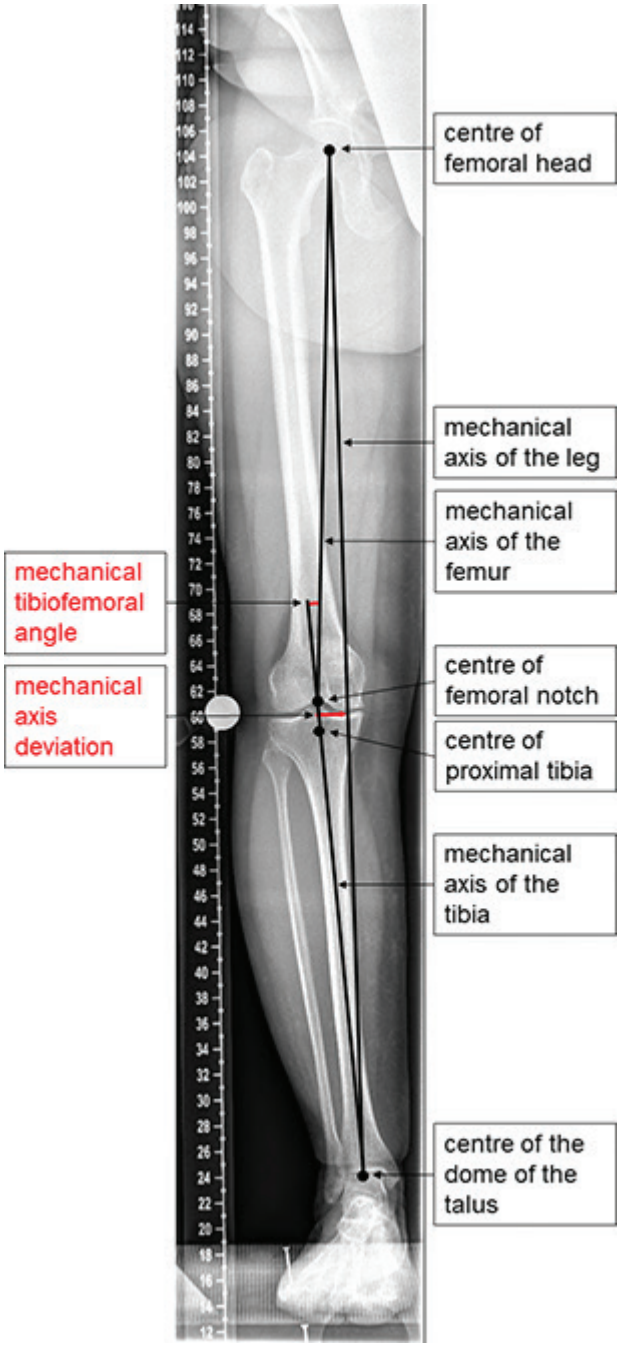

Fig. 1. Mechanical tibiofemoral axis and mechanical axis deviation in a full-leg standing radiograph.

Patients with symptomatic medial knee osteoarthritis were recruited from the outpatient orthopaedic clinic of Heidelberg University Hospital. Over a period of 16 months (May 2018 to August 2019), 42 participants were included. All participants provided written informed consent. Inclusion criteria included the following:

- age: at least 18 years of age;
- medially accentuated knee osteoarthritis stage 1–3 according to Kellgren & Lawrence (26);

- no previous orthotic treatment due to knee osteoarthritis;
- no previous surgery to treat knee osteoarthritis;
- ability to walk.

In a cross-over design, each patient received both interventions for six weeks each in a randomized order. The treatment sequence was assigned by two researchers with a 1:1 balanced, block-wise randomized allocation list in MATLAB (The Math Works, Inc., Natick, MA, USA). Patients were assigned to the next allocation spot on the list according to their baseline examination date. This randomization was known to patients and researchers. Following randomization, the participants received one of the following aids on the side of symptomatic knee osteoarthritis:

- Agilium Freestep orthosis (Otto Bock HealthCare, Duderstadt, Germany): Ankle-foot orthosis with a footplate that is adapted to the patient's shoes. The ankle joint complex is bridged via a hinged joint with free motion in the sagittal plane and subtotal restriction in the frontal and transverse planes. There is a connection to the flat lateral shank inlay, which is adjusted to the individual anatomy to control the pressure applied to the proximal shank. It was provided in combination with neutral soft foam insoles with longitudinal and transverse arch support (Hepuflex Business Mikrofaser, Art.-Nr. 5513-022, HEMA Orthopädische Systeme GmbH, Tunzenhausen, Germany).
- Long-sole insoles with longitudinal and transverse arch support with a high-shore 5-mm lateral wedge.

When both knees met the inclusion criteria, both knees received the same intervention simultaneously.

The supply of aids, adaptation and training in use were conducted by the Department of Technical Orthopaedics at Heidelberg University Hospital (certified according to ISO 13485). After adaptation of the first aid, the participants were instructed to use it in everyday life for a period of six weeks before changing to the other aid for another six weeks. After completing the twelve-week study protocol, the participants were left with the option to continue using any one of the two aids tested.

Patients underwent three examinations: at baseline, after six weeks (end first intervention), and after twelve weeks (end second intervention). The outcome measure evaluated in this analysis was knee pain on the affected side in the last seven days on a numerical rating scale from 0 (none) to 10 (worst). Knee pain was documented on all 3 examination dates and was compared with the baseline values.

In case of bilateral use of the intervention, only the knee with the higher baseline pain level was included in the data analysis. In case of bilaterally equal symptoms and equal radiographic severity on both sides, the assessed side was randomized by a coin toss (one case).

A standardized clinical examination was conducted at baseline to evaluate the passive range of motion of hip, knee, and ankle joints. The following foot deformities were assessed on a semi-quantitative scale (none – slight – marked): pes equinus, pes valgus, pes varus, pes planus, pes transversoplanus, pes adductus, pes excavatus, and hallux valgus.

Limb alignment analysis

X-ray analysis of limb alignment was based on full weight-bearing long-standing anterior-posterior radiographs with approximately equal loading on both limbs. Only patients who had these radiographs before the start of the study were included in the analysis ($n=28$). The evaluation was conducted with the planning software TraumaCad version 2.5 (Brainlab Ltd., Petach-Tikva, Israel). The process was conducted separately by two authors, whose values for the MAD of each patient were averaged. The distance between the centre of the knee and the mechanical axis defines the MAD and is proposed to be normal with 10 mm of medial deviation (range 3−17 mm) (23). The mechanical tibiofemoral angle was determined likewise by 1 author; here, normal values of 1.0° to 1.3° varus have been reported (27, 28). In this article, positive values for the MAD and tibiofemoral angle represent a varus alignment, while negative values indicate valgus alignment. The definition of the different measures is shown in Fig. 1.

Statistical analysis

Statistical analysis was performed using SPSS 27 (IBM Deutschland GmbH, Ehningen, Germany). The first step included a descriptive evaluation of the anthropometric data of the study cohort as well as the MAD and pain on the numerical rating scale, stating means and standard deviations or median and quartiles for ordinally scaled variables. The data were tested for normal distribution with the Shapiro-Wilk test. As not all parameters were normally distributed, further analysis was carried out non-parametrically. This was followed by a Spearman correlation analysis between MAD and changes in pain with AFO and LWI. The corresponding changes in pain and MAD were graphically displayed in a scatter plot. Receiver operating characteristic curves (ROC curves) were then created for LWI and AFO and finally cut-off values for the MAD were calculated using Youden's index. For this purpose, responders were defined as participants whose pain was reduced compared with baseline after using the respective aid.

For a direct comparison of the effects of both aids on the outcome pain, a two-step analysis was used

considering the special characteristics of the cross-over study design. As proposed by Wellek et al. (29), results were checked for carry-over effects in relation to the treatment sequence. For this purpose, the study group was divided into the cohorts "AFO first" and "LWI first" according to treatment sequence. The sums of pain values at T1+T2 were then compared between the cohorts using the Mann–Whitney *U* test. In a second step, the treatment effects were directly compared by comparing the difference "T2–T1" between the 2 cohorts using a Mann–Whitney *U* test.

Table I. Anthropometric data, age, gender distribution, mechanical axis deviation and intervention side of the study participants

	Treatment sequence		
	AFO first	LWI first	Total
	Mean (SD)	Mean (SD)	Mean (SD)
Parameter			
Age (years)	60.1 (8.4)	56.7 (7.5)	58.3 (8.0)
Height (cm)	172 (11)	174 (10)	173 (10)
Weight (kg)	89.5 (16.0)	91.1 (12.5)	90.4 (14.0)
BMI (kg/m²)	30.2 (4.9)	30.0 (3.8)	30.1 (4.2)
MAD (mm)	12.9 (13.0)	14.0 (12.0)	13.5 (9.9)
Tibiofemoral angle (°)	3.6 (2.5)	3.4 (3.0)	3.5 (2.7)
	Median [quartiles]	Median [quartiles]	Median [quartiles]
Knee pain at baseline (NRS)	5 [4; 7]	4 [3; 7]	5 [3;7]
	n	*n*	*n*
Male	8	8	16
Female	5	7	12
Intervention side			
Right	5	6	11
Left	5	6	11
Bilateral	3	3	6
Kellgren and Lawrence degree (26)			
1	2	5	7
2	7	6	13
3	4	4	8
Total	13	15	28

AFO: ankle-foot orthosis; BMI: body mass index; LWI: laterally wedged insole; MAD: mechanical axis deviation; NRS: numerical rating scale (0 – no pain, 10 – worst pain).

RESULTS

A total of 42 subjects agreed to participate in the study after detailed clarification. Three participants were excluded due to disabling hip pain, knee pain with inability to walk and non-compliance with the AFO. Among the remaining 39 participants, 28 had a long-standing radiograph and could be included in the current analysis. The 28 patients included in the analysis did not differ significantly from the remaining patients regarding age, height, weight, BMI, side of intervention and sex distribution. Table I illustrates baseline data of the study cohort. Fig. 2 depicts the flow diagram of patients in the study according to the CONSORT guidelines.

At baseline, the most common comorbidities were orthopaedic disorders of the lower extremity: Contralateral knee pain (14 cases, including bilateral osteoarthritis), hip pain (7 cases) and foot deformities (8 cases). The most frequent foot deformities were pes planus, valgus and transversoplanus, partly in combination. In the standardized clinical examination, 6 patients presented a knee extension deficit of 3–5 degrees.

The statistical test for carry-over-effects yielded a non-significant result ($p=0.74$ for comparing the sums of T2+T3 between treatment sequence groups).

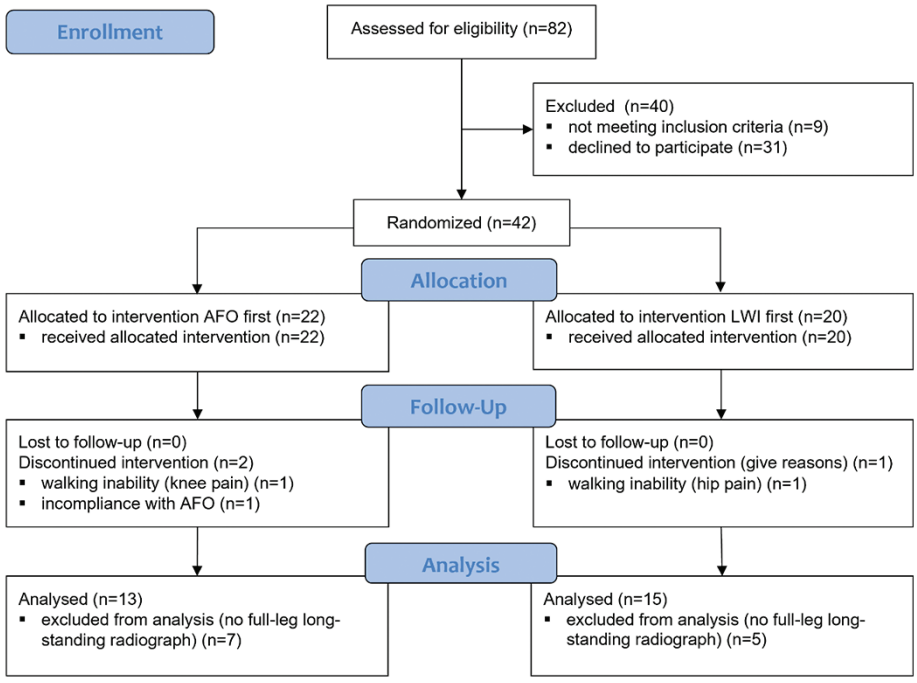

Fig. 2. CONSORT flow diagram of study participants.

As shown in Table II, both aids reduced knee pain significantly, although no significant difference between the 2 aids was found.

The Spearman-rho correlations in Table III show a moderate to strong correlation of the MAD to the pain difference from baseline with both AFO and LWI. The absolute pain score after AFO use was positively correlated with the MAD, while this tendency was weaker for the LWI. Absolute pain after LWI showed a stronger correlation with baseline pain than AFO. Pain at baseline was not clearly correlated with limb alignment. This can also be seen in the scatter plots (Fig. 3). In addition, the changes in pain caused by both aids correlated strongly with each other.

Based on the ROC curves (Fig. 4), cut-off values for the prediction of response to each aid based on the MAD were determined. Optimal cut-off values for the MAD of 14.25 mm (LWI) and 14.75 mm (AFO) were obtained, corresponding to a mechanical tibiofemoral angle of 3.2° and 3.4° varus, respectively (Table IV). A less marked varus deformity predicted response to each aid with over 80% sensitivity.

DISCUSSION

The aim of the study was to evaluate the relationship between MAD and pain reduction with LWI and AFO in individuals with medial osteoarthritis of the knee. The results showed a moderate to strong correlation of MAD with pain reduction. The statistical evaluation allowed a cut-off to be determined for the MAD at approximately 14.5 mm (i.e. tibiofemoral angle < 3.3° varus), which predicted the response to treatment with the aids with a sensitivity above 80%.

While changes in pain with both aids showed a significant correlation to the mechanical axis deviation, this relationship appeared more marked with the AFO than the LWI. In case of the AFO, absolute pain scores after the intervention were correlated more strongly to the MAD, while absolute pain after LWI use was also considerably predicted by baseline pain.

Considering baseline pain, no clear correlation with the MAD was found. Such a correlation could have been expected due to the known causal correlation between knee varus alignment and osteoarthritis progress (20, 30). The sample size was most likely not large enough to detect this correlation without multivariate analyses, but this was not the aim of the study. The use of orthopaedic aids in the treatment of medial osteoarthritis of the knee can be considered an established therapeutic concept. The German S2k guideline for osteoarthritis of the knee recommends treatment with insoles, shoe adjustments or orthoses (31). Other international guidelines recommend the use of orthopaedic aids (32, 33) or not (34, 35). However, the German S2k guideline is the only guideline that contains a section on the use of ankle-foot orthoses and recommends their use in moderate stages of knee osteoarthritis.

In osteoarthritis of the knee, pain is the leading cause of disability. It is exacerbated under physical stress. This makes pain an important parameter in the monitoring of therapeutic effects (24). Since their description in 1987 by Sasaki & Yasuda (6), laterally wedged insoles have been the subject of a large number of scientific publications, the data of which have already been evaluated in several reviews and meta-analyses (8–11, 36–38). In their most recent systematic review, Zafar et al. summarized that there was no consensus regarding a response of the symptom pain to LWI (39).

Table II. Knee pain at baseline and changes after use of each aid. Median (quartiles) of knee pain in the last seven days from 0 (none) to 10 (worst) of all patients (n=28)

Parameter	Knee pain (NRS)	
Knee pain at examination dates		
Baseline	5 (3; 7)	
After LWI use	3.5 (1; 7)	
After AFO use	3 (2; 5)	
Change in knee pain		p-value
LWI – baseline	−0.5 (−3; +1)	0.008[a]
AFO – baseline	−1.5 (−3; +1)	0.004[a]
LWI vs AFO		0.427[b]

NRS: numerical rating scale (0 – no pain, 10 – worst pain); LWI: laterally wedged insole; AFO: ankle-foot orthosis.

[a]Wilcoxon-signed-ranks-test comparing pain at baseline with pain after use of LWI/AFO in all patients.

[b]Mann-Whitney U test comparing the difference in pain between T2 and T1 between the 2 treatment sequence cohorts.

Table III. Correlations of mechanical axis deviation and change in knee pain on a numerical rating scale (0–10) after use of laterally wedged insole and ankle-foot orthosis. Spearman-rho correlation coefficients and p-values. Significant results are shown in bold

Parameter	Tibiofemoral angle	Knee pain after LWI	Knee pain after AFO	Knee pain change LWI	Knee pain change AFO	Knee pain baseline
Mechanical axis deviation	**0.97**	0.28	**0.45**	**0.54**	**0.65**	−0.20
	< 0.001	0.15	**0.02**	**0.003**	**< 0.001**	0.31
Tibiofemoral angle		0.31	**0.42**	**0.48**	**0.56**	−0.13
		0.11	**0.02**	**0.01**	**0.002**	0.51
Knee pain after LWI						**0.58**
						< 0.001
Knee pain after AFO						0.29
						0.13

LWI: laterally wedged insole; AFO: ankle-foot orthosis.

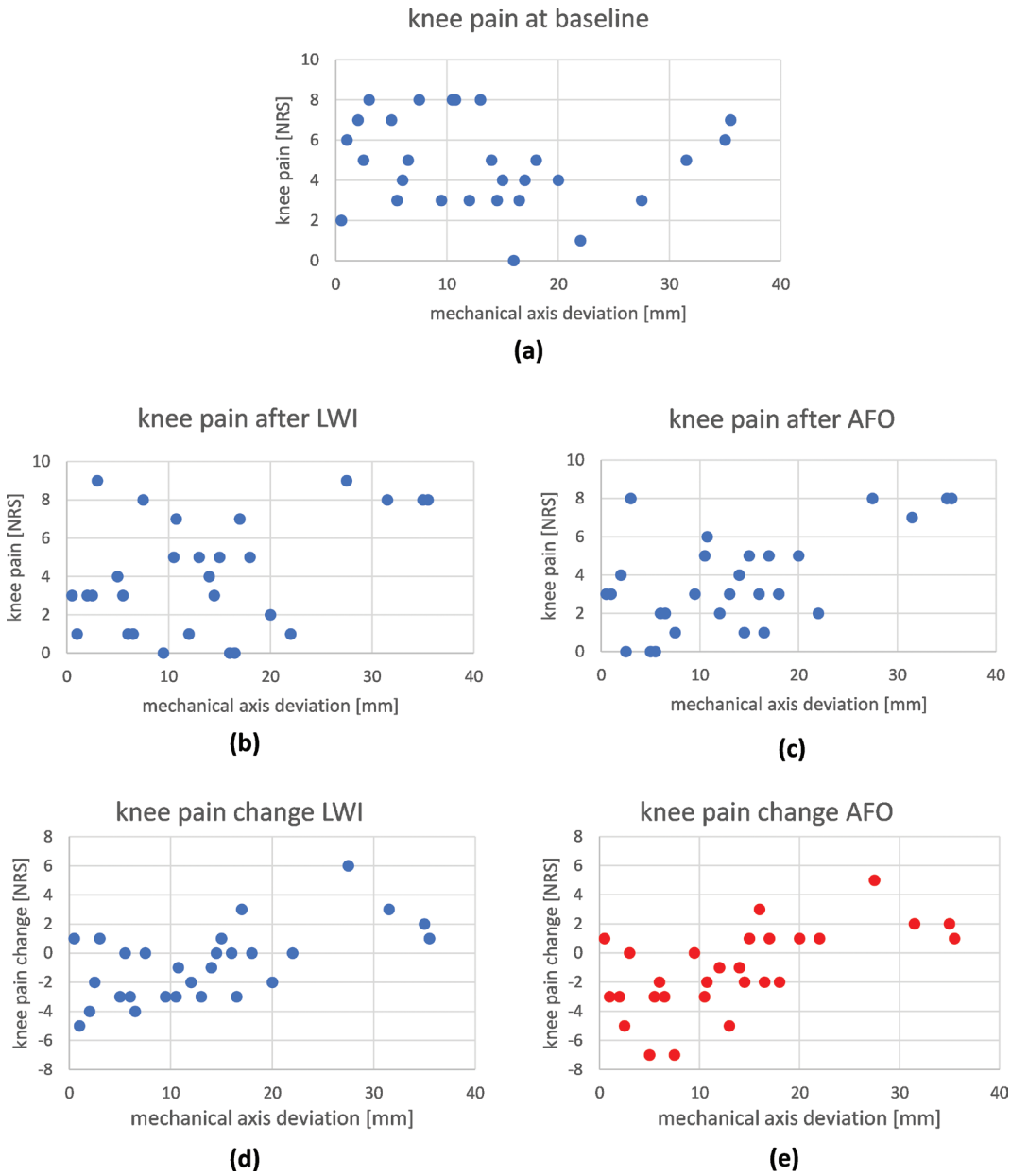

Fig. 3. Scatter plots scaling knee pain on a numerical rating scale (NRS) vs mechanical axis deviation. (a) pain at baseline, (b) pain at follow-up after use of laterally wedged insole (LWI), (c) pain at follow-up after use of ankle-foot orthosis (AFO), (d) change in pain after LWI vs baseline, (e) change in pain after AFO vs baseline.

The readers might wonder how these controversial results can arise. Zafar et al. saw a possible reason in the consequences of pain relief: pain relief reduces the use of analgesics and increases the level of activity, two factors which, in turn, increase pain up to a threshold acceptable to the patient (at a higher level of activity) (39). As influencing factors on biomechanical and clinical response to LWI, the ankle joint and foot alignment, as well as the radiographic severity of osteoarthritis, have been considered (4, 18, 40).

Although Ferreira et al. recently systematically analysed the properties of an "optimal" LWI, they concluded that an individual adaptation might be necessary (41). In the opinion of the authors, not much attention has been paid to patient-side factors in the interpretation of study results. Ferreira et al. concluded that LWI "have a small effect on reducing the forces that cross the medial knee in people with medial knee OA ..." (41). These forces are significantly influenced by the frontal limb alignment. The question that arises here: is there a natural limit of malalignment in which these small mechanical effects come to a limit? The data from the current investigation support this. Both LWI and AFO have a comparable cut-off of 14.25 mm

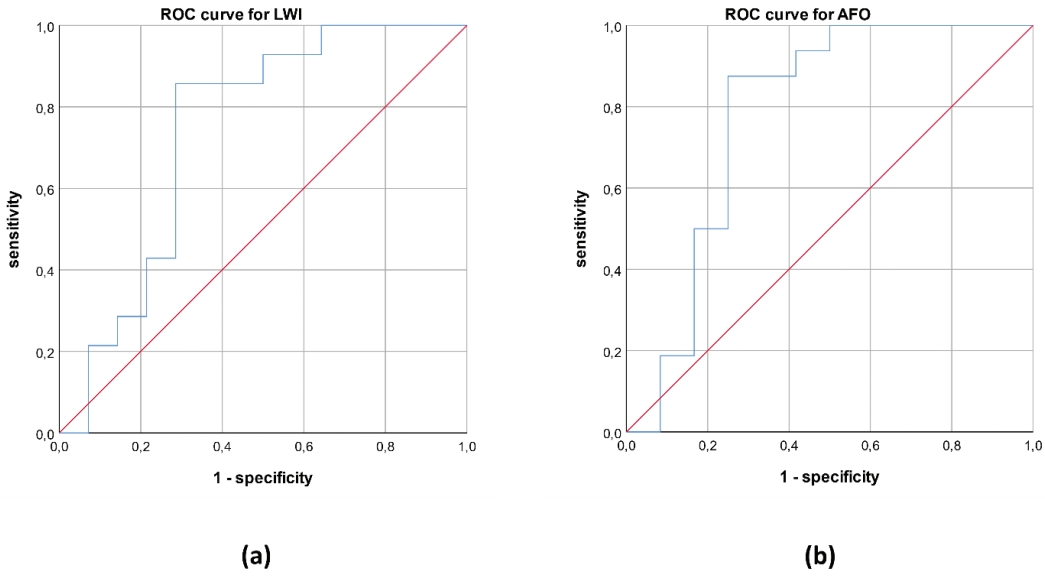

Fig. 4. Receiver operating characteristics curve for prediction of pain response to (a) laterally wedged insole (LWI) and (b) ankle-foot orthosis (AFO) depending on mechanical axis deviation.

Table IV. Responders and non-responders to laterally wedged insole and ankle-foot orthosis with calculated cut-off values for the mechanical axis deviation

Parameter	LWI	AFO
Responders (*n*)	14	16
Non-responders (*n*)	14	12
Cut-off MAD (mm)	14.25	14.75
Sensitivity (%)	85.7	87.5
1 – specificity (%)	28.6	25.0

MAD: mechanical axis deviation; LWI: laterally wedged insole; AFO: ankle-foot orthosis.

and 14.75 mm for the MAD, corresponding to a mechanical tibiofemoral varus alignment of 3.2–3.4°, up to which the majority of patients achieve a slight to moderate pain relief. The authors assume that beyond this cut-off a biomechanical decompensation occurs, which cannot be compensated by such aids.

The similar cut-off value for AFO and LWI is connected to the correlation between the pain reductions with both aids. Patients who responded with a pain reduction to one of the aids were likely to do so with the other. This fact underlines the idea that a change in pain is not only caused by changes in the medial contact forces (19), but must be mediated by additional parameters, one of which appears to be limb alignment. The current results suggest that response to different interventions may be mediated by the same factors. Lim et al. (22) showed the role of limb alignment for a quadriceps training intervention; our data suggest it for LWI and AFO. It remains to be seen if other conservative treatment approaches similar are less effective in the malaligned knee.

Although the AFO's influence on eKAM was significantly higher than the LWI's in our own biomechanical evaluations (25), the MAD cut-off is only slightly higher for AFO than for LWI. In the isolated consideration of the MA and pain, the AFO does not appear to be superior to the LWI, but rather equal. However, effects of the AFO on pain seem to be even more strongly connected to limb alignment than those of the LWI. As far as the authors are aware, there are no comparable results on AFO and limb alignment in the scientific literature. The clinical results of this investigation, however, allow the hypothesis that the positive clinical results described above with pain reduction and functional improvement may be improved by careful patient selection (16, 17).

Study limitations

This study has some limitations. The design of the original study did not mainly target the evaluation of the MAD, but was rather planned to evaluate the biomechanical parameter eKAM. The sample size calculation was also based on the biomechanical outcome (25), while the study may be under-powered for the evaluation of clinical outcomes. Since the current evaluation of the MAD could only be carried out in a significantly smaller proportion (72%) of the participants, the data should not be overinterpreted. This analysis was thus aimed at investigating a hypothesis that may be further examined in prospective designs.

The MAD and tibiofemoral angle were measured with the TraumaCad software, based on full weight-bearing long-standing radiographs. Both values are automatically calculated, provided that the examiner has marked anatomical landmarks on the magnified X-ray image. This procedure depends on the examiner,

although it is widely used in clinical routine. To reduce the effect on the measurement results, a separate measurement was carried out by two investigators with subsequent averaging of the values for MAD.

The measurement parameter of pain on the numerical rating scale is highly subjective and shaped by the patient's pain experience. Placebo effects are likely to represent at least a part of the observed pain reductions. However, since we observed effects with both orthopaedic aids in a magnitude comparable to other investigations with LWI (9), we consider the results to be meaningful.

The trial did not include a wash-out period. This decision was based on the consideration that orthopaedic aids act predominantly while they are being used. Pain as an outcome was assessed only over the last seven days before the respective examination date. An ongoing effect of the previous aid five weeks after switching to the second aid seems improbable. This assumption was supported by our statistical evaluation, which showed no evidence of carry-over effects.

As mentioned in the discussion, activity level and analgesics use are potential confounders in pain assessment, which were not evaluated. Pain relief may increase the activity level and reduce analgesics intake, which may reduce the measurable pain reduction (39). Over the course of several weeks, beneficial effects of an increased activity level are also conceivable (42). While these factors should be included in future investigations, the authors see no reason for an interdependency of analgesics intake and activity with limb alignment. Thus, we consider the correlation between pain and limb alignment meaningful.

CONCLUSION

Both laterally wedged insoles and ankle-foot orthoses can be used successfully to reduce pain in medial osteoarthritis of the knee. The success of the therapy can be predicted with a sensitivity >80% by the mechanical axis deviation on full weight-bearing long-standing radiographs.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of the medical faculty of the Ruprecht Karl University of Heidelberg (protocol code S-021/2018, Jan 30, 2018).

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Conflicts of interest

The authors have no conflicts of interest to declare. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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