Author's response to reviews

Title: A Treatment Applying a Biomechanical Device to the Feet of Patients with Knee OA Results in Reduced Pain and Improved Function. A Prospective Controlled Study

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Author's response to reviews: see over
Dear Tim Shipley,

These are the revisions to our work: “A novel device and treatment methodology for reduced pain and improved function in knee osteoarthritis: a prospective controlled study.” We appreciate all the comments of the reviewers and the time they gave for reviewing our work. We believe that these revisions have greatly improved the quality of the work. Below is a point by point response to every comment.

Reviewer 1: Reinoud W. Brouwer

1. *I do not understand in what way this device changes the location of pressure in the knee and in what way it generates perturbation, which challenges neuromuscular control.*

   The device is made up of two convex elements attached to a foot-worn device. By shifting these elements, the forces on the knee can adjusted. This was illustrated in a recent study
by Haim et al. in a three dimensional gait analysis\textsuperscript{1}. Specifically, by shifting the posterior element laterally, the adduction moment in the knee is decreased. By shifting the posterior element medial, the adduction moment is increased.

We made this clearer in the methods.

Page 7, line 15: “This shifts the center of pressure (COP) in the foot laterally, thereby reducing the magnitude…”

Page 7, line 20: “Perturbation is achieved by walking on two convex shaped elements that create controlled instability in gait.”

2. **I do not understand why the researchers did not go for a RCT, which is nowadays the state of the art.**

The flaw in our randomization procedure was that we did not use a computer program to randomly assign our patients into groups. Instead, we allowed the patients to choose between two days to come to the clinic. In the end, the two groups turned out to be not equal in size. Nevertheless, none of the investigators knew to which group a patient belonged. Moreover, even with the discrepancy in size, there were no baseline differences between the two groups.

3. **The number of patients in each group for a new device seems to be too low.**

   Moreover, the follow-up was only 8 weeks which is relatively short for a chronic disease like knee osteoarthritis.

   With regard to our study size, we consulted with a statistician prior to the study who advised us based on a power calculation what should be our sample size. We are in the process of carrying out a larger study with the device.

   *In regard to the length of our study, this study presents the results of our first phase of research on this device, which was a short intervention of 2 months. Our objective was to test the device in the absence of all other interventions. We are in the process of carrying out a larger and longer study with the device. In our next phase, we have continued to follow our active group for 2 years. Here, however, for ethical reasons we have not been able to stop all other interventions. In 2009 we presented our preliminary results on these patients at the osteoarthritis research society international conference*.

4. **The background is much too long and some parts have to be transferred to the methods part.**

   *The background was shortened.*

   *Removed from paragraph 1:*

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"Knee osteoarthritis is the leading cause of osteoarthritis-related impairment, with an estimated 6.2 million individuals experiencing different levels of pain and functional limitations [3]. Given its association with age, these figures can be expected to rise considerably with the continuous rise in the expected lifespan of the population."

All of paragraph 3 was removed:

"Recent studies suggest that impairment of neuromuscular control precedes clinical symptoms and is initially characterized by quadriceps weakness [16]. In addition, neuromuscular control further deteriorates and quadriceps weakness advances as the grade of osteoarthritis progresses [16]. This probably leads to increased muscle activation [20] and to longer muscle activity patterns in some patients [21]. Cross-sectional studies by Lewek et al. [4] and Hortobagyi et al. [20] suggest that, with further deterioration in neuromuscular control, patients shift from a coordinated motor response to less efficient strategies of joint stabilization, such as global simultaneous concentric contraction of agonist and antagonist muscles, in order to create a bracing effect for the unstable damaged compartment (co-activation/co-contraction). This likely creates a counter-intuitive strategy in which compressive forces are increased across the joint’s damaged compartment and knee adduction moment is increased [22-23]. This leads to further cartilage destruction and exacerbation of joint pain [4]."

5. Has this new device been tested in the laboratory with e.g. gait analysis?

Thank you for pointing this out. The study we cited by Haim et al. examined the device
using a three dimensional gait analysis.

We modified our introduction.

Page 5, line 4: “Recently, a novel foot-worn biomechanical device that incorporates the logic of both types of non-invasive interventions was examined by Haim et al. using a three-dimensional gait analysis”

6. There is no method of randomization performed and the senior orthopaedic surgeon included the patients. When was the study performed and during which period were the patients included?

Our randomization procedure in assigning patients into groups was that we allowed the patients to choose between two days to come to clinic. The senior orthopedic surgeon was blinded to the selection of the patients and did not know who in the end was in each group.

This was made more clear in our methods:

Page 6, line 9: "The patients from both groups, the senior orthopedic surgeon, the investigators and the administrative secretary did not know to which group the patients were assigned. Only the therapist applying and calibrating the device knew to which group a patient belonged."

Our study dates and the schedule of recruitment were added to our methods section.

Page 6, line 3: The study was conducted between December 2005 and February 2006. In
December 2005 a total of 57 patients were allocated to the study…”.

7. The inclusion criteria are not accurately defined. What was the reason to include only patients with bilateral medial knee OA? How do we know which knee has been scored? Was the OA of both knees the same? And if not, which knee has been scored? What was the alignment of the leg, because most patients with medial OA of the knee have varus alignment? How do we know that this device unloaded the medial compartment? Moreover, the degree of varus influences the adduction moment.

We included only patients with bilateral medial compartment knee OA because we wanted our group to be as homogenous as possible. This would allow us to interpret our results as narrowly as possible. Patients were told to score the questionnaires according to the pain and function of their worse knee according to them.

All patients had a varus alignment. In addition, we were only concerned with the compartment affected since this directs the type of configuration used for treatment with the device.

Our knowledge in regard to the device’s ability to unload the medial compartment comes from a study by Haim et al. In this study the researchers showed that shifting the posterior biomechanical element laterally reduces the adduction moment.

This was added to our methods section.

Page 5, line 20: “All patients had varus knee alignment.”
Page 9, line 7: “Patients were told to score the questionnaires according to the pain and function of their worse knee according to them.”

8. Were the patients blinded?

Our patients were blinded to the group allocation. This was clarified in the methods.
Page 6, line 9: “The patients from both groups, the senior orthopedic surgeon, the investigators and the administrative secretary did not know to which group the patients were assigned. Only the therapist applying and calibrating the device knew to which group a patient belonged.”

9. Were the devices for both the intervention and the control group optically identical?

Yes, the devices were identical. The only difference was that the control group did not have biomechanical elements attached to their identical shoes. The patients from the control group never interacted with patients from the research group and reported that they honestly thought they were being treated. In fact, at the end of the study, some participants were upset that they were in the control group and did not want to participate in the second phase of the study.

We modified Figure 2 in order to clarify this further.
10. What was the compliance of the allocated treatment?

In order to achieve full compliance from the patients, we followed up on all patients once a week over the phone to make sure they were following the treatment protocol. All patients reported walking with their shoe on a daily basis according to the instruction of the therapist.

11. Why did the author not perform an ITT analysis?

We initially carried out an ITT analysis. However, because of the low drop-out number of patients we decided to present results without ITT. We understand this point and have changed our results and statistical methods according to the ITT principle.

Changed were made in the abstract.

Statistical methods: Page 10, line 10: “To avoid various misleading artifacts we checked our hypotheses based on the intention to treat (ITT) analysis.”

Results: all values were changed based on the ITT analysis.

12. The author described the consumption of acetaminophen and other medications were monitored. How was this monitored and why are the results not presented?

At baseline each patient received a rescue analgesic (acetaminophen). At first and
second follow-ups, a pill-count was carried out by the examining physician. After 4 weeks, the active group as a whole consumed 145 rescue pills whereas the control group consumed 281 pills. After 8 weeks, the active group consumed 128 pills and the control group consumed 366 pills. Overall the active group consumed 273 pills and the control group consumed 647 pills.

This data was added to our results.

Page 12, line 21: “Patients from the control group use more of the rescue medication given to them at the start of the study than did the active group. After 4 weeks, the active group as a whole consumed 145 rescue pills whereas the control group consumed 281 pills. After 8 weeks, the active group consumed 128 pills and the control group consumed 366 pills. Overall the active group consumed 273 pills and the control group consumed 647 pills.”

13. It is remarkable the control group showed no effect. Normally there is some placebo effect. The effect of the new device is outstanding high, which is unusual in treatment of medial compartment OA. These effects have not been shown in RCT studying other devices like unloading insoles or braces.

Our intervention is unique in that it is applied with a specific “work-out” protocol given to each patient. Each patient was required to walk a certain amount of time each week with the device. This was applied even if the patients were in pain. We assumed therefore that this caused a worsening of symptoms in the control group. For this reason, we believe that any placebo effect that may have occurred was counteracted by the
worsening of symptoms due to walking while in pain. Another reason may be that any placebo effect was not captured in the study. The most typical placebo effect that we envisioned with our intervention would probably occur within the first week or two after the beginning of the study. Our first follow-up, however, was after 4 weeks and the placebo effect may have already disappeared.

A paragraph to this effect was added to the discussion.

Page 15, line 10: “The control group in our study did not demonstrate any placebo effect. This may be explained in two ways. First, because according to the protocol the control group was told to walk with the device even while in pain, we assumed that this worsened their symptoms and balanced out any placebo effect. Second, it may be that any placebo effect only occurred in the first two weeks and as a result our first evaluation at four weeks did not capture the placebo effect.”

14. The side effects of both treatments have not been scored.

None of the patients reported any side effects. Therefore we did not mention this in our results. We understand that this information is important and a clarifying sentence was added to the results.

Page 12, line 10: “In addition, no side effects were reported by any of the patients.”

15. Table 1: Leg alignment outcomes are missing.
According to the inclusion criteria, all patients had bilateral medial compartment knee OA. Therefore all patients had varus alignment. Measurement of varus alignment was done as part of the knee society score.

According to the knee society score, all patients were diagnosed with varus knee alignment. This score does not measure the exact degree of varus, but gives categories of different degrees. For this reason, we do not have the exact value of varus alignment of each patient.

16. Table 2 is too extensive and has to be summarized.

We have summarized Table 2.

17. Are the p values presented between group difference or pre-post analysis?

We clarified the p values in the legend of Table 2.

Page 24, line 6: “The vertical p-value represent the time by treatment interaction results. This represents the difference between the groups at different points in time. The horizontal p-value represents group differences in the three examination points. This represents the differences in the active group across the three follow-ups. No significant differences were found in the control group.”
18. Figure 2: a photograph of the device probably will give more information.

We have modified Figure 2 as requested.
1. In general, a large shortcoming of the study is that no data have been assessed after the intervention stopped. Therefore it is not known whether the intervention is only successful when the devices are used. I hope the authors are performing a long-term study at this moment.

We continued to follow our active group for 2 years. In 2009 we presented our results on these patients at the osteoarthritis research society international conference.³

2. In my opinion the title does not reflect the intervention which was investigated. I would prefer something like: “the effects of applying a biomechanical device to the feet of patients with knee OA” or “applying a biomechanical device to the feet of patients with knee OA results in reduced pain and improved function.”

We appreciate your suggestion for a change in the title of the paper. We believe however that the nature of the treatment itself is a dominant factor in the ability of the device to reduce pain and improve function. We therefore added the word ‘treatment’ to the beginning of the title.

The new title: “A treatment applying a biomechanical device to the feet of patients with knee OA results in reduced pain and improved function.”

3. In the summary information is missing whether significant difference were found between control group and intervention group.

This information was added to the results section of the abstract:

“There were no baseline differences between the groups...Significant differences were found between the active and control groups in all the parameters of assessment.”

4. During the whole manuscript the references need to be check.

We have checked and corrected all references in the manuscript.

5. It is not clear to me whether the control group felt the difference when using normal footwear or the foot worn platform. Was the foot worn platform also a kind of intervention? Did I understand it right that the control group also was advised to walk according to the same schedule as the intervention group?

We modified figure 2 to add a photograph of the device for further clarification. The same shoe was used by the control and experimental group. The only difference is that the elements were removed from the shoes of the control subjects. We assumed that once
the elements were removed, the shoe acts like any other shoe. Therefore, for all intents and purposes, the foot worn platform alone was not intended as a type of intervention.

The control group had the same exercise routine as prescribed to the active group.

We added this clarification to our methods.

Page 8, line 15: “Patients in the control group were fitted with an identical foot worn platform that did not include the biomechanical elements or the movement rails. Without these, the shoe is left with a regular rubber sole. We assumed that once the elements were removed, the shoe acts like any other walking shoe.”

Page 8, line 20: “Therefore, for all intents and purposes, the foot worn platform alone was not intended as a type of intervention. It was a complete control aside from the walking routine of the patients.”

6. I do not really understand the choice to stop the medication. Patients will use medication in the future, therefore you should be interested in the supervalue of the device above the medication. I expected some discussion about this in the discussion section.

We wanted to evaluate the effectiveness of the device as a stand-alone treatment without the use of any other interventions or medications. Since we cannot ask patients to refrain from taking medications for a long period of time, we made our study only 8 weeks. In our long term follow up study on this device we have allowed patients to use other medication in order to evaluate the supervalue of the device above and beyond other
interventions and medications\textsuperscript{4}.

We have added this to our discussion:

Page 15, line 5: “Patients in our study were told not to consume any medications aside from the rescue pills given to them at the start of the study. This was done in order to evaluate the effectiveness of the device as a stand-alone treatment without the use of any other interventions or medications. Since we cannot ask patients to refrain from taking medications for a long period of time, we made our study only 8 weeks.”

We also added to our results the amount of rescue medication consumed by each group (page 12, line 21).

7. \textbf{Were these performed according to the intention-to-treat principle?} This information should be written in this section. I have read that you did not perform ITT in results section. I do not understand why you did not perform ITT.

Furthermore, this information needs to be replaced to statistical analysis section.

We initially carried out an ITT analysis. However, because of the low drop-out number of patients we decided to present results without ITT. We understand this point and have changed our results and statistical methods according to the ITT principle.

\textit{Changed were made in the abstract.}

Statistical methods: Page 10, line 10: “To avoid various misleading artifacts we checked our hypotheses based on the intention to treat (ITT) analysis.”

Results: all values were changed based on the ITT analysis.

8. I do not understand the 3rd hypothesis: I assume you mean: advantage in scale for the active group (instead of no advantage??)

This third hypothesis is for the group difference at baseline. We clarified the statement in our statistical section.

Page 10, line 19: “c) no advantage in scale at baseline for the active group compared to the control group.”

9. In the results section I miss information on the adherence to the protocol: How much did the intervention group walk during these 8 weeks: did they perform their schedule as was advised? And was there a difference in walking between intervention group and control group? The same for intake of medication.

Both groups received the same walking protocol. In order to achieve full compliance from the patients, we followed up on all patients once a week over the phone to make sure they were following the treatment protocol. All patients reported walking with their device/sham on a daily basis according to the instruction of the therapist.
10. I miss information on the clinical relevance and follow-up of this study. What needs to be done next?

This information was added to our discussion.

Page 15, line 16: “The results of this study introduce a device that resulted in significant reduction of pain and function, which is the focus of knee OA treatment. As such, this device and methodology may be a possible treatment for patients with knee OA. Future studies should examine the long term effect of the device on patients with medial compartment knee OA and patients with other musculoskeletal pathologies.”

11. I expected a discussion whether the device benefits more for a higher Kellgren and Lawrence score, or not…

Due to the poor correlation between K&L score and symptomatic knee OA, we did not compare the effect of the device at different levels of K&L. Nevertheless, we agree that this would be an interesting comparison and we hope to analyze it in future studies.

12. There are too many tables. I suggest to make a selection of the figure 3-5.

Table 2 was shortened.

Figures 4 and 5 were removed.
1. The authors need to explain the section on Interventions. Second sentence reads “The device is calibrated to the individual patient according to pathology and motion characteristics.” This needs to be expanded and we need to know if they did the same measurements comprising pathology and motion characteristics on the control group. Lastly, if they did, how did the groups compare? Where they similar with respect to pathology and motion characteristics or not. These points should also be commented on in the discussion section. They also need to broaden the discussion of “recalibration.” How was this done? How many needed adjustment at first third and six weeks. Did they do the same measurements on the controls at first third and six weeks and even if they couldn’t calibrate (since no device was applied) Did the control group change?

The pathology of all our patients was bilateral medial compartment knee OA with varus alignment. In this case the treatment methodology is to “calibrate” the device and shift the posterior element laterally in order to reduce the adduction moment acting on the knee joint. This is based on the findings of Haim et al. Since all our patients had the same pathology their motion characteristics were, for the most part, identical.

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Nevertheless, if a patient presented with different motion characteristics, the device was further calibrated. For example, if the patient had flexion contraction of the knee, the therapist added spacers to the posterior element of the device.

Both the control group and active group were evaluated at first, third and six weeks. All patients were asked to walk away from and then back toward the therapist while the therapist took note of their gait with the biomechanical device. The biomechanical device was recalibrated appropriately according to the treatment methodology (page 7, lines 13-19) for the active group. No recalibration of the device was done to the control group since there were no biomechanical elements attached to their shoes. Nonetheless, the control group, as with the active group, came in for “recalibration meetings” at first, third and six weeks and was again asked to walk back and forth by the therapist. For this reason the “pathology and walking characteristics” of the groups were not compared.

A clarification was added to the methods section.

Page 6, line 23: “Each patient is asked to walk away from and then back towards the therapist. A visual gait evaluation is carried out by the therapist and the device is appropriately calibrated.”

Sincerely,

Dr. Yuval Ran (corresponding author)

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