Comment on: varus malalignment negates the structure-modifying benefits of doxycycline in obese women with knee osteoarthritis

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In the current issue, Mazzuca et al. report, from a trial of the effect of doxycycline on medial joint space narrowing, the results of post hoc treatment group comparisons in subgroups of varus and non-varus osteoarthritic knees. These analyses were undertaken to ascertain whether varus malalignment decreased the structure-modifying effect of doxycycline. The sample included 379 obese, 45–64-year old women with unilateral knee osteoarthritis (OA). Mazzuca et al. found that, in the non-varus osteoarthritic knees, 16-month joint space narrowing was 44% slower and 30-month narrowing was 39% slower in the doxycycline group than in the placebo group. In contrast, in the varus osteoarthritic knees, this difference was blunted; the rate of joint space narrowing was unaffected by doxycycline.

The study, a randomized, placebo-controlled trial of doxycycline, has a number of strengths in its design and methodology as well as in its performance, e.g., state-of-the-art methods to acquire knee radiographs optimizing conditions for measurement of medial tibiofemoral joint space and outstanding participant retention especially given the long duration of the study. While alignment was measured from the knee film, great care was taken in the measurement protocol and in transforming the measurement to an estimate of the mechanical axis angle.

As the authors acknowledge, there are some limitations as well. For compelling reasons, the trial was performed in obese women, but this may limit generalizability of these findings. Varus alignment was less frequent than might be expected, which the authors attribute to the exclusion of Kellgren and Lawrence (K/L) grade 4 knees and to the method of measuring alignment from relatively short visualized segments of the tibial and femoral shafts on the knee radiograph. The frequency of varus was less than the 27% frequency in the Rotterdam study in which K/L grade 3 and 4 knees had been excluded and which had also relied on knee X-rays with offset correction to estimate full-limb alignment. Alignment influences tibiofemoral load distribution, but alignment as it is typically measured is a static parameter. Varus knees had more severe osteoarthritic disease at baseline and, on this basis, may have been more likely to experience OA progression than the non-varus knees.

This study illustrates some caveats inherent to radiographic joint space measurement as a measure of outcome in studies of knee OA. The magnitude of change in joint space width was small, even by 30 months, and it is difficult to know whether this increment of change is important. And, joint space loss in the osteoarthritic knee may reflect meniscal tissue damage or extrusion, conditions which may be exacerbated by malalignment.

The outcome measure of medial joint space narrowing was well chosen for the primary goals of the trial but creates some challenges for these post hoc analyses. The non-varus group included valgus knees. Valgus osteoarthritic knees may include knees with medial tibiofemoral OA but are more likely (than varus or neutral knees) to have lateral OA. The measurement of medial joint space in a knee with lateral OA is difficult to interpret. Knees with lateral OA may experience some medial narrowing (presumably less than lateral narrowing), no change in medial joint space width, or medial pseudowidening that is reciprocal to lateral narrowing. The authors acknowledge that valgus knees may not have been well suited to demonstrate a disease-modifying effect in the medial compartment, and provide evidence that, on average, the valgus knees experienced some medial narrowing over time. The heterogeneity of outcomes in the medial compartment of the valgus knees with lateral OA makes this aspect of the study difficult to interpret. Radiographic methods are inherently limited in their ability to assess disease status or progression in the uninvolved or less involved tibiofemoral compartment. By providing direct visualization of medial and lateral articular cartilage and menisci, MRI bypasses these limitations of radiography.

The study by Mazzuca et al. is important – it illustrates the type of approach that will be essential towards an ultimate goal of solving a significant problem. The problem is that certain mechanical environments may reduce the effectiveness of pharmacologic therapy.

Varus–valgus alignment is one important determinant of this mechanical environment. In a varus aligned knee, the load-bearing axis passes medial to the knee, creating a moment arm that increases forces across the medial tibiofemoral compartment; in...
a knee with valgus alignment, the load-bearing axis line passes lateral to the knee, and the moment arm created increases forces across the lateral compartment. Due to a stance phase knee adduction moment, even during normal gait in healthy knees, 70% of forces pass through the medial compartment. Varus alignment is a key determinant of the magnitude of this adduction moment. Varus alignment (in several studies) and the adduction moment\(^5\) have each been associated with a greater risk of subsequent medial OA progression. An increase in the adduction moment may lie in the causal pathway between varus alignment and disease progression.

Malalignment is important for reasons in addition to these direct effects at the knee. First, malalignment stresses not only articular hyaline cartilage but also other knee joint tissues, including the menisci, subchondral bone, and ligaments, which may contribute to the development and progression of OA. Second, there is evidence that malalignment alters the effect of other risk factors. Third, whether or not malalignment precedes OA development, it may participate in a vicious cycle with worsening of knee OA. From a biomechanical perspective, it is likely that the relationship between malalignment and knee OA worsening is bidirectional. It is difficult to imagine how pharmacologic therapy could alter the natural history of an osteoarthritic knee in this vicious cycle, given the magnitude of the mechanical forces at work and the frequency with which they are transmitted during weight-bearing activity.

Felson and Kim attributed the failure to develop chondroprotective pharmacologic treatment to the assumption that pharmacologic therapy would work regardless of the mechanical environment\(^3\). However, this thoughtful conceptualization of the problem in the literature does not seem to have spurred specific investigation within trials. In fairness, how to handle elements of the mechanical environment is not a straightforward issue. Logical alternatives include stratified analyses (such as those performed by Mazzuca et al.), excluding knees that are malaligned, or providing a co-intervention that addresses the malalignment-associated load imbalance\(^5\). Of these, the second and third options are less desirable at present. In terms of the second option, depending upon how malalignment is defined, a substantial number of knees could be excluded. Even mild deviation from neutral alignment may have an impact – this is not known but stratified analyses would help to elucidate this. In terms of the third option, while several non-invasive interventions are being developed or are under study, there is insufficient data upon which to base a choice. There are also limiting issues of tolerability (e.g., unloading braces) and uncertainty regarding optimal design of wedge insoles. At this point in time, the third option does not seem practical, although it is an excellent goal for the future.

The paper by Mazzuca et al. is an important step and should stimulate more consistent consideration of the mechanical environment within future trials. It is crucial to continue down this path; some drugs may have a substantially better effect in knees that are more neutrally aligned. There are at least four categories of studies that are needed to begin to address the problem that pharmacologic therapy may have no or a reduced chance of being effective unless key elements of the mechanical environment are addressed.

First, trial design needs to support analyses within key mechanical factor (such as alignment) strata; this strategy will be more informative than only testing knees with an optimal mechanical environment. With careful attention to methodology (as in the study by Mazzuca et al.), knee X-rays can provide a reasonable estimate of the mechanical axis angle. Given this, investigators of completed trials should consider repeating analyses within strata, especially since there may be no future trials for certain drugs. Although these investigators will face the same inherent limitations of radiography as described above, the existing images and data are a rich resource to begin to tackle this complex issue.

Second, studies need to identify other important mechanical factors or determinants of the mechanical environment, perhaps even under dynamic conditions. Ultimately, inexpensive and practical methods to measure such factors will have to be developed.

Third, efforts should continue to develop MRI-based outcome measures that can function as the primary outcome in a trial. There are inherent limitations to radiography that acquisition and reading protocols cannot overcome. It is not possible using X-ray to determine at early disease stages which tibiofemoral compartment will be predominantly involved. It is unclear how to assess progression in the compartment not predominantly involved. It is not clear how much radiographic joint space narrowing represents meniscal damage or extrusion; the meniscal contribution may differ between knees. Our heavy reliance on radiographic medial joint space narrowing makes it challenging to examine effect modification by a factor like alignment that has effects specific to each tibiofemoral compartment. MRI, in its potential to measure cartilage loss and in its potential to measure cartilage dysfunction that precedes loss is vastly superior.

Fourth, non-invasive interventions to optimize key elements of the mechanical environment should be developed further and tested towards an ultimate goal of using them together with pharmacologic therapy in clinical trials.

Conflict of interest
The author has no conflict of interest.

References


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