Bout of the corner men and not the boxers? Contextual effects flex their muscles

Martin Englund[1,2]

Increased use of MRI in the quest to explain symptoms, and patients' hope for a 'quick-fix', often challenge healthcare professionals in their choice of treatment for the painful ageing knee. In the USA, there are about one million knee arthroscopies per year and the majority involve removal of torn meniscal tissue in middle-aged patients. The absolute number of arthroscopic partial meniscectomies (APMs) in Europe is unknown but may be even greater due to the larger European population. The popularity of this procedure is understandable — multiple case series and randomised controlled trials (RCTs), not to mention doctors' personal observations of patients, show sustained improvement after APM. However, the last few years, the efficacy of the *actual therapeutic element*, resection of meniscal tissue, has been called into question.

A hallmark RCT is the exquisitely designed, randomised, double-blinded, sham-surgery-controlled Finnish Degenerative Meniscal Lesion Study (FIDELITY).[1] The main findings of the trial so far are summarised in these short film clips:

- FIDELITY New Engl J Med 2013
- FIDELITY Ann Intern Med 2016

In the provocative *New Engl J Med* article from 2013, Sihvonen *et al* reported that outcomes in the middle-aged patients, where resection of meniscus was only simulated during the diagnostic arthroscopy, were very similar to those of actual APM. Patients in *both* the APM arm and the sham-surgery arm improved substantially and sustainably, indicating that the improvement observed after APM is attributable to what are collectively referred to as *contextual effects*. Thus, it was *not* the actual therapeutic element of the surgery, which is resection of torn meniscal tissue. Now, in the present 2-year follow-up of the FIDELITY patients,[2] Sihvonen *et al* strengthen their original findings. The investigators report that the lack of treatment effect of APM compared with sham surgery is sustained even at longer follow-up. Further, they found no support that patients with the so-called 'mechanical symptoms' or certain meniscal tear characteristics would have larger improvement.

Contextual effects in chronic pain conditions predominantly include *placebo response* and the *regression to the mean* phenomenon. Although placebo remains an utterly complex entity that is not fully understood, it is likely to be very powerful in surgical interventions. It fact, it has even been suggested that surgery may offer the 'ultimate placebo'.[3] Additionally, regression to the mean is highly likely to contribute, given that the patient with chronic knee pain often shows a natural history of flares followed by periods of improvement, and that he/she consults and gets included in a trial when he/she is in a bad phase (figure 1). This phenomenon, which substantially may contribute to the total treatment effect, is unknown or forgotten by many researchers and clinicians (and unknown to most medical writers and patients), who often tend to attribute improvement solely to the treatment provided.

The lack of treatment effect of removal of torn meniscal tissue per se in the painful ageing knee may be explained by the misguided reason for which the surgery is often performed. Meniscal lesions confirmed by MRI are typically assumed to explain the patients' knee symptoms. The term 'symptomatic meniscus tear' is heavily misused. Evidence does not support such clear-cut assumption of causality.[4 5] Additionally, as pointed out by Neogi *et al*,[6] a factor can be strongly causally associated with pain in osteoarthritis, yet it may not be a strong predictor of the pain on its own because several other factors may contribute to the pain experience. Thus, deductive reasoning that removal of meniscal tissue somehow would resolve the pain is unfortunately often too simplistic. Naturally, on one end of the spectrum of meniscal tears, there exist cases where a large dislocated longitudinal (bucket-handle) tear of the meniscus (typically a result of major knee trauma) causes painful locking of the knee. Here, arthroscopy is indicated for repair or removal of the torn piece of meniscus. However, there is a grey zone between such an acute *traumatic* meniscal tear and the more slowly developing *degenerative meniscal lesion*.[7] The latter is a frequent incidental finding suggestive of incipient osteoarthritis or simply an ageing joint.[8]

In 2016, the European Society of Sports Traumatology, Knee Surgery and Arthroscopy released new treatment guidelines with the message to refrain from surgery in favour of non-surgical management as the first line of treatment in patients having knee joint symptoms and a degenerative meniscal lesion.[9] Further, most recently, after an extensive meta-analysis, the *BMJ* has also released its clinical guidelines firmly recommending *against* APM in this patient category.[10] Thus, there is

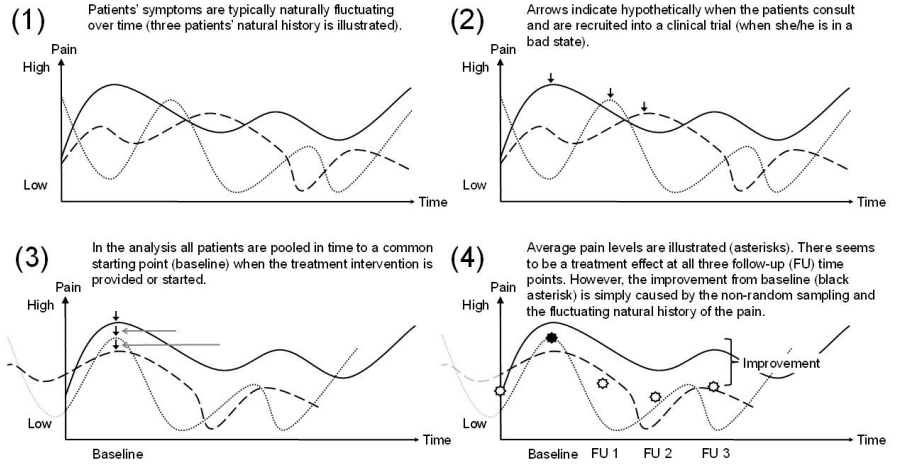


Figure 1 Illustration of regression to the mean.

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currently a strong movement for *non-surgical* management of the painful knee — this is typically through a supervised or non-supervised exercise intervention. However, while the effect of APM per se has had its fair share of attention, there is as of yet *no* RCT demonstrating any effect of an exercise intervention above placebo, either for the osteoarthritic knee or for the hip. In contrast, the two RCTs that specifically addressed this topic have *failed* to demonstrate any effect of exercise above a placebo intervention.[11 12] Various claims can be made of the two studies' limitations, but the fact remains (in line with APM) that there is currently *no* evidence that supports a treatment effect on patient-relevant outcomes above placebo, even for exercise therapy. In addition, the concept of strong muscles as preventive of knee osteoarthritis has recently been challenged by observational data.[13] Vested interests, publication bias and wishful thinking may not only exist in the field of orthopaedic surgery.

Interestingly, so far, the *only* clinical trial comparing exercise versus APM *without* added exercise after APM yielded essentially the same outcomes in *both* arms.[14] Now, what does that tell us? If the effect of APM per se is virtually 'nothing', as strongly suggested by the FIDELITY trial (and applauded by the exercise community), is exercise *also* all about placebo and regression to the mean? Or is the placebo response slightly weaker in the exercise intervention arm, supplemented by some true treatment effect? Nota bene, the randomisation is expected to have balanced the two arms with respect to regression to the mean. Thus, that particular component of the total effect is expected to be equal in both treatment arms. Unfortunately, we do *not* yet know how the placebo responses compare between a single arthroscopic intervention and being cared for at regular intervals by a physiotherapist. Still, I think it is fair to conclude that the added *true* component effect attributable to exercise per se seems, at best, to be very modest, if present at all. Thus, it would be intriguing to tease out the true component effect of exercise on the total effect on patient-relevant outcomes. Double-blinded, placebo-intervention trials in this field may be challenging to design and execute but are far from impossible. The challenge is to remove the actual therapeutic element(s) of exercise in the sham arm while keeping the other circumstances of the treatment interventions as identical as possible. In fact, one could consider a trial comparing a very 'low dose' versus 'therapeutic dose' of exercise. 'Too low dose of exercise', after all, is the most commonly heard argument[15] to explain disappointing results such as those from the two placebo-controlled trials already performed.[11 12]

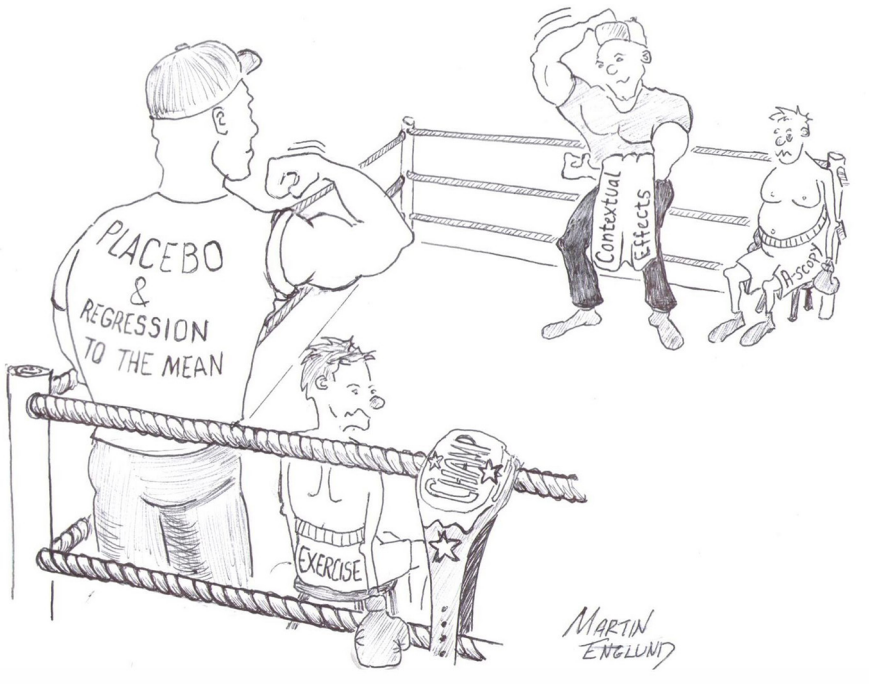


Figure 2 The bout of the corner men and not the boxers?

Nevertheless, a strong, and in my opinion pivoting advantage for an exercise intervention as one of the current primary treatment modalities for the painful ageing knee, is that it is *safe*. Furthermore, increased physical activity, especially if the patient has previously been sedentary, will most likely have a general positive effect on both mental and physical health. Consequently, in a *pragmatic* view, there is in my mind no doubt that exercise should be the treatment offered early on given the current limited availability of other treatment options. Somewhat cynically — and provocatively I might add — to tailor and optimise the most cost-effective, patient-compliant and safe placebo intervention for this massive patient category should perhaps become an important research agenda? (figure 2).

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