Beyond the joint

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Chapter 7

General Discussion and Future Perspectives

Introduction

Aim of this thesis was to investigate the measurement of signs of sensitization in knee and hip osteoarthritis (OA) patients, and to assess the effects of targeted treatment of this phenomenon on long-term outcome after total knee or hip arthroplasty (TKA/THA). Sensitization expresses itself, among other things, through neuropathic-like symptoms.

The first part of this thesis focused on measurement of signs of sensitization in OA by assessing the reliability and validity of the modified PainDetect Questionnaire (mPDQ). The mPDQ is a self-report questionnaire aiming to discriminate between nociceptive and neuropathic pain(1). It does this by focusing on peripheral, neuropathic-like symptoms in- or around the OA affected joint. As neuropathic-like symptoms are not exclusively seen in patients with sensitization, this offers indirect evidence of sensitization or altered central nociceptive processing, hence the term signs-of-sensitization(2,3). Based on the findings in **chapter 2**, the Dutch mPDQ (mPDQ-NL) seems to be a reliable measurement tool. It seems to be able to distinguish patients from each other despite measurement error, including knee or hip OA patients with subtle neuropathic-like symptoms, which is an important feature of the mPDQ-NL because it helps to identify subtle signs of sensitization within the broader spectrum of OA-symptoms. In **chapter 3**, construct validity was assessed using elaborate hypothesis testing in a considerable sample size of OA patients. As 80% of the predefined hypotheses concerning the association with other self-reported questionnaires were confirmed, the findings endorse the validation of the construct measured by the mPDQ-NL. It needs to be mentioned that the item on 'pain pattern' forms an exception, as this does not seem to fit the overall construct.

The second part of this thesis focused on the effects of targeted treatment of sensitization on long-term outcome after TKA/THA by describing the long-term outcome of the Duloxetine in OsteoArthritis (DOA) trial, including the responsiveness and interpretability of its primary outcome measure: the Pain Subscales of the Knee and Hip Osteoarthritis Outcome scale (KOOS and HOOS). This trial was set up because in a recent systematic review chronic residual pain was reported in up to 23% of patients after THA, and up to 34% after TKA, and sensitisation is among the most important risk factors of poor outcome after TKA and THA, especially the risk of chronic residual pain(17). As described in **chapter 4**, a multi-centre, pragmatic, prospective, randomized clinical trial was conducted including patients with end stage primary knee/hip OA with signs of sensitization who were planned for TKA/THA. Pre-operative treatment of seven weeks with 60 mg of Duloxetine was compared to usual care. The primary outcome measure was pain, measured by the Pain Subscales of the KOOS and HOOS. The long-term effect of this pre-operative Duloxetine treatment was described in **chapter 5**. One hundred and eleven participants were included. No significant postoperative effects in pain were found up to one year after TKA/

THA between the intervention and usual care group. Lastly, in **chapter 6** responsiveness and interpretability of the pain subscales of the KOOS and HOOS were reported following COSMIN (COnsensus based Standards for the selection of health Measurement INstruments) guidelines. A considerable response shift was found in Minimally Important Change (MIC) scores after conservative treatment and after TKA/THA. From that it was concluded that the KOOS pain subscale might be able to detect the MIC at an individual level after arthroplasty, but both the KOOS and HOOS pain subscales seem to be unable to do so after conservative treatment.

This general discussion addresses key themes for both parts of this thesis. Concerning the first part, the measurement of signs of sensitization in knee or hip OA patients will be discussed in a broader view including the position of the mPDQ, the questionnaire that was used for that purpose in this thesis. With respect to the second part, the relation between targeted treatment of signs of sensitization and chronic residual pain after TKA/THA will be discussed, and also the role of response shift in pain for OA patients undergoing TKA and THA. For each part of the thesis implications for clinical practice will be considered, and recommendations for future study will be given.

Part one

Measurement of signs of sensitization in patients suffering from knee or hip OA using the mPDQ

It is important to notice that there is no gold standard for the measurement of sensitization. This is not a problem specifically for OA patients, but for all diseases and syndromes in which sensitization is believed to play a role. As already elaborated in the general introduction of this thesis, in the measurement of peripheral sensitization, a distinction is made between elaborate protocols for physical examination of neuropathic symptoms (such as Quantitative Sensory Testing, QST) and self-report questionnaires. To my knowledge, at this moment the mPDQ is the only self-report questionnaire that is specifically modified to address neuropathic-like symptoms in patients suffering from knee or hip OA(2,4–7). When considering the etiological theory of sensitization in OA as described in my general introduction, I personally think that it is logical to focus specifically on the neuropathic-like symptoms in the region of the OA affected knee or hip if you want to relate these signs of sensitization to the OA process, rather than addressing neuropathic-like symptoms in the whole body(32, 37-40). Therefore, the mPDQ seems to be the most suited measurement tool available at this moment to assess signs of sensitization specifically in knee or hip OA patients(2,3,8).

However, the scientific world concerning of measurement of sensitization is not uniformly partial to the PDQ, the original questionnaire of which the mPDQ was deducted. This is mostly due to critical concerns about whether the PDQ addresses the actual construct of sensitization,

particularly its specificity. Timmermans et al. recently investigated whether the PDQ (amongst other measurement instruments) could validly measure the neuropathic pain component in patients suffering from chronic low back pain, neck-shoulder-arm pain, and pain in patients with suspected peripheral nerve damage(9). They particularly focused on patients with a suspected mixed type of pain (so partly nociceptive and partly neuropathic) and used a criterion validity method by comparing with the rating of two experienced physicians as the 'Reference Standard'. Conclusions were that the PDQ is not an effective screening tool for a neuropathic pain component because of moderate sensitivity and low specificity. It should be noted that there was little agreement between both physicians, as well as between the other measurement entities (other questionnaires as well as the international Grading System for neuropathic pain, and bedside examination), confirming again, for several different disorders, the lack of a solid Reference Standard for the measurement of a neuropathic pain component as an expression of sensitization(9–14).

So, does the PDQ measure signs of sensitization? More particular, does the modified PDQ measure neuropathic-like symptoms as an expression of sensitization in patients with hip or knee OA? Based on the present thesis, the confirmed hypotheses of chapter 3 indicate that there is a joint specific tendency in the mPDQ, and also that correlation with the measurement instrument that converged more with the concept of neuropathic-like pain was higher than with measurements with more diverging constructs. Realizing the method of construct validity is no holy grail, it is an accepted method to assess validity in lack of a Gold Standard(15).

However, it is possible that the mPDQ-hip is less specific in screening for possible signs of sensitization than the mPDQ-knee. In the DOA study, the degree of chronic residual pain was relatively low in patients after THA as compared to literature (14.3% after 6 months and 19% after 12 months compared to 23% in literature)(16–18). It is unlikely that this is due to a less prominent association between sensitization in hip OA and the development of chronic residual pain after THA, as Blikman et al. recently found a strong association between these two factors in a comparable population(19,20). If the mPDQ-hip is less specific in screening for possible signs of sensitization than the mPDQ-knee, the hip OA population in the DOA trial was less enriched than the knee OA population, possibly explaining the divergence between percentages of chronic residual pain in THA and TKA patients (19% vs 38% resp.).

Despite all the ambiguity concerning the measurement of sensitization, the presence of an OA phenotype with 'pain sensitization' has been rather well established(21–24). In a recent study from 2019 by Carlesso and Neogi, Quantative Sensory Measurers (QST) were recommended for the identification of this 'enhanced pain susceptibility phenotype'. They used longitudinal data on pain sensitisation in patients with or at risk of developing knee OA(21,22). Because of the longitudinal nature of the data they were able to provide insights in the causes of the development

of chronic persistent pain in OA, rather than features that are associated with sensitization (which were more centrally oriented features, catastrophising, depressive symptoms, widespread pain and sleep quality). The QST measures that were assessed formed comprehensive indicators of the sensitization including both facilitatory (positive-) and inhibitory (negative-) signs. The QST abnormalities were present prior to the development of persistent knee pain in this cohort. However, up to date, QST measures are still not suited for clinical practice(3,25,26). As a result, Carlesso et al. recommend future studies to develop easy-to-use QST measures including good reference data or a validated questionnaire that is an adequate substitute to identify the 'sensitisized OA phenotype'(21). I believe a valid questionnaire to substitute QST is an oxymoron. There is a substantial body of literature indicating that QST measures different aspects of the neuropathic-like pain experience compared to patient-reported assessment. It is suggested that measuring a subjective phenomenon as pain experience through patient reported outcomes is sounder than trying to objectify it though QST measures(25–29). The weak correlations between the selective QST measures and the mPDQ scores in the results of several chapters of the present thesis also seem to indicate that QST entities measure different aspects of the pain experience compared to patient-reported assessment of pain experience (though this was not a primary research question).

Implications for Future Studies and Clinical Implications

Future studies should either focus on further confirmation of the construct validity of the mPDQ by comparing it with other measurement tools for sensitization specifically in knee and hip OA patients. Or, if the specificity of the mPDQ remains to be questionable, other questionnaires, like the DN4 which showed better criterion validity in recent research by Timmermans et al., should be modified in order to provide specific measurement tools for sensitization for knee and hip OA patients(10,25,26,30–32). The results of the present thesis also indicate the necessity for future studies to further compare the phenomenon and measurement of sensitization in knee versus hip OA patients as these two groups appeared to be distinctly different entities. Also, comparing the QST measures and the patient-reported questionnaires considering signs of sensitization remains an interesting, though ambiguous field for future studies(27).

What are the present recommendations for clinical practice for the identification of a dominant role of sensitization in a knee or hip OA patient? As stated by Lluch et al. in 2018, it is important for clinicians to realize that sensitization is no single entity that is either present or absent, but rather that it forms a continuum(3). The results in chapter 2 and 3 of the present thesis indicate that when a patient has a mPDQ score suggesting a substantial amount of neuropathic-like symptoms, sensitization may play a dominant role in the pain experience of these patients, especially in knee OA patients. Despite its limitations as elaborated in the previous section of this general discussion, the results presented in chapter 2 and 3 of this thesis support the clinical applicability

of the mPDQ in knee or hip OA patients for the screening of neuropathic like symptoms as an indicator for possible sensitization. However, the moderate specificity of the mPDQ should be taken into consideration when applying it to clinical practice. These findings can be placed within the broader recommendations presented by Lluch et al. reporting clinical descriptors for the recognition of sensitization in patients with knee OA(3). When a patient reports a high score on the mPDQ, this combined with relatively high pain intensity, disproportionate to the structural damage, enlarged areas of pain and an unpredictable pain pattern, this indicates the presence of sensitization. Furthermore, if such a patient has shown an inconsistent or unsuccessful response to nociception-targeted pain treatment the suspicion should rise further. In these patients it would be prudent to perform a thorough physical examination assessing QST-like measures to further quantify the extent of sensitization.

Part two

Relation between targeted treatment of signs of sensitization and chronic residual pain after TKA/THA

In the DOA study, it was hypothesized that with sensitization in knee and hip OA being an important risk factor for the development of chronic residual pain after TKA/THA, it is plausible that targeted treatment aimed at desensitization prior to surgery will reduce (the risk of) chronic residual pain. However, as shown in chapter 5, a 7-week pre-operative targeted treatment with duloxetine in a study population of end-stage knee/hip OA patients with signs of sensitization did not show an effect on postoperative chronic residual pain after arthroplasty. In exploring the reasons behind this lack of effect, two paths might be taken, which are discussed below.

It could be possible that duloxetine treatment prior to surgery in itself is a successful treatment in the prevention of chronic residual pain after arthroplasty, but methodological aspects of the DOA trial led to the negative results that were found. These methodological aspects have been explained elaborately in the discussion of chapter 5. For example, it is possible that the treatment period, timing, and dosage of duloxetine was not vigorous enough to generate a substantial enough effect on desensitization. However, as can be read in chapter 4 and 5, at the time of designing the DOA trial the available evidence about dosage, timing and treatment period were taken into account. Also, in line with the discussion about the method of measurement of sensitization in OA patients as described in this general discussion, it is possible that our study-population was not as sensitized as was intended, especially the hip OA group.

A reason for the lack of treatment effect found in the DOA trial can be derived from the idea of there actually being no treatment effect of duloxetine treatment prior to surgery on chronic residual pain after arthroplasty. There might not be a causal effect of sensitization on chronic

residual pain, but rather both expressions might be caused by an underlying proneness to enhanced pain experience. This is in line with the 'trait or state' theory as described previously by Neogi et al(33). Rather than the OA process inducing neurobiological changes leading to sensitization (therefore sensitization being a 'state' induced by OA), it seems that sensitization is more of a 'trait' that is present irrespective of OA pathology and leads to a higher capacity of pain experience in OA. This trait might for example be caused by genetic or other systemic predispositions(33). If sensitization is more of a 'state', it might be probable that treatment of the sensitization (caused by the OA process) might lead to less chronic residual pain after TKA/THA, assuming that the pathophysiological mechanisms of OA are removed after arthroplasty. However, based on the 'trait' theory of Neogi et al., the inherent 'trait' of sensitization would still be present after the pathology of OA was removed by arthroplasty, and the process of sensitization could cultivate once again in the peri- and postoperative period of surgical tissue damage and recovery, again leading to chronic (residual) pain. The negative findings of the long-term follow up of the DOA study in this thesis therefore endorse the 'trait' theory rather than the 'state' theory.

Implications for Future Studies and Clinical Implications

These possible explanations bring with them implications for future studies. Firstly, future studies could investigate whether a longer pre-operative treatment duration or a different timing of pre-operative duloxetine treatment continued up to (or shortly after) TKA/THA has a different effect on chronic residual pain, and secondly, there is an evident lack of studies concerning the treatment of sensitization in hip OA patients.

For clinical practice, the results of the present thesis discourage the use of duloxetine in OA patients prior to surgery if the aim is to prevent the development of chronic residual pain after arthroplasty in the treatment dosage, timing and duration as used in the DOA-trial. Depending on the results of the abovementioned future research suggestions regarding other treatment regimens with duloxetine, it is possible that there is a place for the use of duloxetine in the treatment of chronic residual pain after TKA/THA.

Alternatively, Neogi et al. recommends a multidisciplinary, patient-centred, behaviour-oriented treatment, following the biopsychosocial model and early on in the OA process, for the treatment of sensitization. This is in line with her 'trait' theory, Neogi proposes that this will probably be more successful in treating sensitization on the long term rather than the more symptomatic treatment of sensitization by neuromodulating medication(33). Such treatment may provide patients with strategies and self-management tools to fall back on if sensitization should present itself again in their future due to another physical or mental catalyst. Such programmes include elaborate patient education about the sensitization process and its possible influencing factors, coping strategies, social factors that can provoke or protect from enhanced pain experience, and awareness of

physical well-being. Apart from this, the present thesis shows that the complex causal pathways in the development of chronic residual pain need further investigation(33,34).

Response shift in patients undergoing TKA and THA

When investigating an effect of pre-operative treatment on post-operative pain after knee/hip arthroplasty using patient reported outcomes, as was attempted in the DOA trial, it is important to consider a possible response shift after surgery. Response shift is a term for the changes in which patients perceive their health status, and consequently interpret and respond to questions, based on cognitive psychological mechanisms(15). In chapter 6, a considerable difference was found in the MIC that patients reported after conservative treatment and six months after TKA. This could be explained as a form of response shift. The phenomenon of response shift has been reported before in knee OA patients by Razmjou et al.(35,36). As far as I know, no previous studies concerning response shift in hip OA patients are available. Razmjou et al. found that six months after TKA patients judged their pain and disability prior to surgery worse compared to how they rated their complaints preoperatively, especially their pain(36). This implicates that the way patients recall their previous pain experience (when they were suffering from OA) seems to be affected by the change of the internal standard of measurement of pain relief after arthroplasty. What the present thesis adds to this knowledge is the fact that the MIC itself also seems to be subject to a shift in the internal measurement frame of pain. In literature, several mechanisms are mentioned that can cause response shift(15). Reconceptualization, reprioritization and scale recalibration are common mechanisms described to cause response shift, a detailed description of all these mechanisms is beyond the scope of this general discussion but can be read elsewhere(15). Considering the response shift in the MIC after conservative treatment and after arthroplasty found in chapter 6, it is most likely that scale recalibration took place. It is possible patients experience so much pain-relieve after arthroplasty, that their reference framework of pain changes and their internal 'pain scale' recalibrates. Another phenomenon also needs to be taken into account regarding the change in MIC after arthroplasty, namely the effort-justification hypothesis(35). The choice of acceptance of the risks, stress and efforts of undergoing surgery lead to effort justification by a positive attitude shift towards the goal and thereby a tendency of reporting more positive changes in health.

The mechanisms of response shift can influence the clinimetric properties of patient reported outcomes, especially when they are used in longitudinal studies to assess change over time or the effect of an intervention(35). In the case of TKA, the treatment effect seems to become amplified, but after adjustment for response shift the effectiveness of TKA on pain and physical functioning remains undisputed(35,36). However, after other interventions or considering other outcome scores, an improvement (or deterioration) might go undetected without adjustment for internal scale recalibration. In the DOA trial, we did not account for response shift after TKA/THA

including any change in MIC, therefore we cannot determine whether the treatment effect of pre-operative duloxetine treatment was obscured by it.

Implications for Future Studies and Clinical Implications

In future longitudinal studies, response shift is a phenomenon that needs to be taken into consideration, including the realization that the MIC scores of patient reported outcomes might differ considerably depending on the type of treatment (conservative versus operative treatment). It would give valuable information to have reference data of MIC scores after different treatments and for different patient groups for the interpretation of intervention trials in OA patients. Also, future studies can investigate whether OA patients with signs of sensitization experience a different magnitude or direction of response shift than OA patients without signs of sensitization. In clinical practice it is important to realize that response shift depends on personal characteristics and psychological mechanisms that are different for each individual.

Concluding Remarks

This thesis provides insights into the measurement of signs of sensitization in hip and knee OA patients, and the effects of targeted treatment of sensitized hip and knee OA patients on long term outcome after THA/TKA. The research results from the present studies demonstrate a need for more specified measurement tools for signs of sensitization in hip and knee OA patients, and the need to further explore the difference between sensitization in hip versus knee OA patients. Future research regarding the treatment of sensitization in knee and hip OA patients should be focused on exploring different treatment regimens with duloxetine, or different neuromodulating medication, to investigate whether such medication has a role in the treatment of chronic residual pain after TKA/THA. Future research as well as clinical practice could also focus on providing patients who seem prone for sensitization with behaviour-oriented strategies to fall back on if sensitization should present itself again in their future due to another physical or mental catalyst, for example surgery. When studying effects of pre-operative treatments on the development of post-operative pain after hip or knee arthroplasty, it is important to realize that the effect of the arthroplasty itself likely induces a change of the internal standard of measurement of pain relief in the patients.

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