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ORIGINAL STUDY

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Correlations in radiographic and MAKO Total Knee Robotic-Assisted Surgery intraoperative limb coronal alignment

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Robotic-assisted arthroplasty has become increasingly established in recent years. The aim of the study is to determine if intraoperative coronal alignment during robotic-assisted total knee arthroplasty correlates with radiographic alignment. We prospectively compared the pre- and postoperative limb alignment values measured on long leg standing radiographs with intraoperative robotic-assisted measurements for 100 patients who underwent primary total knee arthroplasty. Two-tailed bivariate Pearson correlations were performed to evaluate the strength of the association between radiographic and robotic-assisted alignment. The intraclass correlation coefficient (ICC) was used to estimate interrater reliability. There was a male/female ratio of 1.16 and the mean age was 67 years (range 42-88). Robotic-assisted measurements slightly overestimated the degree of varus relative to radiographs. Radiographic and robotic-assisted measurements were strongly correlated ($r = 0.915$, $p < 0.001$) preoperatively, with a difference of 1.6 ± 3.2°. The average measure ICC was 0.996 with a 95% confidence interval from 0.995 to 0.997 ($p < 0.001$). Postoperatively a bigger difference was measured (3.1° ± 1.9°), comparing radiographic and MAKO alignment. A moderate correlation was observed between the postoperative radiographic and MAKO outcome alignment ($r = 0.604$, $p < 0.001$). The average measure ICC was 0.977 with a 95% confidence interval from 0.967 to 0.984 ($p < 0.001$). There is a strong correlation in the preoperative setting between radiographic and robotic-assisted lower limb alignment and a moderate correlation in the postoperative setting. The values measured by the MAKO Total Knee application were considerably more in varus.

Keywords : Total knee arthroplasty; robotic-assisted surgery; coronal limb alignment; long leg standing radiographs; MAKO.

INTRODUCTION

Robotic technology has become more widely used in joint arthroplasty during the past decades. It has rapidly evolved during the last several years as almost every implant company is developing or offering a robot *(1,2)*. Introduction of robotic-assisted arthroplasty in orthopedics may result in multiple benefits: improved implantation accuracy, reduced

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instrumentation, improved soft tissue balancing, lower complication rates, increased implant survival and finally improved patient satisfaction scores *(3-6)* Additional research regarding robotic-assisted surgery is currently awaiting to further objectify these potential benefits. Longer term outcomes are paramount to investigate improved function and implant durability, the most important outcome parameters of joint arthroplasty.

The MAKO robotic system is a closed, semi-active, CT-based system and is available for assisting Total Knee Arthroplasty (TKA), Unicompartmental Knee Arthroplasty (UKA) and Total Hip Arthroplasty (THA). The surgical plan is determined preoperatively. A robotic arm assists in bone resection based on stereotactic references below and above the joint. The resection plan can be adjusted intraoperatively based on real-time referencing. When the surgeon deviates from the planned resection plane during bone resection, he will be prevented from doing this through feedback on the computer screen and spatial limits *(7)*.

Restoration of neutral mechanical axis has since long been accepted as a prognostic factor for long-term implant survival in TKA. It was assumed that a valgus or varus alignment of more than 3° was associated with an inferior outcome and lower implant durability *(8,9)*.

However, this was nuanced by more recent research. Alignment outliers did not always adversely influence implant survival, especially residual varus alignment *(10,11)*.

To avoid this malalignment, reliable and reproducible measurements of limb alignment are therefore useful in the planning, performance and evaluation of total knee arthroplasty to avoid this malalignment.

The use of long leg standing radiographs have been shown as well to be reproducible for measurements of coronal plane limb alignment, despite the well-known sources of error such as limb rotation, knee flexion contractures or other positional errors during radiograph acquisition *(8-14)*.

With the introduction of navigation-assisted systems it became possible for orthopedic surgeons to obtain a real time intraoperative limb alignment measurement. Navigation-assisted surgery has already shown promising results in reliability of reporting mechanical axis, although patients are measured in a prone position in contrast to the standing radiographs *(15)*.

Recent study showed an acceptable correlation between intraoperative navigation and radiographic lower limb alignment *(16,17)*. We hypothesized that this correlation holds true for robotic-assisted surgery as well. Only limited data was available on this subject given the novelty of this technology *(18,19)*. The aim of the present study was therefore to evaluate the pre- and postoperative correlation between long leg standing radiographs and intraoperative robotic-assisted limb alignment.

MATERIALS AND METHODS

Pre- and postoperative limb alignment values measured on long leg standing radiographs were compared with intraoperative robotic-assisted measurements for 100 patients who underwent primary RATKA for osteoarthritis (OA) of the knee. Data were collected prospectively of all patients undergoing primary TKA from July 2019 until January 2020 in our hospital, regardless of the cause of OA. Five patients were excluded from the final analysis. Three patients were lost to follow up because they did not consult for the postoperative radiograph and two patients were not positioned correctly for the long leg preoperative standing radiograph. The study was in accordance with institutional rules for ethical review. All patients signed informed consent to participate in the study with anonymization of their data.

The total knee arthroplasty and intraoperative analysis was performed with the MAKO Total Knee Arthroplasty system (Stryker, USA). Preoperatively all patients underwent a CT-scan of the knee according to the MAKO protocol. The surgical approach which was used is a modified subvastus approach. The cases were all performed by a single surgeon (GL) with great experience in robotic-assisted surgery, using a ligament balancing technique. Alignment target was neutral, however residual varus/valgus alignment was accepted in severe deformed limbs. Limb alignment was registered before bone cutting and after prosthesis implantation (Triathlon CS, Stryker).

Long leg standing radiographs were taken preoperatively and between 6 weeks and 3 months postoperatively. All radiographs were taken with the legs fully extended and the patella and feet facing forward on a single long cassette *(8)*. The mechanical axis was independently measured pre- and postoperatively by 2 orthopedic surgery residents and 1 medical trainee. The mean of these 3 values was used in the analysis. The mechanical axis was defined as the angle measured between the line drawn from the center of the femoral head to the center of the knee and the line drawn from the center of the knee to the center of the talus *(20)*. These angular values were measured using Centricity Universal Viewer (GE Healthcare, United States). Varus alignment was defined as a positive angulation, whereas valgus alignment was defined as a negative angulation.

The mechanical axis given by the MAKO system is automatically generated by the computer when the leg is fully extended. It is based on the CT landmarks, verified by the surgeon before each procedure. Intraoperative measurements were registered before any cuts were made and again postoperatively after the robotic-assisted cuts were made and definitive implants were inserted.

The primary outcome measure in this study was to determine the correlation between robotic-assisted and pre- and postoperative radiographic measurements in terms of mechanical alignment. Two-tailed bivariate Pearson correlations were performed to evaluate the strength of the association between pre- and postoperative radiograph and robotic-assisted alignment. The strength of correlation was indicated by the correlation coefficient (r) as strong (>0.7), moderate (0.4-0.7), or weak (<0.4). The intraclass correlation (ICC) was used to estimate interrater reliability between the three independent observers. An analysis was performed on pre- and postoperative radiographic and robotic assisted measurements to determine mean values, standard deviation, minimum, maximum and the difference between the means. Statistical significance was assumed at a threshold of $p < 0.05$. All statistical analyses were performed using SPSS version 24 (IBM, USA).

RESULTS

For the 95 patients who underwent primary RATKA from July 2019 until January 2020 there was a male/female ratio of 1.16 and the mean age was 67 years (range 42-88 years). Of the arthroplasties 43 (45.3%) were conducted left-sided and 52 (54.7%) right-sided, 82 (86.3%) were cemented and 13 (13.7%) were cementless (Table I).

Table I. – Patient demographics

Mean age (years) (range)	67 (42-88)
Sex (male/female)	51/44
Side (left/right)	43/52
Cement (cemented/cementless)	82/13

Table II. – Pre- and postoperative radiograph and robotic-assisted measurement of mechanical alignment

Measurement	Mean	Minimum	Maximum	Standard deviation
Preoperative				
MAKO (°)	3.1	-7	13	4.4
Radiograph (°)	1.5	-16	18	6.7
MAKO:radiograph difference (°)	1.6	-5.0	10.7	2.3
Postoperative				
MAKO (°)	2.4	-3	8	2.0
Radiograph (°)	-0.7	-5.3	5.7	2.4
MAKO:radiograph difference (°)	3.1	-1.6	8.3	1.9

Varus: >0° and valgus: <0°

As pathophysiologically expected the mean preoperative radiographic alignment was in slight varus (1.5° ± 6.7°). Varus alignment was observed in 56 knees (59.0%) and valgus alignment in 39 (41.1%). Only 22 patients (23.2%) had a normal preoperative radiographic alignment between 3° of varus and 3° of valgus. The MAKO system registered a mean preoperative varus alignment of 3.1° ± 4.4°. Robotic-assisted measurements slightly overestimated the degree of varus relative to radiographs (1.6° ± 2.3°). Radiographic measurements had a greater range and variability than the MAKO data (Table II). Radiographic and robotic-assisted measurements were strongly correlated ($r = 0.915$, $p < 0.001$) (Table III; Figure 1). A high degree of reliability was found between radiographic and robotic-assisted measurements. The average ICC was 0.996 with a 95% confidence interval from 0.995 to 0.997 ($p < 0.001$) (Table III).

Postoperatively there was a MAKO alignment between 3° of varus and 3° of valgus in 73 patients (76.8%). These results are inherent to the ligament balancing technique. The mean postoperative radiographic alignment was slightly in valgus (-0.7° ± 2.4°), in contrast to the MAKO alignment where a varus alignment is observed (2.4° ± 2.0°). There was a greater discrepancy between radiographic and MAKO alignment postoperatively (3.1° ± 1.9°) than preoperatively (1.6° ± 2.3°). A moderate correlation was observed between the postoperative radiographic and MAKO outcome alignment ($r = 0.604$, $p < 0.001$) (Table II, Figure 2). Postoperatively a high degree of reliability was found between radiographic and robotic-assisted

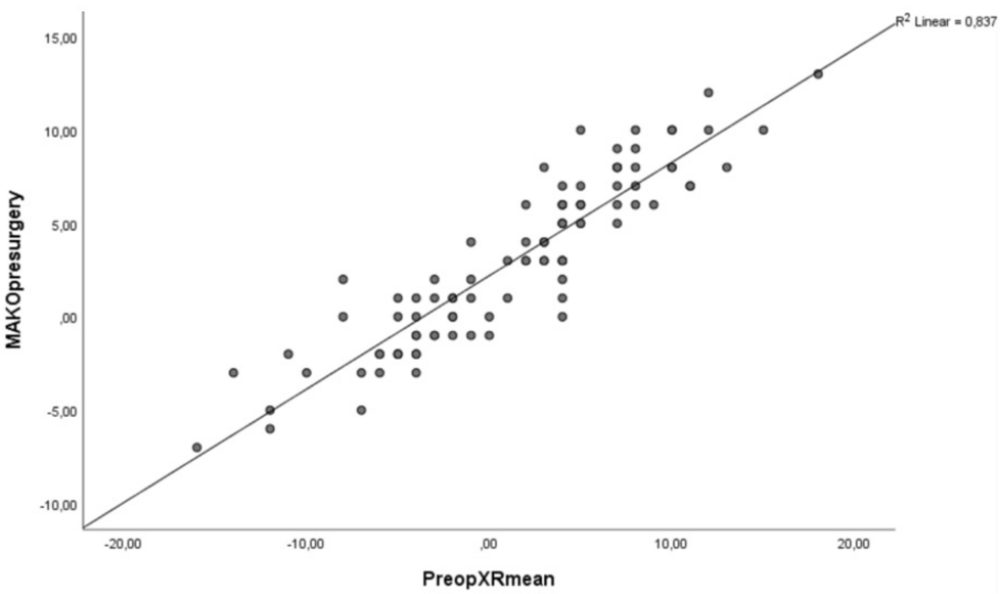

Figure 1. — Correlation between preoperative long standing radiographic and MAKO limb alignment.

Table III. — An analysis of radiograph to MAKO correlation and interobserver reliability

Alignment measurements	Radiograph: MAKO Pearson correlation coefficient*	Observer 1: Observer 2: Observer 3 Intraclass correlation coefficient**
Mechanical axis preoperative	0.915	0.996 (95% CI 0.995 - 0.997)
Mechanical axis postoperative	0.604	0.977 (95% CI 0.967 - 0.984)

* Correlation is significant at the 0.01 level (two-tailed). ** Reliability is significant at the 0.01 level (two-way mixed effect model, average measure)

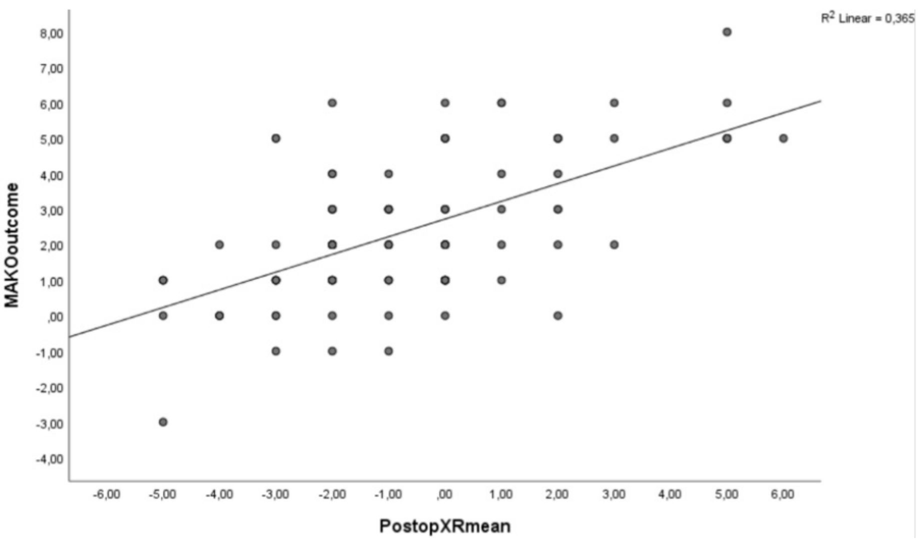

Figure 2. — Correlation between postoperative long standing radiographic and MAKO limb alignment.

measurements. The average ICC was 0.977 with a 95% confidence interval from 0.967 to 0.984 ($p < 0.001$) (Table III).

DISCUSSION

A number of unproven theories exist to explain the increased joint pain with changing weather conditions.

A first theory states that tendons, muscles, bones and areas of scarring have different densities. Cold and damp weather may influence expansion and contraction of these tissues differently. This might lead to micro-traumas and pain *(27)*.

An increase of stiffness in the joints could be caused by alterations in barometric pressure and temperature. This triggers subtle movements that enhance a nociceptive respons *(27,50)*. Changes in barometric pressure may also cause a transient dis-equilibrium in body pressure that may sensitize nerve endings. Sensitized type 4 mechanoreceptors, important nociceptors in the joint, may intensify the pain *(17,56)*.

Finally, as mentioned before, pain could be caused by mood fluctuations due to seasonal weather patterns *(1,27,40)*.

The belief of OA patients in the phenomenon that meteorological conditions can alternate their pain intensity is strong *(10,23,26,27,38,44,45)*. Components that are mentioned the most, are low temperature, humidity and precipitation. Furthermore, patients feel that their pain intensifies most with changes in weather conditions. Barometric pressure is not mentioned as an important cause for worsening pain. This can be explained by the fact that change in pressure is not noticed in daily life and has to be actively searched for. The influence of meteorological conditions on OA symptoms was frequently significantly present. Although different studies show conflicting results, an increase in barometric pressure *(8,14,23,34,53)*, a decrease in temperature *(10,23, 34,48,50)* and an increase of humidity *(14,48,50)* are found to have a significant effect in various studies. The only two studies that came to the same conclusion, are those of Strusberg et al. (2002) and Timmermans et al. (2015), where temperature and humidity show to have an effect *(48,50)*. Only two studies show an effect of both barometric pressure and temperature *(23,34)*. But these studies differ on the significance of precipitation on OA symptons *(23,34)*. Some studies reach to the conclusion that there is no correlation between pain complaints and meteorological variables *(20,45)*. The variety of meteorological conditions that are of influence, is characteristic for the studies on this subject. Weather sensitivity is not greater in colder climates *(27,38,49,50)*. The effect of the variables is greater in colder climates, but higher pain scores are given in warmer climates (50). The effect of meteorological changes seems to be nearly absent in warm, stable climates (20,52,53).

An explanation for this diversity in results is the great importance of factors that might cause differences in pain perception. Due to these motives and the fact that every study has a different geographic location, climate, disease group, methodology and statistical evaluation, the evidence regarding the effect of the weather on OA pain remains small. No general conclusion can be drawn from previous studies. But since the belief of patients is great, influence of weather conditions has to be taken into account in every day clinical practice. The magnitude and clinical impact of changing meteorological conditions is questioned by several studies, but could be clinically significant on a population level due to the high prevalence of OA (14,34,53). To provide further evidence, repetition of a particular study design on the same geographic location or in the same climate would be required.

Central sensitization mechanisms share a causative role with peripheral mechanisms, related to the cause of pain in OA (5,17).

Patients with high WOMAC-scores display more mechanical hyperalgesia at the knee joint and at far distant joints when compared with controls and patients with low WOMAC-scores (29). When placing their hand in a cold water bath, patients with high WOMAC-scores also report higher pain intensity ratings (29).

Pain threshold measures are a part of quantitative sensory testing (QST), a form of testing that indicates the presence of sensitization in OA(5). Cold pressure thresholds (CPT) in subjects with knee OA exhibit to be significantly higher. Furthermore, subjects with knee OA exhibit significantly reduced pressure pain thresholds (PPT) compared to controls. Moreover, higher PPT are observed with higher VAS-scores (36). When knee OA patients are divided into four groups, constructed by dichotomizing clinical knee pain scores and radiographic knee OA Kellgren and Lawrence Scores. Patients reporting high levels of clinical pain in the absence of moderate-to-severe radiographic knee OA, exhibit hyperalgesia when PPT and CPT are measured (21).

The results of these studies suggest the influence of central sensitization in OA patients and show a correlation between severer OA and a greater importance of central sensitization.

Cold hyperalgesia, caused by central sensitization, could explain the heightened pain response in colder weather conditions by OA patients. Cold and general hyperalgesia are important factors to be considered in the treatment of OA. Currently used medication might not adequately tackle the pain caused by sensitization. Centrally acting pharmacological treatments are suggested to be more effective (29). Further research on the use of this medication is required.

The processes responsible for OA are cartilage destruction and inflammation. Breakdown of cartilage is provoked by the action of catabolic cytokines, such as Interleukin 1 (IL-1), Interleukin 17 (IL-17) and Tumor Necrosis Factor alpha (TNF-α). They act by modulating the expression of the matrix metalloproteinases and the cartilage extracellular matrices (2).

Growing evidence is available that certain cytokines predominate in OA with symptoms of central sensitization. Levels of Interleukin 6 (IL-6) are associated with heat - and cold hyperalgesia (32). In addition, cytokines such as IL-1β, IL-6 and TNF-α, contribute to pain hypersensitivity. All produce heat hyperalgesia after injection (28). TNF-α and IL-1β, in contrast to IL-6, show no interaction with any type of QST (32). This may be due to the different mechanisms by which the cytokines contribute to the sensitization mechanisms.

More research is required to understand the relation of these cytokines to the central sensitization mechanisms and to treat hypersensitivity with therapeutic agents directly guided at the cytokines.

More bone damage and a higher expression of Vascular Endothelial Growth Factor (VEGF) and IL-1 in cartilage cells of the ankle joint was observed in rats when they were exposed to prolonged changes in humidity and temperature (6). This indicates that environmental factors can influence the pathological course of arthritis, possibly due to synovial lesions caused by VEGF and IL-1.

Nociceptive neurons are functionally characterized by the type of sensory receptors and ion channels expressed on the plasma membrane through-out the cell body and nerve fibres *(35)*. These receptors and channels are vital for the detection of noxious stimuli. These nociceptive membrane proteins, belonging to the Transient Receptor Potential (TRP) family, constitute the major group of molecular detectors and transducers of pain-causing stimuli, including cold stimuli. Transient receptor potential ankyrin 1 (TRPA-1) was found to be activated by cold stimuli *(35)*. In addition, TRPA-1 showed to be mechano-sensitive and to be found in non-neuronal cells *(35,39)*. Functional activity of the channel has been observed in chondrocytes and synoviocytes in OA joints, where they mediate OA-related pain, inflammation and cartilage destruction *(39)*. IL-1 seems to have a vital role for the functioning of the TRPA-1 channel. IL-1 induces production of metallopreinases and IL-6 in chondrocytes *(39)*. These two were previously mentioned as important factors for OA-pathogenesis and hyperalgesia, respectively *(2,32)*. This induction is less than half in TRPA-1 deficient mice or with the association of a TRPA-1 antagonist *(39)*.

The current through the TRPA-1 channel only mildly increases when temperature reduces from 25 °C to 10 °C, but is much larger when a TRPA-1 channel agonist is added *(9)*. The same results were seen *in vivo* with administration of Freund's Complete Adjuvant (CFA), which causes intra-articular induction of joint inflammation. The mice then displayed more nocifensive behaviour and mechanical pain sensitivity after placement on a cold plate or exposure to cold temperatures (10°C) *(3,18)*. This suggests that TRPA-1 is a key mediator of cold hypersensitivity in pathological conditions *(3)*. This theory is supported by non-appearance of cold hypersensitivity in TRPA-1 knock-out mice and a decrease of cold hypersensitivity with the administration of a selective TRPA-1 antagonist *(9,18,19,25)*.

The role of TRPA-1 was confirmed with over-expression of the TRPA-1 protein and - mRNA after treatment with CFA *(11)*. This overexpression and the long lasting mechanical and cold hyperalgesia are both inhibited by the pre-treatment of a TRPA-1 antagonist *(11,16,19,42)*.The TRPA-1 channel induces the hyperalgesia through mediation of TNF-α *(19)*.

Pharmacological blocking of the TRPA-1 channel might be an interesting method to ease sensitized pain. So far, only Go-sha-jinki-Gan (GJG), a Japanese herb, is successfully examined regarding the effect on TRPA-1 channel mediated pain. GJG reduces hyperalgesia in mice by suppressing the TRP channels and TRPA-1 expression, and thereby suppressing TNF-α. Administration of TNF-α counteracted the effects of the drug. No adverse effects were seen with treatment of GJG *(37)*. The possibility of the use of this medicine for pain hypersensitivity and cold hyperalgesia in daily practice, requires further investigation. Similar cytokines seem to be responsible for TRPA-1 function and sensitization, which justifies further research on this topic.

Presence of pre-operative widespread sensitization, which can be suspected in patients with pain at rest and low thresholds with QST, is associated with a higher prevalence of pain and WOMAC-pain scores 1 year post-operative *(13,33,57)*. However, one study concluded that there was no correlation between pre-operative low PPT and chronic post-operative pain *(58)*.

Contrary to the previously mentioned studies, there are studies that have indicated that pain related to sensitization, improves after TJA. QST normalized in studies after replacement of the hip - or the knee joint *(4,22,30)*. The studies conclude that the central pain processes are maintained by peripheral input, and thus disappear when these peripheral tissues are replaced by prosthetic material. It has to be mentioned that the sample sizes in these studies are small : no more than 20 patients with TJA are investigated in each study.

One study concludes that knee OA patients with greater widespread hyperalgesia benefit less from TJA than patients with lesser widespread hyperalgesia. Conversely, hip patients with greater widespread hyperalgesia benefit more from surgery *(59)*.

The study by Kosek et al. (2000) concluded that cold hyperalgesia reduced after TJA. Only one other study investigated cold hyperalgesia following TJA *(30,55)*. They concluded that persistent pain after TJA is associated with widespread pressure and cold hyperalgesia. Patients with chronic pain showed to have a 5°C higher pain threshold than their controls at the knee and the elbow.

Sensitization turns out to be a dominant factor in the undissolved pain after revision TJA *(46)*. Some studies discussed that central pain processes are maintained by peripheral input *(4,22,30)*. How would this explain ongoing pain and sensitization in other studies *(13,33,41,55,57,58)*? A suggestion is made that the peripheral input arises from tissue that has not been replaced by prosthetic material, such as adjacent muscles, connective tissue, and/or adipose tissue *(46)*. A low pain pressure tolerance, supports this theory. Additionally, central mechanisms could be involved in the maintenance of the sensitization *(46)*.

Pain due to sensitization mechanisms can be treated surgical, by TJA, and non-surgical. Non-surgical treatment consists out of educating the patient, exercise, insoles, dietary advice and pain medication. Combining non-surgical- with surgical treatment is more efficacious at treating pain hypersensitivity. PPTs are significantly lower in patients that receive non-surgical treatment following their TJA, but more serious adverse events are associated *(47)*.

We conclude that TJA can play an important role in the treatment of hypersensitivity, but strong evidence is present regarding the role of sensitized pain in chronic pain after TJA. Therefore, further research on the use of the earlier mentioned centrally acting agents is justified.

CONCLUSION

Although the majority of the studies conclude that at least one of the meteorological variables have an influence on pain in OA patients, no general conclusion can be drawn. Repetition of a particular study design on the same geographic location or in the same climate would be required. Possible explanations for greater pain intensities due to cold weather are central sensitization mechanisms and the function of the TRPA-1 channel. Other treatments than TJA might be required if centrally mediated pain is present, due to possible persistency of centrally mediated pain after TJA. Further research is needed on this topic. In addition, further research is needed on the treatment of cold hyperalgesia caused by the function of the TRPA-1 channel and possible treatment options in this area.

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