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*ORIGINAL STUDY*

# The influence of weather conditions on osteoarthritis and joint pain after prosthetic surgery

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**The purpose of this narrative review was to highlight the research on the influence of weather conditions on patients with osteoarthritis, the pathophysiological mechanisms and the therapeutic consequences. A search was conducted using the Pubmed, Medline and Web of Science databases. Barometric pressure, temperature and humidity are the weather conditions that are found to be correlated most to the worsening of pain complaints. But, due to the difficulty of measuring the impact of these variables and the great diversity in study protocols, an analysis of studies regarding this topic shows conflicting results. Central sensitization mechanisms and the function of a Transient Receptor Potential channel might explain the pain hypersensitivity to cold weather. Joint pain, caused by central sensitization mechanisms, cannot always be treated with joint arthroplasty. When pain remains present after joint arthroplasty, centrally mediated pain constitutes an important role.**

**Keywords** : Osteoarthritis ; weather ; hypersensitivity ; central sensitization ; arthroplasty.

## INTRODUCTION

In daily practice, a clinician is often confronted with osteoarthritis (OA) patients who feel that their symptoms worsen with certain meteorological conditions. The first description of this phenomenon in academic literature is found in a study by Edström (1948), who revealed that rheumatoid arthritis (RA) patients showed improvement of signs and symptoms, when living in a constantly hot and dry environment*(15)*. Hollander and Yeostros (1963) later confirmed the influence of meteorological changes on arthritic pain. In a room with controlled air pressure, temperature and humidity, OA and RA patients experienced worsening of their symptoms when they were exposed to humidity increase and barometric pressure decrease *(24)*. Since then, several studies have aimed to depict the influence of meteorological changes in OA patients.

This literature review intends to discuss the evidence concerning this topic. Hypotheses concerning the cause of the influence of the meteorological conditions will be reviewed. Possible pathophysiological mechanisms, such as central sensitization mechanisms and a functionally active channel in OA, will be discussed. In addition, the

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chances of total joint arthroplasty (TJA) on the resolution of pain symptoms caused by sensitization mechanisms, will be analysed.

## METHODS

This literature review is written after bibliographic database research of Pubmed, Web of Science and Medline. Furthermore, manual search was performed in the reference lists of the articles and reviews selected until December 2016. The main focus in this review is OA, therefore articles that only described RA were excluded.

The following Mesh-terms or a combination of Mesh-terms were used : "Osteoarthritis", "Barometric pressure", "Temperature", "Weather", "Pain", "Hyperalgesia", "Arthroplasty", "Pain threshold", "Central Nervous System sensitization", "Pain measurement", "Arthralgia", "Arthritis", "Cold temperature", "Climate", "Joint diseases", "Depression", "Hip joint", "Chronic pain" "Transient Receptor Potential channels'' "Oxidative stress", "Interleukin 1" and "Cytokines".

## RESULTS

Different types of studies have been conducted to investigate the effect of meteorological conditions on OA pain. They will be discussed separately.

In 1992, 70 chronic pain patients completed the Weather and Pain Questionnaire (WPQ) and a Visual Analog Scale (VAS). Patients reported temperature (87%), weather changes (76%), humidity (73%) and precipitation (72%) as conditions that influenced their pain the most. Sunshine and thunderstorms were less reported. In addition, patients were divided into 2 groups : high or low weather sensitivity. High weather-sensitive patients reported greater pain intensity and longer pain duration*(44)*no standardized measures of weather sensitivity have been developed. We describe the development and use of the Weather and Pain Questionnaire (WPQ.

Three years later, 588 chronic pain patients, divided over four cities with different climates in the United States of America (USA), filled out the same WPQ. The majority (68%) believed that changes in weather affected their pain. Patients stated that their symptoms worsened either during, or after, changing weather conditions. Cold (61%) and humid (73%) conditions were considered to have the greatest influence. Hot weather and changes in temperature and barometric pressure were less frequently perceived to have influence. The belief that living in a colder climate worsens pain, was not supported in this study. The study suggests that the body establishes an equilibrium in relation to the local climate, so that changes in weather trigger an increase in pain, regardless of the prevailing meteorological conditions *(27)*.

Of 137 patients (16% OA) interviewed by Asian researchers, 74% reported to be weather sensitive. Again, humidity and cold weather, were said to have the biggest effect *(38)*.

In a Japanese study, patients were divided in four different climate clusters. Clusters with lesser sunshine and more precipitation showed to have a higher incidence of patients with joint pain. This study furthermore mentions that the type of work a patient performs, is of great importance to their arthralgia *(51)*. There has not been any correction for this pain worsening factor in this study, nor in any other.

In an Australian survey, conducted in 2014, patients with arthritis (69% OA) reported cold weather as the element with the greatest impact on their pain and quality of life *(26)*.

The disadvantages of these retrospective studies have to been taken into account. Sociocultural differences have been ignored in all of the studies. In some cultures, pain perception might be expressed quicker and easier than in others *(12)*. Exposure to the weather could be greater in warmer climates ; therefore patients could be more affected by the weather. The way people adapt to the weather (clothing, use of a heater) has not been considered either.

The perception of pain might also be affected by the mood of a patient. The impact of meteorological factors on the risk of causing depressive symptoms has been described *(40)*. In addition, pain perception and mood are two frequently associated aspects *(1)*. Therefore it is not unreasonable to speculate that weather conditions may affect pain in part via changes in mood. Jamison et al. (1995) found that

patients who reported to be weather sensitive, also were more likely to have emotional distress *(27)*. They were not able to correct this factor in any of these studies.

Patients feel less helpless if they can relate their pain to external conditions *(7)*. They tend to perceive correlations between uncorrelated random sequences. There is a tendency to seek for an explanation for the worsening of pain and ignore arguments that disconfirm that explanation *(43)*. For example, if patients were told they had arthritis, they tend to be more sensitive to the weather *(27)*. So called confirmation bias could explain why weather conditions are remembered to cause pain, and other factors are forgotten or ignored.

The use of analgesic medication and comorbidities, which could affect pain perception, are not taken into account in any of the studies. Another strong disadvantage in these studies is the use of average measured temperatures, hence the impossibility to examine the effect of changing weather conditions.

In the following studies, when not described differently, daily filled out pain scores were compared to local meteorological conditions.

In the first prospective study to appear, no association could be made in any of the VAS-scores with any of the investigated weather variables, including the regularly discussed variables in this review *(45)*.

Contradictive to the previous study, temperature, precipitation and atmospheric pressure were noted to influence pain in 62 patients with arthritic symptoms over a 30 day study period. 83% of the OA patients reported to have worsening pain due to weather conditions. Precipitation was found to be the most significant factor. Humidity was not considered as an influencing factor *(23)*.

A longer study period has been assessed in a study in Argentina, where 151 patients (52 OA) filled out a VAS and a questionnaire over the period of one year. Pain correlated with low temperature and high humidity *(48)*.

A study investigating the effect of temperature, barometric pressure and precipitation on the symptoms of 154 OA patients in 2003, showed no effect for temperature or precipitation. Barometric pressure resulted to be significantly relevant in women. Barometric pressure only resulted to have a significant relationship with OA symptoms in men, when the pressure kept rising over 3 consecutive days. The study was conducted in Florida, in the presence of a stable climate, with relatively few days of precipitation and the study treated mild OA patients with overall lower pain scores. These are three explanations for possible underestimation *(53)*.

In 2007, over a period of 3 months, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) was compared with meteorological conditions for patients diagnosed with knee OA. Patients were spread out over the USA, thus different climate conditions were analysed in this study. Temperature, barometric pressure, dew point, precipitation, and humidity were measured each day. Only temperature decrease and barometric pressure increase showed interaction with a diminution of the WOMAC-score *(34)*.

Barometric pressure showed to be correlated to a higher VAS-score in 53 patients diagnosed with end stage OA of the hip in an one month study period. No correlation was found for precipitation and temperature *(8)*. Earlier, Wingstrand et al. (1990) showed that atmospheric pressure is responsible for stabilising the hip joint *(54)*. With elimination of the effect of atmospheric pressure, the hip could be slightly subluxated. If significant pathology is present, effusion might follow. This counteracts the stabilising effect and could lead to micro-instability and unfavourable loading, explaining the heightened sensation of pain *(54)*.

Dutch researchers found that humidity was associated with WOMAC pain scores, and baro- : metric pressure was associated with WOMAC function scores. In this study in 2014, 118 patients with hip OA were asked to fill out a WOMAC-score every 3 months, during 2 years *(14)*.

The largest study on meteorological influences in OA pain, asked 810 OA patients to fill out a VAS for 2 weeks *(50)*. This was done in five countries, after the baseline interview and after 6 and 12-18 months. Changes in temperature and humidity over a 3-day period were associated with a higher VAS-score. Barometric pressure and precipitation were not. When VAS-scores were compared to changes in meteorological conditions on 2 consecutive days,

no significant correlation was found. Furthermore, warm-dry climates showed higher VAS-scores, but the effect of meteorological variables tended to be higher in cold-wet climates *(50)*.

Australian patients, diagnosed with knee OA, did not show any correlation between exacerbation of their pain and weather conditions. They were asked to fill out a VAS, every tenth day for three months. Disadvantages of this study are the relatively stable climate, the ten-day measurement period and the study method (big changes in weather conditions were needed to be categorised as change of a weather condition) *(20)*.

For the prospective studies, the same disadvantages apply as for the questionnaires regarding socio-cultural influences, inter- and intra-individual pain perception differences, daily mood swings, the use of analgesic medication and comorbidities. Although in the study by Strusberg et al. (2002), results were left out if exacerbation of their disease was due to other mechanisms than changing weather conditions *(48)*. Timmermans et al. (2015) excluded patients with signs of depression and heavy changes in medication use *(50)*. Confirmation bias will not play such an important role as it does in the questionnaires, since in most studies patients did not know their pain reports were compared to weather conditions. Though patients could still sense the weather, and it could have shaped their judgement. Except for the study conducted by Strusberg et al. (2002), no study has taken into account the fact that patients could have spent their follow-up period at another location *(48)*.

In these studies, OA patients are compared to healthy subjects, or weather sensitive patients are compared to non-weather sensitive patients. The same disadvantages, as described above, are applicable for the following studies.

In 1986, weather sensitive OA patients from Chicago city and rural North Dakota were compared to non-weather sensitive OA patients. The non-weather sensitive rural subjects showed not to be affected by any of the weather variables regarding to pain, whereas weather sensitive subjects had more pain-related stress with a change in the temperature or barometric pressure. Precipitation correlated with pain in the urban weather sensitive subjects, wind speed did so in the non-weather sensitive group. For both urban groups, different weather variables showed to cause more pain-related stress *(31)*.

OA patients reported to have more pain with a decrease in atmospheric pressure in a study conducted over the period of one month in Barcelona. This is contradictive to other studies, where an increase of barometric pressure was correlated to intensification of pain. The biggest disadvantage of this prospective study is the stable climate without much fluctuations of the weather variables *(52)*.

Using the results of a study mentioned above, weather sensitive patients were compared to non-weather sensitive patients *(49,50)*. The two-third of the patients that were weather sensitive, were more dominantly present in a warm-dry climate (77%) than in a cold-wet climate (57%). They were older, tended to suffer more of anxiety and/or depression and had a lower capacity to cope with pain. Women tended to be more sensitive to the weather than men. Weather sensitive patients scored higher on a VAS and reported damp, rainy and/or cold weather as affecting their pain the most.

## 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 carti-

lage 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 throughout 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.

## REFERENCES

1. **Adams N, Field L**. Pain management 1 : psychological and social aspects of pain. *Br J Nurs.* 2001 ; 10 : 903-911.
2. **Aignera T, Sachseb A, Gebharda PM, *et al.*** Osteoarthritis: Pathobiology – targets and ways for therapeutic intervention. *Adv Drug Deliv Rev.* 2006 ; 58 : 128-149.
3. **Andersson DA, Gentry C, Moss S, *et al.*** Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress. *J Neurosci.* 2008 ; 28 : 2485-94.
4. **Aranda-Villalobos P, Fernández-De-Las-Peñas C, Navarro-Espigares JL, *et al.*** Normalization of widespread pressure pain hypersensitivity after total hip replacement in patients with hip osteoarthritis is associated with clinical

and functional improvements. *Arthritis Rheum* 2013 ; 65 : 1262-1270.

5. **Arendt-Nielsen L, Nie H, Laursen MB, *et al.*** Sensitization in patients with painful knee osteoarthritis. *Pain* 2010 ; 149 : 573-581.
6. **Bai Y-J, Jiang D, An N, *et al.*** Effects of cold-damp and hot-damp environment on VEGF and IL-1 expression in joint cartilage cells in adjuvant arthritis in rats. *J Tradit Chinese Med.* .2012 ; 32 : 256-260.
7. **Blécourt A de, Knipping A, Voogd N de, *et al.*** Weather conditions and complaints in fibromyalgia. *J Rheumatol.* 1993 ; 20 : 1932-1934.
8. **Brennan SA, Harney T, Queally JM, *et al.*** Influence of weather variables on pain severity in end-stage osteoarthritis. *Int Orthop.* 2012 ; 36 : 643-646.
9. **Camino D, Murphy S, Heiry M, *et al.*** TRPA1 Contributes to Cold Hypersensitivity. *J Neurosci.* 2011 ; 30 : 15165-15174.
10. **Çay HF, Sezer I, Firat MZ, *et al.*** Which is the dominant factor for perception of rheumatic pain: Meteorology or psychology? *Rheumatol Int.* 2011 ; 31 : 377-385.
11. **da Costa DSM, Meotti FC, Andrade EL, *et al.*** The involvement of the transient receptor potential A1 (TRPA1) in the maintenance of mechanical and cold hyperalgesia in persistent inflammation. *Pain* 2010 ; 148 : 431-437.
12. **Cruz-Almeida Y, Sibille KT, Goodin BR, *et al.*** Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis Rheumatol.* 2014 ; 66 : 1800-10.
13. **Dave AJ, Selzer F, Losina E, *et al.*** The association of pre-operative body pain diagram scores with pain outcomes following total knee arthroplasty. *Osteoarthr Cartil.* 2016 : 1-9.
14. **Dorleijn DMJ, Luijsterburg PAJ, Burdorf A, *et al.*** Associations between weather conditions and clinical symptoms in patients with hip osteoarthritis: A 2-year cohort study. *Pain* 2014 ; 155 : 808-813.
15. **Edstrom G, Lundin G, Wramner T**. Investigations into the Effect of Hot, Dry Microclimate on Peripheral Circulation, etc., in Arthritic Patients. *AnnRheumDis.* 1948 ; 7 : 76-82.
16. **Eid SR, Crown ED, Moore EL, *et al.*** HC-030031, a TRPA1 selective antagonist, attenuates inflammatory- and neuropathy-induced mechanical hypersensitivity. *Mol Pain* 2008 ; 4.
17. **Felson DT**. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol.* 2005 ; 17 : 624-628.
18. **Fernandes ES, Russell FA, Alawi KM, *et al.*** Environmental cold exposure increases blood flow and affects pain sensitivity in the knee joints of CFA-induced arthritic mice in a TRPA1-dependent manner. *Arthritis Res Ther* 2016 ; 18.
19. **Fernandes ES, Russell FA, Spina D, *et al.*** A distinct role for transient receptor potential ankyrin 1, in addition to transient receptor potential vanilloid 1, in tumor necrosis factor alpha-induced inflammatory hyperalgesia and Freund's complete adjuvant-induced monarthritis. *Arthritis Rheum.* 2011 ; 63 : 819-829.
20. **Ferreira ML, Zhang Y, Metcalf B, *et al.*** The influence of weather on the risk of pain exacerbation in patients with knee osteoarthritis e a case-crossover study. *Osteoarthr Cartil.* 2016 ; 24 : 2042-2047.
21. **Finan PH, Buenaver LF, Bounds SC, *et al.*** Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. *Arthritis Rheum.* 2013 ; 65 : 363-372.
22. **Graven-Nielsen T, Wodehouse T, Langford RM, *et al.*** Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum.* 2012 ; 64 : 2907-2916.
23. **Guedj D, Weinberger A**. Effect of weather conditions on rheumatic patients. *Ann Rheum Dis.* 1990 ; 49 : 158-159.
24. **Hollander JP, Yeostros SY**. The Effect of Simultaneous Variations of Humidity and Barometric Pressure on Arthritis. *AIBS Bull.* 1963 ; 13 : 24-28.
25. **Horváth Á, Tékus V, Boros M, *et al.*** Transient receptor potential ankyrin 1 (TRPA1) receptor is involved in chronic arthritis: in vivo study using TRPA1-deficient mice. *Arthritis Res Ther.* 2016 ; 18.
26. **Hunter DJ, Riordan EA**. The impact of arthritis on pain and quality of life: An Australian survey. *Int J Rheum Dis.* 2014 ; 17 : 149-155.
27. **Jamison RN, Anderson KO, Slater MA**. Weather changes and pain: perceived influence of local climate on pain. *Pain* 1995 ; 61 : 309-315.
28. **Kawasaki Y, Zhang L, Cheng J-K, *et al.*** Cytokine mechanisms of central sensitization: distinct and over-lapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. *J Neurosci.* 2008 ; 28 : 5189-94.
29. **King CD, Sibille KT, Goodin BR, *et al.*** Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthr Cartil.* 2013 ; 21 : 1243-1252.
30. **Kosek E, Ordeberg G**. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. *Eur J Pain* 2000 ; 4 : 229-238.
31. **Laborde JM, Dando WA, Powers MJ**. Influence of weather on osteoarthritics. *Soc Sci Med.* 1986 ; 23 : 594-554.
32. **Lee YC, Lu B, Bathon JM, *et al.*** Pain sensitivity and pain reactivity in osteoarthritis. *Arthritis Care Res.* 2011 ; 63 : 320-327.
33. **Lundblad H, Kreicbergs A, Jansson KA**. Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg Br.* 2008 ; 90 : 166-171.
34. **McAlindon T, Formica M, Schmid CH, *et al.*** Changes in barometric pressure and ambient temperature influence osteoarthritis pain. *Am J Med.* 2007 ; 120 : 429-34.
35. **Mickle AD, Shepherd AJ, Mohapatra DP**. Nociceptive TRP channels: Sensory detectors and transducers in multiple pain pathologies. *Pharmaceuticals* 2016 ; 9 : 1-26.

36. **Moss P, Knight E, Wright A**. Subjects with Knee Osteoarthritis Exhibit Widespread Hyperalgesia to Pressure and Cold. *PLoS One* 2016 ; 11.
37. **Nakanishi M, Nakae A, Kishida Y, *et al.*** EXPRESS: Go-sha-jinki-Gan (GJG) ameliorates allodynia in chronic constriction injury-model mice via suppression of TNF-expression in the spinal cord. *Mol Pain* 2016 ; 12 : 1-16.
38. **Ng J, Scott D, Taneja A, *et al.*** Weather changes and pain in rheumatology patients. *APLAR J Rheumatol.* 2004 ; 7 : 204-206.
39. **Nummenmaa E, Hämäläinen M, Moilanen LJ, *et al.*** Transient receptor potential ankyrin 1 (TRPA1) is functionally expressed in primary human osteoarthritic chondrocytes. *Arthritis Res Ther.* 2016 ; 18.
40. **O'Hare C, O'Sullivan V, Flood S, *et al.*** Seasonal and meteorological associations with depressive symptoms in older adults: A geo-epidemiological study. *J Affect Disord.* 2016 ; 191 : 172-179.
41. **Petersen KK, Arendt-Nielsen L, Simonsen O, *et al.*** Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain* 2015 ; 156 : 55-61.
42. **Petrus M, Peier AM, Bandell M, *et al.*** A role of TRPA1 in mechanical hyperalgesia is revealed by pharmacological inhibition. *Mol Pain* 2007 ; 3.
43. **Redelmeier DA, Tversky A**. On the belief that arthritis pain is related to the weather. *PNAS* 1996 ; 93 : 2895-2896.
44. **Shutty MS, Cundiff G, DeGood DE**. Pain complaint and the weather: weather sensitivity and symptom complaints in chronic pain patients. *Pain* 1992 ; 49 : 199-204.
45. **Sibley JT**. Weather and arthritis symptoms. *J Rheumatol.* 1985 ; 12 : 707-710.
46. **Skou ST, Graven-Nielsen T, Rasmussen S, *et al.*** Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. *Pain* 2013 ; 154 : 1588-1594.
47. **Skou ST, Roos EM, Simonsen O, *et al.*** The effects of total knee replacement and non-surgical treatment on pain sensitization and clinical pain. *Eur J Pain* 2016 ; 20.
48. **Strusberg I, Mendelberg RC, Serra HA, *et al.*** Influence of weather conditions on rheumatic pain. *J Rheumatol.* 2002 ; 29 : 335-338.
49. **Timmermans EJ, van der Pas S, Schaap LA, *et al.*** Self-perceived weather sensitivity and joint pain in older people with osteoarthritis in six European countries: results from the European Project on OSteoArthritis (EPOSA). *BMC Musculoskelet Disord.* 2014 ; 15.
50. **Timmermans EJ, Schaap LA, Herbolsheimer F, *et al.*** The influence of weather conditions on joint pain in older people with osteoarthritis: Results from the European project on osteoarthritis. *J Rheumatol.* 2015 ; 42 : 1885-1892.
51. **Tokumori K, Wang DH, Takigawa T, *et al.*** The relationship between joint pain and climate conditions in Japan. *Acta Med Okayama* 2011 ; 65 : 41-48.
52. **Verges J, Montell E, Tomas E, *et al.*** Weather conditions can influence rheumatic diseases. *ProcWest PharmacolSoc*. 2004 ; 47 : 134-136.
53. **Wilder F V, Hall BJ, Barrett JP**. Osteoarthritis pain and weather. *Rheumatology* 2003 ; 42 : 955-958.
54. **Wingstrand H, Wingstrand A, Krantz P**. Intracapsular and atmospheric pressure in the dynamics and stability of the hip. A biomechanical study. *Acta Orthop Scand.* 1990 ; 61 : 231-5.
55. **Wright A, Moss P, Sloan K, *et al.*** Abnormal Quantitative Sensory Testing is Associated With Persistent Pain One Year After TKA. *Clin Orthop Relat Res.* 2015 ; 473 : 246-254.
56. **Wyke B**. The neurology of joints. *Ann R Coll Surg Engl.* 1967 ; 41 : 25-50.
57. **Wylde V, Palmer S, Learmonth ID, *et al.*** The association between pre-operative pain sensitisation and chronic pain after knee replacement: An exploratory study. *Osteoarthr. Cartil* 2013 ; 21 : 1253-1256.
58. **Wylde V, Sayers A, Lenguerrand E, *et al.*** Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: A cohort analysis. *Pain* 2015 ; 156 : 47-54.
59. **Wylde V, Sayers A, Odutola A, *et al.*** Central sensitization as a determinant of patients' benefit from total hip and knee replacement. *Eur J Pain* 2016 ; 21 : 1-9.