MECHANISMS INVOLVED IN THE SOUNDS PRODUCED BY MANIPULATION IN SYNOVIAL JOINTS: POSSIBLE ROLE OF PH CHANGES IN LESSENING PAIN LEVELS

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ABSTRACT
The exact mechanisms involved in the sounds produced by manipulation of synovial joints have not been unequivocally elucidated but a number of explanations have been put forward. We have reviewed experiments designed to explain these sounds, with results that were quite unexpected. We have also considered the composition of synovial fluid and how its pH may potentially change locally after the release of CO_2 by physical manipulation. The insights gained provide a rational explanation for the sounds generated by joint manipulation and the beneficial effects of manipulation on patients with joint disorders and pain. We recommend that joint manipulation should be prescribed as first-line therapy before drug therapy and expensive surgery is considered. (*Chiropr J Australia 2017;45:203-216*)
Key Indexing Terms: Cavitation; Chiropractic; Osteopathic Manipulative Treatment; Synovial Joints

INTRODUCTION
Many people notice that when they move their joints, particularly after a period of inactivity, they hear pops and cracks. In fact, most people experience this phenomenon – especially in their fingers, neck and knees. Usually joint cracking and popping requires no treatment. However, if the cracking and popping in the joints is accompanied by swelling and pain, a licensed health care professional should evaluate the patient. The joints most affected by these popping (cracking) sounds include the ankles, knees, IP joints, neck and the lower back. The sounds can be very disconcerting to some individuals, who believe they are a portent of joint diseases to come such as rheumatoid arthritis. Experimental scientists and healthcare professionals have not unequivocally elucidated the exact mechanism(s) underlying these sounds and indeed a number of conflicting explanations have been put forward to explain this phenomenon. In this review, we examine both historical data and recent experiments that used modern instrumentation in attempts to explain this interesting phenomenon, with results that were quite unexpected. We have also considered the composition of synovial fluid and speculated how its pH may transiently and locally change after physical manipulation. The insights gained have provided a rational explanation for the sounds generated by joint manipulation and the beneficial effects of manipulation on patients with various types of joint and pain disorders.

DISCUSSION
Synovial Joints
The types of joints that can readily produce sounds are termed diarthrodial joints, also known as synovial joints, and are freely movable. Synovial joints

are the most common movable types of joints in the body and are characterized by the presence of a layer of hyaline cartilage lining the opposing bony surfaces, as well as a lubricating synovial fluid within the synovial cavity.
Six types of synovial joints are found in the human body: pivot joints, hinge joints (elbow), saddle joint (thumb), planar joints, the radiocarpal joint of the wrist, and ball-and-socket joints (shoulder, hip). All contain synovial fluid.

Composition of Synovial Fluid

Synovia, more often referred to as synovial fluid, is a viscous fluid found in the cavities of synovial joints. The main role of synovial fluid is to reduce friction between the articular cartilages of joints during movement and also to act as a source of nutrients for the cells that maintain the joint cartilage. Specialized secretory cells, termed synoviocytes, produce the components of the synovial fluid, including matrix constituents, hyaluronic acid and salts, collagens, fibronectin for the intimal interstitium, and synovial fluid (1). The synoviocytes also contribute to the local production of cytokines, small-molecule mediators of inflammation, and proteolytic enzymes that degrade the extracellular matrix, therefore being key components of the inflammatory rheumatoid arthritis pathways that can affect joints (2). Together, the cartilages and the synovial fluid protect the bones, reducing the friction between them during movement. Synovial fluid also provides the nutrients and lubrication for the joints. Biochemically, the synovial fluid is an ultrafiltrate of plasma across the synovial membrane enriched with various compounds produced by the synoviocytes. In normal physiological conditions, the biochemical composition of the synovial fluid is similar to that of plasma (3). In addition, the synovial fluid contains dissolved gases, including CO_2, oxygen and nitrogen. When a joint is popped or cracked, it is due to stretch or compression of the joint capsule. The gases are released rapidly from solution, which then form bubbles. In order to crack the same joint again, it is necessary to wait for a short period of time until the gases redissolve in the synovial fluid.

Composition of Synovial Fluid During Disease and After Injury
The composition and function of synovial fluid are altered in joint injury and disease, both due to direct changes in the synovial fluid and alterations in the tissues of the synovial joint. Synovial fluid is in direct physical contact with cartilage and synovium, and in some joints, meniscus and ligament. Synovial fluid interacts with and mediates interactions between synovial joint tissues. These tissues may themselves be altered in injury and disease. Changes in cellular metabolism and structure in these tissues may be reflected by changes in synovial fluid composition and function. Such changes in synovial fluid may result in a reduced ability to lubricate articulating cartilage and a catabolic environment within the joint, together contributing to joint deterioration. Alterations in joint tissues may be detrimental, driving the synovial fluid to an abnormal state (decreased pH i.e. acidification), leading to joint pathology. For example, Farr et al. (4) showed that the pH of synovial fluid approximated to that of the blood in osteoarthritis patients, but was significantly lower in the synovial fluid in rheumatoid arthritis patients. Thus,

the disease-associated changes observed in synovial fluid are likely to be both exacerbated by and contribute to the pathology of the synovial joint.

Effects of Hydrogen Ion Concentration (Ph) on Pain Neurons
It has long been known that acid can elicit pain (5,6), and there is plausible evidence that acidosis contributes to the pain associated with inflammation and ischemia, for example in synovial joints. Cho et al. (7) evaluated the expression of acid-sensing ion channels (ASICs) in the capsule and synovial fluid of patients with frozen shoulder and reported that the mRNA expression of ASIC1, ASIC2 and ASIC3 in the capsule were significantly increased in frozen shoulder patients compared with controls. The ASIC3 subunit is particularly expressed in nociceptive neurons that innervate skeletal and cardiac muscle, joints, and bone (8-10). Thus, there is a growing body of evidence, which strongly suggests that ASICs play a significant role in the generation of inflammatory joint pain (8,11,12). As a consequence, acid sensing is an important property of afferent neurons, in particular unmyelinated and thinly myelinated nerve fibres that convey pain signals. In recent years, a variety of acid sensing ion receptors have been identified on sensory neurons that are responsible for the transmission of pain impulses (13). One particular class of receptors is termed acid sensing ion channels (ASICs). It is interesting to note that ASICs are activated by changes in pH only if the changes occur extracellularly, the threshold for activation being as low as a decrease of pH to 7.2 (14,15). One interesting possibility is whether the intermittent local release of CO_2 in painful joints can produce a transient increase in acidity due to carbonic acid formation, perhaps eventually being converted to sodium (or potassium) bicarbonate and thus deactivating previously excited pain fibers through the alkalizing effect of sodium or potassium bicarbonate. This could be the reason why people get (temporary) relief by self “cracking” of painful joints and/or relief by specific manipulation performed by a licensed healthcare provider.

Ph and Synovial Fluid
It is well known that there is a reversible equilibrium between:

1. Dissolved CO_2 and H_2O
2. Carbonic acid and hydrogen and bicarbonate ions, thus

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

This chemical reaction can then go on to combine or potentially exchange with other ions such as sodium (thus, sodium bicarbonate) or potassium (thus, potassium bicarbonate) both of which are buffers against low pH (or acids) and/or with oxygen, which also results in a neutralizing effect.

In addition to carbonic acid formation, it is possible that the pH of synovial fluid *in vivo* would always be slightly lower than that of blood owing to the production of lactic acid by the chondrocytes of articular cartilage. Clearly, the manipulation of the spinal joints will almost certainly have an effect on the immediate local area around this manipulation. Because the spinal nerves are located next to these joints at every level of the spinal column, this mechanical action (manipulation) is, indirectly, likely to result in a normalization of the chemistry around the spinal nerves, due to better blood flow and thus the flushing of noxious chemicals away from sensory nerve endings. This effect combined with the CO_2/HCO_3 interaction with other entities may result in a generalized increase in the local pH levels and a consequent reduction in the frequency of sensory (nociception) impulses reaching the brain pain processing regions (16,17) suggested that local changes in damaged tissues may bring about a lowering of the nerve threshold for pain and that the organs ordinarily concerned with other forms of sensation are altered in such a way that the impulses originated by them evoke the sensation of pain. In rheumatoid arthritis, a number of pain mechanisms are involved and it is reasonable to posit that a low synovial fluid pH is one of the mechanisms responsible for joint pain. The chronic inflammatory process in rheumatoid arthritis patients is known to produce a local increase in acidity; the pH in synovial fluids from patients with rheumatoid arthritis is significantly lower than that in patients with osteoarthritis or controls (16). Thus, it is not unreasonable to hypothesize that a lowered pH in joints is also involved in the generation of joint pain in non-rheumatoid patients. The average pH in normal synovial fluid is circa 7.2-7.4. In underused joints and inflamed joints the pH falls to acidic levels circa 6.7-6.8. In part, this is likely to be due to poor blood flow. It is probable that joint manipulation in these patients will raise the pH towards normal levels – *circa* 7.0–7.4. In addition, many other local pain mediators, such as ATP, will be flushed away. One interesting question that remains is whether sodium and/or potassium ions can interact with joint gases to create an acid buffer system followed by a neutral acid-base environment in the joint and surrounding areas. At present, there is no published literature on this concept but it needs to be further explored in future studies to determine whether this phenomenon is involved in nurturing a healthy synovial joint. However it is possible that this is the reason for the positive results seen in Appendix 1 after specific joint manipulation was applied to patients where no other previous therapy had provided significant relief from their pain and dysfunction problem(s).

Noises Produced by Joint Manipulation

The noise or crack heard during the manipulation is an important signal that joint cavitation has occurred and that CO_2 has been released. In fact, most professional manipulators will admit that there is a better healing response to the treatments if this event occurs. Most researchers seem to agree that cracking noises arise from cavitation but there are a few studies suggesting that this phenomenon arises from the stretching of ligaments. When the 2 articulating surfaces of a synovial joint are separated from each other, the volume within the joint capsule increases and a negative pressure results. The small volume of synovial fluid within the joint is insufficient to fill the expanding volume of the joint and gases dissolved in the synovial fluid (mainly CO_2) are liberated and quickly fill the empty space, leading to the rapid formation of a bubble. This process is known as cavitation, which in synovial joints results in a high frequency 'cracking' sound (18).

It might be thought, intuitively, that the main dissolved gas coming out of solution would be nitrogen by analogy with Caisson’s disease, sometimes experienced by scuba divers who ascend from depth to rapidly producing excruciating joint pain (hence the term the bends), and even by aviators at high altitudes. The symptoms occur when nitrogen bubbles form in the blood

(particularly dangerous in arterial blood and/or the brain) and other tissues. However, measurements at normal atmospheric pressure on human synovial fluid have shown that most of the liberated gas is actually CO_2. For example, gas analysis of synovial fluid, performed on 7 human subjects, revealed that the average gas content was 15% by volume, and over 80% was CO_2 (19). Similarly, Raymond Brodeur in the Ergonomics Research Laboratory at Michigan State University reported that if an X-ray of the joint is taken after cracking, that a gas bubble can be visualized inside the joint. This gas increases the joint volume by 15 to 20 percent and consists mainly (about 80%) of CO_2 (19) (Brodeur, personal communication).
Metabolic evidence of ischemia provides a second instance when the delivery and removal of small solutes becomes clinically relevant. In normal joints and in most pathologic effusions, essentially full equilibration exists between plasma and synovial fluid. The gradients that drive net delivery of nutrients (glucose and O_2) or removal of waste (e.g. lactate and CO_2) are too small to be detected. In some cases, however, the synovial microvascular supply is unable to meet local metabolic demand and significant gradients develop. In these joints, the synovial fluid reveals a low oxygen pressure (PO_2), low glucose, low pH, high lactic acid and high CO_2 pressure (PCO_2). The clinical implications of local ischemia remain under investigation but decreased synovial fluid pH, for example, was found to correlate strongly with radiographic evidence of joint damage in rheumatoid knees. This finding suggests that normal use of swollen joints may create a cycle of ischemia and reperfusion that leads to tissue damage by toxic oxygen radicals, that can be relieved by joint manipulation (which will improve the joint microcirculation).

Most of the dissolved gas in synovial fluid is likely to be CO_2, which is probably why it is assumed that the bubbles formed during cavitation are mostly produced by CO_2. As the small molecules in synovial fluid are believed to be in rapid equilibrium with those in blood, one would expect that the dissolved gases would resemble those found in blood plasma. The pH is determined by the CO_2/bicarbonate ratio. Synovial fluid from normal freshly opened joints is around pH 7.3-7.4, but quite quickly goes more alkaline (pH rises) on exposure to air as the dissolved CO_2 in it escapes. It is highly possible that this is what is felt and observed immediately after a joint is manipulated and the patient experiences less pain as evidenced in Appendix 1. Furthermore, this alkalizing effect in and around a joint that has just been manipulated has a positive ripple – wave effect on the adjacent spinal nerves and nerve receptors, alkalizing these structures, including the parasympathetic and sympathetic nerve fibres located in the immediate areas of the spinal joints. The end result of this manipulation – an alkalizing effect producing less pain and better function as experienced by most patients after professional manipulation – is evidenced further in Appendix I.

A study by Cseuz et al. (20) reported that an alkaline supplement improves function and reduces pain in rheumatoid arthritis patients, and may represent an easy and safe addition to the usual severe drug treatment of rheumatoid arthritis. One mechanism will be raising the pH in synovial fluid to above neutral, thus reducing sensory nerve stimulation due to for example ASIC activation.

One also has to consider whether joint manipulation can lead to the release of endorphins. In addition to a pain-reducing direct effect of endorphins in the brain and spinal cord, one has to consider the alternative explanation that a more alkaline environment in the local surroundings of the joints will lower the degree of pain receptor stimulation, which is known to be very sensitive to small pH changes. It is noteworthy that significant changes in pH have been shown to occur in the interstitium without detectable changes in blood pH (21).

Possible Causes of Popping/Cracking

One of the most popular explanations is that the synovial fluids in popping joints cavitates — as external forces are put on the synovial fluid as a result of movement, tiny bubbles form in the fluid and implode. This is the phenomenon that is believed to generate the popping and cracking sounds. Cavitation is one of the most popular theories because a number of scientific studies back it up. Two other possible causes of popping and cracking noises when a synovial joint is moved are that the tendons are shifting in and out of place with the movement, or that ligaments are being stretched too fast. A third scenario for popping and cracking noises is the movement of the joint rubbing against rough surfaces. Specifically, the movement of the joint against rough surfaces indicates that the cartilage has been worn away and the two bones in the joint are rubbing against each other, a sign of arthritis, particularly when accompanied by pain.

Another source of popping and cracking sounds is the tendons and ligaments that are intimately associated with the joints. Tendons must cross at least one joint in order to cause motion. But when a joint moves, the tendon's position with respect to the joint is forced to change. It is not uncommon for a tendon to shift to a slightly different position, followed by a sudden snap as the tendon returns to its original location with respect to the joint. These noises are often heard in the knee and ankle joints when standing up from a seated position or when walking up or down stairs.

Recent Studies

A new study appears to confirm what really happens when knuckles are cracked. Scientists have used ultrasound machines to determine exactly what is going on in joints when they are cracked. MRI imaging of finger joints being cracked suggest that the popping sound is caused by the **collapse of air bubbles** that form in the synovial fluid rather than their formation. Ultrasound machines can record up to 100 times faster than MRIs, so another team of scientists decided to investigate this claim further. Led by radiologist Robert D. Boutin from the University of California, Davis, the team recruited 40 healthy participants, 30 of whom were regular joint-crackers, and 10 who were not (22). The participants were asked to crack their knuckles at the base of each finger, known as the metacarpophalangeal joint (MPJ), while being studied by ultrasound. They ended up imaging 400 MPJ cracks, and recorded the sounds so they knew which ones came with a 'pop'. The flashes in the ultrasound were coupled so consistently with the popping sound that the researchers could predict with 94% accuracy which MPJ cracks 'popped' just by looking at the images. The researchers suspect that the cracking and visual flash in the ultrasound images is related to changes in pressure that occur in the synovial fluid, and concluded that the cracking sound and the bright flash on ultrasound were related to the dynamic changes in pressure associated with a gas bubble in the synovial joint.

In the late 1940s, a paper reported that the popping sound occurred when a bubble first formed in the synovial fluid of the joint (23). This hypothesis was refuted 30 years later when another group of researchers said it made more sense that the sound came from the bubble bursting (24).

In April, the University of Alberta team backed up the bubble-collapsing hypothesis with their MRI recordings (25), but they still hadn’t come up with any conclusive proof. So which is it, does the sound result from a bubble popping in the joint or from a bubble being created in the joint? After all these years, there is doubt and we await a definitive answer to the origins of popping/cracking sounds.

Drug Treatment for Joint Pain

For moderate-to-severe joint pain with swelling, an over-the-counter or prescription nonsteroidal anti-inflammatory drug (NSAID) such as aspirin, ibuprofen, or naproxen sodium, can provide relief. A newer generation of NSAIDs known as Cox-2 inhibitors (celcoxib) are also effective in providing pain relief, but all except one of these drugs (*Celebrex*) have been removed from the market because of an increased risk of heart attack, stroke, and other cardiovascular events. NSAIDs also produce side effects, such as increasing the risk of gastrointestinal ulcers and bleeding.

If a patient has milder pain without any swelling, acetaminophen can be effective. Because of the risks, these pain medications should be taken with caution.

If the pain is so severe that NSAIDs and cox-2 medicines are not effective, a doctor may prescribe a stronger painkiller (opioid). Because opioid drugs can cause drowsiness, they should only be used carefully and may also cause constipation, and in particular be addictive after moderate to long-term use. This is the main reason that highly skilled and professional manipulation, and the pain relieving effects that it provides, is a much better alternative than the above described medications.

Other drugs that may help to relieve joint pain include:

- Muscle relaxants to treat muscle spasms
- Some antidepressants and antiepileptic drugs (which both interfere with pain signals)

CONCLUSION

The exact mechanisms involved in the sounds produced by manipulation of synovial joints have not been unequivocally elucidated but we have reviewed a number of theories developed from experiments in humans. It is clear that the build up of lactic acid and other assorted metabolic products may acidify local areas in a synovial joint leading to the activation of sensory nerve terminals. Because of the alkalizing effects that is provided and previously elucidated in this paper, the joint manipulation patient often experience a decrease in pain and an increase in joint function. We have also considered the composition of synovial fluid and how its pH may change after the removal of acidic materials by physical manipulation and their subsequent clearance, which reduces the acidity of synovial fluid producing a less painful joint. It is difficult to determine the validity of this hypothesis in humans and further research is required in this difficult to prove area of interest. Nevertheless, the ideas put forward in this review provide a rational explanation for the sounds generated by joint manipulation and the beneficial effects of manipulation on patients with joint problems and pain. We recommend that joint manipulation, carried out by a well trained and licensed provider, should be prescribed as first line therapy before drug therapy and expensive surgery.

Note the following as well.

1. Auto manipulation; that is, patient self-manipulation, is often carried out by an individual with pain in, for example, the neck or back. It is possible that this self "cracking" accomplishes similar effects to those described in the present review (thus providing pain relief), but it is highly probable that this "self-cracking" does not reach the area of irritation or gives the maximum gas release and gas exchange; thus for maximum pain relief it must be carried out by an individual every few hours.
2. As third-party payers search for (and pay for) therapies that work and stop payment for ineffective therapies, this paper attempts to explain in a logical manner the mechanisms underlying the beneficial effects of joint manipulation, why there is immediate pain relief, and the potential healing process experienced by the patient.
3. This paper was funded solely by the authors and patients; therefore there was no control group i.e. patients that were not "sham" manipulated at the same time. However, we can conclude that 98% of these patients '**did receive**' other treatments before this study commenced and this fact leads to a "control" group being present in this study. However, it is obvious that the controls were not performed at the same time.
4. There are many different types of chiropractic and osteopathic "manipulation" variation treatments. Many of these do not involve actual joint manipulation. That is manipulations (or treatments) that do not produce an audible sound or "crack". If there are no sounds or crack during the manipulative process the gas exchange - pH enhancement process described in this review will not occur. This finding may account for the enormous difference in the success rates achieved in treatments by different types of providers. It is also important that the manipulation should be carried out in the body region where the pain is perceived. In other words, if there is a

pain-producing problem in the lumbar area and the practitioner only has the technical ability to manipulate the thoracic spine, the pH effect produced by this manipulation would obviously be much less or indeed non-existent. It is probable that this is one of the factors resulting in the marked variations of outcomes seen in these types of treatments by different providers. This is another reason why money should be invested in the training of people that are capable of performing effective manipulations that will produce the desired type of response in the correct body region.

REFERENCES

1. Iwanaga T, Shikichi M, Kitamura H, Yanase H, Nozawa-Inoue K. Morphology and functional roles of synoviocytes in the joint. Arch Histol Cytol 2000;63(1):17–31
2. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. Immunol Rev 2010;233(1):233–255.
3. Strasinger SK, Di Lorenzo MS. Urinalysis and Body Fluids. 5th ed. Philadelphia, Pa: FA Davis; 2010:177–199
4. Farr M, Garvey K, Bold AM, Kendall MJ, Bacon PA. Significance of the hydrogen ion concentration in synovial fluid in rheumatoid arthritis. Clin Experimental Rheumatol 1985;3:99–104
5. Steen KH, Reeh PW. Sustained graded pain and hyperalgesia from harmless experimental tissue acidosis in human skin. Neurosci Lett 1993;154:113–116
6. Steen KH, Reeh PW, Kreysel HW. Topical acetylsalicylic, salicylic acid and indomethacin suppress pain from experimental tissue acidosis in human skin. Pain 1995;62:339–347
7. Cho C, Lho Y, Hwang I et al. (2015). Up-regulation of acid-sensing ion channels in the capsule of the joint in frozen shoulder. Bone Joint J 2015;97-B:824–829
8. Kweon HJ, Suh BC. Acid-sensing ion channels (ASICs): therapeutic targets for neurological diseases and their regulation. BMB Rep 2013;46:295–304
9. Ikeuchi M, Kolker SJ, Burnes LA, Walder RY, Sluka KA. Role of ASIC3 in the primary and secondary hyperalgesia produced by joint inflammation in mice. Pain 2008;137:662–669
10. Noël J, Salinas M, Baron A, et al. Current perspectives on acid-sensing ion channels: new advances and therapeutic implications. Expert Rev Clin Pharmacol 2010;3:331–346
11. Izumi M, Ikeuchi M, Ji Q, Tani T. Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis. J Biomed Sci 2012;19:77, doi: 10.1186/1423-0127-19-77
12. Li WG, Xu TL. ASIC3 channels in multimodal sensory perception. ACS Chem Neurosci 2011;2:26–37
13. Holzer P. Acid-sensitive ion channels and receptors. Handb Exp Pharmacol 2009;194:283–332
14. Kress M, Waldmann R. Acid sensing ionic channels. Curr Top Membranes 2006;57:241–276

15. Wemmie JA, Price MP, Welsh MJ. Acid-sensing ion channels: advances, questions and therapeutic opportunities. Trends Neurosci 2006;29:578–586
16. Goldie I, Nachemson A. Synovial pH in rheumatoid knee joints: II. The effect of local corticosteroid treatment, Acta Orthop Scand 1970;41(3):354–362
17. Revici E, Stoopen E, Frenk E, Ravich RA. The painful focus. II. The relation of pain to local physiochemical changes. Bull Inst Appl Biol 949;1:21–38
18. Protapapas M, Cymet T. Joint cracking and popping: Understanding noises that accompany articular release. J Am Osteop Assoc 2002;102(5):283-286
19. Unsworth A, Dowson D, Wright V. 'Cracking joints' A bioengineering study of cavitation in the metacarpophalangeal joint. Ann Rheum Dis 1971;30:348–358
20. Cseuz R, Barna I, Bender T, Vormann J. Alkaline mineral supplementation decreases pain in rheumatoid arthritis patients: a pilot study. Open Nutr J 2008;2:100–105
21. Street D, Nielsen J-J, Bangsbo J, Juel C. Metabolic alkalosis reduces exercise-induced acidosis and potassium accumulation in human skeletal muscle interstitium. J Physiol 2005;566:481–489
22. Boutin RD, Netto AP, Nakamura D et al. “Knuckel cracking”: can blinded observers detect changes with physical examination and sonography? Clin Orthop Relat Res 2017;475:1265-1271
23. Hunzinger W, Sullman H, Viollier G. [Effect of ultrasound on synovial fluid]. Experientia 1949;15:479
24. Kremer H, Schierl W, Schattenkirchner M, Baumann D, Metz I, Zollner N. [Echography of knee joint cysts]. MMW Munch Med Wochenschr 1977;119:1183-1186
25. Kawchuk G, Fryer J, Jaremko JL, Rowe L, Thompson R. real-time visualization of joint cavitation. PLoS One 2015;10:e0119470

APPENDIX I

Background

The questionnaire was placed in the Muscle-Joint Center Netherlands in Eindhoven from 1 July 2016 to 31 December 2016. It was left on the waiting room table of the practice and made available for any patient that would like to voluntarily complete it.
If patients were satisfied with their treatment they were allowed to complete the questionnaire and likewise if they were unhappy or further had no opinion on the treatment received they were also encouraged to complete the questionnaire without compulsion.

Questionnaire

The questionnaire is reproduced below:

Spier-gewrichtologie
Bredalaan 75
5652 JB Eindhoven
Tel: +31 (0)40 243 35 71
Gsm: +31 (0)6 25 17 47 77
www.spiergewrichtologie.nl

Dear Patient

We have started a project in the Muscle-Joint Center to ensure our treatments and theories available in the basic insurance program. To reach this goal we must have some basic facts on paper, namely that the treatment works. We have proven the muscle portion of this treatment with our extensive PhD degree research into the activity of the *iliopsoas* muscle. Now we must investigate the joints of the human body. You can help us in our endeavor by giving a '*yes*' or '*no*' answer to the following questions, which would help us with the continuation of this project. It is very important that you give non-biased answers.

Question

How was your pain level changed immediately after manipulation treatment (please circle your experience of pain):

1. The pain was gone Yes/No

2. The pain was less Yes/No

3. The pain was unchanged Yes/No

4. The pain level increased Yes/No

Name (you can remain anonymous) Date

We thank you for your feedback

At the end of a 6-month time frame the questionnaires were collected (without further review by practice members) and sent to an independent senior scientist in Oxford University, who was blinded to the treatment regimens, to correlate the results. The data from 123 patients is shown graphically in Figure 1.

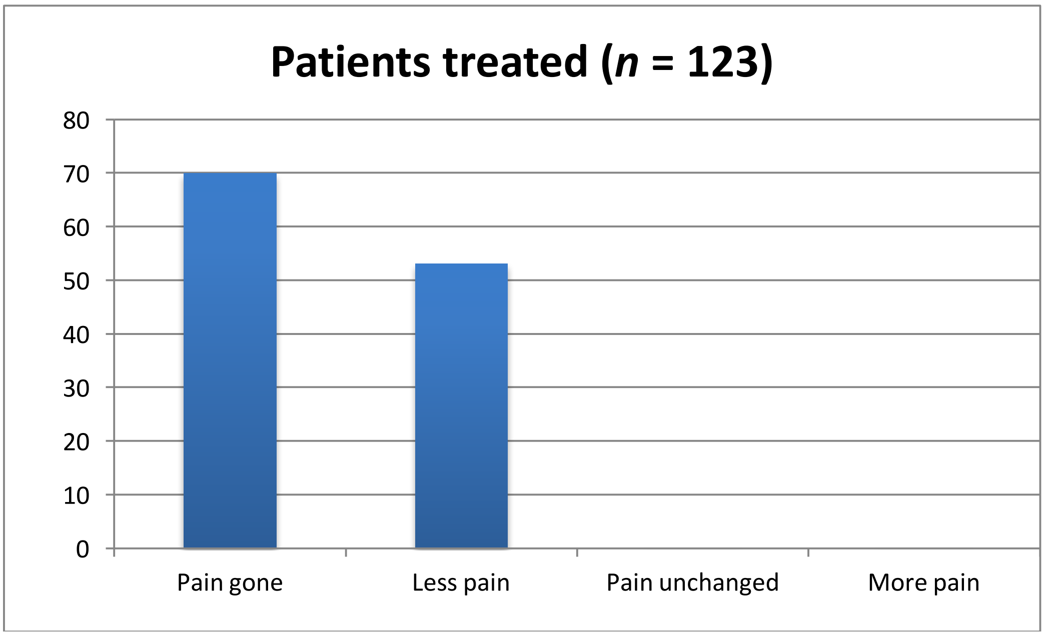

Figure 1. Survey results from 123 patients who received manipulation treatment. This shows the responses of patients who circled 'Pain gone' in the survey. However, it should be noted that 32 patients circled points 1 and 2, namely pain gone or less pain, respectively.

One can safely conclude that in this cohort of patients that manipulation therapy was very effective in pain relief.

Analysis of survey results

All treated patients were invited to complete the questionnaire without coercion. A total of 123 patients completed the survey and the results are shown in Figure 1.

Where ever the patient reported the location of pain that is where the manipulation was performed. It could be anywhere in the body but typically the most common places were the lower back, hip, middle back, neck, shoulders and knees. In the survey, the patients treated involved roughly 20% of each of these five classes. Of the patients included in the survey, **circa 95% came to our clinic because they were experiencing pain**.

All treated patients experienced either complete absence of pain or significantly less pain. Of interest, is that no patient reported that his or her pain was unchanged or exacerbated.