General discussion
Low back pain is a leading health care problem of our times with the prevalence of 9.17%, with 9.64% among men, and 8.7% among women. Although the low back pain can be caused by fractures, osteoporosis or inflammatory spondyloarthrosis, in the majority of cases the specific diagnosis remains unclear, and is often classified as non-specific low back pain. Last decade we contributed to improvements in the diagnosis of low back pain. The research presented in this thesis focused on the pain anatomy of SI joint, and the diagnostic criteria of the pain originating from SI joint. For this purpose we started with the review of the anatomical literature to find out the innervation of the SI joint. Thereafter, we took a closer look on the distribution of the nociceptors in the SI joint, using immunohistochemistry-staining techniques. Then, we performed a meta-analysis to find out the validity of diagnostic criteria for SI joint pain, as proposed by International Association for the Study of Pain. According to these criteria, SI joint pain refers to patients with pain in the area of the SI joint, which should be reproducible by performing specific pain provocation tests, or should be completely relieved by infiltration of the symptomatic SI joint with local anaesthetics. From our meta-analysis we found out that some of the IASP criteria need further elaboration. Therefore, we attempted to validate the pain perception in the region of SI joint, which we assigned to the first IASP criterion, by means of the pressure algometry. Furthermore, as there is no consensus in the literature about the medications used for SI joint diagnostic infiltration (the third IASP criterion), we compared frequently used medication with placebo in an RCT. As we have learned from our anatomical study that nociceptors are spread throughout the synovial and peri-synovial part of the SI joint, we performed a cadaveric study to find out the distribution of contrast medium in peri-synovial part of the joint. Additionally, we treated our patients with this injection technique, and measured the long-term efficacy.

**SI joint anatomy and implications for diagnostic infiltration**

Proper anatomical knowledge is essential for performance of invasive pain therapies. Considering the SI joint anatomy, there is an on-going discussion of the exact joint innervation. Earlier research was focused on the dissection of the SI joints, whereas later staining techniques were introduced. Accordingly, Solonen followed the idea of Hilton (a British surgeon and anatomist), who postulated that the same nerve roots
supplying the skin and muscles extending directly through and acting at a given joint, also give innervation to this joint. Based on this premise, Solonen suspected that the lumbo-sacral plexus provides the innervation to SI joint. During the anatomical cadaveric dissection, he found that the innervation of SI joints is not always the same; even left and right side may differ from each other, extending from lumbar nerves L3 to sacral nerves 2 and the superior gluteal nerve. Solonen also found that the ventral side of the joint was innervated by the ventral spinal nerves L5, and in the majority of the cases also by L4 and S1. In a subsequent study of Ikeda, based on macroscopic examination, it was found that the upper part of the joint on the ventral side was innervated mainly by the ventral ramus of the spinal nerve L5, whereas the lower part were innervated by the dorsal sacral nerves. These findings are consistent with those of Solonen. However, the results of a subsequent study, based on microscopic preparation and histological staining of adult and foetal pelvises, did not confirm previous results. According to this study, the dorsal part of SI joint receives nerves from spinal S1 to S4, but on the ventral part no nerves originating from the sacral plexus have been found. In another histological study, in which the samples were obtained from the ventral ligamentous SI joint capsule, revealed the presence of nerve fascicles and individual myelinated and unmyelinated nerve fibres. Vilensky and colleagues conducted a histological and immunocytochemical study on the posterior parts of the SI joints. They found different types of mechanoreceptors and nerve fibres, but no structures positive for substance P, nor protein gene product 9.5. Finally, by means of substance P immunostaining, positive structures were found in the posterior SI joint ligament obtained from two patients undergoing SI joint arthrodesis. Summarizing above findings, the sacral nerves S1-S4 dorsally innervate SI joint. Dorsal ligaments contain mechanoreceptors, myelinated and unmyelinated nerves, which are also found in ventral capsule. Since the above findings do not provide a rationale of the effectiveness of intra-articular SI joint infiltration, in this thesis we present the results of our own anatomical and immunohistochemical studies on innervation of SI joint. We extrapolated from general anatomical knowledge, and concentrated our study on finding nociceptors in intra-articular SI joint structures such as the ventral capsule, as well as peri-articular structures such as anterior, posterior, and interosseous ligaments, subchondral bone of the ilium, and the sacrum. For this reason, we used the most sensitive and most specific immunohistochemistry technique to visualize the sensory
nerves related to pain perception. We have chosen for antisera against Substance P and calcitonin gene related peptide (CGRP), tyrosine hydroxylase (TH) and non-phosphorylated neurofilaments (SMI-32). The choice was made for substance P and CGRP. These neuropeptides are recognized mediators of pain transmission, and were used in our study with the aim of finding nociceptors. TH and SMI-32 antibodies were used to obtain an overall picture of the presence of neurofilaments in the studied specimens. We found substance P, CGRP, TH, and SMI-32 positive structures in ligaments adjoining the synovial cavity of the SI joint. Substance P immunoreactive nerve bundles were found in the anterior capsular sacroiliac ligament and ligamentous tissue adjacent to the bone and cartilage. Also, mechanoreceptors found in the anterior capsular ligament contained single substance P positive axons. CGRP immunoreactive structures, predominantly single nerve fibers, were found in the anterior and interosseous sacroiliac ligaments as well as in the mechanoreceptors. SMI-32 and TH positive bundles were detected in the anterior sacroiliac ligament, indicating the overall presence of neurofilaments as well as presence of sympathetic nerves. Comparing to earlier mentioned histological studies reporting the presence of “myelinated” and “unmyelinated” axons in SI joint ligaments 5-7, with the immunostaining technique applied in our study, physiological classification of stained structures could be performed. Additionally, the morphology of substance P and CGRP positive fibers found in our specimens, particularly their thickness (0.8-4.4μm) indicates their possible nociceptive character. Our results complete the finding of substance P in posterior sacroiliac ligaments as described by Fortin et al.8, as we found substance P and CGRP positive fibers in the ligaments bordering the SI joint intra-articular space, i.e. interosseous ligament. Our findings, however, do not exactly explain the mechanism of action of intra-articular infiltrations, since these infiltrations do not involve the interosseous ligament. However, it has been proven that during the SI joint arthrography, medication injected intra-articularly can leak to the nearby structures.9 Three of the leakage patterns involved communication between the SI joint and nearby neural structures, including posterior extravasation into the dorsal sacral foramina, superior extravasation to the fifth lumbar nerve sheath, and ventral extravasation to the lumbosacral plexus.9 At this point we hypothesized that if we cannot find any nociceptors in the synovial part of the joint, for example the subchondral sacral, or iliac bone, then the positive infiltration effect maybe ascribed to reaching the neural
structures bordering to synovial part of the joint. Searching for an explanation of SI joint pain generators, we extended our immunohistochemical study in human cadavers to examine the distribution of substance P and CGRP immunopositive structures in iliac and sacral subchondral bone of SI joints in humans.\textsuperscript{10} The microscopic analysis revealed substance P and CGRP positive fiber-like structures in the iliac and sacral cartilage and immunoreactivity in chondrocytes. Immunoreactive fibers were also identified in the fibrous ligamentous tissue adjacent to the cartilage and bone. The bone itself was weakly immunoreactive for the used antisera. Our results support the theory that nociceptive signals may originate from the intra-articular structures of the SI joint; therefore infiltrating synovial part of SI joint makes sense. However, the intra-articular injection technique is criticized because of missing data about specificity and sensitivity and is therefore not considered valid for diagnosing SI joint pain.\textsuperscript{11} This statement results probably from the inconsistency between the studies in performance of the SI joint diagnostic blockade, as discussed in our review.\textsuperscript{12} Although in all of the reviewed studies contrast enhanced intra-articular injection is used, the volume of the injected contrast agent varies substantially. The injected volume ranges from a small, used only for confirmation of the intra-articular position of the needle, to enough volume to obtain SI joint arthrography, ranging from 0.5-1cc, to a maximum of 4cc in one study.\textsuperscript{13} There is also a discrepancy between the use of single vs. double injections and the medication used, short acting vs. long acting local anesthetics, with or without corticosteroids.\textsuperscript{12} Furthermore, a predefined positive effect of the diagnostic infiltration varied considerably between studies, and ranged between 50-90\% pain reduction.\textsuperscript{12} Taking all these differences into account, we agree with the statement of Berthelot and colleagues \textsuperscript{11} that there is no evidence to regard SI joint intra-articular injections as a golden standard for diagnosing SI joint pain. Moreover, according to the literature, SI joint painful pathology involves not only intra-articular causes (such as arthritis), but also peri-articular causes (for instance ligamentous injury, enthesopathy, fractures, and myofascial pain).\textsuperscript{14} Consequently, some investigators involve peri-articular structures in diagnostic process, applying different techniques to infiltrate posterior ligamentous complex of SI joint.\textsuperscript{15-18} Recently a cadaveric study was designed to localize nerve location with the aim to optimize clinical outcomes of lateral branch radiofrequency ablation or blocks for SI joint.\textsuperscript{19} According to this study's results, sacral nerves S1-S2 contributed to SI joint innervation in all morphologically examined specimens, S3 in
88%, S4 in 4%, and lumbar nerve L5 in 8% \(^1\)\(^9\), which data are actually consistent with previous anatomical studies.\(^3\)\(^-\)\(^5\) However, the added value of the meticulous work of Roberts et al. is that they describe the SI joint innervation in relation to bony landmarks in 3 dimensions, identifying reference points visible under ultrasound and fluoroscopy for optimal needle placement. Anesthetizing nerves, however, differs completely from anesthetizing synovial space of the joint. Do we need to banish the intra-articular technique then, and focus on the infiltration of the nerves? First of all, we need to determine whether intra-articular technique gives the same pain relief as the selective nerve infiltration. The peri-articular techniques described so far, are not selective.\(^1\(^5\)\(^-\)\(^1\(^8\)\(^,\)\(^2\(^0\)\)

With the technique van Luukkainen et al., the dorsal part of SI joint is targeted, 3 to 4 cm caudally from the postero-superior iliac spine and 6 to 7 cm from the middle line of the sacrum until contact with the bone.\(^1\(^5\),\(^1\(^6\)\) Yin at al. with their technique aimed to infiltrate interosseous ligaments.\(^1\(^8\)\) The technique used in the study of Murakami et al. was more extensive than that used by Yin, and consisted of 4 dorso-cranial injections of the SI joint.\(^2\(^0\)\) Finally, the infiltration performed by Borowsky and colleagues, targeted structures under posterior SI joint ligament, whereby the S1-3 lateral branches and the posterior ligaments soak in the infiltrate.\(^1\(^7\)\) All these different techniques are not selective for individual nerves. For the purpose of this thesis we used intra-and peri-articular infiltration techniques. The long-term effect of intra-articular injection with different medications was evaluated in a RCT. Patients with benign chronic low back pain were allocated to one of the groups, lidocaine, lidocaine in combination with methylprednisolone acetate, and placebo. After completing the study, patients were offered to receive another intra-articular infiltration, and finally a peri-articular infiltration. The intra-articular infiltration was performed under the fluoroscopic guidance, whereby the most caudo-dorsal part of the synovial SI joint was targeted. The peri-articular infiltration consisted of two separate injections, to the dorso-cranial and dorso-caudal parts, to reach posterior ligaments and nerves. As in case of intra-articular injections there is no one-way to perform the peri-articular injections. Yin et al.\(^1\(^8\)\) performed deep interosseous ligamentous injections with 5 mL of 0.5% bupivacaine containing 4 mg/mL of triamcinolone, in an attempt to more specifically diagnose dorsally mediated SI joint pain. In the discussion they mention that the specificity of their technique has never been formally evaluated. However, there are two limitations of this study, the technique is not adequately described, making a reproduction
impossible. Secondly, the image they presented in the paper shows posterior ligament spreading of the contrast medium, rather than the interosseous one. In another study of Borowsky et al.\textsuperscript{17} we read an adequate description of the peri-articular technique, but again the targeted tissue reflects posterior aspect of the ligamentous compartment of the SI joint and not the posterior synovial joint. What's the point of targeting deep ligamentous structures with an invalidated injection technique? In the case of Borowsky at al., peri-articular injection was used, to give more evidence of existence of extra-articular sources for SI joint pain. In the case of Yin et al., the goal of their injections differed as they used non-selective diagnostic peri-articular infiltration as a prognostic tool for selective SI joint denervation. Diagnostic infiltration of individual nerves would be probably more accurate, but on the other hand it is probably more painful to the patient. We have some recommendation for the future research, but first we would like to discuss the diagnostic value of non-invasive diagnostic tests.

**Diagnostic validity of the non-invasive tests**

According to our systematic review, physical examination tests for SI joint pain are usually validated with the intra-articular infiltration.\textsuperscript{12} Beginning with the presence of pain in the area of the SI joint, the first IASP criterion, most of the studies were consistent with this criterion, as the posterior aspect of the SI joint was frequently reported as the area of pain. However, the occurrence of radiation to the buttock, groin and lower limb was also described. According to conclusions of our review, pain mapping or pain referral patterns have an ability to correctly identify patients with SI joint pain, though they fail in discriminating patients without SI joint pain.\textsuperscript{12} It is well known that discogenic pain or facet joint pain, are both capable of producing referred pain in the buttock region.\textsuperscript{21,22} At this point we are facing a major clinical problem to differentiate between SI joint pain and other pain sources related to the lumbar and buttock region. For the need of this thesis we went a step forward, as we were interested whether the intensity of pressure pain in the anatomical SI joint region can differentiate between the persons with and without SI joint pain. For this reason, we first tested the inter-rater reliability of the pressure algometer, followed by establishing the pain pressure thresholds in patients with SI joint pain. According to our results,
manual pressure algometer is reliable in measuring pressure in the SI joint region. Furthermore, it has the ability to distinguish between not affected and painful SI joints. The last statement is based on the significantly lower pain pressure thresholds measured in patients with SI joint pain comparing to healthy volunteers. Until now, one study tested the palpable tenderness of the posterior pelvic sacroiliac region, immediately medial to the posterior superior iliac spine, showing this test has a high sensitivity but low specificity of 95% and 9% respectively.\textsuperscript{23} In another study a prompt force was applied on the posterior superior iliac spine (PSIS) in medial-to-lateral direction to produce or aggravate SI joint pain. This so called PSIS distraction test showed 100% sensitivity and specificity of 89%.\textsuperscript{24} However, in both studies human hands were used instead of a reliable measure instrument. Further, using a digital instead of analogue pressure algometer could possibly improve the accuracy of the measurement. The digital pressure algometers are more sensitive, measure lower thresholds (the sensitivity of 10gr), and give the exact threshold result up to second decimal place on the digital display. Although the pressure algometry seemed to be reliable we would like to make a remark that this instrument should be validated against an alternative diagnostic test, such as SI joint diagnostic blockade or physical examination tests.

Further in this thesis we describe the diagnostic accuracy of physical examination tests which we assign to the second IASP criterion.\textsuperscript{12} Two individual pain provocation tests, the compression and thigh thrust test, are helpful in diagnosing of SI joint pain. Patients with a positive thigh thrust test or compression test are more likely to suffer from SI joint pain. Studies validating a comprehensive set of stressing tests proved good diagnostic validity of a threshold of three positive tests for diagnosing SI joint pain. Using a threshold of three or more positive stressing tests, the diagnostic odds ratio of three positive provocation tests is high in patients with SI joint pain (DOR 17.2). However, when applying pain provocation tests, it is nearly impossible to define which structures actually are stressed.\textsuperscript{47,54} Even structures like the iliolumbar ligament or piriformis muscle cannot be excluded as potential source for this pain, since they are functionally related.\textsuperscript{3,53} Consequently, it is very difficult to distinguish whether the provoked pain is exclusively intra-articular, or related to capsular ligaments. This is essential information to know, as all the diagnostic tests are validated with the
diagnostic intra-articular infiltration. Again we come back to the discussion whether the infiltration should involve intra-, or peri-articular structures. In the recent systematic review the validity of the intra-articular infiltration is again put into question. In this review authors concluded, that the image-guided intra-articular diagnostic injections of local anesthetics do not predict a positive response to a therapeutic agent. They also found the overall quality of evidence for therapeutic SI joint injections to be moderate.

**Situation in the Netherlands**

**RF treatments for SI joint pain**

In general there are three different interventional treatment options for patients with SI joint pain, the conventional monopolar and bipolar RF, cooled RF and the so-called simplicity technique. With monopolar RF, SI joint nerves are targeted whereby a lesion at 85°C is made. With the cooled RF, circulating fluid internally cools the electrodes but surrounding tissue is still exposed to destructive temperatures. Also with this technique more electrodes need to be placed to create a reliable SI joint denervation. However, the cooled lesion creates a lesion twice as large as conventional monopolar needles, i.e. 8 to 10 mm versus 3- to 4-mm lesions. With the bipolar technique, a so-called “palisade” lesion is created, whereby needles are placed side by side, spacing 10 mm from each other, allowing the RF current to run between two nearby electrode tips. The Simplicity probe involves a multi-electrode RF probe which, in opposite to above techniques, requires one entry point, permitting a large denervation. The problem is, however, that the evidence for effectiveness of denervation techniques is scarce. Based on the results of two RCTs, RF denervation of SI joint had no effect over the short term and a smaller effect (based on one study) one to six months after treatment when compared with placebo.

*“Minimal interventional Treatment” study.*

Infiltration techniques are frequently used in the Netherlands for treatment of mechanical low back pain. In 2011 the Dutch Health Insurance Council (CVZ) published a report about approaches to treatment of non-specific low back pain. This report was based on the results of systematic literature review of different treatment modalities. Therefrom it appeared that there is no strong evidence for the effectiveness of the invasive treatments for non-specific low back pain, and should not be insured from
basic insurance policy. An important principle hereby is that only "state of the science and practice" treatments should belong to basic insurance package. Starting from January 2012, the Minister of Health in the Netherlands temporarily admitted these treatments to the insurance package under the condition, that the (cost-) effectiveness of this care will be prospectively studied. After the expiration of the conditional period, practitioners had to present new data to determine whether the generally practiced care can be definitively part of the insurance policy.

For this reason a clinical multi center research was set up. The goal of the study was to establish cost-effectiveness of pain interventions in patients with chronic mechanical low back pain, originating from SI joint(s), lumbar facet joint(s), and/or lumbar discs. Only patients with chronic low back pain who do not benefit from a conservative treatment in primary care would be subject of the study.

Considering the SI joint, patients with presumed SI joint pain, in whom at least 3 positive provocation tests were positive, received peri-articular diagnostic block with lidocaine 2%, as described by Patel et al.28, whereby lateral branches of S1-S3 and dorsal ramus L5 were targeted. The infiltration was regarded positive if patient experienced at least 50% pain reduction. After that, patients were allocated to one of the treatment groups. One group followed a multidisciplinary pain program including physical and psychological treatment, and another one received the multidisciplinary pain programs in addition to the radiofrequency lesion. For the radiofrequency (RF) treatment, three different techniques were applied: a palisade technique, cooled RF or simplicity technique. Patients were followed up to one year after RF treatment.

There were 16 clinics participating in the study, with the estimated inflow of 5000 potential participants (http://mintstudie.nl). The inclusion was terminated at the end of 2015. The results from the study were published in a preliminary report for the Dutch Ministry of Health. According to the results, 228 patients with SI joint pain participated in the RCT, whereof 116 were allocated to the group with invasive treatment. Statistically significant, but not clinically relevant difference in pain intensity, in favor of the interventional technique was found 3 weeks and 3 months after the start of the intervention. There was a statistically significant difference between the groups as...
measured with global perceived effect 3 weeks, 6 weeks, and 3 months after the intervention, whereas for the functional status 3 weeks after the intervention. Mean total societal costs for the intervention group were €7116, and for the control group €5276 per patient. The difference in costs between the two groups was statistically significant. The cost-effectiveness analyses at 12-month follow-up showed that the costs were significantly higher in the intervention group.

Speaking in the terms of cost-effectiveness, the study results are negative, which will have major implication for our patients, as the Dutch Health Insurance Council (CVZ) considers recommending not including these procedures in the public health insurance. However, as in all large scale multicenter trials, factors contributing to baseline variance have to be taken into account in the interpretation of the results, such as: heterogeneity between patients and interrater reliability factors for performance of diagnostic techniques and interventional therapeutic techniques.

Limitations of this thesis

The limitations of the present thesis involve both the anatomical and clinical studies. For the anatomical studies we were able to obtain tissues only from specimens older than 60 years. Therefore our finding could be underestimation of the real density of the nociceptors in the SI joint region, as it is found that with aging the number of myelinated and unmyelinated fibers may be decreased. Furthermore, from our findings we can only conclude that SI joint is capable to produce the pain sensation, but we failed to describe the greater nerves, like spinal nerves contribution to SI joint innervation. As mentioned above, a recent report of cadaveric study, whereby dissection techniques were used, gives more information about topography of sacral nerves S1-S2 contributing to SI joint innervation in all morphologically examined specimens, S3 in 88%, S4 in 4%, and lumbar nerve L5 in 8%. This provides some perspective to development of selective nerve blockades techniques, using radio-frequent modalities.

Another limitation is the small sample size of the pressure algometry and the RCT studies. With regard to the pressure algometry study we cannot use the low pain
pressure threshold as the only diagnostic tool. Basically, relying only on the low-pressure pain threshold could lead to overestimation of SI joint pain cases (type 1 error). On the other hand, measuring high pain pressure thresholds in a patient with SI joint pain, could lead to under-treatment of this particular subject (type 2 error). Therefore, we suggest using the pressure algometry together with other diagnostic tools. Another limitation of the pressure algometry study is the instrument itself, as Wagner Force Dial FPK algometer, is capable to measure a pressure from 2.0 kgf upwards. This means that all patients have at least a PPT of 2.0, and no lower thresholds could be detected. For clinical practice, it would be recommendable to use an algometer with a lower detection threshold, optimally the digital one.

The small sample size was also the problem affecting the results of our RCT. We failed to include estimated number of 67 patients in our trial. This problem we explained by very secure inclusion criteria, and also the fact of the use of placebo in our study. The small number of the included patients has serious consequences for the ability to draw conclusions from our RCT. However, even with these limited numbers we found indications for efficacy in the group infiltrated with corticosteroids, and not in the other two groups.

**Recommendation for the further studies**

Taking above into account we would like to make some recommendation for the future research. The diagnosis of the SI joint pain can be made based on the presence of the pain in SI joint region whereby three or more positive physical examination/pain provocation tests are positive. Patient with chronic SI joint pain, as confirmed by physical examination could be a candidate for invasive pain treatments. The intra-articular infiltration should involve therapeutic medium, i.e. corticosteroids. If the pain relief is not achieved, peri-articular diagnostic infiltration should be considered. The technique for peri-articular infiltration needs to be standardized, and it should depend on the denervation technique. As according to anatomical findings, lateral branches of the dorsal rami of S1-S3 innervate the posterior aspect of the SI joint, we propose the para-foraminal sacral S1-S3 infiltration with a small volume of local anesthetic, following by RF lesion19. The long-term efficacy of different RF techniques needs to be
established in the prospective study. The multi center study design would be a good choice, as the recruitment problems were already recognized during the performance of the Dutch MINt study. The future techniques should probably be developed for ultrasound techniques, what could eliminate the risk of ionizing radiation from fluoroscopy guidance techniques.

Summarizing, with our research we contributed to better anatomical knowledge regarding distribution of nociceptors in SI joint, emphasizing the role of peri-articular structures as possible pain generators. Further the results of our meta-analysis give the clear directions for making the diagnosis of SI joint pain. Also, we describe the value of a simple diagnostic test, the pressure algometry in diagnosing SI joint pain. Finally, we provide evidence for the superior effect of SI joint intra-articular infiltration with lidocaine and corticosteroids compared to placebo and lidocaine.
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