Clinical and neuropsychological characterization of persistent postherniotomy pain

Eske Kvanner Aasvang, MD

Section for Surgical Pathophysiology
Rigshospitalet – Copenhagen University Hospital
Preface

The studies behind this thesis were done during my work as a research fellow at Hvidovre Hospital at the department of Anesthesiology, and were later continued at Rigshospitalet at the Section for Surgical Pathophysiology. This thesis was only possible due to the close guidance, inspiration and invaluable help from professor Henrik Kehlet. I am deeply grateful for his beliefs in the project and me, and for his friendship.

The collection of data would not have been possible without the willingness and endurance of research nurse Jeanette Birch Hansen, and psychologists Eliza and Bjorn Gmaehle, thank you all.

For lending their surgical expertise I would like to thank Professor Reinhard Bittner, and surgeons Jørgen Malmstrøm and Torsten Asmussen.

For introducing me to Henrik Kehlet and giving me a place to be at Hvidovre Hospital, I wish to thank Claus Lund, Head of Department of Anesthesiology, Hvidovre Hospital.

I wish to thank Jakob Trier Møller, Head of department, Centre of Head and Orthopaedics, Department of Anaesthesia, Rigshospitalet, for giving me a place to be at Rigshospitalet, and introducing me to my two good friends Dan Lou Isbye and Christian Sylvest Meyhoff. Thanks for numerous discussions and laughs, no one could ask for better roommates.

A warm thanks to secretary Tina Calundan for her artistic skills and technical help with posters, and to my co-authors for the inspiring collaboration.

A special thanks to the staff at Hørsholm Hospital for allowing me to intrude on a very busy workplace, and always meeting me with a smile regardless of whatever extra favour I asked for.

A very special thank to all the many patients who gave their time and endured pain to help others. Kindness as this restores faith and cannot be valued highly enough.

My thoughts go to my grandfather Arnold Kvanner for inspiring me to study medicine and enjoying life.

Finally, my deepest gratitude and love to my wife Lene, who always encouraged and supported me throughout the years.

This thesis and the works behind it, was supported by grants from The Lundbeck Foundation, Læge Fritz Karners og Hustru Edith Karners fond, Grosserer Chr. Andersen og Hustru Ingeborg Andersen, f. Schmidts legat, Overlæge Dr. Med Edgar Schnohr og Hustru Gilberte Schnohrs fond and the Faculty for Health Sciences, Copenhagen University.

To Liv and Gry

Eske Kvanner Aasvang
Copenhagen, October 2011.
Contents

Papers on which this thesis is based ................................................................. 4
Definitions and abbreviations ........................................................................ 5
Aim ....................................................................................................................... 8
Background ...................................................................................................... 9
Definition of persistent postherniotomy pain .................................................. 11
Definition of chronic and neuropathic pain: ................................................... 11
Definition of persistent postherniotomy pain .................................................. 11
Clinical characterization of postherniotomy pain ............................................ 13
Methodology - pain and discomfort questionnaires ........................................ 13
Clinical Characterization .............................................................................. 14
   Localization .................................................................................................... 14
   Frequency and intensity ................................................................................ 14
   Postherniotomy pain related activity impairment ....................................... 15
Postherniotomy sexual dysfunction and dysejaculation .................................. 16
Psychology ...................................................................................................... 17
Prediction of persistent postherniotomy pain .................................................. 24
Sensory function and dysfunction .................................................................. 25
Methodology in sensory assessment ............................................................... 25
Preoperative sensory function ....................................................................... 26
   Early postoperative sensory function ......................................................... 29
   Late postoperative sensory function in pain-free patients .......................... 29
   Late postoperative sensory function in persistent postherniotomy pain patients ........................................................................ 31
Prevention of persistent postherniotomy pain ................................................ 36
   Pharmacological prevention ....................................................................... 36
   Surgical technique ....................................................................................... 37
Treatment of persistent postherniotomy pain ................................................ 39
   Pharmacological treatment ......................................................................... 39
   Surgical treatment ...................................................................................... 39
Perspectives ..................................................................................................... 41
Comments and corrections to tables and articles .......................................... 45
References ...................................................................................................... 51
Papers on which this thesis is based


Definitions and abbreviations

AAS: The Activity Assessment Scale.
Alldynia: Lowered pain threshold, so that pain occurs with a normally non-painful stimulus.
CDT: Cold detection threshold, the temperature when cold can be sensed.
CI: Confidence interval.
COMT: Catechol-O-methyl-transferase gene.
CPT: Cold pain detection threshold, the temperature when cold becomes painful.
DFSN: German Research Network on Neuropathic Pain.
DNIC: Diffuse Noxious Inhibitory System.
Dysejaculation: Pain occurring in relation to ejaculation.
Dysesthesia: An unpleasant abnormal sensation spontaneous or evoked.
FU: Follow Up.
GWAS: Genomic-Wide Association Studies.
HADS: Hospital Anxiety and Depression Scale.
HPT: Heat pain threshold, the temperature when warmth becomes painful.
Hyperesthesia: Increased sensitivity to stimulation/increased detection threshold.
Hyposalgesia: Less pain from a normally painful stimulus/Increased pain detection threshold.
Hyposthesia: Decreased sensitivity to stimulation/increased detection threshold.
IASP: International Association for the Study of Pain
IPQ: The Inguinal Pain Questionnaire.
Lichtenstein: A tension free open herniotomy technique with implantation of a mesh.
n: number of patients.
Neuropsychological: (in this thesis understood as) the perception/cognition of a stimulus.
NRS: Numerical Rating Scale.
OR: Odds Ratio.
Paresthesia: tingling, burning, pricking, or numbness of the skin.
PCS: Pain Catastrophizing Scale.
PDI: Pain Disability Index
Pressure algometer: An apparatus that allows application of a measurable pressure to an area.
PPT: Pressure pain detection threshold, the point when pressure that becomes painful.
PPtol: Pressure pain tolerance threshold, the point when pressure pain becomes intolerable.
p-value: A statistical estimate of the likelihood that the observation in the study occurs by chance.
rho: A statistical estimate of correlation between values.
QST: Quantitative Sensory Testing
SF36: The Short Form (36) Health Survey
Shouldice,Bassini, McVay: Non-mesh based sutured (tension) herniotomy techniques
S-LANSS: The Leeds Assessment of Neuropathic Symptoms and Signs pain scale.
SNP: Single-nucleotide polymorphism.
TAPP: TransAbdominal PrePeritoneal laparoscopic herniotomy technique.
**TEP**: Total ExtraPeritoneal laparoscopic herniotomy technique.

**Thermotester**: An apparatus that allows precise measurable heating/cooling of a peltier thermode and thus stimulation of patients.

**VAS**: Visual Analogue Scale.

**von Frey fiber**: a nylon filament of varying diameter and buckling force, used, among other areas, for testing mechanical detection and pain detection thresholds.

**VRS**: Verbal Rating Scale.

**WDT**: Warmth detection threshold, the temperature when warmth can be sensed.

**Wind-up**: new pain from repetitive non-painful stimulation or increased pain from repetitive painful stimulation, due to a cumulative response of spinal posterior horn neurons leading to hyper-excitability.
Introduction

It is now recognized that persistent pain after groin hernia surgery affects everyday activities in 5-8% of patients more than 6 months after groin hernia surgery (1-4). Furthermore, groin hernia surgery is one of the most frequently performed operations, with annual rates of about 2800 per million inhabitants (5,6). When these numbers are combined with the lowest estimated 5% risk of moderate/severe pain, it translates into an annual number of new cases of persistent pain patients of 600, 3,700 and 34,000 for Denmark, the United Kingdom and The United States of America respectively (5), making persistent postherniotomy pain not only a personal misfortune for the individual patient, but also a socio-economic problem as it may result in job-loss and increased use of healthcare services.

However, the underlying pathogenic mechanisms why some patients end up with pain that affects their ability to work, carry out everyday activities and even results in sexual dysfunction, have not been the focus of research until the last decade.

Thus, there are challenges that needs to be addressed to achieve a better understanding and treatment of postherniotomy pain

1. the definition of persistent postherniotomy pain and how to measure it must be agreed upon if studies are to be truly compared and treatment strategies tested (7).
2. the details of pain related functional impairment with regards to intensity and specific impairments, i.e. sexual pain related dysfunction (8,9).
3. the understanding of the relative role of pre-, intra- and postoperative factors in relation to persistent postoperative pain (10-13).
4. the location of pain, where is the generator for ongoing nociceptive input (peripheral vs. central, cutaneous vs. deep) (14).
5. the effect of preventive and treatment strategies (pharmacological or surgical) (4,13,15,16).
Aim

The main aim of this research project was to describe the clinical and neuropsychological characteristics of postherniotomy patients with emphasis on

- Pain related sexual dysfunction, including frequency, severity and neuropsychological characterization
- Preoperative sensory function in hernia patients, including prediction of pain by nociceptive testing.
- Acute postoperative sensory function in hernia patients
- Late sensory function in both pain and pain-free hernia operated patients
- Identification of predictive factors for persistent postherniotomy pain related impairment.
- The effect of re-operation for persistent postoperative pain on sensory function and pain related impairment.

These issues are reviewed based upon the existing literature and the eight papers (8-11,13-15,17) that form this thesis, by:

- Describing the incidence, severity and clinical characteristics of patients with postherniotomy pain related sexual dysfunction (8)
- Describing the detailed sensory characteristics of persistent postherniotomy patients with dysejaculation (9)
- Describing the detailed sensory characteristics and its relation to pain, in hernia patients before surgery (13,17,18)
- Describing the detailed sensory characteristics of pain-free patients more than a year after surgery, and constructing normative data from these findings (11)
- Describing the detailed sensory characteristics of persistent postherniotomy pain patients when compared to pain-free patients on a group-to-group level (10,13)
- Describing a heterogeneous sensory outcome in persistent postherniotomy patients by individual characterization using normative data from pain-free patients (14)
- Identifying predictive factors for development of persistent postherniotomy pain (13)
- Describing the effect of re-operation for persistent postherniotomy pain on the sensory function (15)
Background

Galen first described treatment of inguinal hernias in the 2nd century A.D. Primary application of compressive bandages and different drugs were the primary treatment. However, if these were ineffective, surgery was recommended, where an impressive anatomical understanding was applied; the patient was positioned horizontally with legs lifted, the hernia pushed back, an oblique incision was made, and the subcutaneous membranes (externus aponeurosis?) dissected so that the hernia sac was prepared. Any remaining intestines were pushed out of the sac, which was then ligated around the base, where after the loose peritoneum was removed and the skin closed by 2-3 sutures. Unwashed sheepswool soaked in vinegar and olive oil was applied, and finally bandages. Throughout the Byzantine era hernias were operated on in hospitals, known as Xenones, where a special category of lower surgeons called celotome (= surgeon for hernias), dealt exclusively with this kind of operation (19). Apart from the introduction of meshes and laparoscopy, the principles of the surgical technique remain the same.

The first reports of pain following surgery and other trauma in the inguinal region came as early as 1895 when Roth, Bernhardt, and Freud published reports separate regarding neuropathies of the lateral femoral cutaneous nerve; called meralgia paresthetica. In 1942 Magee (20), and in 1945 Lyon (21) reported of genitofemoral related pain called “genitofemoral causalgia”, in most cases occurring after previous appendectomies. Laha reported in 1977 a patient with radiating pain from the groin to the right testes 14 days after an inguinal hernia operation, and a subsequent contralateral operation resulted in the same symptoms (22).

Thus, persistent pain has long been reported as an adverse outcome after groin surgery, but even in the beginning of the 1980’s it was considered rare (22-24). In the 1990’s several studies from hernia and pain clinics reported that persistent pain of any intensity was experienced in as many as 60% of patients a year after groin hernia repair whilst others reported that none of their patients had persistent pain (2,25), an obscure difference mainly due to lack of a definition of persistent postherniotomy pain. In the 2000’s large scale national questionnaire surveys have reported a frequency of moderate to severe pain occurring in 5-12% of patients (26-28), and these rates have been confirmed by prospective data (13).
Definition of persistent postherniotomy pain

“If something defines everything then it defines nothing”

Definition of chronic and neuropathic pain:

Chronic pain is defined by the International Association for the Study of Pain (IASP) as:

“Pain lasting longer than 3 months” (32).

Furthermore, neuropathic pain is defined by IASP as:

“Pain initiated or caused by a primary lesion or dysfunction in the nervous system.”(33).

Which recently has been suggested revised to:

“Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (34).

With these definitions, one could ask; what is not neuropathic pain? For instance, an inflammation surrounding a peripheral nerve results in spinal inflammation (35), much as a partial axonal lesion would (36), both resulting in pain that may not be perceived different to the patient and one is a disease and the other a lesion, but both affects the somatosensory system. However, as noted by the authors behind the new definition (34), even the refinement is not evidence based, as no specific test for neuropathic pain exists. The suggested grading system in the same paper should be seen as a working/scientific tool for hypothesis generation, which in turn is expected to result in a more robust mechanism based definition of various pain types, and ideally in mechanism-based treatment strategies.

Definition of persistent postherniotomy pain

A uniform-agreed upon definition of persistent postoperative/herniotomy pain such as the those mentioned above does not exist, resulting in the undesirable situation where studies investigating persistent postherniotomy pain are heterogeneous in definitions and outcomes leading to difficulties when comparisons and reviews are attempted, and huge spans in incidences (0-60%) as evidenced by reviews on persistent postherniotomy pain (2,3).

Macrae et al. (37) defined pain as chronic postoperative pain if:

1. the pain developed after a surgical procedure.
2. the pain is of at least 2 months duration.
3. other causes for pain should have been excluded (e.g. continuing malignancy or chronic infection).
4. the possibility that the pain is continuing from a pre-existing problem had been explored, and exclusion attempted.

In this thesis the term persistent rather than chronic pain will be used, to emphasize that the pain reported by patients acutely and several months after surgery may share several pathogenic mechanisms, and should not per se be seen as separate entities. Furthermore, although neuropathic changes may occur at some point, we do not know exactly when and therefore it would be wrong to postulate that pain is acute or chronic after a certain time point, like the IASP definition of three months (32). Acute pain does lead to neuroplastic spinal changes after a very short while (2 days) in animal models of neuropathic pain (38), and some patients have pain states that lasts for months or years and then disappears spontaneously (12,39) much as acute pain resolves spontaneously in the majority of injuries. However, for methodological reasons it is necessary to define a point at which pain is considered to have lasted longer than normal, even if such a time point at this moment is only a qualified guess. In hernia repair, where implantation of meshes is standard, animal studies shows that an inflammatory reaction is expected to last longer than 3 months. Melman and colleagues (40) have shown in a porcine hernia model with commonly used mesh types, that inflammation peaks at 1 month and gradually resolves until 5 months where only minimal inflammation persists. For this reason 6 months follow-up seems desirable, although inflammation may occur even after this time point as shown by an MRI study of patients with and without persistent pain more than a year after inguinal herniotomy (41), but should be considered abnormal.
Thus, for persistent postherniotomy pain, the IASP definition of “pain lasting longer than 3 months” (32) or the 2 months suggested by Macrae et al. (37) is not optimal and should be changed to “pain lasting longer than 6 months”.

The definition of persistent pain by Macrae et al. (37) demands that pain has “... developed after a surgical procedure”. However, as noted by Macrae et al. (37) many hernia patients experience pain before surgery (13,17,27,42-44) and the pain itself may be part of the pathogenic mechanism that results in persistent pain (see later section). At this time point in our quest for understanding postherniotomy pain, it would seem wise to include patients with pain before surgery, but investigate if: A. the pain has changed character or localization, and B. the pain has changed in intensity, frequency and when it is provoked. It is highly interesting to understand why pain intensifies in some and disappears in others, but a persistent but less intense pain than before should perhaps also be seen as a sub-optimal healing process that may require intervention if the pain is to disappear completely. The potential for intensification of pain later in the postoperative period is evidenced by a 6 year follow-up study of 1 year pain by Aasvang et al. (39) and a 5 year prospective trial by Reinpold et al. (12), where a subgroup of patients in both studies had more pain at the late than at the earlier postoperative follow-up.

In conclusion, persistent postherniotomy pain should be considered if the pain 6 months after groin hernia surgery is different from the pre-operative hernia pain, either in localization, character, intensity or frequency.

Suggested new definition of persistent postoperative pain:

1. pain occurring after a surgical procedure
2. pain lasting longer than 6 months
3. postoperative pain different from preoperative pain with regards to
   a. character and/or
   b. localization and/or
   c. intensity and/or
   d. frequency
4. other causes of pain excluded such as malignancy or infection
Clinical characterization of postherniotomy pain

"A difference is only a difference if it makes a difference"

Methodology - pain and discomfort questionnaires

Discomfort vs. pain vs. pain related functional impairment.

The subjective nature of pain makes exact objective measurement impossible. There is no sharp definition of pain vs. discomfort so the result relies on the patient’s interpretation with the obvious bias this imposes. Furthermore, commonly used pain scales as the Visual Analogue Scale (VAS) or Numeric Ranking Scale (NRS), may be troublesome for some patient categories with less abstract abilities (elderly, cognitive impaired) potentially leading to bias (45).

Most studies on postherniotomy pain use simple questionnaires with dichotomous ‘yes/no’ answers to pain or use rating scales (VAS, NRS) (2,3,46). These scales do not assess the impact of health on quality-of-life, which in the end is the only meaningful outcome. Thus, even though measuring the pain related impairment of everyday activities has been recognized as a relevant clinical outcome and used early on in the study of postherniotomy pain (47), the majority of studies still only investigates the occurrence of pain, resulting in a need for an agreement on a uniform standardized questionnaire and recording of data for comparison across studies (7). General and non-surgery specific questionnaires like the Short Form 36 (SF36) (48), McGill Pain Questionnaire (MPQ) (49) or the Pain Disability Index (PDI) (50,51) are the most frequently used questionnaires in clinical and experimental pain trials. When it comes to postsurgical pain – including postherniotomy pain – these general questionnaires are not ideal as they do not investigate limitations in everyday activities specifically impaired by the surgical procedure of interest, or allow quantification of impairment. Furthermore, their inferiority to disease specific questionnaires with regards to assessment of the health related quality of life has been shown by Velanovich (52).

Thus, over the last decade, different groups have developed specific questionnaires for assessment of postherniotomy pain:

The pain and functional impairment questionnaire. A validated questionnaire from the Swedish hernia database with 4 physical activities and rating of impairment of each activity on 4 levels (29). It has not been used in other studies than the original report, which was based upon the questions used in the nationwide postherniotomy pain study by Bay-Nielsen et al. (26).

The Carolinas Comfort Scale (CCS). A validated questionnaire developed specifically for patients scheduled for mesh-based hernia repair (not only inguinal), with good correlation to the SF-36 scales. It consists of a total of 23 questions, specifically investigating impairment in movement in 6 well-defined activities and 2 that are open for interpretation (activities of everyday living, and exercise). Despite claims from the developers of the CCS that it is translated and used in 10 countries, a standardized PubMed search did not reveal studies on persistent postherniotomy pain using the CCS except for the original article, where no details of impairment is given, but only validation information is presented (53).

The Inguinal Pain Questionnaire. A validated questionnaire based upon a modification of the questionnaire suggested by Kehlet et al. (7), used in nationwide surveys on persistent postherniotomy pain (26,39). The IPQ uses a pain scale of seven ratings that are linked to pain-related affection of behaviour rather than numbers or pain word descriptors, to assess pain. Impairment is assessed in 6 activities with a yes/no/not applicable answer, along others recordings for instance description of pain-scores at rest or activity and use of analgesics (54). It was used by Eklund but without detailed data on impairment incidence (55) as was the case with the study by Frisen et al (56).

The Activity Assessment Scale (AAS). A validated questionnaire, evaluating pain related impairment in 13 different activities, pain related impairment is rated on five levels for each activity, and a total score or subscales can be constructed. It has proven validity in the assessment of pre- vs. postoperative pain related impairment (31) and used in a prospective trial by
Fitzgibbons et al (57) and in a modified version by Aasvang et al (11) and Bittner et al (58). However, based upon erroneous information from the primary author of the AAS (personal e-mail correspondence), the scale were inversed in the studies by the Aasvang group, so that 0% meant no impairment and 100% meant maximal impairment.

In conclusion: Specific questionnaires, investigating activities known to cause pain related impairment in postherniotomy patients should be used when assessing the outcome of groin hernia operations. A questionnaire with detailed assessment of impairment of everyday activities and multilevel quantification for each activity is to be preferred and should be agreed upon by the hernia surgical community for future trials. Subsequent validation studies for different languages, and establishment of background data in non-hernia and non-operated hernia patients should be made.

**Clinical Characterization**

An almost complete description of the typical clinical presentation of a persistent postherniotomy pain patient was given by Laha et al (22) already in 1977:

The patient had “...pain in the lower quadrants of the abdomen, radiating to groins and testes for the past six years... Pain recurred several times a day and lasted from only a few minutes to one-half hour. Extension of the hip, climbing stairs or walking aggravated the pain...” showing the localization, frequency, duration and impairment caused by postherniotomy pain.

**Localization**

Harms reported in 1984 on the location of persistent postherniotomy pain in two patients who had had previous groin hernia repair. The pain was located to the upper thigh and lateral to the pubic tubercle, a description that still fits the majority of patients. Thus, in a nationwide questionnaire study regarding pain 1 year after groin hernia surgery, Bay-Nielsen showed that persistent postherniotomy pain in the majority of cases (88%) is located around the surgical scar (26) and confirmed by Massaron et al (28). However, Other localizations are also seen with isolated or combined involvement of the pubic tubercle, thigh, penis and scrotum (8,9,26,28) (Figure 1). One in four patients report pain being superficial, whilst the majority report that pain arises from deeper structures (about 70%) (10).

The point with maximum pain intensity is almost always near the external inguinal annulus (10). Figure 1 shows the location of severe persistent postoperative pain as reported by patients (10).

**Frequency and intensity**

It is beyond the scope of this thesis to give a review of the literature on pain intensity and duration of postherniotomy pain. Large scale studies show, that 1-3 years after groin hernia surgery about 1-2% of patients report severe pain during activity, 7-12% moderate pain and 13-25% light pain (26,59). These numbers are lower when measured during rest, again showing the importance of defining and presenting the method of measurement. Pain occurs occasionally in 15-25% of patients, and always/nearly always in 3-5% (26,59). In these studies the frequency of how often the patient experiences pain, is not defined in the methods section, and the presented frequency is also loosely defined as “seldom”, “occasionally”, “regularly”, leaving room for individual interpretation and thus bias. A better choice is to have firm definitions such as “never”, “less than weekly”, “weekly” and “daily”.

The combination of intensity/frequency/duration should be assessed to give a multidimensional picture of the scale of pain experienced by the patient. An example of a combined pain frequency matrix is suggested in the study by Aasvang et al. of preoperative hernia pain (17).

In conclusion: pain intensity/frequency/duration are important variables, but should not be the primary outcome measurement in future hernia trials.
Postherniotomy pain related activity impairment

The key question is when is enough pain enough to be categorized as relevant? The patients can only answer this. Table 1 summarizes the major studies on pain related impairment in persistent postherniotomy pain patients (8,12,13,25-27,29,39,43,47,54,57,60-67). The first large scale study to assess not only pain but also consequences, were reported by Cunningham et al. (25) in 276 patients seen at the 1 year follow-up visit after open groin hernia repair (Bassini, McVay or Shouldice repair techniques). Pain was defined as moderate if it prevented return to normal pre-hernia activities (golf, tennis, lifting without pain) or severe if it incapacitated the patient at frequent intervals, for instance during walking. Pain of such severity (moderate/severe) was found in 11.9% at 1 year and 10.6% at 2 years. However the general incidence of any pain was very high in this study (62.9 and 53.6% at the 1 and 2 year follow up respectively), but a very low follow-up rate of only 48.6% hinders firm conclusions. In a nation-wide cohort study of 1166 patients (80.8% follow-up), Bay-Nielsen et al (26) found that one year after surgery 11% of patients had pain related impairment to one or more pre-specified activities. Age was a significant discriminator with patients 65 years old or less reporting pain related impairment more often than older patients. Pain was most frequently reported when standing (32.0%) or climbing stairs (27.7%) and most seldom when travelling by bus or train (6.8%). A follow-up study by Aasvang et al (39) in the pain cohort from the previous study (26) study showed that the incidence of pain related impairment in the original 166 patient cohort was 5% even after 6 years (assuming no new pain had occurred in the pain-free patients), again with less pain if patients were older than 65 years. In this study the patients’ activity level was assessed, and 90% of patients reported full activity level and only 2% required daily help, but most studies fail to take the patients activity level into consideration. However, good questionnaires such as the IPQ or AAS will systematically adjust for this (31,54). In the study by Frånneby et al (27,54) where the IPQ was used in 2456 patients, an overall 6% of patients reported pain related impairment, however 8% reported sports related impairment, whilst only 3% had impairment in sitting. In another study using the IPQ, Kalliomäki et al (43) found that 11% had pain related impairment, again with sports as the most impaired function. The AAS questionnaire was first used by McCarthy et al, but the cohort of 2164 patients were assessed after 3 months and therefore do not fit our definition of persistent postherniotomy pain (31). Fitzgibbons et al also used the questionnaire in 354 patients primarily scheduled for a hernia repair or crossing over from a group where watchful waiting was attempted (57). Postherniotomy pain related impairment was found in 3.1% of patients after 2 years, but without details on specific activities, a very low figure compared with the other available literature on open herniotomy and impairment (table 1). Interestingly, pain related impairment was more frequent in patients who had crossed over from the watchful waiting group (8.6% vs. 1.5%, in primary vs. cross-over patients respectively) suggesting that preoperatively established impairment may continue (see later sections). Another explanation for this difference is a shorter observation period for the cross-over group. The first study to use pain related impairment as the primary outcome was reported by Aasvang et al (31). They used a modified version of the AAS in a 442 patient (95.3% follow-up) prospective study. Two activities (walking around inside” or “walking around outside”) were replaced by one ("standing for more than 30 minutes") since this was the most troublesome activity in the study by Bay-Nielsen et al. (26). The total number of

Figure 1. Pain location in persistent postherniotomy pain

activities was thus 12. An AAS score of more than 8.3 was represented substantial pain related impairment, as this was equivalent to a score if a task could not be performed. The same score could also be achieved by less maximum impairment, but in several categories. Fifty-five patients (12.4%) had substantial pain-related impairment at the 6-month follow-up. Ten (2.2%) had “a little” difficulty in five or more activities, 33 (7.5%) had “some difficulty” in three or more activities, 10 (2.2%) had “a lot” of difficulty in two or more activities, and 4 (0.9%) were “unable” to perform the activity due to pain. Overall, the operation reduced pain-related impairment of any degree from 66.3% before operation to 23.3% after (P < 0.001). Thirty-five patients (7.9%) reported a higher degree of pain-related impairment after 6 months than before surgery.

In conclusion: Impaired function due to pain 1 to 6 years after groin hernia surgery is reported by 5±2% of patients, whereof about 8% report an increased impairment compared to their preoperative function.

Postherniotomy sexual dysfunction and dysejaculation

Pain related sexual dysfunction

A specific pain syndrome is genital pain and dysejaculation (painful ejaculation) following groin hernia repair with subsequent sexual dysfunction. This syndrome had only been described sporadically (42,62,68-80) until a nationwide questionnaire study by Aasvang et al (8) investigated the incidence of persistent postherniotomy pain related sexual dysfunction, location, severity and impairment in 1015 eligible young male patients (18 - 40 years) with a groin hernia operation 1 year before. The response rate was 68.4%, which may be explained by the nature of the questions. Any kind of pain during sexual activity was reported by 224 (22.1%) patients, and 68 (6.7%) reported that pain occurred every third time or more with an intensity of >3 points out of 10. The location of pain during sexual activity reported by the patients is shown in figure 2. Thirty-three percent of patients with operation for recurrence reported pain during sexual activity as opposed to 20% of those with a primary operation, a finding identical to the increased risk for non-sexual persistent postherniotomy pain in recurrence operations (26,43). Impairment of sexual function as a consequence of pain was reported by 95 (42.2%) of the 224 patients, whereof 28 (18.9%) found the impairment moderate or severe. A key question is to what extent preoperative pain related sexual impairment occurs. Thus, preoperative hernia related impairment of sexual function has been described by Zieren et al (73) in 224 patients where 52 (23%) had unspecified sexual dysfunction. This was reduced to 36 (16%) postoperatively that resolved or improved over the next 6 months. The cohort was older (53±/- 33 years, making direct comparison difficult due to possible reduced sexual activity and erectile dysfunctions. In a prospective trial were 442 patients were operated in high volume expert hernia centres and followed until 6 months after groin herniotomy, Aasvang et al. (13) found that preoperatively, 52 (11.7%) patients reported pain from the hernia during sexual activity, with 6 (1.3%) patients reporting a moderate and 6 (1.3%) a severe impairment of sexual function. Postoperatively 37 (8.4%) reported pain during sexual activity, whereof 25% (5.6%) where new cases). In this study only 3 (0.7%) found that pain impaired their sexual activity moderate/severely. This difference may be explained by the latter study being performed in an older and perhaps less sexually active cohort (33 vs. 55 years) or a different surgical technique in half of the patients (TAPP with glue fixation vs. mainly open sutured or mesh herniotomy). Staal and colleagues (66) also showed that preoperative pain affects sexual behaviour and is reduced but not removed by groin hernia repair when measured by the PDI questionnaire. However, without explanation the authors reported that patients without pain also had pain related sexual activity disability.

Dysejaculation: From figure 2 it can be seen that a total of 41 (18.3%) patients in the study by Aasvang et al. (8) reported pain during ejaculation (dysejaculation), whereof 17 (7.5%) only had this specific pain syndrome. Thirteen patients with dysejaculation reported severe pain related sexual impairment (9).

Dysejaculation was further clinically investigated in a specific series of 10 patients with ejaculatory pain (9), where a psycho-sexological interview concluded that the pain was definitely of somatic origin, and no other causes for pain (i.e. recurrence) could be found at the clinical examination . Eight of 10 patients had pain during sexual activity and all at the moment of ejaculation, with pain persisting from minutes to hours after the sexual activity had stopped. All patients reported a maximum pain at the external inguinal annulus. Very little data exists on preoperative
dysejaculation, but Aasvang et al. (13) found that 6 (1.3%) of patients had preoperative dysejaculation, and 6 months later this had disappeared in 5/6, but 5 new cases of dysejaculation had occurred after surgery. Dysejaculation in relation to inguinal herniotomy was already reported by Bendavid in 1992 (68) where injury to the vas deferens during surgery was suggested as a pathogenic mechanism, a finding supported by the post-vasectomy pain syndrome (84) although there were no details on dysejaculation in this article. Another explanation has been the contact between the mesh and vas deferens which may cause inflammation (82) and/or compression which has also been reported in surgical exploration of severe persistent postherniotomy pain and dysejaculation patients, when decompression was performed by mesh removal (15,83). The sensory details of dysejaculation are analysed in the later “sensory function and dysfunction section”.

In conclusion: Sexual function and the occurrence of dysejaculation should be assessed in studies on inguinal hernia repair, as pain during sexual activity may affect patients severely and have consequences on family and social life.

**Figure 2: Pain location in postherniotomy persistent pain related sexual dysfunction**

![Image of pain location diagram]


**Psychology**

It would be suspected that persistent pain and pain related impairment including sexual dysfunction could have an adverse impact on the psychological status of patients. However, cohort studies by Aasvang et al. (10,13) using the Hospital Anxiety and Depression Scale, has shown a relative low incidence of depression (3 - 5%) and anxiety (5-10%) respectively, in patients with persistent postherniotomy pain. These studies suffer from the lack of data from pain-free postherniotomy patients, but even when caution is taken, due to the different questionnaires and screening tools are used in the studies, the incidence of depression and anxiety is low compared to the well-described about 60% prevalence in a cross-sectional study from a pain clinic (84). These findings have been confirmed by Kalliomäki et al (43) who investigated anxiety and depression in 100 pain and 100 pain-free postherniotomy patients and found a 4% incidence of depression and anxiety, and only in pain patients. Furthermore, an in-depth psychological interview did not revealed psycho-sexual disturbances in patients with severe pain related dysfunction and dysejaculation, or other psychopathology (9).

In conclusion, despite persistent pain, leading to pain related impairment of activities, the prevalence of anxiety and depression is low in the hernia pain population when compared to other chronic pain populations.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up period</th>
<th>Measurement</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham (1996) (25)</td>
<td>276</td>
<td>2 yr</td>
<td>Study specific questionnaire</td>
<td>53.6% had pain after 2 years, 10.6% had moderate/severe pain defined as pain related impairment. Five patients reported pain related sexual impairment</td>
<td>Well defined impairment categories, but a very low follow-up rate of 48% hinders firm conclusion.</td>
</tr>
<tr>
<td>Gillion (1999) (47)</td>
<td>490</td>
<td>3.2 yr</td>
<td>(1 – 5 yr) Study specific questionnaire</td>
<td>15% (n=71) had pain, 0.2 (n=1) ejaculatory pain, 13% pain related impairment</td>
<td>“Impairment” was general i.e. not specified, and ranged from “do not hinder activities” to “prevents certain activities (which)”. No data on age or activity level.</td>
</tr>
<tr>
<td>Bay-Nielsen (2001) (26)</td>
<td>1166</td>
<td>1 yr</td>
<td>Study specific questionnaire</td>
<td>29% (n=335) had pain, 17% (n=194) had pain related impairment, less pain if age over 65</td>
<td>Nine predefined activities answered by “yes/no/not applicable”. Age, gender and recurrence operation stratified. Data on impairment in table and text do not match</td>
</tr>
<tr>
<td>Haapanemi (2002) (29)</td>
<td>218</td>
<td>3 yr</td>
<td>The pain and functional impairment questionnaire</td>
<td>16% (n=34) had pain, 3% (n=7) pain related impairment of everyday activities, and 6% pain related impairment of sport</td>
<td>Pain or pain related impairment not primary outcome. Impairment not stratified and only yes/no answer possible. No age or activity stratification.</td>
</tr>
<tr>
<td>Kumar (2002) (60)</td>
<td>454</td>
<td>1.8 yr</td>
<td>(0.7 – 2.7) Study specific questionnaire</td>
<td>8% had pain and 23% discomfort, 18% had pain/discomfort related impairment</td>
<td>Four predefined activities answered by “no problem/limits a little/yes very limiting”. No age or activity stratification.</td>
</tr>
<tr>
<td>Lau (2003) (61)</td>
<td>261</td>
<td>2 yr</td>
<td>(2 – 3) Study specific questionnaire</td>
<td>10% (n=24) had pain, 0.4% (n=1) had pain related impairment, 0% had sexual impairment</td>
<td>Follow-up by telephone interview. “Impairment” was general i.e. not specified except for “work”, “daily activities” and “sexual activity”. No data on age or activity level. Only laparoscopic</td>
</tr>
<tr>
<td>Mikkelsen (2004) (62)</td>
<td>72</td>
<td>9.5 mo.</td>
<td>Study specific questionnaire</td>
<td>28% (n=20) had pain, 15% (n=11) reported significant pain related impairment of everyday activities, 3% (n=2) spontaneously reported ejaculatory pain and sexual impairment.</td>
<td>Primary objective was sensory disturbances.</td>
</tr>
<tr>
<td>O’Dwyer (2005) (63)</td>
<td>284</td>
<td>1 yr</td>
<td>SF36</td>
<td>Moderate/severe pain in 3.5% Social activity affected in 13%, work in 22% and sexual activity in 33% of pain patients</td>
<td>Pain related questions not specified. Unknown if pain was the cause for impairment. No age or activity stratification.</td>
</tr>
<tr>
<td>Fitzgibbons (2006) (57)</td>
<td>354</td>
<td>2 yr</td>
<td>AAS</td>
<td>3.1% (n=11) had functional impairment</td>
<td>Validated questionnaire with 13 predefined activities and 5 possible levels of impairment for each. No patient or activity related details given in article</td>
</tr>
<tr>
<td>Bringmann (2006) (64)</td>
<td>494</td>
<td>3 yr</td>
<td>Study specific questionnaire</td>
<td>24 had pain, 6% had pain related impairment of everyday activities and 9% of sports</td>
<td>Questionnaire not referenced but claimed to be validated. No data on age or activity level.</td>
</tr>
<tr>
<td>Reference</td>
<td>Patients</td>
<td>Follow Up</td>
<td>Questionnaire</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fränneby (2006) (27)</td>
<td>2456</td>
<td>2 – 3 yr</td>
<td>IPQ</td>
<td>30% had pain. 6% pain that interferes with activities. 8% pain related impairment of sport, 5% standing, 3% in sitting</td>
<td></td>
</tr>
<tr>
<td>Fränneby (2008) (55)</td>
<td></td>
<td></td>
<td></td>
<td>“yes/no/don’t know/not applicable” answers to 6 predefined activities. Primary outcome pain and not impairment. Problem that pain intensity defined by impairment and frequency of impairment do not match</td>
<td></td>
</tr>
<tr>
<td>Aasvang (2006) (39)</td>
<td>210</td>
<td>6 yr</td>
<td>Study specific questionnaire</td>
<td>6% (n=72) had pain, 5% had pain related impairment, less pain if age &gt;65 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Percentages based on original cohort, excluding re-operations, (n=1122). Nine predefined activities answered by “yes/no/not applicable”. Activity level defined. Age, gender and operation stratified</td>
<td></td>
</tr>
<tr>
<td>Aasvang (2006) (8)</td>
<td>1015</td>
<td>1.4 – 1.7 yr</td>
<td>Study specific questionnaire</td>
<td>456 (45%) had pain, 18% substantial pain during activity, 7% had VAS&gt;3 during sexual activity, 4% had dysejaculation, moderate/severe pain related sexual impairment in 3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Predefined location and dysfunction scale. Detailed description of location of pain, intensity and duration, correlation with other pain syndromes. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>van Veen (2007) (65)</td>
<td>153</td>
<td>10 yr</td>
<td>Study specific questionnaire</td>
<td>12% (n=18) had pain during intense activity, but no case of pain related impairment reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51% follow up, mainly due to 30% mortality, making firm conclusions difficult. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>Staal (2008) (86)</td>
<td>146</td>
<td>3 mo</td>
<td>PDI and VAS</td>
<td>32% (n=47) had pain, 21% (n=30) VAS &gt;3. 29% (n=42) pain related impairment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PDI not developed to hemia population. Chronic pain defined as VAS&gt;3 regardless of positive PDI score. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>Kalliomäki (2008) (43)</td>
<td>1669</td>
<td>6 mo – 7 yr</td>
<td>IPQ</td>
<td>31% had pain (n=519), 11 or 7% (n=183 or 121) pain related impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Numbers on impairment not similar in text (11%) and table 2, (5%). Primary outcome not impairment, but pain. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>Aasvang (2010) (13)</td>
<td>442</td>
<td>6 mo.</td>
<td>AAS**</td>
<td>27% had pain (n=117), 12.4% substantial pain related impairment. 8% more impairment than before operation. 1.5% with moderate/severe sexual impairment, dysejaculation by 1.3%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Substantial pain defined as a total AAS-score equal to not being able to perform a task. No details on specific activities accept sexual. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>Reinpold (2011) (12)</td>
<td>645</td>
<td>5 yr</td>
<td>Study specific questionnaire</td>
<td>16% (n=104) had pain, 2% NRS&gt;3, 1% had pain related impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No details on questionnaire or questions. No age or activity stratification.</td>
<td></td>
</tr>
<tr>
<td>Pierides (2011) (67)</td>
<td>232</td>
<td>5 yr</td>
<td>Study specific questionnaire</td>
<td>11% (26) had pain. 2% had pain related impairment of everyday life and 6.4% impairment of sports.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No details on questionnaire or questions. No age or activity stratification.</td>
<td></td>
</tr>
</tbody>
</table>

n = patients completing the study. FU = Follow Up, SF36 = The Short Form (36) Health Survey
AAS = Activity Assessment Scale, VAS = Visual Analogue Scale, PDI = Pain Disability Index, IPQ = Inguinal Pain Questionnaire, NRS = Numerical Rating Scale, ** a modified AAS version with 12 items instead of 13.
Pathogenic mechanisms

The previous sections have shown that persistent postherniotomy pain impairs life in some unfortunate patients, but leaves the question; Why? Why do the majority of patients improve after surgery while 8-12% continue having pain or even worsens? This main focus of this thesis is the role of nerve injury and sensory function, but several other patient related factors have been suggested to play a role in the development of persistent postherniotomy pain and will briefly be presented below.

Genetic – The role of genetic variation on the risk for chronic pain is a topic of major interest (85). Single-nucleotide polymorphism (SNP) variations in several genes have been proposed as the reason for the observed variation in pain experiences. One candidate gene is the COMT gene (catechol-O-methyl-transferase) that encodes for the protein that is responsible for the breakdown – and thereby the duration/effect of catecholamines. Zubieta et al reported that polymorphism in the val158met codon was associated with pain scores after experimental saline injections into the maseter muscle (86), a finding supported by Diatchenko et al in other experimental pain models and the clinical temporo-mandibular disorder (87). However, these findings have been challenged by others (88,89).

No association between the postulated high pain COMT variant was seen in experimental or a third molar surgical model by Kim et al (90). Another candidate gene is GCH1, encoding for GTP-hydrolase regulating the synthesis-rate of tetrahydrodoprinoterin, where Tegeder and colleagues have shown that there is a reduced risk of persistent radicular low back pain in patients with a specific variant of GCH1, seen in 15.4% of the population. Again this finding was challenged by Kim et al who did not find the same protective association (or any other) in the third molar surgical model (91).

The initial encouraging results have been hard to reproduce, with associations at different SNP’s or phenotypes, gender differences etc (92), but is beyond the scope of this text (85). A review of the data on the importance of variation in the OPRM1 gene (encoding the my-opioid receptor), did not find any effect of the genotype with regards to opioid consumption or pain-levels and even in a highly selected analysis did they only find that 7% of the variance was explained by the genetic variation of OPRM1 (93).

Thus, it does not seem plausible that a single “pain-gene” can explain the variation in pain experience. The case may be that there is a large number of genes that each contribute to result in a given phenotype, each contributing with a small but measurable effect (e.g. pain). For this reason a new approach is necessary and is called Genomic-Wide Association Studies (GWAS) where the interaction and variation between millions of SNP’s are investigated (85). No available studies have examined the role of genetics during hernia surgery. However, as part of a prospective trial of predisposing factors for persistent postherniotomy pain (13), blood samples for genetic analysis have been collected and are currently being analyzed.

Age – several studies have suggested that with increasing age comes a reduced risk for persistent pain after surgery (26,94,95) . A major obstacle in interpretation is the lack of data on physical activity between age groups. The age related risk for persistent postherniotomy pain was investigated in the prospective hernia study by Aasvang et al. (13) where younger age was found to be significantly correlated to persistent postherniotomy pain when analyzed as a simple bivariate outcome (rho = -0.13, p = 0.009). However this effect disappeared in the logistic regression analysis (p = 0.21, OR 1.02 (0.99- 1.05)). The study gave a possible mechanism based explanation for the observed age effect, since correlation analysis showed that part of the age-pain effect may be explained from a lower pain response to noxious stimuli (47 degree heat) suggesting that with increasing age comes a less vigilant nociceptive function (13). This finding needs confirmation from other studies.

Gender - Hernia repair is in 90% of cases performed in men, however women may be at particular risk for persistent postherniotomy pain, if the findings in other pain conditions can be transferred to the hernia setting (96). A possible explanation for this gender difference in pain has been reviewed by Popesku et al. (97) who looked at gender differences in activation of the Diffuse Noxious Inhibitory Control system (DNIC) (98,99), where men were found to have better DNIC activation and thereby better pain-control than women. Bay-Nielsen et al. found that women operated for a groin hernia had an increased risk for persistent pain of 38%
compared with 28% in men (26). Similarly, in a retrospective study of 594 men and 56 women, 3% of males and 11% of female patients had persistent postherniotomy pain (100). A finding confirmed in another study from the Swedish Hernia Register (n = 1793), where 11.1% of men and 23% of women reported pain related impairment of activities (43). Thus there is a need for studies specific on pain in the female hernia patient population, regarding mechanisms and consequences.

Pre-operative pain - A relationship between preoperative pain and persistent postoperative pain has been found in herniotomy (13,44,101) and other surgical models including hysterectomy (102) and limb amputation (103). Assessing pain from the hernia area before operation is important for several reasons. Obviously, it is crucial to know in detail the intensity and frequency of preoperative pain, in order to assess how much has been caused or relieved by the surgical procedure, including the impact preoperative pain has on activities. Thus, although pain at the hernia area before surgery has been suggested as a predisposing factor for later persisting postherniotomy pain in several reviews (2,3,94), and supported by studies in other surgical procedures (5,95,104), most studies are either retrospective with the inherent recall bias, or only assess preoperative pain dichotomously (yes/no). However, a few detailed prospective studies do exist. Page and colleagues (105) found that patients with a preoperative (0-100) VAS score of 0 points had a 1.6% risk of pain a year postoperatively compared to a 4.8% risk in those who had a VAS score >10 (p<0,01), although one could argue that a difference of 10 points on a 0-100 scale may not be clinically relevant. Eklund and colleagues reported that pre-operative impairment in specific physical manoeuvres (climbing stairs, squatting, rising from bed) affected the risk of 5 year persistent pain in a multivariate analysis (11.2% vs. 19.2%, OR 1.86) (55). However, whether this was pain-related was not reported. Lien et al found that in a randomized controlled trial of open vs. laparoscopic repair in 994 patients, there was an overall 9.4% risk of persistent pain, and preoperative pain significantly increased the risk (OR 1.67) (78). In a prospective multifactor trial in 442 patients, preoperative pain related impairment independently predicted postoperative pain related impairment (p=0.004) (13).

Besides pain from the hernia area, pain from other body regions have been shown to correlate to the occurrence of persistent postoperative pain in general (95) and postherniotomy pain in particular (8,74), suggesting that a general pain alertness exists in certain individuals, putting them at risk for development of any kind of persistent pain. However, in a prospective study of persistent postherniotomy pain, preoperative pain from other body regions was seen in 33% of patients, but was not a significant factor either in a univariate analysis or logistic regression analysis (13), a finding that is in contrast to a prospective study in hysterectomy where preoperative pain from other body regions (e.g. low-back pain, headache etc) was significantly correlated to the existence of persistent pain (p = 0.004) (106). Identical data comes from a prospective study of persistent post-prostatectomy pain, where preoperative pain from “urological body areas” (not defined) as well as other areas where reported more often in those that went on to have pain 6 months after prostatectomy (107).

In conclusion, preoperative pain in the area to be operated upon predicts persistent pain and in some patients a generalized increased responsiveness to nociceptive input may exist. However, the underlying mechanisms are unclear, and the local and generalized sensory function in patients with and without preoperative pain needs further investigations and will be discussed in detail in later sections.

Nociceptive function - The above discussion of preoperative pain is closely related to evaluation of the preoperative nociceptive function and will be discussed later in the thesis.

Psychology - Due to the subjective nature of pain, it is should be considered highly relevant to study the effect psychological variables have on persistent postherniotomy pain. However, the only available prospective data comes from a cohort study by Aasvang et al. (13) where the relative role of anxiety and depression were examined by the Hospital Anxiety and Depression Scale, and pain coping strategies by the Pain Catastrophizing Scale. Before surgery 5.0% of patients had possible or definite depression, and possible or definite anxiety was seen in 9.7%. These rates were similar to the estimated background prevalence of 6.4 – 10.0% (108). When examined in an univariate analysis both depression and anxiety were significantly correlated.
to severe persistent pain related activity impairment 6 months postoperatively (p = 0.03, and p = 0.001, respectively). However, in a logistic regression model neither proved to be independent predictors for persistent postherniotomy pain. Neither pain coping strategies were predictive of persistent postherniotomy pain related impairment at 6 months. The relevance of psychological factors for development of persistent pain appears to be procedure related. Thus, in thoracotomy Katz et al. did not find a relation between preoperative anxiety or depression and the development of persistent pain, in 30 patients assessed by the Beck Depression Inventory and Spielberger State and Trait Anxiety Assessments (109). Maguire and colleagues did not find any correlation between the preoperative Hospital Anxiety and Depression Scale scores and 3 months persistent postthoracotomy pain in a population of 33 thoracotomy patients (110). The number of patients was small in both studies and larger prospective trials are required to make final conclusions. In contrast to hernia and thoracotomy, Tasmuth et al. found that in patients undergoing mastectomy, the rate of preoperative anxiety and depression were higher in patients with chronic symptoms (pain, paresthesia, strange feeling etc.) one year after surgery (111).

In conclusion, preoperative anxiety and depression may not play a major role in the development of persistent postherniotomy pain.

**Re-operation** - Several studies have shown that herniotomy for a recurrence has an increased risk for persistent postherniotomy pain of (2,3,8,43) The previous surgical trauma makes nerve identification difficult during the second open procedure potentially due to scar tissue and anatomical changes, increasing the subsequent risk of nerve entrapment and injury. An early operation for a recurrent hernia also inflicts a new nociceptive input in a region that may not have recovered from the primary operation, and thus is in a sensitized nociceptive state, with increased ascending pain facilitation. In conclusion, reoperation increases the risk of persistent postherniotomy pain, but the pathogenic mechanisms have not been investigated.

**Hernia size or type** - In a retrospective study of persistent postherniotomy pain in 355 patients, Courtney et al. reported that patients that did not recall having a palpable visible bulge before surgery had higher risk of pain at 6 months (p=0.001) (74). Later studies did not confirm that hernia size or type (femoral/medial/lateral/other) is of relevance to persistent postherniotomy pain. Kalliomäki et al. combined the Inguinal Pain Questionnaire and perioperative data from the Swedish Hernia Register in 1744 patients out of 2583 (72.1% response rate) and did not find a difference in hernia diameters over or under 3 centimetres or type of hernia (43) and the risk of pain, a finding confirmed by Alfieri et al. (112). However, Bay-Nielsen et al found a significant difference in the incidence of one year pain related activity impairment, between patients operated for an indirect and direct hernia ((9.7% (95% CI 7.4-12.5) vs. 13.0 (95% CI 10.0-16.5)). Thus, the hernia size may not be of major importance to the risk for persistent postherniotomy pain, but the role of the hernia type remains unsolved.

**Acute pain** - No factor has been as closely and consistently related to the development of persistent pain as the occurrence of high acute pain scores after various surgical procedures (95,104) and herniotomy in particular (13,61,113,114). Thus, in a prospective trial of 500 patients Callesen et al. (114) found that the risk of pain after 12 months overall was 19% with 6% reporting moderate/severe pain. Patients with high acute pain scores during the first week had a 9% risk of moderate/severe pain compared to a 3% risk in those with low acute pain scores. Aasvang et al. (13) found that for each increase in NRS point (0-10) on day 7 or 30 the risk of persistent postherniotomy pain increased by 27% and 28 % respectively, in a combined cohort of open and laparoscopically treated patients ( n = 442).

The key question regarding acute and persistent postoperative pain is whether there is a causal relationship, perhaps due to neuromuscular sensitization from intense postoperative nociceptive input, or it is merely the effect of the underlying mechanisms that also results in persistent pain (genetics, nerve entrapment).

In conclusion, the pathogenetic association between acute and persistent postoperative pain is not clarified. The role of acute hyperalgesia on the risk for persistent pain needs to be assessed and the effect of treating acute pain also remains unsolved.
Potential factors for persistent postherniotomy pain
Prediction of persistent postherniotomy pain

There are several studies showing that acute postoperative pain can be predicted by variable preoperative testing methods (115), but the available data from persistent postoperative pain is scarce (13,116,117). Yarnitsky et al. (116) tested the preoperative pain response to heat in thoracotomy and Lundblad et al. (117) evaluated the response to electrical stimulation before knee joint replacement surgery. Both found that the response to preoperative nociceptive stimulation contributed to the prediction of postoperative pain. In contrast, Bisgaard et al. did not find that the pain response to a cold pressor test predicted pain 1 year after laparoscopic cholecystectomy (118).

These studies did not test the robustness of the nociceptive response against other potential factors for persistent pain. In hernia surgery, only the study by Aasvang et al. (13) has investigated the relative role of postulated factors for persistent postherniotomy pain. Twenty-three predefined factors for 6 months persistent postherniotomy pain related activity impairment were analyzed in a logistic regression model in a cohort of 442 patients (95% follow-up). Four factors were independently related to the development of persistent pain related impairment in the primary analysis of both pre- and postoperative factors; the pain response to 47 degree heat stimulation, the preoperative modified AAS-score, pain on day 30 and the degree of sensory deficit between the pre-operative and postoperative warmth detection. If only pre-operative factors were analysed, the pain response to 47 degree heat stimulation, the preoperative modified AAS-score and the surgical technique were independent predictors for persistent postoperative pain related impairment (13) (see page 27 for further details on the predictive value of sensory testing).
Sensory function and dysfunction

Methodology in sensory assessment

Persistent pain is in itself a dysfunction, as the pain no more has relevance to bodily protection and behaviour modulation, the key features behind why we normally experience pain.

Based on the observations of sensory dysfunction from early on, postherniotomy pain has been suggested to be a neuropathic pain state (25,47). However, detailed sensory assessment is necessary to understand if sensory dysfunction is unique in pain patients or a common finding in all operated (11), to understand what role the peripheral and central nervous system plays in the amplification or inhibition of nociceptive input, and whether the localization of pain is cutaneous or coming from deeper structures. And ultimately to provide the basis for selection of patients for specific preventive interventions and mechanism based therapies.

As shown in table 2, there are more than 55 studies with information on inguinal heruiotomy and sensory function. However, the vast majority are of methodological poor quality and without details on what questions that were asked or how the patients were instructed, so that even though the results section states that “numbness” “dysesthesia” or the unspecific “sensory changes” was reported, interpretation and conclusions are impossible (28,47,119-122). The same is the case in the majority of studies that states that a physical examination was performed, where in most studies, only patients with complaints (in the questionnaire or at the telephone interview) were given the possibility of a physical examination, and no details is given on how sensory modalities were investigated (28,47,64,65,76-78,80,113,123-142).

However, as also shown in table 2, an increasing proportion of studies in groin hernia surgery have sound methodology with the use of Quantitative Sensory Testing (QST) (9-11,13-15,17,30,62,143-146). QST is a standardized, objective, scalable quantification of the central nervous response to activation of the peripheral sensory system. QST can assess and quantify various subsets of peripheral nerve fibers selectively (a-delta, a-beta, c-fibers etc) (147), but also allows testing of both positive- (hyperalgesia, allodynia) and negative- (hypoesthesia, anaesthesia) sensory dysfunction.

Furthermore, the occurrence of (central?) sensitization can be assessed through repetitive stimulation, to assess if there is new- or increased pain (temporal summation) and especially if there is continuous pain after cessation of stimulation (painful after-sensation) (148-150). QST should ideally be preceded by sensory mapping (or Qualitative sensory testing) to determine the area of sensory dysfunction, or with intact sensory function. Furthermore, the sensory mapping technique can quantify sensory deficits/hyperphenomena by measurement of the area of interest, allowing comparison with other patient-groups or within-patient assessment over time.

QST is a test of the whole neuroaxis, involving the 1, 2 and 3’rd order neuron as well as the whole central nervous nociceptive system, and therefore these tests cannot point to the anatomical location of dysfunction. Furthermore, QST is a concept rather than a strict uniform test, evidenced by the different testing protocols that exists (10,62,147,151-153), again making comparisons difficult. This issue has been addressed by the German Research Network on Neuropathic Pain (DFSN) where a testing protocol with instructions and training programme has been set up (154), in the hope to form a uniform platform for future QST trials. However, whether this is the ideal model or if it should be expanded or reduced needs to be investigated.

Furthermore, despite the appealing idea of a mechanism-based approach, it still needs to be shown that an effective treatment strategy or mechanism based definition of pain syndromes, can be formed from the findings from QST. When looking at table 2, there is an overwhelming trend in that the more basic sensory assessment is (i.e. questionnaires) the less sensory disturbances are reported, whereas QST finds sensory dysfunction in almost all patients. Until there is a study showing that the patients self-report of disturbances equals that found by QST, self assessment should be reduced to asking patients if they have experienced sensory disturbances that bothers them, but should not waste time questioning patients on sensory deficits in an attempt to assess the incidence and severity of sensory dysfunction. This should for now be restricted to studies with quantitative and/or qualitative sensory testing.
Preoperative sensory function

Four studies have documented that nerve injury (sensory dysfunction) is present in both pain- and pain-free patients operated on for groin hernia (25,59,62,155) (Table 2). Furthermore, preoperative hernia pain has been shown to be related to development of persistent pain (13,44,101), which may suggest that pre-operative hernia pain induces nociceptive neuroplastic changes that facilitates nociceptive signalling to the central nervous system (CNS) and ultimately leads to continuation of pain after surgery. Pre-operative neuroplastic changes are reported in other visceral pain syndromes (gallstone and appendicitis) (156-158), where sensory changes such as hyperalgesia in the painful or referred area are related to pain intensity. Thus, the hernia could potentially affect the preoperative peripheral sensory function in groin hernia patients, either due to the physical protrusion, causing stretching of the tissue or more likely from nociceptive induced neuroplasticity.

Evidence from Aasvang et al. shows that the preoperative peripheral sensory function is overall unaffected, in a preherniotomy study of 41 patients (17). The correlation between pain and sensory function in patients scheduled for herniotomy was assessed by a standardized QST protocol assessing large and small fiber function as well as temporal summation to repetitive stimulation (17). To stratify pain, a matrix combining pain and frequency was constructed, both for average and maximum pain reported by the patients. No correlation between any test (mechanical- or thermal detection or pain detection or pressure pain detection) and pain on the hernia side was found, with a trend towards hypoalgesia/hypoesthesia with increasing pain for all modalities. The sensory function on the contralateral side was also without correlation to pain intensity/frequency. Three patients (7.5%) experienced new pain during repetitive von Frey fiber stimulation, but again without any correlation to reported pain from the hernia. Besides the lack of correlation between pain and sensory function, the study showed that the two sides were highly identical with respect to sensory detection – and pain detection thresholds. Warmth and cold detection thresholds were significantly different, but the numerical differences were small (maximum 0.4 degrees Celcius) and the confidence intervals very narrow (less than 1 degree Celcius for detection and 1.5 degrees for heat pain detection). In general, the sensory function in the groin was remarkable robust and homogenous regardless of pain, not only reflecting inter-individual homogeneity, but also the robustness of the quantitative sensory testing protocol (18).

In a larger study (n = 442), testing the warmth- and heat pain detection thresholds (WDT and HPT) and response to a tonic 47 degree Celcius heat stimulation on the arm and groin, Aasvang et al. (17) found that preoperative pain was not associated with alterations in local preoperative nociceptive function in the groin. Thus, insignificant correlations between preoperative pain matrix score and WDT, HPT or response to a five second 47 degrees stimulation, were found (Rho<0.08, p>0.1 for all). The finding that the sensory function in the groin and arm were closely related (rho = 0.77, p<0.001) also supports that the preoperative pain does not cause local hyperalgesia (13).

Two other studies report data of pre-herniotomy sensory function. Mui et al. (143) assessed numbness by a questionnaire (none-mild-moderate-severe) in patients scheduled for ilioinguinal neurectomy during Lichtenstein’s herniotomy. Seven patients (7%) reported preoperative numbness, but no details on the relationship to pain were presented. Although sensory deficits were examined by von Frey fibers at the postoperative follow-up, this was not done preoperatively (143). Negro and colleagues (133) performed a physical examination in patients having sutured mesh repair or glue fixation, and found preoperative numbness in about 24% in the suture group vs. 13% in the glue fixation group. These two studies are methodologically problematic and firm conclusion can not be drawn from them. A histological study of nerves removed as part of a modified Lichtenstein’s procedure found “ilioinguinal neuritis” in 34% of cases (159). This was histologically seen as fibrosis with axon and myelin loss according to the authors, a finding also reported by others investigating nerves in relation to groin hernias in cadavers (160). Although intriguing, the study has several methodological problems that hinder firm conclusions. Firstly, this was not a protocolized trial, that is, only selected nerves were excised (80% of ilioinguinal nerves). Secondly, the neurectomy itself may have induced changes seen at the histological examination. Lastly there is no data on sensory function or pain, and therefore a correlation to pre-operative pain cannot be made. Thus, the local preoperative sensory function
found in groin hernia patients is intact, without any signs of pain-induced neuroplasticity or other changes when compared to the naive side. In this sense hernia patients do not exhibit the hyperalgesia seen in other pain syndromes (gallstone, migraine, appendicitis) (156,158,161-163). Compared to groin hernia pain, the pain intensity in gallstone disease and migraine are far more intense even resulting in referred pains (157) suggesting that neuroplastic changes may only occur during intense and/or prolonged and frequent pain. Patients with hernia pain of such intense character would normally undergo emergency surgery, and thus would be not included in the available investigations. Furthermore, the pain seen in appendicitis is caused by inflammation directly sensitizing nearby nociceptors (164) representing a different pathogenic mechanism than in hernia pain.

In conclusion: Sensory detection thresholds are unaffected by the hernia and/or the pain arising from it and there are no signs of peripheral nociceptive sensitization before surgery. Any changes seen in persistent postherniotomy pain must be related to the surgical procedure.

**Preoperative sensory function to predict pain - Heterogenic pain responses to uniform stimuli**

Although there is no evidence for local preoperative sensory changes in persistent postherniotomy pain, it has been shown by Aasvang and colleagues that a high preoperative pain response to a fixed nociceptive stimulus predicts patients at risk for persistent postherniotomy pain (13), presumably by testing the combined ascending/descending nociceptive function. Patients were given four 5-seconds 45, 46, 47 and 48 °C heat stimuli to the groin and arm (16 stimuli at each location). In contrast to the above-described small variation in detection thresholds, there was a large inter-individual variation in the pain response to heat stimulation. The response to the 47 °C stimuli was chosen due to more ideal normal distribution both from the groin and arm testing, but pain response to all four degrees (45-48 °C) where closely correlated (rho >0.8, For each NRS point the odds ratio for persistent postherniotomy pain was 1.34 (95% CI 1.15 - 1.57) (p=0.0002). Despite the 47 degree stimulus being a simple method it tests the complete nociceptive system, including peripheral nociceptors (c-fibers), first, second and third order neurons and pain modulation including the diffuse noxious inhibitory system (DNIC) (98,99), reflecting a more clinically relevant function than the simple thresholds testing. The finding that the responses to 47 degree stimulus to the arm or groin were closely correlated (rho = 0.77, p<0.001) shows that the pain response reflects a central mechanism rather than a peripheral sensitization. Furthermore, the finding that there was no significant correlation between preoperative pain and response to the 47-degree stimulus supports that the 47 degree response reflects a true inter-patient variation in pain perception rather than a reporting bias when using pain scales.

Further, support for the testing of the patients response to preoperative pain in prediction of persistent pain comes from Yarnitsky and colleagues, where testing of the DNIC system was shown to predict persistent post-thoracotomy pain (166). These findings from persistent pain studies are in accordance with the demonstrated correlation between acute preoperative pain response to a standardized noxious heat-, pressure or electrical stimulation and acute postoperative pain response after knee surgery, abdominal hysterectomy or caesarean section (155,153,165-168). In conclusion; although the preoperative pain response to a fixed noxious stimulus shows a wide inter-individual variation, it is not systematically affected by the preoperative pain intensity, suggesting that this is an inherent trait within the patient.
Table 3. Sensory function in patients before and after open and laparoscopic surgery

<table>
<thead>
<tr>
<th></th>
<th>open</th>
<th>laparoscopic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>warmth detect-groin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop.</td>
<td>36.1 [35.9 – 36.3]</td>
<td>35.6 [35.4 – 35.8]</td>
<td>0.001</td>
</tr>
<tr>
<td>postop.</td>
<td>41.1 [40.4 – 41.6]</td>
<td>35.6 [35.4 – 35.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ</td>
<td>5.2 [4.6 – 5.9]</td>
<td>-0.3 [-0.6 – -0.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>warmth detect-arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop.</td>
<td>35.8 [35.6 – 36.1]</td>
<td>35.8 [35.6 – 36.1]</td>
<td>0.9</td>
</tr>
<tr>
<td>postop.</td>
<td>35.9 [35.4 – 36.1]</td>
<td>35.5 [35.3 – 35.9]</td>
<td>0.08</td>
</tr>
<tr>
<td>Δ</td>
<td>0.1 [-0.2 – 0.4]</td>
<td>-0.3 [-0.6 – 0.1]</td>
<td>0.06</td>
</tr>
<tr>
<td>heat pain detect-groin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop.</td>
<td>46.0 [45.6 – 46.4]</td>
<td>46.0 [45.6 – 46.4]</td>
<td>0.9</td>
</tr>
<tr>
<td>postop.</td>
<td>48.6 [48.2 – 48.9]</td>
<td>46.6 [46.1 – 46.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ</td>
<td>2.4 [2.0 – 2.9]</td>
<td>0.5 [0.1 – 0.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>heat pain detect-arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop.</td>
<td>46.1 [45.6 – 46.5]</td>
<td>46.0 [45.6 – 46.5]</td>
<td>0.8</td>
</tr>
<tr>
<td>postop.</td>
<td>46.0 [45.5 – 46.3]</td>
<td>46.0 [45.6 – 46.4]</td>
<td>0.8</td>
</tr>
<tr>
<td>Δ</td>
<td>-0.2 [-0.6 – 0.2]</td>
<td>0.0 [-0.3 – 0.3]</td>
<td>0.5</td>
</tr>
<tr>
<td>pain 47 °C - groin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-op.</td>
<td>5.3 [4.9 – 5.5]</td>
<td>5.1 [4.7 – 5.5]</td>
<td>0.8</td>
</tr>
<tr>
<td>pain 47 °C - arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-op.</td>
<td>5.4 [5.1 – 5.6]</td>
<td>5.1 [4.7 – 5.5]</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Postoperative function

Early postoperative sensory function

Acute postoperative pain is correlated to and predicts persistent postherniomy pain (13,61,113,114), as described previously (see page 24). Information on acute postherniomy sensory function would benefit our understanding of why acute pain predicts persistent pain, and if it could be due to nociceptive plasticity. In a 20 patients pilot study of the role of DNIC on acute and postoperative pain and hyperalgesia after abdominal surgery Wilder-Smith et al. (169) reported that acute pressure hyperalgesia was seen more often (p=0.06) in patients who later reported pain at 6 months and at that time also had pressure hyperalgesia. However, the data are not clear as hyperalgesia was seen more often in the pain-free group at 3 months, and the surgical group consisted of various upper and lower abdominal and urogenital surgical procedures, making the findings intriguing, but inconclusive. No studies exist on the role of acute postoperative hyperalgesia and persistent postherniomy pain and hyperalgesia.

The only available detailed sensory data comes from a study by Aasvang et al. (144) where they compared sensory function between the operated and contralateral side by QST before surgery, one week after and 2.5 years postoperatively. The data is from an randomized clinical trial regarding the analgetic effect of intraoperative instillation of purified capsaicin (18).

When data from the operated groin in the available 16 control patients were analyzed separately, there were significantly decreased (P < 0.01) pressure pain threshold (PPT) (pressure hyperalgesia) on the operated side at the 1-week follow-up, and a significant increase (hypoesthesia) was seen for all other modalities (thermal and mechanical detection and pain detection thresholds both when compared to the pre-operative values and the 1-week data from the contralateral side. Sensory function was improved at the 2.5 year follow-up when compared to the 1 week data, but compared to preoperative values there were significant hypoesthesia and hypoalgesia to thermal and mechanical (von Frey) stimulation (p < 0.02 for all), but not cold pain thresholds due to a floor effect. Pressure pain detection threshold were significantly lower (hyperalgesia) at 2.5 years compared to preoperative values (p < 0.004).

Changes on the operated side were significantly correlated to sensory function on the contralateral side both in mechanical and pressure pain detection thresholds. Unfortunately, no prospective individual data on those patients with a painful and hyperalgesic late (2.5 years) outcome are available, hindering conclusions on the relation between acute and late hyperalgesia. Two other studies have reported less sensory dysfunction over time. In a questionnaire study, Vestaete et al. (79) found that 5% of patients reported paresthesia lasting less than 3 months, 20% had paraesthesia up to a year and in 13% par aesthesia lasted longer than a year. Grant et al. (170) found a similar trend in a study of 750 patients treated by Lichtenstein or TEP, where the incidence of numbness after Lichtenstein was 39.6% at 1 year and 25.7% at 5 years, and in TEP 18.8% at 1 year and 12.7% at 5 years.

In conclusion: inguinal herniomy results in acute cutaneous hypoesthesia and deep hyperalgesia with bilateral changes suggesting spinal nociceptive changes, and both phenomena are reduced over time. There is a need for studies into the role of acute hyperalgesia in the risk for persistent pain and hyperalgesia.

Late postoperative sensory function in pain-free patients

In order to fully understand the specific role of sensory dysfunction in patients with persistent postherniomy pain, information on the sensory function in pain-free patients is crucial. Table 2 shows that the majority of studies do not investigate the relationship between pain and sensory dysfunction, despite having investigated both parameters, and again showing the overall poor methodological quality, resulting in remarkable findings. For instance that despite having performed neurorctomies both Crea et al. (140) and Malekpour et al. (119) reported that not a single patient had sensory disturbances. However, when looking at the data from studies with better methodology and claimed examination (although not specified), there is a clear trend of sensory disturbances in both pain and pain-free patients with more frequent sensory disturbances in pain patients. Cunningham and colleagues reported that postoperatively numbness was not restricted to patients with persistent pain (25). Three-hundred-and-two patients were examined, although the details how are
not reported, and 52.5% of patients with pain had numbness, whereas this was the case in 40% of pain-free patients (25). Loos et al. (59) used a questionnaire to investigate various outcomes in 1766 patients and found a 44.6% incidence of “sensory disorder” (not detailed) in patients with persistent pain about three years postoperatively of pain and a 11.3% sensory disorder incidence in those without pain. Similar findings were reported by Verstraete et al. (79) where 23% of pain-free patients reported “paraesthesia” as opposed to 50% of pain-patients, or from Reinpold et al. (12) where the incidence for “sensory disorder” (a mix of paresthesia, numbness or foreign body sensation) were 48.9% and 10.6% in pain and pain-free patients respectively, 5 years postoperatively. Finally, Pierides et al. (67) found that sensory disorders (not detailed) were more frequent in pain vs. pain-free patients (23.1% vs. 7.3%). Despite these findings, there is still a remarkable high number (about 70%) of patients, both pain and pain-free, that has fully restored the sensory function after 6 months according to these studies.

Detailed quantitative sensory assessment in pain-free patients is available from only a handful of studies with the overall primary objective of investigating sensory function in postherniotomy pain patients and will be discussed later in that section (10,13,14,30,62). A study by Aasvang et al. (11) was dedicated to assessment of sensory function in pain-free patients and establishment of normative data for future research into individual sensory profiling (14). Forty pain-free patients unilaterally operated 2.1 (1-2.4) years before by Lichtenstein’s technique were investigated by a standardized QST protocol (10). Sensory mapping on the operated side showed 52% of patients had areas of cold hypoesthesia, 40% brush hypoesthesia, 35% pinprick hypoesthesia, 5% increased pinprick hyperalgesia and 5% pinprick hyperalgesia. Except for one patient, with bilateral hyperalgesia to pinprick, no other patients had sensory dysfunction on the contralateral side. The study showed that thermal thresholds were normally distributed but mechanical, pressure and pinch thresholds required log-transformation to achieve normal distribution. Cold pain and pressure tolerance were never normally distributed, not even after log-transformation due to a floor and ceiling effect respectively. When the two sides were compared, a significant increase in detection and pain thresholds (hypoesthesia/hypoalgesia) to cold, warmth, heat and mechanical (von Frey) stimulation were found on the operated side. Pressure and pressure tolerance thresholds were significantly lower (hyperalgesia) on the operated side compared to the contralateral. Pain thresholds on both sides were correlated and the standard deviation from the naïve side in pain-free operated patients, was much larger when compared to that of unoperated hernia patients (17). This suggest that the clinically irrelevant cutaneous hypoalgesia and deep hyperalgesia found in pain-free operated patients may sensitize contralateral neurons on a central nervous level, similar to what is seen other nerve injuries (171,172). However, there is little if no indication of central nociceptive hyperexitability in pain-free operated patients as evidenced by the finding that although repetitive 2 Hz stimulation with a von Frey fiber elicited pain in 15% (n=6) of patients (up to 45 out of 100 points on a VAS scale), pain ceased when stimulation stopped in all patients, and without after-sensations.

In conclusion, these findings show that hernia surgery leads to cutaneous hypoesthesia and hypoalgesia, but also deep hyperalgesia in pain-free patients. These findings are similar to those reported from other surgical models, including thoracotomy (173) mastectomy (174,175) and traumatic peripheral nerve injury after various surgical procedures (176). The reason why these patients do not experience pain despite having reduced pain thresholds is not clarified, but may be that a relevant pain stimulus like the pressure algometry does not occur in everyday life, or that these patients have a better inhibitory pain modulation than pain patients (177). The thresholds found on the naïve side were comparable to those reported by Rolke et al. (178) and from the naïve side in hip replacement surgery (179), with minor variations possibly explained by the differences in QST protocols. However, the findings from the operated side clearly shows that a pain-free operated control group is essential when sensory findings in persistent postherniotomy, and possibly also other persistent postoperative pain syndromes, are interpreted, and that reference data from an unoperated side should be used with caution. Assessment of sensory function should thus, not only compare side-to-side differences, adjusting for mirror-effects or generalized sensitization, but also perform individual characterization based upon normative data from the pain-free postherniotomy patients.
Late postoperative sensory function in persistent postherniotomy pain patients

Out of more than 55 studies that report sensory function in patients with persistent pain after groin hernia surgery (table 2), only 10 of these have detailed quantifiable information specific for pain and pain-free patients and will be the focus of the following section.

Group-to group comparison:
It is now well-established that pain patients compared to pain-free patients as a group not only have a higher incidence of sensory disturbances (10,62), assessed by sensory mapping, but also that the disturbances are more severe and includes positive phenomena such as hyperalgesia and temporal summation wind-up like pain. Three studies that describe the use of a QST, only have limited sensory information: Kalliomäki et al. (43) found significant higher incidences of sensory disturbances in 92 pain patients compared to 92 pain-free patients and with predominantly hypoesthesia to thermal stimulation and hyperalgesia to pinprick and pressure algometry. The study used sensory mapping and thus cannot present quantitative data. Mui et al. (143) assessed sensory function by von Frey fibers in patients having prophylactic ilioinguinal neurectomy during Lichtenstein’s hernia repair. However, there is no details on findings, but only that there was no difference in the incidence of sensation changes or loss (55.3% vs. 66.0%), despite the fact that half of the patients had a neurectomy. Beldam et al. (155) also investigated sensory function by von Frey fibers and as one of the few studies have defined mechanical detection and pain detection thresholds. However, again only incidences are reported and pain patients had hypoesthesia more frequently than pain-free patient in this study.

The first detailed QST study involving a combination of persistent pain patients and pain-free operated cohort, was reported by Mikkelsen et al. (62) where 20 patients with pain and 52 without pain were examined with a median follow-up of 9.3 months. Only the operated side was tested and data from a control area is not given in the article. Twelve pain-free patients (23%) were found to have hypoesthesia vs. 35% in pain patients (p>0.3), and allodynia was seen in 33% of pain-free vs. 50 % of pain patients. However, cutaneous detection thresholds were not different between the two groups when average values were compared, but pressure pain thresholds were lower (145 vs. 178 kPa) although also not significant. Pain patients had an increased pain response to dynamic stimulation both by brush and von-Frey fibers, but with very low pain score (2-5 out of 100). A methodological concern in this study is that the absence of sensory differences could be caused by the fact that pain patients only suffered from mild pain (median VAS 22, range 12-30), thereby not including those patients that may have more severe nerve damage and/or nociceptive sensitization. High pain intensity patients were selected in the study by Aasvang et al. (10) of 46 (nine bilateral and 37 unilateral operated) patients with moderate/severe persistent postherniotomy pain related functional impairment and ten pain-free controls. Sensory function was assessed by a standardized QST protocol. When the operated and contralateral sides were compared in the 37 patients with unilateral hernia operation and the pain-free controls, a significant hypoesthesia to cold, warmth, and mechanical (von Frey) and hypoaesthesia to heat stimulation was seen in both pain and pain-free patients. Both groups also had hyperalgesia to mechanical (von Frey) and pressure stimulation. When the relative differences between the two sides were compared (thus correcting for intra-individual variation and mirror-effects) between pain and pain-free patients, hypoesthesia to cold, warmth and tactile mechanical stimulation and hyperalgesia to pressure stimulation was confirmed, but not mechanical (von Frey) hyperalgesia and heat hypoalgesia. However, this study did not use log-transformed mechanical (von Frey) values and non-parametric testing with the invariable reduced sensitivity to differences performed statistical comparison. Pressure pain detection threshold was the stimulation most closely correlated to spontaneous pain reported by the patients, but just not reaching statistical significance (p=0.05).

An identical sensory distribution was seen when the similar group-to-group analysis was performed in 70 persistent postherniotomy pain patients and 40 pain-free hernia operated patients by Aasvang et al. (14). In this study mechanical (von Frey) and pressure modalities were log-transformed. Mechanical- and pressure pain thresholds were significantly lower (hyperalgesia) in pain patients and thermal thresholds were significantly increased (hypoesthesia-/algesia), when compared to values from pain-free patients.

Further support for nerve injury as a characteristic feature in postherniotomy pain, comes from the large-scale prospective study by Aasvang et al. (13) in 442 patients. By measuring the warmth detection thresholds
pre- and postoperatively, the study gave information on the relative role of nerve injury, measured as sensory dysfunction, in the development of persistent postherniotomy pain. A logistic regression analysis of 23 postulated patient- and surgery related risk factors showed that sensory deficit (pre- vs. postoperative warmth detection) was one of only four factors that survived the analysis as an independent predictor for significant pain related activity impairment 6 months postoperatively. For each degree Celsius of sensory loss in warmth detection, the risk for significant pain related impairment increased by 7% (OR 1.07, 95% CI 1.01-1.14, p=0.029), with a maximum sensory loss was 16 °C. When patients were divided into those with a good outcome (equal or less pain related impairment than before surgery) and those who favoured less well (more pain related impairment than before surgery), there was a significant increase in warmth detection (4.8 vs. 2.7 °C) and heat pain detection (2.5 vs. 1.5 °C) thresholds in patients with a poor vs. good outcome. Further analysis showed that changes in sensory function before and after surgery was local in the groin (mean WDT change 5.2 °C, and mean HPT change 2.4 °C) as seen by the robust intact sensory function on the arm (mean WDT change 0.1 °C, and mean HPT change -0.2°C) (table 3). These findings again show that changes must have occurred as a result of surgical trauma and not as part of a generalized alteration of the sensory system.

Individual characterization of pain patients
Several pain states shows signs of heterogeneous pain processing despite a common ethiology. This has been shown in persistent postherniotomy pain (14), postmastectomy pain syndrome (174), postthoracotomy pain (173,180) and postherpetic neuralgia (181). Thus, from the detailed sensory studies of persistent postherniotomy pain patients (10,62) there is an evident large inter-individual variation in sensory function on the operated side in pain patients (10) in contrast to the smaller variation in pain-free operated patients (10,11), and especially when compared to hernia patients before surgery (14), suggesting that the patient group may be heterogeneous.

Aasvang et al. used normative sensory data from 40 pain-free operated patients (11) to construct individual sensory profiles in a cohort of 70 persistent postherniotomy patients with moderate to severe pain, with the aim of identifying sensory-specific subpopulations.

The unique QST data for each patient was Z-transformed (182) which in turn allows comparison across scales and units. Any Z-score below “-2” and above “2” is statistically significantly different (+/- 2 standard deviations) from the normative material, which practically means that the specific sensory function for the specific patient being analyzed, is statistically significantly different from the group of pain-free operated patients. The patients were examined by QST on 11 different modalities, whereof 2 were not z-transformed (cold pain detection and pressure tolerance). From the z-scores it was found that 80% had hyperalgesia (5% to two or more modalities and 29% had uni-modal hyperalgesia) and 20% did not. The study showed that nociceptive heterogeneity exists for parameters where a group-to-group difference is not detected (heat pain detection) and where a difference was shown (mechanical pain detection). In the latter case, 37% had hyperalgesia, 6% hyperalgesia and 57% were not statistically different from the pain-free population. One in four (25%) of patients had a combination of significant sensory loss and hypersensitivity, suggesting that partial deafferentation and subsequent sprouting may have occurred or that c-fiber excitation inhibit the non-noxious input from the periphery on presynaptic spinal neurons (183).

Based on the responses to the individual sensory tests, patients were divided into those who only had cutaneous hyperalgesia (cold, heat, mechanical) (6%), only pinch (6%) only pressure (17%), combined cutaneous and pinch (3%), or combined cutaneous, pinch and pressure hyperalgesia (48%). These findings suggest that sensory assessment of cutaneous function may not be the right place to look, as pain may more likely origin from deeper structures. The study also shows that the degree of sensory hyperexibility is very variable, with some only having a slightly reduced pain detection threshold (Z = -2), whilst others had a severe sensory disturbance (Z < -8). However the degree of sensory dysfunction could not be related to pain intensity, evidenced by the fact that despite all having moderate to severe pain, 20% were within the normal range of sensory function seen in pain-free patients, showing that the QST protocol does not cover all the factors for pain processing, in particular it may not sufficiently assess central modulating mechanisms (177). Another important note is that the sensory profile is based upon assessment in one location. The possibility for other sensory profiles within the same patient and the same region is not described in
persistent postherniotomy pain, but should be investigated.

In conclusion, the persistent postherniotomy pain population consists of sensory subgroups with the involvement of cutaneous and deeper nociceptors, and may allow for mechanism- rather than aetiology based treatment. Twenty percent cannot be discriminated in sensory characteristics from pain-free patients, suggesting that factors not elucidated by QST play a vital part in the pain modulation.

Dysejaculatory pain

A special group within the persistent postherniotomy pain population is those who suffer from ejaculatory pain. Ten patients with severe pain related sexual dysfunction and dysejaculation were examined by QST and compared to 20 persistent postherniotomy pain patients without dysejaculation by Aasvang et al. (9). All dysejaculatory patients located their maximum pain to the external inguinal annulus. The general finding was thermal and mechanical hypoesthesia and pressure hyperalgesia in both groups. The groups differed when the operated sides were compared, with the dysejaculatory group showing significantly (62 vs. 151 kPa, p =0.002) lowered pressure pain- and tolerance detection thresholds. However, this effect was no longer present when the relative difference between the sides was compared. Wind-up like pain during repetitive pinprick stimulation was seen in 80% of dysejaculatory patients and 55% of controls, with 30% of dysejaculatory and 20% of controls reporting painful after-sensations more than a minute after stimulation had stopped. The conclusion was that dysejaculatory pain may be caused by a lesion to the vas deferens or nearby nervous structures. A hypothesis supported by the pathology seen during reoperations for persistent postherniotomy pain and dysejaculation (9,15). The combination of hypoesthesia, hyperalgesia and wind-up like pain, suggest this to be a neuropathic pain syndrome with central sensitization and is maintained by ongoing peripheral pathology.

Local or general – peripheral or central sensitization

The key question is of course what maintains pain and from where? The sensory finding from QST studies in postherniotomy pain clearly shows that there is a peripheral sensory dysfunction. However, the location of the continuous nociceptive input to the CNS is not clarified. It is well known from other pain conditions that pain sometimes occurs away from the lesion or pathological area/organ (referred pain) i.e. arm pain in a heart attack, or shoulder pain in gall-bladder pathology. The most obvious location in persistent postherniotomy would be periphery as this is where the initial trauma (the operation) is. The hypoesthesia and hyperalgesia to cutaneous and/or deep stimulation seen in 80% of patients (14) suggests that the pain is peripherally driven, perhaps due to ongoing ectopic activity in surgically injured neurons after transsections or entrapment by sutures or other material, or by ongoing inflammation from the mesh. Mesh related inflammation is well-known (40) and has been shown in pain and pain-free postherniotomy patients (41) and is known to sensitize neurons (35).

However, the QST findings, especially the wind-up like pain response (10,14,62), also suggest a central nervous component in persistent postherniotomy pain. When persistent postherniotomy pain patients were subjected to repetitive peripheral stimulation (temporal summation) 80% had new or increased pain (10) to pinprick and/or brush stimulation. However, increased/new pain to repetitive pinprick stimulation is also seen in pain-free operated patients, but only with moderate pain (VAS < 45 points), in contrast about 50% of persistent postherniotomy pain patients have a VAS ≥ 45 VAS points (14). Furthermore, continuous pain after stimulation cessation (painful after-sensations) is only found in pain patients where it is seen in about 15% (10,14). These phenomena may reflect a general and preoperative reduced pain inhibition or increased pain facilitation, or a constant peripherally driven nociceptive input that sensitizes spinal nociceptors (84).

The wind-up like response to cutaneous stimulation indicates a central nervous sensitization and is also seen in other surgical models of persistent postoperative pain such as amputation (185) and mastectomy (174). Further support for a central component/sensitization comes from the finding of bilateral changes in about 50% of unilaterally operated patients. Thus, in persistent postherniotomy pain, but also pain-free patients, it has been shown by Aasvang et al. (11,14) that changes on the operated side is accompanied with changes on the contralateral side, evidenced by the presence of sensory disturbances on the unoperated side and the correlation between sensory thresholds on the operated and unoperated sides (13,14,144). This suggests a mirror effect
where spinal changes due to peripheral stimulation are reflected on the contralateral neurons (186), a phenomenon also seen in other nerve injuries (171,172,187). Support for sensitization at the peripheral or spinal level comes from a study by Kupers et al. (145) of PET-scan evaluated cortical activation during repetitive stimulation of persistent postherniotomy patients. Wind-up like pain during repetitive stimulation in persistent postherniotomy pain patients was shown not to activate specific cortical structures other than what is seen in intensity matched tonic (pressure) pain stimulation. Thus, the mechanisms behind wind-up like pain must be spinal or peripheral.

It could be argued that the contralateral changes were due to a general rather than local sensitization, but the available data supports the regional effect, as seen in the study by Aasvang et al. (13), where patients with increased pain related impairment had local sensory dysfunction after surgery, but the control area on the arm was unaffected (table 3). The only study of bilateral and extra regional QST measurements and persistent postoperative pain comes from Nikolajsen et al. (179) where sensory mapping and QST were performed on both hips and the thenar in patients with or without persistent post-hip arthroplasty pain. The only difference between pain and pain-free patients were the higher incidence of pinprick hyperalgesia ($p = 0.02$) in pain patients, but mechanical hyperalgesia was not confirmed by QST and QST did not reveal any other differences between the two groups, when compared across the test sites. However, the study was small with 18 patients in each group.

Additional support for persistent postherniotomy pain being peripherally driven, albeit centrally modulated, comes from the finding that mesh-removal and selective neurectomy leads to reduced pain related impairment and pain-scores which is accompanied by development of hypoesthesia and reduced hyperalgesia (15).

In conclusion: Sensory disturbances are present in most patients after inguinal herniotomy, pain-free as well as those with severe pain. Preoperatively, sensory function is intact without signs of pain related neoplastic changes. In the acute postoperative phase, sensory function is more severely affected than later, where an incomplete remission towards preoperative values is seen. Pain-free patients as a group show signs of hypoesthesia to cutaneous stimuli, but a hyperalgesic response to pressure stimulation, a condition that also affects the contralateral side suggesting a spinal activation and neuromodulatory changes even without pain. Prospective data shows that the degree of nerve injury predicts persistent pain again clearly showing that sensory changes occurs as a result of surgery, and not from preoperative pain. In contrast to pain-free patients, pain patients show signs of a combination of hypoesthesia and hyperalgesia and central sensitization found only in this group. The pain is most likely of peripheral origin and related to deeper rather than cutaneous structures, due to ectopic nociceptor activity from surgically injured neurons or inflammation most likely arising from the mesh, but with central nervous sensitization. Furthermore, the hyperalgesic condition seems to be partly reversible evidenced by the combination of reduced pressure hyperalgesia and pain in patients with mesh removal and selective neurectomy. The combination of sensory loss and pain is essential in neuropathic pain (188,189), and according to definition (33,34) persistent postherniotomy pain should therefore be categorized as a neuropathic pain state.

34
Main sensory conclusions in persistent postherniotomy pain

- The preoperative sensory function is intact without signs of pain related neuroplastic sensory changes
- The preoperative heat pain response to 47 °C predicts persistent pain
- The degree of nerve injury predicts persistent pain
- Persistent cutaneous hypoesthesia and –algesia and pressure hyperalgesia is seen in pain and pain-free patients
- Sensory dysfunction is more pronounced in persistent pain patients vs. pain-free patients
- Unilateral nerve injury results in bilateral sensory changes
- Central sensitization primarily found in pain-patients
- Pain-patients are a heterogeneous group of sensory dysfunction with:
  - ~50% having combination of cutaneous and pressure hyperalgesia
  - ~15% having only cutaneous hyperalgesia
  - ~15% only deep hyperalgesia
  - ~20% no hyperalgesia
- Sensory function in pain-patients is partly restored by re-operation
Prevention of persistent postherniotomy pain

Hernia surgery is performed as an emergency procedure in case of incarceration or electively mainly due to pain, discomfort or for cosmetic reasons. Even in non-troublesome hernia, there may be indication for performing an operation as evidence suggests that a diagnosed hernia will eventually lead to pain or discomfort resulting in surgery in 50% of patients after 5 years, and in up to 70% of patients within 7.5 years (190). Thus, as the previous sections have shown that preoperative pain is an important predictor for persistent postherniotomy pain (13,44,101), this could imply that patients would either benefit from a pharmacological preoperative pain-reduction, which has not been proven so far (191), or from operation when the hernia is not painful. This strategy would be in disagreement with the idea of watchful waiting for minimal or asymptomatic hernias (57) where there is a low risk of incarceration (0.3%) (57,75,102,193). However, in all three studies operated patients reported a greater increase in quality of life than those in the watchful waiting group, and patients that crossed over from watchful waiting to repair, reported pain related impairment as the reason in 47% of cases (57). These patients had a 2-year incidence of persistent postherniotomy pain related impairment of 8.1% vs. 1.5% of those operated to begin with (57).

In combination with the prospective data on preoperative pain related impairment and subsequent pain-related impairment after 6 months by Aasvang et al. (13), these findings suggest that persistent pain could be reduced if the hernia was operated before pain is of such severity that it impairs function.

In conclusion: A groin hernia may be treated preferably before it becomes painful. The evidence for a positive effect of early surgery on the risk for persistent postherniotomy pain is not available and should be assessed in a prospective trial.

Nerve identification and handling

Three to four nerves transverse the surgical field in groin hernia surgery, depending on the surgical approach. Thus, in open repair the ilioinguinal, iliohypogastric and genitofemoral nerve, and in laparoscopic, also the lateral femoral cutaneous nerves are at risk. If one were to avoid nerve injury it would seem obvious to identify nerves before potentially putting them at harm by placing sutures, tacs or dissecting tissues. Due to the nature of surgery, injury of cutaneous sensory fibers and nociceptors is invariable and may induce pain and changes even on spinal level in animal models (38). An attempt should be made to identify major nerves that transverse the surgical field, and at least ensure that when a fixation is made (e.g. suture) this does not crush, ligate or otherwise injure a nerve. Again, this is challenging due to the variation in anatomical distribution, a finding reported as early as 1977 when Mosmann et al. reported that the ilioinguinal nerve had an aberrant origin, course and direction in 40% of 424 cadaver dissections. The sparse data supports the identification of nerves. Smeds et al. found that in a study of 525 patients, that non-identification of nerves was significantly associated with postoperative pain at 3 months. In a cohort of 895 patients (973 hernioplasties), there were no cases of moderate or severe pain in the 380 patients where all three nerves were identified, but in the 40 patients where all three nerves were transected there was a 10% incidence of moderate/severe pain at 6 months (p=0.02) (112).

Several large scale studies with data on the preventive effect of nerve transection on pain are available (table 2). The results vary with studies reporting less pain after transection, but also a paradox absence of sensory disturbances in nerve transected patients (126,140,143) raising questions about the study validity. In a prospective cohort study of 241 patients with open repair followed for 5 years, 16% of those with an ilioinguinal neurolysis had pain in contrast to only 1.4% of those without neurolysis (12). Picchio et al (194) found an incidence pain after 1 year of 27% vs. 23% in those with or without ilioinguinal nerve resection.

In conclusion: nerve identification should be attempted whenever possible, and nerves should be spared rather than transected.

Pharmacological prevention

Anesthesia and analgesia in relation to persistent postherniotomy pain may involve both the pre-, peri- and postoperative period. A widely appreciated hypothesis has been that of pre-emptive analgesia, where the main aim is to block/reduce a nociceptive input before it reaches the central nervous system, in order to reduce sensitization and pain. Brennan and Kehlet (191)
reviewed the data of pre-emptive anaesthesia studies and persistent pain, and found a discrepancy between acute and persistent pain studies. Most studies suffer from insufficient methodology, especially regarding the length of treatment resulting in the conclusion that pre-emptive analgesia remains controversial for the prevention of persistent postoperative pain (191). Since then the focus has shifted towards the concept of preventive analgesia, with a focus on the duration and efficacy of an analgesic, rather than the timing of administration (104,195,196). Thus, in a randomized study on persistent pain after abdominal surgery, Lavand’homme et al. found a superior effect at 6 and 12 months in patients treated with epidural analgesia administered before surgery, compared to patients treated with an epidural postoperatively (6 months 48% vs. 0%, and 12 months 28% vs. 0%) (197). However, the perioperative anaesthetic technique did not affect the development of persistent postherniotomy pain in a large Danish nationwide study by Bay-Nielsen et al. (26).

In a recent double blind randomized placebo controlled study in 240 patients (95% follow-up) scheduled for total knee arthroplasty. Administration of oral pregabalin 1-2 hours before surgery and 14 days postoperatively significantly reduced the incidence of neuropathic pain (0% vs. 5%), allodynia (0% vs. 8%) and hyperalgesia (2% vs. 11%) at 6 months, assessed by the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (198). A randomized double-blind study on the effect of a single dose of preoperative gabapentin on persistent postherniotomy pain, showed significantly lower NRS pain scores at 6 months compared to placebo (p<0.05), but the pain scores were very low (NRS 1 vs. 2) and no difference in postherniotomy pain related impairment were seen at 6 months (incidence not reported) (199).

Numerous other studies, however, have failed to show the same effect of preventive analgesia, raising the question why the concept works in some conditions and patients and not in others (104,191,200,201).

A potential reason may be that in surgeries with preoperative pain such as herniotomy, the nociceptive sensitization has already occurred making preventive analgesics less effective, although this is not supported by pre-operative QST data (17). Furthermore, if there is continuous peripheral nociceptive input after the analgesic treatment is stopped, for instance from mesh-related inflammation (40), the neuroplastic changes leading to persistent pain will occur hereafter, implying that pharmacological treatment should be given for a substantial period (198).

Large epidemiological studies have show that there is no difference between general, local or regional anaesthesia with regards to the risk for persistent postherniotomy pain (26,43,112). However, regional anaesthesia is not warranted for groin hernia repair due to the potential for urological adverse events (202).

In conclusion, there is no available data to recommend a specific analgesic regimen in herniotomy with regards to the risk for persistent postherniotomy pain. Future trials should target patients with increased preoperative risk for persistent postherniotomy pain, for intense pre, peri- and postoperative multimodal pain treatment, to assess if this reduces persistent postherniotomy pain.

**Surgical technique**

The current evidence suggests that a laparoscopic approach is superior to an open with regards to the risk for persistent postherniotomy pain (2,3,13,43,46,203-205). There is a general trend towards lower reports of pain in small scale studies and/or studies without pain as the primary outcome, some even reporting no pain in either laparoscopic or open repair. (2,3). Larger studies (>300 patients) and studies designed to assess pain by pain-scales or questionnaires (3,13,203,205) report lower incidences of persistent postherniotomy pain after laparoscopic repair and with incidences of pain after open repair similar to what has been shown in epidemiological studies. However, a single high volume study (n=1696) failed to find a difference in pain or pain related impairment from two weeks and until two years postoperatively between laparoscopic and open hernia repair (206).

The main hypothesis is that laparoscopic surgery is a less traumatic procedure, especially with regards to cutaneous injury. Laparoscopic repair still has a risk for persistent postherniotomy pain, although lower than in open repair (207). Studies suggest that the mesh fixation technique may play an important role, since sutures, tacs or clips may entrap a nerve, whereas fixation by fibrin glue or self-gripping meshes may not. Aasvang et al. (13) showed that laparoscopic repair with glue fixation of the
mesh, resulted in significantly less nerve injury (change in warmth detection threshold) than open, Lichtenstein, repair (relative change in WDT -0.3 vs. 5.2 °C, p<0.001) (table 3). Furthermore, logistic regression data were used to construct preoperative risk estimates for persistent postherniotomy pain. The analysis showed that patients with high preoperative pain response to 47 degree heat stimulation and a high level of preoperative pain related impairment, had a theoretically 30 % (63% vs. 43%) reduced risk for pain if they were operated by the laparoscopic rather than open technique. In low risk patients there were no difference between the two surgical techniques with regards to the risk of persistent postherniotomy pain techniques.

An early criticism of the superior results from the laparoscopic technique with regards to persistent postherniotomy pain was that laparoscopic repair was performed by more experienced surgeons performing. However, the prospective trial by Aasvang et al. was performed in two expert centres and laparoscopic surgery had a more favourable outcome than open repair (13). Further evidence for the role of surgical technique itself being important for the risk of persistent pain rather than expertise, comes from a randomized trial of persistent pain after Lichtenstein groin hernia repair by surgeons-in-training versus a specialized surgeon, where the trainee group had 21.3 % incidence of persistent postherniotomy pain and the expert group 37.1% (p=0.01) (56).

In conclusion, laparoscopy surgery leads to less persistent postherniotomy pain due to less nerve injury, and this may even be more pronounced in high-risk patients.
Treatment of persistent postherniotomy pain

Little data exists on postherniotomy pain related use of healthcare resources, but Aasvang et al. (8) reported that only 38 (8.3%) of 456 patients with persistent postherniotomy pain had consulted a physician because of the pain, and that analgesics had been used by 35 (7.7%). Patients with pain related sexual dysfunction are even more reluctant to consult a physician, evidenced by the fact that only 18 (8.0%) of the 224 patients had seen a physician, but 86 (38.4%) wished to be contacted an interview regarding the sexual dysfunction. A similar finding was also reported by Kalliomäki et al (43), where only 2% of patients took analgesics despite 30% reporting persistent postoperative pain, suggesting that choose patients to reduce their activity level rather than take analgesics.

Pharmacological treatment

No specific therapy for persistent postherniotomy pain exists, and thus patients should be treated according to the general recommendations for treatment of neuropathic pain (208,209). However, persistent postherniotomy pain represents a unique model for assessment of mechanism based therapeutic trials due to the possibility of classification based upon QST-results.

Surgical treatment

Firstly, acute intense pain immediately after surgery, or after the effect of any local anaesthetic has resided, should always be suspected to represent nerve entrapment and the need for an acute exploration should be considered.

Various invasive procedures have been attempted to accomplish pain relief in persistent postherniotomy pain. A non-destructive method is pulsed radiofrequency stimulation, where the mechanism behind pain relief remains debatable but is suggested by some to be through activation and upregulation of the c-Fos gene (210). Two small case series of pulsed radiofrequency stimulation of nerve roots achieved 75-100% pain relief lasting at least 6-9 months, was reported by Rozen and Parvez (n=5) (211) and Cohen and Foster (n=3) (212).

Several studies have suggested re-operation with neurontomy and/or mesh removal to be a potential treatment for persistent postherniotomy pain with success rates ranging from 0 to 100%, but the lack of methodology and follow-up has precluded conclusions (16) . Based on the fact that patients were treated with an operation without any evidence for effect and the potential for further harm, a study of selective neurectomy and mesh removal was undertaken, recruiting 21 patients with severe pain related activity impairment after hernia surgery (15). Patients were assessed by the modified AAS and SF-36 questionnaire and QST before and after surgery. A total of 58% had the mesh twisted and adherent to the funicle. Moreover, in 19 patients (90%) the ilioinguinal nerve could be identified, where it was entrapped in sutures or a mesh conglomerate in 16 cases. The iliohypogastric nerve could be identified in 10 patients (48%), with entrapment in nine of these cases, and the genitofemoral nerve could be found in only six patients (29%) where it was entrapped in four cases. On a group level there was a significant improvement in pain-scores and activity (as assessed by the modified AAS score) at the 3 and 6 months follow-up. A subanalysis showed that three patients had worsened, five reported no improvement and 13 experienced less pain related impairment of everyday activities. The postoperative pain and physical-related components of the SF-36 also showed significant improvement compared to preoperative values. Use of analgesics was also reduced. Five used opioids and one pregabalin preoperatively, which was reduced to three using opioids at the six-month follow-up. Four cases of dysejaculation were resolved by the reoperation, but two new cases were also seen. Importantly, pain and pain-related impairment was accompanied by changes in nociceptive function. Warmth, cold and mechanical detection- and pain detection thresholds, as well as pressure pain detection thresholds, showed significant changes towards hypoesthesia and hypoalgesia, but patients with an outcome worse than before the operation had significantly less normalization of pressure thresholds compared to patients with a neutral or improved outcome. The same trend was observed after repetitive stimulation where nine patients reported increased pain and two patients had painful after-sensations. Postoperatively, five patients still had wind-up like pain whereas none had painful after-sensations. None of the preoperative sensory tests significantly predicted the 6 month outcome, but patients with wind-up like pain during repetitive stimulation had a trend towards a less favourable outcome. Despite these
encouraging results, that have since been reproduced by other groups (16,213) the main worry is that the surgical pain may reoccur and even increase as seen in other pain conditions (214). Thus, in a study on the effect of tailored neurectomy for persistent postherniotomy pain, 16% of patients reported that the operation worsened pain (215), corresponding to the 14% found by Aasvang and Kehlet (15). The mechanism and hypothesis behind neurectomy is removal of the peripheral “pain-generator”, either due to inflammation caused by the mesh, or from the partial nerve lesion from a cut, crush or entrapment.

In conclusion: Neurectomy may be an effective treatment for persistent postherniotomy pain in the majority of patients, but data from other pain conditions warrants care in assuming a long-lasting effect, why large-scale trials from dedicated centres need several years of follow-up. The main focus should be to identify predictive factors for a positive and especially a worse outcome, where QST may be valuable as a predictive tool.
Perspectives

Despite the conclusions on nerve injury as a prerequisite for persistent postherniotomy pain and the indirect evidence for nociceptive sensitization, this thesis also raises a number of questions regarding the need for future studies to increase the knowledge and subsequent possibility for treatment and prevention of persistent postherniotomy pain. Quantitative sensory testing has revealed a number of sensory characteristics in this pain syndrome, but the heterogeneity of the pain patient population also shows the shortcomings of QST, evidenced by the 20% sensory overlap between pain-free patients and those with persistent postherniotomy pain. Thus, as suggested by the commentary by Giber and Barkley (216) to the article of heterogenic sensory function in persistent postherniotomy pain by Aasvang et al. (14) there is a need for additional investigations beyond QST.

Deep sensory function assessment
One way forward may be to include direct assessment of the sensory function and especially sensitization of deeper structures than the skin. This may imply invasive methods such as heat probes that allow quantification of warmth and heat pain thresholds as well as responses to tonic stimuli with comparison to cutaneous sensory function. Such studies may elucidate the relationship between deep nociception, spinal modulation and cutaneous referred pain.

The role of inflammation
The sensory investigations may be supplemented by microdialysis to assess the occurrence of inflammation by measuring inflammatory mediators (217), which so far has only been shown directly in animals and indirectly, by radiology, in humans. The relation between inflammation and sensory function, especially sensitization should be explored. The studies should again include persistent postherniotomy pain patients as well as pain-free patients.

Nerve injury
The potential for phenotypic switching and/or receptor modulation in injured nerves may occur (35) and could be investigated in patients where a neurectomy is performed for treatment of postherniotomy pain, thus expanding the understanding of peripheral and central nociceptive sensitization and the potential for a mechanism targeted treatment.

The role of peripheral vs. spinal sensitization
This could also be investigated by ultrasound guided blockades and/or regional anaesthesia, thus revealing if the disease is related to the primary- or secondary neuron or both. Furthermore, the observation that pain occurs or intensifies after several months in some patients (12,39) suggests that these patients may have a time dependent loss of ascending inhibition, a theory that could be challenged by administering opioid receptor antagonists.

Acute vs. late hyperalgesia:
Based on the established fact that acute pain correlates and predicts persistent pain, future studies should investigate the sensory characteristics of acute pain and their role in persistent pain, thus forming a mechanism based strategy for intense analgesic treatment in patients at risk for persistent pain.

Prevention and treatment:
The effect of an early operation, i.e. before the hernia becomes painful, or the effect of minimizing the preoperative pain on the risk for persistent pain reduction needs to be explored. Also, the promising results from re-operation for persistent pain should be expanded and confirmed in other large scale studies, with the aim of identifying those that have a risk of further pain intensification from the re-operation, thus resulting in a safe surgical procedure. The long-term effects should be monitored in detail. Similarly, the results from QST assessments should be used to allocate patients to treatment trials to test the usefulness of QST-findings in selecting those that may benefit from a certain treatment. For instance, a trial of the effect of a topical treatment of lidocaine or capsaicin patches should include patients with- and without signs of cutaneous hyperalgesia.

The theoretical effect of laparoscopic surgery for minimizing the risk of persistent postherniotomy pain in high-risk patients should be confirmed in a randomized trial where both high risk- and low-risk patients are randomly allocated to Lichtenstein’s or laparoscopic surgery with mesh-glue fixation.
Summary
The aim of this thesis has been to describe clinical and neuropsychological outcomes in patients with persistent postherniotomy pain, and draw evidence based rational conclusions on areas where future studies should be focused. The impact persistent postherniotomy pain has on everyday life is well described showing that this is a pain syndrome with adverse personal consequences (8,9). Data on the socioeconomic burden are lacking and could further encourage research into preventive and treatment strategies. The studies show the need in future trials for clinically relevant outcomes on the impact pain has on everyday activities. Preoperative sensory function is intact with respect to detection thresholds and absence of central sensitization, and it is not affected by pain from the hernia. Pain responses to a fixed 47 °C stimulation display normal distribution, but again is not correlated to pre-operative pain (13). The pain response to the 47 °C is an independent predictor for pain after 6 months with about 30% increased risk per pain point reported (0-10 possible points). Other significant risk factors for persistent pain related impairment include intensity of pre-operative pain-related functional impairment and choice of surgical technique, with less pain after laparoscopy than after Lichtenstein’s repair. Postoperative independently significant variables are pain intensity on day 30 and the degree of nerve injury assessed as the difference between preoperative and postoperative warmth detection thresholds. For each degree of sensory loss (maximum 16 degree loss) the risk for persistent pain is increased by 7%. Even though low risk patients do not seem to have a different outcome depending on the surgical procedure, high-risk patients may have a reduced risk for persistent pain of 30% if operated by a laparoscopic technique rather than by an open repair. This finding needs to be confirmed in a randomized clinical trial. Sensory dysfunction is more severely affected in the acute postoperative phase and only partly restored when assessed years later (14), but more data is needed on the importance of acute hyperalgesia. The late sensory function is significantly affected in operated pain-free patients (10,14) including signs of neuroplastic changes on a spinal level, evidenced by the correlated bilateral changes in sensory function (14). However, sensory function is more severely affected in patients with persistent postherniotomy pain than in pain-free patients, with deep rather than cutaneous hyperalgesia being the focus for pain.

Furthermore, persistent pain patients have central nervous sensitization with wind-up like pain and regional but not general bilateral sensory changes (13,14). This implies that the treatment and future studies should target the function of deep nociceptors, and their role on spinal and cutaneous nociceptive function. Despite a uniform trauma, individual characterization of patients shows heterogeneous pain processing (14), and that 20% of patients cannot be discriminated from a pain-free population by QST, suggesting that QST should not stand alone, but methods for investigating more central nociceptive activation should be investigated. The heterogenous response has evident implications for treatment trials, as it allows for a mechanism-based stratification of patients. Evidence based pharmacological treatment specifically effective in persistent postherniotomy pain is not available, but surgical exploration with or without neurectomy and/or mesh removal seems promising (15). However, it carries the risk for increased pain in a minority of patients and methods to identify those at risk should be investigated. Furthermore, the permanent effect of surgery for persistent postoperative pain needs to be established before it can be recommended as a routine procedure.

In conclusion: inguinal herniotomy results in a neuropathic pain state with pain related impairment of everyday activities occurring in 5-10 percent of patients.
Dansk resumé

Smerter, der hæmmer hverdagsaktiviteter, forekommer hos 5 til 8% procent af patienterne mere end et halvt år efter lyskebrokoperation (herniotomi). Operationen foretages årligt på ca. 2800 per million indbyggere i den vestlige verden. Dette medfører at der i Danmark, Storbritannien og USA årligt påføres vedvarende smerter hos henholdsvis 600, 3.700 og 34.000 patienter. Således er vedvarende postherniotomi smerter ikke kun en personlig ulykke for den enkelte patient, men udgør ligeledes et socio-økonomisk problem, da de kan medføre tab af arbejdsveje og øgede sundhedsudgifter.

Vedvarende smerter efter lyskebrokoperation er ikke veldefinerede, men bør mistænkes, hvis: 1. der er opstået smerter efter operationen 2. smerter er intensiveret og/eller har skiftet karakter, lokalisation eller hyppighed efter operationen, 3. smerter har varet mere end 6 måneder efter operationen, og 4. der ikke er andre årsager til smerten.


Patienter med vedvarende smerter efter lyskebrok operation har hyppigere og alvorligere tegn på nerveskade end patienter uden smerter. Dog er det ikke nerveskaden alene, som definerer smerter, da nerveskade i form af nedsat og/eller ændret

Forebyggelsen af smernerne bør begynde allerede ved erkendelsen af lyskebrok, og tendensen er i dag, at man bør operere tidligt, da de fleste patienter alligevel ender med operation. Dog er der ikke data på hvorvidt en tidlig operation mindsker risikoen for vedvarende smerner. Under operationen bør man forsøge at identificere nerverne i området og skåne dem, da der ikke er evidens for at overskæring af nerver mindsker risikoen for sene smerner. Ligeledes er der ikke evidens for anvendelse af såkaldt præ-emptiv analgesi, men dette skyldes muligvis at behandlingen har været for kortvarig og effekten af længevarende behandling med centralt virknende smertestillende midler bør undersøges hos risiko patienter.

Der er ikke data, der kan retfærdiggøre specifik medicinsk behandling af vedvarende smerner efter lyskebrokoperation, og indtil videre må disse patienter behandles efter de gængse retningslinier for kroniske smerner, men denne gruppe bør undersøges nærmere for at optimere behandlingsstilbuddet. Derimod er der en gavnlig effekt af at fjerne nettet og evt. nerver, der er kommet i klemme i arvæv eller suturer hos udvalgte patienter med svær smertebetinget hæmning af deres hverdagsaktiviteter. De umiddelbare positive resultater bør dog følges nøje, da tidligere forsøg på operativ behandling af andre smertetilstande ikke har haft vist samme positive langtidseffekter.

Operation for lyskebrok medfører en risiko for udvikling af vedvarende smerner, der kan påvirke både hverdagsaktiviteter og seksualfunktion i svær grad. Risikoen er højest hos patienter med et øget smerterespons og smerner før operationen samt ved nerveskade under operationen. Højrisikopatienter kan identificeres, og betydningen af at operere dem med en teknik med minimal risiko for nerveskade bør undersøges for at reducere antallet af patienter, der invalideres. Der er ligeledes et behov for at identificere og udvikle behandlingsstilbud til de patienter, der trods forebyggende tiltag alligevel påføres disse smerner.
Comments and corrections to tables and articles

1. The term "tactile" is used in several of the articles when a stimulus was applied by von Frey fibers. The correct term is "mechanical" and will be used in the thesis.

2. In the article "Aasvang, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. Acta Anesthesiol Scand. 2010;54:291-8" there is an error in table 1, where "painful" should have been "operated"

3. In the article "Aasvang, Mohl B, Kehlet H. Ejaculatory pain: a specific postherniotomy pain syndrome? Anesthesiology 2007;107:298-304." there is an error in the methods section, on page 299, second column, line 22, where the algometer neoprene tip was reported to be "0.18 cm²", but the correct size is "1.0 cm²". A correction letter has been sent to Anesthesiology, and a Corrigendum will be made according to the editorial office.

4. In the article "Aasvang EK et al. Neurophysiological characterization of postherniotomy pain. Pain 2008;137;173-181." there is an error in the methods section, on page 175, second column, line 20, where the algometer neoprene tip was reported to be "0.18 cm²", but the correct size is "1.0 cm²". A correction letter has been sent to Pain, and a Corrigendum will be made according to the editorial office.

5. In the article "Aasvang, Mohl B, Kehlet H. Ejaculatory pain: a specific postherniotomy pain syndrome? Anesthesiology 2007;107:298-304." there is an error in the methods section, on page 175, second column, line 20, where the algometer neoprene tip was reported to be "0.18 cm²", but the correct size is "1.0 cm²". A correction letter has been sent to Pain, and a Corrigendum will be made according to the editorial office.

6. In the article "Aasvang, Mohl B, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. Acta Anesthesiol Scand. 2010;54:291-8" there is an error in the methods section, on page 298, first column, line 12, where the pressure algometer neoprene tip was reported to be "0.18 cm²", but the correct size is "1.0 cm²". A correction letter has been sent to annals of Surgery, and a Corrigendum will be made according to the editorial office.

7. In the article "Aasvang et al. Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010; 112:957–69" there is an inconsistency on page 965, second column, line 16, between the confidence intervals and figure 2 and 3. The text reads: "approx. 30% vs. approx. 70% (95% CI 0.1-0.6 vs. 0.35-1.0, P = 0.05) after laparoscopic versus open repair, respectively." Upon recognizing this error, the calculations were redone and the figures were correct, but the text should now read: "43% vs. 63% (95% CI 0.22-0.67 vs. 0.38-0.83, P = 0.04) after laparoscopic versus open repair, respectively." The new numbers show that the relative reduction is reduced from 57% to 31%, however the correct p-value of 0.04 shows that this finding is robust, more so than the previously stated p<0.05. The other data, including the assessment of the predictive potential (power), in the article are not affected. A correction letter has been sent to Anesthesiology, and a Corrigendum will be made according to the editorial office.

8. In the article "Aasvang et al. Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010; 112:957–69", the AAS scale was inverted compared to the original article on the AAS. This was due to an error in the formula supplied by the author of the original article (personal e-mail), for transforming raw data to the 0-100 scale. Thus 0 = no impairment and 100 = maximum impairment.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Primary endpoint</th>
<th>FU</th>
<th>Sensory finding</th>
<th>Sensory assessment</th>
<th>Post-op pain</th>
<th>Sensory findings in relation to pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu, 2008</td>
<td>100</td>
<td>pain at 6 mo.</td>
<td>any discomfort</td>
<td>any numbness and allodynia</td>
<td>QST</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Aasvang, 2009</td>
<td>36</td>
<td>occurrence of hypalgesia</td>
<td>NRS score &gt; 2/3</td>
<td>Sensory finding</td>
<td>QST</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Aasvang, 2009</td>
<td>41</td>
<td>pain and numbness</td>
<td>NRS score &gt; 6</td>
<td>Sensory finding</td>
<td>QST</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Aasvang, 2010</td>
<td>242</td>
<td>identification of risk factors for pain related impairment</td>
<td>AA-score &lt; 26.2</td>
<td>Sensory finding</td>
<td>QST</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Aasvang, 2010</td>
<td>19</td>
<td>case description</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Harms, 1994</td>
<td>2</td>
<td>case description</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Cornet, 1994</td>
<td>60</td>
<td>complications to hernia</td>
<td>NRS 21</td>
<td>Sensory finding</td>
<td>interview</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Cunningham, 1996</td>
<td>292</td>
<td>pain and numbness</td>
<td>any pain</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Cunningham, 1996</td>
<td>25</td>
<td>any pain</td>
<td>any pain</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Tuntupl, 1998</td>
<td>15</td>
<td>not defined</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Tuntupl, 1998</td>
<td>18</td>
<td>not defined</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Pagsanjan, 1999</td>
<td>15</td>
<td>not defined</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Pagsanjan, 1999</td>
<td>128</td>
<td>not defined</td>
<td>not defined</td>
<td>Sensory finding</td>
<td>questionnaire</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
<tr>
<td>Wiesner, 2000</td>
<td>141</td>
<td>not defined</td>
<td>134</td>
<td>Sensory finding</td>
<td>not defined</td>
<td>no data</td>
<td>Lichtenstein +/−, Groin pain and sensation of electrical shock like pain aggravated by extension of leg and relieved by flexion.</td>
</tr>
</tbody>
</table>

Table 2: sensory function in persistent postherniotomy pain.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study Details</th>
<th>Population</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bay-Nielsen</td>
<td>2001 (202)</td>
<td>Incidence of pain in 1 yr post-operatively</td>
<td>any pain</td>
<td>Pain questionnaire</td>
<td>12% at rest, 20% during activity</td>
</tr>
<tr>
<td>Poobalan</td>
<td>2007 (42)</td>
<td>Frequency and characteristics of pain</td>
<td>any pain</td>
<td>Pain questionnaire</td>
<td>46% neuropathic pain, 21% non-neuropathic pain</td>
</tr>
<tr>
<td>Verstraete</td>
<td>2003 (79)</td>
<td>Not defined</td>
<td>undefined</td>
<td>Pain questionnaire</td>
<td>Postop: 13% paraesthesia &gt; 1 yr, 20% paraesthesia &lt; 1 yr</td>
</tr>
<tr>
<td>Hindmarsh</td>
<td>2003 (125)</td>
<td>Severity of pain</td>
<td>any pain</td>
<td>Chart review</td>
<td>Tenderness at pubercle or scar</td>
</tr>
<tr>
<td>Malekpour</td>
<td>2003 (119)</td>
<td>Pain after ilioinguinal nerve excision</td>
<td>NRS ≥1</td>
<td>Pain questionnaire</td>
<td>No pain or sensory changes in either group</td>
</tr>
<tr>
<td>Bell</td>
<td>2003 (76)</td>
<td>Effect of staples on recovery, pain and recurrence</td>
<td>not described</td>
<td>Exam</td>
<td>0.5% numbness</td>
</tr>
<tr>
<td>Brinckman</td>
<td>2003 (136)</td>
<td>Time to recovery</td>
<td>not defined</td>
<td>10% Lichtenstein 3% TEP 4% mesh-plug</td>
<td>Sensory loss (Lichtenstein) 1% sensory loss, 1% hyperesthesia (mesh-plug)</td>
</tr>
<tr>
<td>Douek</td>
<td>2003 (77)</td>
<td>Complications to herniotomy</td>
<td>not defined</td>
<td>10% Lichtenstein 2% TAPP</td>
<td>23% numbness (Lichtenstein) 3% numbness (TAPP)</td>
</tr>
<tr>
<td>Liem</td>
<td>2003 (78)</td>
<td>Complications to herniotomy</td>
<td>&quot;pain in groin, scrotum or thigh&quot;</td>
<td>14% open 5% TAPP</td>
<td>No detailed information, but at least 12.3% with sensory disturbance.</td>
</tr>
<tr>
<td>Anderson</td>
<td>2003 (138)</td>
<td>Costoperative pain in Lichtenstein vs. TEP</td>
<td>NRS ≥1</td>
<td>26% Lichtenstein 18% TEP</td>
<td>44% Lichtenstein 10% TEP</td>
</tr>
<tr>
<td>Muldoon</td>
<td>2004 (80)</td>
<td>Complications to herniotomy</td>
<td>not defined</td>
<td>6% Lichtenstein 9% Read-Rives</td>
<td>10% Lichtenstein 12% (Read-Rives)</td>
</tr>
<tr>
<td>Ditteck</td>
<td>2004 (129)</td>
<td>Neuralgia and paraesthesia</td>
<td>NRS ≥1</td>
<td>Interview or Chart review</td>
<td>11% (resected) vs. 8% (preserved); paraesthesia severity (0-10); 3.5 vs. 4.0 (resected vs. preserved).</td>
</tr>
<tr>
<td>Heikkinen</td>
<td>2004 (113)</td>
<td>Complications to herniotomy</td>
<td>not defined</td>
<td>5% numbness, 10% pricking (Lichtenstein) 0% numbness, 2% pricking (laparoscopic)</td>
<td>no data</td>
</tr>
<tr>
<td>Tsaikayannis</td>
<td>2004 (137)</td>
<td>Pain and numbness</td>
<td>any pain</td>
<td>Exam – ND interview</td>
<td>6% numbness, 1% sensory loss</td>
</tr>
<tr>
<td>Grant</td>
<td>2004 (170)</td>
<td>Pain and numbness</td>
<td>any pain</td>
<td>Questionnaire</td>
<td>Numbness: Open 1 yr 40%, 5 yr 25%, TEP 1 yr 18%, 5 yr 13%</td>
</tr>
<tr>
<td>Mikkelsen</td>
<td>2004 (62)</td>
<td>Association between chronic pain and sensory disturbances</td>
<td>VAS ≥ 1</td>
<td>G QT mapping questionnaire</td>
<td>26% hypoesthesia 38% tactile alldynia</td>
</tr>
<tr>
<td>Picchio</td>
<td>2006 (194)</td>
<td>Incidence of pain 1yr post-operatively</td>
<td>any pain</td>
<td>Exam – ND</td>
<td>Resected: numbness 4%, loss of touch sensation 11%, loss of pain sensation 9% preserved: numbness 6%, loss of touch sensation 4%, loss of pain sensation 8%,</td>
</tr>
<tr>
<td>Study</td>
<td>Primary n</td>
<td>FU</td>
<td>Sensory findings in post-op pain</td>
<td>Sensory findings in post-op dysesthesia</td>
<td>Sensory findings in post-op hypoesthesia</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>----</td>
<td>---------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Aasvang 2006</td>
<td>210</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Bringman 2006</td>
<td>494</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Loos 2006</td>
<td>494</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Lichtenstein, Shouldice, TAPP, Beldi 2007</td>
<td>307</td>
<td>12 mo</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Loos 2007</td>
<td>153</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Butters 2007</td>
<td>140</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>van Veelen 2007</td>
<td>140</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Measor 2007</td>
<td>140</td>
<td>6 yr</td>
<td>yes/no</td>
<td>yes/no</td>
<td>yes/no</td>
</tr>
</tbody>
</table>

**Comment**
- **Neuropathic pain descriptors used by 95%**: Sensory finding by no data, and TAPP Hennia pain specific questionnaire including a MRI.
- **51%**: Sensory finding by no data, and TAPP Hennia pain specific questionnaire including a MRI.
- **64%**: Sensory finding by no data, and TAPP Hennia pain specific questionnaire including a MRI.
- **25%**: Sensory finding by no data, and TAPP Hennia pain specific questionnaire including a MRI.
- **7%** hypoesthesia or hyperesthesia.
- **3%** Neuragia and 2% pain upon palpation.
- **6.5 yr post-operation**: Sensory finding by no data, and TAPP Hennia pain specific questionnaire including a MRI.
- **6%** pubic and 7% scrotal numbness (open).
- **20%** neurological descriptors.
- **74%** insensitivity.
- **20%** insensitivity.
- **6%** pubic and 7% scrotal numbness (open).
- **7%** hypoesthesia.
- **15%** numbness (Lichtenstein).
- **20%** neurological descriptors.
- **45%** hypoesthesia.
- **11%** numbness.
- **89%** hypesthesia.
- **3%** neurological descriptors.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **20%** neurological descriptors.
- **45%** hypoesthesia.
- **11%** numbness.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
- **9%** neuragia.
- **18%** numbness.
- **7%** hypesthesia.
- **89%** hypesthesia.
- **7%** hypesthesia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Conditions</th>
<th>Method</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazeh 2008</td>
<td>2008</td>
<td>not reported</td>
<td>exam – ND interview</td>
<td>&quot;No complaints suggesting nerve injury were reported&quot; &quot;no cutaneous nerve injury&quot;</td>
<td>no data</td>
</tr>
<tr>
<td>Kalliomäki 2009(30)</td>
<td>2009</td>
<td>association between chronic pain and sensory disturbances</td>
<td>exam questionnaire</td>
<td>Any sensory disturbances: 81% in pain vs. 43% pain-free patients</td>
<td>Lichtenstein, Shouldice, laparoscopic, other. Sensory testing not quantified but qualitative yes/no but with strict methodology. McGill and SF-36</td>
</tr>
<tr>
<td>Aasvang 2009(15)</td>
<td>2009</td>
<td>effect of mesh removal/neurectomy on persistent pain</td>
<td>QST questionnaire</td>
<td>Increased detection and pain thresholds (hypesthesia, and hypeoalgia). Preoperative painful after sensations to stimuli, not postoperatively present.</td>
<td>Operation for persistent pain. Standardized QST protocol of thermal and mechanical detection, pain and tolerance thresholds</td>
</tr>
<tr>
<td>Kucuk 2010(130)</td>
<td>2010</td>
<td>complications to herniotomy</td>
<td>exam - ND</td>
<td>1% sensory loss</td>
<td>Lichtenstein vs. Dam procedure</td>
</tr>
<tr>
<td>Faraj 2010(131)</td>
<td>2010</td>
<td>recurrence</td>
<td>exam - ND</td>
<td>4% hypesthesia</td>
<td>Prolene Hernia System. sensory assessment not detailed but operated side compared to contralateral</td>
</tr>
<tr>
<td>Caliskan 2010(139)</td>
<td>2010</td>
<td>postoperative pain</td>
<td>exam - ND</td>
<td>21% numbness/floss of touch (preserved) 21% numbness/floss of touch (resected)</td>
<td>Lichtenstein +/- illhyp. resection</td>
</tr>
<tr>
<td>Creu 2010(141)</td>
<td>2010</td>
<td>neuralgia and hypesthesia</td>
<td>exam - ND</td>
<td>0% numbness at 6 and 12 months in both groups.</td>
<td>no data</td>
</tr>
<tr>
<td>Aasvang 2010(11)</td>
<td>2010</td>
<td>sensory function in pain-free herniotomy patients</td>
<td>exam - ND</td>
<td>not applicable</td>
<td>Lichtenstein. Standardized QST protocol of thermal and mechanical detection, pain and tolerance thresholds</td>
</tr>
<tr>
<td>Aasvang 2010(14)</td>
<td>2010</td>
<td>individual sensory characterization of postherniotomy pain patients</td>
<td>exam - ND</td>
<td>a standardized procedure results in heterogeneous combinations of hypo- and hypeoalgia</td>
<td>Lichtenstein. Standardized QST protocol of thermal and mechanical detection, pain and tolerance thresholds. Findings compared to normative data **</td>
</tr>
<tr>
<td>Reinpold 2011(12)</td>
<td>2011</td>
<td>disabling postoperative pain and/or numbness</td>
<td>exam - ND</td>
<td>+ pain: + sens. dysf. 49% - sens. dysf. 51% - pain: + sens. dysf. 10% - sens. dysf. 89%</td>
<td>Shouldice and Lichtenstein +/- neurolysis. Only 5 yr. examination of patients who reported sensory disorder or pain. No details on questionnaire.</td>
</tr>
<tr>
<td>Negro 2011(133)</td>
<td>2011</td>
<td>complications to herniotomy</td>
<td>exam - ND</td>
<td>no data</td>
<td>Lichtenstein suture vs. glue fixation. Sensory method not described, but data presented</td>
</tr>
<tr>
<td>Linderoth 2011(146)</td>
<td>2011</td>
<td>description and classification of sensory disturbances</td>
<td>exam - ND</td>
<td>a standardized procedure results in heterogeneous combinations of hypo- and hypeoalgia</td>
<td>TAPP. Standardized QST protocol of thermal and mechanical detection, pain and tolerance thresholds</td>
</tr>
<tr>
<td>Perides 2011(67)</td>
<td>2011</td>
<td>complications to herniotomy</td>
<td>exam - ND</td>
<td>+ pain: + sens. dysf. 23% - sens. dysf. 77% - pain: + sens. dysf. 7% - sens. dysf. 93%</td>
<td>PHS vs. Lichtenstein Sensory assessment: &quot;abnormalities in skin sensory function (YN)&quot;. Only examination of patients who reported sensory disorder or pain.</td>
</tr>
<tr>
<td>Kupers 2011(145)</td>
<td>2011</td>
<td>cerebral response to wind-up pain</td>
<td>exam - ND</td>
<td>no data</td>
<td>assessment of cerebral activation assessed by Positron Emission Tomography</td>
</tr>
</tbody>
</table>

**Notes:**
- **ND** = Not defined
- **QST** = Quantitative Sensory Testing
- **VAS** = Visual Analog Scale
- **PHS** = Prolene Hernia System
- **MH** = Mesh Hernia
- **Lichtenstein** = Lichtenstein Herniotomy
- **Shouldice** = Shouldice Herniotomy
- **Darn** = Darn Herniotomy
- **Caliskan** = Caliskan Herniotomy
- **Kucuk** = Kucuk Herniotomy
- **Faraj** = Faraj Herniotomy
- **Aasvang** = Aasvang Herniotomy
- **Reinpold** = Reinpold Herniotomy
- **Negro** = Negro Herniotomy
- **Linderoth** = Linderoth Herniotomy
- **Perides** = Perides Herniotomy
- **Kupers** = Kupers Herniotomy

**Methodology:**
- **Exam** = Examination
- **Interview** = Patient interview
- **Questionnaire** = Patient questionnaire
- **Surgery** = Surgical procedure
- **MRI** = Magnetic Resonance Imaging
- **CT** = Computed Tomography
- **PET** = Positron Emission Tomography
- **SPECT** = Single Photon Emission Computed Tomography
- **EEG** = Electroencephalography
- **ECoG** = Electroencephalography
- **MPS** = Motor Performance Score
- **HVS** = Hyperalgesia
- **Hypalgia** = Hypoalgesia
- **Normal** = Normal
- **Abnormal** = Abnormal
- **+** = Positive
- **-** = Negative
- **%** = Percentage
- **mo.** = Months
- **yr.** = Years
- **VS** = Visceral Sensation
- **VRS** = Verbal Response Scale
- **HVS** = Hypoalgesia
- **Hypalgia** = Hyperalgesia
- **NRS** = Numerical Rating Scale
- **SLT** = Sensory Loss Test
- **TST** = Tactile Stimulation Test
- **TAPP** = Total Abdominal Perineal Perineal Herniotomy
- **TEP** = Transversus Abdominis Perineal Perineal Herniotomy
- **PHS** = Prolene Hernia System
Legend to table 2:

Studies on sensory function and herniotomy, excluded are case reports: FU = Follow-up, QST = Quantitative Sensory Testing, ilioing. = ilioinguinal nerve, iliohyp. = iliohypogastric nerve, TEP = laparoscopic Total ExtraPeritoneal, TAPP = Laparoscopic TransAbdominal PrePeritoneal, exam = physical examination, ND = no details, Sens. = sensory, PPP = persistent postherniotomy pain, VAS = Visual Analogue Scale, VRS = Verbal Rating Scale. Standardized QST protocol: warmth-, cold- and mechanical detection and pain detection thresholds; pressure algometry with pain and pinch thresholds and pressure tolerance; repetitive brush and pinprick stimulation. WU = wind-up (increased pain from repetitive stimulation). Sensory mapping: Areas of sensory deficits mapped with; 20 °C cold-roll, pinprick and brush. PHS = Prolene Hernia System. * Separately reported in ref. 17, ** follow up to ref. 127, *** follow up to ref. 202.
References


Kreiner F, Galbo H. Elevated muscle interstitial levels of pain-inducing substances in symptomatic muscles in patients with polymyalgia rheumatica. Pain 2011;152:3127-32