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# A national center for persistent severe pain after groin hernia repair

## Five-year prospective data

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**Abstract**

Severe persistent pain after groin hernia repair impairs quality-of-life. Prospective, consecutive cohort study including patients with pain-related impairment of physical and social life. Relevant surgical records were obtained, and examinations were by standardized clinical and neurophysiological tests. Patients demonstrating pain sensitivity to pressure algometry in the operated groin underwent re-surgery, while patients with neuropathic pain received pharmacotherapy. Questionnaires at baseline (Q0) and at the 5-year time point (Q5Y) were used in outcome analyses of pain intensity (numeric rating scale [NRS] 0–10) and pain-related effect on the activity-of-daily-living (Activities Assessment Scale [AAS]). Data are mean (95% CI).

Analyses were made in 172/204 (84%) eligible patients. In 54/172 (31%) patients re-surgery (meshectomy/selective neurectomy) was performed, while the remaining 118/172 (69%) patients received pharmacotherapy. In the re-surgery group, activity-related, and average NRS-scores at Q0 were 6.6 (5.6–7.9) and 5.9 (5.6–5.9), respectively. Correspondingly, NRS-scores at Q5Y was 4.1 (3.3–5.1) and 3.1 (2.3–4.0; Q0 *vs.* Q5Y: $P < .0005$), respectively. Although both groups experienced a significant improvement in AAS-scores comparing Q0 *vs.* Q5Y (re-surgery group: 28% (4–43%; $P < .0001$); pharmacotherapy group: 5% (0–11%; $P = .005$)) the improvement was significantly larger in the re-surgery group ($P = .02$).

This 5-year cohort study in patients with severe persistent pain after groin hernia repair signals that selection to re-surgery or pharmacotherapy, based on examination of pain sensitivity, is associated with significant improvement in outcome. Analyzing composite endpoints, combining pain and physical function, are novel in exploring interventional effects.

ClinicalTrials.gov Identifier NCT03713047

**Abbreviations:** AAS = Activities Assessment Scale, ADL = Activities of Daily Living, GHR = groin hernia repair, HADS = Hospital (A = anxiety; D = depression) Scale, NRS = Numeric Rating Scale, PCS = Pain Catastrophizing Scale, PPP = Persistent Postsurgical Pain, Q0 = questionnaire at baseline, Q5Y = questionnaire at 5-year time point, QST = quantitative sensory testing, RCT = randomized controlled trial.

**Keywords:** chronic post-surgical pain, groin, hernia repair, longitudinal study, neuropathic pain, nociceptive pain, pathophysiology, patient-reported outcomes

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## 1. Introduction

Severe persistent postsurgical pain (PPP) after groin hernia repair causes psychophysical disability and impairs quality-of-life for a considerable number of individuals each year.[1–3] In the USA 600,000 groin hernia repairs (GHR) are performed annually, and a conservative estimate is that 2%, corresponding to 12,000 individuals, each year will develop this debilitating pain condition.[4,5] The management of PPP often requires multidisciplinary efforts.[1,6,7] Several surgical procedures have suggested substantial pain-relieving effects in PPP,[1,8] however, few well-powered, controlled studies have been presented.[9,10] In pharmacological and neuromodulation procedures, most studies are still case-based or uncontrolled.

In 2010, the authors established a dedicated tertiary national center for PPP-patients. The objectives were, *first*, to analyze the pathophysiological mechanisms behind the pain, *second*, to implement optimal medical and surgical pain treatment and *third*, to perform clinical randomized controlled-research projects. Standardized clinical and neurophysiological tests guided the management paradigm for each patient. Individuals with a high pain sensitivity to pressure algometry in the primary surgical area were allocated to re-surgery, while individuals with a predominant neuropathic component were allocated to pharmacotherapy. Treatment outcomes were evaluated prospectively using baseline questionnaires (**Q0**) and a 5-year questionnaire (**Q5Y**) mailed at the end of 2014 to all patients.

The focus of the present consecutive follow-up cohort of 222 patients, was first, to present clinical, neurophysiological and psychometric data on PPP-patients based on **Q0**. Second, to evaluate the functional and pain-related outcomes of re-surgery or pharmacotherapy determined based on **Q5Y**.

## 2. Methods

### 2.1. Research ethics

The study protocol was approved by the Regional Committee on Health Research Ethics (H-2–2011-023 [NCT03713047]) and the Danish Data Protection Agency (2012-41-0008). Patients were included after informed written consent (Fig. 1).

### 2.2. Center: structure and organization

The center was staffed by a senior anesthesiologist specialized in pain management (MUW) and clinical research associates (EKJ, JMB, TKR). All patients were examined by MUW. Two senior hernia surgeons (HK, JR) were affiliated as consultants evaluating patients eligible for surgery and in addition performing the re-surgical procedures.

### 2.3. Referral

PPP-patients were referred according to the Danish Hernia Database' website[11] (http://www.herniedatabasen.dk/; Supplemental Digital Content 1; http://links.lww.com/MD/D169; Fig. 2). Principal requirements for admission to the center were PPP (activity-related or maximal pain intensity >7 NRS-scores [numeric rating scale 0-10]) and PPP-related serious impairment of working and social life.

### 2.4. Ambulatory Visit

**2.4.1. Baseline questionnaire (Q0).** Before the ambulatory visit the patient completed a descriptive questionnaire (**Q0**) on characterization, intensity (NRS; resting/average/activity-related/maximal) and site of pain, pain-related groin hernia

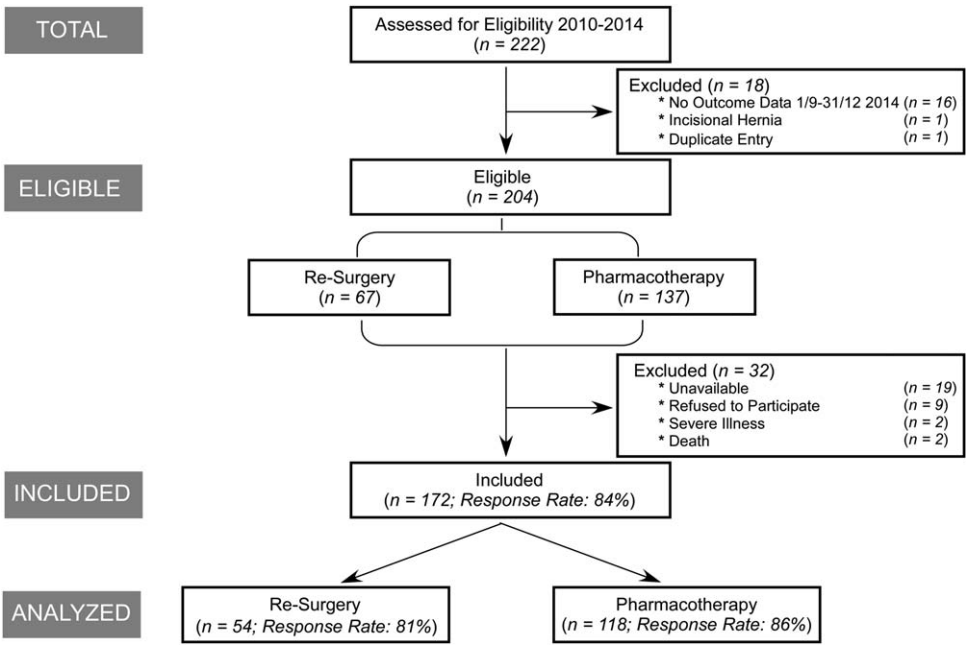


**Figure 1.** A flow diagram of patients with severe persisting pain after groin hernia repair (PPP) referred consecutively to the national center from January 1, 2010, to December 31, 2014. The overall response rate to the 5-year questionnaire was 84% (172/204). Re-surgeries were performed in 33% (67/204) of the patients (anterior/laparoscopically assisted surgeries = 62/5). The response rate in the re-surgical group was 81% (54/67). The response rate in the pharmacotherapy group, representing 67% (137/204) of the patients, was 86% (118/137; $P = .45$).

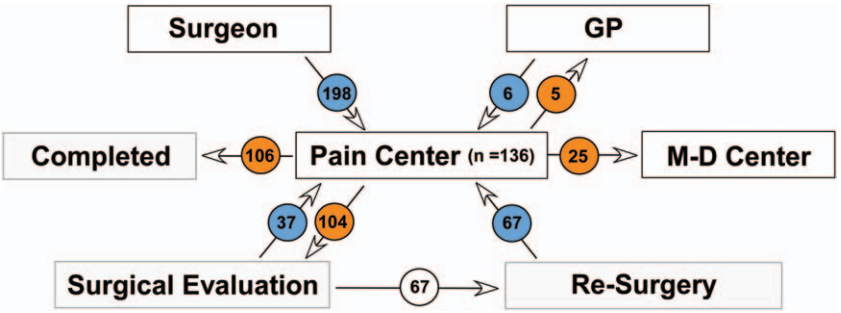


**Figure 2.** Algorithm illustrating the patient-flow (n = 204) following referral from the surgeon or the general practitioner (GP) to the national center (Pain Center) for severe persistent pain after groin hernia repair. Blue filled circles indicate patient flows into the Pain Center. The brown filled circles indicate patient flows out from the Pain Center and the white circles patients receiving re-surgery. At the Pain Center, 136 patients were undergoing medical treatment or were included in scientific trials at the time of completion of the 5-year questionnaire (Q5Y). Patients with significant psychosocial issues or with failing pharmacotherapy were referred to the multidisciplinary pain center (M-D Center) for multidisciplinary pain therapy.

specific Activities of Daily Living (ADL)-function scores (Activities Assessment Scale [AAS];[12] Supplemental Digital Content 2, http://links.lww.com/MD/D169) and psychometrics (Hospital Anxiety and Depression Scale [HADS],[13] Pain Catastrophizing Scale [PCS][14]). AAS-scores were summed for specific activities ($AAS_{A\text{-}D}$) and *overall* activities ($AAS_{E\text{-}H}$). Cut-off scores for HADS and PCS are indicated in Supplemental Digital Content 2, http://links.lww.com/MD/D169.

***2.4.2. Medical records and interview.*** Complete surgical records of primary groin hernia procedures and relevant results of previous scans were acquired. A structured medical interview emphasizing the functional and psychosocial consequences of the PPP was performed.

***2.4.3. Clinical and neurophysiological examinations.*** A standardized physical examination of the groin areas and the external genitals were carried out (Supplemental Digital Content 3, http://links.lww.com/MD/D169). Finally, a neurophysiological examination including sensory mapping and quantitative sensory testing (QST; mechanical and thermal thresholds; [Supplemental Digital Content 4, http://links.lww.com/MD/D169]) of both groins and a control area on the lower arm, were performed, as previously described in detail.[15,16]

### *2.5. Pathophysiological analysis*

Our understanding of the pathophysiology of PPP is still in a formative phase making a differentiation between an inflammatory or neuropathic pain origin difficult.[17–19] The authors, therefore, used the terms inflammatory and neuropathic "components" signifying deep and cutaneous pathological sensory constituents, respectively.

The analysis was based on a pragmatic examination algorithm (Fig. 3): if the patient upon gentle palpation experienced distinctly tender areas in the groin at or near the superficial inguinal ring or along the spermatic cord, corroborated by significantly decreased pressure algometry thresholds in the area compared to contralateral groin, a tentative diagnosis of a deep inflammatory "component" was made. The QST-requirement for an inflammatory "component" was a pressure algometry pain threshold

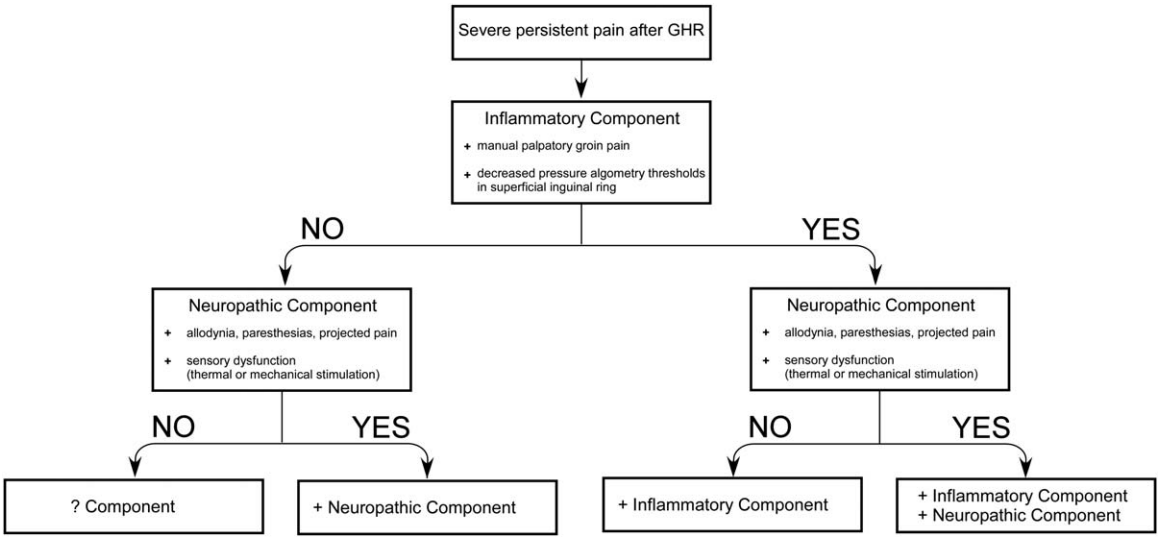


**Figure 3.** Examination algorithm regarding the presence of inflammatory and neuropathic components in the primary surgical area (see text for detailed explanation).

(PPT) difference, compared to the contralateral side >50 kPa (PPT<150 kPa) or >100 kPa (PPT >150 kPa) (Supplemental Digital Content 4, http://links.lww.com/MD/D169). The deep tissue tenderness was anticipated to relate to a "meshoma", an entrapped or dilated spermatic cord, a neuroma or a combination of these. If pain characteristics included evoked sensory symptoms (allodynia, hyperalgesia), projected pain in an area with a neuroanatomically plausible distribution and signs of sensory dysfunction (increased thermal and pinprick thresholds, temporal summation phenomena [Supplemental Digital Content 4, http://links.lww.com/MD/D169]), a neuropathic "component" was inferred.[20] The QST-requirements for a neuropathic "component" were fulfillment of at least 3 of the 4 criteria, using the contralateral side as a control:

1) >3 increased thermal thresholds (CDT, WDT, HPT, CPT [detection thresholds: >1°C; pain thresholds: >2C°])
2) reduced numerical difference between tactile pain threshold and tactile detection threshold (Δ[TPT-TDT]; <2 ordinal values)
3) temporal summation (i.e., "wind-up phenomenon"): >2 NRS-values pain during repetitive pinprick or brush stimulation
4) aftersensation: pain >60 s after cessation of repetitive pinprick or brush stimulation.

Clinical significant psychosocial factors were evaluated by the medical interview and the psychometrics.

### 2.6. Treatment

**2.6.1. Pharmacological management.** Primarily, treatment with capsaicin (8%) patches[21] or systemically administered drugs targeted at neuropathic pain were tried.[22–24] Patients with significantly interfering psychosocial issues were referred to a multidisciplinary pain center (Fig. 2).

**2.6.2. Re-surgery.** The decision to perform re-surgery was based on validation of a significant inflammatory "component" and fulfillment of the referral criteria (cf. above), by the surgeons (HK, JR) performing all surgeries. The anterior surgical procedure was performed through the prior groin incision, and complete resection of the mesh and the suture material was performed (as previously described in detail).[25] In the case of visually confirmed nerve entrapment by the mesh, scar tissue, sutures, or staples, the involved nerve was transected 3 to 5 cm rostrally to the lesion, and tissue samples were sent for histopathological verification. A conventional Bassini repair was performed after mesh removal. The posterior re-surgical procedure was performed with a laparoscopic transabdominal preperitoneal technique. Total meshectomy was attempted in all patients, but in 3 laparoscopic patients, only a partial removal of the mesh could be obtained because of ingrowth in vital structures such as the iliac vein. Most permanent tacks were removed under intraoperative radiologic guidance. Peritoneal coverage of the groin area could be obtained in 3 patients, and in these patients peritoneal closure was done with fibrin sealant. In 2 patients the peritoneum could not be closed and the groin area was left uncovered. A new mesh was not inserted.

### 2.7. Follow-up

The re-surgical group was followed by repeat questionnaires, identical to **Q0**, at 3, 6, 12, 24, 36, and 60 months after the procedure, as previously reported.[25] The pharmacotherapy group was followed by phone by the senior pain specialist (MUW), prescribing dose-adjustments or drug-changes obtaining the optimal therapeutic result.

### 2.8. Five-year questionnaire

The 5-year questionnaire (**Q5Y**) was an abbreviated and modified version of **Q0**. The **Q5Y** was delivered to the patient by conventional mail. If a response was not obtained after 2 months, re-mailing followed by telephone contact was tried. If no contact was established or participation was refused, the patient was excluded.

The **Q5Y** contained the following parts:

1) pain characteristics (intensity, pattern, localization on an anatomical chart)
2) use of analgesics (drug type, treatment efficacy)
3) pain-related impairment of ADL-function (modified AAS-scores).[12,25]

### 2.9. Data handling

Data were manually transferred from questionnaires into a database (Microsoft Access 2013, Microsoft, Redmond). Data entries were confirmed by 2 independent observers.

### 2.10. Statistical procedures

Data distribution was checked for normality with standard tests and by visual inspection of residual plots. Overall data analyses were made with 2-way repeated measures analysis of variance (ANOVA) (groups: **Q0** *vs.* **Q5Y** | re-surgery *vs.* pharmacotherapy; factors: pain intensity [NRS-scores], ADL-function [AAS-scores]). In ANOVAs indicating statistical significance, paired or un-paired sample *t* tests, or non-parametric signed-rank tests depending on data distribution, were used. Fisher's exact test was used in the analysis of contingency tables.

The fractional changes in pain intensity (summed NRS-scores) and ADL-function (summed AAS-scores) were calculated as:

$$\frac{NRS_{Q0} - NRS_{Q5Y}}{NRS_{Q0}} \text{ and } \frac{AAS_{Q0} - AAS_{Q5Y}}{AAS_{Q0}}$$

The fractional scores, AAS *vs.* NRS, were analyzed by simple linear correlation and regression techniques. In the predictive analyses, multiple regression was applied to predict the dependent variables, AAS ($AAS_{A\text{-}D}$-scores, $A_{E\text{-}H}$-scores), contentment (NRS: diagnosis and the management; **Q5Y**), and pain intensity (NRS: **Q5Y**; Δ[**Q0** – **Q5Y**]) from the independent variables: age, re-surgery (posterior/anterior), gender, pain intensity (NRS), primary procedure (laparoscopic procedure/Lichtenstein technique/other), pathophysiologic "components" (inflammatory/neuropathic/mixed/other), psychometrics (Hospital Anxiety and Depression Scale—Anxiety [HADS-A]/ Hospital Anxiety and Depression Scale—Depression [HADS-D]/PCS), time (from primary repair to **Q0** and from **Q0** to **Q5Y**).

The level of significance was set at $P < .05$. Data are given as mean or median (95% CI).

## 3. Results

### 3.1. General characteristics

The total number of consecutively referred patients, from January 1, 2010, to December 31, 2014, was 222 (Fig. 1). Eligible patients (n = 204) were divided into a re-surgical group (n = 67 [anterior/laparoscopically assisted surgeries = 62/5]) and a pharmacotherapy group (n = 137). The **Q5Y**-response rates for the re-surgery

**Table 1**

**Resting, average, activity-related, and maximal pain intensity scores.**

| | Pain at Rest | Average Pain | Activity-related Pain | Maximal Pain |
|---|---|---|---|---|
| **Q0 all patients** | **4.1 (3.8–4.5)**$^{****}$ | **5.5 (5.2–5.9)**$^{****}$ | **6.3 (5.9–6.7)**$^{****}$ | **7.8 (7.5–8.2)**$^{****}$ |
| - Q0 re-surgery | 4.2 (3.7–4.8)$^{****/n.s.}$ | 5.9 (5.6–5.9)$^{****/n.s.}$ | 6.6 (5.6–7.9)$^{****/n.s.}$ | 8.6 (8.3–9.0) $^{****/***}$ |
| - Q0 pharmacotherapy | 4.1 (3.7–4.6)$^{****/}$ | 5.3 (4.9–5.8)$^{****/}$ | 5.9 (5.4–6.4)$^{****/}$ | 7.5 (7.0–8.0)$^{****/}$ |
| **Q5Y all patients** | **1.8 (1.4–2.3)** | **3.0 (2.5–3.6)** | **3.5 (2.9–4.2)** | **4.9 (4.1–5.9)** |
| - Q5Y re-surgery | 1.9 (1.3–3.3) /$^{*}$ | 3.1 (2.3–4.0) $^{/n.s.}$ | 4.1 (3.3–5.1) $^{/n.s.}$ | 5.6 (4.6–7.0) $^{/n.s.}$ |
| - Q5Y pharmacotherapy | 3.3 (2.6–4.1) | 2.9 (2.3–3.7) | 3.3 (2.6–4.1) | 4.6 (3.6–5.8) |

Resting, average, activity-related and maximal pain intensity scores from the baseline questionnaire (**Q0**) and the 5-year questionnaire (**Q5Y**) (NRS, 0 to 10; data logarithmically transformed and back-transformed, geometric mean (95% CI), paired or unpaired *t* tests, as appropriate). Pain scores with NRS-values of 0 were transformed to 0.1 prior to the logarithmic procedure. Comparisons between **Q0** and **Q5Y** for all patients, divided into re-surgical and pharmacotherapy groups, are indicated by the first superscript position. Comparisons between the re-surgical and pharmacotherapy groups, within **Q0** and **Q5Y** are indicated by the second superscript position (preceded by a forward slash). Complete, comparable pain scores (**Q0** and **Q5Y**), were obtained from the responders in 98% (53/54) of the re-surgical group and in 92% (109/118) of the pharmacotherapy group. n.s. = non-significant; $^{*}P<.05$; $^{**}P<.01$; $^{***}P<.005$; $^{****}P<.0005$.

and the pharmacotherapy groups were 81% and 86%, respectively ($P=.45$).

The gender ratio (M/F) was 13.6 (190/14), and the median age was 50.1 (49.0–53.8) yrs. Time from the primary surgical procedure related to the development of PPP to the first ambulatory visit in the center was median 1.8 (0.8–4.0) yrs with a range of 0.5 to 22.0 yrs. The time from the first visit at the center (**Q0**) to the response to the 5-year questionnaire (**Q5Y**) was median 2.2 (1.9–2.8) yrs with a range of 0.2 to 4.9 yrs.

### 3.2. Baseline characteristics (Q0)

***3.2.1. Surgical record.*** The initial repairs considered to be pathophysiologically related to the development of PPP were an anterior procedure in 80% (164/204), a laparoscopic procedure in 18% (37/204) and undecided, due to repeat surgeries in 1% (3/204). The anterior procedures were Lichtenstein 78% (160/204), mesh-and-plug 1% (2/204) and Onstep 1% (2/204). The laparoscopic procedures were by transabdominal preperitoneal repairs. The GHRs were primary in 87% (178/204) and due to recurrence in 13% (26/204).

The GHR performed on the PPP-side (before referral) were single repairs in 59% (121/204) of the patients, 2 repairs in 25% (51/204), 3 repairs in 11% (22/204) and more than 4 repairs in 5% (10/204). Re-surgical procedures due to pain after the groin hernia operation had been performed in 32% (66/204) before referral.

***3.2.2. Pain characteristics.*** Regarding the pain trajectories, 76% (156/204) experienced the onset of PPP immediately after, 4% (9/204) weeks after, 10% (21/204) months after and 9% (18/204) years after, the primary surgical procedure. The PPP was right-sided in 56% (115/204), left-sided in 30% (61/204) and bilaterally in 14% (28/204). Pain intensity NRS-scores are presented in Table 1.

***3.2.3. Pathophysiological analyses.*** The clinical and neurophysiological examinations showed that 48% (98/204) experienced a mixed inflammatory and neuropathic PPP "component", 25% (50/204) an inflammatory "component", 11% (23/204) a neuropathic "component", and 16% (33/204) with no inflammatory or neuropathic "components". Interestingly, 98% (199/204) demonstrated signs of sensory dysfunction in the groin, external genitalia, lower abdomen, or the anteromedial aspect of the thigh.

***3.2.4. Pain-related impairment in ADL-function (AAS-scores).*** The summed-scores of the specific activities ($AAS_{A\text{-}D}$: lying in bed, sitting in a chair >30 min, climbing stairs, lifting 5 to 10 kg) and the overall activities ($AAS_{E\text{-}H}$: sedentary activities, light physical activities, moderate physical activities, strenuous physical activities) are presented in Table 2. Highly significant differences were demonstrated between single activity levels (A-D: $P<.005$; E-H: $P<.0001$).

***3.2.5. Psychometrics.*** Median HADS-A scores were 6.0 (5.0–7.0). HADS-A scores indicating probable or definite anxiety were seen in 19% (30/154) and 16% (25/154), respectively. Median HADS-D scores were 4.0 (3.0–5.0). HADS-D scores indicating probable or definite signs of depression were seen in 17% (24/138) and 13% (18/138), respectively. Mean PCS scores were 23.2 (21.2–25.2). PCS scores indicating catastrophizing behavior were seen in 30% (46/155).

**Table 2**

**Summed scores of the Activities Assessment Scale (AAS).**

| | Baseline Questionnaire (Q0) | | Five-year Questionnaire (Q5Y) | |
|---|---|---|---|---|
| | Activities A-D | Activities E-H | Activities A-D | Activities E-H |
| **All patients** | 10.0 (10.0–11.0)$^{*****}$ (n = 161) | 12.0 (12.0–13.0)$^{*****}$ (n = 161) | 9.0 (8.0–10.0) (n = 161) | 11.0 (10.0–12.0) (n = 50) |
| - re-surgery | 11.0 (10.0–12.0)$^{****}$ (n = 50) | 13.0 (12.0–14.0)$^{***}$ (n = 50) | 8.0 (6.6–10.0) (n = 50) | 10.0 (8.0–12.0) (n = 50) |
| - pharmacotherapy | 10.0 (10.0–11.0)$^{*}$ (n = 111) | 12.0 (11.0–13.0)$^{*}$ (n = 111) | 10.0 (8.0–11.0) (n = 111) | 11.0 (10.0–12.0) (n = 111) |

Summed scores of the Activities Assessment Scale (AAS; cf. text (3.2.4) and Table 1) for the specific activities **A-D** and the overall activities **E-H**, from the baseline questionnaire (**Q0**) and 5-year questionnaire (**Q5Y**), split into all patients, the re-surgical group and the pharmacotherapy group. The longitudinal comparisons are between **Q0** and **Q5Y**, indicating a highly significant decrease in AAS-scores, particularly regarding the re-surgical group.

$^{*}P<.05$.
$^{***}P<.005$.
$^{****}P<.0005$.
$^{*****}P<.0001$.

Simple regression analysis of HADS-A *vs.* HADS-D demonstrated a coefficient of determination ($R^2$) of 0.65 ($P<.0001$). Multiple regression analysis (PCS *vs.* HADS-A or HADS-D) demonstrated an $R^2$ of 0.42 ($P<.002$) indicating an association between the variables. Simple regression analysis of HADS-A *vs.* HADS-D and multiple regression analysis PCS *vs.* HADS-A/HADS-D demonstrated coefficients of determination ($R^2$) of 0.65 ($P<.0001$) and 0.42 ($P<.002$) respectively, indicating an association between the variables.

***3.2.6. Analgesics.*** Forty-eight percent (82/172) of the patients used analgesics on a daily basis (Supplemental Digital Content 5, http://links.lww.com/MD/D169) and 37% (30/82), 37% (30/82), and 27% (22/82) medicated with 1, 2, or 3 different drugs, respectively.

### *3.3. Five-year questionnaire (Q5Y)*

***3.3.1. Analgesics (re-surgery/pharmacotherapy groups).*** Forty-six percent (25/54) of the re-surgery and 48% (57/118) of the pharmacotherapy patients used analgesics on a daily basis at **Q5Y** (Supplemental Digital Content 6, http://links.lww.com/MD/D169).

***3.3.2. Predictors (multiple regression analyses).*** The regression model demonstrated an inverse correlation between age and magnitude of pain intensity scores ($R^2=0.279$; $P=.004$). Furthermore, HADS-A scores were a significant predictor for ADL-functions ($AAS_{A\text{-}D}$: $R^2=0.34$ [$P=.003$], and, $AAS_{E\text{-}H}$: $R^2=0.20$ [$P=.02$]).

### *3.4. Five-year vs. baseline questionnaires (Q5Y vs. Q0)*

***3.4.1. Pain intensity scores.*** Complete comparable pain NRS-scores (**Q0** and **Q5Y**) were obtained from 98% (53/54) of the re-surgical group and 92% (109/118) of the pharmacotherapy group. Significant pain intensity differences between testing conditions (pain at rest, average pain, activity-related pain, maximal pain) were demonstrated at **Q0** and **Q5Y**, respectively, and, between **Q0** and **Q5Y** ($P<.00001$; Table 1). A significant reduction in the summed scores between **Q0** and **Q5Y** was demonstrated ($P<.0005$; Fig. 4A). The decrease in NRS-scores from **Q0** to **Q5Y** did not differ between the re-surgery and the pharmacotherapy groups ($P=.07$; Fig. 4A/B).

***3.4.2. Pain-related impairment (ADL-function).*** Comparing Q0 *vs.* **Q5Y**, the $AAS_{A\text{-}D}$-scores and $AAS_{E\text{-}H}$-scores, respectively, differed significantly ($P<.0001$; Table 2), indicating improvement in the self-perceived physical function. The improvement in summed $AAS_{A\text{-}H}$-scores was more pronounced in the re-surgery group (28% [4–43%]) compared to the pharmacotherapy group (5% [0–11%]; Fig. 4A/B; $P=.02$).

***3.4.3. Correlation and regression analyses (composite outcome analyses).*** Scatter diagrams of the regression analyses of the fractional NRS-scores, and AAS-scores demonstrated 41%

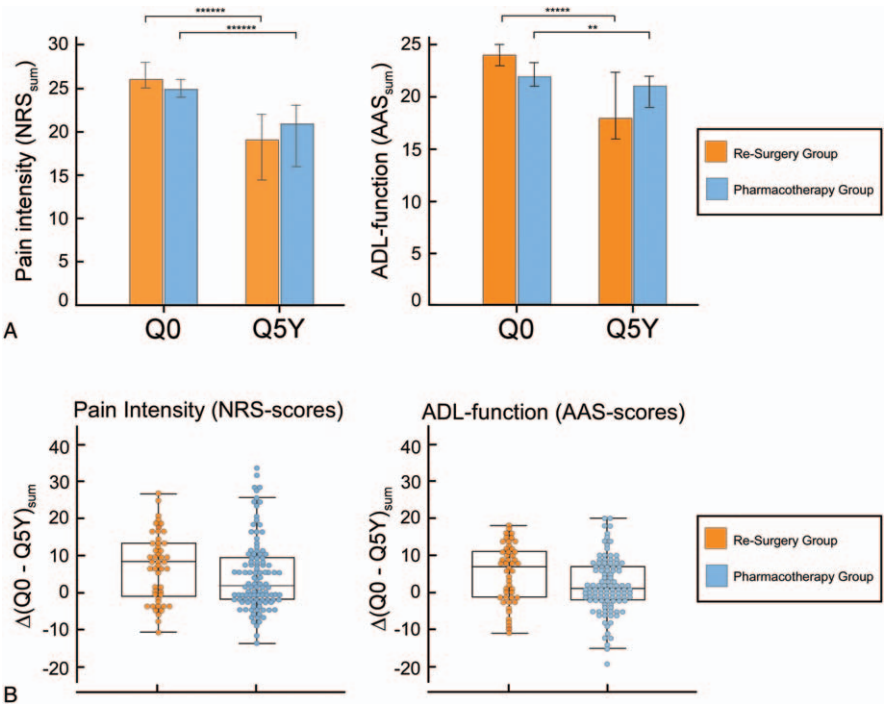


**Figure 4.** (A, B). Upper panel row (A): median (95% CI) values for pain intensity (left panel) and ADL-function (right panel), in the re-surgical and pharmacotherapy groups. The pain intensity given as summed NRS-scores (numeric rating scale [$NRS_{summed}=NRS_{resting}+NRS_{average}+NRS_{activity\text{-}related}+NRS_{maximal}$]) is presented at Q0 and Q5Y. ADL-function assessed as summed $AAS_{A\text{-}H}$-scores (Activities Assessment Scale; activities A-H [Supplemental Digital Content 2, http://links.lww.com/MD/D169]) is presented at baseline (Q0) and 5-year questionnaire (Q5Y). The higher the score, the more impairment in ADL-function (minimum score 8). Lower panel row (B): clustered multiple variables graph for Δ(Q0-Q5) for summed pain intensity scores (left) and summed AAS-scores (left) in re-surgery *vs.* pharmacotherapy group. A positive value indicates an improvement in pain and physical function. There was no difference between groups in NRS-scores ($P=.07$) however a slight difference in AAS-scores was observed with higher ADL-function in the re-surgery group ($P=.02$). A rough "bimodal" data-clustering is suggested by visual inspection of NRS-scores and AAS-scores in both groups. $^{**}P<.01$; $^{*****}P<.0005$; $^{******}P<.0001$.

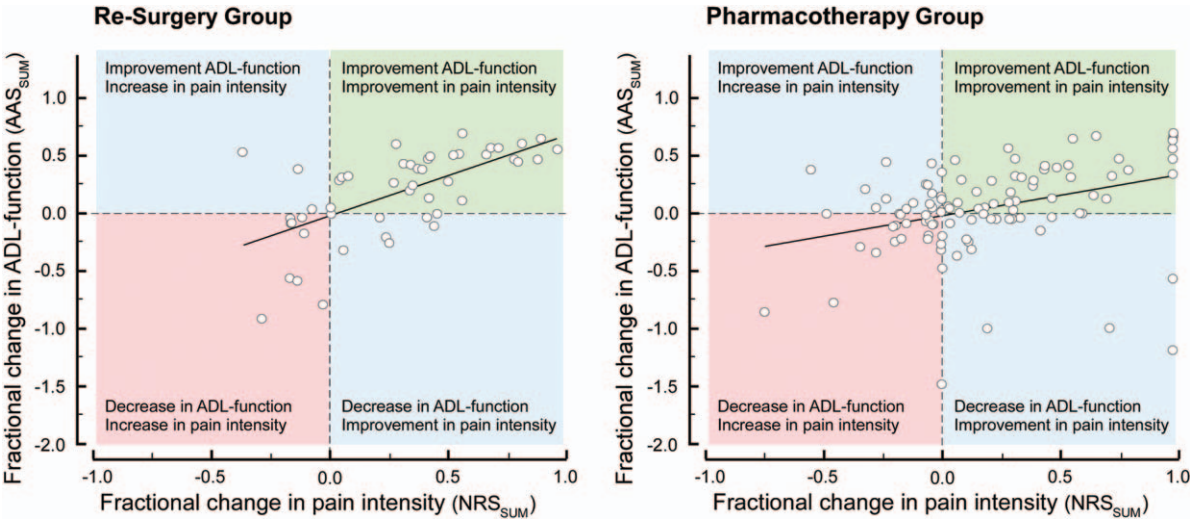


**Figure 5.** Composite outcome analyses. Linear regression graphs of fractional changes in ADL-function (assessed by the summed scores of the modified Activities Assessment Scale [AAS]) *vs.* fractional changes in pain intensity (assessed by the summed numeric rating scale [NRS] scores [please, consult the text for explanation]), for the re-surgery group (left panel) and the pharmacotherapy group (right panel). The fractional changes for ADL-scores were calculated as $\frac{AAS_{Q0}-AAS_{Q5Y}}{AAS_{Q0}}$ and for pain intensity as $\frac{NRS_{Q0}-NRS_{Q5Y}}{NRS_{Q0}}$ (Q0 = baseline questionnaire; Q5Y = 5-year questionnaire). A fractional change >0 indicate improvement at Q5Y compared to Q0, while a fractional change <0 indicate a deterioration. The regression coefficient in the re-surgery group was significantly larger than in the pharmacotherapy group (0.71 [0.45 to 0.96] *vs.* 0.35 [0.17 to 0.52]; $P = .03$).

of the variance in AAS-scores was explained by the NRS-scores in the re-surgery group *vs.* 13% in the pharmacotherapy group (Fig. 5; Supplemental Digital Content 7, http://links.lww.com/MD/D169). The regression slope in the re-surgery group was significantly steeper than in the pharmacotherapy group ($P = .03$) confirming a better ADL-outcome per increment pain reduction compared to the pharmacotherapy group.

***3.4.4. Sub-group analysis (pharmacotherapy group).*** Comparing the non-medication with the medication group significantly larger decreases in $\Delta(Q0\text{-}Q5Y)_{NRS}$ and $\Delta(Q0\text{-}Q5Y)_{AAS}$ (summed values) were demonstrated in the non-medication-group (Supplemental Digital Content 8, http://links.lww.com/MD/D169).

***3.4.5. Predictors (multiple regression analyses; re-surgery/pharmacotherapy groups).*** The regression model demonstrated that time between **Q0** and **Q5Y**, contentment with management (Supplemental Digital Content 7 and 9, http://links.lww.com/MD/D169*)*, and primary procedure (Lichtenstein *vs.* other surgical procedures) *inversely* predicted summed $\Delta(Q0\text{-}Q5Y)_{NRS}$-values ($R^2 = 0.137$; $P = .001$).

## 4. Discussion

This longitudinal prospective study contains descriptive characteristics and management outcomes for 172/204 eligible patients with severe persistent pain after groin hernia repair, referred to a dedicated national PPP-center. Main findings are *first*, that in patients allocated to receive re-surgery or pharmacotherapy, based on pain sensitivity in the operated groin, significant improvements in pain intensity and ADL-function are demonstrated. *Second*, in patients allocated to re-surgery, the recovery in ADL-function is enhanced. *Third*, a substantial number of patients will experience spontaneous improvement irrespective of treatment allocation.

### *4.1. Pathophysiology behind PPP*

Groin surgery consistently demonstrates sensory dysfunction, indicating peripheral nerve damage.[17,26] However, only a minority of individuals proceed to develop persistent postsurgical pain. A recent histopathological study in explanted meshes demonstrated neo-innervation of nerve fibers and a significantly higher nerve fiber density in specimens obtained due to pain than after re-surgery for a non-pain hernia recurrence.[18] Another recent study summarized that an inflammatory response may be the most important for the development of PPP.[19] Our analyses based on interpretation of quantitative sensory assessments indicated a mixed inflammatory and neuropathic "component" in 48%, an inflammatory "component" in 25%, a neuropathic "component" in 11% and were undecided in 16%. Nearly all patients irrespective of the primary surgical procedure demonstrated signs of sensory dysfunction. In a recent PPP-study using a pain questionnaire (Douleur Neuropathique 4 [DN4]), 30% had probable or definite neuropathic pain.[5] Using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale a probability of 50% for neuropathic pain was reported.[27] Our data infer that signs of sensory dysfunction in a PPP-patient do not necessarily imply a neuropathic pain state.

### *4.2. Pharmacotherapy in PPP*

Severe persistent pain after GHR is generally considered neuropathic of origin[28] although the exact potential role of nerve injury is unknown.[29] Neuromodulation techniques, infiltration blocks and drug therapy have been advocated, but only 5 RCTs are available: 2 on infiltration blocks[16,27] and 3 on drug therapies.[21,30,31]

### *4.3. Re-Surgical procedures in PPP*

Neurectomy,[32] mesh removal with selective neurectomy,[25,33] retroperitoneal triple neurectomy,[2,34,35] or a combined anterior

and laparoscopic approach[36] are advocated procedures. No outcome studies across surgical techniques have been presented.[1] A recent controlled study, however, demonstrated a significantly better outcome of selective neurectomy *vs*. local anesthetic injection therapy.[27]

### 4.4. Baseline characterization (Q0)

The demographics are consistent with the GHR-population[37] except for younger age (50.1 *vs*. 66.1 yrs) documented in previous PPP-research.[38] The surgical record and PPP-intensity details are in agreement with recently published data.[9,27] The QST-method has previously been used to characterize PPP-patients,[26,39] but the present study is the largest using the method in an attempt to interpret the pathophysiological aspects. Unfortunately, the QST-method did not demonstrate any specific mechanism or any predictive potential in PPP.

### 4.5. Pharmacotherapy group (Q5Y vs. Q0)

Pain intensity scores (NRS) and ADL-function scores (AAS) improved significantly in the present non-medication (57%) *vs*. medication (43%) sub-groups ($P < .0001$). It is generally believed that analgesic therapy is a symptomatic treatment only masking pain perception until, eventually, tissue regeneration allows normalization of sensory functions.[40]

Thus, it seems reasonable to conclude that the improvement in pain intensity and ADL-function in the non-medication subgroup may represent spontaneous recovery. A change in pain phenotype, that is, a spontaneous decrease in pain intensity, has been reported in other longitudinal post-surgical studies, in GHR,[41] and breast cancer.[42,43]

The level of recovery in the non-medication subgroup regarding pain intensity (average NRS) and ADL-function (summed AAS) was 40% and 22%, respectively. In comparison, in neuropathic pain trials, the baseline pain intensity is at least 5 (NRS),[44] and the measure of analgesic efficacy corresponds to at least a 30% reduction in pain intensity,[45] which is in accordance with the non-medication-subgroup.

### 4.6. Re-Surgery vs. pharmacotherapy group (Q5Y vs. Q0)

Comparing treatment efficacies between the re-surgery and non-medication pharmacotherapy group, the level of recovery in the former regarding pain intensity (average NRS) and ADL-function were 48% and 28%, respectively. Analyzing these data as composite endpoints, a recent pharmacological review in non-surgical neuropathic pain reported a responder outcome of at least 20% improvement in pain intensity and at least 30% improvement in physical function, represented significant changes in RCTs.[46] From a surgical point of view, this is quite intriguing. While the outcome in pain relief did not differ between the re-surgery and non-medication pharmacotherapy subgroup, the composite responder outcome showed a statistically significant difference in favor of a re-surgery procedure. Composite endpoints, combining pain and physical function, is a dynamic way of exploring interventional effects and may even improve assay sensitivity in research issues.[46]

Furthermore, in the neuropathic pain review[46] the correlation between pain and physical outcome was rather weak ($R^2 = 0.05$),[46] in contrast to the present study where the correlation between the fractional changes in pain intensity and ADL-function in the re-surgery group was considerably higher ($R^2 = 0.44$). However, it should be realized that the non-randomized design in the present study, warrants caution in interpreting statistical differences between the re-surgery and pharmacotherapy groups.

### 4.7. Strengths of the study

*First,* our study illustrates a neat cooperation with pain specialists and experienced surgeons with a fairly good outcome regarding pain and ADL-function, particularly in the re-surgery group (Fig. 5).[47] In comparison, a randomized, controlled 12 months outcome study of drug treatment in chronic neuropathic pain in a tertiary center showed that less than 25% attained clinically significant improvement in pain and function.[48]*Second*, a limited number of investigators collected clinical data (MUW) and QST-data (TKR, EKJ), and, performed the re-surgery procedures (HK, JR), decreasing data variability. *Third*, extensive information on clinical, physical function, psychometrics, and sensory variables enabled construction of putative pathophysiological profiles, guiding pragmatic pain management. *Fourth,* the study was well-powered, prospective in design, with responder rates >80% and a median follow-up period >2 yrs. *Fifth*, composite outcome analyses assessments of pain and physical function are recommended in studies of chronic post-surgery pain.[44,49]

### 4.8. Limitations of the study

*First*, confounding is likely, due to lack of blinding and randomization with regard to re-surgical or pharmacotherapy. As an example, baseline **Q0** maximal pain intensity was significantly higher in the re-surgery group compared to the pharmacotherapy group. This could hypothetically be explained either by higher pain intensity in PPP-states with a significant inflammatory "component" or that a high pain intensity *per se* may influence the surgical decision of undertaking a re-surgery procedure. *Second*, the study is questionnaire-based, and although all **Q0**-data were validated during the first ambulatory visit, **Q5Y**-data are subject to recall bias. In a test-retest dichotomized questionnaire in PPP a moderate reliability was found (Cohen's $\kappa = 0.58$).[37]

## 5. Conclusion

Our data corroborate the role of re-surgery in patients with severe persistent pain after groin hernia repair with an inflammatory "component". Composite responder analyses showed a better outcome for the re-surgery group regarding pain and physical function. However, the spontaneous recovery demonstrated in the pharmacotherapy group is an incentive to develop more efficacious non-interventional therapies.

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