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Impact of different mesh parameters on chronic pain and foreign body feeling after open inguinal hernia repair

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Impact of different mesh parameters on chronic pain and foreign body feeling after open inguinal hernia repair

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Department of Surgery, University of Tartu, Estonia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Nikkolo C, Lepner U, Murruste M, Vaasna T, Seepter H, Tikk T. Randomised clinical trial comparing lightweight mesh with heavyweight mesh for inguinal hernioplasty. Hernia 2010;14:253–258

II Nikkolo C, Murruste M, Vaasna T, Seepter H, Tikk T, Lepner U. Three-year results of randomised clinical trial comparing lightweight mesh with heavyweight mesh for inguinal hernioplasty. Hernia 2012;16:555–559

III Nikkolo C, Vaasna T, Murruste M, Seepter H, Kirsimägi Ü, Lepner U. Randomized clinical study evaluating the impact of mesh pore size on chronic pain after Lichtenstein hernioplasty. J Surg Res 2014;191:311–317

IV Nikkolo C, Vaasna T, Murruste M, Seepter H, Suumann J, Tein A, Kirsimägi Ü, Lepner U. Single-centre single-blinded randomised study of self-gripping versus sutured mesh in open inguinal hernia repair. J Surg Res DOI: 10.1016/j.jss.2014.09.017

Author's contribution:
Conception and study design, data collection, participation in data analysis, writing the papers

ABBREVIATIONS

BMI	body mass index
EHS	European Hernia Society
HW	heavyweight mesh
ITT	intention-to-treat population
LW	lightweight mesh
NSAID	non-steroidal anti-inflammatory drug
OM, OLP	Optilne® LP mesh
PP	per protocol principle
PPG	Parietex Progrip™ mesh
SF36	Short Form 36
TAPP	transabdominal preperitoneal
TEP	totally extraperitoneal
UM	Ultrapro® mesh
VAS	visual analogue scale

I. INTRODUCTION

In recent decades there has been considerable debate on inguinal hernias – etiology of the disease, indications for surgery, selection of the surgical approach and technique, selection of the prosthetic material and reduction of recurrences and chronic posthernioplasty symptoms.

Although the well known and by far the most widely used mesh material polypropylene was developed 60 years ago [Coda et al., 2012; Earle and Mark, 2008] and more than 160 different meshes for hernia repair are in the market [Coda et al., 2012], with millions of prosthetic meshes used worldwide each year [Bay-Nielsen et al., 2001a; Weyhe et al., 2007], we do not yet know the parameters of an ideal mesh [Simons et al., 2009].

After the widely used alloplasty in inguinal hernia surgery, the most common complication is chronic pain whose rates reach 51.6 % [O'Dwyer et al., 2005]. The rate of foreign body feeling occurs in up to 43.8 % of patients after inguinal hernia repair [Post et al., 2004].

Considering the high rate of chronic pain and foreign body feeling after inguinal hernioplasty, which can have major influence on the patients' quality of life, as well as serious socio-economic impacts, different mesh characteristics should be studied in order to identify the mesh whose usage results in lower rates of long-term pain and foreign body feeling.

2. REVIEW OF THE LITERATURE

2.1. Definition of inguinal hernia

The musculo-aponeurotic layer of the abdominal wall is formed in order to retain the organs of the abdominal cavity. However, there are some limited areas, including the groin region, where the anatomical structures are often deficient resulting in hernia development.

Inguinal hernia is defined as a protrusion of the contents of the abdominal cavity or preperitoneal fat through the hernia defect in the inguinal region [Simons et al., 2009] (Figure 1).

Inguinal hernias can be direct or indirect, depending on their relationship to the inferior epigastric vessels. Direct or medial hernias occur medial to the inferior epigastric vessels and indirect hernias protrude lateral to the inferior epigastric vessels. There can also exist a combination of direct and indirect hernia – a pantaloon hernia [Matthews and Neumayer, 2008].

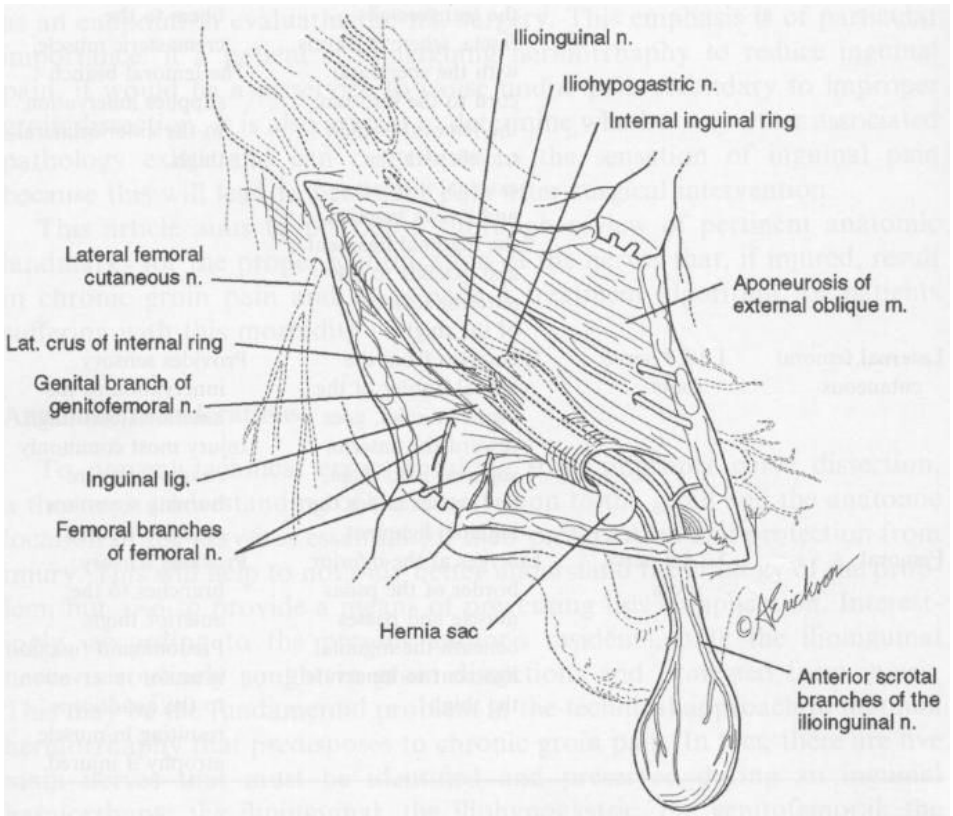

Figure 1. Groin anatomy during the anterior inguinal hernioplasty approach [Ferzli et al., 2008] (Reproduced with the permission of Elsevier)

2.2. Etiology of inguinal hernia

The fundamental mechanism of formation of abdominal wall hernia is the loss of structural integrity at the musculo-aponeurotic layer [Franz, 2008].

The cause of hernia formation is multifactorial, but many studies have identified pathological changes in collagen, resulting in development of a hernia [Bendavid, 2004]. Also in a systematic review of Henriksen et al. hernia formation is associated with a decreased type I:III collagen ratio [Henriksen et al., 2011].

According to the European Hernia Society (EHS) guidelines on the treatment of inguinal hernia, smokers, patients with positive family hernia history, patent processus vaginalis, collagen disease, after an open appendectomy and prostatectomy, with ascites, on peritoneal dialysis, after long-term hard work or with chronic obstructive pulmonary disease have an increased risk of inguinal hernia development [Simons et al., 2009].

2.3. Frequency of inguinal hernia

Inguinal hernioplasty is one of the most common operations in general surgery. The incidence and prevalence of inguinal hernia is not exactly known [Rutkow, 1998]. Inguinal hernias are more common in males than females (8–20:1) [Kingsnorth and Leblanc, 2003]. The lifetime risk for inguinal hernia operation is estimated to be 27 % in men and 3 % in women [Primatesta and Goldacre, 1996].

The rates of inguinal hernia repair (primary and recurrent hernias) in Estonia have been stable in the last decade (Figure 2). In 2012, there were 148 inguinal hernia repairs per 100,000 inhabitants in Estonia [TAI, 2012].

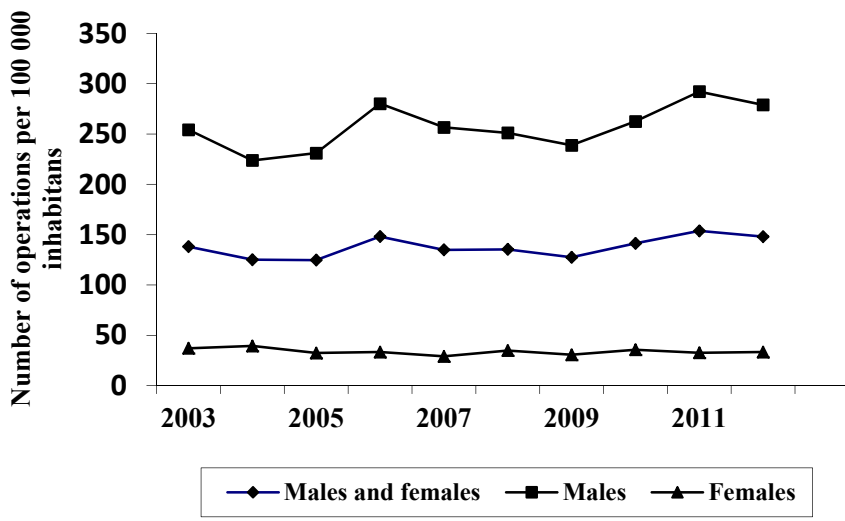

Figure 2. Number of inguinal hernia operations per 100 000 inhabitants in 2003–2012 in Estonia [TAI, 2012]

2.4. Diagnostics of inguinal hernia

Patients with symptomatic inguinal hernias report a lump in the groin region, which might disappear in the supine position and they also have complaints about pain and discomfort in the groin, which are usually related to physical exercise and effort.

However, inguinal hernias can also be asymptomatic. In a study of Gallegos et al. the cumulative probability of strangulation of inguinal hernias after 3 months was 2.8 %, rising to 4.5 % after 2 years [Gallegos et al., 1991]. Considering the low risk of strangulation of inguinal hernias, watchful waiting is considered an acceptable and safe option in asymptomatic inguinal hernias [Simons et al., 2009]. However, we have to consider the fact that in more than 70 % of cases patients will cross over from the group of watchful waiting to the group of surgical treatment because of development of symptoms [Miserez et al., 2014].

Acute complications of inguinal hernias beyond the scope of this thesis.

In most cases the diagnosis of inguinal hernia is based on physical examination and other investigations are usually not needed. According to Kraft et al., the sensitivity of preoperative examination is 92 % and specificity 93 % [Kraft et al., 2003]. In case of unclear diagnosis, ultrasound is recommended. If ultrasound is negative, then MRI with Valsalva should be performed [Simons et al., 2009] (Figure 3a, 3b).

Differentiating between a direct and an indirect hernia preoperatively is not necessary, but it is important to distinguish a femoral hernia from an inguinal hernia because of the high risk of incarceration in the former case [Simons et al., 2009].

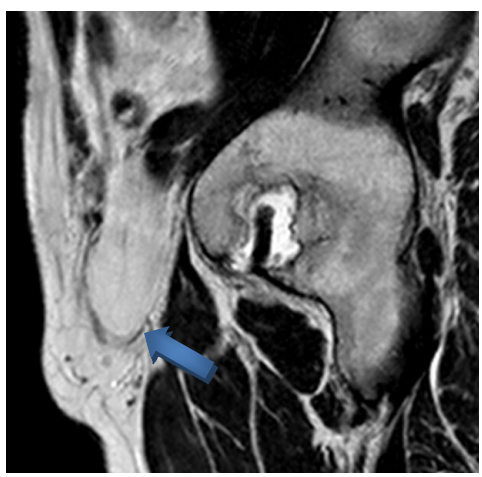

Figure 3a

Figure 3b

Figure 3a, 3b MRI of a 67-year old male patient with right-sided inguinal hernia

2.5. Treatment of inguinal hernia

Hernias can be repaired only by surgical means. Many different types of inguinal hernia repairs have been described in history. Inguinal hernias can be repaired via an open or a laparoscopic approach. However, a consensus opinion regarding which method is the most advantageous has not been reached and the method used is often based on surgeon's preference [Sanders and Waydia, 2014].

In the case of open inguinal hernia repair, tissue-based repairs or prosthetic repairs can be performed. Probably the best known tissue repairs are the Bassini technique and the Shouldice repair.

Bassini reported his series of open tissue repairs in 1885 [Matthews and Neumayer, 2008]. The Bassini technique is based on repair of the posterior wall of the inguinal canal with interrupted non-absorbable sutures [Wantz, 1989].

The Shouldice repair, originally described in 1953, is based on the Bassini repair, but uses several layers of running non-absorbable sutures [Simons et al., 2009; Welsh and Alexander, 1993]. The Shouldice repair is considered to be the best conventional technique [Simons et al., 2009; Simons et al., 1996], but in general practice it results in high recurrence rates up to 15 % [Beets et al., 1997].

The more widespread laparoscopic approaches are transabdominal preperitoneal (TAPP) repair and totally extraperitoneal (TEP) repair. In TAPP repair the mesh is placed into a preperitoneal position from the peritoneal cavity. In TEP repair the hernia is approached in the preperitoneal space and the peritoneum is not opened [Matthews and Neumayer, 2008].

According to the EHS guidelines on the treatment of inguinal hernia, the Lichtenstein and endoscopic inguinal hernia techniques are recommended as the best evidence-based options for primary inguinal hernia repair [Miserez et al., 2014; Simons et al., 2009].

2.5.1. Lichtenstein technique

Lichtenstein was a pioneer in the use of mesh in open inguinal hernia repair and his technique has become the gold standard of open inguinal hernia repair [Simons et al., 2009]. Lichtenstein had a theory that tissue–based repairs create tension in tissues and increase the likelihood of hernia recurrence [Lichtenstein et al., 1989].

In the Lichtenstein technique a 5–6 cm skin incision is made, which starts from the pubic tubercule and extends laterally within the Langer's lines [Amid, 2004a].

The external oblique aponeurosis is opened. The lower leaf of the external aponeurosis is freed from the spermatic cord and the upper leaf is freed from the underlying internal oblique muscle and aponeurosis for a distance of 3–4 cm above the inguinal floor. The iliohypogastric nerve is visualized. The spermatic cord with its cremaster covering is separated from the inguinal floor of the

inguinal canal and the pubic bone for a distance of about 2 cm beyond the pubic tubercle. When lifting the cord, the ilioinguinal nerve, the external spermatic vessels and the genital nerve should be included [Amid, 2004a].

To explore the internal ring for indirect hernia sacs, the cremasteric sheath is incised longitudinally at the deep ring. Complete stripping and excision of the cremasteric fibers is unnecessary and can result in injury to the nerves, small blood vessels and vas deferens. Indirect hernia sacs are freed from the cord to a point beyond the neck of the sac and inverted without ligation. To minimize the risk of postoperative ischemic orchitis, complete non sliding scrotal hernia sacs are transected at the midpoint of the canal, leaving the distal section in place. The anterior wall of the distal sac is incised to prevent postoperative hydrocele formation. In large direct hernias the sac is inverted with an absorbable suture [Amid, 2004a].

A 7 x 15 cm mesh is used. With the cord retracted cephalad, the lower medial corner of the mesh is placed over pubic tubercle, overlapping the pubic tubercle by 1.5–2 cm. The medial corner of the mesh is sutured to the rectus sheath above the pubic bone, avoiding the periosteum of the bone. This suture is continued as a continuous suture with no more than 3–4 passes to attach the lower edge of the mesh to the inguinal ligament up to a point just lateral to the internal ring. This prevents folding and movement of the mesh in the mobile area of the groin. A slit is made at the lateral end of the mesh, creating two tails (two-thirds wide above and one-third wide below). The cord is positioned between the two tails of the mesh. With the cord retracted downward and the upper leaf of the external oblique aponeurosis retracted upward, the upper edge of the mesh is sutured in place with two interrupted sutures (one suture to the rectus sheath and the other to the internal oblique aponeurosis, just lateral to the internal ring). While the mesh is fixed in place, it is important to give the mesh a dome-shape configuration. The tails of the mesh should be sutured with crossing the tails with a single non-absorbable monofilament suture, which creates a new internal ring made of mesh. The excess mesh on the lateral side is trimmed, leaving at least 5–6 cm of mesh lateral to the internal ring and it is placed underneath the external oblique aponeurosis [Amid, 2004a] (Figure 4).

The external oblique aponeurosis is closed over the cord with an absorbable suture. The skin is closed [Amid, 2004a].

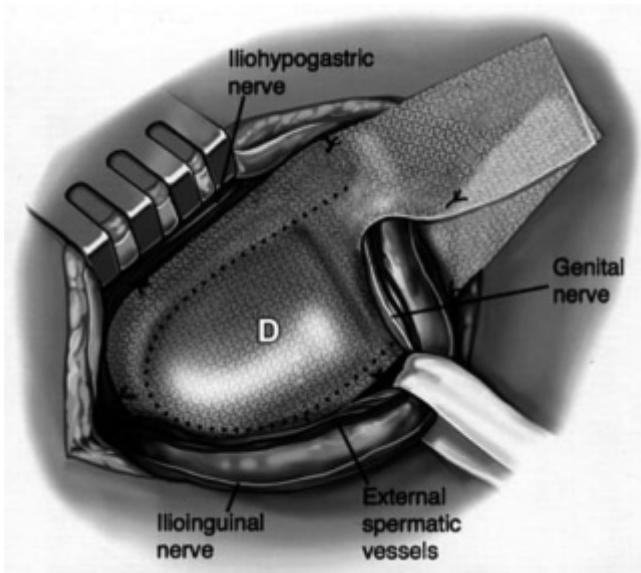

Figure 4. Extension of the mesh beyond the inguinal floor (dotted line) and the dome-shaped centre of the mesh (D) [Amid, 2004a] (Reproduced with the permission of Springer)

2.5.2. Lichtenstein versus laparoscopic repair

The Working Group of EHS guideline performed a meta-analysis of studies comparing the Lichtenstein technique and endoscopic inguinal hernia repair (TEP/TAPP). The results of long-term recurrence rates were lower in the Lichtenstein group, but were insignificant after excluding the data of one surgeon in a study of Eklund et al. [Eklund et al., 2009; Miserez et al., 2014]. In the study of Eklund et al. one surgeon was responsible for 33 % of recurrences in the endoscopic repair group [Eklund et al., 2009].

Also chronic pain was evaluated in above mentioned meta-analysis and the results of severe chronic pain did not differ between the open and the laparoscopic mesh repair groups [Miserez et al., 2014].

It is well known that endoscopic inguinal hernia repair results in lower rate of wound complications but there can be, although infrequently, more serious complications (vascular and visceral injuries) after endoscopic repair [McCormack et al., 2005; Paajanen et al., 2010].

Although the learning curve of surgical operations is surgeon specific, the learning curve of endoscopic inguinal hernia repair has been estimated at 50–100 cases [Matthews and Neumayer, 2008; Simons et al., 2009], with the first 30–50 being the most critical [Simons et al., 2009]. In the study of Eklund et al. the learning curve was estimated to be 25 TEP operations, resulting in a situation that one surgeon was responsible for 33 % of recurrences in the laparoscopic group [Eklund et al., 2009]. Also in the update of EHS guideline on the

treatment of inguinal hernia it is stressed that endoscopic hernia repair, especially TEP, has a long learning curve [Miserez et al., 2014].

The learning curve of the Lichtenstein repair has not been evaluated in many studies, but in a study of Wiese et al. the Lichtenstein repair has been estimated as a safe and effective operation to be performed under supervision even by junior residents [Wiese et al., 2010]. Also in a study of Paajanen, which evaluated the results of the Lichtenstein repair done by senior consultants and surgical trainees, there was no difference in the long-term outcome and the learning curve was estimated to be relatively short [Paajanen, 2003; Paajanen and Varjo, 2010].

2.6. Classification of inguinal hernias

There have been developed many different inguinal hernia classifications. Use of classifications is important for the description of the groin anatomy and the type of hernia. Also use of a general classification enables to analyse research data.

According to the EHS guideline on the treatment of inguinal hernia, it is advisable to use the EHS classification [Simons et al., 2009]. In the EHS classification the size of the hernia orifice is registered as 1 (1 finger or <1.5 cm), 2 (2 fingers or <3 cm) and 3 (more than two fingers or >3 cm). Anatomic localisation is registered as L (lateral or indirect hernia), M (medial or direct hernia), F (femoral hernia). For a combined hernia, it is recommended to note the different hernias. Letter P or R should be used for a primary or recurrent hernia, respectively [Miserez et al., 2007].

2.7. Meshes used for hernia repair

> If we could artificially produce tissues of the density and toughness of fascia and tendon, the secret of the radical cure of hernia would be discovered.
> Theodore Billroth (1829–1894) [Earle and Mark, 2008]

In 1935 nylon (trade name Polyamid) was discovered and the first hernia prosthetics were produced. The first reports in which nylon was used as a prosthetic are from 1944 and 1948. In 1941 polyethylene terephthalate (trade name Dacron) was patented. In 1954 polypropylene was discovered and the chemists Natta and Ziegler won in 1961 the Nobel Prize in Chemistry [Coda et al., 2012]. Usher reported the use of polyethylene mesh (trade name Marlex) in incisional hernia repair in 1958 [Bringman et al., 2010]. For years surgeons could choose from among a few prosthetics until in the 1990s companies began producing many different kinds of products which were mostly produced from polypropylene [Coda et al., 2012].

According to Coda et al., there are more than 160 meshes available on the market [Coda et al., 2012], making it complicated to choose a mesh whose

usage would result in the best outcome. There are meshes with 2D and 3D structures, flat meshes and plugs, monofilaments and multifilaments, absorbable and non-absorbable, with pores and without pores, with surface coating and combinations of these [Klinge and Klosterhalfen, 2012]. Despite the wide selection of brands available, nearly all meshes use one of the three basic materials – polypropylene, polyester or expanded polytetrafluoroethylene (ePTFE). These are used in combination with each other or with a range of additional materials [Brown and Finch, 2010].

It was assumed that mesh was a material which could be used for abdominal wall reinforcement with formation of scar tissue. Earlier it was expected that the best meshes would be those made of very strong material and able to induce the most of fibrosis. However strong fibrotic reaction led to pain and movement restriction [Brown and Finch, 2010].

Today an ideal mesh should be cost-effective, have no adhesion potential, have excellent tissue integration, minimal shrinkage, good memory and be easy to use. Ideal meshes should not promote infection, fistula or seroma formation and should not limit or negatively affect patient's normal activity [Bringman et al., 2010]. The requirements for an ideal mesh in hernia surgery are known, but mesh that satisfies all requirements has not yet been found [Conze et al., 2008]. Each product has its own unique advantages and disadvantages and therefore one product might never address the wide spectrum of inguinal hernia disease [Cavazzola and Rosen, 2013].

Soon after companies started to produce many different prosthetics, the weight of meshes became the most widely discussed topic in hernia surgery and the goal of all mesh developers was to produce lighter meshes in order to improve biocompatibility [Weyhe et al., 2007]. Implants were classified according to the weight of the material in grams per square metre [Weyhe et al., 2007]. Differences in weight vary and in a study of Klinge and Klosterhalfen the weight of available meshes ranged between 11 and 130 g/m² [Klinge and Klosterhalfen, 2012]. However, there is no general definition for „lightweight" and „heavyweight". Nowadays the term „lightweight" is used to describe a product with larger pores resulting in a smaller surface area [Bringman et al., 2010].

Heavyweight meshes are designed with thick polymer fibres, smaller pores, high tensile strength and large surface area [Klosterhalfen et al., 2005]. The mean distension of the anterior abdominal wall at 16 N is in the range between 11 % and 32 % for all directions [Junge et al., 2001]. Textile analysis of heavyweight meshes revealed an elasticity of 4–16 % at 16 N [Klosterhalfen et al., 2005]. Lighweight meshes were found to be superior due to their increased flexibility and reduction in discomfort [Brown and Finch, 2010]. After the introduction of lightweight meshes there was concern about their lower tensile strength. However, the tensile strength of surgical meshes in large incisional hernias, where the fascia cannot be closed and the bridging technique is used, is theoretically 32 N/cm at a maximum. In the case of abdominal wall augmentation in small hernias, the tensile strength of the mesh is 16 N/cm

[Klosterhalfen et al., 2005]. Therefore, tensile strength of heavyweight meshes more than 100 N/cm is disproportional and leads to low flexibility of the abdominal wall [Klosterhalfen et al., 2005; Welty et al., 2001].

Klinge and Klosterhalfen have classified the meshes used for hernia repair, based mainly on porosity (Table 1). The aim of this classification is to group the different meshes so that the impact of material can be evaluated systematically from the data of studies and registries [Klinge and Klosterhalfen, 2012].

Weyhe et al. reported in their experimental study that the main determinant of biocompatibility was the pore size of mesh rather than the amount implanted [Weyhe et al., 2006]. The inflammatory intensity of foreign body reaction depends on the porosity of meshes [Klinge et al., 2002b; Muhl et al., 2008]. As reported by Klinge et al., increased pore size had a major impact on the biological response [Klinge et al., 2002b]. In the case of small pores a dense scar plate will develop around the entire mesh [Klinge et al., 2002b; Muhl et al., 2008] and the extent of foreign body reaction does not permit the ingrowth of the local tissue [Klinge et al., 2002b]. Larger pores are filled with the local fat tissue and a thin scar network will form, resulting in the proper elasticity of the implant (Figure 5) [Klinge et al., 2002b; Muhl et al., 2008]. If a mesh with large pores is used then large pores will guarantee preserving of elasticity and will hamper the bridging of inflammation across the pores [Klinge et al., 2002b].

The porosity of meshes is measured as the percentage of the area of the mesh, which is not covered by filaments, reflected as textile porosity. Effective porosity represents the area of the „good pores“ where bridging of the scar tissue is avoided by a sufficient interfilamentary distance. [Klinge and Klosterhalfen, 2012; Muhl et al., 2008]. Porosity decreases if foreign body reaction is considered [Muhl et al., 2008]. For polypropylene meshes, 1000 μm is the least distance that prevents bridging of the scar tissue, which then fills out the entire pore [Conze et al., 2008].

While one possible reason for development of groin pain is non-absorbable sutures which are used for fixation of the mesh in Lichtenstein hernioplasty, other fixation solutions, among them self-gripping meshes, have been developed to reduce the rate of chronic pain. Self-gripping meshes have microgrips across mesh surface area, which ensure gripping between muscle fibres and the connective tissue and therefore no fixating sutures are needed [Chastan, 2009].

An important feature to be emphasized is shrinkage of meshes. The mesh itself does not shrink, but the surface is reduced due to reduction in the fibrotic scar tissues surronding the mesh. Shrinkage must be taken into consideration in the hernia repair technique [Klosterhalfen et al., 2005].

Table 1. Classification of meshes used for hernia repair [Klinge and Klosterhalfen, 2012]

Class	Description of class
Class I Large pore meshes **Ia monofilament** **Ib multifilament** **Ic mixed structure or polymer**	✓ Textile porosity >60 % ✓ Effective porosity >0%
Class II Small pore meshes **Ia monofilament** **Ib multifilament** **Ic mixed structure or polymer**	✓ Textile porosity <60% ✓ Without any effective porosity
Class III Meshes with special features	E. g. meshes with barrier function for intraperitoneal use
Class IV Meshes with films	Film-like meshes without porosity or submicronic pore size or secondarily excised pores
Class V 3D meshes	Pre-shaped, pre-formed, 3D devices
Class VI Biologicals	

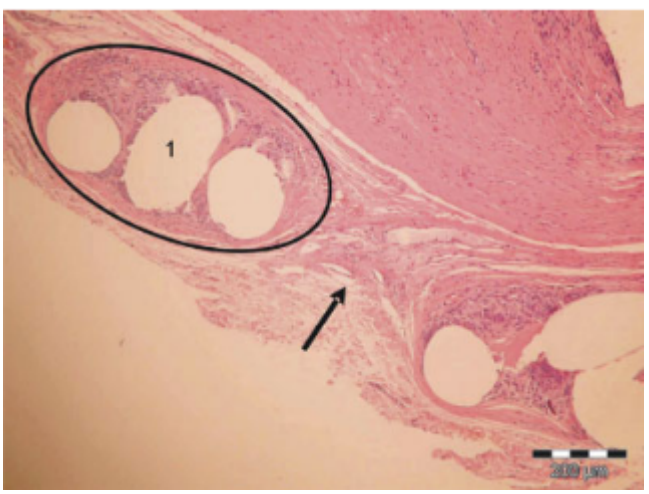

Figure 5. A monofilament polypropylene mesh after incorporation with typical granuloma formation of inflammatory cells and fibrotic capsule (line) around the filament (1) and bridging scar tissue within the pore (arrow) (light microscopy, staining with haematoxylin and eosin, standard measure 200 µm) [Muhl et al., 2008] (Reproduced with the permission of John Wiley and Sons)

2.8. Hernia recurrence

In the earlier period when tissue-based repairs were performed, the most widely discussed complication of hernia surgery was recurrence rate. Although some studies have reported low recurrence rates of tissue-based repairs (Shouldice repair) [Glassow, 1986; Paul et al., 1994], others have not obtained similar results [Beets et al., 1997; van Veen et al., 2007].

Tension-free mesh repair has become the gold standard because of lower recurrence rates compared with conventional suturing techniques. According to literature data, recurrence rates after non-mesh repairs vary between 4.4 and 17 % [Grant, 2000; van Veen et al., 2007]. Recurrence rates for mesh repairs vary between 0.3 and 2.2 % [Grant, 2000; van Veen et al., 2007].

In a study of van Veen et al. half of the recurrences occurred more than 3 years after operation, which made the authors speculate that in many studies recurrence rates were underestimated because of the lack of long-term follow-up [van Veen et al., 2007].

2.9. Chronic pain after inguinal hernia repair

After the widespread use of mesh repairs the recurrence rates after inguinal hernia surgery have become acceptable and attention has been focused, instead of recurrence rates, on chronic pain.

Although we can control pain with analgesics, chronic postsurgical pain is a major clinical problem, which can significantly influence patient's quality of life. The rate of chronic pain after inguinal hernia mesh repair may occur in 51.6 % of patients [O'Dwyer et al., 2005].

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [Merskey and Bogduk, 1994].

Distinction between acute and chronic pain is usually based on time. Acute pain is characteristic of all hernia operations. Benzon et al. defined chronic pain as the pain that persists beyond the course of an acute disease or a reasonable time for an injury to heal, or that is associated with a chronic pathologic process that causes continuous pain, or the pain recurs at intervals of months or years [Benzon et al., 2011]. IASP has defined chronic pain as the pain lasting longer than 3 months [Merskey and Bogduk, 1994]. According to Aasvang and Kehlet, the usage of synthetic materials for hernia repair may lengthen the inflammatory response and therefore chronic pain is defined as the pain lasting $\geq$6 months [Aasvang and Kehlet, 2005]. A similar definition can also be found in a guideline published by Alfieri et al. [Alfieri et al., 2011].

2.9.1. Causes of chronic pain

The reasons for posthernioplasty chronic pain are often unclear. It has been linked to nerve injury and nerve entrapment, but there is also association between the rate of chronic pain and the type of mesh used for hernia repair.

Chronic pain after inguinal hernia repair can be fundamentally divided into neuropathic pain and non-neuropathic pain (nociceptive pain) [Kehlet et al., 2006; Massaron et al., 2007].

To understand the etiology of nerve injury and to prevent nerve entrapment in inguinal hernia repair, a complete knowledge of the nerves located in the inguinal region is necessary. When the inguinal region is explored through the anterior approach, the ilioinguinal nerve, the genital branch of the genitofemoral nerve and the iliohypogastric nerve are at a risk of damage [Ferzli et al., 2007]. With open surgery the ilioinguinal nerve can be identified lateral to the internal ring, and between the ring and the anterior superior iliac spine. The iliohypogastric nerve is identified within the anatomic cleavage between the external and internal oblique aponeurosis. The inguinal segment of the genital branch of the genitofemoral nerve can be identified between the cord and the inguinal ligament and traced laterally to the internal ring [Bjurstrom et al., 2014]. The ilioinguinal nerve, the genital branch of the genitofemoral nerve and the iliohypogastric nerve are present at a mean of 96, 90 and 94 %, respectively [Alfieri et al., 2011]. Although there exist great variations in the nerves [Amid, 2004b], in 70–90 % of cases it is possible to identify all three inguinal nerves as three separate nerves [Alfieri et al., 2011].

According to the IASP, neuropathic pain is initiated or caused by primary lesion or dysfunction of the nervous system [Merskey and Bogduk, 1994]. The causes of neuropathic pain are nerve entrapment by mesh or sutures and neuroma formation associated with partial or complete transection of the involved nerve [Amid, 2004b; Ferzli et al., 2007].

Neuropathic pain can occur immediately after operation but not infrequently it can also occur after months or years. The pain is burning and radiates to the area supplied by the sensory nerve [Merskey and Bogduk, 1994].

For the iliohypogastric nerve, the pain radiates to the midline above the pubis and laterally to the hip region. For the ilioinguinal and the genitofemoral nerves, the pain radiates from the groin into the scrotum and penis or into the anterior part of the labia major and on the inside or the anterior surface of the thigh. Usually the pain is continuously present, but it is activity induced and therefore can be intensified by stretching of the hip joint, coughing, sneezing, sexual intercourse and general tension in the abdominal muscles, which results in nerve traction or compression [Loos et al., 2007; Merskey and Bogduk, 1994].

The diagnostic criteria for neuralgia in the inguinal region are burning pain with superimposed paroxysms in the distribution of the involved nerve, increased sensation of light touch or pinprick sensation, reproduction of paroxysmal pain by tapping neuromata at the site of nerve injury and transient pain relief from proximal local anaesthetic block [Merskey and Bogduk, 1994].

Nociceptive pain results from activation of high threshold peripheral sensory (nociceptor) neurons from local activation of inflammatory mediators [Kehlet et al., 2006] due to continuous inflammatory reaction around the mesh [Aasvang et al., 2008; Alfieri et al., 2011]. According to Amid, nociceptive pain is caused by the mechanical pressure of mesh on the adjacent tissue including vas deferens and nerves [Amid, 2004b]. Nociceptive pain is described as aching, stabbing, throbbing, sharp or gnawing [Massaron et al., 2007] and it is constant pain aggravated by strenuous exercise [Vuilleumier et al., 2009].

2.9.2. Risk factors for development of chronic pain

The risk factors for development of chronic pain are younger age, preoperative pain, severe early postoperative pain and female sex [Simons et al., 2009]. According to Reddi et al., mild preoperative pain is not a risk factor for development of chronic pain; postoperatively also acute moderate pain, not only acute severe pain, is a predictive factor for development of chronic pain [Reddi and Curran, 2014].

Poobalan et al. found that patients who were aged under 40 years had an increased risk for development of chronic pain [Poobalan et al., 2001]. Also in a systematic review of Nienhuijs et al. and in a study of Bay-Nielsen et al. chronic pain was associated with lower mean age [Bay-Nielsen et al., 2001b; Nienhuijs et al., 2007]. This can be explained by the fact that younger people are usually more active [Kalliomaki et al., 2008].

In a study of Poobalan et al. patients who reported pain preoperatively had an increased risk for development of chronic pain [Poobalan et al., 2001]. In another study preoperative pain had a predictive value for development of chronic pain [Wright et al., 2002].

In a study of Callesen et al. the rate of chronic pain at 1-year follow-up was higher in patients who had a high pain score 1 week after operation [Callesen et al., 1999].

In a review of Aasvang et al. it was found that females are at a higher risk of developing chronic pain than males [Aasvang and Kehlet, 2005].

2.9.3. Assessment of chronic pain

Pain is a highly subjective experience and is therefore difficult to objectify. Several different scales (visual analogue scale (VAS), numeric rating scale, McGill pain questionnaire, Short form McGill pain questionnaire, chronic pain grade scale, Short form 36 bodily pain scale) have been developed to quantify pain.

The VAS is a continuous scale comprising a horizontal or vertical line, usually 100 mm in length. For pain intensity, the scale is most commonly anchored by „no pain“ (score of 0) or „worst imaginable pain“ (score of 100) (Figure 6). To avoid clustering of scores around a preferred numeric value,

numbers or vertical descriptors at intermediate points are not recommended [Hawker et al., 2011; van Hanswijck de Jonge et al., 2008]. Patients are asked to mark a point on the line where they think their pain is [van Hanswijck de Jonge et al., 2008].

Figure 6 Visual analogue pain scale

2.9.4. Impact of different mesh parameters on chronic pain

Usage of foreign material in hernia surgery can induce stronger inflammatory reaction [Klinge et al., 1999], which can result in chronic pain. The pain may be caused by damage to the inguinal nerves, but there is also association between the rate of chronic postoperative pain and the type of foreign material used for alloplasty.

Different mesh characteristics have been studied, among them weight of mesh has probably gained the most attention. The rate of chronic pain varies significantly in different studies. In a study of O'Dwyer et al. 39.5 % of patients in the LW (lightweight) group and 51.6 % in the HW (heavyweight) group reported pain of any severity at the site of hernia repair 12 months after operation (P=0.033), among them 3 % of the patients in the LW group and 4 % of the patients in the HW group experienced severe or very severe pain [O'Dwyer et al., 2005]. Also Post et al. reported that usage of lightweight mesh in a subgroup analysis of 70 physically active patients was associated with significantly less pain on exercise at 6-month follow-up, whereas no patient reported severe pain but, unfortunately, the exact rates of chronic pain were not presented [Post et al., 2004]. In a study by Bringman et al. groin pain was experienced by 10.3 % in the LW group and 12.2 % in the HW group at 1-year follow-up (P=0.49) [Bringman et al., 2005]. At 3-year follow-up less patients in the LW group reported pain during different activities (at rest, on coughing, when rising from lying to sitting and during physical activity), but it reached statistical significance only during rising from lying to sitting [Bringman et al., 2006]. According to Smietanski et al., there was no statistically significant difference in terms of pain between the LW and HW groups at 6- and 12-month follow-up. Of the patients 10.7 % in the LW group and 9.9 % in the HW group suffered from pain 6 months after operation. The rates of chronic pain at 12-month follow-up were 3.8 % and 6.2 %, respectively [Smietanski, 2008] and at 3-year follow-up 2.6 % and 2.5 %, respectively [Bury and Smietanski, 2012]. In

the most recent study comparing lightweight and heavyweight mesh, the rate of chronic pain in the LW group was 16.7 % and in the HW group 21.8 % at 6-month follow-up, but it did not reach statistical significance. Although the difference between the two study groups was insignificant also at 1-year follow-up, the rates of chronic pain decreased to 7.4 % in the LW group and to 5.5 % in the HW group [Yazdankhah Kenary et al., 2013].

Also several systematic reviews and meta-analyses comparing lightweight and heavyweight meshes have revealed reduced rates of chronic pain in the LW group [Li et al., 2012; Sajid et al., 2012; Smietanski et al., 2012; Zhong et al., 2013; Uzzaman et al., 2012]. Li et al. included open and laparoscopic repairs in their study [Li et al., 2012], which in the opinion of Memon et al. is like comparison of apples and oranges [Memon et al., 2012]. Smietanski et al. evaluated also severe chronic pain but found no significant difference between the two mesh types concerning severe pain [Smietanski et al., 2012].

When reduction in weight has resulted in lower chronic pain rates in many studies, self-gripping meshes have not yielded promising results. In a prospective study the usage of self-gripping mesh resulted in a 2.8 % rate of chronic pain at 6-month follow-up [Garcia Urena et al., 2011] and 4 % at a median follow-up of 17 months [Pedano et al., 2012]. In a randomised study of Jorgensen et al., comparing self-gripping and sutured mesh for the open inguinal hernia repair, the rate of pain at 1-year follow-up was 9.9 % in the self-gripping group and 7.7 % in the sutured mesh group (P=0.561) [Jorgensen et al., 2013]. A study of Pierides et al. found no difference between the self-gripping and the sutured mesh group in terms of chronic pain one year after hernia repair, either [Pierides et al., 2012]. Although in a study of Kingsnorth et al. there were significant differences in the change of VAS scores at discharge and at one week follow-up, compared with baseline, there were no differences in VAS scores or in the rate of chronic pain at 3-month follow-up [Kingsnorth et al., 2012]. Chatzimavroudis et al. reported higher rates of chronic pain in the self-gripping mesh group at 1- and 2-year follow-up (16 % versus 12 % and 8 % versus 4 %, respectively), but the differences were statistically insignificant [Chatzimavroudis et al., 2014].

There are also several systematic reviews and meta-analyses comparing self-gripping mesh and sutured mesh, where self-gripping mesh has failed to demonstrate reduced rates of chronic pain after open inguinal hernia repair [Fang et al., 2014; Li et al., 2014; Pandanaboyana et al., 2014; Sajid et al., 2014; Zhang et al., 2013].

Like the usage of self-gripping mesh, also the usage of absorbable sutures has not resulted in lower rates of chronic pain after inguinal hernia repair. In a study of Paajanen 26 % of the patients in the study group where absorbable sutures were used and 24 % of the patients in the group where non-absorbable sutures were used reported pain at 2-year follow-up [Paajanen, 2002].

Several studies compared meshes with different pore sizes, however, the investigated meshes differed not only in pore size but also in weight [Bringman et al., 2006; Bury and Smietanski, 2012; O'Dwyer et al., 2005].

2.9.5. Surgical treatment of chronic pain

The choice of adequate therapy for chronic groin pain after inguinal hernia repair is controversial [Campanelli et al., 2013]. The EHS recommends to consider a multidisciplinary approach at a pain clinic for treatment of chronic postoperative pain [Simons et al., 2009]. It should be recognized that chronic post hernioplasty pain may be multifactorial and it is possible that specific etiology is not identifiable [Ferzli et al., 2008].

Although surgical treatment of chronic post hernioplasty pain is restricted because of the lack of scientific data, resection of entrapped nerves, mesh removal in mesh-related pain or removal of fixating sutures can be considered [Simons et al., 2009]. According to the international guidelines for prevention and management of chronic posthernioplasty pain the reasonable time point for surgical treatment is 1 year postoperatively, when the inflammatory response has decreased. Surgical treatment should be considered only when pain curtails activities [Alfieri et al., 2011] and conventional non-invasive treatment has failed [Alfieri et al., 2011; Palumbo et al., 2007]. Although there is no good evidence of the efficacy of local anaesthetic blocks in chronic posthernioplasty pain, the potential for local anaesthetic blocks should be considered in predicting surgical outcome: if a diagnostic nerve block is ineffective, patients will most likely not benefit from surgical treatment [Werner, 2014].

It is difficult or even impossible to pinpoint the involved nerve because of common peripheral communication between the three nerves [Amid, 2004b; Hakeem and Shanmugam, 2011]; the innervation field of the three nerves overlaps and frequently more than one nerve can cause postoperative neuropathic pain [Amid, 2004b]. Therefore, when surgical treatment is indicated, triple neurectomy, including the intramuscular segment of the iliohypogastric nerve, should be performed [Alfieri et al., 2011]. However, search for the nerves involved in the scar tissue can be extremely difficult [Palumbo et al., 2007]. Neurectomy does not address the nociceptive component caused by meshoma or neuropathic testicular pain [Bjurstrom et al., 2014].

Earlier, a two-stage operation, including ilioinguinal and iliohypogastric neurectomies through an inguinal approach and genitofemoral neurectomy through a posterior flank approach, has been advised [Starling and Harms, 1989].

According to Amid, surgical treatment of chronic posthernioplasty pain consists of one-stage resection of the entire length of the nerves as far proximal and distal as possible in order to include the involved segment. The transected nerve ends should be ligated in order to prevent neuroma formation. The ligated ends of the ilioinguinal and iliohypogastric nerves should be implanted within the internal oblique muscle, which prevents adherence of the cut ends to the inguinal ligament and external oblique aponeurosis, in order to prevent recurrence of pain. In the case of the genital branch of the genitofemoral nerve, the proximal cut end of the nerve is ligated with the nerve under tension in order to allow retraction of the nerve into the internal ring. As reported by Amid, 80 % of the patients recovered completely after one-stage triple neurectomy

[Amid, 2004b]. The advantages of the open approach are the possibility to perform a single stage operation for triple neurectomy, as well as to remove meshoma when necessary. The disadvantage of the approach is its technical difficulty when operating within the scarred field, placing the spermatic cord and vascular structures at a higher risk of compromise [Bjurstrom et al., 2014].

In a study of Campanelli et al. a simultaneous double approach (ilioinguinal and iliohypogastric nerves by the anterior approach, genitofemoral trunk by posterior pre-peritoneal approach from the same skin incision) triple neurectomy (in 44/46 cases) was used, resulting in resolution of pain in 87 % of cases [Campanelli et al., 2013].

Endoscopic retroperintoneal neurectomy for chronic pain after inguinal hernia repair has also been described [Giger et al., 2009; Muto et al., 2005]. According to Giger et al., the severity of chronic pain decreased significantly after endoscopic neurectomy in 37 of the 39 patients compared to preoperative values [Giger et al., 2009].

However, the unreasonable failure to treat pain is an abrogation of fundamental human rights [Brennan et al., 2007] and therefore surgical treatment of chronic posthernioplasty pain should definitely be considered for patients in whom conservative pain management treatment has failed.

2.10. Foreign body feeling

Many patients report a feeling of a foreign body after implantation of mesh in the groin [Post et al., 2004], which is probably the result of foreign body reaction. Therefore, it is speculated that meshes whose usage causes less foreign body reaction cause also less chronic symptoms, including foreign body feeling, which results in subjective improvement [Post et al., 2004]. According to Bringman et al., a successful procedure is one in which a patient has no sensation of foreign body and can return quickly to normal activities [Bringman et al., 2010]. However, according to Smietanski et al., the clinical relevance of foreign body feeling is unknown and although it is reported by patients, it is not likely to influence daily activities and quality of life [Smietanski et al., 2012].

Foreign body feeling is usually assessed as a yes-or-no question [Bringman et al., 2006; Post et al., 2004].

In a study of Post et al. significantly less patients reported foreign body feeling in the LW group compared with the HW group after the Lichtenstein repair (17.2 versus 43.8 %) at 6-month follow-up [Post et al., 2004]. Also Bringman et al. reported less foreign body feeling in the LW group compared with the HW group (14.7 versus 22.6 %) at 3-year follow-up [Bringman et al., 2006]. In meta-analyses comparing lightweight and heavyweight meshes the presence of foreign body feeling was dominating in the LW group [Smietanski et al., 2012; Uzzaman et al., 2012]. However, in a study comparing self-gripping mesh and sutured mesh, there was no difference in foreign body feeling between the study groups at 1-year follow-up [Pierides et al., 2012]. In a

prospective study self-gripping mesh resulted in a 8.9 % rate of foreign body feeling at 6-month follow-up [Garcia Urena et al., 2011]. Also in a prospective study of self-gripping mesh the rate of foreign body feeling at a median follow-up of 17 months was 2 % [Pedano et al., 2012].

2.11. Quality of life

Quality of life is a measure increasingly used to evaluate the success of treatment [Pierides et al., 2013]. Different questionnaires have been developed and used to assess quality of life and its changes after treatment, including inguinal hernia repair (RAND SF 36; Short Form 36, SF36; Core Outcome Measures Index, COMI; EuroQol; EQ-5D) [Palmqvist et al., 2013; Staerkle and Villiger, 2011].

The RAND SF36 1.0 questionnaire is a generic quality of life questionnaire. It is the same as the Short Form Health Survey, except for the scoring algorithm of two domains. The RAND SF36 measures 8 domains of health: general health, vitality, bodily pain, mental health, social functioning, physical functioning, emotional role (limitations caused by emotional problems) and physical role (limitations caused by physical health). The RAND SF36 questionnaire's score 100 represents the best possible health [Hays et al., 1993]. The RAND SF36 has been validated for the Estonian population [Lai, 2012].

According to Post et al., there was no difference in the quality of life scores between the LW and HW groups, but regardless of the type of mesh implanted, the quality of life scores improved significantly in most domains after surgery at 6-month follow-up, compared with the preoperative scores [Post et al., 2004]. Also in a study of Bringman et al. there were no differences in the quality of life scores between the LW and the HW groups at 1-year follow-up [Bringman et al., 2005].

Although quality of life assessment is frequently used to evaluate the effects of treatment, Mathur et al. have measured quality of life in patients with inguinal hernia on the elective waiting list for repair. According to their study, patients with inguinal hernia have significantly impaired quality of life compared with age-, sex- and comorbidity-matched controls [Mathur et al., 2006].

3. AIMS OF THE STUDY

1. To evaluate the rate of chronic pain after open inguinal hernia repair in the case of using different meshes and to clarify which mesh parameters have a significant influence on the development of chronic pain.
2. To evaluate the rate of foreign body feeling after open inguinal hernia repair in the case of using different meshes and to clarify which mesh parameters have a significant influence on the development of foreign body feeling.
3. To evaluate patients' quality of life after inguinal hernia repair.

4. MATERIAL AND METHODS

4.1. Inclusion and exclusion criteria

All patients scheduled for inguinal hernia repair at the Surgery Clinic of Tartu University Hospital, Department of General Surgery, in the following time periods, who met the inclusion criteria, were eligible to participate in the studies:

from 1/2007 to 7/2008 (I, II)
from 1/2011 to 4/2012 (III)
from 1/2012 to 6/2013 (IV)

The eligible patients were adults aged 18 years or older with unilateral primary reducible inguinal hernia, providing consent for participation in the study. Patients younger than 18 years and patients with irreducible, strangulated or recurrent hernia were excluded. Also patients who were unable to understand the questionnaire or who were unwilling to participate in the study were excluded.

4.2. Randomisation

The patients were randomised to 1 of 2 parallel study groups. Randomisation was done using a set of sealed opaque envelopes, which were all prepared by one investigator (CN) prior to commencement of the study. The envelopes were kept in an arranged location in the operating room. Before operation, the surgeon took randomly a sealed envelope that contained a label of mesh. The patients were blinded to which mesh they received.

4.3. Meshes and operation technique

4.3.1. Lightweight versus heavyweight mesh (I, II)

In the HW group the patients received Premilene® Mesh (B. Braun Melsungen AG, Melsungen, Germany); in the LW group the patients received Optilene® Mesh LP (B. Braun).

Premilene® Mesh is a monofilament polypropylene mesh with a pore size of 0.8 mm and a weight of 82 g/m². Optilene® Mesh LP is monofilament polypropylene mesh with a pore size of 1.0 mm and a weight of 36 g/m².

A tension-free hernioplasty, using the modified Lichtenstein technique, was performed in both study groups. The operative technique was based on the description of Amid [Amid, 2004a], except that indirect hernia sacs were freed from the cord, ligated and resected and the upper edge of the mesh was sutured in place with more than two interrupted sutures. In both groups a mesh of 4.5 x 10 cm was applied and polypropylene 2/0 suture material was used for mesh implantation. All nerves in the inguinal canal were identified and preserved when possible.

4.3.2. Pore size study (III)

In the UM group the patients received Ultrapro® mesh (Ethicon, Hamburg, Germany); in the OM group the patients received Optilene® LP mesh (B. Braun).

Ultrapro® is a lightweight partially absorbable mesh consisting of polypropylene and polyglecaprone with a weight of 28 g/m² and a pore size of 3–4 mm. The resorption time of polyglecaprone is 84–140 days [Klosterhalfen et al., 2005]. Optilene® LP mesh is a monofilament polypropylene lightweight mesh with a weight of 36 g/m² and a pore size of 1 mm.

A tension-free repair using the modified Lichtenstein technique was performed in both study groups. The operative technique was based on the description of Amid [Amid, 2004a], except that indirect hernia sacs were freed from the cord, ligated and resected and the upper edge of a mesh was sutured in place with more than two interrupted sutures. A mesh with measurements 4.5 x 10 cm was applied, while Optilene® LP mesh was commercially preshaped and Ultrapro® mesh was shaped by the surgeon during the operation, by using a stencil. Polyprolylene 2/0 suture material was used for mesh implantation. All nerves in the inguinal canal were identified and preserved when possible.

4.3.3. Self-gripping versus sutured mesh (IV)

In the OLP group the patients received Optilene® LP mesh (B. Braun); in the PPG group the patients received Parietex ProGrip mesh (Covidien, Trevoux, France).

Optilene® LP mesh is a monofilament polypropylene lightweight mesh with a weight of 36 g/m² and a pore size of 1 mm. Parietex ProGrip™ mesh is a partially absorbable monofilament mesh consisting of polyester and polylactic acid with a weight of 74 g/m² before resorption and 38 g/m² after resorption and a pore size of 1.1 x 1.7 mm. Parietex ProGrip™ mesh has microgrips across its surface area, which ensure gripping between muscle fibres and the connective tissue. The resorption time of polylactic acid is 12 months [Chastan, 2009]. Both meshes are commercially preshaped. Optilene® LP mesh with measurements 6 x 14 cm and Parietex ProGrip™ mesh with measurements 8 x 12 cm were used.

A tension-free hernioplasty, using the modified Lichtenstein technique, was performed in the OLP group. The operative technique was based on the description of Amid [Amid, 2004a], except that indirect hernia sacs were freed from the cord, ligated and resected and the upper edge of the mesh was sutured in place with more than two interrupted sutures. Polyprolylene 2/0 suture material was used for mesh implantation. In the PPG group the inguinal canal was prepared and the wound was later closed as in the standard Lichtenstein operation. The mesh was placed in position in the inguinal canal, the flaps were closed around the cord and pressure was applied to the mesh for fixing it. All nerves in the inguinal canal were identified and preserved when possible in both study groups.

4.4. Preoperative data and follow-up visits

The patients were examined after 7 days, 1 month, and 6 months. In the study comparing the weight of the meshes, follow-up examination was performed also 3 years after the operation.

The preoperative and postoperative data were documented using standardised forms. The data included demographic data, body mass index, duration of the disease, method of anaesthesia, type of hernia (direct or indirect), size of hernia, hernial sac handling, mesh used, duration of operation, length of hospital stay and experience of the surgeon (trainee or staff surgeon).

The patients were examined for any evidence of wound infections, haematomas, seromas and recurrent hernia at every postoperative follow-up visit. The patients were inquired about postoperative analgesic consumption.

4.5. Chronic pain

The primary endpoint of three randomised studies was the rate of chronic groin pain at 6-month follow-up, taking into account all patients who reported pain during different activities (yes-or-no questions).

The pain questionnaire was completed before the operation and during follow-up visits at week 1, month 1 and month 6 and, in the case of the study comparing the weight of the meshes, also at year 3.

The pain questionnaire included questions about pain at rest, on coughing, when rising from lying to sitting and during physical effort and exercise (all yes-or-no questions). When patients' response to the questionnaire was positive, the pain scores were measured on a visual analogue scale (VAS) ranging from 0 mm (no pain) to 100 mm (worst imaginable pain). A score less than 10 was graded as mild pain, a score 10–50, as moderate pain, and a score more than 50, as severe pain. Such gradation has been used in similar studies [Page et al., 2002]. The analysis of the distribution of pain severity was based on the highest score on the visual analogue scale during different activities (at rest, on coughing, when rising from lying to sitting, and during physical effort and exercise). Data about whether pain influenced the patients' everyday activities were recorded as well.

4.6. Foreign body feeling

Foreign body feeling was a secondary outcome measure.

Foreign body feeling was registered as a yes-or-no question and the data were collected at follow-up visits at week 1, month 1 and month 6 and, in the case of the study comparing weight of meshes, also at year 3.

4.7. Quality of life

Quality of life was a secondary outcome measure.

Quality of life was evaluated using the RAND SF36 questionnaire, which was completed before the operation and 6 months after the operation. The SF36 questionnaire is a generic quality of life questionnaire, which measures 8 domains of health: general health, vitality, bodily pain, mental health, social functioning, physical functioning, emotional role and physical role. The SF36 questionnaire's score 100 represents the best possible health [Hays et al., 1993].

4.8. Statistical analysis

4.8.1. Lightweight versus heavyweight mesh (I, II)

A sample size of 114 eligible patients (57 in each group) was necessary to ensure the 80% power to detect a benefit of 25% for lightweight mesh for primary efficacy (rate of chronic pain at 6 months: HW mesh, 40%; LW mesh, 15 %).

The study groups were analysed per protocol principle. Patients who were lost during follow-up were excluded from the analysis; only the patients who completed the questionnaire were included.

The data of 1-week, 1-month and 6-month follow-up visits were analysed using the Statistica® version 8.0 software package (StatSoft, Tulsa, USA) for Windows XP Professional (Microsoft Inc., USA), the data of 3-year follow-up were analysed using the Statistica® version 10.0 software package for Windows XP Professional. The χ^2 and Fisher's exact tests were used to assess differences between categorical data. Scores on the VAS were compared by the Mann-Whitney U test. To analyse quality of life scores, the *t*-test was used. All statistical tests were two-sided and $p \leq 0.05$ was considered significant.

4.8.2. Pore size study (III)

In the study comparing the weight of the meshes the rate of chronic pain in the group, where also Optilene® LP mesh was used was 47.8 % [Nikkolo et al., 2010]. In a study of Smietanski et al. the rate of pain (VAS>0) after inguinal hernia repair with Ultrapro mesh was 21.2 % [Śmietański et al., 2009]. Based on previous research, to show that the difference in the rate of chronic pain for OM 48 % vs UM 21 % would be about 27 % according to Fisher's exact test at the 5 % significance level (power 80%), a sample size of 56 patients was necessary. Considering the drop-out rate to be 5 %, a minimum of 118 participants were needed for the study.

The study groups were analysed per protocol principle. The patients who were lost during follow-up were excluded from the analysis; only the patients who completed the questionnaire were included.

The data were analysed using the Statistica® version 10.0 software package for Windows XP Professional. To test the primary hypothesis (rate of chronic

pain in the two study groups at 6-month follow-up), Fisher's exact test was used. To describe associations for the binary outcome variables, risk ratios with 95% confidence intervals were reported. A logistic regression model was used to control for confounding variables (adjusting for sex, age groups (age <65 vs. ≥65 years) and severe preoperative pain). VAS scores were analysed by fitting a linear mixed model with the explanatory between-group variable (mesh usage) and the within-group variable (time) to the data. Analysis of covariance was used to evaluate association between quality of life scores at 6-month follow-up and type of mesh, while adjusting for the effect of the preoperative quality of life scores. All statistical tests were two-sided and $P \leq 0.05$ was considered significant.

4.8.3. Self-gripping versus sutured mesh (IV)

To demonstrate that the rate of chronic pain between the study groups would decrease by 25 % according to Fisher's exact test at the 5 % significance level (power 80%), a sample size of 65 patients was calculated (the rate of chronic pain in the OLP group 48 % and in the PPG group 23 %). The rate of chronic pain in the OLP group was based on the results of our previous study [Nikkolo et al., 2010].

The study groups were analysed per intention-to-treat principle. The patients' data which were lost because of drop-out were replaced with data from the last completed follow-up, except for the quality of life scores where the median scores for the study group were used.

The data were analysed using the Statistica® version 12.0 software package for Windows XP Professional. Fisher's exact test was used to test the primary hypothesis. To describe associations for binary outcome variables, risk ratios with 95% confidence intervals were reported. A logistic regression model was used to control presence of pain at 6 months for confounding variables (adjusting for age groups (age <65 vs. ≥65 years), severe preoperative pain (VAS≤50 vs. VAS>50), severe early postoperative pain (VAS≤50 vs. VAS>50 at 1-week follow-up)). VAS scores were analysed by fitting a linear mixed model with the explanatory between-group variable (mesh usage) and the within-group variable (time) to the data. Analysis of covariance was used to evaluate association between quality of life scores at 6-month follow-up and type of mesh while adjusting for the effect of the preoperative quality of life scores. All statistical tests were two-sided and $P \leq 0.05$ was considered significant.

5. RESULTS

5.1. Lightweight versus heavyweight mesh (I, II)

The study flow chart is presented in Figure 7.

The patient and operative data are presented in Table 2.

According to the primary endpoint, 59.4 % of the patients in the HW group and 47.8 % of the patients in the LW group experienced pain of any severity (VAS score ≥1) during any physical activity at 6-month follow-up (P=0.221). The respective results at 3-year follow-up were 17.2 % and 29.3 % (P=0.132). Comparison of the results of 6-month follow-up and 3-year follow-up revealed that the rate of chronic pain had decreased significantly in the HW group (P<0.001) and as well as in the LW group (P=0.03).

Positive responses to the pain questionnaire at 6-month follow-up are presented in Table 3 and at 3-year follow-up in Table 4. Differences in the median VAS scores for the study groups were statistically insignificant. Mean VAS scores and 95 % confidence intervals based on the highest VAS score for different activities before operation, and at 1-week, 1-month and 6-month follow-up, are presented in Figure 8. At 3-year follow-up the mean VAS scores were 34.3 in the HW group and 32.5 in the LW group. There was no significant difference in the distribution of pain severity between the HW group and the LW group at 6-month follow-up (Table 5). As only a few patients reported pain during different activities (at rest, on coughing, when rising from lying to sitting and during physical activity) at 3-year follow-up, the distribution of pain severity is not informative and will not be presented. Comparison of the 6-month follow-up VAS scores and the three-year follow-up VAS scores for the most painful activity showed that there were 6 patients in the HW group and 12 patients in the LW group who had reported stronger pain at three-year follow-up (P=0.135).

Of all studied patients under the age of sixty-five, 25.7 % reported chronic pain at three-year follow-up. The corresponding result for patients over the age of sixty-five at 3-year follow-up was 16.7 % (P=0.26).

At three-year follow-up 42.9 % of the patients who had had severe pain (VAS score >50) preoperatively also reported pain during different activities and 19.6 % of the patients who had not had severe pain preoperatively (VAS score <50) reported pain during different activities (P=0.048).

Of the patients 41.7 % who had severe pain on the 7th postoperative day had also pain at three-year follow-up. However, 20.2 % of the patients who did not report severe pain on the 7th postoperative day had pain during different activities at three-year follow-up (P=0.081)

Only 9.4% of patients in the HW group and 6% of the patients in the LW group had pain at the operation site after 6 months, which influenced their daily activities (p=0.463). At three-year follow-up 5.2 % of the patients in the HW group and 6.9 % of the patients in the LW group had pain at the operation site, which influenced their daily activities (P=0.999).

There was no difference in analgesic consumption between the study groups. The analgesics used against pain were non-steroidal anti-inflammatory drugs (NSAID); no combination of a NSAID and an opioid was used in this study. Altogether 93.8% of the patients in the HW group and 98.5% of the patients in the LW group did not use any analgesics after 6 months. Only one patient in the HW group used analgesics for groin pain at 3-year follow-up.

Foreign body feeling at the operation site was experienced by 32.8% of the patients in the HW group and by 20.9% of the patients in the LW group after 6 postoperative months (p=0.123). At 3-year follow-up, there were also more patients in the HW group than in the LW group who stated that they could feel the mesh in the groin (27.6 vs. 20.7 %, *P*=0.397). Among them 11 patients in the HW group and 8 patients in the LW group reported foreign body feeling at 6-month follow-up but no foreign body feeling at three-year follow-up. Eight patients in the HW group and 9 patients in the LW group had no foreign body feeling at 6-month follow-up but had developed it by three-year follow-up. Of the patients 37.5 % in the HW group who reported foreign body feeling had also pain during different activities at 3-year follow-up. At the same time, 9.5 % of the patients in the HW group who had no foreign body feeling at three-year follow-up reported pain during different activities (*P*=0.011). In the LW group the respective results at 3-year follow-up were 58.3 % and 21.7 % (*P*=0.016). Comparison of the relevant data for the two study groups revealed no significant difference.

There were no significant differences in any dimension of quality of life on the SF36 questionnaire between the two study groups 6 months after surgery. However, both study groups showed a significant improvement in the postoperative scores, in comparison with the preoperative scores, in all dimensions except for general health (Table 6).

At three-year follow-up there was 1 hernia recurrence in the HW group and 1 hernia recurrence in the LW group. The overall recurrence rate, expressed with respect to the number of patients who completed postoperative follow-up, was 1.7 %.

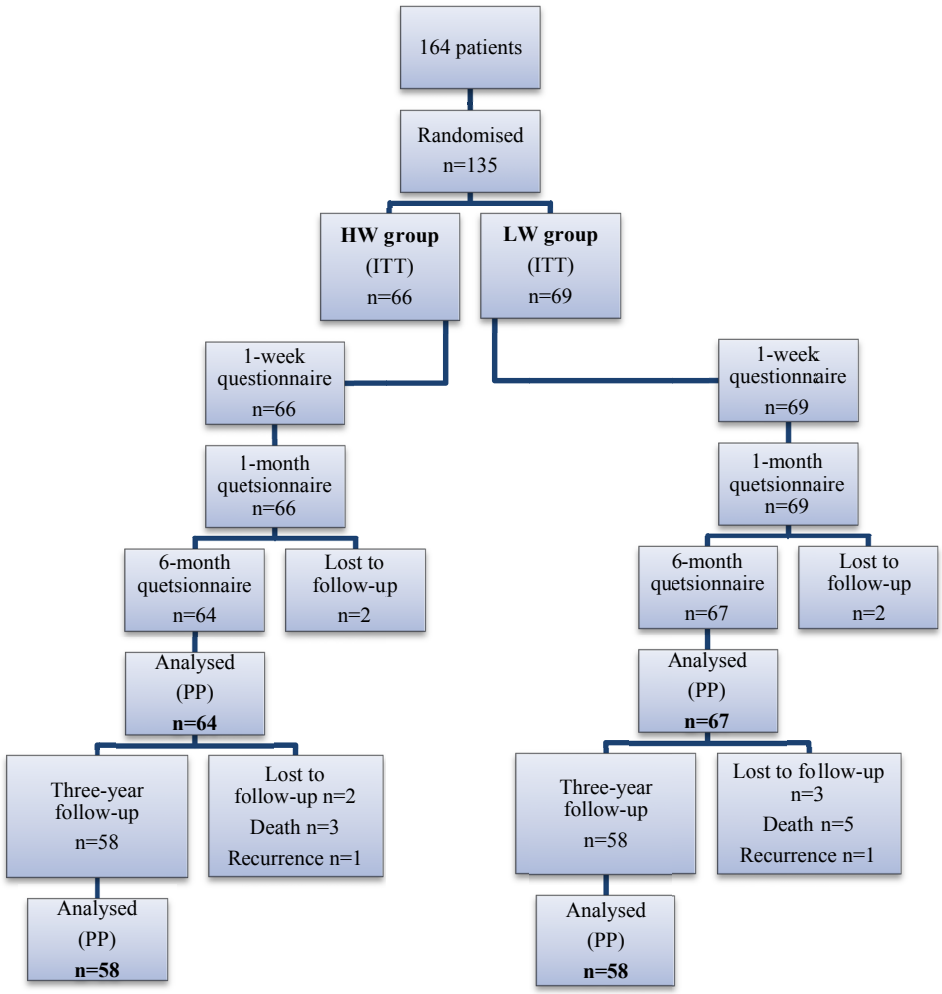

Figure 7. Study flow chart (lightweight versus heavyweight mesh I, II)
HW heavyweight mesh, *LW* lightweight mesh, *ITT* intention-to-treat population, *PP* per protocol principle

Table 2. Patient and operative data (lightweight versus heavyweight mesh I, II)

	HW group (n=64)	LW group (n=67)
Mean age (years)	57.2	59.2
Sex ratio M:F	60:4 (93.8:6.3 %)	61:6 (91:9 %)
BMI (kg/m²)	25.5 (17.7–33.6)[a]	25 (17.5–32.9)[a]
Mean time from hernia occurrence to operation (months)	14.3 (0.5–360)[a]	21.5 (0.4–360)[a]
Hernia		
Direct	23 (35.9 %)	34 (50.8 %)
Indirect	38 (59.4 %)	31 (46.3 %)
Combined	3 (4.7 %)	2 (3 %)
Size of defect (cm)		
<1.5	13 (20.3 %)	11 (16.4 %)
1.5- 3	43 (67.2 %)	49 (73.1 %)
>3	8 (12.5 %)	7 (10.5 %)
Anaesthesia		
Spinal	20 (31.3 %)	28 (41.8 %)
Mask	4 (6.3 %)	1 (1.5 %)
Laryngeal mask	33 (51.6 %)	35 (52.2 %)
Endotracheal	5 (7.8 %)	2 (3 %)
Local	2 (3.1 %)	1 (1.5 %)
Mean operating time (min)	53 (31–111)[a]	49 (20–73)[a]
Hernial sac		
Resected	40 (62.5 %)	31 (46.3 %)
Non-resected	24 (37.5 %)	36 (53.7 %)

[a] Minimal and maximal values are shown in the parentheses
HW heavyweight mesh, *LW* lightweight mesh, *BMI* body mass index

Table 3. Positive answers to the pain questionnaire at 6-month follow-up after inguinal hernioplasty (lightweight versus heavyweight mesh I, II)

	HW group (n=64)	**LW group (n=67)**	***P* value***
Primary endpoint**	38 (59.4 %)	32 (47.8 %)	0.221
Pain in the groin at rest	4 (6.3 %)	0	0.054
Pain in the groin on coughing	2 (3.1 %)	3 (4.5 %)	0.999
Pain in the groin when rising from lying to sitting	5 (7.8 %)	3 (4.5 %)	0.486
Pain in the groin during physical activity	15 (23.4 %)	13 (19.4 %)	0.671

*Fisher's exact test
**The rate of chronic groin pain at 6-month follow-up, taking into account all patients who reported pain during different activities
HW heavyweight mesh, *LW* lightweight mesh

Table 4. Positive answers to the pain questionnaire at 3-year follow-up after inguinal hernioplasty (lightweight versus heavyweight mesh I, II)

	HW group (n=58)	**LW group (n=58)**	***P* value***
Primary endpoint**	10 (17.2 %)	17 (29.3 %)	0.132
Pain in the groin at rest	2 (3.5 %)	2 (3.5 %)	0.999
Pain in the groin on coughing	0	3 (5.2 %)	0.999
Pain in the groin when rising from lying to sitting	5 (8.6 %)	0	0.999
Pain in the groin during physical activity	7 (12.1 %)	14 (24 %)	0.999

*Fisher's exact test
**The rate of chronic groin pain at 3-year follow-up, taking into account all patients who reported pain during different activities
HW heavyweight mesh, *LW* lightweight mesh

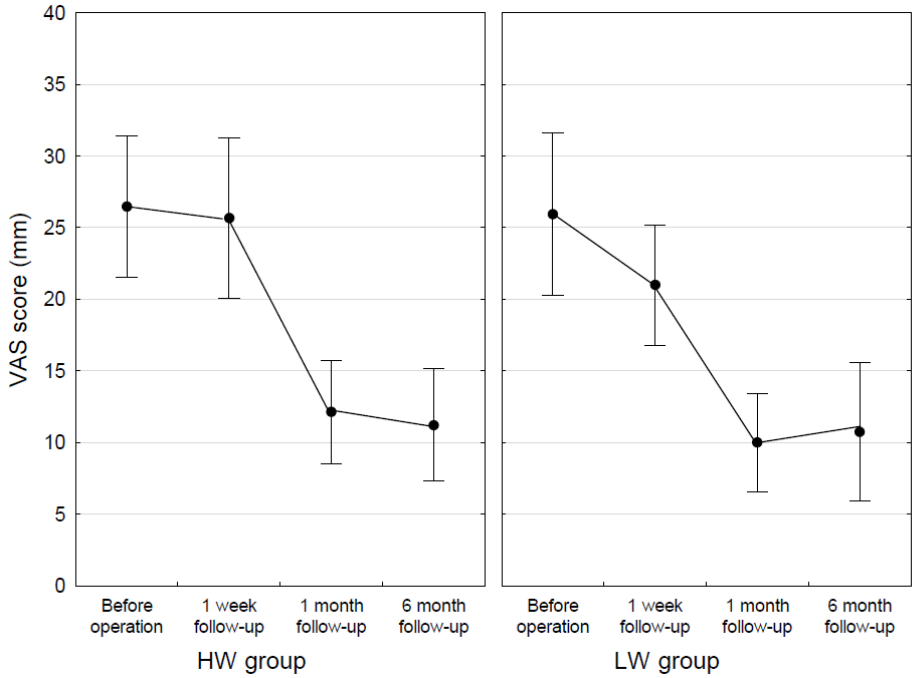

Figure 8. Mean visual analogue scale scores and 95 % CI based on the highest score for different activities before and after operation (lightweight versus heavyweight mesh I) *VAS* visual analogue scale, *HW* heavyweight mesh, *LW* lightweight mesh

Table 5. Distribution of pain severity based on the highest pain score on the visual analogue scale during different activities (lightweight versus heavyweight mesh I, II)

	HW group (n=64)	LW group (n=67)	*P* value*
Preoperative pain			
None (0)	5 (7.8 %)	10 (14.9 %)	
Mild (1–10)	13 (20.3 %)	17 (25.4 %)	0.347
Moderate (11–50)	40 (62.5 %)	32 (47.5 %)	
Severe (>50)	6 (9.4 %)	8 (11.9 %)	
Postoperative pain Week 1			
None (0)	5 (7.8 %)	3 (4.5 %)	
Mild (1–10)	14 (21.9 %)	23 (34.3 %)	0.128
Moderate (11–50)	36 (56.3 %)	38 (56.7 %)	
Severe (>50)	9 (14.1 %)	3 (4.5 %)	
Postoperative pain Month 1			
None (0)	14 (21.9 %)	22 (32.8 %)	
Mild (1–10)	31 (48.4 %)	30 (44.8 %)	0.527
Moderate (11–50)	18 (28.1 %)	14 (20.9 %)	
Severe (>50)	1 (1.6 %)	1 (1.5 %)	
Postoperative pain Month 6			
None (0)	26 (40.6 %)	35 (52.2 %)	
Mild (1–10)	23 (35.9 %)	23 (34.3 %)	0.252
Moderate (11–50)	15 (23.4 %)	9 (13.4 %)	
Severe (>50)	0	0	

*χ^2 test
HW heavyweight mesh, *LW* lightweight mesh

Table 6. Comparison of the quality of life: mean scores according to the Short Form 36 questionnaire (lightweight versus heavyweight mesh I, II)

	Type of mesh (HW group n=64 LW group n=67)	Preoperative scores	Scores at 6 months	Preoperative scores versus scores at 6 months (*P*-value)*	Scores at 6 months HW versus LW (*P*-value)**
General health	HW LW	60.8 59.8	64.2 62.2	0.111 0.234	0.558
Vitality	HW LW	67.2 68.6	72.7 72.5	0.008 0.06	0.968
Bodily pain	HW LW	69.5 63.7	84.3 80.1	<0.001 <0.001	0.241
Mental health	HW LW	75 75.8	80.1 80.7	0.013 0.017	0.827
Social functioning	HW LW	81.1 83.2	87.7 91	0.015 0.003	0.254
Physical functioning	HW LW	67.9 67.4	86.1 84.4	<0.001 <0.001	0.637
Emotional role	HW LW	63.5 66.7	85.4 86.1	<0.001 <0.001	0.892
Physical role	HW LW	53.5 44	77.7 75.4	<0.001 <0.001	0.706

* paired *t* test
** unpaired *t* test
HW heavyweight mesh, *LW* lightweight mesh

5.2. Pore size study (III)

The study flow chart is presented in Figure 9.

The patient and operative data are presented in Table 7.

According to the primary endpoint, 46.3 % of the patients in the UM group and 34.3 % of the patients in the OM group reported having experienced pain during different activities at 6-month follow-up (P=0.165). This suggests that chronic pain was about 1.35 (95 % CI 0.89, 2.06) times more likely to occur in the UM group but not at a statistically significant level.

There were no significant differences in the results of the pain questionnaire for different activities between the study groups at follow-up visits. Positive answers to the pain questionnaire at 6-month follow-up are presented in Table 8. Differences in the VAS scores for the two treatment groups were statistically insignificant (P=0.699). Mean VAS scores and 95 % confidence intervals based on the highest VAS score for different activities before operation and after operation are presented in Figure 10. There was no significant difference in the distribution of pain severity between the UM group and OM the group, either (Table 9).

In general, 54.3 % of the patients who had had severe pain (VAS>50) at one-week follow-up also reported chronic pain during different activities at 6-month follow-up. However, 41.8 % of those who had not reported severe pain at one-week follow-up had pain during different activities at 6-month follow-up (P=0.169).

Using logistic regression, we found that after adjusting for sex, age group (age <65 vs ≥65 years) and severe preoperative pain (VAS>50 vs. VAS≤50), type of mesh had no independent relationship (P=0.254) with chronic pain at 6-month follow-up. The analysis revealed that the rate of chronic pain was higher for younger patients (OR 3.83; 95 % CI 1.71, 8.59; P=0.001) and for patients with severe preoperative pain (OR 2.69; 95 % CI 1.16, 6.21; P=0.021). At the same time, sex did not affect the primary endpoint (P=0.424).

Of the patients, 11.9 % in the UM group and 1.5 % in the OM group had pain in the inguinal region, which influenced their everyday activities (P=0.018).

None of the patients used analgesics at 6-month follow-up.

The feeling of a foreign body in the inguinal region was experienced by 47.8 % of the patients in the UM group and by 31.3 % of the patients in the OM group at 6-month follow-up (P=0.052). The risk ratio for foreign body feeling was 1.52 (95 % CI 1.00, 2.37). Of the patients, 59.4 % in the UM group who reported foreign body feeling at 6-month follow-up also had pain during different activities. At the same time, 34.3 % of the patients in the UM group who had no foreign body feeling at 6-month follow-up reported pain during different activities (P=0.040). In the OM group, the respective results were 57.1 and 23.9 % (P=0.008). Comparison of these data for the two study groups revealed no significant difference.

There were no significant differences in any dimension of quality of life according to the SF36 questionnaire between the two study groups at 6-month

follow-up. However, in both study groups the quality of life scores improved after operation significantly for all dimensions, except for the social functioning score in the OM group (Table 10).

There were no hernia recurrences during the study period.

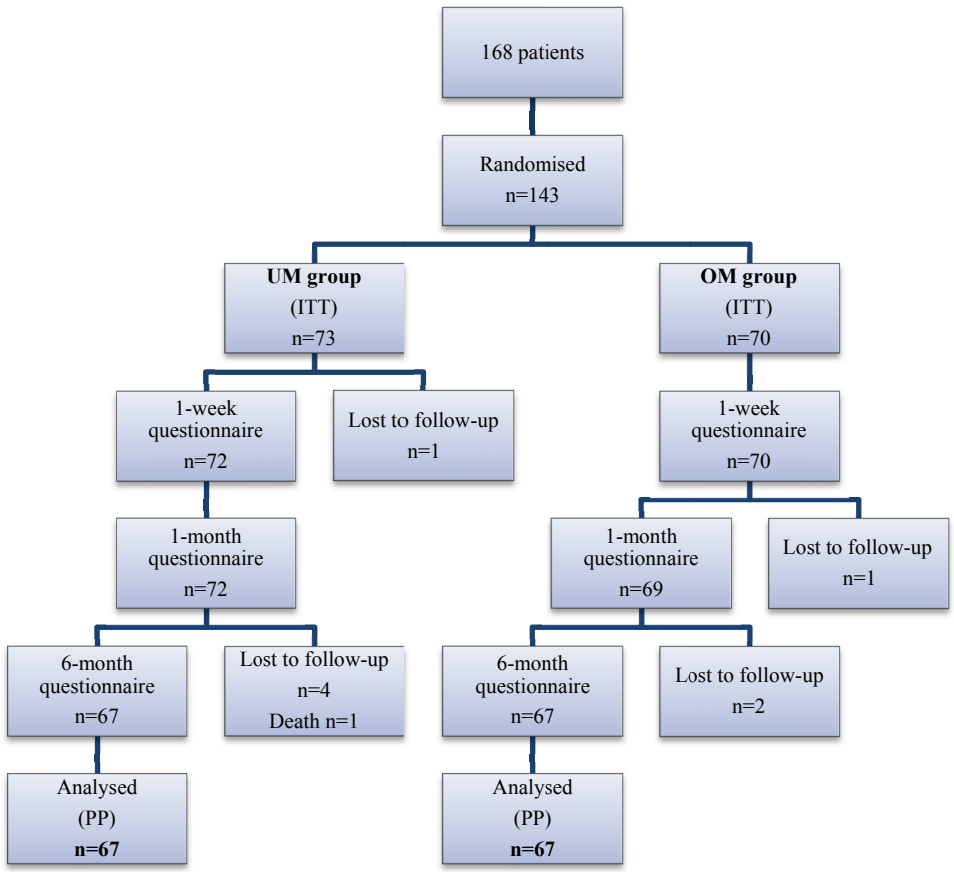

Figure 9. Study flow chart (pore size study III)
UM Ultrapro mesh, *OM* Optilene LP mesh, *ITT* intention-to treat population, *PP* per protocol principle

Table 7. Patient and operative data (pore size study III)

	UM group (n=67)	OM group (n=67)
Mean age (years) ±SD	57.4±15.0	60.7±13.8
Age ranges (years)	18–79	19–85
Sex ratio M:F	55:12 (82.1:17.8 %)	64:3 (95.5:4.5 %)
BMI (kg/m²)	26.3 (18.6–35.6)[a]	25.3 (19.3–33.4)[a]
Time from hernia occurrence to operation (months)	9.4 (0.3–96)[a]	13.1 (0.1–120)[a]
Hernia		
Direct	23 (34.3 %)	23 (34.3 %)
Indirect	40 (59.7 %)	38 (56.7 %)
Combined	4 (6 %)	6 (9 %)
Size of defect (cm)		
<1.5	11 (16.4 %)	15 (22.4 %)
1.5- 3	45 (67.2 %)	38 (56.7 %)
>3	11 (16.4 %)	14 (20.9 %)
Anaesthesia		
Spinal	1 (1.5 %)	6 (9 %)
Laryngeal mask	66 (98.5 %)	52 (77.6 %)
Endotracheal	0	9 (13.4 %)
Mean operating time (min)	49.8 (27–86)[a]	51.8 (27–94)[a]
Hernial sac		
Resected	46 (68.7 %)	45 (67.2 %)
Non-resected	21 (31.3 %)	22 (32.8 %)

[a] Minimal and maximal values are shown in the parentheses
UM Ultrapro mesh, *OM* Optilene LP mesh, *BMI* body mass index

Table 8. Positive answers to the pain questionnaire at 6-month follow-up after inguinal hernioplasty (pore size study III)

	UM group (n=67)	OM group (n=67)	*P* value*
Primary endpoint**	31 (46.3 %)	23 (34.3 %)	0.165
Pain in the groin at rest	7 (10.5 %)	3 (4.5 %)	0.210
Pain in the groin on coughing	3 (4.5 %)	3 (4.5 %)	0.999
Pain in the groin when rising from lying to sitting	5 (7.5 %)	4 (6 %)	0.746
Pain in the groin during physical activity	29 (43.3 %)	21 (31.3 %)	0.159

* Fisher's exact test

** The rate of chronic groin pain at 6-month follow-up, taking into account all patients who reported pain during different activities

UM Ultrapro mesh, *OM* Optilene LP mesh

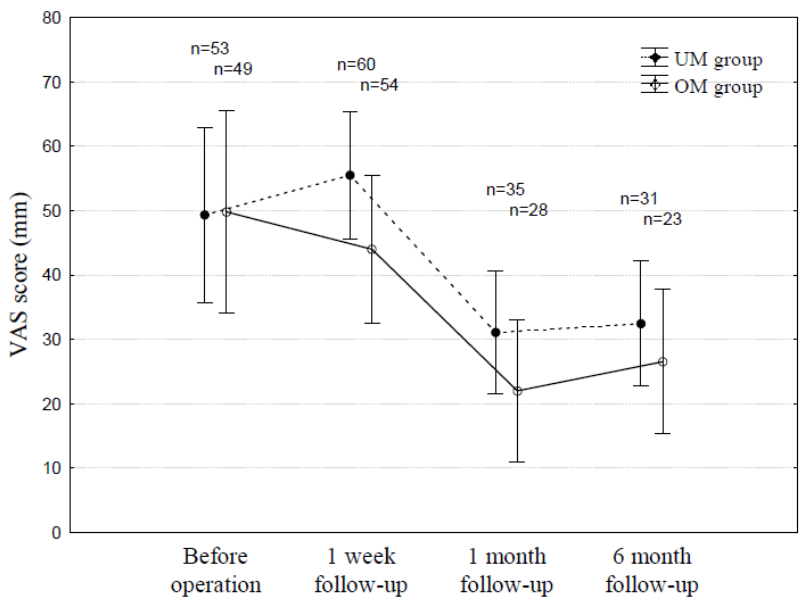

Figure 10. The mean visual analogue scale scores and 95 % CI based on the highest score for different activities before and after operation (linear mixed model) (pore size study III)

VAS visual analogue scale, *UM* Ultrapro mesh, *OM* Optilene LP mesh

Table 9. Distribution of pain severity based on the highest pain score on the visual analogue scale during different activities (pore size study III)

	UM group (n=67)	OM group (n=67)	*P* value*
Preoperative pain			
None (0)	14 (20.9 %)	18 (26.9 %)	
Mild (1–10)	3 (4.5 %)	2 (3 %)	0.418
Moderate (11–50)	31 (46.3 %)	30 (44.8 %)	
Severe (>50)	19 (28.4 %)	17 (25.4 %)	
Postoperative pain Week 1			
None (0)	7 (10.5 %)	13 (19.4 %)	
Mild (1–10)	2 (3 %)	5 (7.5 %)	0.146
Moderate (11–50)	38 (56.7 %)	34 (50.8 %)	
Severe (>50)	20 (29.9 %)	15 (22.4 %)	
Postoperative pain Month 1			
None (0)	32 (47.8 %)	39 (54.9 %)	
Mild (1–10)	3 (4.5 %)	8 (11.9 %)	0.226
Moderate (11–50)	27 (40.3 %)	16 (23.9 %)	
Severe (>50)	5 (7.5 %)	4 (6 %)	
Postoperative pain Month 6			
None (0)	36 (53.7 %)	44 (65.7 %)	
Mild (1–10)	9 (13.4 %)	5 (7.5 %)	0.159
Moderate (11–50)	18 (26.9 %)	16 (23.9 %)	
Severe (>50)	4 (6 %)	2 (3 %)	

***** Fisher's exact test
UM Ultrapro mesh, *OM* Optilene LP mesh

Table 10. Comparison of the quality of life: mean scores according to the Short Form 36 questionnaire (pore size study III)

	Type of mesh	Preoperative score ±SD (n=67)	Score at 6 months ±SD (n=67)	Difference between preoperative score and score at 6 months ±SD (n=67)	Significance of type of mesh according to ANCOVA (*P* value)**
General health	UM OM	54.1±19.6 56.1±18.9	61.2±20.3 60.3±22.6	7.1±17.3* 4.2±16.5*	0.396
Vitality	UM OM	60.6±18.6 61.6±21.1	69.7±20.1 70.8±19	9.1±18.3* 9.2±17*	0.853
Bodily pain	UM OM	63±25.8 64.1±24.3	81.1±22.9 79.6±25.4	18.1±24.8* 15.5±24.1*	0.577
Mental health	UM OM	69.3±17.5 70.9±18	74.4±19 76.4±18.1	5.1±13.5* 5.5±19.1*	0.689
Social functioning	UM OM	75.7±21.6 76.9±24.5	86.2±20.9 80.6±24.4	10.4±20* 3.7±23.2	0.061
Physical functioning	UM OM	63.5±26.3 63.8±26.6	82.7±19.5 77.2±26	19.2±25.4* 13.4±27.9*	0.126
Emotional role	UM OM	60.2±38.2 67.7±38.5	73.6±39.2 80.1±36.3	13.4±48.9* 12.4±45.6*	0.455
Physical role	UM OM	47±43.6 49.3±41.3	69±39.2 66.4±42.1	22±56* 17.2±45.1*	0.645

* Statistically significant change (paired *t* test)

** Quality of life scores at 6-month follow-up as the dependent variables, type of mesh as the categorical independent variable, preoperative quality of life score as the continuous predictor variable

UM Ultrapro mesh, *OM* Optilene LP mesh

5.3. Self-gripping versus sutured mesh (IV)

The study flow-chart is presented on Figure 11.

The patient and operative data are presented in Table 11.

According to the primary endpoint, 45.3 % of the patients in the OLP group and 31.4 % of the patients in the PPG group experienced pain during different activities at 6-month follow-up (*P*=0.092). The risk ratio for the primary endpoint is 1.44, 95 % CI 0.82, 2.59 (*P*=0.184).

Positive responses to the pain questionnaire at 6-month follow-up are presented in Table 12. Differences in the VAS scores for the study groups were statistically insignificant (*P*=0.350). Mean VAS scores and 95 % CI, based on the highest VAS score for different activities before operation, and at 1-week, 1-month and 6-month follow-up, are presented in Figure 12. There were no statistically significant differences in the distribution of pain severity between the two study groups (Table 13).

In logistic regression analysis, adjusting for the age groups (age <65 vs ≥65 years), severe preoperative pain (VAS ≤50 vs. VAS>50) and severe early postoperative pain (VAS≤50 vs VAS>50 at 1-week follow-up), type of mesh was not associated with chronic pain at 6-month follow-up (*P*=0.099). The analysis demonstrated an increased rate of chronic pain for patients with severe early postoperative pain (OR 4.22; 95 % CI 1.85, 9.58; *P*=0.001).

At 6-month follow-up, 8 % of the patients in the OLP group and 4.3 % of the patients in the PPG group had pain at the operation site, which influenced their everyday activities (*P*=0.496).

At 6-month follow-up, 5.3 % of the patients in the OLP group and 1.4 % of the patients in the PPG group used analgesics (*P*=0.368). Of the analgesic users at 6-month follow-up, one patient used paracetamol and four patients used NSAIDs.

Overall, 22.7 % in the OLP group and 40 % in the PPG group reported foreign body feeling at the operation site at 6-month follow-up (*P*=0.031). The risk ratio for foreign body feeling was 0.57, 95 % CI 0.29, 1.07 (*P*=0.073). Of the patients 76.5 % in the OLP group who experienced foreign body feeling at 6-month follow-up also had pain during different activities. At the same time, 36.2 % of the patients in the OLP group who had no foreign body feeling reported pain during different activities (*P*=0.005). In the PPG group, the respective results were 39.3 % and 26.2 % (*P*=0.298).

There were no significant differences in any domain of quality of life according to the SF36 questionnaire between the two study groups at 6-month follow-up, except for the social functioning domain (*P*=0.035). In the OLP group the quality of life scores improved significantly after operation in all domains except for general health and mental health. In the PPG group the quality of life scores improved significantly after operation in the domains of bodily pain, physical functioning and physical role (Table 14).

There were no recurrences during the study period.

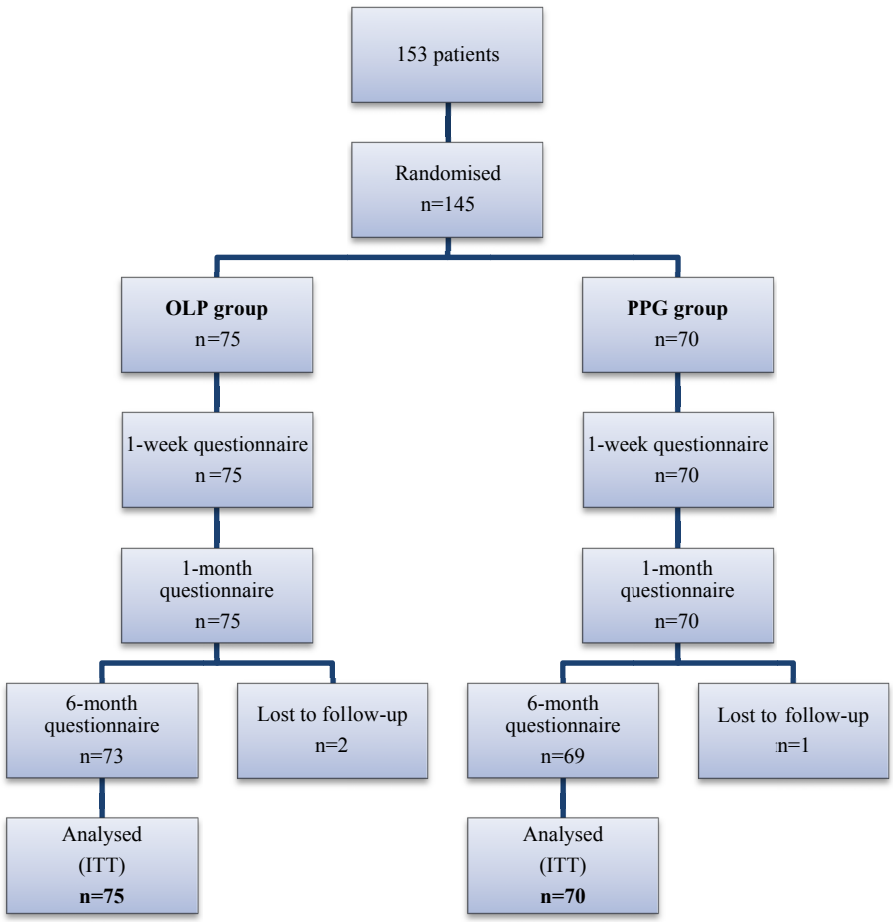

Figure 11. Study flow chart (self-gripping versus sutured mesh IV)
OLP Optilene LP mesh, *PPG* Parietex ProGrip mesh, *ITT* intention-to-treat population

Table 11. Patient and operative data (self-gripping versus sutured mesh IV)

	OLP group (n=75)	PPG group (n=70)
Mean age (years) ±SD	54.4±17.3	57.9±17.4
Age ranges (years)	19–84	20–81
Sex ratio M:F	68:7 (90.7:9.3 %)	65:5 (92.9:7.1 %)
BMI (kg/m²)	25.1 (16.6–34.7)[a]	25.0 (17.4–38.1)[a]
Median time from hernia occurrence to operation (months)	6 (0.3–384)[a]	5 (0.3–240)[a]
Hernia		
Direct	20 (26.7 %)	21 (30 %)
Indirect	52 (69.3 %)	46 (65.7 %)
Combined	3 (4 %)	3 (4.3 %)
Size of defect (cm)		
<1.5	23 (30.7 %)	15 (21.4 %)
1.5- 3	39 (52 %)	46 (65.7 %)
>3	13 (17.3 %)	9 (12.9 %)
Anaesthesia		
Spinal	8 (10.7 %)	5 (7.1 %)
Laryngeal mask	65 (86.7 %)	62 (88.6 %)
Endotracheal	2 (2.7 %)	2 (2.9 %)
Local	0	1 (1.4 %)
Mean operating time (min)*	50.7 (27–95)[a]	40.1 (15–65)[a]
Hernial sac		
Resected	51 (68 %)	47 (67.1 %)
Non-resected	24 (32 %)	23 (32.9 %)

[a] Minimal and maximal values are shown in the parentheses
*$P<0.001$ (Mann-Whitney *U* test)
OLP Optilene LP mesh, *PPG* Parietex ProGrip mesh, *BMI* body mass index

Table 12. Positive answers to the pain questionnaire at 6-month follow-up after inguinal hernioplasty (self-gripping versus sutured mesh IV)

	OLP group (n=75)	PPG group (n=70)	*P* value*
Primary endpoint**	34 (45.3%)	22 (31.4 %)	0.092
Pain in the groin at rest	4 (5.3 %)	6 (8.6 %)	0.523
Pain in the groin on coughing	8 (10.7 %)	1 (1.43 %)	0.034
Pain in the groin when rising from lying to sitting	9 (12 %)	3 (4.3 %)	0.132
Pain in the groin during physical activity	31 (41.3 %)	21 (30 %)	0.170

*Fisher's exact test
**The rate of chronic groin pain at 6-month follow-up, taking into account all patients who reported pain during different activities
OLP Optilene LP mesh, *PPG* Parietex ProGrip mesh

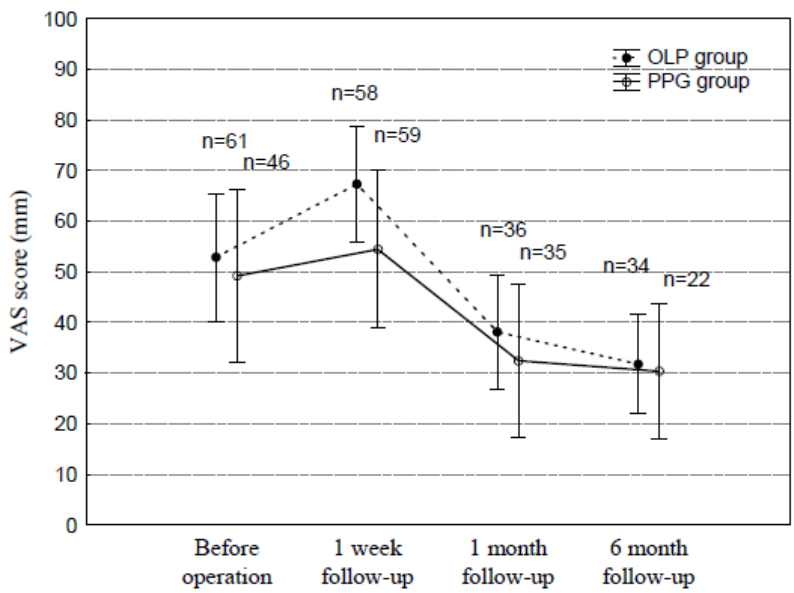

Figure 12. The mean visual analogue scale scores and 95 % CI based on the highest score for different activities before and after operation (linear mixed model) (self-gripping versus sutured mesh IV)
VAS visual analogue scale, *OLP* Optilene LP mesh, *PPG* Parietex ProGrip mesh

Table 13. Distribution of pain severity based on the highest pain score on the visual analogue scale during different activities (self-gripping versus sutured mesh IV)

	OLP group (n=75)	PPG group (n=70)	*P* value*
Preoperative pain			
None (0)	14 (18.7 %)	24 (34.3 %)	
Mild (1–10)	2 (2.7 %)	4 (5.7 %)	0.112
Moderate (11–50)	35 (46.7 %)	26 (37.1 %)	
Severe (>50)	24 (32 %)	16 (22.9 %)	
Postoperative pain Week 1			
None (0)	17 (22.7 %)	11 (15.7 %)	
Mild (1–10)	3 (4 %)	3 (4.3 %)	0.714
Moderate (11–50)	34 (45.3 %)	37 (52.9 %)	
Severe (>50)	21 (28 %)	19 (27.1 %)	
Postoperative pain Month 1			
None (0)	39 (52 %)	35 (50 %)	
Mild (1–10)	6 (8 %)	4 (5.7 %)	0.831
Moderate (11–50)	22 (29.3 %)	25 (35.7 %)	
Severe (>50)	8 (10.7 %)	6 (8.6 %)	
Postoperative pain Month 6			
None (0)	41 (54.7 %)	48 (68.6 %)	
Mild (1–10)	5 (6.7 %)	3 (4.3 %)	0.314
Moderate (11–50)	24 (32 %)	14 (20 %)	
Severe (>50)	5 (6.7 %)	5 (7.1 %)	

*Fisher's exact test
OLP Optilene LP mesh, *PPG* Parietex ProGrip mesh

Table 14. Comparison of the quality of life: mean scores according to the Short Form 36 questionnaire (self-gripping versus sutured mesh IV)

	Type of mesh OLP group n=75 PPG group n=70	Preoperative score ±SD	Score at 6 months ±SD	Difference between preoperative score and score at 6 months ±SD	Significance of type of mesh according to ANCOVA (*P* value)**
General health	OLP PPG	59.5±22.1 55.6±18.6	59.5±23.8 59.1±21.5	0.07±17.7 3.6±16.8	0.337
Vitality	OLP PPG	63.3±19.1 64.6±17.7	67.4±19.8 67.6±19.2	4.1±17.7* 3±16	0.812
Bodily pain	OLP PPG	64.1±19.8 63.7±24.3	77.1±24.1 75±24.6	13.0±25.3* 11.3±29.9*	0.622
Mental health	OLP PPG	74±18.5 72.1±15.7	76.3±16.8 74.1±17.6	2.2±12.9 2.1±14.5	0.699
Social functioning	OLP PPG	80.5±21.7 79.5±20.7	89.3±19.9 81.6±23.8	8.8±22* 2.1±21.3	0.025
Physical functioning	OLP PPG	65.1±26.3 70.2±23.8	77±26.1 80.4±25.5	11.9±25.8* 10.2±30.5*	0.733
Emotional role	OLP PPG	66.2±37 59±41.8	76.9±33.3 67.6±39.3	10.7±42.9* 8.6±45.3	0.218
Physical role	OLP PPG	44.7±39.1 46.4±40.4	63.7±44.1 69.3±38.6	19±45.4* 22.9±48.9*	0.445

*Statistically significant change (paired *t* test)
**Quality of life scores at 6-month follow-up as the dependent variables, type of mesh as the categorical independent variable, preoperative quality of life score as the continuous predictor variable
OPL Optilene LP mesh, *PPG* Parietex ProGrip mesh

6. DISCUSSION

Recent evolution in hernia surgery and the usage of meshes has resulted in acceptably low recurrence rates. However, search for an ideal prosthetic mesh, associated with reduced chronic pain, requires extensive further research. As more than 160 different meshes for hernia repair are in the market [Coda et al., 2012], it is plausible that we do not yet know the parameters of an ideal mesh. Because inguinal hernia repair is performed very frequently any morbidity associated with surgery can result in significant human, economic and societal burdens [van Hanswijck de Jonge et al., 2008].

The aim of our studies was to determine whether the theoretical advantage of using lightweight meshes, meshes with larger pores and self-gripping meshes in inguinal hernioplasty would result in reduced rate of chronic groin pain and foreign body feeling.

The International Association for the Study of Pain has defined chronic pain as the pain lasting longer than 3 months [Merskey and Bogduk, 1994]. Considering the use of synthetic meshes for hernia repair and taking into account the fact that inflammatory response to foreign material may last longer [Aasvang and Kehlet, 2005], we defined chronic pain as the pain lasting 6 months after operation. Unfortunately, the definition of chronic pain and the methology of its evaluation are highly variable among different publications. Therefore, also the rate of chronic pain varies significantly in different studies, which makes comparison of trials difficult.

In a study of O'Dwyer et al. the rate of chronic pain at 1-year follow-up was 39.5 % in the LW group and 51.6 % in the HW group (P=0.033) [O'Dwyer et al., 2005]. The results of our studies were similar. In our studies the rate of chronic pain at 6-month follow-up varied from 31.4 % (Pore size study PPG group) to 59.4 % (Lightweight versus heavyweight mesh HW group). However, Smietanski et al. demonstrated much lower rates of chronic pain 6-months after inguinal hernioplasty in 10.7 % of the patients in the LW group and in 9.9 % of the patients in the HW group [Smietanski, 2008]. Although the above trial did not indicate whether the pain was evaluated at rest or during physical activity, it is obvious that the rate of pain is different in these two situations. In our studies we noted low rates of chronic pain at rest at 6-month follow-up (0–10.5 %), but the rate of pain was much higher in all our studies during physical activities (up to 43.3 %). Likewise, Bringman et al. reported lower rates of chronic pain at rest (LW group 6.4 %, HW group 7.4 %) than during physical activities at 3-year follow-up (LW group, 17.9 %; HW group, 23 %) [Bringman et al., 2006]. Unfortunately, in the same study of Bringman et al. it remains unclear whether the reported rates of chronic pain at 1-year follow-up (LW group, 10.3 %; HW group, 12.2 %) are general pain rates, rates of pain at rest or during physical activities [Bringman et al., 2005].

In our studies, all patients who reported pain during different activities (VAS>0) were considered as patients with chronic pain. In another study of

Smietanski et al. VAS> 2 (on a scale ranging from 0 to 5) was defined as chronic pain, resulting in a rate of chronic pain of 11.1 % [Śmietański et al., 2009]. If chronic pain had been defined as in our studies, its rate would have increased to 21.2 %. In a study of Jorgensen et al., comparing self-gripping and sutured mesh, pain was defined as a VAS score exceeding 30 mm (on a scale ranging from 0 to 100), which resulted in lower rates of chronic pain (self-gripping mesh group, 9.9 %; sutured mesh group, 7.7 %) [Jorgensen et al., 2013]. Also in an observational study of self-gripping mesh chronic pain was defined as a VAS score exceeding 3, but the range of the scale remained unclear [Garcia Urena et al., 2011]. In comparison, in our study comparing self-gripping and sutured mesh the rates of chronic pain at 6-month follow-up were 31.4 % and 45.3 %, respectively. If we had excluded patients with mild pain (VAS scores 1–10), the rates of chronic pain would had remained still higher than in a study of Jorgensen et al. [Jorgensen et al., 2013]. As in our studies the distribution of pain severity was determined using the grading system after Page et al. [Page et al., 2002], it is not possible to compare the results with those of Jorgensen et al. However, variation in the definition of chronic pain and its measurement may lead to underestimation of patients with chronic pain.

According to the European Hernia Society guidelines on treatment of inguinal hernia in adult patients, the risk factors for development of chronic pain are preoperative pain and severe early postoperative pain. It has also been found, that the risk of chronic pain after hernia surgery decreases with age [Simons et al., 2009].

Younger age was a risk factor for development of chronic pain also in other studies [Bay-Nielsen et al., 2001b; Poobalan et al., 2001] and in a systematic review of Nienhuijs et al. [Nienhuijs et al., 2007]. Among our studies younger age was a significant risk factor only in the pore size study.

Poolaban et al. and Wright et. al have reported that preoperative pain increases the risk for development of chronic pain [Poobalan et al., 2001; Wright et al., 2002]. As most of the patients in our studies had pain preoperatively, we decided to evaluate whether severe preoperative pain (VAS>50) is a risk factor for development of chronic pain. The analysis revealed that in the study comparing the weight of the meshes the only statistically significant risk factor at 3-year follow-up was preoperative severe pain. Also in the pore size study severe preoperative pain was a risk factor for development of chronic pain.

Similarly to a study of Callesen et al. [Callesen et al., 1999], the analysis of our study comparing self-gripping mesh and sutured mesh demonstrated increased rate of chronic pain in patients with severe early postoperative pain. In our lightweight versus heavyweight mesh study there was also a trend towards more patients having chronic pain among those who had severe pain on the 7th postoperative day, although this trend did not reach statistical significance.

It has been shown that the amount of the material and the structure of mesh influence significantly scar tissue formation and chronic inflammatory reaction. According to Klinge et al., reduced amount of polypropylene showed pronounced reduction in inflammation and improved integration into the surrounding tissue [Klinge et al., 1999]. Consequently, implantig LW mesh will presumably diminish chronic pain and foreign body feeling.

However, O'Dwyer et al. [O'Dwyer et al., 2005] reported higher recurrence rates in the LW group at 12-month follow-up compared with the HW group (5.6 versus 0.7 %, P=0.037). The authors speculated that the reason for the higher recurrence rate in the LW group was not associated with mesh but with technical error during operation. Although the recurrence rate in the HW group was low, one must keep in mind that the follow-up period was only one year and the recurrence rate may increase over time as shown in another study by Bringman et al. [Bringman et al., 2006]. These authors found no significant difference in the recurrence rates between the HW group and the LW group, however, the recurrence rates had almost doubled by the time of 3-year follow-up compared with one-year follow-up. Our study confirms a similar trend: there was no recurrence at 6-month follow-up while the recurrence rate was 1.7 % at three-year follow up, whereby there was no difference in the recurrence rates between the LW and HW groups.

In several studies the authors concluded that use of lightweight meshes would reduce the rate of chronic pain [Bringman et al., 2006; O'Dwyer et al., 2005]. Regrettably, the meshes used in the above mentioned randomised studies differed not only in weight but also in pore size. This raises the question whether their finding (less pain in the lightweight mesh group) depended on the weight or the pore size of mesh. Considering this, it is evident that also other mesh characteristics should be explored.

According to Weyhe et al., the size of pores rather than the amount of mesh is the main determinant of successful incorporation and diminished foreign body reaction [Weyhe et al., 2006]. Mühl et al. also found that inflammatory reaction largely depended on pore size [Muhl et al., 2008]. According to Klinge et al., mesh with large pores was integrated in a loose network of perifilamentary granulomas and the fat tissue, and mesh with small pores was embedded into granulomas and the scar tissue, which bridged the pores completely [Klinge et al., 2002b]. Our study demonstrated that the use of the mesh with larger pores compared with the mesh with smaller pores did not reach significance in terms of chronic pain. Nevertheless, although the difference was statistically insignificant, there were more patients reporting pain in the group where the mesh with larger pores was used. The meshes used in the pore size study had different composition at implantation. Interestingly, when in a study of Orenstein et al. the mesh consisting of polypropylene and polyglactin induced a significant chronic inflammatory response [Orenstein et al., 2012], then in a study of Klinge et al. the inflammatory response of the mesh of polypropylene combined with polyglactin was considerably reduced compared to other polypropylene

meshes [Klinge et al., 1999]. One explanation could certainly be that Oreinstein's study was an experimental study on mice while the study of Klinge et al. involved removal of meshes during revision operations. Another explanation could be that the study of Klinge et al. explored Vypro® mesh and and the study of Orenstein et al. used Ultrapro® mesh. Although both meshes are made of polypropylene with an addition of polyglactin, Vypro® mesh is a multifilament mesh [Post et al., 2004] and Ultrapro® mesh is a monofilament mesh [Bury and Smietanski, 2012]. Monofilament and multifilament meshes have been studied in terms of infection [Klinge et al., 2002a] but not in terms of chronic pain. However, as polyglactin, one component of Ultrapro® mesh, was already absorbed at 6-month follow-up [Klosterhalfen et al., 2005], it is therefore unlikely that the different composition of the meshes is the reason for the above mentioned trend.

The suture fixation of a mesh has been postulated to impact development of chronic groin pain after inguinal hernia surgery. To exclude suture fixation as the cause of chronic pain and to reduce the rate of chronic pain, alternative fixation methods, such as tissue glue and self-gripping meshes, have been developed.

Kingsnorth et al. have reported potential benefits of self-gripping mesh compared with sutured mesh [Kingsnorth et al., 2012]. Also other studies have demonstrated promising results for self-gripping meshes in terms of chronic pain [Quyn et al., 2012]. In a study of Kingsnorth et al. the change in VAS scores compared to baseline was significantly different between the self-gripping and sutured mesh groups only at early postoperative visits, but not at 3 months; nor was the rate of chronic pain significantly different between the study groups at 3-month follow-up [Kingsnorth et al., 2012]. Also, considering our definition of chronic pain (6 months postoperatively), further results from the Kingsnorth's study would be needed. Kingsnorth et al. performed also subgroup analysis. In the self-gripping mesh group a single stitch over the pubic bone was used in 25.5 % of the patients; at 3-month follow-up the VAS scores were significantly more reduced compared with baseline in the subgroup where no fixation was used. This indicates the importance of sutures in development of postoperative pain. Another study whose results would favour the use of self-gripping mesh is a study of Quyn et al. where the rate of chronic pain at 6-month follow-up was 7.9 % in the self-gripping mesh group and 21 % in the sutured mesh group. The respective results at 1-year follow-up were 6.3 % and 18.8 % [Quyn et al., 2012]. Unfortunately, as that study was not a randomised study its level of evidence is lower.

At the same time, in several studies the use of a self-gripping mesh did not result in decreased rate of chronic symptoms [Jorgensen et al., 2013; Pierides et al., 2012]. Definitely, one strength of the study of Pierides et al. is the fact that they recorded patients' type of work (sedentary versus physical); yet they did not perform subgroup analysis in order to evaluate the association of chronic pain with character of everyday work [Pierides et al., 2012]. In a study of

Jorgensen et al. the primary aim was to address moderate or severe pain and/or numbness and/or discomfort at 1-year follow-up. The reason for using a composite endpoint was to make more powerful statistical assessment, because each complication occurs infrequently. Moderate to severe symptoms occurred in 17.4 % of the patients in the self-gripping mesh group and in 20.2 % in the sutured mesh group (P=0.573) [Jorgensen et al., 2013]. Although in the study of Pierides et al. there was no difference between the two study groups either, the reported rate of chronic symptoms was much higher (36.3 % in the self-gripping mesh group, 34.1 % in the sutured mesh group) than in the study of Jorgensen et al. One reason for this could be that Pierides et al. included all patients with complaints, unlike the study of Jorgensen et al. where patients with mild symptoms were excluded from the analysis of the primary endpoint [Jorgensen et al., 2013; Pierides et al., 2012]. Similarly to Pierides et al., we included all patients who reported pain (VAS>0) in evaluation of the primary endpoint. In a study of Chastan only 1 of 52 patients reported pain at 1-year follow-up [Chastan, 2009]. The reason how Chastan achieved such a low pain rate remains unclear. However, Chastan's study was not randomised and another limitation of that study is that it included not only primary unilateral hernias as most studies do but also recurrent hernias and bilateral hernias [Chastan, 2009]. In a prospective study of Pedano et al., evaluating the results of usage of self-gripping mesh, the rate of chronic pain was also only 4 % at a median follow-up of 17 months. Again, it should be stressed that only patients who had invalidate pain were included in assessment of chronic pain. Unfortunately, the definition of invalidate pain was not specified [Pedano et al., 2012].

According to previous systematic reviews and meta-analyses, self-gripping mesh has been associated with shorter operating time (15–17). Li et al. suggested that reduced operating times with shorter exposure times of the mesh may result in decreased rate of wound infections [Li et al., 2014]. Also in our study of self-gripping versus sutured mesh, the operating time was 10 minutes shorter in the PPG group. However, considering the fact that the rate of wound infection was exceedingly low (1 case in the PPG group at 1-month follow-up), we cannot make any conclusion about it. In a study of Kapischke et al. the mean operating time was 12.2 minutes shorter in the self-gripping mesh group than in the sutured mesh group and the authors speculate that the increased costs of self-gripping meshes are compensated for by the reduced utilization of the operating room [Kapischke et al., 2010] Evidently, analysis of cost-effectiveness would be useful to evaluate the benefit of shorter operating time and the usage of more expensive mesh compared to standard mesh.

Significantly less patients in our study experienced pain during different activities at three-year follow-up in the LW group as well as in the HW group compared with the results of 6-month follow-up. This finding is important in management of postoperative chronic pain following inguinal hernia surgery. International guidelines recommend to resort to surgical treatment not earlier than 1 year after operation when the inflammatory response has decreased

[Alfieri et al., 2011]. Unfortunately, we had not planned follow-up at 1 year, but we can speculate that, considering the high rate of chronic pain at 6-month follow-up, the rate of chronic pain would have been high also at 1 year. Also in a population-based cohort study of Kalliomäki et al. less than three years from operation was associated with an increased risk for chronic pain [Kalliomaki et al., 2008]. Therefore, it might be necessary to postpone surgical treatment even more than one year after primary operation.

Foreign body feeling after inguinal hernia repair has not gained as much attention as chronic pain. Although according to Smietanski et al., the clinical relevance of foreign body feeling is unknown and it might not influence daily activities [Smietanski et al., 2012], patients report it often. Considering that Bringman et al. have stated that a successful procedure is one in which a patient has no sensation of foreign body and can return quickly to normal activities [Bringman et al., 2010], they seem to disagree with the opinion of Smietanski et al. opinion about the relevance of foreign body feeling.

In a study of Post et al., which is one of the few studies where foreign body feeling is the primary outcome measure, more patients had the feeling of a foreign body after hernia repair at 6-month follow-up with HW mesh compared with LW mesh (43.8 *vs.* 17.2 %, P=0.003). Our study comparing meshes with different weights revealed a similar trend (32.8 versus 20.9 %) but the difference was statistically insignificant. As the lightweight versus heavyweight mesh study presented also 3-year follow-up results, it was possible to evaluate the time factor in occurrence of chronic symptoms. While the time factor was important in reducing the rate of chronic pain, the rate of foreign body feeling remained immutable. At 6-month follow-up 32.8 % of the patients in the HW group and 20.9 % of the patients in the LW group experienced foreign body feeling; at 3-year follow-up the respective results were 27.6 % and 20.7 %. Interestingly, although the rate of chronic pain had reduced significantly by the time of 3-year follow-up, the rate of foreign body feeling had not diminished. However, in a study of Paajanen et al., comparing three meshes with different weights, foreign body feeling was more common at 1-year follow-up than at 2- or 5-year follow-up [Paajanen, 2007; Paajanen et al., 2013].

In the pore size study the results of foreign body feeling were unexpected. Surprisingly, mesh with larger pores even revealed a trend of higher rate of foreign body feeling. The reason why more patients experienced foreign body feeling in the study group where mesh with larger pores was used is unclear. We speculate that one explanation could be the unequal distribution of female patients between the two study groups. According to a meta-analysis, women respond more readily with pain to a stimulus that men may report as not painful [Riley III et al., 1998]. Therefore, considering also the fact that there was correlation between chronic pain and foreign body feeling, the trend towards higher rate of foreign body feeling in the UM group with more female patients would be explainable. Yet logistic regression did not confirm our speculation: sex did not affect the primary endpoint. Another explanation could lie in the different

composition of the meshes (Ultrapro® consists of polypropylene and polyglecaprone and Optilene® LP consists of polypropylene). However, taking into account that the absorbable component of Ultrapro, polyglecaprone, is fully absorbed during 84–140 days [Klosterhalfen et al., 2005], the meshes will have a similar composition at 6-month follow-up. In an experimental study by Orenstein et al. Ultrapro mesh, which is a lightweight macroporous material, caused a surprisingly strong chronic inflammatory response [Orenstein et al., 2012]. Although similar results with Optilene LP mesh are not available, the finding of Orenstein et al. might also account for the higher rate of foreign body feeling in the UM group in our study.

Also the results of our study comparing self-gripping mesh and sutured mesh in terms of foreign body feeling were surprising. The rate of foreign body feeling was higher in the study group where self-gripping mesh was used. It should be noted that as Parietex ProGrip™ mesh has microgrips across its surface area, the resorption time of which is 12 months [Chastan, 2009], this might account for the higher rate of foreign body feeling in the PPG group at 6-month follow-up. Therefore, we planned another follow-up three years after operation.

Although the rates of chronic pain in our studies were high, we noted a significant improvement in the quality of life scores after surgery compared with preoperative scores in most domains of the lightweight versus heavyweight mesh study and in the pore size study. Also in a study of Bringman et al. comparing the weight of meshes there was no difference between the study groups, but the quality of life scores improved postoperatively [Bringman et al., 2005].

Interestingly, when quality of life was evaluated in several studies comparing the weight of different meshes [Bringman et al., 2005; Post et al., 2004; Smietanski, 2008], then it seems that interest in evaluating quality of life has been lost in studies comparing self-gripping and sutured meshes, except in a study of Jorgensen et al. where SF12 was used [Jorgensen et al., 2013]. In our study comparing self-gripping mesh and sutured mesh only the scores which describe pain and physical health, i.e. bodily pain, physical functioning and physical role, improved in both study groups. Smietanski et al. had similar results in a study comparing the weight of meshes, except that in their study also the role emotional domain improved significantly in both study groups [Smietanski, 2008]. In a study of Post et al., besides improvement in scores of the domains associated with pain and physical health, there improved, additionally, the domain of social functioning [Post et al., 2004]. Surprisingly, in the ANCOVA analysis of our study comparing self-gripping mesh and sutured mesh, the type of mesh influenced the quality of life scores in the domain of social functioning. The reason why the type of mesh influenced only one domain are unclear. Taking account of the fact that this domain can be influenced by many factors, it is unlikely that the type of mesh had actually a significant effect on this result.

Considering the variability in results, there raises the question about whether it is necessary to evaluate the full range of SF36 or RAND SF36 or only the domains describing bodily pain and physical health. Although several studies on the same topic have used a modification of SF36 [Yazdankhah Kenary et al., 2013], further research is needed to find out an optimal questionnaire to evaluate the outcome of hernia surgery.

Still, improvement in most quality of life scores after inguinal hernia surgery indicates the importance of prompt elective repair of symptomatic inguinal hernias that could significantly restrict patients' physical activities without operation. It also demonstrates that inguinal hernias have a greater influence on the quality of life than is generally thought.

The high rate of chronic pain in our studies as well as in several other studies [O'Dwyer et al., 2005; Śmietański et al., 2009] raises the question about the surgical treatment of asymptomatic inguinal hernias. According to the EHS guidelines on the treatment of inguinal hernia, watchful waiting is an acceptable option in the case of asymptomatic inguinal hernias; in particular, it should be considered for older patients and for patients with major comorbidities [Miserez et al., 2014]. In a study of Fitzgibbons et al. 23 % of the patients had crossed over from the watchful waiting group to the surgical treatment group after 2 years, mostly because of the increase of hernia related pain [Fitzgibbons et al., 2006]. In a study of Chung et al. 72 % of the patients initially randomized to the observation group underwent conversion to operation at 7.5 years [Chung et al., 2011]. In a study of Kalliomäki et al. 34 % of the patients were pain-free before the operation and of these 21 % reported having pain at follow-up [Kalliomaki et al., 2008]. However, considering the low risk of incarceration of 0.3–3 % per year [Simons et al., 2009] and the risk for development of chronic postoperative pain, whose rate in our studies reached 59.4 % at 6-month follow-up, inguinal hernia repair should probably be postponed in asymptomatic cases until there develop complaints.

A limitation of our studies could be that we did not record if the nerves in the inguinal canal were sacrificed and hence we cannot make any conclusions about nerve damage and chronic pain. Another limitation might be related to the study comparing self-gripping mesh and sutured mesh: the material of the sutured mesh used in that study was polypropylene and the material of the self-gripping mesh was polyester. Still, in some studies, polypropylene and polyester meshes yielded similar results in terms of chronic pain [Sadowski et al., 2011]. On the other hand, in experimental studies polyester meshes induced more chronic inflammation and marked foreign body reaction [Orenstein et al., 2012]. Although in a study of Klinge et al. polyester mesh and polypropylene mesh with reduced weight resulted different thicknesses of collagen capsules around the mesh fibres, the inflammatory infiltrate was similar in both cases [Klinge et al., 1999].

In order to improve the results of inguinal hernia repair and to reduce the rate of chronic pain, further research is definitely needed. Considering that usage of meshes has significantly reduced recurrence rates, it is evident that meshes will remain in use for a longer period of time. Consequently, further research to develop meshes with optimal parameters is of vital importance and should be encouraged.

One drawback of published studies is the lack of consensus on definition of chronic pain, which makes it complicated to compare the results of different studies and to conduct meta-analyses and systematic reviews. Therefore, a uniform definition of chronic pain and its best assessment methods should be developed in order to conduct top quality multicentre randomised trials.

Most published studies on inguinal hernia repair comparing different meshes have presented short- or mid-term results. However, longer follow-up of , e. g. 5 and 10 years, would be useful in order to evaluate the rate of chronic pain and its impact on quality of life.

7. CONCLUSIONS

1. According to our studies, the weight, pore size and suture fixation of a mesh have not a significant influence on development of chronic pain. However, other mesh parameters, particularly, their combinations should be explored.
2. Considering the high rate of early severe postoperative pain (papers III and IV) and the association between early severe pain and development of chronic pain (paper IV), a better postoperative pain control strategy is needed.
3. Significantly less patients experienced pain during different activities at three-year follow-up compared with the results of 6-month follow-up (papers I and II). Therefore, if surgical treatment of chronic pain is considered, it should be postponed for more than one year after primary operation.
4. Considering the high rate of chronic postoperative pain in asymptomatic cases, postponement of hernia repair until possible development of complaints should be considered.
5. Improvement in quality of life scores after inguinal hernia surgery indicates the importance of prompt elective repair of symptomatic inguinal hernias and demonstrates that inguinal hernias have a greater influence on quality of life than is generally thought.

8. SUMMARY IN ESTONIAN

Alloplastika võrkude mõju kroonilise valu ja võõrkehatunde tekkimisele kubemesonga ravis

8.1. Sissejuhatus

Viimastel aastakümnetel on palju diskuteeritud kubemesongade etioloogia, kirurgilise ravi näidustuste, kirurgilise ravimeetodi valiku, erinevate võrkude kasutamise, songaretsidiivide ja krooniliste herniotoomiajärgsete sümptomite üle.

Kuigi kõige enam levinud võrgumaterjal polüpropüleen avastati 60 aastat tagasi ja turul pakutakse üle 160 erineva võrgu [Coda et al., 2012], ei ole ideaalse võrgu omadused ikkagi teada [Simons et al., 2009].

Peale alloplastika võidukäiku songade ravis on sagedaseks probleemiks muutunud krooniline valu, mida esineb kubemesonga plastika järgselt kuni 51,6 % patsientidest [O'Dwyer et al., 2005]. Võõrkehatunne esineb ingvinaalherniotoomia järgselt kuni 43,8 % patsientidest [Post et al., 2004].

Arvestades kroonilise valu ja võõrkehatunde sagedast esinemist kubemesonga plastika järgselt, mis võivad oluliselt halvendada patsientide elukvaliteeti, on kindlasti vajalik võrgu erinevate omaduste uurimine, et leida võrk, mille kasutamisel esineks kroonilisi sümptomeid vähem.

8.2. Uuringu eesmärgid

1. Hinnata kroonilise valu esinemist erinevate võrkude kasutamisel ja selgitada, millised võrgu parameetrid omavad olulist mõju kroonilise valu tekkimisele ingvinaalherniotoomia järgselt.
2. Hinnata võõrkehatunde esinemist erinevate võrkude kasutamisel ja selgitada, millised võrgu parameetrid omavad olulist mõju võõrkehatunde tekkimisele ingvinaalherniotoomia järgselt.
3. Hinnata patsientide elukvaliteeti ingvinaalherniotoomia järgselt.

8.3. Uuritavad ja meetodid

Uuringusse kaasati Tartu Ülikooli Kliinikumi Kirurgiakliiniku üldkirurgia ja plastikakirurgia osakonnas opereeritavad vähemalt 18-aastased patsiendid, kellel oli ühepoolne reponeeritav kubemesong ning kes andsid nõudoleku uuringus osalemiseks. Uuringusse ei kaasatud alla 18-aastaseid patsiente ega mittereponeeritava songaga, pitsunud songaga ja retsidiivsongaga patsiente. Uuringusse ei kaasatud ka neid patsiente, kes ei olnud võimelised küsimustikust aru saama või ei soovinud uuringus osaleda.

Patsiendid randomiseeriti ühte kahest uuringugrupist.

Esimeses uuringuetapis võrreldi kahte erineva kaaluga monofilamentset polüpropüleen-võrku. Raske võrgu grupis kasutati Premilene® võrku (B. Braun Melsungen AG, Melsungen, Germany), mille kaal on 82 g/m² ja poori suurus on 0,8 mm. Kergvõrgu grupis kasutati Optilene®LP võrku (B. Braun), mille kaal on 36 g/m² ja poori suurus on 1 mm.

Teises uuringuetapis võrreldi erineva poorisuurusega võrke. Uuringus kasutatud suurema pooriga võrk oli Ultrapro® võrk (Ethicon, Hamburg, Germany), mis koosneb polüpropüleenist ja resorbeeruvast polüglekaproonist. Ultrapro® võrgu poori suurus on 3–4 mm ja kaal 28 g/m². Kasutatud väiksema pooriga võrk oli eelpool kirjeldatud Optilene®LP võrk.

Uuringu kolmandas etapis, kus hinnati võrgu fikseerimiseks kasutatavate õmbluste rolli kroonilise valu tekkimisel, kasutati samuti eelpool kirjeldatud Optilene®LP võrku ja isetakerduvat Parietex ProGrip™ võrku (Covidien, Trevoux, France). Isetakerduv võrk on tehtud polüestrist ja resorbeeruvast polülaktikhappest. Parietex ProGrip™ võrgu kaal on 38 g/m² ja poori suurus 1,1 x 1,7 mm ning selle pind on kaetud resorbeeruvate mikrokonksukestega, mis tagavad võrgu fikseerumise kudede külge.

Kõikidele patsientidele tehti kubemesonga plastika Lichtensteini järgi. Isetakerduva võrgu kasutamisel olid operatsiooni etapid sarnased Lichtensteini plastikale, välja arvatud see, et ei kasutatud võrku fikseerivaid õmblusi.

Uuringu esmaseks tulemusnäitajaks oli kroonilise valu esinemine 6. Postoperatiivsel kuul. Võõrkehatunne ja elukvaliteet olid uuringu teisesed tulemused.

Enne operatsiooni, 7. postoperatiivsel päeval, 30. postoperatiivsel päeval, 6. postoperatiivsel kuul ja esimese uuringuetapi puhul ka 3. postoperatiivsel aastal registreeriti valu esinemine erinevate tegevuste korral: rahuolekus, köhimisel, lamamisasendist tõusmisel ja füüsilisel koormusel. Valu tugevus märgiti visuaalanaloogskaalal (VAS) 0 (valu puudub) kuni 100 (maksimaalne valu).

Samuti registreeriti kõikidel postoperatiivsetel järelkontrollidel võõrkehatunde esinemine (jah-ei küsimus).

Elukvaliteedi hindamiseks täideti enne operatsiooni ja 6. postoperatiivsel kuul elukvaliteedi küsimustik (RAND SF36 küsimustik). Antud küsimustikuga hinnatakse järgmisi elukvaliteedi valdkondi: üldine tervisehinnang, vitaalsus, kehaline valu, vaimne tervis, sotsiaalne toimetulek, füüsiline toimetulek, emotsionaalse seisundi probleemidest tingitud piirangud, füüsilise tervise häiretest tingitud piirangud.

8.4. Tulemused

Uuringu esimeses etapis, kus võrreldi erineva kaaluga võrke, esines 6. Postoperatiivsel kuul valu (VAS skoor ≥1) erinevate tegevuste korral raske võrgu grupis 59,4 % ja kergvõrgu grupis 47,8 % patsientidest (P=0,221). Vastavad tulemused 3. postoperatiivsel aastal olid 17,2 % ja 29,3 % (P=0,132). Võõrkehatunne esines 6. postoperatiivsel kuul raske võrgu grupis 32,8 % ja kergvõrgu grupis 20,9 % patsientidest (P=0,123) ning 3. postoperatiivsel aastal

vastavalt 27,6 % ja 20,7 % patsientidest (*P*=0.397). Elukvaliteedi skooride osas kahe grupi vahel statistiliselt olulisi erinevusi ei olnud. Postoperatiivselt paranesid mõlemas grupis oluliselt elukvaliteedi skoorid, välja arvatud üldise tervisehinnangu valdkonna skoorid.

Uuringu teises etapis, kus võrreldi erineva poorisuurusega võrke, esines 6. Postoperatiivsel kuul valu suurema pooriga võrgu grupis 46,3 % ja väiksema pooriga võrgu grupis 34,3 % patsientidest (*P*=0,165). Võõrkehatunnet esines 6. postoperatiivsel kuul vastavalt 47,8 % ja 31,3 % patsientidest (*P*=0,052). Elukvaliteedi skooride osas kahe grupi vahel statistiliselt olulisi erinevusi ei olnud. Postoperatiivselt paranesid mõlemas grupis oluliselt elukvaliteedi skoorid, välja arvatud sotsiaalse toimetuleku skoor väiksema pooriga võrgu grupis.

Uuringu kolmandas etapis, kus võrreldi õmblustega fikseeritavat võrku ja isetakerduvat võrku, esines 6. postoperatiivsel kuul valu õmblustega fikseeritava võrgu grupis 45,3 % ja isetakerduva võrgu grupis 31,4 % patsientidest (*P*=0,092). Võõrkehatunnet esines 6. postoperatiivsel kuul vastavalt 22,7 % ja 40 % patsientidest (*P*=0,031). Elukvaliteedi skooride osas kahe grupi vahel statistiliselt olulisi erinevusi ei olnud, välja arvatud sotsiaalse toimetuleku skooride osas. Postoperatiivselt paranesid õmblustega fikseeritava võrgu grupis oluliselt elukvaliteedi skoorid, välja arvatud üldise tervisehinnangu ja vaimse tervise skoorid. Isetakerduva võrgu grupis paranesid oluliselt kehalise valu, füüsilise toimetuleku ja füüsilise tervise häiretest tingitud piirangute skoorid.

8.5. Järeldused

1. Meie uuringute tulemusena ei oma võrgu kaal, poori suurus ja võrku fikseerivad õmblused olulist mõju kroonilise valu tekkimisele. Kindlasti on vajalik võrkude teiste omaduste ja eelkõige võrkude erinevate omaduste kombinatsioonide edasine uurimine.
2. Arvestades varajase tugeva valu esinemist ja seost varajase tugeva valu ning kroonilise valu tekkimise vahel ingvinaalherniotoomia järgselt, on vajalik postoperatiivse valuravi parema skeemi väljatöötamine.
3. Kuna kolmandal postoperatiivsel aastal esines kroonilist valu oluliselt vähem kui 6. postoperatiivsel kuul, siis juhul kui kaalutakse kroonilise valu kirurgilist ravi, tuleks see võimalusel edasi lükata rohkem kui aasta peale esmast operatsiooni.
4. Arvestades kroonilise valu sagedast esinemist ingvinaalherniotoomia järgselt, peaks asümptomaatiliste kubemesongade puhul kirurgilist ravi edasi lükkama kuni sümptomite tekkimiseni.
5. Kuna patsientide elukvaliteet paranes oluliselt ingvinaalherniotoomia järgselt, siis sümptomaatilisi kubemesongasid on soovitav opereerida plaanilises korras esimesel võimalusel. Samuti näitab elukvaliteedi paranemine kubemesonga alloplastika järgselt seda, et kubemesongadel on suurem mõju elukvaliteedile, kui seni on üldiselt arvatud.

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