Aspects on the use of slowly degradable mesh in inguinal hernia surgery

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Cover illustration “Mesh over mesh” by Fernando Ruiz Jasbon

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Dedicado a mis amores / Dedicate to my loves

Luis Fernando, Sofia, Danaela, Adiela, Alcira and Miguel
“Our deepest, most indubitable convictions are the most questionable. They mark our limitations and our frontiers, they are our prison”

*Jose Ortega y Gasset, writer.*
Abstract

**Background:** Synthetic non-degradable mesh used in inguinal hernia surgery can cause chronic inflammation, which in turn can lead to chronic post-operative pain (CPP). Theoretically, a degradable mesh could reduce the risk of chronic pain.

**Aims:** To explore the possibility of keeping viable human peritoneum tissue in contact with hernia meshes for several weeks. Evaluate the feasibility and the safety of a slowly degradable mesh in open and endoscopy inguinal hernia repair.

**Methods:** Four publications are included in the doctoral thesis: an experimental method study on peritoneal tissue and three prospective clinical safety studies using a slowly degradable mesh in the repair of patients with inguinal hernias.

**Results:** *Ex vivo* model: Peritoneal tissue in contact with a mesh could be kept viable between 26 and 56 days. Safety Studies: At 3-year control, no patient experienced CPP. The recurrence rates in patients operated with the open technique were 44% for medial inguinal hernias and 0% for lateral inguinal hernias. In patients operated with the endoscopy technique, the recurrence rate for lateral inguinal hernias was 8.8%.

**Conclusions:** Peritoneal tissue can be kept viable in contact with mesh during weeks in a human ex vivo model. Using slowly degradable mesh in the repair of medial inguinal hernia is not safe due to an increased recurrence risk. This mesh seems safe regarding the risk of chronic post-operative pain in patients with lateral inguinal hernias, but the risk of hernia recurrence should be further studied.

**Keywords:** Slowly degradable mesh, inguinal hernia, chronic pain, hernia recurrence, ex-vivo model.
Sammanfattning på svenska

Bakgrund


Nätimplantat ger upphov till en mer eller mindre kronisk inflammation och flera studier har visat att mängden kvarvarande främmande material efter bråckoperation är relaterad till postoperativ smärta. Således kan det finnas en relation mellan icke resorberbart nät och kronisk postoperativ smärta och teoretiskt sett skulle ett nedbrytbart nät kunna minska risken för kronisk postoperativ smärta. Alla nya bråcknät testas först i experimentella djurmodeller. Först därefter kan dessa användas på människa. Tyvärr saknas det tillförlitliga humana experimentella modeller som studerar bland annat cellinväxt, innan nätet används på människor.

Hypoteser

Att mänsklig bukhinna från ljumskbråckssäcken kan behållas levande i vävnadskultur under flera veckor, och att man därmed i en experimentell miljö kan studera interaktion mellan human peritoneal vävnad och olika typer av nätimplantat.

Att ett långsamt resorberbart nät medför färre komplikationer i form av långvarigt post-operativ smärta än ett kvarvarande syntetiskt nät utan att öka recidiv frekvensen vid öppen ljumskbråckskirurgi.
Att ett långsamt resorberbart nät medför färre komplikationer i form av post-operativ smärta än ett kvarvarande syntetiskt nät utan att öka recidiv frekvensen vid operation av ljumskbråck med endoskopisk teknik.

Frågeställningar


2. Är långsamt nedbrytbart syntetiskt nät säkert att använda vid öppen operation av mediala och laterala ljumskbråck? Klinisk prövning, studie II


4. Är långsamt nedbrytbart syntetiskt nät säkert att använda, ur ett bråckåterfallperspektiv, vid endoskopisk operation av laterala ljumskbråck? Klinisk prövning, långtidsresultat. Studie IV

Metoder och Resultat

1. Studie I

Experimentell metodstudie på bukhinna från bråcksäckens. Modellen bestod av ett 25x25 mm stor preparat av bukhinna som fixerades mellan 2 olikstora plastrningar, där nätet placerades på antingen främre eller bakre sidan av bukhinnan. Hela ex-vivo uppsättningen sänktes ner i odlingsmediet. Åtta uppsättningar av modellen studerades, varav fem av dessa i kontakt med ett nät. Monitorering av alla preparat gjordes med upprepade fotografieringar. Inverterat faskontrastmikroskop nyttjades för att kunna studera morfologi, cell viabilitet och cellproliferation. Efter en vecka kunde man observera att enstaka celler migrerade till nätet och detta ökade med tiden. Efter 48 dagar var stora delar av nätet
täckta med fibroblaster och dessa celler kunde ses även i botten av cellodlingsplattan. Preparat kunde behållas levande i minst 26 dagar.

2. **Studie II**

Prospektiv klinisk genomförbarhet- och säkerhetsstudie av ett långsamt resorberbart syntetiskt nät vid öppen operation av ljumskbräck på 40 manliga patienter. Patienterna följdes upp tre år efter kirurgi avseende post-operativa komplikationer, bland annat smärta och bräckåterkomst. Postoperativ smärta minskade med tiden och värderades i samtliga fall lägre jämfört med den preoperativa smärta. Vid 3-års kontroll upplevde ingen patient smärta som påverkade dagliga aktiviteter. Ingen av de opererade patienterna med lateralajhumskbräck fick recidiv, vilket däremot drabbade 44% av de opererade patienterna med mediala ljumskbräck.

Detta studieresultat medförde att den initialt planerade randomiserade fortsättningsstudien mellan icke resorberbart och långsamt nedbrytbart nät inte kunde genomföras. Det beslutades då att gå vidare med ytterligare en klinisk prövning där endast patienter med lateralajhumskbräck inkluderades. Detta för att säkerställa de positiva resultat som första studien visade på patienter med lateralajhumskbräck.

3. **Studie III och IV**

Prospektiv, klinisk genomförbarhet- och säkerhetsstudie av långsamt resorberbart nät vid endoskopisk operation avlumskbräck på 35 patienter med enbart lateralajhumskbräck. Prövningen hade två delmål. Det första delmålet var utvärdering av peroperativa och tidiga postoperativa komplikationer samt utvärdering av kronisk post-operativ smärta vid 1-års uppföljning, studie III. Det andra delmålet, studie IV, var en långtidsuppföljning upp till 3 år för utvärdering av sena komplikationer såsom bräckåterfall. Inga allvarliga peroperativa eller omedelbart postoperativa komplikationer vid användning av långsamt resorberbart nät vid endoskopisk bräckkirurgi påträffades i studie III. Studien visade att den postoperativa smärta minskade jämfört med preoperativt och att ingen patient hade kronisk postoperativ smärta enligt definition i ”International Guidelines for Groin Hernia Management”.
Studie IV visade att 8.8% av patienterna fick kliniskt bräckåterfall inom 36 månader efter operationen med långsam resorberbart nät samt att ytterligare 11.7% hade ultraljudsmässiga tecken på bräckåterkomst utan klinisk relevans. Ingen patient hade kronisk postoperativ smärta vid 3-års kontroll.

**Konklusion**

Dessa publicerade studier har delvis kunnat svara på frågeställningar i det här forskningsprogrammet:

Bukhinnan kan tillsammans med nät hållas viabel i odlingskultur i en *ex vivo* modell under 28-56 dagar. Ex-vivo modellen kan möjliggöra framtida studier avseende integration av ljumskbräcknät med bukhinna.

Långsamt resorberbart nät är inte lämpligt att använda vid operation av medialt ljumskbräck på grund av utökad recidivrisk.

Ur kronisk smärtsynpunkt föreföll långsamt resorberbart nät vara fördelaktigt att använda vid laterala ljumskbräck men risken för bräckåterfall bör studeras vidare.

Nya randomiserade studier jämförande standard permanent nät mot långsamt resorberbara nät är nödvändiga för att kunna veta om resorberbara nät ger mindre risk för kronisk postoperativ smärta med bibehålleden låg recidiv risk på patienter med lateralt ljumskbräck.
List of articles

This thesis is based on the following published studies, referred to in the text by their roman numerals.


*An ex vivo model using human peritoneum to explore mesh-tissue integration.*

Biology Open. 2017 Sep; 15; 6(9):1391-1395.

II. Ruiz-Jasbon F, Norrby J, Ivarsson M-L, Björck S.

*Inguinal hernia repair using a synthetic long-term resorbable mesh: results from a 3-year prospective safety and performance study.*


III. Ruiz-Jasbon F, Ticehurst K, Ahonen J, Norrby J, Ivarsson M-L.

*TEP with long-term resorbable mesh in patients with indirect inguinal hernia.*

JSLS. 2018 Jan-Mar; 22(1).


*Results at 3-year follow-up of totally extraperitoneal (TEP) hernia surgery with long-term resorbable mesh.*

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIP</td>
<td>Chronic inguinal pain</td>
</tr>
<tr>
<td>CPP</td>
<td>Chronic post-operative pain</td>
</tr>
<tr>
<td>CPIP</td>
<td>Chronic post-operative inguinal pain</td>
</tr>
<tr>
<td>EHS</td>
<td>European hernia Society</td>
</tr>
<tr>
<td>IASP</td>
<td>International association for the study of pain</td>
</tr>
<tr>
<td>IPQ</td>
<td>Inguinal pain questionnaire</td>
</tr>
<tr>
<td>LIH</td>
<td>Lateral inguinal Hernia</td>
</tr>
<tr>
<td>MIH</td>
<td>Medial inguinal Hernia</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
</tr>
<tr>
<td>P4HB</td>
<td>Poly-4-hydroxybutyrate</td>
</tr>
<tr>
<td>PGA</td>
<td>Polyglycolide</td>
</tr>
<tr>
<td>PLA</td>
<td>Poly-lactide</td>
</tr>
<tr>
<td>PTC</td>
<td>Polymer of trimethylene carbonate</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>SHR</td>
<td>Swedish hernia register</td>
</tr>
<tr>
<td>STD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Transforming growth factor-beta 1</td>
</tr>
<tr>
<td>TAPP</td>
<td>Trans-abdominal pre-peritoneal</td>
</tr>
<tr>
<td>TEP</td>
<td>Totally extra-peritoneal</td>
</tr>
<tr>
<td>TIPP</td>
<td>Transinguinal pre-peritoneal</td>
</tr>
<tr>
<td>TMC</td>
<td>Trimethylene carbonate</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analog scale</td>
</tr>
</tbody>
</table>
1. Introduction Inguinal Hernia

1.1 Definition

Inguinal hernia is the protrusion of intra-abdominal organs or tissues such as bowel through a defect in the abdominal wall at the level of the inguinal canal in the groin. When the intra-abdominal content protrudes through the hernia defect, it can produce discomfort or pain. In some cases, blood supply to an intraabdominal organ is strangulated by the ring formed for the hernia defect, leading to necrosis of the tissues outside the hernia defect.

In clinical practice, a broader term, groin hernia, is used that includes femoral and inguinal hernia. This expression is possibly used due to the difficulty in differentiating between femoral, lateral and medial inguinal hernias by physical examination alone. A fifth of men suffer of a groin hernia during their lifetime compare to 3% of women.

1.2 Anatomy, Classification, Etiology and Incidence

Anatomy

The inguinal canal is a tube-like structure in the groin through which the testicular vessels and the spermatic duct in male and the round ligament of the uterus in female pass. Access to the inguinal canal from the abdominal cavity is the deep inguinal ring (annulus inguinalis profundus) and exit to the scrotum or the labia majora is the superficial inguinal ring (annulus inguinalis superficialis). The most important tissues of the inguinal canal from the inguinal hernia perspective are: 1. Fascia transversalis, 2. Tractus ilipubicus 3. Muscoloaponeurotic tissues of the external obliquis, the internal obliquis, and the transversus abdominis muscles, fig 1. The aponeurotic fibres of some of these muscles, alone or in combination, form strong ligaments as the Inguinal, lacunar and Cooper ligaments.
The femoral canal, contending the femoral vessels, is located inferior and medial to the inguinal canal, these canals are separated by the iliopubic tract and the inguinal ligament. This explains the difficulty in diagnosing the type of hernia by palpation of the groin alone.

Figure 1 Anatomy of inguinal hernia.

Netter illustration used with permission of Elsevier Inc. all rights reserved. www.netterimages.com
Classification

Groin hernias are traditionally divided into lateral inguinal hernia, medial inguinal hernia and femoral hernia\(^1,2,6\). A combined hernia implies coexisting types of hernia in the same groin. A pantaloon hernia is a combined lateral and medial hernia.

The lateral (indirect) inguinal hernia occurs when an intraabdominal organ involved in a peritoneal integument (hernia sac) protrudes through the deep inguinal ring. Lateral hernias represent about 55% of all groin hernia in both male and female\(^7\).

The medial (direct) inguinal hernia is formed by penetration of any intra-abdominal content throw the fascia transversalis at the level of Hesselbach triangle, that means medial to the deep inguinal ring and the inferior deep epigastric vessels, and superior to the iliopubic tract and the inguinal ligament. A medial inguinal hernia does not form a hernia sac as does the lateral. In men, 35% of groin hernias are medial inguinal hernias, and 18% in women. Nevertheless, if combined hernias are included, the proportion of medial hernias is 43% in male and 21% in female\(^7\). Medial inguinal hernias have almost double the risk of recurrence after repair compared to lateral inguinal hernias\(^8\).

In a femoral hernia, the abdominal organ protrudes through the femoral canal. Femoral hernias are 25% of all groin hernias in women but only 2% in men\(^7\). Femoral hernias have a higher risk for acute incarceration than other groin hernias and this may be the cause why 13% of all groin hernia operations in women are acute, but only 4% in men\(^9\).

Usually it is an intraperitoneal organ that bulges through the hernia defect, if it is a pre-peritoneal organ or part of this such as sigmoid colon, rectum fallopian tubes or urinary bladder, it is called sliding groin hernia\(^10,11\). These hernias are usually associated with a higher risk for surgical complication and recurrence because the organ is part of the hernia sac\(^12\).

Additionally to the above description of the groin hernias, there are several systematic groin hernia classifications\(^1,2,6,13,14\). These classifications aim to grade the severity of the hernia. Grading of the inguinal hernias allows comparison between different studies and between different repair techniques and consequently establishes which hernia repairs should be recommended at different grades of severity.
The most used classifications are the Nyhus classification and the classification of the European Hernia Society (EHS) (table 1 and 2). Both classifications are based in traditional concepts as lateral (indirect), medial (direct), femoral, primary and recurrent hernia. Moreover, both classifications ranks the complexity of the hernia. The EHS classification ranks the sized of the hernia defect, while the Nyhus classification ranks the grade of dilation of the deep inguinal ring and how this affects the fascia transversalis.

**Table 1. European Hernia Society Classification of Groin Hernias in form of a cross table to fill with P, R, X or 0**

<table>
<thead>
<tr>
<th>Type of hernia</th>
<th>Size of hernia orifice by numbers of fingers</th>
</tr>
</thead>
<tbody>
<tr>
<td>L: lateral</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>M: medial</td>
<td></td>
</tr>
<tr>
<td>F: femoral</td>
<td></td>
</tr>
<tr>
<td>X:</td>
<td>The existence of a type of hernia is unclear</td>
</tr>
<tr>
<td>0:</td>
<td>Confirmed absence of a type of hernia</td>
</tr>
<tr>
<td>P:</td>
<td>Primary hernia</td>
</tr>
<tr>
<td>R:</td>
<td>Recurrent hernia</td>
</tr>
</tbody>
</table>

**Table 2. Nyhus Classification of Groin Hernias**

Type I  Indirect inguinal hernia, normal deep inguinal ring

Type II Indirect inguinal hernia, dilated deep inguinal ring, normal fascia transversalis and no displacement of the inferior deep epigastric vessels

Type III A. Direct inguinal hernia
   B. Indirect inguinal hernia, dilated deep inguinal ring affecting the fascia transversalis

Type C  Femoral hernia

Type IV Recurrent hernias
Inguinal Hernia in Children

In the male fetus, the testicles reside in the abdominal cavity. By the time of birth or just after, the testicles migrate to the scrotum by an elongation of the peritoneum into the inguinal canal called processus vaginalis. The processus vaginalis is usually obliterated after descent of the testicle, preventing others intraabdominal organs from passing into the scrotum. In the female fetus, a small processus vaginalis is also obliterated by the end of pregnancy forming the round ligament. Failure in the obliteration of the processus vaginalis can lead to the formation of an inguinal hernia, hydrocele or cyst of Nuck.

Not all the children with a patent processus vaginalis develop an inguinal hernia, thus other factors must be implicated in the etiology of the inguinal hernia in children.

The incidence rate of groin hernia in infants younger than 1 year is around 10% in boys and less than 2% in girls. The rates of groin hernia prevalence stratified by age and gender are shown in figure 2. The risk of inguinal hernia is higher on the right side compared with the left side. It is suggested that this is in part due to later descent of the right testicle into the scrotum and consequently later obliteration of the processus vaginalis on that side.

Inguinal Hernia in Adults

Patent processus vaginalis and high intra-abdominal pressure have been proposed to be a major cause of lateral inguinal hernia in adults. Others factors such as acquired or genetic alterations in connective tissue metabolism also play an important role, especially in the development of medial inguinal hernias.

Connective tissue disorders as exfoliative syndrome, Ehlers-Danlos syndrome and Marfan syndrome has been associated with inguinal hernia.

There are several studies showing a relationship between alterations in the collagen and/or elastin fibres and inguinal hernia. Altered levels of regulators of these fibres, including matrix metalloproteinase (MMP), transforming growth factor beta (TGF- β1) and lysil oxidase, have mostly been associated with medial inguinal hernia.

Other risk factor such as high age and male gender has been demonstrated in various studies.
The cumulative incidence of inguinal hernia tends to increase with age and the highest prevalence of inguinal hernia repair is found at the age of 70-80 years $^{5,19}$. A fifth of men suffer of an inguinal hernia during their lifetime compared to less than 2.5% of women $^{4,5}$. Patients operated for an inguinal hernia have higher risk of a new primary hernia in the contralateral side. A study in New York State and a Danish register study found that 10% of the patients repaired for a unilateral inguinal hernia were operated for a contralateral hernia within ten years after $^{35,36}$. A study on patients undergoing unilateral endoscopic inguinal hernia repair showed 22% to have an occult hernia on the contralateral side $^{37}$.

![Figure 2. Prevalence of inguinal hernia repair stratified by age and gender](Reprinted with permission from PLOS ONE 8(1): e54367 (CC-BY license))
1.3 Management of Inguinal Hernia

Treatment in Children

Surgical treatment of confirmed inguinal hernias in children is recommended because of the risk for incarceration in untreated hernias during infancy is high (6-30%) and especially because incarcerated hernia has a 9% risk of irreversible lesion of the testis and the potential risk of ischemia of intestine or ovary. Premature infants and infants are traditionally planned for hernia surgery as soon as possible. In older asymptomatic children, surgery is usually carried out on an elective basis.

There are two established operating techniques, open and laparo-endoscopic approach. Both methods perform a ligation of the hernia sac, called herniotomy. If the deep inguinal ring is dilated, narrowing of the ring with stitches or loops is usually carried out, called herniorrhapsy. Open surgery is more common than laparo-endoscopic. Meta-analysis studies have not found any substantial difference in recurrence or complication rates, but the laparoscopic approach has a shorter operation time for bilateral hernias, and the advantage of being able to explore the contralateral side in unilateral repair.

Treatment in Adults

In male adults, unlike in children, watchful waiting management is an alternative for asymptomatic inguinal hernias because the risk for acute incarceration is less than 2.4% over 2-4 years. The International guidelines for groin hernia management recommended an individual approach in men with asymptomatic hernias. A discussion with the patient on the appropriated timing of surgery is important because the risk for an acute surgery, moreover the hernias can become symptomatic within a 7-year period in 70% of patients selecting a watchful waiting approach.

In women, data show a higher frequency of emergency inguinal hernia surgery compared to men; 9.5% vs 4.6% respectively. However there...
are no data on the risk of incarceration in asymptomatic radiologically confirmed inguinal hernia without femoral component in women.

The international guidelines for groin hernia management recommends operation of asymptomatic groin hernias in women, taking in consideration that 25% of all groin hernias are of femoral type and that acute femoral surgery comprises 40% of all acute groin hernia procedures in women.\textsuperscript{7,9}

A summary of the principal indications for each surgical technique according to the international guidelines for groin hernia management is presented in table 3.\textsuperscript{2}

\textit{Table 3. Indication for each surgical technique according to the international guidelines for groin hernia management.} Totally extra-peritoneal (TEP), Trans-abdominal pre-peritoneal (TAPP)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lichtenstein</th>
<th>TEP</th>
<th>TAPP</th>
<th>Shouldice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral Primary Male</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Recurrence after open</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Recurrence after TEP/TAPP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Previous pelvic surgery/pathology</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Surgery</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Contraindication for mesh</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
1.4 Surgical techniques for inguinal hernia repair in adults

The treatment of inguinal hernia has changed over time. Throughout most of the nineteenth century the method recommended was herniorrhaphy, that means resection of the hernia sac, closure of the hernia defect and eventually reinforcement of the fascia transversalis with sutures.\textsuperscript{43,44}

Since the late 1900s the recommended method has been mesh hernioplasty, i.e. resection or invagination of hernia sac and reinforcement of the abdominal wall with some mesh implant\textsuperscript{43}. The implant can be placed ventral to fascia transversalis, in which case it is called the on-lay or anterior approach. If the mesh is placed dorsal the fascia transversalis it is called, sub-lay, pre-peritoneal or posterior approach.

The pre-peritoneal mesh can be positioned by open, laparoscopic or endoscopy methods.\textsuperscript{43,44} Historic and the principles of the main techniques are described below.

Herniorrhaphy

Marcy

Marcy (1871) was the first to describe the resection of the hernia sac at the level of the deep inguinal ring and narrowing of the ring with sutures. This was a breakthrough at the time since the hernia sac was previously resected at the superficial ring without opening the extern oblique aponeurosis and the deep inguinal ring was thus not visualized during the surgery. Despite the advances made by Marcy, recurrence rate sometime were almost 100\%\textsuperscript{43,44}.

Bassini

Bassini (1889) reported a technique where a reinforcement of the posterior wall of the inguinal canal was performed with 3 suture layers: fascia transversalis, conjoint tendon and internal oblique muscle to the inguinal
ligament. This procedure reduced markedly the recurrences rate to around 20%, however pain product of the tension of the repaired tissue and still elevated recurrence rate motived the search for better surgical techniques.\(^{43,44}\)

**Shouldice**

*Shouldice* published 1953 a method using 4 suture lines with 2 stainless steel wire. Two suture lines were placed between the fascia transversalis and the iliopubic tract and a further two suture lines from the internal oblique and transversus abdominis muscle to the inner part of the external oblique aponeurosis. Shouldice also pleaded for the use of local anaesthesia and early mobilisation. The last recommendation was surprising at a time when the majority of surgeons advice physical inactivity for several weeks after surgery.\(^{44,45}\) Recurrence rate in specialized clinics such as the Shouldice Clinic in Canada has been as low as 1% but those results have not been reproduced in others hands.\(^{45}\) A recurrences of 4% have been found in the Swedish hernia register.\(^7\)

**Mesh Hernioplasty**

The idea of using an implant to reinforce weak points in the groin was introduced relative early. Marcy for example tested tendons from various animals in 1887. In the first half of the 20th century, several surgeons tested autologous implants from rectus fascia and fascia lata. At the same time other surgeons began using synthetic materials: first polyamide (nylon) then polyester and in the1950s polypropylene.\(^{43,44}\)

The existence of synthetic mesh facilitated apply the idea of patching the hernia defect dorsally in the abdominal wall, this gave rise to two new operation methods: Anterior and posterior mesh repair of inguinal hernia; the latter could be performed as an open, laparoscopic and endoscopic technique.

A short introduction of the four commonly used procedures today is given below.
**Lichtenstein**

This is an approach using a polypropylene mesh fixed to the inguinal and lacunar ligament, covering the fascia transversalis and the internal oblique muscle around the deep inguinal ring. Initially the method was advocated for recurrence and complex hernias but in 1989 Lichtenstein named the technique as “the tension-free hernioplasty” and recommended it to all types of inguinal hernias. The modified Lichtenstein technique was later established by Parviz Amid, a pupil of Lichtenstein. This technique, along with other modifications, includes suturing of the fascia transversalis in medial inguinal hernias.

This method is the most used in the world today possibly because for its reproducible low recurrences rate even in the hand of surgeons with limited experience in hernia surgery.

**Open pre-peritoneal**

There are two ways to access to the pre-peritoneal space with an open technique: Transinguinal pre-peritoneal (TIPP) and the Nyhus approach. In the TIPP procedure, access is via the hernia defect itself or by incision of the fascia transversalis. After this the hernia sac and the rest of the peritoneum is dorsally separated from the fascia transversalis. The dissection is extended from the retropubic space to the anterior superior iliac spine including the iliac vessels and the femoral canal. A mesh of approximately 10 x 15 cm is placed without fixation covering the whole dissected pre-peritoneal space including the hernia defect.

In the Nyhus technique, extension of the dissection of the peritoneum including the peritoneal sac and placement of the mesh is similar to the TIPP technique but access to the pre-peritoneal space is via an incision of the rectus muscle and the mesh is fixated to the fascia transversalis.

**Laparoscopic pre-peritoneal: Transabdominal Pre-Peritoneal (TAPP)**

In this approach, the operation begins with a laparoscopy; afterwards the surgery is carried out from inside the abdominal cavity. Dissection of the peritoneum is performed by an incision cranial to the inguinal zone to form a pocket. Dissection of the peritoneum and placement of the mesh is similar to other pre-peritoneal procedures, however with TAPP the peritoneal incision must be closed with sutures or tacks.
An advantage of the TAPP procedure is it enables inspection of the abdominal cavity during the surgery, facilitating, for example, reposition of incarcerate intestine during acute hernia surgery\textsuperscript{50,51}.

*Endoscopic preperitoneal: Totally Extra-Peritoneal (TEP)*

This procedure is very similar to TAPP but surgery is carried out in the pre-peritoneal space without entering the abdomen. First an incision is made in the anterior rectus fascia few centimetres below the umbilicus. A balloon or the laparoscopic camera is then introduced between the rectus muscle and the posterior rectus fascia in a distal direction as far as the superior pubic ligament. When the camera passes the arcuate line, the posterior rectus fascia fades out and the camera is now in the preperitoneal space. With blunt dissection, space is created to introduce directly 2 trocars into the pre-peritoneal space. The rest of the procedure is similar to other pre-peritoneal approaches\textsuperscript{52,53}. An advantage compared to TAPP is that the peritoneum remains intact during the procedure, thus there is less risk of intestinal lesion or adherence formation after the surgery. However, TEP has a longer learning curve than TAPP\textsuperscript{54,55}.

### 1.5 Surgical Complications

Complications can be classified as early or late. Complications during the first month after surgery are generally accepted as early and complications later than three months after surgery are considered late. There is no generally accepted classification of complications occurring between 1 and 3 months after surgery. The most frequent complications are hematoma, seroma, superficial incision infection, acute and chronic postoperative pain, urinary retention and recurrence. The overall risk for early complication is between 2.9–8\% but of these only around 20\% need some form of intervention\textsuperscript{54,56–59}. There are rare but serious complications such as lesion of intra-abdominal vessels and organs, and fistula formation\textsuperscript{59}.

The most common late complications, hernia recurrence and chronic post-operative pain, are discussed below. A summary of other frequently occurring complications is given in table 4.
### Hernia Recurrence

The rate of hernia recurrence has fallen in recent decades. At the end of last century, the risk for re-operation five years after surgery according to the Swedish Hernia Register (SHR) was 5%. Since then it has fallen to 3% in patients operated between 2010-2013. Risk factors for recurrence are both technical and patient related.

#### Technical risk factors for recurrences

**Mesh:**
The main factor leading to reduction of the recurrence rates is possibly the widespread use of mesh in hernia procedures. This statement is supported by the fact that the percentage of recurrence repairs was reduced from 17% prior to 1995 to around 10% after 2006. At the same time the percentage of mesh hernia repairs increased significantly from 5% in 1992 to 78% in 2003.

Furthermore several studies have shown a lower recurrence rate after mesh repair compared to suture repair.

**Surgical Technique:**
Randomised studies at specialised hernia centres have not demonstrated any significant difference in recurrence rates between the diverse mesh repairs for primary inguinal hernia in men.

---

**Table 4. Summary of post-operative complications other than recurrence and chronic pain**

<table>
<thead>
<tr>
<th></th>
<th>Open repair</th>
<th>Laparoscopy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>1.4</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3.5</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Seroma</td>
<td>2.5</td>
<td>0.5-12</td>
<td>2.5</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0.6</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe acute pain</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>
In register studies, there is clearly better result after TEP/TAPP compared with Lichtenstein in women 65-67. However in men with primary inguinal hernia, register studies tend to slightly favour Lichtenstein over TEP/TAPP 57. On the other hand, TEP/TAPP procedures have better outcomes than Lichtenstein regarding repair of recurrences after open surgery. 68-70.

Differences between randomised and register studies could be explained by the fact that studies at a specialised hernia centre include surgeons experienced in a specific approach, whereas register studies includes less experienced surgeons. This suggests that a risk factor for recurrence is not only the approach per se but also the experience of the surgeon in that technique. This statement also is supported by studies that show higher risk for recurrence in surgeons with less experience in hernia surgery 71,72.

Patient related risk factors:
Smoking, recurrent hernia, medial inguinal hernia and female sex have been found to be the most important patient related risk factors for recurrence. The relative risk for recurrence for smokers is 2.53, for recurrent hernia 2.22, for medial inguinal hernia 1.9 and for female 1.4 compared with non-smoker, primary hernia, lateral hernia and male respectively 73. The higher risk of recurrence for smokers, medial inguinal hernia and recurrent hernia may be explained in part by the association of these factors with collagen defects 73. As regards female sex as a risk factor for recurrence, it is speculated that neglected femoral hernias at primary repair could be a reason 65,73.

Chronic Postoperative Pain (CPP)
Others terms with the same meaning are chronic postsurgical pain (CPSP) and persistent post-surgical pain (PPSP) 74,75. Chronic postoperative inguinal pain (CPIP) means chronic pain after inguinal hernia repair.
There is no generally accepted definition of CPP. It is reflected in the wide range of CPP rates after hernia repair found in clinical studies (5-63%) 76,77. There is not a uniformed assessment of pain in inguinal hernia surgery studies. Variables such as intensity and duration of pain, pain effect on the quality-of-life, interval between surgery and follow-up, as-
essment method per se and exclusion of pain no caused by surgery are not standardised in studies on CPIP.\textsuperscript{76,77}

Although the International Association for the Study of Pain (IASP) and the HerniaSurge Group (HSG) have established definition of CPP and CPIP respectively, there is a lack of uniformity in studies assessing CPP after inguinal hernia repair.\textsuperscript{76}

CPP is defined by the IASP as pain persisting more than three months, at least three months after surgery, with increased intensity postoperatively or not present preoperatively, localised to the surgical site or a referred area and with pain from non-surgical causes excluded.\textsuperscript{75,78}

CPIP is defined by HerniaSurge Group as CPP in the groin but requires that the intensity of the pain must be at least moderate and have impact on daily activities.\textsuperscript{2}

Despite the vast number of studies on inguinal chronic pain and hernia surgery, it is surprising that meta-analyses performed to date have not used a strict definition of CPP or CPIP.\textsuperscript{77,79,80} This is because most studies included in meta-analyses had not excluded patients with others cause of inguinal pain or patients with similar or greater groin pain preoperatively. Moreover most studies include patients with mild pain that does not affect daily activities. Consequently meta-analysis show the rate of chronic inguinal pain sometime after hernia repair but this is not the same as the rate of chronic inguinal pain due to hernia repair.\textsuperscript{74,81}

\textit{Risk factors for chronic inguinal pain (CIP) after hernia repair}

The following risk factors have stronger level of evidence for CIP after hernia repair: Intensive or chronic preoperative pain, intensive pain directly after surgery, young age, female gender, open hernia repair and surgery of recurrent hernia.\textsuperscript{82} Other risk factors with lower level of evidence include: heavyweight mesh in open repair, complication after surgery and preservation of inguinal nerves in open mesh repair.\textsuperscript{82,83}

A study from the Swedish Hernia Register show that the hazard ratio for reoperation due to CPP was almost twice as high in women compared to men, three times as high for Lichtenstein compared to TEP and three times as high for patients younger than 61 years compared to those older.\textsuperscript{84}
1.6 Type of mesh for inguinal hernia repair

Non-resorbable meshes
Nowadays the most commonly used material for production of surgical meshes is polypropylene followed by polyester. However there are different types of polypropylene meshes because the mesh can be constructed in different ways. This influences the mesh properties specially tissue integration.
At the end of the last century, most meshes were so-called heavyweight *i.e.* mesh with a weight greater than 90 gr/m². This type of mesh is less flexible and carries a higher risk for CPP when used in open hernia repair compare with lightweight meshes (< 50 gr/m²). It is possibly for this reason that lightweight meshes are most used in open hernia repair today. However, lightweight meshes have been associated with higher recurrence rate than heavyweight meshes in endoscopic hernia repair.
In recent decades, mesh research has focused on other factors and their effect on integration with host tissues. Factors such as the size of mesh pores, the used of biological or resorbable synthetic meshes have been studied. Meshes with larger pores (pore size > 1 mm) integrate better with the surrounding tissue than meshes with small pores.

Resorbable meshes
Resorbable meshes can be divided into biological and synthetic.

*Biological meshes*
Biological meshes are mostly composed of an acellular collagen matrix extracted from porcine, bovine or human tissue. Few biological meshes have been tested in inguinal hernia surgery, possibly due to the high cost of these implants.
The best studied biological mesh in inguinal hernia was made of porcine intestinal submucosa. Randomised studies comparing this mesh with standard non-degradable meshes showed no difference in recurrence rates when using the Lichtenstein procedure but higher recurrence rates using the TEP procedure. Nowadays, biological meshes are not routinely used in inguinal hernia repair.
Synthetic resorbable meshes

Synthetic resorbable meshes are principally made of derivatives from polyesters (polyglycolides and polylactides) or copolymer of trimethylene carbonate. Many of these meshes combine different resorbable materials.

Synthetic resorbable meshes can have different degradation time. In hernia surgery the most important thing is not how long it takes for complete degradation of the mesh but rather how long it takes for the mesh to lose its capacity to resist intra-abdominal pressure. To this end the concept of time taken for the mesh to lose 50% of its strength is often used. A list of short- and long-term resorbable meshes is given in Table 5.

There are studies on inguinal hernia repair using meshes with relatively rapid resorption. These have either shown a high recurrence rate or the follow-up of the patients was too short to demonstrate a realistic recurrence rate.

Some short-term degradable meshes such as Vicryl and Dexon with degradation times less than 3 months have been tested in animal studies on incisional hernia, showing higher rates of recurrence or strong peritoneal adhesions. A pilot study on open inguinal hernia repair using the short-term resorbable Bio A mesh showed a recurrence rate of 37% at the 3-year follow-up.

The commercially available mesh with the longest resorption time and longest time to lose 50% of strength is the TIGR Matrix. This mesh was used in all the clinical studies in the present doctoral thesis.

Table 5. Synthetic resorbable meshes in inguinal hernia surgery

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Composition</th>
<th>Degradation time</th>
<th>50% Strength</th>
<th>Long-term studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vicryl</td>
<td>Polyglactin</td>
<td>2-3 m</td>
<td>&lt; 1 m</td>
<td>no</td>
</tr>
<tr>
<td>Dexon</td>
<td>PGA</td>
<td>2-3 m</td>
<td>&lt; 1 m</td>
<td>no</td>
</tr>
<tr>
<td>Bio A</td>
<td>PGA + TMC</td>
<td>6 m</td>
<td>1-2 m</td>
<td>yes</td>
</tr>
<tr>
<td>Phasix</td>
<td>P4HB</td>
<td>12-18 m</td>
<td>3-4 m</td>
<td>no</td>
</tr>
<tr>
<td>TIGR</td>
<td>PGA+PLA+PTC</td>
<td>36 m</td>
<td>9 m</td>
<td>yes</td>
</tr>
</tbody>
</table>

1.7  Properties of the mesh used in the present clinical studies.

Composition of the mesh
TIGR Matrix mesh is a macroporous multifilament mesh with 2 types of co-polymer fibres. Fibre 1 is mainly composed of polyglycolide, plus some polylactide and polytrimethylene carbonate. Fibre 2 is mainly composed of polylactides plus a minor amount of polytrimethylene carbonate. Fibre 1 (rapid degradation) constituted 40% of the mesh. This fibre loses 50% of its residual strength after approximately 14 days and is completely resorbed at about 4 months. Fibre 2 (slow degradation) constituted 60% of the mesh. This fibre loses 50% of its residual strength after approximately 9 months and is completely resorbed at about 3 years.\textsuperscript{109,110}

Mechanism of degradation of the mesh
The mesh is degraded by bulk hydrolysis, \textit{i.e.} the surface and inside of each fibre are eroded equally by contact with water.\textsuperscript{109,110} Water reacts with bonds in the co-polymer chain breaking it up into smaller chains; subsequently these chains are degraded to small particles that are finally metabolised in the Krebs cycle to carbon dioxide and water.\textsuperscript{99,111}

Early studies of the slowly degradable mesh
A comparative study between slowly degradable mesh and polypropylene mesh in sheep revealed that both elicited formation of collagen fibres around the mesh. The collagen formed during the first 12 months was principally type I, while the proportion of collagen type III increased with time. At 24- and 36-month follow-up the total collagen and the ratio of collagen I/III were higher around the slowly resorbable mesh compared to the tissue formed around the polypropylene mesh.\textsuperscript{109}
This animal study and a complementary *in vitro* study showed that the mesh was completely degraded 36 months after implantation$^{109,110}$. 
2. Aims

The general purpose of the present thesis was to evaluate the safety and the feasibility of a new slowly resorbable mesh in the surgical treatment of inguinal hernia.

2.1 Specific Aims

The specific aims of the studies included in this thesis were:

I. Explore the possibility of keeping human peritoneum tissue alive for several weeks during culture conditions, and thus be able to study the interaction between human peritoneal tissue and different types of mesh in an experimental environment.

II. Evaluate the feasibility and the safety of a slowly resorbable mesh in open inguinal hernia surgery.

III. To investigate the feasibility and the safety of endoscopic lateral inguinal hernia repair using a slowly resorbable mesh, focusing on early complications and chronic postoperative pain.

IV. To investigate the feasibility and the safety of endoscopic lateral inguinal hernia repair using a slowly resorbable mesh, focusing on recurrence and late complications.
2.2 Problem statements

I. Can peritoneum’s reaction after mesh implants be studied experimentally with a human ex vivo model?

II. Is slowly degradable synthetic mesh safe and feasible to use in open inguinal hernias surgery?

III. From a short-term and chronic pain perspective, is slowly degradable synthetic mesh safe to use in endoscopic lateral inguinal hernia surgery?

IV. From a long-term and recurrence perspective, is slowly degradable synthetic mesh safe to use in endoscopic lateral inguinal hernia surgery?
3. Patients and Methods

3.1 Studies’ designs in relation to the problem statements

Study I: Can human peritoneum be kept viable for several weeks in a culture solution in order to study its reaction to different meshes?

An *ex vivo* experimental model was used to answer this question. Peritoneal tissue from the hernia sac of five patients was used. A 25x25 mm patch of peritoneum was placed between two acrylic rings of different sizes and the mesh was placed in front of or behind the peritoneum. The entire setup was immersed in a culture medium, figure 4. Total 8 sets of the model were constructed: 5 setups in contact with a synthetic mesh and 3 without mesh. Monitoring of all preparations was done by repeated photographs. An inverted phase contrast microscope was used to study morphology, cell viability and cell proliferation. Follow-up was planned until contamination was suspected.

![Cell culture plate](image)

**Figure 3. The ex vivo model**

The peritoneal tissue is positioned between two acrylic rings and submerged in culture medium.

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Study II: Is slowly degradable synthetic mesh safe and feasible to use in open surgery of inguinal hernias?

A prospective clinical feasibility and safety study of TIGR ®Matrix mesh was planned to respond this issue. Forty male patients with primary unilateral inguinal hernia were included in the study. Patients underwent Lichtenstein hernia repair using TIGR-mesh by surgeons experienced in hernia surgery. Patients were followed up three years after surgery for adverse events and complications including pain and hernia recurrence. The assessment of adverse events was monitored by anamnesis taking and physical examination at 14 days, 6, 12 and 36 months after surgery. The assessment of pain was done by validate pain questionnaires 112,113; Visual Analog Scale (VAS) at different activities was used pre and post-operatively. Moreover, an analgesic diary and the Inguinal Pain Questionnaire (IPQ) during the first week and at 36 months after surgery respectively were planned. A symptom questionnaire was also used to assess other aspects of the quality of life of the patients. Recurrence was evaluated by physical examination 6, 12 and 36 months after surgery. The 36-month follow-up included an ultrasound examination by an experienced radiologist.

Study III: In the short term, is slowly degradable synthetic mesh safe to use in endoscopic lateral inguinal hernia surgery?

In order to reply this problem statement a prospective, clinical safety and feasibility study on patients with a lateral inguinal hernia was organized. Patients attending for primary inguinal hernia and suitable for TEP repair were enrolled for the study. During surgery, patients with pure lateral inguinal hernia were repaired with TIGR®Matrix mesh, otherwise patients were repaired with a permanent mesh and excluded from the study. A total of 35 lateral inguinal hernias were included in the study. Early complications were recorded by anamnesis taking and physical examination one week and 12 months after surgery. Postoperative pain and its effect on quality-of-life were assessed preoperatively and at 3 and 12 months after surgery using the validated pain questionnaires: IPQ and VAS during various daily activities.
Chronic postoperative pain was predefined as moderate or higher pain intensity that disturbed normal daily activities and persisted longer than three months.

Study IV: In the long term, is slowly degradable synthetic mesh safe to use in endoscopic lateral inguinal hernia surgery?

With the intention of answering this issue, a prospective clinical safety study on the same cohort of patients in study III was planned. This study includes a 3-year follow-up.
Later complications were recorded by anamnesis taken at a visit to the outpatient clinic and by data obtained from the Swedish Hernia Register. Recurrences were assessed at 3-year follow-up by physical examination by an experienced surgeon and ultrasound examination by an experienced radiologist. Chronic post-operative pain was evaluated at the 3-year follow-up in the same way as in study III.

3.2 Methodological Considerations

Background and methodology
The background of this thesis was that permanent implants, used as gold standard in hernia surgery, have not only positive effects such as less risk of recurrences but also negative effects. Mesh related complications such as fistula formation, nerve entrapment, and chronic postoperative pain have been found in several studies. It was therefore important to know whether slowly resorbable meshes have less risk for such complications without increasing the risk for recurrence. The best way to answer this question scientifically would be to perform a multicenter double blind randomized control trial (RCT) on hernia surgery comparing permanent with slowly resorbable mesh. This has been the definitive goal of the present research project all the time.
At the time of the start of Study II there were no studies published on synthetic long-term resorbable mesh in inguinal hernia surgery. Study II
was thus a first-in-man study. At this phase of knowledge, an RCT was not considered ethical. However, it was considered relevant to run a pilot study in selected patients with focus on feasibility and safety.

The role of pilot studies and statistical analysis

The purpose of a pilot study is not to measure the efficacy of an intervention but rather the feasibility of the intervention, in other words how practicable and reasonable the intervention is. An important methodological consideration is how much new knowledge does a clinical pilot studies provide. The answer depends on several factors: how much is known about the issue in question, what is the specific goal of the pilot study, and how robust is the outcome in relation to the number of patients included and to outcomes in similar populations.

Specific methodological considerations of Study I

If the ex-vivo model was intended to be applied to studies on hernia mesh and human tissue integration, why use human peritoneum and not human muscles fascia or aponeurosis? The first simple answer is the ease of access to peritoneal tissue. The peritoneal hernia sac is commonly resected during open hernia repair but aponeurosis tissue and muscle fascia are rarely resected during benign surgery. The second reason is that open pre-peritoneal and laparo-endoscopic techniques place the mesh in direct contact with the peritoneum.

Another aspect is why not use an experimental model based on human cells instead of human peritoneum? It was considered that tissue with several cell layers such as peritoneum would provide more information about the integration or reaction to meshes than a single cell culture.

Specific methodological considerations of Study II

It was decided to include 40 patients in Study II. This number of patients was insufficient to give realistic rates of rare or infrequent complications but large enough to reveal any frequently occurring complication or adverse event.
In this respect, a recurrence rate of around 2% and chronic inguinal pain rate of around 16%, normally seen after inguinal hernia repair, should be considered infrequent complications.

If the rates of recurrence and chronic inguinal pain with slowly resorbable mesh were expected to be similar to or less than traditional permanent mesh, it would not be possible to draw any significant conclusion about recurrence or chronic post-operative inguinal pain from a pilot study including as few as 40 patients. Study II was thus meant as a safety and feasible study, but even so, to assess recurrence and chronic post-operative inguinal pain.

Specific methodological considerations of Studies III and IV

After completion of pilot Study II, it was initially planned to proceed with a randomised controlled trial comparing non-resorbable and slowly degradable mesh. However, Study II soon revealed a high complication rate for patients operated for medial inguinal hernia with degradable mesh, and it was thus not possible for ethical reasons to go on with the RCT planned. A broad explanation of ethical considerations is found in the following section.

Of the cohort of 40 patients in Study II, 14 patients were operated for lateral inguinal hernia. No serious adverse events were found in this subgroup. However, an RCT based on patients with a lateral inguinal hernia alone was not possible because this subgroup of 14 patients was considered too small, even for a safety and feasibility study.

Thus, the methods of Studies III and IV were influenced by the outcome of Study II.

Instead of an RCT, it was decided to proceed with a further safety trial on patients with a lateral inguinal hernia in order to see if the preliminary positive results in this subgroup of patients in Study II could be confirmed in a larger cohort of patients.

It was considered important to focus the trial on two outcomes but using the same cohort of patients. To this end, Study III focused on early complications and chronic post-operative pain while Study IV focused on late complications and recurrence. This decision was based on methodological problems seen in Study II. One problem was that most recurrences developed between the 1- and 3-year follow-up, thus assessment of recurrence at 3 years was most important. On the other hand, assessment of chronic pain at 3 years was affected negatively by the exclusion of a group of patients that had been re-operated with a permanent implant,
thus assessment of chronic post-operative inguinal pain was more reliable at the 1-year follow-up.

The decision to use endoscopic repair for Studies III and IV instead of an open approach as in Study II was based on two considerations: First, there were concerns that the lack of recurrence seen in patients with a lateral inguinal hernia in Study II was not due to the mesh per se but to factors related to open repair such as resection of the hernia sac and reinforcement of the internal ring. By using an endoscopic approach without fixation of the mesh, these confounders did not exist, leaving only the mesh to explain the recurrence rate. Second, by using endoscopic repair it was possible to observe possible serious side-effects of the new mesh that could not be investigated in Study II because of the open technique itself. For example, complications related to contact of the mesh with the peritoneum or possible protrusion of the mesh into the hernia defect may be investigated in an endoscopic repair trial but not when using an open technique.

3.3 Ethic

Ethical Approvals

Study I: The Local Ethics Committee at Sahlgrenska Academy approved the study. Ö 728-03.

Study II: The Regional Ethical Review Board in Gothenburg, Sweden, approved the study. DNR751-08

Study III and IV: The Regional Ethical Review Board in Lund, Sweden, approved the study. Protocol 2014/2
Ethical Considerations

Ethical discussions on the probable benefits versus possible complications related to the mesh are necessary before testing a new mesh in humans.

In Study II, the most important discussion concerned the probable benefits of a slowly resorbable mesh (less pain, less risk for fistula and other mesh-related complications) versus the possible risk of a higher recurrence rate once the mesh has been completely degraded.

There had not been studies on the type of mesh we planned to use in humans, but there were studies on biological mesh with presumably comparable properties. Those studies showed similar recurrence rate to standard permanent meshes, thus it was possible to start a safety study from an ethical point of view.

When preparing for Studies III and IV, the major ethical consideration was whether to begin a new safety study or go directly to a randomized controlled trial on patients with a lateral inguinal hernia only. Since Studies III and IV were to use a different technique to that in Study II (TEP instead of open repair), it was decided that a new feasibility safety study would be the best for patients included in those studies.

There are differences between ethical and scientific considerations in this case. Study II did not find any serious complication in patients with a lateral inguinal hernia, thus an RCT was possible from the scientific point of view. From an ethical perspective, however, this was a new mesh not tested in humans, and it was better to advance slowly keeping the safety of the patients in mind. We therefore decided on a new safety study on patients with a lateral hernia only.

3.3 Statistical Considerations

Since all studies included in this doctoral thesis were feasibility studies, statistical handling was principally description of the sum of continuous data.

Comparison of pain before and after surgery was based on continuous dependent variables and thus evaluated using the non-parametric Wilcoxon signed-rank test.

In this case, repeated pain assessments in the same patient were compared before and after surgery. The difference in those “populations”
cannot be considered normally distributed and consequently a paired Student’s t-test was considered not suitable and the non-parametric Wilcoxon signed-rank test more appropriate.
4. Summary of Results

4.1 Study I: Ex Vivo model of peritoneal tissue

Eight set-ups of peritoneal tissue with and without mesh could be kept alive in culture medium for at least 26 days. Two set-ups with mesh remained viable at 56 days with no signs of contamination. The viabilities of the different set-ups are shown in Figure 4.

Monitoring of viability with inverted phase contrast microscopy showed that after one week, cells began to migrate towards the mesh and this increased with time.

After 48 days, large areas of the mesh were covered with fibroblasts, and these were seen at the bottom of the cell culture plate.

![Figure 4. Viability of the different set-ups in the ex vivo model. Each arrow indicates a duplicate of experimental set-ups (n=2-3) of ex vivo models (n=4-6 for each group). *indicates one (of two) set-up that was discarded after 60 days in culture due to suspected bacterial contamination. Samples from the culture medium revealed no bacterial growth. Reprinted with permission from Biol Open 6:1391-1395 (CC-BY license).](image-url)
4.2 Study II: Lichtenstein surgery with TIGR-mesh: a 3-year follow-up.

Of the 40 patients included in the study, 35 completed the 3-year follow-up. No serious adverse events were recorded during the early postoperative period. One patient suffered urinary retention and dysuria. No hematoma, seroma or wound infection requiring management was seen. Postoperative pain decreased over time and was lower than that experienced preoperatively. At the 3-year follow-up, no patient experienced pain affecting daily activities. Pre- and postoperative pain scores on a VAS are showed in Table 6.

Table 6. Pre and postoperative pain scores on a VAS (0-10)

<table>
<thead>
<tr>
<th>Action</th>
<th>Before Surgery (n=39)</th>
<th>12 months (n=38)</th>
<th>36 months (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>1.0 (2.5)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>On coughing</td>
<td>1.5 (4.0)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.8)</td>
</tr>
<tr>
<td>When rising from lying to sitting</td>
<td>2.2 (5.5)</td>
<td>0.2 (0.2)</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>When climbing one step in a flight of stairs</td>
<td>1.3 (2.9)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>When taking a 30m indoor walk</td>
<td>1.6 (3.3)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.6)</td>
</tr>
<tr>
<td>Overall (mean of above scores)</td>
<td>1.5 (0.2)</td>
<td>0.1 (0.0)</td>
<td>0.1 (0.0)</td>
</tr>
</tbody>
</table>

Values are mean (std).
At the 3-year follow-up, eight (22.8%) patients had hernia recurrence. None of the patients with a lateral inguinal hernia had recurrence, while 38% of patients with a medial inguinal hernia alone or a combined hernia suffered a recurrence. During the study period, five patients were re-operated for medial recurrences (Table 7).

Table 7. Type of primary hernia defect and type of recurrence 3 years after surgery

<table>
<thead>
<tr>
<th></th>
<th>Lateral</th>
<th>Medial</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Operation</td>
<td>14 (40.0)</td>
<td>9 (25.7)</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>Total Recurrences</td>
<td>0 (0.0)</td>
<td>4 (44.4)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Type of Recurrence</td>
<td>Medial 4(100)</td>
<td>Medial 3 (75)</td>
<td>Unclear 1 (25)</td>
</tr>
</tbody>
</table>

Percentages within parentheses

4.3 Study III: TEP with TIGR-mesh: 1-year follow-up

Fifty-five patients were initially included for this study. During the TEP procedure, 28 patients with medial, combined or femoral hernias were excluded from the trial. Twenty-seven male patients with 35 lateral inguinal hernias were finally operated with a long-term resorbable mesh. All patients completed the 1-year follow-up. No serious perioperative or immediate post-operative complications were seen. Complications in the early post-operative time were local hematoma 5 (18.5%), seroma 2 (7.4%), urinary retention 1(3.7%). Only the patient with urinary retention required treatment consisting of a single urinary drainage.
The study also showed that the post-operative pain score on the VAS decreased for the absolute majority of patients. No patient had increased pain and two patients had post-operative pain scores similar to that pre-operatively (fig 6).

Two patients had pain at rest at the 3-month follow-up but no patient had pain at rest or chronic post-operative pain as defined in the “International Guidelines for Groin Hernia Management” at the 1-year follow-up. Table 8 shows the number of patients with VAS $\geq 2$ before and after surgery. No hernia recurrence was seen during the first post-operative year.

*Figure 6 Scatter-plot of pain on the VAS for each patient before and 3 years after surgery*

*Patients with equal pain trend are shown on one trend colored line only. Bilateral hernias are counted twice, one VAS-form per side.*

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### Table 8. Number of patients with inguinal pain ≥ 2 (VAS 0-10)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Preoperatively n=35</th>
<th>3 months post-operatively n=30</th>
<th>1 year post-operatively n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>7 (20.0)</td>
<td>2 (6.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>On coughing</td>
<td>18 (51.4)</td>
<td>1 (3.3)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>At sitting</td>
<td>15 (42.9)</td>
<td>2 (6.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>When climbing one step in a flight of stairs</td>
<td>8 (22.9)</td>
<td>1 (3.3)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>When taking a 30m indoor walk</td>
<td>12 (34.3)</td>
<td>1 (3.3)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>When rising from lying to sitting</td>
<td>12 (34.3)</td>
<td>2 (6.6)</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

*Value: number of patients (%).

Patients with bilateral hernias count twice, one pain questionnaire per side.

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### 4.4 Study IV: TEP with TIGR-mesh: a 3-year follow-up

Of the cohort of 27 patient with 35 hernias included in the Study III, all patients completed the 3-year follow-up regarding late complications and pain questionnaires, but one patient was lost to the ultrasound and physical examination.

Three (8.8%) symptomatic hernia recurrences were found during the first three postoperative years. Two recurrences were found 18 months after primary surgery and one recurrence after 28 months.

At the 3-year follow-up, four (11.7%) new recurrences were found by ultrasound examination, but none of those patients had hernia symptoms or recurrence by physical examination.

No chronic post-operative pain or other late complications were found at the 3-year follow-up.
5. Discussion

5.1 Keeping viable human peritoneum in an *ex vivo* model to explore mesh-tissue integration

Study I showed that a human peritoneal tissue can be preserved up to 56 days in an *ex vivo* model. Prior to this study, the longest time reported for preservation of peritoneum in culture medium had been 4 days\(^{120}\). Keeping human peritoneum viable during practically 2 months would help in the study of integration of new meshes with the peritoneum.

In this study the setups with longest culture time were finished because of suspicions of culture contamination but bacterial analysis of those samples were negative. This indicates that peritoneal tissue may be preserved *ex vivo* for more than 2 months.

The reason for the longer viability of peritoneum in the present study compared to previous studies is not clear. In contrast to previous trials, in the present study the peritoneum was directly immersed in buffered sterile culture medium E199 instead of saline solution after excision\(^{120}\). Whether this factor played a role in the viability of peritoneum should be investigated in future studies.

In Study I, the number of fibroblast around the mesh and in the culture medium increased over time. Because the study was planned as a proof-of-concept model it did not intend to investigate in detail the function of the different cells that comprise the peritoneum. However several studies have demonstrated that fibroblast cell formation is an important part of the healing process of the mesothelial line\(^{121,122}\). Thus, the findings in Study I are consistent with those of previous studies on peritoneum\(^{123-125}\).
5.2 Slowly resorbable synthetic mesh as repair material in inguinal hernia

Studies II and IV found that of 75 inguinal hernias repaired using slowly resorbable mesh, 54 (72%) hernias showed no sign of recurrence at physical or ultrasound examination at the 3-year follow-up. As the mesh should have been fully degraded by this time, an important issue is why did not those patients develop hernia recurrence? The present doctoral thesis was not intended to study the biological effect of the slowly resorbable mesh in the abdominal wall but a discussion about this is necessary to understand the present results.

Degradation time of the mesh

An important issue in the present thesis was whether the TIGR mesh used in these studies had been completely degraded three years after implantation.

In studies II and IV, 8 patients were re-operated for recurrence. Macroscopic residual material was not found during surgery, and biopsy of fascia transversalis from these patients did not show microscopic signs of residual material.

Degradation of TIGR mesh occurs by hydrolysis and the intervention of macrophage cells is not necessary. On the contrary some studies on similar degradable mesh found that the time taken for degradation was reduced by other factors such as infection or inflammation. This was probably due to macrophages, other inflammatory cells and cytokines accelerating the degradation process of the mesh. Moreover an animal study and an in vitro study showed that degradation of the mesh was complete within 3 years. In conclusion there are several facts that indicate that TIGR mesh is fully resorbed during the first 3 years after implantation.

Effect of slowly resorbable mesh on the hernia defect

Nondegradable mesh patches the weakness in the abdominal wall thus repairing permanently the hernia defect - but what happens in the case a resorbable mesh? Animal studies have shown that slowly resorbable mesh can stimulate the formation of strong connective tissue. This tissue continues to patch the weakness in the abdominal wall when the
mesh has disappeared in the same way as a permanent mesh. This process possibly explains why 72% of the hernia repairs in Studies II and IV showed no signs of recurrence three years after surgery.

5.4 Hernia recurrence in patients with a medial inguinal hernia

In Study II, 8 (38%) of 21 patients with isolate medial or combined inguinal hernia, *i.e.* defect of the fascia transversalis, had suffered a recurrence by the 3-year follow-up. In the SHR the percentage of re-operations for recurrence of a medial or combined hernia 5 years after primary surgery is around 3.7% ⁷. The key question is: was this large difference in recurrence rates (38% vs 3.7%) solely due to aleatory factors inherent in a pilot study.

Validation of the rate of recurrence in patients with MIH in Study II

In order to approach this issue, it is necessary to compare the study population with a similar population operated with a permanent mesh, which was not the intention of Study II. A post-study analysis was performed when preparing for the present doctoral thesis to resolve the question: could aleatory factors alone explain the large number of recurrences seen in the Study II (Appendix 1). This post-study analysis compared the recurrence rate of medial inguinal hernia repairs between patients included and those not included in Study II. Patients not included in the study were operated by the same surgeons and using the same technique but using a permanent mesh. Using the Chi2-test/Fisher-test, this analysis showed that the difference in recurrence rates was highly significant <0.001, confirming that the high rate of recurrence in patients operated for medial inguinal hernia with slowly resorbable mesh was not due to chance.

Possible causes of the high rate of recurrence in patient with MIH

Studies have shown that collagen defects are more frequent in patients with MIH compared to patients with LIH ⁸,²⁵.
These studies have shown lower collagen levels, higher levels of collagen degradation enzymes such as MMP-2 and TGF-β1, lower levels of tissue inhibitors of MMP-2, and lower copper levels in tissues of patients with MIH compared to LIH. These aberrations in collagen metabolism could lead to the connective tissue stimulated by the resorbable mesh not having the strength to resist intra-abdominal pressure once the mesh has disappeared. An indication of this in Study II was that 7 of 8 recurrences occurred around 18 months after surgery at which time the mesh had lost its capacity to resist intra-abdominal pressure.

5.5 Hernia recurrences in patients with lateral inguinal hernias

Fourteen patients with a lateral hernia were operated with an open technique in Study II, and none developed a clinically or ultrasound verified recurrence. Of 35 lateral inguinal hernias operated with the TEP technique in Study IV, 3 (8.8%) patients developed a clinically verified recurrence at the 3-year follow-up. In the Swedish Hernia Register the risk for reoperation for recurrence after lateral hernia repair is 2% 5 years after surgery.

Two technical facts differ between the open study and the endoscopic one. When using the endoscopic approach, no stitches are used to close the hernia defect and the hernia sac is invaginated not resected. The rate of recurrence in patients with lateral hernia repair using the open approach cannot be compared with that in the endoscopy study, but the difference in the handling of the hernia defect and the hernia sac between those surgical approaches must be considered when planning future trials on slowly resorbable mesh in order to select the more appropriated approach for resorbable meshes.

A relevant issue is once again whether the relatively high recurrence rate (8.8%) after lateral inguinal hernia repair using TEP with slowly resorbable mesh can be explained by aleatory factors alone.
Recurrence verified by ultrasound examination alone.

In Studies II and IV an ultrasound examination was performed 3 years after surgery in order to verify any hernia recurrence. The ultrasound examinations in both studies were performed by the same experienced radiologist.

In Study II, there was good agreement between clinical and ultrasound verified recurrence. In Study IV, however, four patients (11.7%) had an ultrasound verified recurrence despite lack of signs or symptoms on clinical examination.

The specificity and the sensitivity of ultrasound examination for inguinal hernia recurrence after TEP in asymptomatic and non-palpable hernias has not been studied before. It is therefore not clear what the clinical significance of these recurrences was. However, the fact that ultrasound examination has good sensitivity for hernia recurrence in symptomatic patients after TEP indicates the need for longer follow-up of patients with recurrence verified by ultrasound examination alone 129-132.

5.6 Chronic postoperative pain and slowly resorbable synthetic mesh

Chronic pain in the total population of the Studies II-IV.

At a 1-year follow-up, 56 patients (73 hernias) included in Studies II and III did not suffer chronic post-operative pain, defined as a score ≥3 on a VAS-scale, during any activity, and no patient had pain affecting daily activities. A recent study from the SHR showed that 15.2% of patients had pain affecting daily activities 12 months after hernia surgery 133. Another study from the German Herniamed register showed that between 7.8% and 10% of patients had pain on exertion 12 months after hernia surgery 134.

It is not fair to compare the results of chronic pain from those register studies with the studies in the present thesis because of different selection criteria. Still as far, it shows a god performance of slowly resorbable mesh on the rate of chronic post-operative pain at 12-month follow-up.
Seven patients of in total 73 hernias include in this doctoral thesis who developed clinical recurrence, also suffered chronic pain or discomfort 18 months after surgery for which reoperation was required. Thus, recurrence affects the rate of chronic postoperative pain. Therefore, keeping long-term low recurrence rate is an important factor when analysing the impact of slowly resorbable mesh on chronic postoperative pain.

**Chronic pain in patients with lateral inguinal hernias and without clinical recurrence.**

Not a single patient with LIH without clinical recurrence had suffered chronic postoperative pain by the 3-year follow-up of Studies II and III.

On one hand, we need to take in consideration that those patients were selected among patients without inguinal pain unrelated to the hernia (median preoperative pain 2.66 on the VAS). Comparing that with a median of 3.4 found in a study from the German Herniamed Register, it seems possible that the selection criteria in the present studies could have influenced the chronic postoperative pain rate.

On the other hand, around 40% of the patients in Study II and III had preoperatively inguinal pain related to the hernia that affecting some aspects of daily activity. Thus, the present studies show a firm reduction in chronic pain after repair with slowly resorbable mesh in this selected patient group.

The hypothesis that slowly resorbable mesh reduces the rate of chronic postoperative pain compared to permanent meshes cannot be fully supported using the results from the studies in the present doctoral thesis. However, our results may server as a base when selecting inclusion criteria in future randomized controlled trials on slowly resorbable mesh, in order to maximize the possible benefits on chronic postoperative pain and reduce the risk for hernia recurrence in the patients included.
5.7 Strengths and limitations:

Strengths

The results of the clinical studies included in the present doctoral thesis are the first and only available data in the literature of the performance of synthetic slowly resorbable mesh in inguinal hernia surgery. This is positive but at the same time, it is a limitation because the present studies cannot be compared with similar studies.

Assessments

A substantial strength of these studies lies in the careful assessment of the different preoperative and postoperative variables: two validated pain questionnaires, two validated methods for assessment of hernia recurrence and the multidisciplinary assessment of per-operative and others post-operative complication. The multidisciplinary follow-up included surgeons, specialist nurses and the local coordinator of the Swedish Hernia Register.

Follow-up

Another strong point is the long follow-up of 3 years, which allowed more realistic evaluation of recurrence rates and other late complications.

Competence of the health personal involved in the study

A third strength is the extensive experience in hernia care and surgery of those treating the study patients. That all surgeons were experienced in hernia surgery reduced the risk of bias related to selection of the patients or to the quality of hernia repair. Nurses experienced in hernia care can better interpret early signs of complication after surgery.

External evaluation of the studies

An independent confirmation of the quality of the clinical studies in this doctoral thesis is that Study II was included in a review article on the
quality of chronic pain assessment after open inguinal hernia repair. In this review, Study II was ranked for its methodological quality among the nine best among 234 articles screened by the authors 76. Studies III and IV, which were published after that review, used a similar methods for pain assessment.

Another independent evaluation of the impact of Study II is that the U.S. Food and Drugs Administration (FDA) did a Class 2 Device Recall where TIGR-mesh was advised against in patients with a medial inguinal hernia. This recall was based on the results of Study II 135.

**Limitations**

**Pilot studies**
All the present studies have the usual limitations inherent in pilot studies i.e. low numbers of samples or patients and the absence of randomisation. These aspects, discussed in the Methodological Considerations section, implies that the present results must be taken with caution because aleatory factors can influence the outcome and there is not enough power for real evaluation of the long-term efficacy of slowly resorbable mesh in lateral inguinal hernia repair.

**Viability of cells**
An important limitation of Study I was that the viability of different cell types in the peritoneum was not assessed by methods other than photography and observation by inverted phase contrast microscopy. Consequently, it was not possible to know which types of cell in the peritoneal tissue were viable at the end of the observation period.

**Follow-up**
Another limitation was the time of follow-up especially regarding the recurrence rate. A three-year follow-up is normally accepted for assessment of recurrence in the literature. However, it is well known that recurrence can occur after 3 years 136,137.
If the efficacy of slowly resorbable mesh on hernia repair is based on replacement by strong connective tissue stimulated by the implant, it is essential that this regenerated connective tissue maintains its strength throughout life. It is possible, however, that the strength of the regenerated connective tissue changes over time leading to recurrence of the hernia.

*Subgroup results*

Study II included patients with all types of inguinal hernia; consequently, the number of patients in each hernia group was low. This affected the statistical value of differences in recurrence rates between medial and lateral inguinal hernia repairs.
6. Conclusions

The published studies in this doctoral thesis partly answered the questions posed in the problem statements section:

1. Peritoneal tissue samples, even those in contact with a mesh, can be kept viable for 28-56 days in culture medium. This observation facilitates future studies on integration of inguinal hernia mesh and peritoneum in an *ex vivo* model.

2. Slowly resorbable meshes seem unsuitable for open hernia repair of medial inguinal hernia due to the increased risk of recurrence.

3. The use of slowly resorbable mesh in lateral inguinal hernias repair seems safe regarding the risk of chronic post-operative pain, but recurrence rate should be studied further.
7. Future Perspective

Peritoneal ex-vivo model

In the future, it would be interesting to compare quality of integration with the peritoneum between different meshes. This is made possible by the \textit{ex vivo} model developed in this thesis. The \textit{ex vivo} model also makes it possible to study more closely which cells are involved in the remodeling process, as well as collagen and elastin distribution. Future ex vivo studies on peritoneum and mesh could include analyses of the differences in viability and reactions to the mesh of the diverse cells that comprise the peritoneum. \textit{Ex vivo} studies may be combined with clinical studies on cell changes in the peritoneum or on biological markers related to hernia recurrence or other complications.

Clinical studies of slowly resorbable meshes

Prolonged follow-up of the patients included in the clinical studies in the present thesis was planned to assess very late recurrence or other complication.

Further randomised trials comparing slowly resorbable and permanent meshes in patients with lateral inguinal hernia are necessary to confirm that slowly resorbable mesh reduces the risk for chronic post-operative pain while maintaining a low recurrence rate.

Since very late recurrence rates of slowly resorbable mesh in patients with a lateral inguinal hernia are unknown, future studies should select patients likely to benefit from the mesh as regards chronic post-operative pain. At the same time, the unknown risk for recurrence using resorbable mesh must also be considered. For example, patients with greater risk for
chronic postoperative pain would benefit more from being included in a study using slowly resorbable mesh than those with lower risk.

Future randomised controlled trials on slowly resorbable mesh should include some form of tissue or blood collagen test in order to include only patients with normal collagen status. This would reduce the potential risk of hernia recurrence and remove at least one confounding factor.
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References

28 Abci, I., Bilgi, S. & Altan, A. Role of TIMP-2 in fascia transversalis on development of inguinal hernias. *Journal of investigative surgery : the official...
29 Henriksen, N. A. Systemic and local collagen turnover in hernia patients. Danish medical journal 63 (2016).


84 Hallen, M., Sevonius, D., Westerdahl, J., Gunnarsson, U. & Sandblom, G. Risk factors for reoperation due to chronic groin postherniorrhaphy pain. *Hernia*


Ansaloni, L. et al. Inguinal hernia repair with porcine small intestine submucosa: 3-year follow-up results of a randomized controlled trial of Lichtenstein’s repair with polypropylene mesh versus Surgisis Inguinal Hernia


Appendix
Articles