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Autologous full-thickness skin graft as reinforcement material in the repair of complex hernias

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Learning is the discovery that something is possible

Fritz Perls

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Abstract

Introduction

Abdominal wall hernia is a common issue in the realm of surgery. Many patients suffering from a hernia require surgical intervention, and over 8000 abdominal hernia repairs are performed each year in Sweden. Since the introduction of synthetic materials for reinforcement of the abdominal wall, hernia repair has improved considerably, and patient satisfaction is high. Repair of some types of hernia, however, is still associated with high recurrence rates and considerable risk for complications.

The risk for developing an incisional hernia after elective abdominal surgery is around 10% and the risk is even higher after emergency surgery. Most incisional hernias are small, but some patients develop a giant hernia, defined as a hernia aperture measuring more than 10 cm across. Management of giant incisional hernia is challenging, and surgical repair is plagued by high recurrence rates and serious postoperative complications.

Parastomal hernia is a common stomal complication that develops in more than half of patients that receive a stoma. Even though most patients experience little or no problem with their hernia, some experience considerable depreciation in their quality of life. Current surgical methods of repair for parastomal hernia are associated with high recurrence rates and are prone to complications that in some cases may be fatal.

In many cases, complications associated with the treatment of giant incisional hernia and parastomal hernia can be linked to the introduction of foreign prosthetic material placed in the abdominal wall as reinforcement. These include mesh infection, fistula formation, visceral adhesions, pain, and discomfort. Our hypothesis was that the use of autologous full-thickness skin grafting instead of the synthetic meshes used today would improve outcome in these cases.

Aim

The overall aim of this thesis was to investigate the use of autologous full-thickness skin grafts as reinforcement material in the repair of complicated types of hernia.

Methods

Studies I and II. A randomised controlled multicentre trial where the use of autologous full-thickness skin grafting in giant incisional hernia repair was

compared to methods using synthetic material. Study I focused on abdominal wall function measured objectively with the Biodex™ system one year after surgery. Study II explored patient-reported quality-of-life in a long-term follow-up using validated questionnaires.

Study III. A laboratory study in which the mechanical properties of fresh full-thickness skin were investigated and compared to currently available synthetic and biological reinforcement materials. The study was a link in a translational chain of studies leading up to human trials investigating the repair of complex abdominal wall defects.

Study IV. A feasibility pilot study, where the development of a novel method for parastomal hernia repair using autologous full-thickness skin for reinforcement was evaluated in four patients.

Study V. Protocol for a randomised controlled multicentre trial on parastomal hernia repair comparing the full-thickness skin grafting method developed in Study IV with conventional methods using synthetic mesh.

Results

In Studies I and II, the randomised controlled multicentre trial showed no significant differences between the groups overall. No improvement in abdominal muscle strength was observed after repair in Study I, nor was there any difference between the treatment allocations. Study II showed a numerical trend towards improvement in quality-of-life in general. Some domains were significantly improved, mainly those describing physical ability and prevalence of pain. No relevant differences according to treatment allocation were seen. At clinical follow-up three years after surgery, there were a total of 5 recurrences in the full-thickness skin graft group and 3 in the synthetic mesh group, but this difference was not significant.

In Study III, the tensile strength and resistance to suture tearing of full-thickness skin was shown to be superior to conventional synthetic and biological meshes.

In Study IV, there were no major procedure-related complications in the four patients that underwent parastomal hernia repair with intraperitoneally applied autologous full-thickness skin graft. Two patients developed a recurrent hernia during a mean follow-up time of 18 months.

Study V presents details of an upcoming randomised controlled trial and thus no results are available.

Conclusions

Full-thickness skin in giant incisional hernia repair produced similar outcomes as synthetic mesh repair. There was little or no difference according to treatment allocation regarding complications, recurrences, abdominal wall muscle strength, and quality-of-life. Further evaluation is needed to identify a potential subgroup of patients where repair using full-thickness skin grafting would be more beneficial than synthetic mesh.

Study IV, on the feasibility of a novel method for parastomal hernia repair, was based on results from Study III along with previous animal studies. This method was deemed feasible, leading to the conclusion that there is enough evidence to proceed with a larger randomised clinical trial. Details of the upcoming trial are presented in Study V.

Abbreviations

ADL: Activities of daily living

CT: Computerised tomography

EHS: European Hernia Society

EORTC C30: European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire

EORTC CR29: European Organisation for Research and Treatment of Cancer questionnaire module for colorectal cancer

FTSG: Full-thickness skin graft

MMP: matrix metalloproteinase

Preop: Preoperatively

PSH: Parastomal hernia

QoL: Quality-of-life

RCT: Randomised controlled trial

SHIFT: Stomal Hernia Intraoperative Full-Thickness skin

VAS: Visual analogue scale

VHPQ: Ventral hernia pain questionnaire

List of publications

This thesis is based on the following publications and manuscripts, referred to in the text by their Roman numerals

- I. Holmdahl V, Stark B, Clay L, Gunnarsson U, Strigård K. One-year outcome after repair of giant incisional hernia using synthetic mesh or full-thickness skin graft: a randomised controlled trial. *Hernia*. 2019 Apr;23(2):355-361.
- II. Holmdahl V, Stark B, Clay L, Gunnarsson U, Strigård K. Long-term follow-up of full-thickness skin grafting in giant incisional hernia repair: a randomised controlled trial. (Submitted)
- III. Holmdahl V, Backman O, Gunnarsson U, Strigård K. The Tensile Strength of Full-Thickness Skin: A Laboratory Study Prior to Its Use as Reinforcement in Parastomal Hernia Repair. *Front Surg*. 2019 Dec 4;6:69.
- IV. Holmdahl V, Gunnarsson U, Strigård K. Autologous full-thickness skin graft as reinforcement in parastomal hernia repair: a feasibility study. *Tech Coloproctol*. 2021 Jan;25(1):131-136.
- V. Holmdahl V, Gunnarsson U, Strigård K. Autologous full-thickness skin graft as reinforcement in parastomal hernia repair: a randomised controlled trial. (Study-Protocol) (Submitted)

Enkel sammanfattning på svenska

Ett bräck uppstår till följd av en försvagning i bukväggens hårda bindvävshinnor. Bukinnehåll, vanligen tarm eller fettväv, kan tränga ut genom försvagningen och ge upphov till symptom såsom ömhet eller obehag. Är bräcket stort kan bukväggsfunktionen försämrats så att personen får problem med vardagliga kroppsrörelser och smärtor. En fruktad komplikation till bräck är risken för inklämning då blodcirkulationen stängs av till organet i bräcket. Detta leder i sin tur till svåra smärtor och kan vara mycket allvarligt om bräcket exempelvis innehåller tarm. Vilka symptom som uppkommer varierar beroende på bräckets typ, lokalisation och storlek.

De bräck som studeras i denna avhandling är stora ärrbräck och stomibräck.

Ärrbräck uppstår, som namnet antyder, i ett ärr efter tidigare bukkirurgi. Man beräknar att cirka en av tio som opererats i buken kommer att utveckla ett ärrbräck. Andelen är ännu högre efter akut kirurgi eller vid sårläkningskomplikationer i samband med den ursprungliga operationen. De flesta ärrbräck är små och det finns idag bra behandlingsmetoder för de dessa bräck där man i regel förstärker bukväggen med ett syntetiskt plasträt. Resultaten vid operation av patienter som utvecklat mycket stora ärrbräck är inte lika bra, ingreppen är mer komplexa och risken för komplikationer och bräckåterfall större.

Stomibräck uppstår i anslutning till en stomi ("påse på magen"), där tarmen lyfts upp genom bukväggen för att avföringen av någon anledning inte kan passera den normala vägen. Stomibräck är en mycket vanlig komplikation till att ha en stomi och graden av symptom varierar påtagligt. Har man mycket besvär av sitt bräck kan kirurgi vara ett alternativ. Tyvärr är resultaten vid de idag tillgängliga operationsmetoderna otillfredsställande. De bästa behandlingsmetoderna idag innefattar precis som vid ärrbräck en förstärkning av bukväggen med ett plasträt. Ingreppen är förenade med relativt hög risk för att få tillbaka bräcket, men också potentiellt farliga komplikationer som i vissa fall kan ha en dödlig utgång.

En del av de komplikationer som ses vid dessa komplexa bukväggsbräck är kopplade det syntetiska förstärkningsmaterialet i bukväggen. Min ambition i studierna som ingår i denna avhandling har därför varit att försöka hitta ett alternativ till dessa syntetiska nät. Att använda sig av autolog (patientens egen) hud som förstärkningsmaterial kan erbjuda ett säkrare alternativ. Detta är inte en ny idé utan något man studerade och använde sig av i viss utsträckning i början av 1900-talet. Även med dagens mått mätt redovisades relativt goda resultat vid en rad olika bräckoperationer i dessa äldre publikationer. Dock minskade

intresset för användning av fullhud påtagligt efter introduktionen av förstärkning med olika typer av plastnät på grund av de goda resultat som uppnåddes, speciellt vid de okomplicerade bräckoperationerna.

Med tanke på de problem som uppdragats vid reparation av stora ärrbräck och stomibräck kan en rekapitulering av dessa äldre kirurgiska metoder vara av värde. Teoretiskt skulle patientens egen hud i egenskap av kroppsegen vävnad minska risken för svårbehandlade infektioner, fistelbildning och obehag samt ge upphov till en förbättrad inläkning i bukväggen och därmed också bättre funktion efter kirurgin.

För att utvärdera autolog fullhud som förstärkningsmaterial vid stora ärrbräck har det genomförts en blindad lottad studie. Totalt lottades 52 patienter mellan att erhålla förstärkning med autolog fullhud eller syntetiskt nät vid bräckreparationen.

- I studie I presenteras resultaten vid ettårsuppföljningen där fokus var bukväggsstyrka före och efter operation. Med Biodex™, som är ett instrument där man objektivt kan skatta bukväggsstyrka, undersöktes alla studiedeltagare före operationen och ett år efter kirurgi. Man såg ingen förbättring av muskelstyrkan hos studiegruppen. Det var heller ingen skillnad i bukväggsstyrka mellan de olika kirurgiska metoderna. Vid den kliniska undersökningen sågs inte någon skillnad avseende återfall och estetiskt resultat. Avsaknaden av förbättring i bukväggsstyrka var förvånande då liknande försök tidigare har visat att patienternas bukväggsstyrka förbättras efter operation. Tänkbara förklaringar är att patientgruppen som inkluderats i denna studie lider av andra sjukdomar som försvårar rehabiliteringen eller att väntetiden på operation ibland varit mycket lång. Den långa väntetiden skulle då kunna medföra att bukmuskelnerna har börjat förtvina.
- I studie II presenteras en långtidsuppföljning med fokus på livskvalitet som även innefattade ett kliniskt återbesök ca tre år efter operationen. Livskvaliteten utvärderades med tre olika självskattningsformulär som patienterna fick fylla i före operationen, tre år, samt i genomsnitt drygt 9 år efter operationen. Vid den kliniska undersökningen såg man att totalt fem återfall hade inträffat i fullhudgruppen och tre i syntetnätgruppen, men skillnaden mellan grupperna var inte statistiskt säkerställd. Vid skattning av livskvalitet sågs förbättring av operationen, framför allt vad gäller smärta och fysisk funktion. Några statistiskt säkerställda skillnader kunde inte uppmätas mellan grupperna.

Avseende behandling av parastomalt bräck innefattar den idag bästa tillgängliga behandlingen applikation av någon slags syntetiskt förstärkningsmaterial, men exakt hur nätet bäst ska appliceras vet man inte med säkerhet. Vissa indikationer tyder på att nätet bör placeras på insidan av bukväggen med ena sidan mot tarmarna. Det finns dock mycket få exempel i litteraturen där man tidigare applicerat autolog fullhud i bukhålan. Därför krävs vissa förkunskaper innan man testar detta på människa. Inom forskargruppen har det tidigare genomförts musförsök där det visat sig att transplanterad fullhud har god överlevnad vid en placering på bukväggens insida.

I studie III utvärderades de mekaniska egenskaperna hos färsk fullhud. Jämförelser gjordes med konventionella förstärkningsmaterial, ett biologiskt och ett syntetiskt. Resultaten visar utmärkta mekaniska egenskaper där huden har långt högre draghållfasthet än såväl kommersiellt syntetiskt som biologiskt förstärkningsmaterial. Fullhud motstår dessutom drag från en sutur lika bra eller bättre än de jämförda materialen.

Mot bakgrund av de tidigare genomförda djurförsöken och resultaten i studie III bedömdes det som möjligt att utvärdera metoden på människa. I studie IV presenteras utvecklingen av en metod för reparation av stomibräck med autolog fullhud som förstärkningsmaterial. Till hjälp vid metodutvecklingen användes bukväggsmodeller utskrivna i en 3D-skrivare där röntgenbilder av patienter med stomibräck användes som mall. Den nyutvecklade metoden testades därefter på fyra pilotpatienter. Vid uppföljning av dessa sågs inte några metodrelaterade komplikationer. Metoden bedömdes därför som tekniskt genomförbar och tillräckligt säker att utvärdera i större skala.

Studie V utgörs av ett studieprotokoll för en lottad studie som skall genomföras på flera centra för utvärdering av den nyutvecklade metoden för reparation av stomibräck jämfört med reparation med syntetiskt nät som används idag.

I denna avhandling presenteras studier som undersöker moderna applikationer av en äldre och till stora delar bortglömd kirurgisk teknik. Resultaten tyder på att användningen av autolog fullhud kan ha en plats i behandlingen av stora ärrbräck, och i en framtida studie kommer dess potential för användning vid reparation av stomibräck att utvärderas.

Background

Hernias

Encyclopædia Britannica defines hernia as “a protrusion of an organ or tissue from its normal cavity” (1). Although hernias arise in several organs in the body including the intervertebral discs and diaphragm, the term is usually applied to protrusions of intra-abdominal contents through the abdominal wall.

Abdominal wall hernias have presumably been a concern throughout human history. The first known description of an abdominal wall hernia and its treatment dates back to ancient Egyptian sources from at least 1550 BC (Fig 1). Fortunately, advances in both surgery and anaesthesiology have meant that patients today receive less painful, safe and effective treatment. However, even though the availability of safe and effective methods for hernia repair has increased, there is still room for improvement, especially in some hernia subgroups.

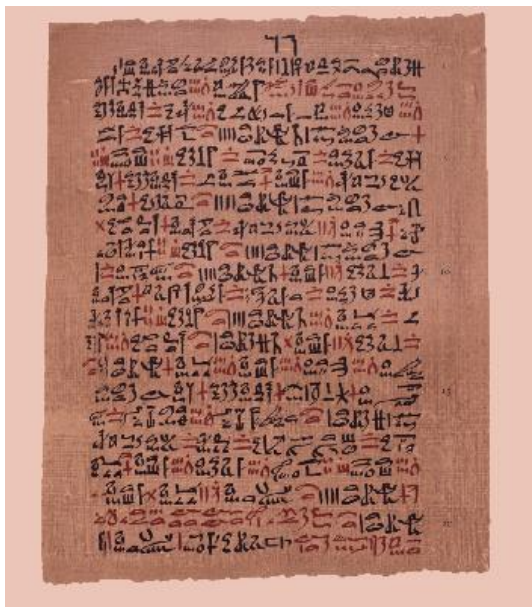


Fig 1. Ebers Papyrus, the oldest preserved medical document.

The abdominal wall

Muscles and their aponeuroses are important for the function of the abdominal wall. There are three flat muscles layers on each side of the abdomen: from the outside inwards, the external oblique, internal oblique, and transversus abdominis, named after the direction of their respective muscle fibres. These flat muscles together with the ventrally located and vertically oriented rectus muscles form a firm but flexible container for the contents of the abdomen (Fig 2). Their combined action not only protects the intra-abdominal organs from injury but together with the lumbar musculature helps us to maintain posture and stability, especially in the erect position.

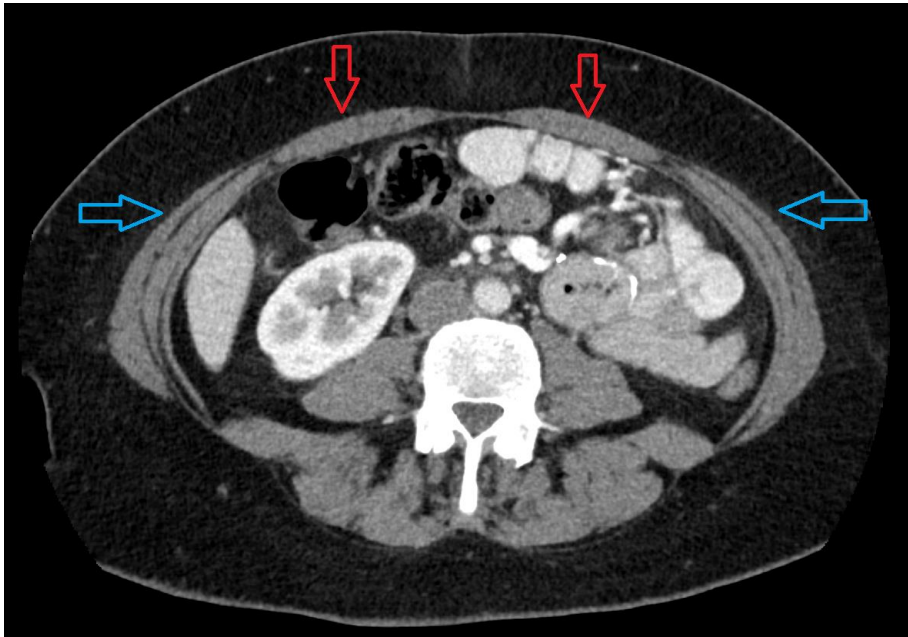


Fig 2. Computerised tomography (CT)-scan with a cross section of the abdomen at the lumbar level. The blue arrows indicate the laterally located flat muscles (external oblique, internal oblique and transversalis abdominis) and the red arrows the ventrally located rectus abdominis muscles.

Contraction of the abdominal wall muscles increases the intra-abdominal pressure. At rest, the intra-abdominal pressure is less than 15mmHg but can reach 150mmHg when coughing (2). The ability to increase intra-abdominal pressure also aids the processes of expiration, vomiting, micturition, parturition, and defaecation. A well-functioning abdominal muscle apparatus is thus most important for the individual's ability to perform activities of daily living (ADL).

Hernia development

A weakening or defect in fascia and muscle aponeuroses will lead to protrusion of intra-abdominal content *i.e.*, a hernia. Since the abdominal wall has natural weaknesses, in some cases iatrogenic, some locations are more prone to the occurrence of hernia. Inguinal hernia is the most common type of hernia, and the life-time incidence of inguinal hernia repair is 27% for men and 3% for women in western populations (3). The umbilicus, site of surgical incision, and stomal orifice are other areas prone to develop a hernia.

When a hernia has developed, the range of symptoms and consequences varies considerably, largely depending on the type and size of the hernia. All symptoms

arise from the displacement of abdominal content which in turn can cause functional disability, pain, or purely aesthetical problems. A feared complication of a hernia is strangulation, where the blood supply to herniated tissue is compromised. Strangulation causes severe pain, and if bowel has herniated it can cause bowel obstruction, necrosis, and ultimately intestinal perforation which is potentially life-threatening and requires emergency repair.

Displacement of large amounts of intra-abdominal content can also alter the centre of balance (Fig 3) contributing to back pain in patients with big hernias (4).



Fig 3. Patient with a giant incisional hernia.

In parastomal hernia (PSH), the stoma can be displaced causing leakage and complicating stomal dressing. This is reflected in the fact that patients with a PSH report poorer quality of life than those without (5).

Biological predisposition

The connective tissue that makes up abdominal wall fascia is under constant remodulation. In response to different forms of strain (or inactivity) the composition of connective tissue is modified to meet current mechanical requirements. Remodulation is a complex biochemical process involving a large number of enzymes and other proteins, primarily managed and orchestrated by fibroblasts. An important group of enzymes involved are the matrix metalloproteinases (MMPs), and their role in hernia development has gained

increasing interest. It has been shown that an imbalance between MMPs and their endogenous inhibitors could be an underlying pathophysiological mechanism behind hernia formation (6). Another important extracellular molecule in connective tissue is hyaluronan, a hygroscopic macromolecule that plays a role in the regulation of water balance in tissue. Hyaluronan and its derivatives also appear to be important in angiogenesis, regulating inflammation, and development of fibrin in chronic wounds, but their exact impact on hernia development and hernia repair is not known (7).

Hernias develop via a complex interplay between endogenous and exogenous factors. When performing hernia repair, patient-related factors and surgical technique combine to determine outcome in the individual patient (8). Improvement in our knowledge of the biology of hernia formation will increase our clinical understanding of the disease and this, in turn, could potentially be used to guide tailored treatment for the individual patient.

Hernia Repair

The aim of hernia repair is to return protruding content to its intra-abdominal origin, to prevent recurrence of the protrusion, and to restore functional integrity of the abdominal wall. The technique used depends on the kind of hernia being repaired and its size. The simplest way to repair a ventral abdominal hernia is to reduce or excise the hernia and to suture the fascial defect. Suture repair may be appropriate for very small hernias or in an emergency situation where the surgical field is potentially contaminated (9). For most hernias, however, it did not take long for surgical research to show that recurrence rates were unacceptably high with suture repair only. This led to the search for suitable reinforcement materials.

Autologous skin

In 1913, Loewe published a paper where he introduced autologous skin as reinforcement material in various surgical procedures (10). Autologous skin was used for sutures, ligatures, and for fixation with generally good results. Loewe and subsequently Rehn used the term “cutis-transplant” indicating that they used manipulated full-thickness skin grafts (FTSG).

Rehn published an article in 1914 describing the use of transplanted skin to repair damaged hand tendons (11). His conclusion was that cutis graft was superior to fascial graft due to its higher regenerative abilities. He furthermore concluded that the tension with which it was applied caused favourable metaplasia. These encouraging results spurred him on to continue his experiments. In 1939, Uihlein reviewed Rehns results including at least 80 hernia repairs (12). Uihlein concluded that Rehns use of cutis graft in hernia surgery was generally successful

and associated with relatively few complications compared to standards of the day (Fig 4).

Preparation of the skin graft

In the early days, different approaches were taken to prepare the skin graft before implantation since the general belief at that time was that implantation of epidermis caused the formation of epidermoid cysts. Loewe used a knife and Rehn a razor blade to scrape away the epidermis. However, removal of the epidermis was probably unnecessary. In 1937, Peer and Paddock published a study where they implanted abdominal skin subcutaneously. They



Fig 4. Patient with incisional hernia who received a FTSG harvested from the lateral aspect of the thigh from Uihlein's publication "Use of the cutis graft in plastic operations" – Reproduced with permission from Archives of Surgery. 1939;38(1):118-130. Copyright© 1939 American Medical Association. All rights reserved.

prepared the skin in the same way as Loewe and Rehn *i.e.*, sharp removal of the epidermis. They studied the metamorphosis process over time by excising the implanted skin graft at various intervals after implantation. They found that no matter how thoroughly the transplanted skin was scraped, there were still remnants of epidermis left in the form of microscopic cysts containing horny material and fragments of hair (13). Most skin adnexa were degraded in a matter of weeks, leaving irregular connective tissue.

Peer followed up that study with another series of patients, but used FTSG instead of cutis grafts. He found that the epidermis was successively degraded and that two months after implantation it was completely absent, leaving epidermoid cysts of little significance and no sign of malignant transformation. Greene and Wollgast confirmed that removal of epidermis was unnecessary and suggested that the main factor preventing clinically relevant epidermoid cysts was suture of the skin graft under tension (14). This was later supported by other authors (15). There are few systematic comparisons from the first half of the 20th century, but one of the most ambitious was by Mair in a series of 454 inguinal hernia repairs, 149 of which used FTSG reinforcement (16). Mair compared the results of

autologous FTSG as reinforcement, with fascia reinforcement and suture repair *ad modum* Bassini, both popular methods at the time. He found the FTSG method to be superior to the others as regards both complications and postoperative morbidity.

Modern uses of FTSG

After the introduction of synthetic mesh material, the use of autologous FTSG decreased and in the second half of the 20th century there have been few scientific publications investigating hernia repair with autologous skin grafting. However, with increasing interest in the scientific evaluation of hernia surgery, it has become evident that results in some hernia subgroups are disappointing, even when using modern synthetic mesh materials. Furthermore, there is a rising awareness of chronic pain and discomfort after hernia repair, partly related to the presence of a foreign body in the abdominal wall (17, 18). The fact that currently available synthetic meshes do not seem to be appropriate for some hernia subgroups may be the reason why autologous FTSG has seen a new dawn, with increasing numbers of publications (19-23).

Synthetic mesh

The development of synthetic meshes to reinforce the abdominal wall has paralleled advances in material science. Development has and always will be an interdisciplinary collaboration between basic researchers, clinical surgeons, mesh manufacturers, and the petroleum industry. In the early 20th century, various metals such as silver, tantalum, stainless steel, and vitallium were tried, but because of considerable morbidity due to fragmentation, these methods were abandoned (24).

Usher's pioneering work with Marlex mesh was a paradigm shift where synthetic mesh began to dominate hernia repair techniques (25, 26). Since then, several synthetic meshes with different properties have been developed. Most synthetic meshes used today are manufactured from polypropylene, polyester, or expanded polytetrafluorethylene, each sort having properties desirable on different occasions (27). Meshes can also be designed with different filament sizes, pore sizes, and architectures that give specific densities. Furthermore, material can be combined or coated with different barrier substances or semi-absorbable materials to obtain a wide variety of properties that enable the surgeon to apply personalised treatment strategies.

Biological mesh

Although generally referred to as biological meshes in the scientific literature, biological prosthetic materials are rather plates of collagen-rich tissues harvested from animals or human cadavers (Fig 5). The theory behind biological mesh is to

provide a scaffold for the endogenous process of connective tissue remodelling. They are supposed to provide initial mechanical support and then to stimulate angiogenesis and deposition of fibroblasts. To enable this, the tissues harvested as xenografts or allografts are processed in different ways to assure biocompatibility and to prevent foreign-body reactions or allergic reactions.

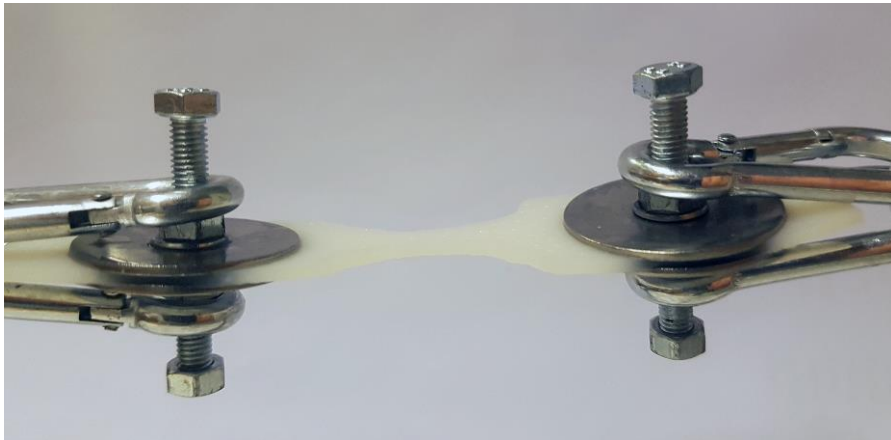


Fig 5. Biological mesh undergoing mechanical testing (from Study III).

However, high expectations were unfortunately not met; the meshes were very expensive and had disappointing recurrence rates (28). Today, biological meshes are mainly limited to selected cases such as a contaminated surgical field.

Vascular ingrowth

Biological meshes undergo transformation after implantation. They provide a scaffold for cells to colonise and regenerate into a functional component of the abdominal wall without recurrence. FTSG is somewhat like a biological mesh, but there is a crucial difference. At the time of implantation, FTSG contains viable tissue but the arterial supply is cut off. The thickness of the graft does not allow for diffusion of oxygen and nutrition to cells, but despite this the graft does not undergo necrosis. The reason is pre-existing blood vessels in the graft that partake in the complex process of revascularisation. This process begins immediately after implantation with a step called inosculation, where the host site's microvasculature and the graft's existing vasculature connect (29). Vascular connection proceeds as the regressing graft vessels are replaced by invading host microvessels, as well as an outgrowth of graft microvessels that connect with the host's microvasculature. Inosculation enables reperfusion of the graft within a few days. In biological meshes no cellular elements are left after bioavailability treatment, making inosculation impossible enabling only the much slower process of neovascularisation

Incisional hernia

Incisional hernia is a matter of concern in the field of abdominal surgery (Fig 7). Approximately one in ten patients develop an incisional hernia after elective abdominal surgery, and the risk is even higher after emergency surgery or postoperative wound complications (30). Incisional hernias cause a wide range of symptoms such as pain, discomfort, problems with personal hygiene, and difficulties in performing activities of everyday life. The number and dignity of symptoms are related to the size of the hernia (4). The size of the hernia also determines the method to be used when repairing the hernia surgically. Incisional hernias with an aperture wider than 10cm are usually labelled “giant” and require considerable thought before attempting surgical repair. The procedure is often complex and associated with higher risk for complications and recurrence than repair of smaller hernias (4, 31).

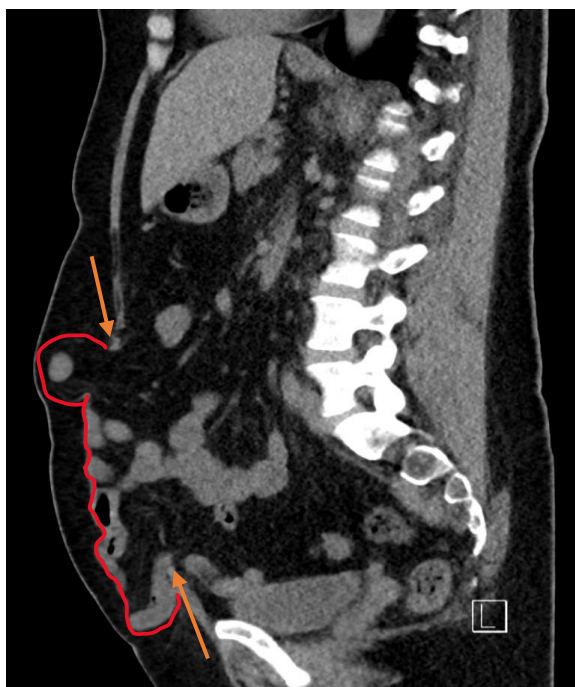


Fig 7. A sagittal CT-image of an abdomen with an incisional hernia. The orange arrows indicate the borders of the fascial defect, and the red line outlines the hernial sac.

Part of this complexity is derived from the fact that a large amount of the intra-abdominal contents can protrude into the giant incisional hernia, causing the abdominal cavity to shrink, a phenomenon referred to as *loss-of-domain*. At surgery, when the herniated abdominal contents are relocated and the hernial defect repaired, an increase in intra-abdominal pressure occurs depending on the grade of *loss-of-domain*, leading to respiratory embarrassment (4, 32). Another problem is the size of the fascial defect, where approximation of the fascial borders often requires the use of special techniques such as component separation

(33). Furthermore, an incisional hernia, by definition, is due to failed healing of an abdominal wall incision. Collagen metabolism impairment may exist in the group of patients with an incisional hernia, further increasing the risk for recurrent hernia.

Treatment of incisional hernia

The treatment of incisional hernia is surgical and for incisional hernias with an aperture wider than 1cm it is recommended to use reinforcement with a prosthetic mesh (34). Even though recurrence rates in smaller incisional hernias have decreased since the introduction of synthetic reinforcement materials, giant incisional hernia repair still has a recurrence rate that can exceed 30% (4, 32). Furthermore, any decrease in recurrence using synthetic mesh reinforcement appears to increase the risk for complication, depending on hernia size (31, 35). The increased interest in long-term complications and pain after hernia repair has shown that care must be taken when choosing a method for surgical reconstruction. There are indications that an implanted unabsorbable mesh could contribute to chronic pain (18).

There are different approaches as to where reinforcement material in the abdominal wall should be placed. The two positions usually used in open incisional hernia repair are:

- Sublay: The reinforcement material is placed in a space created ventral to the peritoneum and fascia transversalis (and the posterior rectus sheath cranial of the arcuate line) and dorsal to the rectus abdominis muscle. The technique is sometimes called Rives-Stoppa after the two French surgeons who developed retrorectus placement of reinforcing mesh in hernia surgery in the 1960s (36).
- Onlay: The reinforcing mesh is placed ventral to the externus fascia after primary closure of the hernial defect. The onlay procedure is sometimes called the Chevrel technique but that is incorrect since the Chevrel technique also includes releasing incisions in the externus fascia to facilitate tension-free closure of the fascia (37).

In a meta-analysis by Timmermans *et al* published in 2014, a number of prospective and retrospective studies were analysed to investigate any differences between the sublay and onlay techniques (38). They found fewer surgical site infections and a tendency towards fewer recurrences in the sublay group, which corroborates with Danish register data published by Helgestrand *et al* (39). In a rat model, mesh placed in the sublay position caused greater foreign body reaction and subsequently stronger incorporation, which could explain the lower recurrence rates seen in clinical studies on humans (40). A more recent meta-analysis could not demonstrate any difference in recurrence rates, but still noted a higher postoperative complication rate, including infection and seroma, in patients with onlay placement of the mesh. This indicates that there may be preventive measures that can be taken to improve outcome after use of the onlay technique (37). Research seems to lean towards the use of the sublay position for

reinforcement in incisional hernia repair, even though it is thought to be more technically challenging. Under certain circumstances, however, an onlay technique is motivated, such as when the anatomy has been distorted by previous surgery or disease and does not allow for safe access to the retrorectus space.

Other positions used for reinforcement material in the abdominal wall include intraperitoneal onlay mesh, commonly used in laparoscopic incisional hernia repair. Laparoscopic repair of incisional hernia has become popular over recent years with promising results, but open repair still seems to be the main choice of approach for incisional hernia repair (41). A less commonly used position is the sandwich method where meshes are used in different positions at the same time.

The association between the position of reinforcing material in the abdominal wall and other important outcomes such as comfort, function, and pain has not received as much attention. Many of the studies included in the meta-analysis by *Timmermans* did not report pain as an outcome, and of those that did, the results were so varied that pain could not be pooled for meta-analysis (38). There are indications that chronic pain may be more prominent if the mesh is placed in the sublay position, possibly due to the higher proximity of nerves and vessels in the retrorectus area (18). Abdominal wall muscle strength, however, does not seem to be affected by mesh positioning, indicating that functional improvement after hernia repair does not depend on the method used (42).

Parastomal hernia

In Sweden, more than 3000 patients receive a stoma each year, most of whom will live with it permanently (43). Living with a stoma can decrease the patient's quality of life, and stomal complications increase this burden (44). A common stomal complication is the occurrence of a PSH, which develops when the diameter of the fascial aperture increases, allowing intra-abdominal content to protrude adjacent to the stoma (Fig 6) (45-47).

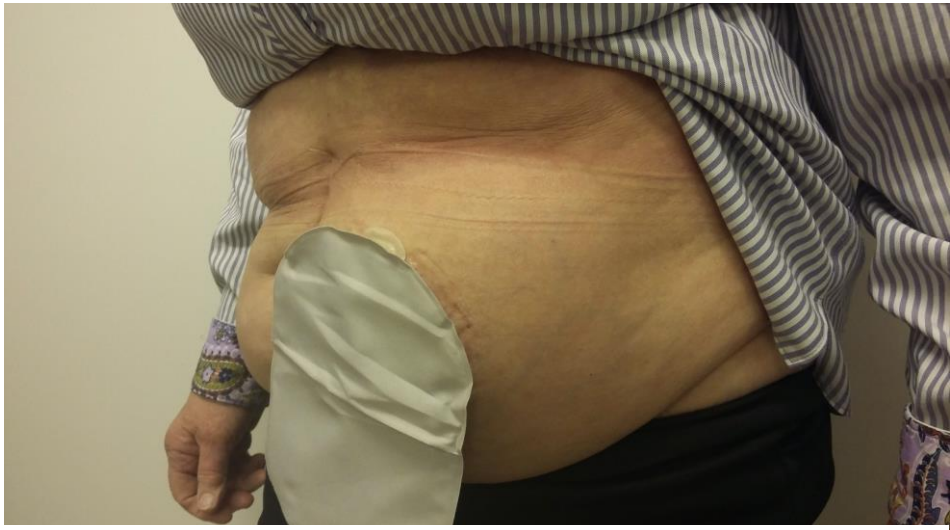


Fig 6. Patient with parastomal hernia.

Epidemiology

The reported rate of PSH varies greatly, in some studies as high as 78% (46-50). This has been due to the lack of a consensus definition of PSH as well as differences in follow-up time. In 2014, a consensus group from the European Hernia Society (EHS) defined a PSH as: “an abnormal protrusion of the contents of the abdominal cavity through the abdominal wall defect created during placement of a colostomy, ileostomy or ileal conduit stoma. It should be distinguished from local stoma problems without a hernia sac, such as mucosal prolapse or a Siphon loop, which is a subcutaneous folding of excess bowel length at the stoma”(51).

There is no gold standard procedure to judge whether a patient suffers from a true PSH or not. In a clinical evaluation, it can be hard to distinguish a hernia from other bulges adjacent to the stoma, this was illustrated by low inter-observer reliability between assessing surgeons (52). CT-scanning increases the sensitivity and accuracy of the diagnosis but has potential disadvantages (48). The patient is usually examined in the supine position, whereas it would be more appropriately

performed in the prone position (or ideally standing). 3D-ultrasonography has been introduced as an alternative means of diagnosing PSH, with high validity compared to findings at surgery (53). 3D-ultrasonography does not expose the patient to ionising radiation and can be performed at the time of clinical examination with the patient standing. A drawback is that the procedure is experienced as uncomfortable or even impossible to perform if the patient's stomal orifice is too small for the ultrasound transducer to pass.

Difficulties in diagnosing a PSH and the large variation in rates reported have also made it difficult to assess potential risk factors, and studies on risk factors for developing a PSH must be interpreted with care. Some authors report that PSH risk factors are the same as for other hernias, including obesity, malnutrition, raised intra-abdominal pressure, and corticosteroid use (54). End-colostomy seems to be more prone to develop a PSH compared to loop-colostomy and loop-ileostomy, but no direct comparative data exist (55). There is also a lack of high-level evidence favouring any of the techniques or locations used in the creation of a stoma *e.g.*, extraperitoneal *vs* transperitoneal, trans-rectus *vs* para-rectus, and ideal size of fascial aperture), though some evidence points to the fact that the fascial aperture should be as small as possible (55-57). Some observations indicate that PSH is more frequent in stomas created laparoscopically than in those using an open technique (58-60).

Treatment of parastomal hernia

As with other hernias, the ultimate treatment of PSH is surgical. A complicating factor in PSH repair, however, is that the origin of the hernia is the aperture created to allow passage of the deviated bowel through the abdominal wall. If this aperture widens a hernia will develop, but its repair must be partial, leaving room for the deviated bowel. The direct proximity to bowel further complicates the procedure.

Previously used surgical techniques in the management of PSH, such as relocation of the stoma and suture repair of the defect, have largely been abandoned since they were associated with unacceptably high recurrence rates (61, 62). In groin and umbilical hernias, reinforcement with synthetic mesh material has been shown to dramatically decrease the risk for recurrence (9, 63). They have now been introduced in the repair of PSH, but recurrence rates are still high; in some reports, up to 46% (62, 64, 65). Furthermore, as with other hernia repairs, the synthetic mesh materials used can cause serious complications such as mesh infection, fistula formation, and bowel erosion, all of which can be related to the presence of foreign material in the abdominal wall. These complications were not seen with the traditional methods of repair mentioned earlier. In a Danish retrospective nationwide study on PSH repair in general surgery, the

procedure was associated with a considerable complication rate and a 30-day mortality rate of 6,3% (66). The complications and technical difficulties in managing PSH have led to surgeons being reluctant to treat these patients, leaving them with life-long suffering (67).

Current recommendations from the EHS on method of repair for PSH lack detail. They advise against the use of simple suture repair but do not recommend any particular mesh material, mesh position or surgical approach, due to the current paucity of knowledge (55). Lack of a gold standard method for PSH repair remains a surgical issue to this day, and better methods are urgently needed.

Prophylactic treatment

The high PSH rate together with the fact that there is no satisfactory treatment has led to several attempts to prevent a hernia from occurring from the outset. “Non-mesh” methods proposed for the prevention of PSH such as trephine sizing of the fascia aperture, circular or cruciate fascia aperture, stoma route through or lateral to the rectus sheath, transperitoneal or extraperitoneal approach, have not provided any notable reductions in PSH (54, 57, 68).

Several randomised trials, small and large, have investigated the placement of a mesh at the time of stoma creation to decrease the hernia rate. Studies have investigated different mesh locations, different mesh materials, as well as different surgical approaches. Pooled results are promising and the use of a prophylactic mesh in the construction of a permanent end colostomy is therefore recommended in the guidelines published in 2018 by the EHS (55, 69). Since then, two large, randomised trials have been published (STOMAMESH and Stoma-Const) where the prophylactic placement of a synthetic mesh in the sublay position did not decrease the PSH rate in routine practice (57, 70). Interestingly, in the STOMAMESH trial the rate of stoma-related problems was lower in the mesh group in a quality-of-life (QoL) follow-up one year after surgery, indicating that there could be beneficial effects of a prophylactically placed mesh, despite the dubious effect on recurrence rate (71).

Aims

The overall aim of this thesis was to investigate if autologous FTSG could serve as an alternative reinforcement material in hernia repair.

The specific aims were:

- To compare the use of FTSG with a conventional synthetic mesh as reinforcement material in the repair of giant incisional hernia. Outcomes considered were:
 - Clinical, with special regard to surgical complications and recurrences
 - Functional, by thoroughly measuring core strength using the Biodex-system™
 - Quality-of-life, in terms of general perception of health and specifically, limitations due to abdominal wall dysfunction
- To investigate whether FTSG has the mechanical properties necessary for use as reinforcement material in hernia repair.
- To develop a novel surgical method using intraperitoneal autologous FTSG as reinforcement material in PSH repair, including evaluation of the method's feasibility in humans.
- To design and present a clinical trial where autologous FTSG will be compared with a conventional method for PSH repair.

Materials and Methods

Studies I and II

Study design

Studies I and II were part of a randomised controlled trial investigating the use of FTSG in giant incisional hernia repair. They were performed at two tertiary level centres profiled in abdominal wall surgery. Patients included in the trial were randomised to either FTSG or the best available treatment option with a synthetic mesh at the time. The randomisation process was managed by a research administrator using opaque envelopes containing a note with either “skin” or “mesh”. Procedure allocation was revealed to the surgeon the day before the planned intervention. The patient, nursing staff and the surgeon performing the follow-up were blinded to treatment allocation until the study was completed. Patients were included between December 2009 and August 2013.

Inclusion criteria: Incisional ventral hernia requiring surgical intervention; hernial orifice width greater than 10 cm; and >18 years of age.

Exclusion criteria: Ongoing immunosuppressive treatment; smoking habit; continuous oxygen therapy; ongoing pregnancy or nursing.

The main outcome of the entire trial was short-term complications at the three-month follow-up (23). In the power calculation, complication rates of 50% in the synthetic mesh group and 20% in the FTSG group at the three-month follow-up was estimated. To obtain 80% power and 95% significance, 50 patients had to be included in the study. The outcomes reported in Papers I and II can thus be considered secondary outcomes.

Preoperative management

The initial work-up included a standardised CT-scan to evaluate the hernia, preoperative assessment by an anaesthetist, and, if deemed necessary, a more detailed cardiac assessment by ergometry and/or echocardiography. Patients included were also equipped with an elastic abdominal girdle to be worn around the clock for three months preoperatively and six weeks postoperatively, followed by six weeks of daytime use only. All patients received oral antibiotic prophylaxis prior to surgery with two tablets of Bactrim® 800mg (sulfamethoxazole 800mg/trimethoprim 160mg) and three tablets metronidazole 400mg. Patients allocated to FTSG also received one tablet clindamycin 300mg since this was used in the preceding feasibility study (22).

Surgical procedures

All patients were operated on under general anaesthesia and received an epidural catheter for per- and postoperative analgesia. The hernia aperture was palpated and measured under muscle relaxation.

Full-thickness skin graft

In cases randomised to the FTSG treatment arm, the procedure began with marking of the skin covering the hernia that was intended to be harvested for the FTSG, including the old scar. The graft was then excised with electrocautery and dissected free from all subcutaneous tissue. The graft was then knife-meshed with multiple incisions (8-15mm in diameter when stretched) to increase the area of the graft and to prevent seroma and haematoma formation, thus increasing the chances of successful healing. There is also reason to believe that graft meshing increases the degree of vascularisation, thereby improving graft adaptation and survival (29). Pending implantation, the FTSG was rolled up in surgical gauze soaked with physiological saline and hydrogen peroxide as bactericide. The operation proceeded with exposure of the anterior rectus fascia with meticulous haemostasis to enable sufficient overlap (>5cm) of the hernia defect by the FTSG. Primary closure of the hernia defect was performed using a continuous polydioxanone monofilament suture size 0. If the defect could not be closed without undue tension, releasing incisions in the anterior rectus fascia (*ad modum* Chevrel) were performed. The FTSG was then placed on the fascia and attached with single, interrupted, absorbable monofilament sutures size 4-0 (Fig 10). The space created under the graft was flushed with hydrogen peroxide, and two exodrain were placed above the graft. The wound was then closed in three layers using absorbable sutures.



Fig 10. FTSG after placement in the onlay position during giant incisional hernia repair.

Synthetic mesh

In procedures allocated to the synthetic mesh treatment arm, the hernia sac was exposed through a midline incision taking care not to enter the abdominal cavity. After exposure of the fascia, assessment was made whether it would be possible to access the retrorectus space safely. If so, the procedure continued with exposure of the retrorectus space to obtain a margin of 5cm around the hernia aperture aiming to perform a hernioplasty according to Rives-Stoppa (36). Primary closure of the hernia defect was performed with a continuous polydioxanone monofilament suture size 2-0. A lightweight polypropylene mesh was trimmed to fit and placed without fixation sutures. The anterior rectus fascia was then closed with a continuous polypropylene monofilament suture size 0. As in the FTSG procedure, releasing incisions in the anterior rectus fascia were made to release tension if deemed necessary. If access to the retrorectus space was judged an unjustifiable risk for complications, the fascia was closed with a continuous polypropylene monofilament suture size 0, and a heavyweight polypropylene mesh was placed in the onlay position. In these cases, the mesh was secured with double rows of absorbable monofilament sutures size 2-0. The wound was subsequently closed in three layers with absorbable sutures, any excess skin was excised to enable satisfactory skin adaptation. Drains were not used in the synthetic mesh group.

Postoperative care

All patients were mobilised early and received prophylactic low molecular weight heparin treatment for one week to prevent thromboembolism. Patients allocated to FTSG continued treatment with clindamycin 300mg *tds* for ten days.

Follow-up

All patients were scheduled for clinical follow-up visits at 3, 12 and 36 months postoperatively, to an experienced surgeon blinded to the method used. The three-month follow-up focused on short-term complications and the results have been published previously (23). At the 12- and 36-month follow-ups, assessment was made of any new or persistent complications, any sign of recurrence, and how well the scar had healed. If the surgeon performing the follow-up was uncertain whether a recurrence was present, the patient was referred for a CT-scan to confirm the diagnosis.

Biodex™

To assess the effect of surgery on abdominal muscle strength, all patients included in the study underwent testing with the Biodex system™ (Biodex Corp. Shirley, NY, USA) preoperatively and as part of the 12-month follow-up. The Biodex system™ measures various strength modalities of the abdominolumbar girdle, and there is a link between an improvement in abdominal muscle strength

and ADL (72). The Biodex system™ has been shown to be reliable and has been validated for patients with giant ventral hernia and abdominal diastasis recti (73, 74). Furthermore, it has been used to show that ventral hernia repair improves abdominal muscle strength (75). The test programme in the present study consisted of abdominal flexion and extension at two different angle speeds (30 and 60 degrees per second) and an isometric static test. All tests were performed five times and the entire programme was repeated twice. The tests were performed by specially trained physiotherapists that followed a standard protocol to ensure standardised and reproducible measurements. The physiotherapists were blinded to which surgical method had been used.

Questionnaires

Three different questionnaires were used to investigate how various aspects of QoL and pain were affected by giant incisional hernia repair; two generic questionnaires assessing general health and one specifically developed for patients undergoing ventral hernia repair. The questionnaires were in Swedish.

The questionnaires used were:

1. EQ-5D. A comprehensive and generic assessment of general health status condensed to five dimensions developed by the EuroQol Group. Patients classify their health on a three-level scale regarding mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and finishes with a rating of their general health perception on a VAS-scale.
2. SF-36. A more thorough evaluation of general health and QoL widely used in medical and other research. The respondent answers 36 questions, often condensed into eight “health concepts” according to an algorithm. The eight concepts consist of physical functioning, role limitation due to a. physical health problems and b. emotional problems, vitality, bodily pain, social functioning, mental health, and general health. (76, 77).
3. Ventral hernia pain questionnaire (VHPQ). A validated tool developed for clinical and research purposes in patients undergoing surgery for ventral hernia. The questionnaire focuses on pain and how it affects ADL (78).

Patients were asked to answer these questionnaires preoperatively and at the three-year follow-up. To obtain an even longer follow-up, the same questionnaires were also sent by mail to all patients alive in September 2020. Patients not answering received up to two reminders a few weeks apart.

Study III

Rationale

Early publications describing the use of cutis grafts and FTSG in hernia surgery vary regarding the surgical method used but positioning of the skin graft has generally been onlay. Since the best available evidence for PSH repair with mesh involves the intraperitoneal position, the natural choice for FTSG should also be intraperitoneal. However, since the experience of how FTSG behaves intra-abdominally is sparse, we need more data before using it in human subjects. Study III was part of a translational chain of studies aiming to develop a method for PSH repair using intraperitoneal FTSG. Previous research involved murine models investigating FTSG survival when applied in different positions in the abdominal wall and subsequent tissue remodelling of the grafts (79). Another important aspect in hernia surgery is the mechanical strength of the reinforcement material implanted and whether it provides sufficient support during the early postoperative period.

Study design

Fresh FTS samples were taken from a wide range of patients undergoing cancer and benign surgery. Our ambition was to represent the diverse population living with a stoma *i.e.*, ranging from young otherwise healthy patients to old patients with disseminated cancer. Fourteen patients donated FTS samples, most of them originating from the abdominal region. Information about the patient's general health and conditions possibly affecting the mechanical properties of skin was gathered from the medical records.

Measurement of tensile strength

Following dissection, the skin sample was immediately collected from the operating theatre, immersed in physiological saline and did not undergo any

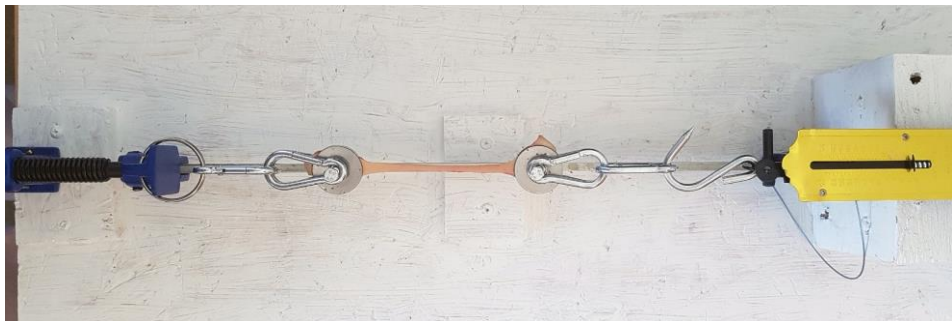


Fig 8. The specially designed test frame with skin sample mounted. The spring-loaded dynamometer is seen on the right.

other chemical treatment prior to testing. Skin samples were prepared by sharp dissection removing all subcutaneous tissue and then cut into a shape resembling a dumbbell leaving a strip of skin with a preformed breaking point of known width. This approach enabled us to control the cross-sectional area at the breakage point. The prepared skin samples were then attached to clamps and mounted in a specially designed frame to allow for testing of tensile strength and suture tearing tolerance (see Fig 8). Measurements were performed using a spring-loaded dynamometer with a precision of 2,5 N.

Tensile strength tests were performed by applying an increasing traction force to the sample at a pace of 10mm/min until reaching the breaking point. Furthermore, 2-0 and 0 monofilament polypropylene (Surgipro™ Medtronic, Dublin, Ireland) sutures were threaded through the skin sample and knotted to form a loop which was then mounted in the testing frame and exposed to traction until the suture broke or tore through the skin.

After skin sample testing, identical tests were performed on synthetic composite mesh and biological reinforcement mesh, both of which are currently used intraperitoneally in hernia repair (80-83). The synthetic composite mesh was a Symbotex™ (Covidien, Dublin, Ireland) which is a monofilament polyester mesh with an absorbable collagen film said to reduce the risk for visceral adhesion when placed intraperitoneally. The biological mesh was a Xenmatrix™ (Bard, Murray Hill, NJ, USA) which is a porcine-derived cross-linked collagen scaffold (Fig 9).

By definition, tensile strength is force per cross-sectional area. However, it is difficult to calculate the cross-sectional area of synthetic mesh since its structure is a woven scaffold from filaments of polyester. Furthermore, it is not possible to adjust the thickness of a skin graft in clinical practice. Therefore, to facilitate



Fig 9. A Xenmatrix™ sample, cut to the dumbbell shape and mounted in the test frame.

interpretation of the results and make the outcome more clinically relevant, the tensile strength is presented as N/cm.

Study IV

Method development

The aim was to develop a surgical method for PSH repair where FTSG is applied intraperitoneally. Results from the publication by *Winsnes et al*, previous clinical experience with FTSG, and the results of Study III were deemed sufficient to proceed with a method description and a pilot trial on patients. Four patients scheduled for PSH repair were invited to participate in this pilot trial.

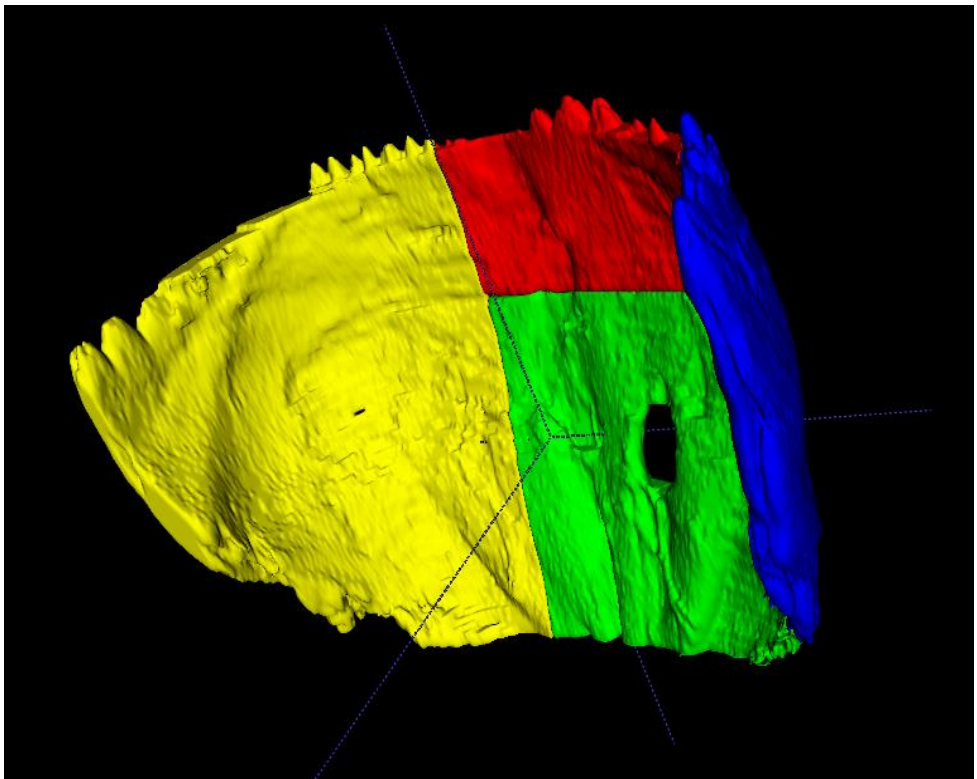


Fig 11. Virtual 3D-model of the dorsal aspect of the abdominal wall of a patient with a parastomal hernia.

3D-printing

Based on CT-scans of patients with a PSH, virtual 3D-models were created (Fig 11) and printed on a 3D-printer. These life-size 3D-models were then used to aid our discussions on the best way to apply the FTSG to the abdominal wall. The 3D printer used was an Ultimaker 2+™ (Ultimaker, Utrecht, Netherlands) which uses a fused filament fabrication technique depositing a thermoplastic material in a X-Y grid in layers forming a 3D-structure from a digital 3D-model (Fig 12).



Fig 12. Final 3D-models from two patients with a parastomal hernia. Dorsal view in the upper row and ventral view in the bottom row. The inferior epigastric artery is seen in the upper left model inferior to the hernia. A small umbilical hernia is also noted in the patient in the right column.

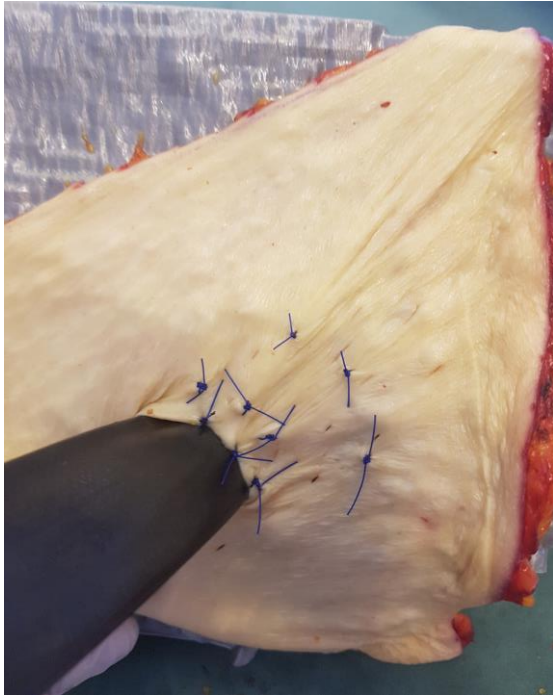


Fig 13. Testing FTSG appliance on a 3D-structure. The bicycle hose represents bowel.

The 3D-models enabled us to see *in vivo* relationships between muscles in the abdominal wall, indicating a suitable position for application of the FTSG (Figs 12 and 13). At the same time as the tests on 3D-models, tests were also performed with surgical tacks. These could potentially decrease operating time considerably, simplify attachment of the FTSG, and facilitate future laparoscopic application. However, standard tacks did not easily penetrate the graft and we decided not to use this method of attachment given the importance of applying the graft under tension to prevent cyst formation (12, 14).

The pilot method

Since open intraperitoneal application of reinforcement material in PSH repair involves a laparotomy, the primary source of skin for grafting should preferably be harvested adjacent to the midline incision. In the trial referred to in Studies I and II, enough skin for grafting could be harvested from the para-midline area in all cases. However, in cases where para-midline skin has poor quality, other potential donor sites are the thigh and medial aspect of the upper arm. In these locations there is usually enough skin available for grafting while still allowing for primary closure of the donor site.

After excision of skin for the intended graft, it was dissected free of all subcutaneous tissue according to previous descriptions on the use of FTSG (Fig 14). To allow for larger coverage aiming at 5cm overlap, the FTSG was meshed with a no. 11 scalpel forming multiple incisions, 0,5 – 1 cm in length. A larger incision was made in the centre of the graft to allow passage of the stomal intestine. Meshing also served to prevent seroma and haematoma formation. Pending implantation, the graft was placed in surgical gauze soaked in saline and hydrogen peroxide to keep the graft moist and to prevent postoperative infection.

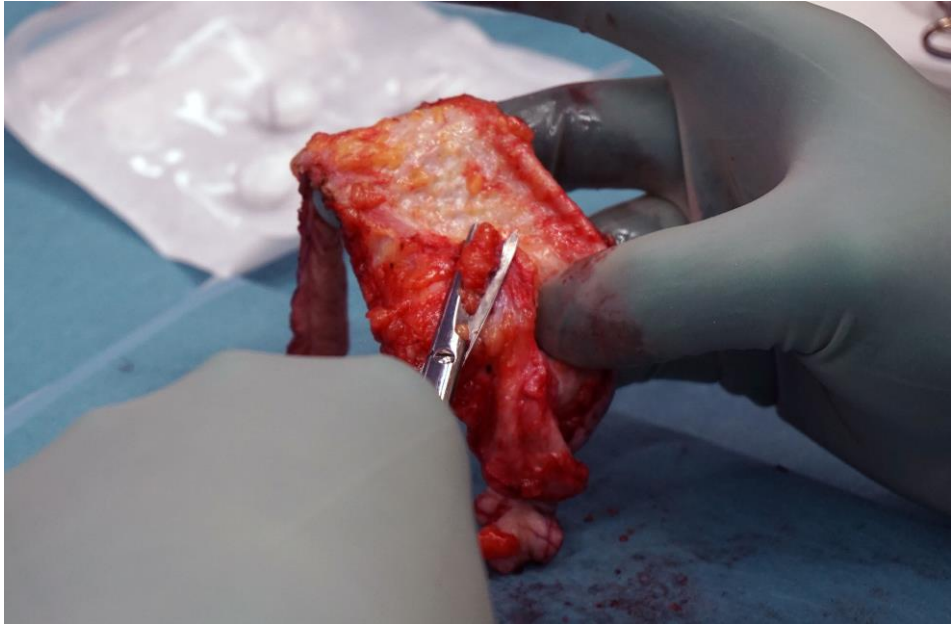


Fig 14. Subcutaneous tissue being sharply removed from harvested FTSG.

The procedure proceeded with a small standard midline laparotomy for inspection of potential adhesions to ensure adequate access. If the procedure was deemed possible without undue risk for complications, the laparotomy wound was extended and draped in sterile dressings to allow for the stoma to be dissected from the skin and sealed with temporary sutures. If necessary, adhesiolysis was performed to allow for graft application. The stoma was then retracted into the abdominal cavity and the fascial defect was reduced with single interrupted, size 2-0 polydioxanone monofilament sutures to allow for snug passage of the stoma bowel (approximately 25-30mm depending on the type of stoma).

Measurements were made to estimate the necessary length of bowel above the fascia plane that would allow appropriate stoma maturation. The prepared FTSG was then applied to the stoma bowel at that position by threading the bowel through the larger incision formed at the centre of the graft. The epidermal side of the FTSG faced the intestines and was anchored to the bowel with four interrupted single size 3-0 poliglecaprone-25 sutures (Fig 15). At this stage, the end of the stoma bowel was exteriorised through the fascial orifice. The FTSG was subsequently anchored under tension to the abdominal wall with interrupted single size 2-0 polydioxanone monofilament sutures around the borders of the graft at intervals of 1-2cm. Sutures were also placed to fuse the fascial plication to the FTSG to further reinforce the repair. The midline incision was then closed with a running polydioxanone monofilament suture, size 2-0.

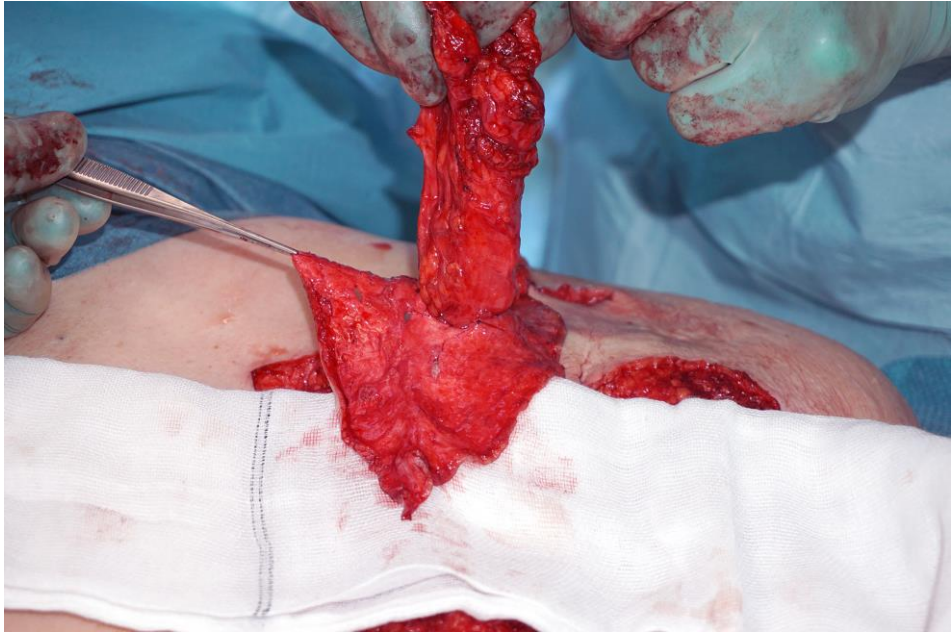


Fig 15. FTSG surrounding and anchored to the stomal intestine.

Perioperative management

All patients received an epidural catheter for per- and postoperative analgesia. Antibiotic prophylaxis with Bactrim® (sulfamethoxazole 800mg/trimethoprim 160mg) and metronidazole 1200mg, routinely used locally for bowel surgery, was given when possible. Postoperatively, all patients received thrombosis prophylaxis with 4500 IE tinzaparin for at least 10 days after discharge.

Follow-up

The plan was to conduct a two-week telephone follow-up, and clinical follow-ups at one month and approximately one year after surgery. However, because of the experimental nature of the study evaluating a novel technique, any complaint or other sign of complication noted by the patient, the ostomy nurse, or any other healthcare provider was followed up immediately. Assessment focused on any surgical complication or PSH recurrence, pain, aesthetic outcome, and patient satisfaction. To further evaluate any possible complication or recurrence, intrastomal ultrasound was performed at the one-year follow-up visit. If this was inconclusive, it was complemented with a CT-scan.

Statistics

Data used in the studies included in this thesis were gathered in Access™ databases (Microsoft, Redmond, Washington, USA). From these, data were extracted for programs designed for statistical analysis. All statistical calculations and tests in Study III were performed in STATA® 14 (StataCorp., College Station, Texas, USA). Studies I, II, IV and V used IBM® SPSS® Statistics v.24 and v.27 (IBM corp., Armonk, New York, USA).

Statistical testing

All grouped continuous variables with normal distribution or sufficient group size were described as means and were compared with independent- or paired *t*-tests. Non-parametric variables were described by medians and compared using the Mann-Whitney *U*- or Wilcoxon's test. Comparison of independent dichotomous variables were conducted with Chi-square statistics or Fischer's exact tests when Chi-square criteria were not met. Paired dichotomous variables were analysed using the McNemar's test. In Study I, both univariable and multivariable linear regression analyses were used to investigate possible correlations between Biodex™ outcome and baseline characteristics. All variables were entered simultaneously in the multivariable analyses. A *p*-value <0.05 was considered significant in all studies included in this thesis.

Ethics and ethical approval

According to Swedish law (SFS 2003:460), all research involving human subjects that includes physical and psychological interventions or the management of sensitive personal data must be approved by the Swedish Ethics Review Authority. Furthermore, whenever possible the study participants must give their informed consent, and this must be documented.

All study participants received verbal and written information of the studies before giving a written consent to participate. An overview of the study plan was explained, and the patient was told that participation could be terminated without having to specify a reason, and that they would then continue with standard care. Because of experimental nature of Studies I, II, IV and V, the information given to potential study participants was as thorough as possible since the risks associated with a novel surgical method can never be fully appreciated in advance. Patients were given the opportunity to ask questions to the researchers responsible for the trial, and were given ample time to consider their participation before consenting.

All study data were stored anonymously to ensure the personal integrity of the participants. When patients had been included in a study and had signed the

consent form, they received a study number which was later used in all study-related documentation and analyses of data. The identification key was stored in a locked cabinet with an access code available only to the researchers responsible and administrators. All digital databases were stored in encrypted form on the Region Västerbotten intranet, with passwords for decryption available only to the researchers responsible and administrators.

Inherent in the design of a randomised controlled trial is the fact that one of the treatment arms may be inferior to the other. Since the hypothesis is that the compared arms differ from each other, the number of participants needed in a trial is always a balance act. Too few patients would not give enough power and pose a risk for type-2 error, and too many would put an unnecessary number of patients at risk for inferior treatment. In the trial presented in Study V, a safety-analysis will be made by external experts after 1/3 of the patients have been operated to ensure the safety of the study participants remaining.

Studies I and II were approved by the Board of Ethics at the Karolinska Institute (reference number 2009/227-31/3 and 2012/1775-32).

Studies III, IV and V were approved by the Regional Board of Ethics, Umeå University (reference number: 2016/450-31 and 2017-251-31 M respectively).

Studies I and II are registered at ClinicalTrials.gov (ID NCT01413412)

Study III is registered at researchregistry.com (UN: researchregistry3338).

Studies IV and V are registered at ClinicalTrials.gov (ID NCT03667287)

Results

Studies I and II

After 50 patients had been included in the study, one patient in the FTSG group had to be excluded due to serious illness making both anaesthesia and surgical intervention too hazardous. To compensate for this loss, an additional ten randomisation envelopes were prepared, and three more patients were included. All three patients were randomised to the synthetic mesh group causing slight imbalance with 24 patients in the FTSG group and 28 in the synthetic mesh group. Characteristics at surgery are presented in Table 1.

Table 1. Patient characteristics at surgery

Age (years)	64 (35 – 77)
BMI (kg/m²)	31 (22 – 46)
Intraoperative hernia area (cm²)	170 (33 – 488)
Female gender (n)	25 (48%) *

There were no statistical differences between the treatment arms. Results presented as means with range in parentheses.

Average duration of surgery was 195 (108 – 324) minutes in the synthetic mesh group and 233 (128 – 414) minutes in the FTSG group, but the difference was not significant ($p = 0.078$). In eight patients randomised to the synthetic mesh group, anatomical conditions did not allow for adequate access to the retrorectus space. In these cases, a heavyweight polypropylene mesh in the onlay position was applied according to the study protocol. The mean postoperative length of hospital stay was 8 (2 – 22) days in the synthetic mesh group and 9 (5 – 29) days in the FTSG group ($p = 0.263$).

12-month follow-up

All patients included in the study participated in the 12-month clinical follow-up. A total of four recurrences were found, two (8.3%) in the FTSG group and two (7.1%) in the synthetic group ($p = 1.000$). There were no significant differences in aesthetical outcome (well-healed scar, presence of excess skin, uneven distribution) between the groups.

Biodex™

Two patients in the synthetic mesh group was lost to the Biodex™ follow-up; one due to increased comorbidity making it impossible to do the examination, and one chose not to participate. One patient in the FTSG group experienced prolonged wound healing necessitating surgical revision and was therefore also lost to the Biodex™ follow-up.

In the population as a whole, no significant change in abdominal muscle strength was seen after surgery in any of the Biodex™ measurements. Nor were there any significant differences between the groups in any of the Biodex™ modalities. In table 2 the mean results from each Biodex™ measurement is presented for each treatment arm.

Table 2. Results of the Biodex™ examination

	FTSG (n = 23)			Synthetic mesh (n = 26)		
	Preop	12-month	p-value	Preop	12-month	p-value
Flexion 30°/s	91 ± (83)	96 ± (74)	0.686	93 ± (58)	98 ± (56)	0.130
Flexion 60°/s	100 ± (73)	98 ± (64)	0.762	105 ± (59)	101 ± (58)	0.611
Extension 30°/s	111 ± (77)	119 ± (77)	0.508	116 ± (54)	116 ± (54)	0.442
Extension 60°/s	121 ± (67)	121 ± (71)	0.819	122 ± (53)	126 ± (58)	0.350
Isometric	65 ± (50)	70 ± (40)	0.506	67 ± (36)	68 ± (40)	0.291
Total	98 ± (67)	101 ± (65)	0.894	102 ± (49)	97 ± (48)	0.271

Results from the Biodex™ examination presented in mean peak torque in Nm (standard deviations). P-values represent paired t-tests for each variable within each treatment arm.

As indicated by the relatively high standard deviations in the table above, inter-individual differences in baseline values were large. In many cases, individual changes between preoperative values and measurements at the 12-month follow-up were small (Fig 16).

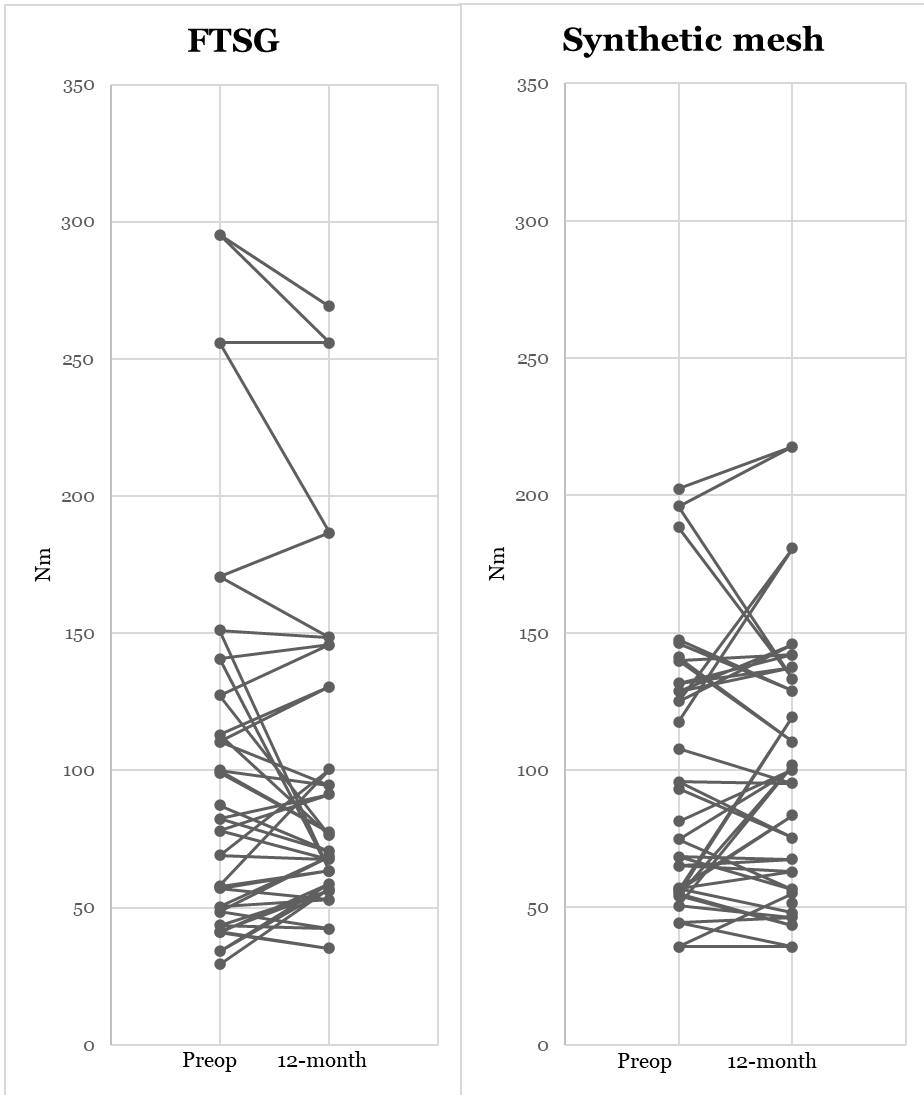


Fig 16. Mean value of Biodex™ measurements. Each dot represents an individual patient, and the lines connects each patient's measurements.

To explore any possible explanation for the considerable diversity in Biodex™ results, a multiple linear regression model was created. None of the variables included showed significant correlation with the average change in Biodex™ values (Table 3).

Table 3. Multivariable linear regression model

	B-Coefficient	95% CI		p-value
FTSG (vs synthetic mesh)	-4.44	-29.40	20.53	0.721
Intraoperative area of hernia aperture (cm²)	0.06	-0.07	0.19	0.344
BMI (kg/m²)	0.74	-1.69	3.17	0.539
Male sex	-4.84	-30.37	20.70	0.704
Age at surgery (years)	-0.37	-1.82	1.09	0.612
Complications (any surgical)	6.15	-19.55	31.85	0.631
Duration of surgery (min)	0.01	-0.18	0.19	0.930

Linear regression analysis on how different baseline characteristics influence average change in Biodex™. CI = Confidence interval, BMI = Body mass index

Long-term follow-up

36-month clinical follow-up

After an average of 37 (28 – 43) months, a total of 42 patients were examined, 19 (79%) from the FTSG group and 23 (88%) from the synthetic mesh group. This corresponded to 84% of the available study population since two patients died from other causes during follow-up. Since the 12-month follow-up, three more recurrences had occurred in the FTSG group and one in the synthetic mesh group, (21% vs. 11%). The difference in recurrence rate was not significant ($p = 0.313$). No new procedure-related complications had occurred between the 12- and 36-month follow-ups.

Quality-of-Life follow-up

The average follow-up time for the 36-month questionnaire was 41 (37 – 48) months, and for the long-term follow-up 112 (88 – 126) months. Numbers of questionnaire respondents are presented in Table 4.

Table 4. Number of respondents to the questionnaires

	FTSG	Synthetic mesh	Total number	Available	Overall response rate
Preop	20 (83%)	23 (82%)	43	52	83%
36-month	14 (58%)	18 (69%)	32	50	64%
Long-term	18 (78%)	14 (61%)	32	46	70%

Two answers having considerable clinical relevance in the VHPQ questionnaires were whether the respondents experienced “pain right now” or “during the last week”. The degree of symptoms is rated on a 7-grade scale where grades 1 and 2 are considered clinically irrelevant. To simplify interpretation, results were dichotomised and are presented in Table 5.

Table 5. VHPQ, main findings

	FTSG			Synthetic mesh		
	Preop (n = 20)	36-month (n = 14)	Long-term (n = 18)	Preop (n = 23)	36-month (n = 18)	Long-term (n = 14)
Pain right now >2	14 (70%)	4 (29%)	5 (28%)	9 (39%)	5 (28%)	4 (29%)
Pain last week >2	14 (78%)	4 (29%)	5 (28%)	9 (41%)	7 (39%)	3 (25%)
Satisfaction						
Satisfied with operation		11 (85%)	10 (59%)		12 (67%)	7 (64%)
Would do it again		10 (77%)	14 (82%)		15 (83%)	7 (64%)

Number of respondents (percentage).

There is a clear numerical decrease in the number of patients complaining of pain between prior to and 3 years after surgery, and this result seems to persist with time. However, differences did not reach statistical significance. Most of the patients expressed satisfaction over their operation and would do it again if asked. A sample of the questions from the VHPQ questionnaire focusing on pain and behaviour also indicated a non-significant increase in QoL with fewer patients complaining of not being able to perform ADL activities (Table 6). However, many patients that did not report pain chose not to answer the functional questions. There were no significant differences in any of the VHPQ results between the treatment arms.

Table 6. VHPQ, selection of function questions

	FTSG			Synthetic mesh		
	Preop	36-month	Long-term	Preop	36-month	Long-term
Function						
Difficulty in rising from a chair	7 (50%)	2 (40%)	1 (25%)	7 (58%)	4 (44%)	2 (33%)
Difficulty in sitting	6 (43%)	3 (60%)	1 (33%)	6 (50%)	3 (33%)	1 (17%)

Number of respondents, percentage of respondents in parentheses.

There was also a numerical trend towards improved self-assessed health in the EQ-5D, especially in the dimensions related to physical activity and pain, but the decrease of complaints was neither significant within the treatment arms nor between them (Fig 17). The EQ-5D questionnaire also includes an assessment of the respondent's overall health using a VAS scale. In this study there was remarkably little change in self-rated overall health at both follow-ups (Table 7).

Table 7. EQ-5D self-rated overall health

	FTSG			Synthetic mesh		
	Preop	36-month	Long-term	Preop	36-month	Long-term
Self-rated health	64 ± (17)	64 ± (26)	71 ± (21)	62 ± (21)	67 ± (18)	69 ± (23)

Average VAS scores; 0 corresponds to worst and 100 to best health possible. Standard deviations in parentheses

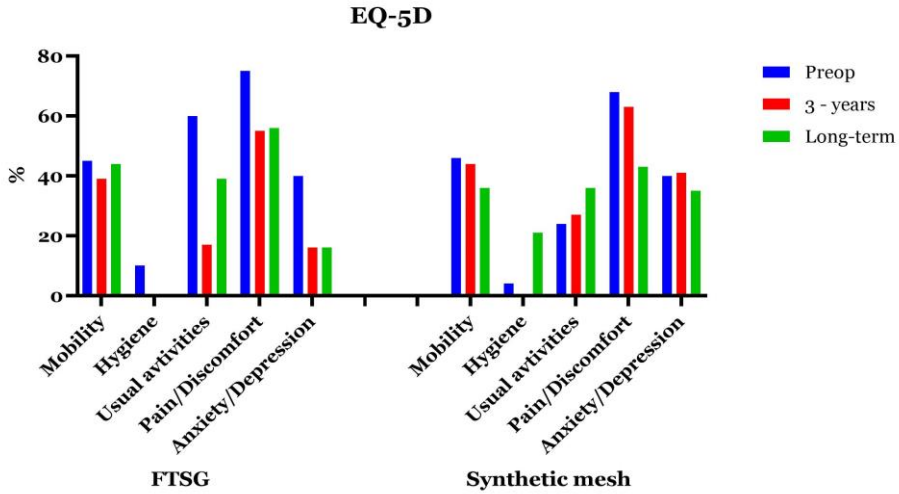


Fig 17. EQ-5D assessment. Percentage of patients reporting problems.

Answers in the SF-36 questionnaire were condensed according to the standard scoring manual. Results are presented as eight dimensions (see Fig 18). As in the other questionnaires, there was a trend towards improvement, where some outcomes were significantly improved, in particular physical ability and pain.

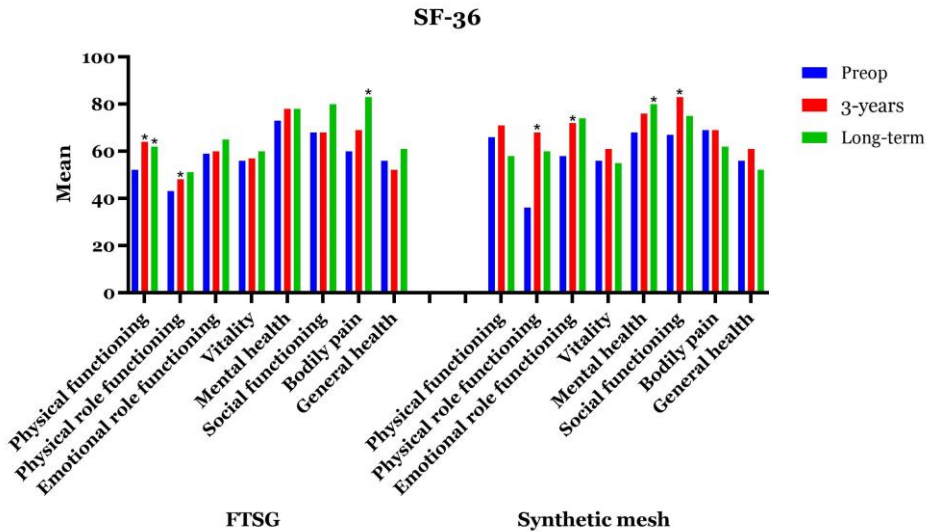


Fig 18. SF-36 scoring after condensation of questionnaire data. The score in each health dimension is graded on a scale from 0 to 100 where 100 is best possible health. * Indicates a statistically significant improvement ($p > 0.05$).

Study III

A total of 14 skin samples were collected from 14 patients between February and August 2017. One sample was lost because of being placed in formalin instead of physiological saline after excision, and one was lost due to malfunction of the test equipment. Thereby, a total of 12 skin specimens were eligible for analysis. For comparison, a total of six synthetic mesh samples and 13 biological mesh samples were tested and analysed. Characteristics of the skin donors are presented in Table 8.

Table 8. Patient characteristics

Age (Years)	65 (31 – 83) *
Cancer surgery	7 (58%)
Skin harvested from abdomen	9 (75%)
Long-term corticosteroid use	2 (17%)
Diabetes	1 (8%)
Radiotherapy to the harvest area	2 (17%)
Thickness of skin graft (mm)	2 (1,3 – 3,7)*

*Characteristics of skin-donor patients, results in number of patients (percentage). Long-term corticosteroid use defined as ongoing treatment for more than 3 months. *: mean (range).*

Two of the FTSG samples broke at the attachment point and not at the preformed waist with the smallest cross-sectional area. The tensile strength was in these two cases calculated from the measurements of the waist since the true value was as high or higher.

FTSG had a tensile strength of 604 N/cm, which was significantly ($p < 0,001$) higher than that of the biological graft (208 N/cm) and of the synthetic mesh (40 N/cm). There was considerable inter-individual variability in the FTSG group (Fig 19). Due to the heterogeneity of the surgical procedures, the amount of sample material available was sometimes insufficient, and not all samples were tested with both size 2-0 and 0 sutures. When both suture sizes were tested, an average of the two values was calculated before analysis. In most cases, the suture material snapped before the skin sample. When the suture did not break, the suture slowly tore a rift through the skin until it reached the edge of the graft. In these cases, the value entered in the analysis was the maximum load during the tear.

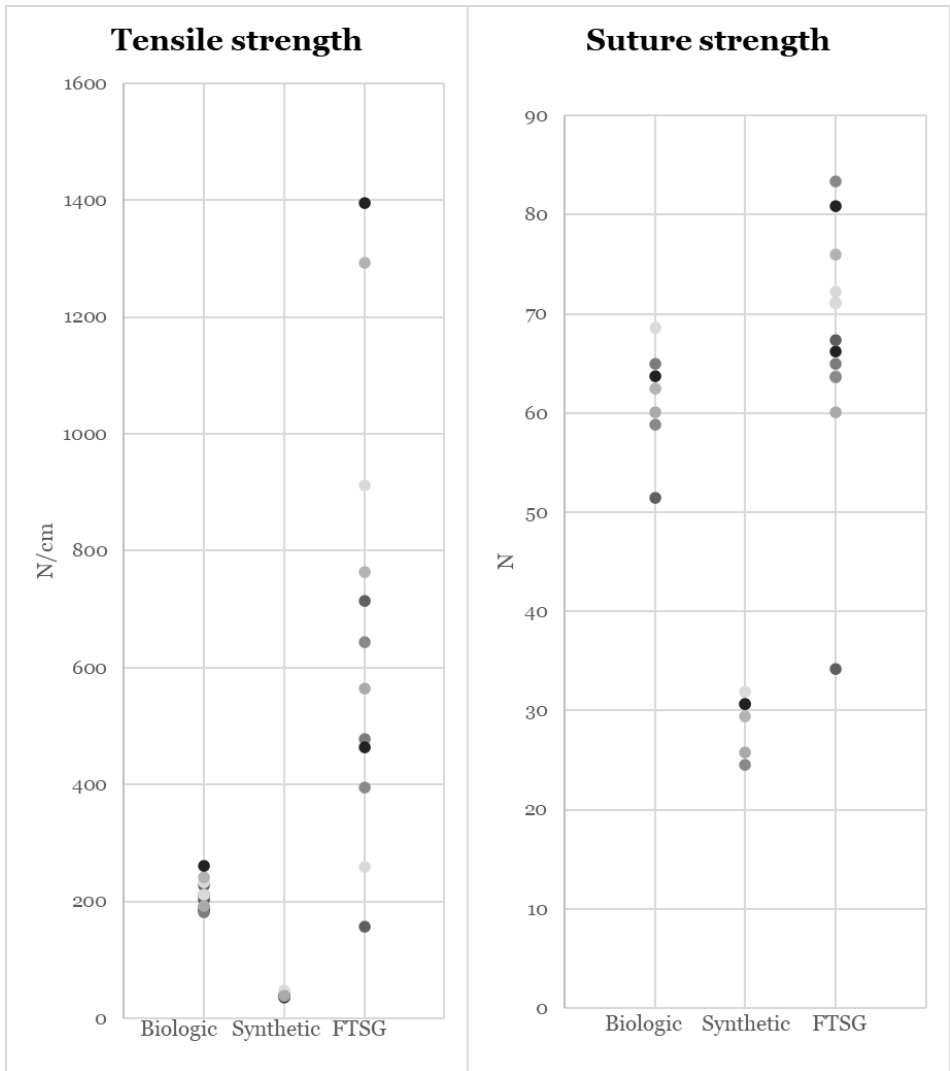


Fig 19. Tensile strength and suture strength measurements, each dot indicates one measurement.

Study IV

Four patients with symptomatic PSH were included as pilot patients, two females and two males with an average age of 70 years (60 – 82). Three of the patients had an end-sigmoid colostomy and one an end-ileostomy.

Intraoperatively, the area of the hernia aperture was measured to be an average of 24 cm² (13 – 50 cm²) and the FTSG used measured on average 101 cm² (94 – 107 cm²). The length of hospital stay varied between 3 and 4 days.

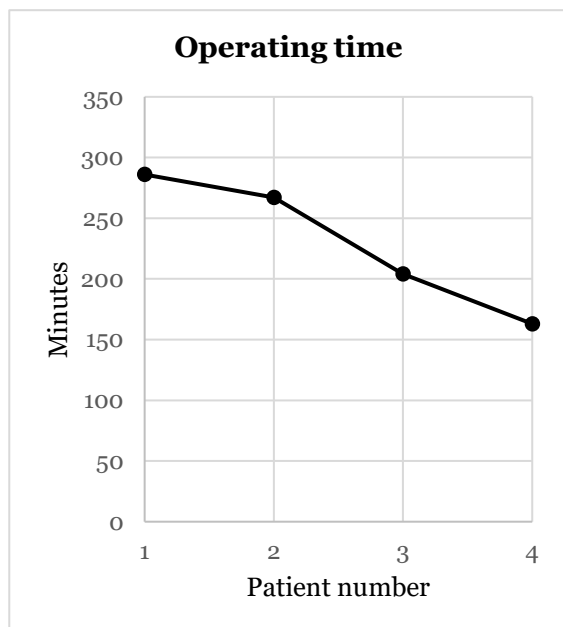


Fig 20. Trend in operation time.

The duration of the surgical procedure decreased remarkably case by case, indicating rapid technique refinement (Fig 20). The operating time for Patient 2 was prolonged by about 30 min due to poor adherence to operating theatre routines.

During the postoperative period on the ward, a small gap adjacent to the stoma was noted in Patient 4 which was easily managed on the ward with a simple suture. No other surgical complications were noted. The patients included were followed up for a total of 25, 23, 12, and 12 months respectively. Around 18

months after surgery, Patient 1 noted a small bulge adjacent to the stoma. At the clinical follow-up at 25 months a small asymptomatic recurrence was confirmed by intrastomal ultrasound. Patient 2 returned to the hospital 21 months after surgery with small bowel obstruction caused by a PSH recurrence which was manually reduced. At this point, a thorough medical history was obtained. This revealed that around one week postoperatively, the patient was admitted to the department of internal medicine because of an attack of acute intermittent porphyria with profuse vomiting. During this hospital stay the patient experienced a sense of something bursting next to the recently operated area. Patients 3 and 4 had well-functioning stomas without any sign of recurrence at the last follow-up.

Study protocol (Study V)

Stoma Hernia Intraperitoneal Full-Thickness skin (SHIFT)

Objective

The feasibility of using FTSG in PSH repair was shown in Study IV and previous publications. To further assess safety and other outcomes compared with present methods of repair, this novel method must be tested in a larger population.

Our hypothesis is that FTSG as intraperitoneally placed reinforcement in PSH repair provides a safer and more comfortable alternative to conventional synthetic mesh. To provide high level evidence, a blinded multicentre randomised controlled trial has been designed and named SHIFT.

Trial design

Initially SHIFT will take place at three Swedish hospitals of different sizes, with the possibility to include additional hospitals to increase inclusion rate. The trial allocation ratio is 1:1 and is designed as a parallel group, superiority trial.

Study participants

Patients eligible for inclusion will be taken from the waiting list for PSH repair. A consultant surgeon with experience in abdominal wall surgery will be responsible for the final inclusion assessment. To be included in SHIFT, the patient must have a PSH associated with a colostomy, ileostomy or urostomy, and diagnosed with intrastomal ultrasonography or CT-scan. They must be at least 18-years-of-age and comprehend enough Swedish to be able to give fully informed consent and fully understand the QoL questionnaires included in the trial. Patients that have comorbidity with undue risk for complications will be excluded. These comorbidities include Crohn's, concomitant ventral hernia requiring mesh repair, other intra-abdominal disease requiring surgical intervention, enterocutaneous fistula, and poor FTSG donor site condition.

Sample size

With an estimated complication rate of 40% in the synthetic mesh group and 15% in the FTSG group, a total of 78 patients must be included in SHIFT to achieve 80% power and 95% significance level. To compensate for expected loss to follow-up, our plan is to include a total of 90 patients, 45 in each intervention arm.

Randomisation

A total of 90 sealed envelopes will be prepared by research administrators containing a note specifying one or other of the study interventions. To prevent skewness in the distribution of a specific allocation at low-volume centres, the envelopes are arranged in a sequence in blocks of five with alternating overweight for either allocation. At inclusion, patients receive a randomisation number corresponding to a prepared envelope, but the patient's allocation is not revealed until the patient is under anaesthesia on the day of surgery.

Blinding

The patient and all staff involved in the care of the patient including the surgeon performing the clinical follow-up are blinded to the treatment allocation. Staff in the operating theatre during the surgical intervention and the researchers performing data analysis are not blinded.

Interventions

The study intervention will be the novel FTSG method thoroughly described in pages 23-25 in this thesis.

The control treatment arm is PSH repair using intraperitoneal onlay synthetic mesh reinforcement. Intraperitoneally placed mesh in PSH repair can be applied in different ways such as the Sugarbaker and keyhole methods, but the EHS states that there is insufficient evidence to favour any particular application (55). To make the control treatment as similar to the study intervention as possible, a DynaMesh®-IPST (FEG Textiltechnik mbH, Aachen, Germany) of appropriate size was chosen for SHIFT.

The surgical procedure in the control arm begins with a small standard midline laparotomy for inspection to ensure adequate access. If the intra-abdominal conditions allow for the procedure to be performed without undue risk for complications, the laparotomy is extended and draped in sterile dressings for protection from stomal contamination. The stoma is dissected from the skin, sealed with a temporary running suture, and retracted into the abdominal cavity. The hernia aperture is reduced to adequate diameter with single interrupted size 2-0 polydioxanone sutures. A Dynamesh® of appropriate size is applied to the stomal intestine which then is exteriorised through the reduced fascial orifice. The Dynamesh® is anchored to the abdominal wall with single interrupted size 2-0 polydioxanone monofilament sutures at 1-2 cm intervals along the edges of the graft and reinforcing sutures fusing the fascial plication to the mesh are placed in the same way as the FTSG method. The midline incision is then closed with a running polydioxanone monofilament suture size 2-0.

Outcomes

All study patients are planned for clinical follow-up at 3, 12, and 36 months postoperatively. The primary outcome of SHIFT is the rate of surgical complications which will be assessed at all clinical follow-ups. Secondary outcomes to be studied are:

-Recurrence rate. Diagnosed clinically and radiologically (intrastomal ultrasonography and/or CT-scan).

-Pain and quality-of-life. As shown by VHPQ and the European Organisation for Research and Treatment of Cancer questionnaire, module for colorectal cancer (EORTC CR29), and the European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC C30).

-Health economy. The cost-effectiveness of each treatment arm will be calculated using data from the hospital healthcare costs system.

Safety analysis

To ensure the safety of the patients included in SHIFT without compromising the scientific power of the study, a safety analysis will be performed after 1/3 of the patients have been included. An independent and scientifically experienced senior surgical research worker will analyse data from case report forms focusing on potential complications graded Clavien-Dindo 3b or worse. If a pattern of serious or otherwise unexpected complications associated with any of the study interventions is noted, the study will be interrupted. If no such pattern is noted, the safety analysis data will not be presented to the researchers responsible for the trial.

Ancillary study

Parallel to the main trial, a translational ancillary study investigating tissue biology in PSH patients will be performed. All patients participating in SHIFT will be asked to participate in the ancillary study using a separate consent form. If included in the ancillary study, the patients tissue biology will be examined in fascial biopsies taken during the primary intervention, and blood samples will be taken Day 1, 3 months, and 12 months postoperatively.

Furthermore, a subgroup of 12 patients will be asked to undergo biopsy of the implanted reinforcement material 12 months after surgery. The biopsy sample will be taken transcutaneously with an ultrasound-guided needle adjacent to the stoma.

Discussion

Main findings and methodological considerations

Study I

The main finding in Study I was that the use of FTSG appears to be comparable to synthetic mesh as reinforcement material in the repair of giant incisional hernia. There was no difference regarding complication rate, recurrence, aesthetic results, and effect on abdominal wall strength. The overall rate of recurrence was relatively low compared to previous publications, but no significant difference was seen between FTSG and synthetic mesh (4, 32).

No increase in abdominal wall strength was seen in either group following surgery. Previous studies have shown an increase in abdominal muscle strength after ventral hernia repair (75, 84). The lack of improvement in Study I could be due to a different population of patients with different prerequisites for postoperative rehabilitation. An attempt was made to explore potential correlations between the average change in Biodex™ results with multivariable linear regression analysis. No significant correlation was seen with the variables included in the analysis, but other potential risk factors such as degree of previous physical activity, severity grading of comorbidity, and degree of loss-of-domain were not available for analysis.

Another factor that could contribute to the lack of improvement is that some of the patients had had their hernia a long time before surgery. Giant incisional hernias cause disruption of the normal anatomy restraining normal activity of the abdominal wall muscles, thereby resulting in muscle atrophy as demonstrated in a rat model by Dubay *et al* (85). We could have investigated atrophy mechanisms in our patients by radiological grading of muscle thickness pre- and postoperatively and comparing these to a matched population without hernia. However, no such measurements were performed in this trial.

The present study did not grade the number and seriousness of comorbidities, nor did it include any data on the age of the hernia. An incisional hernia generally tends to grow over time with subsequent decrease in abdominal muscle strength (86). The position of the graft in the abdominal wall differed between our groups, but previous studies have shown that the positioning of graft material does not have an impact on abdominal wall strength (42).



Fig 21. Person prepared for testing in the Biodex system™

The Biodex system™ is a versatile tool that can be set to exercise and test different muscle groups, producing repeatable objective data on musculoskeletal performance (Fig 21). Practically it is an advanced dynamometer, in many aspects comparable to devices used in similar studies (84). An advantage of the Biodex system™ is the fact that it not only assesses flexor strength in primarily the rectus muscles, but also the entire function of the abdominolumbar girdle. Biodex™ has been validated and used in other studies investigating abdominal wall function (73, 87).

Study II

Results from this long-term follow-up study showed that the FTSG method continued to perform very much like the synthetic mesh method. The slightly higher recurrence rate in the FTSG group did not differ significantly from the synthetic mesh group. Since recurrences can occur several years after surgery with synthetic mesh, we expect an increase in recurrence rates in both groups after the three-year follow-up (88).

Despite few significant improvements, there was a numerical trend towards improvement of QoL and pain after surgery in both groups. There were significant improvements in physical and pain dimensions in the SF-36 in the FTSG group. Studies investigating QoL and pain after giant incisional hernia repair are few and of poor methodological quality with retrospective design and using non-validated questionnaires (89, 90). This study fills that gap in the knowledge of QoL and pain in giant incisional hernia and how it is affected by surgical repair. A strength of this study is the use of validated questionnaires with VHPQ being a tool specially designed for trials like the present. By assessing pain in relation to everyday activities, the VHPQ questionnaire can provide a better description of the actual handicap caused by the hernia.

We know little of how currently used techniques and positioning of reinforcement material determine comfort and function. There are some indications that the sublay position could cause more postoperative pain, thereby affecting the results in this study (18). Crucial details in surgical technique differ between surgeons affecting how positioning of the reinforcement material affects the prevalence of postoperative pain. For example, when applying mesh in the sublay position surgical techniques differ regarding mesh fixation, how lateral the dissection is made and how many vessels that can be preserved. The eight (28,6%) patients in the synthetic mesh group who received an onlay mesh in this trial reported more pain at follow-up. It is difficult to draw any conclusions on the prevalence of pain in this subgroup due to the small size and that the patients were selected since the retrorectus space could not be accessed safely, possibly indicating general frailty.

Overall, there was considerable inter-individual variability among the respondents that may be explained by differences in comorbidity. Results based on long-term QoL assessment will always face the risk of being confounded by comorbidities not related to the intervention investigated. This is especially true when using generic and general assessment tools such as EQ-5D and SF-36 in an older population, as was the case in this study. During the average of 9,3 years that had passed since surgery, it is likely that some of the patients had developed other comorbidities that confounded the results. This could explain the fact that a considerable number of patients reported pain and other QoL complaints after their operation. On the other hand, a more general health perception questionnaire is important for a holistic understanding of a disease or condition.

Large inter-individual variation can be compensated for by a large study population. The power calculation in this trial did not take QoL and pain into account, and therefore the study population was probably too small to detect true differences between the groups. This issue was further aggravated by loss to follow-up. A decrease in response rate always increases the risk for bias, and the study participants did not need to provide a reason for dropping out of the study making analysis difficult. However, the randomisation process should have provided equality between the groups, enabling fair comparison. A questionnaire should be designed so the number of questions maintains balance between gaining enough information before losing the patient's interest.

Study III

We predict that the mechanical properties of FTSG will not limit its use in abdominal wall reconstructive surgery. With outstanding tensile strength and ability to withstand suture loads, combined with its flexible handling properties, FTSG has the potential to become an excellent reinforcement material in PSH

repair. The results of Study III provide the evidence we need to continue investigating FTSG in PSH repair in human subjects.

The maximum physiological forces on the abdominal wall have been estimated not to exceed 16N/cm, which is almost 10 times less than the tensile strength of the weakest skin sample in this study (2). This large margin of safety allows for knife-meshing of the graft without imminent risk for failure of the reinforcement. FTSG also shows high resistance to suture tearing, in most cases stronger than the suture material used in this study. This provides us with information on how closely together the anchoring sutures must be placed. The present study results indicate that relatively long suture intervals can be used when fixing FTSG, thus reducing the number of anchoring sutures and reducing the amount of foreign material in the abdominal wall.

In this study, tensile strength measurements were performed on a home-made test device that was not validated or tested regarding precision and reproducibility. However, the principle behind tensile strength testing is simple, and similar methods have been used in other applications concerning abdominal wall reconstruction, including tests on Xenmatrix™ which yielded similar results (2, 91, 92). Furthermore, the main objective of this study was to compare the mechanical properties of FTSG with conventionally used reinforcement materials, and since all tests were performed using the same device, we presumed the internal validity to be high. The biological graft had a higher tensile strength than the synthetic mesh, both being well above the “physiological threshold”. Since biological grafts undergo transformation after implantation, their safety margin over physiological forces must be greater to prevent late failure of the reinforcement material.

Two of the skin samples broke at the attachment point rather than at the preformed waist. To obtain adequate fixation of the graft to perform the test, the clamp had to be tightened very hard, thus weakening the skin at that point, so the true tensile strength at the waist in these two cases was higher than that measured. There may also be a large variability in tensile strength within the skin graft, but this is less likely.

Study IV

No major procedure-related complication was seen during the follow-up period in the four pilot PSH patients repaired with FTSG as intraperitoneal reinforcement material. The results of Study IV thus indicate that this novel method of repair is feasible in humans.

The only surgical complication noted in the study was that in Patient 4, where a small mucocutaneous gap was discovered and a minor revision of the newly formed stoma with a single suture was performed under local anaesthesia on the ward. This was not necessarily related to the type of surgical intervention.

Two recurrences were noted in this study, but because of the small sample size, no valid conclusion regarding recurrence rate can be drawn. Since recurrence rates of currently available methods of repair can reach 46% after an average of 28 months, recurrence can be expected even in a small sample such as ours (64). The recurrence in Patient 2, that later became symptomatic, presumably occurred in the early postoperative period due to profuse vomiting caused by acute intermittent porphyria. The patient's condition was known prior to surgery, but the disease had been dormant for many years, and care was taken to avoid contraindicated drugs. Major abdominal surgery itself can trigger an attack of porphyria, which may have been the case here.

The surgical method developed in this study involves reduction of the fascial orifice prior to FTSG placement. This was primarily done to provide support for the entire FTSG and to approximate the well-vascularized peritoneum to facilitate rapid ingrowth of the graft. Reduction of the defect also enables a larger overlap, which is an advantage when the amount of available skin for transplantation is limited. EHS guidelines do not provide any recommendation on whether fascial reduction prior to mesh implantation in PSH repair is beneficial (55). Current guidelines for incisional hernia repair recommend fascial closure prior to mesh implantation to reduce the number of recurrences and complications. This should apply to PSH repair as well (34, 55).

This was a pilot project and sample size must be considerably larger than in this study to fully investigate the safety of this novel surgical method. Conventional PSH repair is associated with a relatively high risk for complications and even mortality. This illustrates the need for a better method of repair as well as the risks inherent to the procedure (66). The aim of Study IV was to develop a method of repairing PSH using intraperitoneal FTSG, to ensure its technical feasibility, and to show that it is without major procedure-related complications. In these respects, the results were satisfactory (Fig 22).

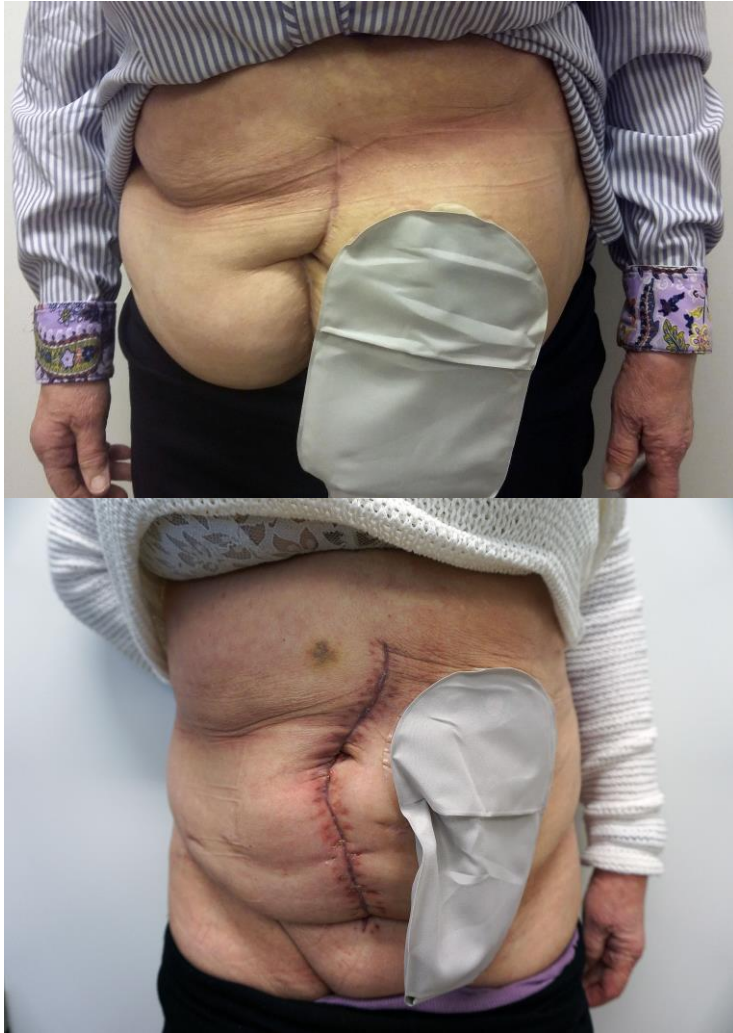


Fig 22. Patient 1 preoperatively and three months after surgery.

Study V

Study V presents the protocol of a trial to assess the novel method of PSH repair described in Paper IV. This will be a trial with a patient group big enough to provide reliable data on complications, recurrence, and other outcomes. Outcomes after PSH repair vary considerably because of differences in study design, and definitions of recurrence, and complications (62, 66). It is thus necessary to test the new method in a well-defined randomised controlled trial if we are to compare FTSG outcomes with conventional methods of repair.

The method of PSH repair developed in Study IV involves FTSG reinforcement applied intraperitoneally with the stoma bowel passing through an orifice in the graft. Based on current knowledge, EHS guidelines do not recommend any mesh application technique for open PSH repair. The mesh used for comparison (Dynamesh®-IPST) was thus chosen to be as similar to FTSG as possible.

Study III showed that FTSG cannot easily be applied via laparoscopy since tacks generally cannot penetrate the grafted skin. Furthermore, laparoscopic suturing can limit the tension necessary under which FTSG must be applied. The reference method in SHIFT therefore uses an open approach to ensure that comparison focuses on reinforcement properties rather than surgical approach. Another aspect is the need to retract the stoma bowel intra-abdominally to enable passage through the reinforcement material. This necessitates a hybrid approach such as the HyPER-technique if the reinforcement is to be placed laparoscopically (93). Furthermore, EHS guidelines do not state any preference for open or laparoscopic techniques (55).

Recurrence is the main outcome in most studies on hernia repair. Although this is a surgical failure, recurrence *per se* may be of minor importance compared to the serious and sometimes fatal complications associated with conventional repair. For this reason, the main outcome of SHIFT is short-term complications. Any recurrence will be noted at clinical follow-up. For more objective diagnosis, patients will be assessed with intrastomal ultrasonography at the 12- and 36-month follow-ups. The questionnaires chosen for QoL assessment will provide hernia repair-specific information. The VHPQ will focus on pain and pain behaviour since many of the problems arising from PSH repair are similar to other ventral hernias. More stoma-specific complaints as well as a general health assessment will be covered by the EORTC questionnaires. These are designed for cancer patients, but have also been used successfully in stoma patients without cancer (71).

Healthcare economy is another important outcome which will be studied in SHIFT. By definition, a FTSG costs nothing, but to fully appreciate the potential economic advantages of FTSG, a thorough healthcare economy analysis is necessary. This will include the cost of extra operating time, extra surgical material, length of hospital stay, risk for complication, cost of subsequent treatment, *et cetera*.

General discussion

When there is disruption of the normal anatomy in the abdominal wall, as occurs in patients suffering from a ventral hernia, the importance of the abdominolumbar girdle in everyday life becomes obvious. Some patients suffering from incisional hernia, especially when it is large, report back pain as the dominant symptom, indicating disruption of abdominolumbar girdle integrity (4). There are no studies on how PSH affects abdominal wall muscle strength, but a PSH can be large, with distorted abdominal wall anatomy, so there is reason to believe that PSH can also affect girdle function and thereby QoL (44).

After repair of a ventral hernia, and thereby an at least partial restoration of the anatomy, an increase in core strength has been observed (75, 84). Even in relatively moderate disruption of the normal anatomy, as in patients suffering from diastasis recti, functional problems occur, and there are both objective and subjective improvements after surgical restoration of the normal anatomy (94, 95). Furthermore, findings in animal models indicate that long-term imbalance of the abdominal muscles, such as with an incisional hernia, can cause irreversible atrophy and fibrosis of the abdominal wall. The strong inverse relationship between hernia size and abdominal wall muscle strength in humans suggests that this is the case (85, 86).

Incisional hernias and PSHs impact the patient's QoL in different ways. We know that surgical repair can provide relief, but a note of caution must be made. Repair of these complicated hernias is a great surgical challenge, and current methods of repair can cause serious complications causing morbidity or even death. While attempting to optimise surgical techniques and different approaches for cure, the patient must never be subjected to undue risk for harm.

FTSG as reinforcement material

The use of FTSG as reinforcement material has seen a renaissance. For many years this technique was almost forgotten following the successful introduction of synthetic mesh materials. However, FTSG is autologous, readily accessible, costs no more than the extra resources for harvesting, and strong (see Study III). Where healthcare resources are limited, skin grafting could provide a useful alternative in the hernia surgeon's toolbox.

In Studies I and II, there was no difference in the rate of subcutaneous infections between FTSG and mesh. However, all operations were elective, only a few patients received any concomitant bowel interventions, and no intra-abdominal infections or mesh extractions were needed (23). Synthetic mesh infection can be difficult to treat and, in some cases, requires mesh removal which is associated with considerable morbidity. FTSG is a living tissue armed with an

immunological infrastructure, so infection of the reinforcement material is less likely to become resistant to treatment. A problem with FTSG is that the skin surface is colonised by bacteria that could theoretically cause infection after implantation. In our procedure, the skin was sterilised preoperatively, and to further reduce the number of bacteria the FTSG was placed in surgical gauzes soaked in saline and hydrogen peroxide solution. Random samples of FTSG were taken for microbiological culture and no growth was seen in any of the samples except one showing sparse skin flora.

FTSG vs Split-thickness skin grafts

Autologous skin transplantation is frequently used in other plastic surgery procedures, predominantly as machine meshed split-thickness grafts. Its main use is wound coverage when replacing absent or damaged skin, such as after burn injuries or when excising malignancies of the skin (96, 97). A split-thickness graft consists of epidermis and part of the dermis (see Fig 23) which enables full recovery of the donor site with little or no scarring, making potential grafting material abundant.

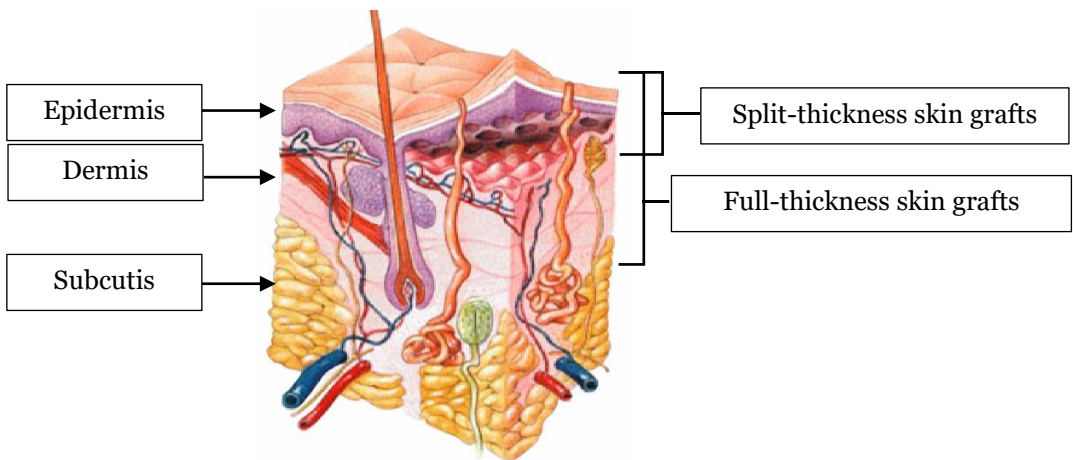


Figure 23. Cross-section of skin

Split-thickness grafts primarily serve as a bridge to secondary skin healing. When applied to a well vascularised surface, it provides rapid coverage of the skin defect. In hernia repair, the mesh or graft applied to the defect initially serves as mechanical reinforcement to the repair and must therefore sustain tensile strength. The dermis is mainly responsible for mechanical strength of the skin, and it is therefore desirable to keep as much dermis as possible when using skin as mechanical reinforcement, as in hernia surgery. Unfortunately, when harvesting FTSG, the donor site must allow for primary closure, which limits the size of the graft.

FTSG harvesting

FTSG must be harvested from a location with enough suitable skin, but without causing undue morbidity at the donor site. For large FTSGs, donor sites are restricted to the thigh and the medial aspect of the upper arm. Unfortunately, this causes an additional wound with subsequent risk for infection and other complications. The abdominal wall can also serve as the primary donor site, in which case it is possible to combine the hernia repair incision with the donor site (Fig 24), such as in Studies I and II, where all FTSGs were taken adjacent to the midline incision. Furthermore, when a hernia is large, the skin over the hernia is often stretched, leaving excess skin after repair. In many cases this must be excised, regardless of surgical method used, to allow for proper skin closure.

Another potential benefit of FTSG as reinforcement material in hernia repair is that the graft costs nothing and is readily available. Healthcare economy assessment was not considered in Studies I and II, but there were no significant differences in operating time and length of hospital stay.



Fig 24. Study IV: picture taken during surgery. After marking the area intended for skin graft harvesting, care is taken that primary closure is possible before making the incision.

Fate of the FTSG

Synthetic mesh as reinforcement material differs from biological mesh or FTSG in that it is made up of inert material. A synthetic mesh hardly transforms during tissue remodelling and repair, the tensile strength relies on the mesh itself and the scar tissue formed around it as response to the foreign body.

FTSG, on the other hand, is a living autologous tissue which undergoes remodulation after implantation. Study III demonstrated the mechanical properties of FTSG at the time of implantation, but how the graft's properties change after implantation is largely unknown. In early histological studies it was shown that all adnexa as well as epidermis gradually degrade over time, leaving only irregular connective tissue (13, 98). A biopsy taken three years after surgery from an FTSG implanted in a patient with an incisional hernia showed complete transformation into fascia-like irregular fibrous tissue without skin adnexa (23). While degradation of skin adnexa is desirable, the mechanical properties of the graft remains unknown. Physiologically, connective tissue such as fascia, dermis, and tendons remodulate in response to strain and adjust their structure to meet current needs. This mechanism may also apply to FTSG used in hernia surgery.

The metamorphosis of implanted FTSG could be what makes it more advantageous than other reinforcement materials. By being integrated into the structures of the abdominal wall, physiological properties may be restored and preserved in a way that is better than introduction of an inert, inflexible synthetic mesh. FTSG should rather be seen as a deposition of autologous connective tissue to reinforce a weakness. In study I, no difference in abdominal muscle strength between the groups could be demonstrated, perhaps indicating that FTSG does not lead to better restoration of the abdominal wall anatomy. On the other hand, no improvement was seen in the population overall. Since previous studies have shown improvement in abdominal wall muscle strength, this could indicate the presence of confounders in our trial that made restoration of abdominal function impossible.

PSH repair poses a unique challenge in that the hernial aperture cannot be closed completely but must allow for passage of the stomal intestine or ileal conduit. Reinforcement material must therefore be equipped with an orifice or a slit, such as in the keyhole technique, or placed in a Sugarbaker position. Because of the stomal orifice, recurrence of the hernia adjacent to the deviated bowel is always possible. Theoretically, transformation and integration of FTSG after implantation would create a continuum with the abdominal wall making recurrence less likely.

There are some indications that hernia patients in general may have suboptimal connective tissue metabolism (6). Add to the fact that patients with an incisional

hernia have already shown defective wound healing, one wonders whether this could be a disadvantage when employing FTSG. However, mechanisms behind synthetic mesh reinforcement also presume ingrowth of connective tissue (99), so patients with defective connective tissue metabolism should be affected regardless. Autologous tissue, such as FTSG, could possibly cause an inflammatory response characterised by healing and integration rather than the foreign body reaction caused by synthetic mesh.

FTSG versus biological grafts

Biological grafts and FTSG have several expectations in common since both are collagen-rich tissues, but there are major differences. Biological grafts are either allografts from cadavers or xenografts that stem from several collagen-rich tissues such as dermis, pericardium, or intestinal mucosa. These tissues are treated chemically, thermally and mechanically to create sterile sheets of collagen matrix that do not induce a foreign body reaction. In theory, the graft should then offer a scaffold for native cells to migrate into, forming long-term reinforcement tissue. However, harsh treatment in preparation of the graft material together with differences in vascularisation (Page 7) could explain the disappointing recurrence rates and biological graft's fall from favour (28).

Future studies

Apart from Study V which has recently started, the results of the studies included in this thesis raises several questions for future studies on the use of FTSG in hernia surgery.

Due to its seemingly more favourable resilience to infection, FTSG deserves more structured assessment of its performance in contaminated surgical fields, including hernia repair in conjunction with bowel surgery, strangulation requiring bowel resection, or in immuno-incompetent patients.

A potential benefit of FTSG is better function and comfort compared to synthetic mesh in cases where the size of reinforcement material necessary is large. No improvement in abdominal muscle strength, regardless of graft or mesh, was seen in Study I, but this was probably due to the aged study population with comorbidities. It would be interesting to investigate the performance of FTSG in a healthier population with incisional hernias having a width of 4-10 cm (Grade 2 according to EHS classification guidelines).

In future studies investigating FTSG as reinforcement in hernia repair, follow-up times must be at least 36 months since recurrence seems to occur later than one year after surgery, as seen in Study II.

Another possible development of FTSG application is laparoscopic repair. While developing the method in Study IV, we found that traditional surgical tacks could not easily penetrate the FTSG. With better tack equipment it could be possible to achieve graft fixation, thereby enabling laparoscopic application of FTSG.

Conclusions

The results of the studies in this thesis contribute significantly to our knowledge regarding the use of FTSG as reinforcement material in complex hernia surgery.

The use of FTSG in giant incisional hernia provided results comparable to conventional repair with synthetic mesh reinforcement and could thereby be useful in selected cases in clinical practice. Further research may help us to find a subgroup of incisional hernia patients where the use of FTSG is advantageous.

Study IV, a pilot study, introduces a novel method for repairing PSH in a human feasibility study. This was the final link in a translational chain investigating the concept of intraperitoneal placement of a FTSG. This novel PSH repair was shown not to have any major method-related complications, and a large trial comparing FTSG to conventional mesh in PSH repair is underway (see Study V).

All things being considered, it is strange that the technique of FTSG in hernia repair fell into obscurity following the introduction of synthetic mesh. This thesis will hopefully lead to a rebirth of the phoenix, opening the way to using FTSG in hernia repair and potentially improve the outcome for patients with complex hernias.

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