From: Holste, Dr. Joerg [MEDDE] <DHOLSTE@its.jnj.com>
Sent: Wed, 22 Apr 2009 12:47:46 GMT
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CC: Hall, Lynn [ETHUS] <LHall2@its.jnj.com>; Landgrebe, Susanne [MEDDE] <SLandgre@its.jnj.com>
Subject: AW: Question on Monocryl absorption

Importance: High

Jonathan,

the border for scar plate formation in small pore standard weight meshes was set around 1000 µm (microns)

So the pore size of ULTRAPRO/PROLIFT+M is far beyond that level, even before MONOCRYL is absorbed at 84days after implantation.

Furthermore MONOCRYL has a positive influence on tissue reaction, minimizing the inflammation and the final fibrosis/scar formation.

See literature attached: please find additional information in the ww marketing e-room in the ULTRAPRO LW folder.

Jörg

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Von: Meek, Jonathan [ETHUS]
Gesendet: Mittwoch, 22. April 2009 14:04

An: Holste, Dr. Joerg [MEDDE]; Meier, Peter [MEDDE]
Cc: Hall, Lynn [ETHUS]
Betreff: Question on Monocryl absorption

Joerg and Peter,
Would you mind guiding me on the answer to a question from a US KOL that I want to get back to with the correct answer.

Q: If the Monocryl in GYNEMESH M takes 84 days to absorb, doesn't that mean that the FBR will be complete before the pore size can be maximized i.e the effect on scar bridging will be the same as any other 2.5mm graft

Please can you craft a response that I can send on to her.
Many thanks
Jonathan Meek
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The Argument for Lightweight Polypropylene Mesh in Hernia Repair

William S. Cobb, MD, Kent W. Kercher, MD, and B. Todd Heniford, MD

The development of polypropylene prosthetics revolutionized surgery for the repair of abdominal wall hernias. A tension-free mesh technique has drastically reduced recurrence rates for all hernias compared to tissue repairs and has made it possible to reconstruct large ventral defects that were previously irreparable. The repair of abdominal wall defects is one of the most commonly performed general surgical procedures, with over 1 million polypropylene implants inserted each year. Surprisingly, little research has been performed to investigate the interaction of abdominal wall forces on a ventral hernia repair or the required amount or strength of the foreign-body material necessary for an adequate hernia repair. The long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial. Reducing the density of polypropylene and creating a "light weight" mesh theoretically induces less foreign-body response, results in improved abdominal wall compliance, causes less contraction or shrinkage of the mesh, and allows for better tissue incorporation. A review of the laboratory data and short-term clinical follow-up is reviewed to provide a strong basis or argument for the use of "light weight" prosthetics in hernia surgery.

A surgeon can do more for the community by operating on hernia cases and seeing that his recurrence rate is low than he can by operating on cases of malignant disease.

—Sir Cecil Wakely, 1948
President
Royal College of Surgeons

The search for an effective repair of ventral hernia has long occupied the general surgeon. Historically, tissue repairs of abdominal wall defects were met with rates of recurrence of up to 50%.[1-3] The work of Dr. Francis Usher with polypropylene (Marlex) in the late 1950s revolutionized the approach to abdominal wall defects and drastically lowered the recurrence rates.[4-6] His experience with polyethylene provided significant advantages over the metallic meshes used at the time. Polyethylene resisted corrosion and migration inherent to tantalum and stainless steel meshes.

In 1962, the weave of the standard polypropylene mesh was changed from woven to a knitted construct. This alteration was made to prevent the ends of the mesh from unraveling when cut.[7] The polypropylene mesh that is used today has remained largely unchanged over the past 45 years. Polypropylene is the most commonly used prosthetic worldwide for the repair of ventral and groin hernias.

The surgical literature is replete with articles describing different mesh repair techniques for ventral and inguinal hernias and their associated rates of recurrence. Despite hernia operations being the most commonly performed procedures by general surgeons over the last 50 years, little data exist concerning the intraabdominal forces generated during normal or strenuous activity and the necessary strength of a prosthetic for repair. The standard polypropylene mesh may in fact be over-engineered or too strong. In addition, the body's reaction to these dense or "heavyweight" meshes results in intense inflammation, mesh shrinkage, and loss of abdominal wall compliance.

By reducing the amount of foreign body material, lighter-weight meshes may provide ample strength for hernia repair with less associated side effects. Second- and third-generation prosthetic biomaterials have been developed that are intentionally less dense, with less tensile strength (N/cm) than standard, nonabsorbable mesh. These bioprosthetics allow more freedom of abdominal wall motion, are more resistant to contraction because of reduced inflammation, and maintain or improve good tissue ingrowth. A strong argument for these "lightweight" meshes can be made from data concerning maximum burst strength, abdominal wall compliance, degree of foreign body response, amount of shrinkage, and advantages of larger pore sizes in the mesh.

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Concept of Lightweight Mesh

Although the reduction in hernia recurrence rates is undeniable when a tension-free mesh repair is performed, the long-term complications of implantation of polypropylene mesh have been well documented.[8] The properties that serve polypropylene well for incorporation after hernia repair can also be detrimental. Polypropylene creates an intense inflammatory response that results in rapid and dense incorporation into the surrounding tissue. This excessive inflammatory reaction to heavyweight polypropylene tends to form a scar-plate around the prosthetic that results in a firm and contracted mesh. Reducing the amount of foreign body material in these meshes may reduce the inflammatory response and decrease the degree of unorganized or reactive scar formation.

Marlex (C.R. Bard, Inc, Murray Hill, NJ) is a standard monofilament heavyweight polypropylene mesh that is commonly used for hernia repair. It contains 95 g/m² of polypropylene, is porous but has very small interstices, and is extremely strong. Several comparable formulations of heavyweight polypropylene are available with a similar polypropylene content as Marlex, including Prolene (Ethicon, Inc, Somerville, NJ), Surgipro (US Surgical, Norwalk, CT), and Prolite (Atrium Medical, Hudson, NH) (Table 1).

Companies have decreased the foreign body material in their mesh by reducing the density of polypropylene filaments that compose the mesh. These bioprosthetics now fall into 3 main categories—heavyweight, middleweight, and lightweight—according to their polypropylene content. Prolene Soft Mesh (Ethicon, Inc) contains less than half the polypropylene (45 g/m²), has larger pores, and is more compliant than heavyweight meshes. Lightweight meshes tend to have 35 g/m² of polypropylene or less. They also have very large pores, in the range of 3 to 4 mm. This reduction in prosthetic makes the mesh much softer and more flexible compared with standard meshes. An example of the available polypropylene hernia prosthetics and their densities is listed in Table 1.

As mentioned, the reduced-mass meshes are very compliant or soft. Although this increase in compliance or decrease in stiffness is an advantage to patients, the dramatic increase in flexibility of the mesh could make it difficult for surgeons to handle or manipulate it in the operating room. A certain stiffness, or ability of the mesh to hold its shape, eases placement of the prosthetic inside or outside the abdomen.

In an effort to improve handling characteristics of these lightweight meshes, manufacturers incorporated absorbable filaments into the weave of the mesh. These absorbable components add stiffness during implantation but then readily absorb. Vypro (Johnson & Johnson) was the first lightweight partially absorbable mesh. It contains lightweight polypropylene interwoven with multifilamented polyglactin 910 (Vicryl, Ethicon, Inc). The Vicryl component begins to dissolve immediately and is microscopically absent in 60 to 90 days.

Because the multifilamented nature of the Vicryl in Vypro may contribute to increased surface area and potentially a higher infection risk, the next generation product included a partially absorbable monofilament woven within polypropylene. Ultrapro (Ethicon, Inc) is a recently introduced mesh that is composed of a weave of lightweight polypropylene and poliglecaprone, the same material that is in Monocryl (Johnson & Johnson) suture (Figure 1). The poliglecaprone, which is a mono-filament, gives the mesh added stiffness for handling and dissolves in approximately 90 days.

Burst Strength

Calculations of intraabdominal pressure and compliance of the abdominal wall have called into question the need for heavyweight polypropylene. Schumpelick and colleagues[9] have attempted to study the elasticity and tensile strength of the abdominal wall. Calculations based on Pascal's principle of hydrostatics have predicted the maximum

Table 1. Polypropylene meshes of differing densities.

Surgipro[a]	110 g/m²
Prolene[b]	105 g/m²
Marlex[c]	95 g/m²
Prolite[d]	90 g/m²
Prolene Soft Mesh[b]	45 g/m²
Vypro II[b]	35 g/m²
Ultrapro[b]	28 g/m²

[a]United States Surgical, Norwalk, CT
[b]Ethicon, Inc, Somerville, NJ
[c]CR Bard, Inc, Cranston, RI
[d]Atrium Medical Co, Hudson, NH

tensile strength of the abdominal wall to be 16 N/cm.[10] Standard heavyweight polypropylene mesh has been shown to have a bursting strength that is 6 to 10 times this calculated force. From their mathematic models and stereotaxy of the human abdomen, it can be hypothesized that the currently available prosthetics are, in fact, too strong, more dense, and less compliant than needed for an optimal hernia repair.[10] However, the abdominal wall pressures in their models are calculated and not a direct measure.

The initial fixation strength of the various surgical techniques and the tissue overlap of the prosthetic are the principal factors in the early success of a mesh hernia repair. Suture or metallic attachment devices must resist maximum intraabdominal pressures, forces of wound contraction, and potential mesh migration.

The long-term success of the repair ultimately depends on the fibrocollagenous ingrowth of the tissue into the mesh. How strong a biomaterial needs to be and the required amount of incorporation of the mesh into the patient's tissues have yet to be determined. In fact, the normal intraabdominal forces prosthetic biomaterials encounter in vivo had not been truly and accurately measured in a quantitative manner. Previous cadaveric models have predicted that the maximum, instantaneous force generated in the abdomen to be about 150 mm Hg[11]; however, the forces acting on the abdomen during everyday activities were relatively unknown.

Figure 1. Electron micrograph at ×60 magnification demonstrating the weave of Ultrapro partially absorbable mesh. The poliglecaprone (Monocryl) appears white and is interwoven with two strands of lightweight polypropylene.

To answer this question, we measured the ranges of maximum intraabdominal pressures (IAP) via bladder catheters in young adults during routine activities.[12] The maximum intraabdominal pressures generated by healthy, non-obese individuals in our study occurred during coughing and jumping. While coughing, the maximum intraabdominal pressures were 127 mm Hg while sitting and 141 mm Hg standing. A pressure as high as 252 mm Hg was obtained while a test subject jumped in place. For Valsalva in this healthy adult population, the maximum pressures were 64 mm Hg while sitting and 116 mm Hg standing.

Considering the abdominal cavity as a cylinder and using Pascal's principle of hydrostatics, the maximum tensile strengths would range from 11 N/cm to 27 N/cm for these exercises. Biomaterials and their fixation should tolerate these pressures to minimize the risk of hernia recurrence. Klinge et al[11,13] demonstrated that the heavyweight polypropylene currently in use tolerates rupture forces of up to 100 N/cm.

We used a porcine model to evaluate the biomechanical properties of heavyweight (Marlex), middleweight (Prolene Soft Mesh), and lightweight (Ultrapro) polypropylene mesh after 5 months of implantation.[14] The burst strengths for all meshes in this study were highly supraphysiologic. The burst load for the native abdominal wall fascia averaged 232 N. The mean burst loads for the lightweight (576 N) and middleweight (590 N) meshes were more than twice this. The heavyweight mesh demonstrated excessive burst loads of greater than 1200 N. These burst strengths far exceed the normal forces acting on the abdominal wall fascia both before implantation and after 5 months within the abdomen.

Recurrences of abdominal wall hernia repairs are rarely due to failure of the mesh itself. Indeed, there is only a single report[15] of central mesh failure with a heavyweight polypropylene mesh. Rather than surmising that the mesh was too weak, the authors postulated that the increased stiffness of the heavyweight mesh at its interface with the compliant abdominal wall resulted in damage to the mesh or a fracture that caused its failure over years.[15] Failure of hernia repairs nearly always occurs laterally at the mesh-tissue interface because of a failure of fixation, incorporation, or lack of overlap.

Abdominal Wall Compliance

There are consequences to the long-term implantation of polypropylene. As previously mentioned, heavyweight meshes elicit an intense inflammatory response that produces a scar plate or thick capsule around the mesh (Figure 2) and results in reduced compliance of the abdominal wall.[16] This was well demonstrated by ultrasound examination and 3D stereography in patients having undergone ventral hernia repair with both heavyweight and lightweight meshes.[17] All meshes showed an increased stiffness of the abdominal wall with reduced height and diminished curvature at maximum abdominal distention. The extent of stiffness significantly increased in direct proportion to mesh weight and was inversely related to pore size, that is, a larger pore size yielded a more compliant or softer mesh in situ.

The curvature of the abdominal wall increased over time with the lightweight mesh, which was not seen with any of the heavyweight meshes.[17] When heavyweight polypropylene meshes were removed from human subjects during reoperations, Klinge and colleagues microscopically confirmed what had been seen in animal experiments: the inflammatory process at the mesh-tissue interface demonstrated pronounced perifilamentous fibrosis and deposition of unorganized collagen fibers. The entire polypropylene mesh was encapsulated by connective tissue that formed a rigid scar plate.[18] This phenomenon is believed to contribute to increased stiffness of the mesh and abdominal wall.

In our in vivo study mentioned previously, the medium- and lightweight meshes demonstrated significant reduction in stiffness as the absorbable component dissolved compared with the heavyweight mesh. Following explantation, the lightweight mesh was significantly more compliant or least stiff. However, before implantation, the absorbable Monocryl (poliglecaprone) component makes the lightweight mesh the stiffest of all the meshes (68.6 N/cm).

As previously stated, the purpose of the poliglecaprone interwoven with the thin polypropylene is to increase stiffness to improve handling during implantation. However, the improvement in compliance demonstrated after degradation of the poliglecaprone much more closely approximates the physiology of the abdominal wall. We are currently prospectively following patients after the implantation of lightweight mesh for large ventral hernia defects. The endpoints of this study will include patient comfort, abdominal wall compliance, complications, and recurrence.

Foreign Body Response

The most important factor influencing the biocompatibility or tolerance of a subject to a foreign body is the intensity and extent of inflammation and the wound healing associated with the material. The degree of inflammatory reaction to a biomaterial affects its incorporation into the implant site. The formation of connective tissue correlates well with the degree of inflammation. Moreover, the extent of the foreign body reaction to mesh prosthetics depends on the amount of the incorporated material.[19]

The increased ingrowth of connective tissue when associated with inflammatory or giant cells does not necessarily translate into strength and durability after hernia repair. Lightweight mesh with reduced polypropylene density and larger pore sizes between filaments has shown a pronounced reduction in inflammation and improved integration into surrounding tissue in humans.[18]

Histologically, in a long-term study in a pig model, we observed more scar plate or capsule formation with heavyweight mesh compared with lightweight mesh (Figure 2).[20] The number of inflammatory cells was statistically less in the lightweight mesh (Figure 3). As a result, the degree of overall tissue incorporation was substantially better with lightweight mesh compared with its heavyweight counterpart.

In a rat model of ventral hernia repair, Klinge et al[21] demonstrated that biomaterials with a larger pore size and decreased polypropylene content exhibited a reduction in inflammation and fibrosis with microscopic attributes of normal healing tissue compared with more dense polypropylene-containing materials. At the cellular level, measurements of apoptosis and proliferation were elevated in the heavyweight mesh groups, implying an increased amount of cellular turnover. The lightweight mesh appears to demonstrate more physiologic levels of turnover.

The foreign-body reaction to nonabsorbable meshes was studied by histologically examining explanted mesh specimens removed during revision operations.[18] The investigators found that permanent heavyweight meshes cause a persistent inflammatory reaction at the mesh-tissue interface for months to years after implantation. The host adapts to the "inert" foreign body to a degree, and then encases the mesh in a surrounding collagen capsule to protect the host tissues.[18] The persistence of this foreign-body reaction is important, especially in young patients in whom the mesh will remain for several decades.

Clinically, the reduction in foreign-body reaction translates into theoretically fewer complaints of paraesthesias and functional complaints. Welty et al[17]demonstrated the superiority of lightweight polypropylene mesh biomaterials for incisional hernia repairs.[17] More complaints were seen in patients younger than 50 years of age. In the heavyweight Marlex group, 58% had complaints of paresthesia compared with only 4% in the lightweight Vypro group.[17]

Degree of Shrinkage

One concern with the long-term implantation of mesh is the amount of shrinkage or passive compression the material undergoes. All available meshes, regardless of their composition, experience a 20% to 50% reduction in their initial size. Factors of the mesh itself and the surrounding tissue inflammatory response contribute to this phenomenon. The reality of mesh contraction, whatever the

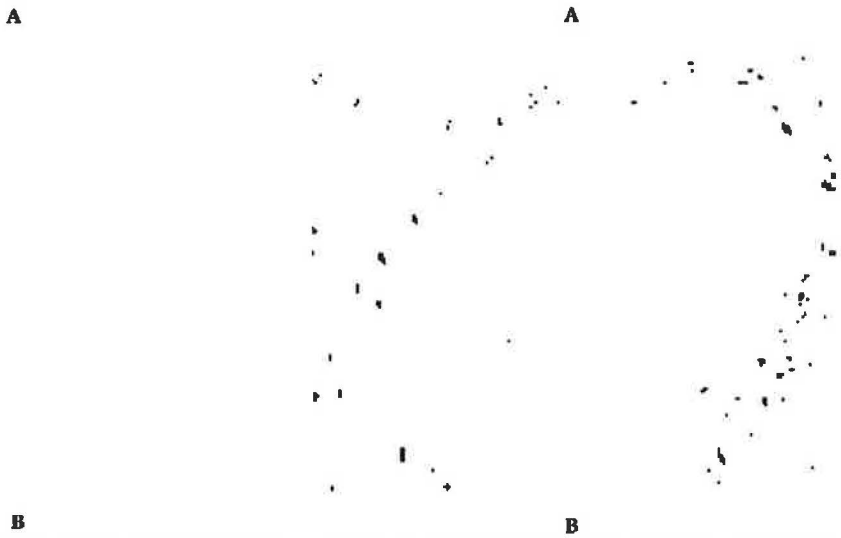

Figure 2. (A) Heavy weight mesh ×40, Trichrome stain) induces a thick scar around the mesh with bridging fibrosis or unorganized collagen between the filaments. **(B)** Lightweight mesh (×40, Trichrome stain) demonstrates better tissue incorporation with less scar plate formation.

Figure 3. (A) Tissue response 5 months after heavy weight mesh implantation (×400, Trichrome stain) demonstrates abundant inflammatory, giant cells. **(B)** The lightweight mesh (×400, Trichrome stain) produces much less inflammation, with more stromal cells and fibroblasts.

reason, strongly supports the concept of wide tissue overlap, which has been long advocated by proponents of the retro-rectus repair and, more recently, the laparoscopic repair.[22]

In a dog model, the shrinkage of heavyweight polypropylene mesh and a lightweight polypropylene mesh with absorbable polyglactin 910 were compared. It demonstrated that all polypropylene meshes shrink 30% to 50% of their original size within 2 to 6 months after implantation. The lightweight mesh showed less inflammatory response and reduced shrinkage (34% vs 46%).[23]

Initially, macrophages are an important cell population associated with the inflammatory reaction to biomaterials. The absorbable fraction of lightweight polypropylene mesh may be responsible for high macrophage counts at day 7 and a pronounced reduction of the macrophage index after 90 days.[19] The presence of the absorbable poliglecaprone in Ultrapro mesh may initially create an inflammatory reaction that resolves as this portion of the prosthetic absorbs. Over a longer period of time, this effect may diminish and result in less passive compression of the lightweight mesh.

Increased Pore Size

The pore size of prosthetic mesh has an important effect on the biocompatibility of the foreign body after implantation. An in vivo study after implantation of heavyweight mesh and an experimental lightweight polypropylene mesh demonstrated a significant increase of total and mature type I collagen deposition with the lightweight mesh containing larger pores. The tensile strength of the large-pore mesh increased after 30-day implantation in the dog, whereas it remained the same for the smaller-pore heavyweight mesh.[24]

A similar study evaluated heavyweight, small-pore Marlex mesh and lightweight, large-pore Vypro mesh with an absorbable component. The large-pore mesh was integrated in a loose network of perifilamentous fibrosis with fat tissue present in between. In contrast, the small-pore mesh was incorporated entirely in perifilamentary granulomas and scar tissue, which bridged the whole pore diameter of less than 1 mm.[21] It appears that the greater distance between pores resists the ability of "bridging fibrosis" (Figure 4), contributing to im-

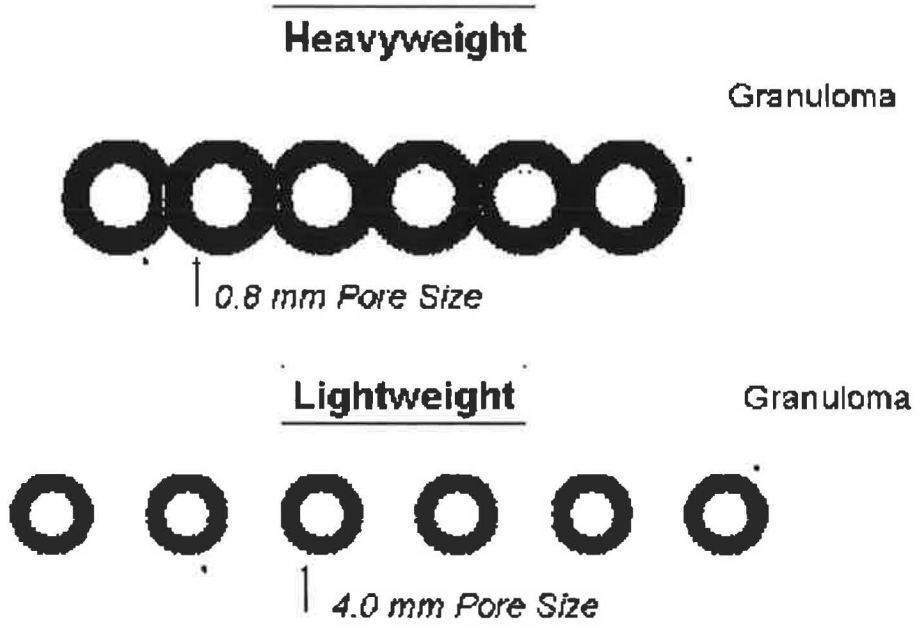

Figure 4. Small pores of heavyweight polypropylene allow for intense peri-filamentous fibrosis with bridging to adjacent filaments. Macroporous meshes that have less polypropylene incite less of a foreign body reaction with less bridging fibrosis.

proved compliance and theoretically less passive compression of the biomaterial.

Conclusion

The use of a polyethylene polymer in a mesh configuration has changed the face of hernia surgery over the past 50 years. The techniques describing the precise method of placement of this mesh are exhausting, and recurrence rates have reached a nadir with the currently available mesh. The continued search for the ideal hernia repair with reduced long-term morbidity will shift away from discussing the type of repair and turn to an evaluation of the type of mesh used in the repair.

The implantation of a macroporous, lightweight polypropylene mesh results in less restriction of abdominal wall compliance while providing more than adequate strength for the repair of ventral hernias. These new class of meshes for abdominal wall hernia repair are lightweight, or more correctly termed, *physiologic-weight* materials. Continued, prospective evaluations of various polypropylene mesh formulations in the clinical setting are required for a more thorough assessment of the role of these promising bioprosthetics in the repair of ventral hernias, and, as well, will determine "how low we can go" with the amount of foreign body material.

References

1. Berger D, Bientzle M, Muller A: Postoperative complications after laparoscopic incisional hernia repair. Incidence and treatment. Surg Endosc 16:1720-17203, 2002.
2. Anthony T, Bergen PC, Kim LT, et al: Factors affecting recurrence following incisional herniorrhaphy. World J Surg 24:95-100, 2000.
3. van der Linden FT, van Vroonhoven TJ: Long-term results after surgical correction of incisional hernia. Neth J Surg 40:127-129, 1988.
4. Luijendijk RW, Hop WC, van den Tol MP, et al: A comparison of suture repair with mesh repair for incisional hernia. N Engl J Med 343:392-398, 2000.
5. Stoppa RE: The treatment of complicated groin and incisional hernias. World J Surg 13:545-554, 1989.
6. Wantz GE: Giant prosthetic reinforcement of the visceral sac. Surg Gynecol Obstet 169:408-417, 1989.
7. Usher FC: Hernia repair with knitted polypropylene mesh. Surg Gynecol Obstet 117:239-240, 1963.
8. Leber GE, Garb JL, Alexander AI, et al: Long-term complications associated with prosthetic repair of incisional hernias. Arch Surg 133:378-382, 1998.
9. Junge K, Klinge U, Prescher A, et al: Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants. Hernia 5:113-118, 2001.
10. Klinge U, Klosterhalfen B, Conze J, et al: Modified mesh for hernia repair that is adapted to the physiology of the abdominal wall. Eur J Surg 164:951-960, 1998.
11. Klinge U, Conze J, Limberg W et al: [Pathophysiology of the abdominal wall]. Chirurg 67:229-233, 1996.
12. Cobb WS, Burns JM, Kercher KW, et al: Normal intra-abdominal pressure in healthy adults. J Surg Res 2005 (in press).
13. Junge K, Klinge U, Rosch R, et al: Functional and morphologic properties of a modified mesh for inguinal hernia repair. World J Surg 26:1472-1480, 2002.
14. Cobb WS, Burns JM, Peindl RD, et al: Textile analysis of heavyweight, midweight, and lightweight polypropylene mesh in a porcine ventral hernia. J Surg Res 121:306, 2004.
15. Langer C, Neufang T, Kley C, et al: Central mesh recurrence after incisional hernia repair with Marlex—are the meshes strong enough? Hernia 5:164-617, 2001.
16. Klinge U, Junge K, Stumpf M, et al: Functional and morphological evaluation of a low-weight, monofilament polypropylene mesh for hernia repair. J Biomed Mater Res 63:129-136, 2002.
17. Welty G, Klinge U, Klosterhalfen B, et al: Functional impairment and complaints following incisional hernia repair with different polypropylene meshes. Hernia 5:142, 2001.
18. Klinge U, Klosterhalfen B, Muller M, et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg 165:665-673, 1999.
19. Rosch R, Junge K, Schachtrupp A, et al: Mesh implants in hernia repair. Inflammatory cell response in a rat model. Eur Surg Res 35:161-166, 2003.
20. Cobb WS, Novitsky YW, Cristiano JA, et al: Biocompatibility of different weight polypropylene meshes in a porcine ventral hernia model. Submitted abstract. Am Coll Surg, 2005.
21. Klinge U, Klosterhalfen B, Birkenhauer V, et al: Impact of polymer pore size on the interface scar formation in a rat model. J Surg Res 103:208-214, 2002.
22. Heniford BT, Park A, Ramshaw BJ, et al: Laparoscopic repair of ventral hernias: nine years' experience with 850 consecutive hernias. Ann Surg 238:391-399, 2003.
23. Klinge U, Klosterhalfen B, Muller M, et al: Shrinking of polypropylene mesh in vivo: an experimental study in dogs. Eur J Surg 164:965-969, 1998.
24. Greca FH, de Paula JB, Biondo-Simoes ML, et al: The influence of differing pore sizes on the biocompatibility of two polypropylene meshes in the repair of abdominal defects. Experimental study in dogs. Hernia 5:59-64, 2001.

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ORIGINAL ARTICLE

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Influence of polyglecaprone 25 (Monocryl) supplementation on the biocompatibility of a polypropylene mesh for hernia repair

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Abstract Background: Supplementary polyglecaprone 25 (Monocryl) monofilaments were added to a lightweight pure monofilament polypropylene mesh (PP mesh) to improve intraoperative handling (PP + M mesh). This study was designed to evaluate the influence of this additional supplementation on the biocompatibility in a rodent animal model.Methods: Two mesh materials, a composite mesh (PP + M) and the pure polypropylene variant (PP), were compared after subcutaneous implantation in a standardized rat model. Histological analysis of the inflammatory response was performed after 28, 56 and 84 days of implantation. Material absorption, inflammatory tissue reaction, fibrosis and granuloma formation were investigated, as well as the percentage of proliferating and apoptotic cells at the interface.Results: Both mesh materials showed a slight foreign body reaction involving mainly macrophages and foreign body giant cells. Total absorption of the Monocryl filaments of the PP + M mesh occurred between 56 and 84 days of implantation. Both the inflammatory and the fibrotic reaction were decreased (n.s.) in the PP + M mesh group compared to the pure PP mesh. Whereas the percentage of proliferating cells showed no significant difference, the rate of apoptotic cells was significantly decreased in the PP + M mesh group over the whole implantation period.Conclusion: Compared to the pure polypropylene mesh, our data confirm that the use of a polypropylene mesh supplemented with absorbable Monocryl filaments is feasible without additional short-term mesh-related complications in the experimental model or negative side effects on biocompatibility.

Keywords Mesh · Polyglecaprone 25 · PolypropyleneBiocompatibility

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Introduction

Mesh materials for abdominal wall hernia repair are probably the most common biomaterials implanted in surgical medicine. Despite proven advantages regarding recurrence rates compared to primary tissue repair there are potential complications related to their implantation. Next to chronic pain and foreign body feeling, infection is the most common complication, occurring in up to 18% [1] of all cases. The development of reduced mesh implants that are adapted to the physiological requirements of the anterior abdominal wall has improved biocompatibility as well as patients' comfort [2, 3]. Compared to conventional heavyweight mesh materials, these so-called lightweight meshes were found to lower levels of prolonged pain and sensory loss [4]. Following Lichtenstein hernioplasty, Post et al. reported that the use of lightweight mesh was associated with significantly less pain on exercise after six months. In addition, fewer patients reported the feeling of a foreign body after repair with lightweight mesh (17.2 versus 43.8% with conventional mesh) [5]. These lightweight mesh materials are constructed as a composite, with a nonabsorbable

polypropylene part for a long-lasting augmentation of the anterior abdominal wall, and an absorbable multifilament polyglactin 910 part that aids surgical handling during operation. The absorbable polyglactin 910 part disappears completely three months after implantation, leaving slightly waved polypropylene filaments [6]. However, despite clinical advantages, there is still concern about the use of multifilaments with regard to possible infection through the interstices of the braided structure. Klinge et al. showed that the increased surface area of a multifilament mesh promotes the persistence of bacteria in the implant bed [7]. This might explain the development of mesh-related infections after a delay of several months or even years, favouring the use of monofilament materials.

Since more than one million mesh implants are performed per year worldwide, and because of the surgical challenge of infection treatment, further improvement of mesh materials seems beneficial. Therefore, a new monofilament lightweight composite mesh was constructed from nonabsorbable polypropylene monofilaments and supplemented with absorbable monofilament polyglecaprone 25 (Monocryl) threads. The aim of the present study was to analyse the influence of polyglecaprone 25 supplementation on the biocompatibility in vivo in a rodent animal model.

Materials and methods

Mesh materials

Two different mesh modifications were investigated. The basic prosthetic material used for the construction of all mesh samples was polypropylene (Ethicon, Norderstedt, Germany). The pure polypropylene mesh was manufactured as a large-pored warpknitted mesh construction with a honeycomb structure consisting of polypropylene monofilaments (PP, Fig. 1A). The composite mesh was constructed using the pure PP mesh, which was supplemented with monofilament USP 6-0 polyglecaprone 25 (Monocryl) threads (PP + M, UltraPro, Fig 2). Compared to the pure PP mesh (25.8 g.m^{-1}) the total amount of material of the PP + M mesh was therefore increased to 49.6 g m^{-1}.

Animal studies

30 male Sprague-Dawley rats (300–350 g) were housed under conditions of constant light and temperature, and received a complete diet of rat feed and water ad libidum throughout the entire study, which was performed according to the rules of the "Deutsche Tierschutzgesetz" and according to the NIH guidelines for the use of laboratory animals. The animals were randomly divided into two groups ($n = 15$ each), corresponding to the use of PP or PP + M mesh as implant.

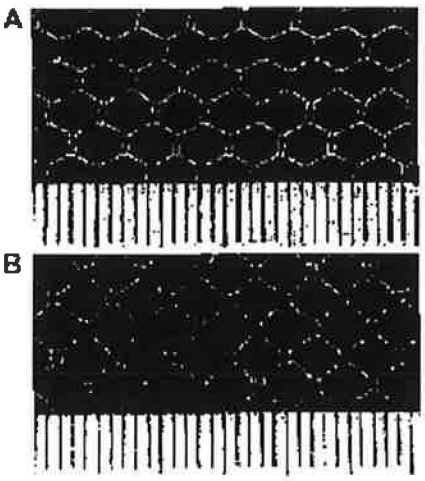

Fig. 1A–B Mesh structure of (A) the pure polypropylene (PP) mesh and (B) the PP mesh supplemented with USP 6-0 polyglecaprone 25 (Monocryl) threads (PP + M). One mark of scale is 1 mm

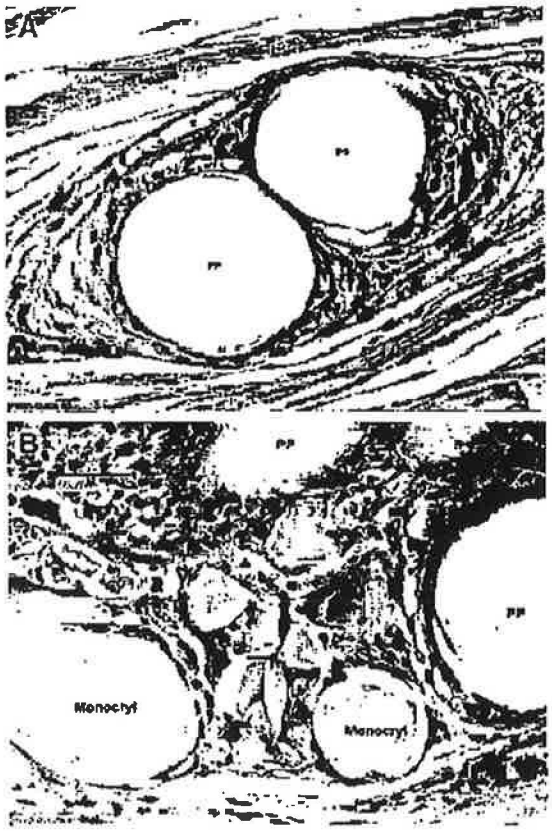

Fig. 2A–B Granuloma formation around the mesh filaments (H&E staining, magnification 400×) 90 days after implantation of (A) PP mesh, (B) PP + M mesh

Surgical procedure

Laboratory rats were anaesthetized (8 mg/100 g Ketamin, 0.8 mg/100 g Xylazin), and the back skin was freed of hair in the shoulder region using a shearing machine. The rats were brought into the prone position and fixed at their limbs on a table. The shorn surgical region was degreased using 70% IPA and disinfected using Kodan spray. The rats prepared in this way were then submitted to the operating surgeon on the operating table. The rat was covered with a sterile covering-cloth within which a small window in the implantation area was cut away. After two transverse incisions of ~25 mm in length ~40 mm apart, the subcutis was tunnelled under between the two incisions. The sterile mesh implant of 25×35 mm size was fixed in the subcutis between the two transverse incisions using single sutures of Prolene USP 4/0. Following fixation the skin was closed using Michel clamps. These were removed after the skin wound had healed up.

Observation periods

During postoperative husbandry the animals and particularly the wounds were inspected on a daily basis. Here, particular attention was paid to wound swelling and fluid accumulation (seroma formation) in the subcutis, and the clinical inspections were recorded.

Sectioning

Five animals from each group were sacrificed 28, 56 and 84 days after implantation, and the implantation zone was removed after skin resection. The preparation was mounted using pins on a carrier before it was fixed in formalin. During sectioning, the presence of a haematoma, seroma formation and the residual mesh area were evaluated and recorded in the sectioning protocol.

Histological analysis

Tissue specimens were fixed in 10% formaldehyde and embedded in paraffin. Histological investigation was performed on 3 µm sections after haematoxylin and eosin staining (H&E). All sections were processed at the same time to reduce internal staining variations. The amount of inflammatory and connective tissue formation was analysed semiquantitatively by measuring the diameters of the inner ring of the granuloma, which represents the inflammatory infiltrate, and the outer ring of the granuloma as a component of the fibrotic tissue reaction. After capturing five granulomas per sample with a digital camera (4/80z, Olympus C-3030, Hamburg, Germany) separate measurements of four quadrants of the inner and outer rings of the granulomas were performed with the help of digital image analysis software (Image-Pro Plus, Media Cybernetics, Silver Spring, MD, USA).

The perifilamentary percentages of proliferating and apoptotic cells were investigated following immunohistochemical staining as well as TUNEL histochemistry as described previously [8]. The percentage of macrophages was analysed immunohistochemically as an additional marker for the inflammatory process. The antibodies used in this study included monoclonal mouse anti-rat Ki67 (MIB5) for cell proliferation rate (1:30, Dako, Glostrup, Denmark) as well as monoclonal mouse anti-rat ED 1 for the selective staining of macrophages (1:250, DPC Biermann, Bad Nauheim, Germany). TUNEL histochemistry for apoptosis and DNA strand breaks was performed using an in situ apoptosis detection kit (ApopTag Peroxidase Kit, S7100, Intergen, Oxford, UK). After capturing 25 perifilamentary regions (100 µm×100 µm directly at the interface of the mesh with the host tissue) for each implantation period and mesh modification, percentages (%) of apoptotic as well as proliferating cells and macrophages from total cell numbers were measured with the help of a digital image analysis software (Image-Pro Plus). To further analyse the quality of the inflammatory process, the following immunohistochemical stainings were performed: T-cells (CD-3, monoclonal mouse anti-rat 1:20, DPC Biermann), granulocytes (CD-15, monoclonal mouse anti-rat, 1:10, DPC Biermann), and macrophages (CD-68, monoclonal mouse anti-rat, 1:250, DPC Biermann).

Statistics

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software. Data was organised according to mesh material and duration of implantation. Results for diameter measurements as well as percentages of proliferating and apoptotic cells were tested for significant differences using an independent *t*-test. *P* values < 0.05 were considered to be significant. All data are presented as means ± standard deviation.

Results

Macroscopic observations

Overall, macroscopic clinical observation after implantation of up to 84 days was uneventful. No infections were found; no animal died after the intervention. 28 days after implantation, three animals of the PP mesh group showed a small haematoma at the implantation site, while one animal of the PP + M mesh group showed the appearance of a seroma formation.

Shrinkage

28, 56 and 84 days after implantation, the PP mesh revealed residual areas of 86.4 ± 6.1%, 91.2 ± 6.6% and 80.6 ± 6.0 %, respectively. The PP + M mesh did not

show any reduction in area (100% residual area) 28 days after implantation, while after 56 and 84 days the area was reduced to 90.0 ± 7.7% and 88.0 ± 2.9%, respectively. Overall, no significant influence of Monocryl supplementation (PP + M mesh) was detected compared to the pure PP mesh.

Histological analysis

Both mesh modifications showed a slight inflammatory tissue reaction limited to the perifilamentary region, involving mainly macrophages and foreign body giant cells (Fig. 2). No degenerative calcifications were found. Just one localized bacterial microabscess was found in the PP mesh group after 84 days. The first signs of degradation of the Monocryl filaments were found 56 days after implantation, leading to complete absorption at the end of the observation period. To evaluate the extent of inflammation and fibrosis, the diameters of the granulomas at the perifilamentary interface were measured. The diameters of the inner granuloma rings, representing the inflammatory infiltrate, decreased over time (Fig. 3). Without being significant, the PP + M mesh showed lowered values of the inflammatory infiltrate at each investigating period compared to the pure PP mesh. The diameters of the outer rings of granulomas were investigated as an indicator of fibrosis. Represented by an overall decrease in the diameters, initial loose accumulation of fibroblasts matured and condensed to a nearby acellular collagenous framework. The connective tissue formed a small scar net surrounding the filaments of the mesh samples, with pores mainly filled with physiological fat tissue. Comparing both mesh modifications, supplementation of Monocryl filaments (PP + M mesh) was not found to induce significantly different levels of connective tissue formation. Cell proliferation rates, as assessed by immunohistochemical staining for Ki67 positivity, revealed nearly constant values over time, with slightly higher proliferation rates for the PP + M mesh (Fig. 4). The percentage of apoptotic cells assessed by TUNEL staining (Fig. 5) showed a constant decrease over time in both groups. Interestingly, in contrast to the higher numbers of proliferating cells in the PP + M mesh group, significantly more apoptotic cells were found in the pure PP mesh group. The significant difference decreased but could still be noted 84 days after implantation.

Discussion

Polyglactin 910 is a 90:10 copolymer of glycolide and lactide. Monofilaments from these polymers are relatively stiff, and therefore braided multifilament threads are mainly used to supplement nonabsorbable lightweight mesh materials for hernia repair. Monocryl (polyglecaprone 25) is a monofilament derived from a

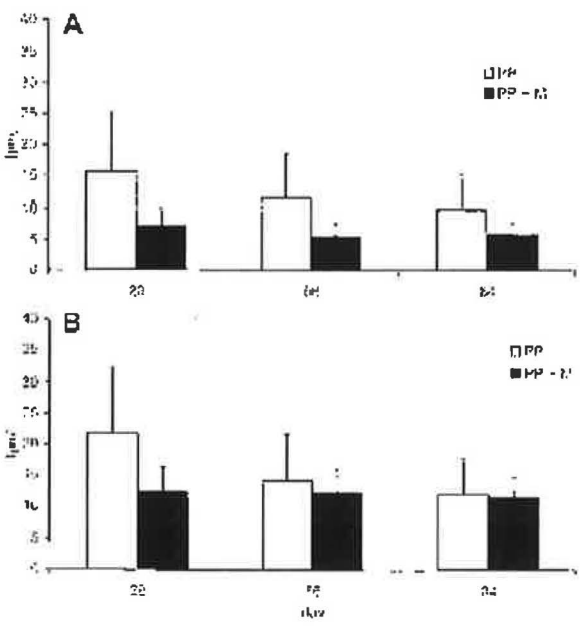

Fig. 3 A Diameter of the inner granuloma ring (µm) indicating the amount of inflammatory tissue. B Diameter of the outer granuloma ring (µm) after implantation of the PP and PP + M mesh, indicating the amount of connective tissue formation. Data are given as means ± SD (significant differences are marked; * indicates $p < 0.05$)

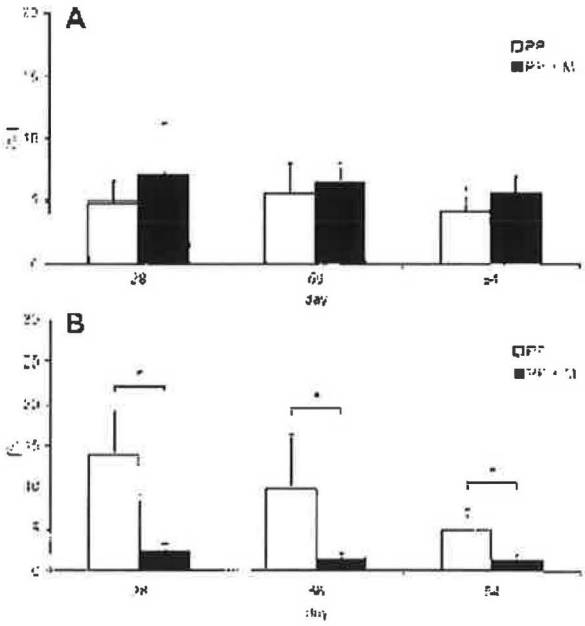

Fig. 4 A, B Percentage of (A) proliferating cells and (B) apoptotic cells after implantation of the PP mesh and the PP + M mesh at the interface of the mesh with the host tissue (400 or 200 µm). Data are given as means ± SD (significant differences are marked; * indicates $p < 0.05$)

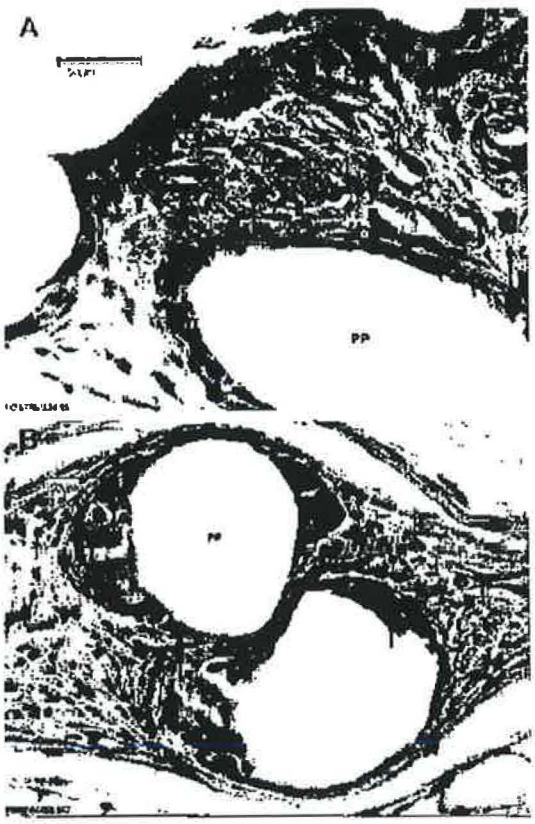

Fig. 5A, B Immunohistochemical staining of apoptotic cells (*arrows*) around the mesh filaments (TUNEL, magnification 400×) 84 days after implantation of (A) the PP mesh and (B) the PP + M mesh

segmented copolymer of ε-caprolactone and glycolide [9]. This complex polymeric system contains soft segments of a random copolymer of ε-caprolactone and glycolide, which provides good handling characteristics, and hard segments of polyglycolide, which provide high strength. Both hard and soft segments are combined in the same polymeric chain. Upon evaluating the toxicity potential of the Monocryl sutures, no genotoxic, cytotoxic, teratogenic, irritating or allergic effects were found [9]. Since being introduced as suture material in 1995 [9] it has showed many advantageous qualities, including a significantly lowered tissue reaction in the early phases of wound healing compared to polyglactin 910 [10, 11, 12, 13].

Although it has been used in surgery for many years now, before this it has never been used for the construction of surgical meshes. We therefore tested a mesh modification constructed from polypropylene monofilaments supplemented with absorbable monofilament polyglecaprone 25 (Monocryl) threads (PP + M mesh) and investigated its histological characteristics compared to a pure polypropylene mesh without any supplementation (PP mesh) in a standardized rat model.

Overall, both mesh materials showed an uneventful macroscopic postoperative course. Shrinkage of mesh implants due to wound contraction was found to be within the ranges observed in other studies [14, 15]. Histological examination revealed the induction of a slight granulomatous chronic foreign body reaction involving at most macrophages and foreign body giant cells. The absorbable polyglecaprone 25 (Monocryl) filaments were essentially degraded 84 days after implantation. This is in agreement with the findings of Bezwada et al., who found a complete absorption of ^{14}C-labelled Monocryl sutures 14 weeks after subcutaneous implantation [9]. Interestingly, in contrast to polyglactin 910, the supplementation of Monocryl filaments did not increase the initial amount of inflammatory and connective tissue reaction, as seen for other composite mesh materials [16]. Furthermore, compared to the pure PP mesh, the PP + M mesh group showed lowered levels of the inflammatory as well as connective tissue part of the chronic foreign body reaction and a significantly reduced percentage of apoptotic cells at the end of the implantation period. Only the proliferation rate, as investigated by Ki67 positivity, was found to be somewhat increased compared to the pure PP mesh.

Summarizing, our data confirm that the use of a polypropylene mesh supplemented with absorbable Monocryl filaments is feasible, with no additional short-term mesh related complications in the experimental model and no negative side effects on biocompatibility. The results from the present investigation showed that this new lightweight mesh modification could be advantageous for optimised hernia repair using monofilamentous materials. However, animal experiments, particularly rodent animal models, have their natural limitations, and results cannot be extrapolated directly to the situation in humans. Furthermore, beneficial effects of this monofilament composite mesh variant compared to conventional mesh materials in regard to the infection rate should be clarified in further prospective randomised trials in humans.

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References

1. Ries A, Rodriguez JM, Minambres V, Alcaraz P, Perez LD, Parrilla P (2001) Antibiotic prophylaxis in mesonomic hernia repair using a prosthesis. Hernia 5:148–152
2. Klinge U, Klosterhalfen B, Conze J, Limberg W, Obolenski B, Ottinger AP, Schumpelick V (1998) Modified mesh for hernia repair that is adapted to the physiology of the abdominal wall. Eur J Surg 164:951–960
3. Schumpelick V, Klosterhalfen B, Muller M, Klinge U (1999) Monocryl polypropylene mesh for preperitoneal net plasty (PNP) of incisional hernias. Chirurg 70:422–430
4. Bringman S, Heikkinen TJ, Wollert S, Osterberg J, Smedberg S, Granlund H, Rauste S, Eriksson G, Anderberg B (2004) Early results of a single-blinded, randomized, controlled, Internet-based multicenter trial comparing Prolene and Vypro II mesh in Lichtenstein hernioplasty. Hernia 8:127–134

5 Post S, Weiss B, Willer M, Neufang T, Lorenz D (2004) Randomized clinical trial of lightweight composite mesh for Lichtenstein inguinal hernia repair. Br J Surg 91:44–48
6. Klinge U, Klosterhalfen B, Müller M, Anurov M, Ottinger A, Schumpelick V (1999) Influence of polyglactin-coating on functional and morphological parameters of polypropylene mesh modifications for abdominal wall repair. Biomaterials 20:613–623
7 Klinge U, Junge K, Spelzenberg B, Piroth C, Klosterhalfen B, Schumpelick V (2002) Do multifilament alloplastic meshes increase the infection rate? Analysis of the polymeric surface, the bacteria adherence, and the in vivo consequences in a rat model. J Biomed Mater Res 63:765–771
8 Junge K, Klinge U, Rosch R, Klosterhalfen B, Schumpelick V (2002) Functional and morphologic properties of a modified mesh for inguinal hernia repair. Worse J Surg 26:1472–1480
9. Bezwada RS, Jamiolkowski DD, Lee IY, Agarwal V, Persivale J, Trenka-Benthin S, Erneta M, Suryadevara J, Yang A, Liu S (1995) Monocryl suture, a new ultra-pliable absorbable monofilament suture. Biomaterials 16:1141–1148
10. LaBagnara J Jr (1995) A review of absorbable suture materials in head & neck surgery and introduction of monocryl: a new absorbable suture. Ear Nose Throat J 74:409–412
11 Kirpensteijn J, Muirchalkerweerd RJ, Kwaram JP, Kooistra HS, van Sluijs FJ (1997) Comparison of two suture materials for intradermal skin closure in dogs. Vet Quart 19:20–22
12 Niessen FB, Spauwen PH, Kon M (1997) The role of suture material in hypertrophic scar formation: Monocryl vs. Vicryl-rapide. Ann Plas Surg 39:254–260
13. Nery EB, Matsumoto MA, Batista AC, Lopes LC, de Goes FC, Consolaro A (2002) Comparative study of tissue response to polyglecaprone 25, polyglactin 910 and polytetrafluoroethylene suture materials in rats. Braz Dent J 13:86–91
14 Scheidbach H, Tamme C, Tannapfel A, Lippert H, Kockerling F (2004) In vivo studies comparing the biocompatibility of various polypropylene meshes and their handling properties during endoscopic total extraperitoneal (TEP) patchplasty: an experimental study in pigs. Surg Endosc 18:211–220
15. Coda A, Bendavid R, Botto-Micca F, Bessoni M, Bona A (2003) Structural alterations of prosthetic meshes in humans. Hernia 7:29–34
16. Rosch R, Junge K, Quester R, Klinge L, Klosterhalfen B, Schumpelick V (2003) Vypro II mesh in hernia repair: impact of polyglactin on long-term incorporation in rats. Eur Surg Res 35:145–150

The lightweight and large porous mesh concept for hernia repair

Bernd Klosterhalfen†, Karsten Junge and Uwe Klinge

In modern hernia surgery, there are two competing mesh concepts which often lead to controversial discussions, on the one hand the heavyweight small porous model and on the other, the lightweight large porous hypothesis. The present review illustrates the rationale of both mesh concepts and compares experimental data with the first clinical data available. In summary, the lightweight and large porous mesh philosophy takes into consideration all of the recent data regarding physiology and mechanics of the abdominal wall and inguinal region. Furthermore, the new mesh concept reveals an optimized foreign body reaction based on reduced amounts of mesh material and, in particular, a significantly decreased surface area in contact with the recipient host tissues by the large porous model. Finally, recent data demonstrate that alterations in the extracellular matrix of hernia patients play a crucial role in the development of hernia recurrence. In particular, long-term recurrences months or years after surgery and implantation of mesh can be explained by the extracellular matrix hypothesis. However, if the altered extracellular matrix proves to be the weak area, the decisive question is whether the amount of material as well as mechanical and tensile strength of the surgical mesh are really of significant importance for the development of recurrent hernia. All experimental evidence and first clinical data indicate the superiority of the lightweight and large porous mesh concept with regard to a reduced number of long-term complications and particularly, increased comfort and quality of life after hernia repair.

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KEYWORDS:
foreign body reaction, heavyweight, hernia repair, lightweight, long-term complications, pores, surgical mesh

Surgical meshes today represent a group of implants used mainly for hernia repair. Modern hernia surgery is no longer imaginable without the application of these special biomaterials, leading to about 1 million implantations each year, worldwide. The net-like alloplastic mesh is used to close the hernial gap and, with extended overlap, to reinforce the abdominal wall.

Since the introduction of surgical meshes for hernia repair in 1959 by Usher [1–3], the main interest of hernia surgeons in the past decades was focused on surgical techniques to optimize hernia repair and the application of the mesh [4–8]. The surgical mesh itself, however, seemed to have little impact on the clinical outcome after hernia repair. The meshes themselves were regarded as biologically inert.

The trend changed in the early and mid 1990s in parallel with increasing numbers of case reports reporting mesh-related complications after heavy mesh-based hernia repair [9–12]. Today, minor local complaints such as seromas, discomfort and decreased abdominal wall mobility are accepted to be frequent and can be observed in about half of the patients. Serious complications such as recurrence, chronic and persisting pain as well as infection, including fistula formation are rare, but sometimes force a surgeon to remove the surgical mesh. Nevertheless, these complications have been the rationale to examine the role of the mesh in hernia repair in detail and to begin to investigate the biocompatibility of different mesh modifications and to challenge old mesh concepts. As a consequence, knowledge

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regarding the biocompatibility of different surgical mesh modifications has dramatically increased in the last 10 years since 1995, based on numerous experimental studies and clinical observations. Two basic problems had to be solved; first, to learn more about the physiology and the mechanics of the abdominal wall to be able to define basic elements of the textile structure and, second, to understand the significance of the mesh construction itself for the integration of the mesh into the recipient tissues after implantation.

As a consequence, today two major mesh concepts are distinguished, the classical concept including so-called heavyweight meshes with small pores and the new concept including lightweight meshes with large pores. Typically, the new mesh generation is characterized by a reduced weight (depending on the specific weight of the basic polymer), a pore size of more than 1 mm, an elasticity of 20–35% (at 16 N/cm) and a physiologic tensile strength of 16 N/cm at minimum.

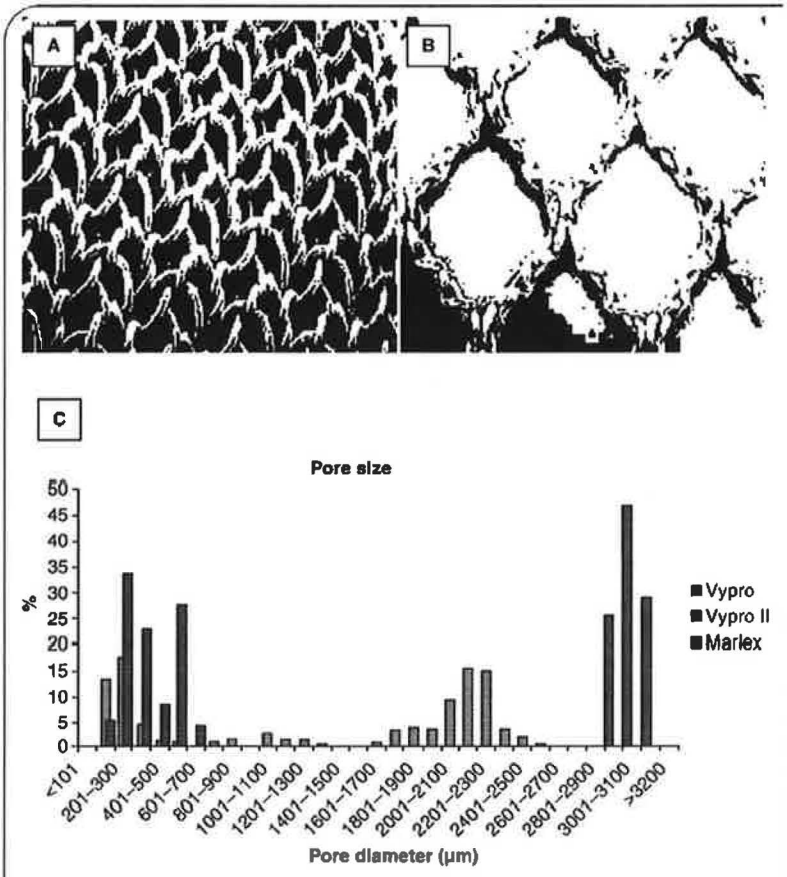

Figure 1. Typical textile structure of the heavyweight small porous mesh Marlex® (A) and the lightweight large porous mesh Vypro® **(B)** in scanning electron microscopy (127x). **(C)** Pore size analysis of Vypro, Vyproll® and Marlex; Vypro exhibits pore sizes between 3 and 5 mm (before absorption of the Vicryl® part), Vyproll between 1 and 2.5 mm (again before absorption of the Vicryl part) and Marlex between 0.2 and 0.7 mm.

Textile & mechanical features of heavy- & lightweight meshes

Small and large porous heavy- and lightweight mesh modifications both represent a totally different pathophysiologic view and concept of hernia repair (FIGURE 1, TABLE 1). Heavyweight meshes have been designed to guarantee a maximum mechanical stability, based on the idea of closing the hernial gap with a stiff, nonflexible device inducing maximum scar tissue [13,14]. In this concept the mesh itself and intense scar tissue formation ensure a durable and resistant repair of the hernia. Accordingly, meshes in the heavyweight group are designed with thick polymer fibers, small pores (<1 mm), a high tensile strength and a large surface area (FIGURE 1A).

In contrast, lightweight meshes are designed to mimic the physiology of the abdominal wall and the inguinal region [15,16]. Meshes in this group are produced with small polymer fibers, large pores (>1 mm) and a high flexibility (FIGURE 1B). The tensile strength is adapted to that of local tissues and the surface area in contact with the host tissues is low. A welcome and major side effect of the sensitive mechanical adoption of these meshes to the abdominal wall is a significant reduction of scar tissue formation resulting in a long-term flexible repair [16-18].

Heavyweight meshes with small pores versus lightweight meshes with large pores

The question of what is the ideal mesh for hernia repair, at the very beginning of the development of the lightweight meshes, led to the following specification: the ideal mesh should; restore the abdominal function, be integrated physiologically into the abdominal wall based on a maximum of biocompatibility, be without serious long-term complications such as recurrence, infection or chronic pain and finally, have optimal handling characteristics for an easy, comfortable and safe hernia repair.

The restoration of abdominal wall function

The abdominal wall and the inguinal region, both main areas for hernia development, are complex systems of fascias and muscles. The whole system reveals certain rates of flexibility in different anatomic directions, which could be measured from autopsy specimens (FIGURE 2A). In order to define the physiologic requirements regarding elasticity, it could be shown that the mean distension at a physiologic strain of 16 N, ranges between 11 and 32% [19,20]. Textile analysis of heavyweight meshes revealed an elasticity of only 4–16% at 16 N (FIGURE 3, TABLE 2). Therefore, a restriction

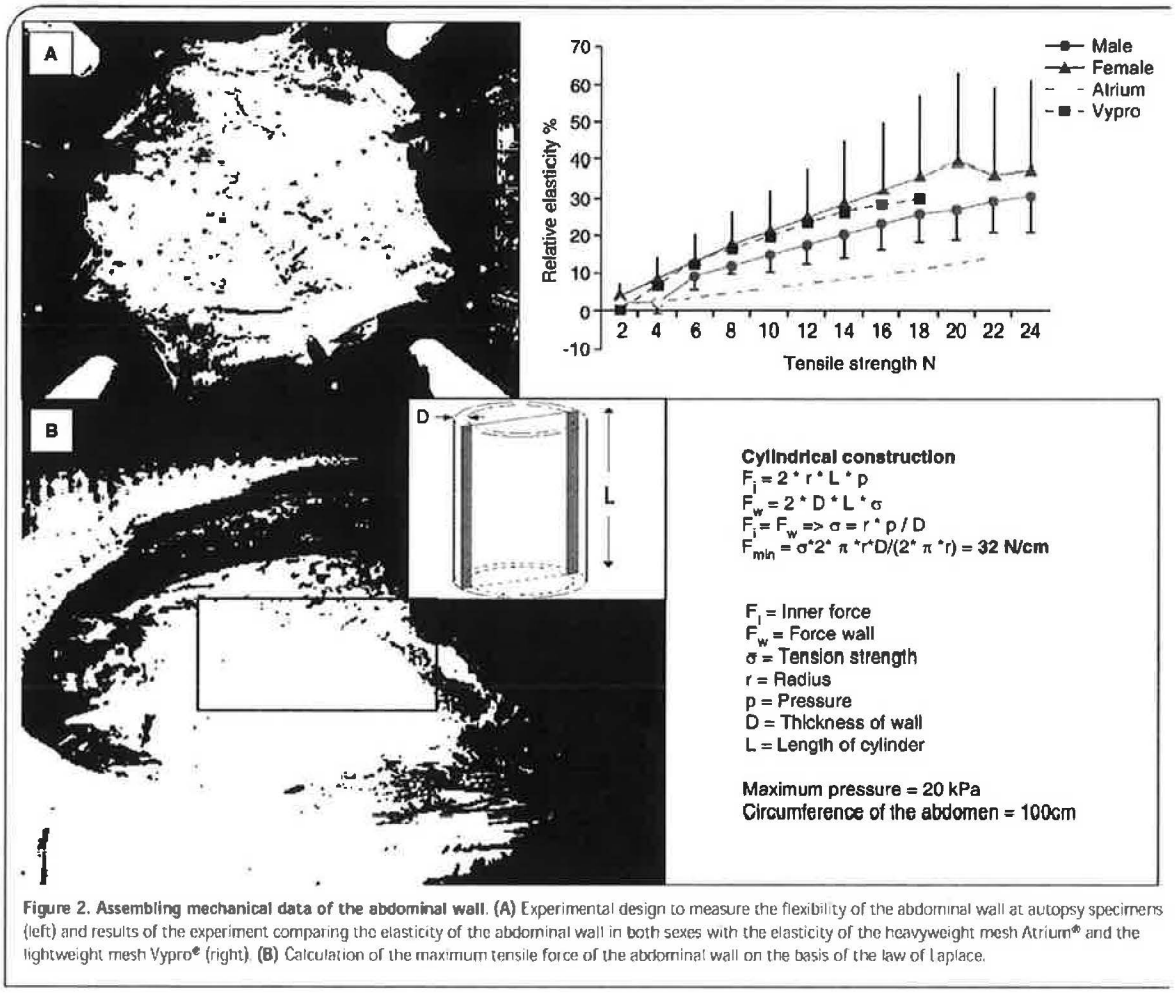

Figure 2. Assembling mechanical data of the abdominal wall. (A) Experimental design to measure the flexibility of the abdominal wall at autopsy specimens (left) and results of the experiment comparing the elasticity of the abdominal wall in both sexes with the elasticity of the heavyweight mesh Atrium® and the lightweight mesh Vypro® (right). **(B)** Calculation of the maximum tensile force of the abdominal wall on the basis of the law of Laplace.

of the abdominal wall is one consequence of the implantation of heavyweight meshes with low elasticity rates [16]. Flexible lightweight mesh constructions with similar elasticity to the abdominal wall demonstrate their superiority with respect to a physiologic abdominal wall repair [21].

After the introduction of the first lightweight mesh (Vypro®) to the German market, one main argument against the mesh appeared to be the significantly lower tensile strength compared with common heavyweight meshes. However, based on the law of Laplace, the tensile strength of surgical meshes for abdominal wall replacement in large hernias (where the mesh has to replace all structures of the abdominal wall and the fascia cannot be closed) is theoretically 32 N/cm at maximum (FIGURE 2B). In abdominal wall augmentation in small hernias (where the fascia can be closed), the tensile strength of the mesh can be reduced to 16 N/cm [19,22,23]. Tensile strengths of more than 100 N/cm of conventional heavyweight meshes are therefore disproportional and not required for an effective fascia closure or augmentation and lead to low flexibility with a subsequent restriction of the abdominal wall and discomfort of the patient (TABLE 2, FIGURE 3) [24,25]. Furthermore, the stiffness of heavyweight and small porous meshes may result in central mesh ruptures [26].

Integration into the abdominal wall: biocompatibility

Modern biomaterials including polymers are physically and chemically inert and stable, nonimmunogenic and nontoxic. However, not all these materials are biologically inert. In contradiction to their physical and chemical stability, the biomaterials trigger a wide variety of adverse responses *in vivo* including inflammation, fibrosis, calcification, thrombosis or infection. The quality of the inflammatory reaction to foreign bodies of a different nature is surprisingly constant, characterized by a rapid accumulation of huge numbers of phagocytic cells, in particular, blood monocytes and tissue-derived macrophages [27,28].

Today, it is not fully clear why inert and nonimmunogenic materials induce this type of inflammation known as a foreign body reaction (FBR). However, the protein absorption theory is

Table 1. A small selection of currently available heavyweight small porous, and lightweight large porous meshes.

Mesh	Producer	Polymer	Fiber
Heavyweight/small pores			
Marlex®	Bard, Inc., USA	PP	Mono
Prolene®	Ethicon, Inc., USA	PP	Mono
Atrium®	Atrium Med. Corp., USA	PP	Mono
Lightweight/Large Pores			
Vypro®	Ethicon GmbH, Germany	PP/PG910	Multi
UltraPro®	Ethicon GmbH, Germany	PP/Monocryl	Mono
TiMesh®	GFE, Germany	PP/Ti	Mono
Others			
DualMesh®	Gore, USA	ePTFE	Foil
Mersilene®	Ethicon, Inc., USA	PET	Multi

Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PP: Polypropylene.

widely accepted in biomaterial research and illustrates an underlying pathophysiologic process responsible for this typical type of chronic inflammation. The aim of this process is to isolate the foreign body or biomaterial from the host tissues by forming an artificial outside world at the site of implantation. The same mechanism is true in tuberculosis for example, here again the host is not able to remove the inflammatory agent namely *Mycobacterium tuberculosis*. The reaction is typical as well as relatively uniform with the formation of granuloma, which is generally found at the interface of implanted biomaterials as well. Characteristic of these granuloma are multinucleated giant cells that originate from fused macrophages and monocytes seeding on the foreign body–recipient host tissues interface [29].

Implant materials very quickly absorb a layer of host proteins after implantation – in a process lasting a few seconds, which occurs well before an initial cellular response to the biomaterial can be observed. It is generally believed that phagocytes interact with these spontaneously absorbed proteins rather than with the material itself. Immunologic activity from degraded proteins, secondary to their absorption of the biomaterial surface, triggers the activation of the attached phagocytes [27]. Depending on the physicochemical properties of the surface area of the implant and the type of absorbed proteins, the rate of protein degradation should be variable and, therefore generates a typical FBR for each type of implant. In particular, fibrinogen and fibrinogen-derived products beside albumin should play a major pathophysiologic role in the occurrence of FBR [28].

Finally, phagocytes may recognize the degradated proteins of the medical implants and respond by releasing a series of inflammatory and wound-healing responses commonly initiated by fibrin clot formation. The initial inflammatory burst caused by the release of a huge cocktail of potent inflammatory mediators attract other cell types including T-cells, polymorphonuclear and

Table 2. Textile and mechanical data of selected heavyweight (Prolene®) and lightweight (Vypro®, Vyproll® and UltraPro®) meshes.

Mesh	Structure	Polymer	Weight	Suture pull out force		Stamp pressure test	
			(g/m²)	*Longitudinal (N)*	*Vertical(N)*	*Burst pressure P max (mmHg)*	*% Stretching at 16 N/cm tension (%)*
Prolene®	Mono + SP	PP	80–85	116	145	1630	6
Vypro®	Multi + LP	PP§	25*	30	24	360	31
Vypro II®	Multi + LP	PP§	30*	40	31	430	28
UltraPro®	Mono + LP	PP§	28*	42	42	650	25

Note the significantly reduced stretching rate of Prolene® at 16 N/cm and the significantly increased burst pressure of the heavyweight mesh compared with all the lightweight meshes included. (Data provided by Ethicon GmbH, Norderstedt, Germany). *Remaining nonabsorbable part of PP. LP: Large pores; Mono: Monofilament; Multi: Multifilament; PP: Polypropylene; SP: Small pores.

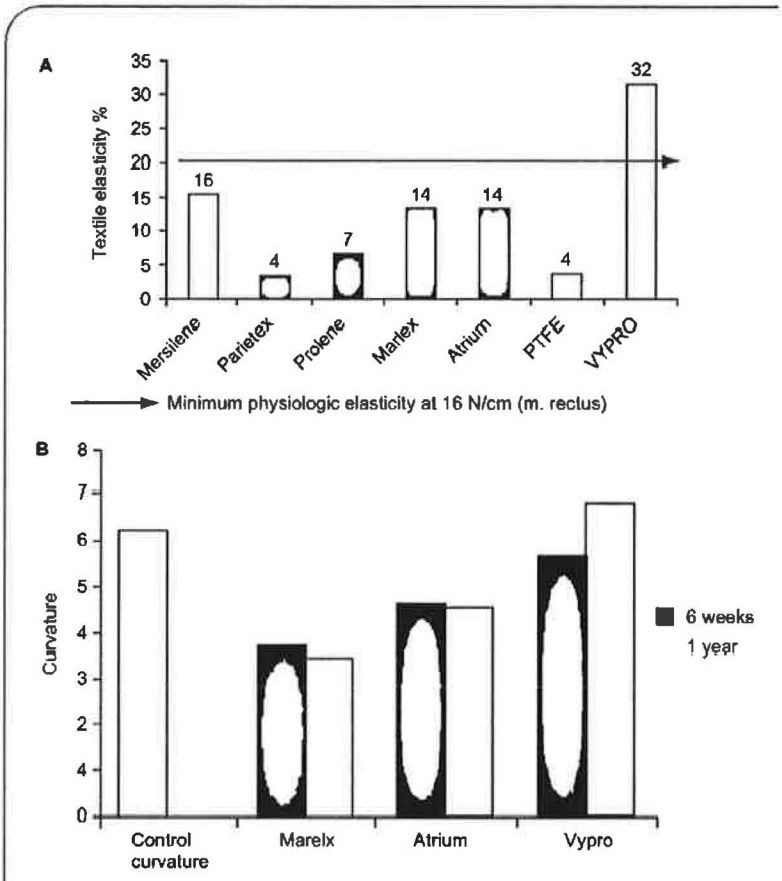

Figure 3. Textile elasticity of various mesh modifications (A) and abdominal wall restriction after mesh implantation (B). The abdominal wall indicates a reduced curvature during pressing after incisional hernia repair with both heavyweight small porous meshes Marlex® and Atrium®, whereas the abdominal wall remains flexible after Vypro® implantation.

eosinophilic granulocytes, plasma cells and fibrocytes [30]. Within a few days this cell cocktail forms the early granuloma with a characteristic stratification of cell layers which can also be identified during maturation recognized by the very typical foreign body giant cells and an outer layer of fibrosis (last stage of inflammation). Moreover, late granuloma is not a static type of chronic inflammation, but represents a chronic wound with an increased cell turnover even years after implantation [31,32]. Monocytes and tissue-derived macrophages at the interface and in contact with the polymer, undergo apoptotic cell death and are replaced by cells at the periphery.

Before the introduction of the lightweight large pore meshes, biocompatibility of meshes has generally been regarded as excellent. The fact that meshes induce a tissue response unfavorable for the outcome of the hernia repair has not been under discussion. Surgical mesh has been regarded as inert and biocompatible.

However, if the foregoing chapters on FBR are correct, surgical meshes should also show the typical inflammatory reaction. In fact, all experimental and clinical studies indicate a typical FBR at the interface of all mesh modifications on the market today [32].

The main polymers for the production of surgical meshes are polypropylene (PP), polyester (polyethylene-terephthalat [PET]) and expanded poly-tetra-fluoroethylene (ePTFE); all of which are nonabsorbable.

Mesh modifications made of PP are frequently used, the majority with small pores. Generally, PP is stable, nondegradable and with an acceptable biocompatibility resulting in a moderate chronic inflammation of the foreign body type with an intense fibrosis. PET histologically reveals an excellent biocompatibility with a decreased FBR compared with PP, however, the long-term stability PET is rather low due to hydrolytically splitting of the polymer. The rate of degradation of PET mesh modifications and its influence on the outcome of hernia repair remains unclear. In contrast to PP and PET, ePTFE again histologically indicates a good biocompatibility. Tissue integration of these patches depends on the microporous modification of one patch surface. Rarely, small particles of ePTFE are detached from the surface (in particular in mesh infection [33]), which may then be found phagocytized in macrophages colonizing the interface.

Due to the disadvantages of PET and ePTFE, today, most of the new mesh modifications are composed of PP. Special mesh modifications are hybrid meshes with an absorbable and nonabsorbable part made of Vicryl® (polyglactine 910) or Monocryl® (polyglecaprone 25). An upcoming new polymer PVDF (polyvinylidenflourid) demonstrates promising results in experimental animal studies [34–38].

However, the FBR depends not only on the polymer, but also the surface area in contact with the host tissues. The surface area again strongly depends on textile properties such as the pore size or the diameter and number of fibers used. The lightweight and large pore size meshes have less surface area than the heavyweight mesh group, consequently, the FBR in the lightweight mesh group is significantly reduced [39]. In addition to this significantly decreased typical chronic inflammatory reaction, the fibrotic reaction around the mesh in total as well as around each single mesh fiber is greatly reduced (FIGURE 4). The fibrotic reaction as a result of the inflammatory response, however, considerably influences the long-term quality of the hernia repair. Today the tissue response to the mesh is understood as a chronic wound persisting over many years at the interface of the

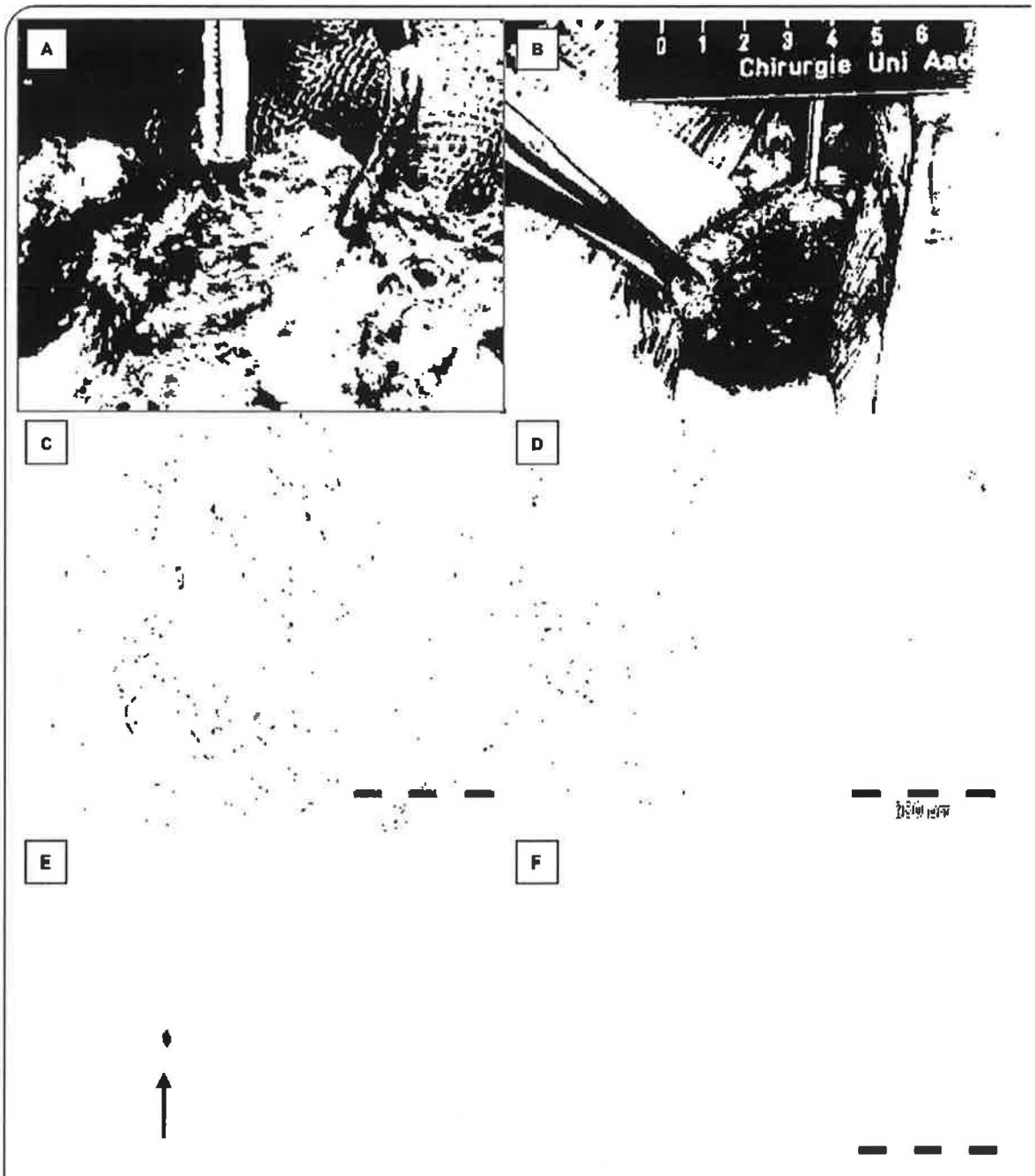

Figure 4. Macroscopical aspect after long-term implantation of a lightweight polypropylene mesh with large pores **(A)** and a heavyweight mesh with small pores **(B)**; note the thin fibrous layer around the lightweight mesh **(A)** all structures of the mesh are still visible. In some cases lightweight meshes with large pores are hardly to identify during relaparatomy, an observation leading to the idiom invisible mesh. In parallel, a specimen of a heavyweight mesh with small pores after long-term implantation **(B)** representing a fibrous mass composed of mesh and recipient tissue due to the increased fibrotic reaction. Typical histological response on lightweight **(C)** and heavyweight **(D)** Polypropylene meshes; note the significantly improved biologic response on the lightweight PP mesh with a significantly decreased chronic inflammation and fibrosis around the polymer fibers (both hematoxylin and eosin, 200×). Comparison of the fibrotic reaction after implantation of mesh modifications with small **(E)** and large pores **(F)**; note that the pores in **(E)** are filled with fibrous tissue skipping from one PP fiber to the next, a phenomenon called bridging; in **(F)** without bridging the mesh pores are filled with fat (both hematoxylin and eosin, 40×).

Table 3. Results of the postretrieval study including 347 explanted mesh specimens [23]; the total number of each mesh was set at 100%; percentage of major complications of each mesh modification leading to explantation of the mesh.

Mesh	Polymer	Features	Fibers	No.	Months	Recurrence (%)	Chronic pain (%)	Infection (%)	Fistula (%)
Mersilene®	PET	LW/SP	Multi	31	28	65	13	26	4
Marlex®	PP	HW/SP	Mono	90	26	57	34	22	8
Prolene®	PP	HW/SP	Mono	90	26	57	40	22	6
Atrium®	PP	HW/SP	Mono	64	20	67	33	17	9
Surgipro®	PP	HW/SP	Multi	17	24	70	35	17	9
Vypro®	PP/PG	LW/LP	Multi	34	15	82	6	12	0
GoreTex®	ePTFE	HW/SP		21	33	57	19	24	0
Total				*347*	*24*	*63*	*30*	*21*	*7*

ePTFE: Expanded poly-tetra-fluoroethylene; HW: Heavyweight; LP: Large pores; LW: Lightweight; Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PG: Polyglactine; PP: Polypropylene; SP: Small pores.

mesh and recipient tissues. In western countries there is increasing acceptance that the activity of this chronic wound should be diminished to the minimum where possible.

Long-term biocompatibility of surgical mesh: complications

Our knowledge concerning the long-term biocompatibility and tissue response of mesh in humans is still poor, although a few reports exist (FIGURE 5, TABLES 3 & 4). Nearly all of the data regarding the biologic behavior of these implants are obtained from animal experiments.

Postretrieval studies of implants allow the possibility to gain a deeper insight into the local tissue reaction after longer implantation intervals and to get an idea of the main complications of each implant type. Serious complications such as recurrence, chronic and persisting pain as well as infection (including fistula formation), are rare, but sometimes force the surgeon to remove a surgical mesh.

Since 1995 the authors have collected explanted meshes, which failed in hernia repair. Meanwhile, the authors' center has more than 700 explants of different meshes on record and has already analyzed more than 300. The results of the study are quite similar to data published in 2000 as a preliminary report with 121 specimens [32].

Briefly, the data demonstrate that heavyweight small porous meshes have to be explanted due to chronic pain more frequently than lightweight large porous meshes (e.g., 40% Prolene® vs. 6% Vypro). Fistula formation is only observed in the heavyweight mesh group. Recurrences can be observed in all mesh modification independently from the mesh construction. After a mean implantation interval of more than 26 months, 99% of all recurrences occurred at the edges and free margins of the mesh. Over 70% of all specimens explanted after recurrence revealed an altered ratio of collagen Types I and III [23], an observation which supports the hypothesis of ECM alterations as a major pathophysiologic reason of hernia recurrence. Furthermore, the data pool of the retrieval study demonstrates that the reaction of different hosts is highly different and individual. These data reflect that the individual reaction of the patient onto an implanted mesh depends on the genetic background of each host [40].

Table 4. Results of the postretrieval study including 347 explanted mesh specimens [23]; the total number of each mesh was set at 100%; biocompatibility assessment of each mesh modification after long-term implantation.

Mesh	Polymer	Features	Fibers	No.	Months	IF (PV %)	CT (PV %)	Ki67 (%)	Tunel (%)
Marlex®	PP	HW/SP	Mono	90	26	36	41	22	9
Prolene®	PP	HW/SP	Mono	90	26	30	31	19	7
Atrium®	PP	HW/SP	Mono	64	20	26	27	13	7
Surgipro®	PP	HW/SP	Multi	17	24	41	39	25	9
Vypro®	PP/PG	LW/LP	Multi	34	15	16	21	7	3
Total	-	-	-	*295*	*22*	*30*	*32*	*17*	*7*

CT: Connective tissue formation; ePTFE: Expanded poly-tetra-fluoroethylene; HW: Heavyweight; IF: Inflammatory infiltrate; Ki67: Ki67 positive, proliferating cells in the interface mesh/recipient tissues; LP: Large pores; LW: Lightweight; Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PG: Polyglactine; PP: Polypropylene; SP: Small pores; Tunel: Tunel-positive, apoptotic cells in the interface mesh/recipient tissues.

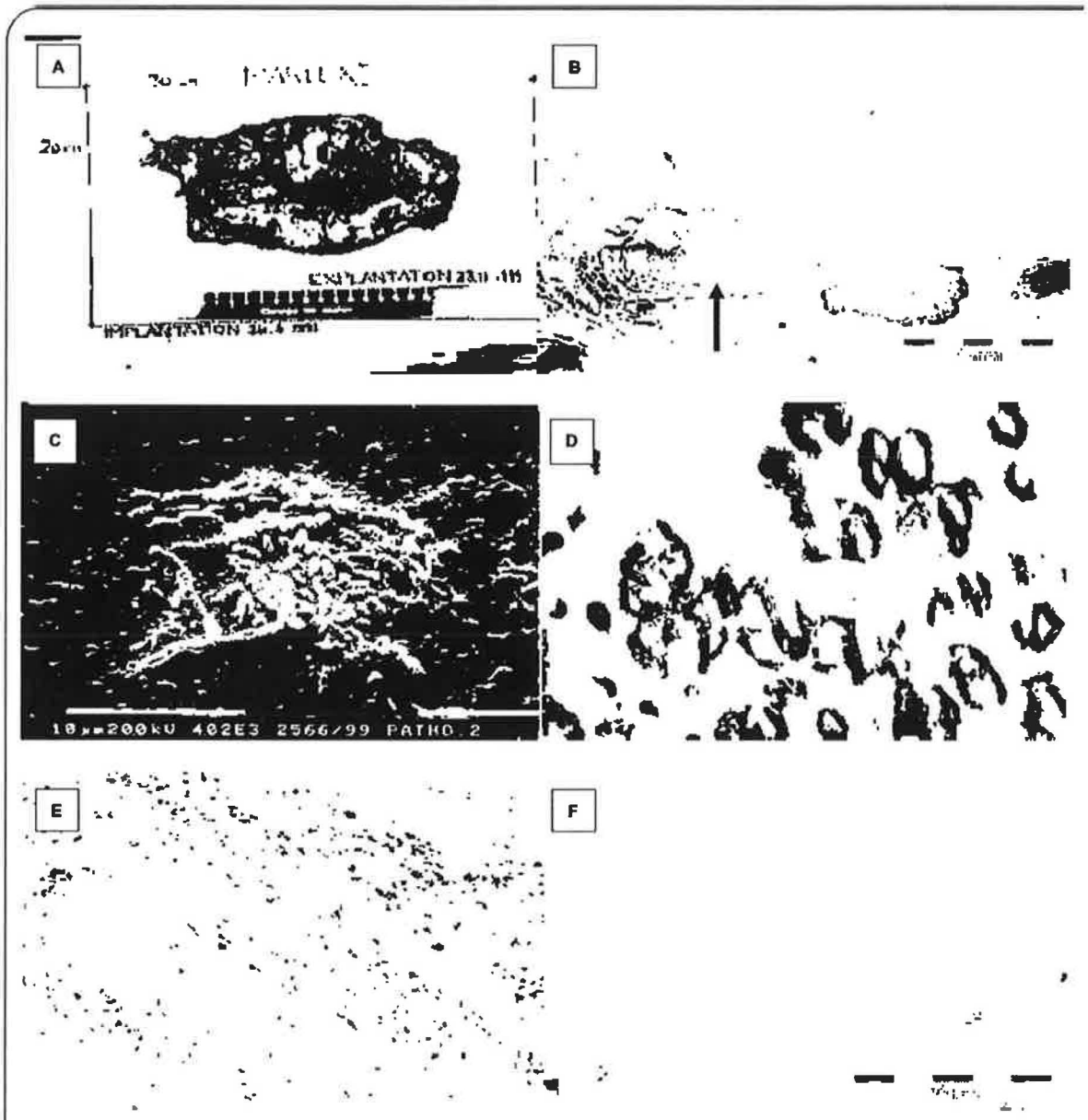

Figure 5. (A) Example of mesh shrinkage after long-term implantation. The mesh surface area was reduced from 20 × 30 cm to 10 × 20 cm after an implantation period of approximately 8 years; it is not the mesh itself undergoing the process of shrinkage, the phenomenon is a result of contracting scar tissues around the mesh. **(B)** Chronic pain in the majority of cases is the result of nerve impairment during implantation, in particular, by clips during fixation or by the mesh itself; in the authors' postretrieval study the involvement of nerve fibers was found in more than 60% of all mesh specimens removed due to chronic pain; in the given example, the mesh traumatically disturbed the nerve, finally forming a post-traumatic neuroma (arrow; S100, 40×). **(C)** Scanning electron micrograph (4020×) indicating a major reason for late mesh infection: persisting bacteria of the staphylococcus family; in the actual example, the mesh was removed 6 years after implantation due to recurrence without signs of infection. **(D)** A frequent observation after long-term implantation in the authors' postretrieval study are calcifications, especially in Gore-tex® and heavyweight polypropylene meshes with small pores. **(E)** Long-term stability of polyethylene-terephthalate is still under discussion in hernia surgery, whereas degradation of polyethylene-terephthalate in vascular prosthesis is a well known phenomenon; in the given example the polyethylene-terephthalate mesh Mersilene® has been implanted for approximately 6 years; after explantation the authors only found polyethylene-terephthalate fragments phagocytized by macrophages (hematoxylin and eosin, 400×). **(F)** Expanded poly-tetra-fluoroethylene histologically elicits an excellent tissue response with a minor chronic inflammatory and fibrotic response on the polymer; microporous ePTFE mesh of the newer generation with an improved tissue in-growth after 3 years of implantation and small detached polymer particles phagocytized by macrophages (hematoxylin and eosin, 400×).

Shrinkage

At the beginning, the concept of shrinkage of the mesh was enthusiastically debated. However, there is now a broad acceptance that shrinkage is a common phenomenon after mesh implantation [41–43]. It is not the mesh that shrinks, but the surface reduction is due to a simple retraction of the fibrotic scar tissues around the mesh. Retraction of the scar is a physiologic reaction of maturing scar started by a constant water loss and a subsequent surface-area decrease to an average 60% of the former wound region. It has been assumed that lightweight meshes with a notably decreased fibrotic tissue reaction demonstrate a lesser degree of shrinkage, a hypothesis that still has to be confirmed. Nevertheless, shrinkage is highly important for the repair technique. Sufficient long-term hernia repairs can only be performed with large meshes overlapping the hernia gap by a minimum of 5 cm each side (FIGURE 5A) [44–46].

Fibrotic bridging

Fibrotic bridging is a phenomenon which is, in the authors' opinion, closely associated with the occurrence of shrinkage. Moreover, the incidence of bridging is unrelated to the textile structure of the mesh. Bridging occurs in all mesh modifications with a granuloma size around each mesh fiber exceeding more than half of the pore size of the mesh [47]. Usually, the phenomenon of bridging is observed in all mesh modifications with pore sizes of less than 1 mm. In all of these cases a granuloma of one fiber starts to become confluent with granuloma formations of the adjacent fibers and thus eventually the whole mesh is incorporated into a larger area of granuloma side by side. Granulomas side by side, however, elicit a common outer fibrotic capsule joining each mesh fiber and forming a scar plate covering the whole mesh (FIGURE 4E & 4F). The scar plate again results in the mesh becoming stiff and nonflexible. Conversely, stiff and nonflexible mesh repairs appreciably manipulate the abdominal wall function and quality of life.

Fibrotic bridging is mostly found in heavyweight small pore size meshes. Due to the parallel orientation of the scar formation to the mesh axis, theoretically, shrinkage in meshes with bridging should be more intense – a theory to be proved in the future.

In contrast, lightweight meshes with large pores are constructed in such a way that the granuloma is always notably smaller than half of the pore size. In some of these meshes, the pore size was increased more than six-times compared with the conventional heavyweight meshes, such that bridging is not possible. Lightweight large pore size mesh modifications are characterized by a localized fibrotic reaction around the mesh fibers, with small granulomas allowing the mesh to stay flexible and smooth after implantation.

Recurrence

In approximately 60% of all retrieved surgical meshes, recurrence is the reason why meshes are explanted [32]. Today, clinical studies indicate that recurrence rates of hernia repair based on the use of surgical meshes are significantly decreased compared with suture repair. However, the same clinical studies reveal increasing recurrence rates over time for all types of hernia repair. Essentially, these findings may be interpreted to suggest that today, none of the procedures currently used protects the patients completely from recurrence but the use of surgical mesh decreases their incidence [4,48].

In the postretrieval study the effectiveness of common mesh modifications on the market is comparable concerning recurrence and infection rate. Here, only the rate of recurrences in the Vypro mesh group seems to be higher, as this mesh is mainly used in incisional hernia and, in particular, this lightweight mesh indicates significantly decreased rates of chronic pain (TABLES 3 & 4).

Recurrence following mesh implantation appears after 26 months (mean value, range 3–180 months). The recurrent hernia develops in 99% of all cases at the free edges of the mesh, emphasizing again the importance of a sufficient overlap of mesh and hernia gap. Hernias in the area of the mesh seem to be rare exceptions.

The main reasons for the recurrences are technical faults during the operation (e.g., inadequate fixation in the first 2 weeks after implantation and insufficient overlap), the shrinkage of the mesh after implantation and, finally, alterations of the ECM that are still under investigation in hernia patients. All data from ECM research in these patients indicate an altered collagen metabolism (decreased ratio collagen I/III) in the majority of patients with recurrent hernia [49–55].

The ratio and extent of intermolecular cross-linkage between collagen Type I and III influences the tensile strength and mechanical stability of connective and scar tissues [56,57]. Hernias are therefore more common in patients with collagen disorders such as Marfan's and Ehlers-Danlos syndrome, cutis laxa, osteogenesis imperfecta and hip dislocation in childhood [58,59]. Other factors suggested to influence the collagen I/III ratio and the recurrence rate of hernias are age, sex, smoking and genetic factors [23].

Chronic pain

Chronic pain is an upcoming issue in the field of hernia repair and will probably become the most important topic to be discussed and addressed by the responsible surgeons [11,60–63]. Clinical trials report high percentages of patients with chronic pain after hernia repair, including mesh repair. In contrast to neuropathy-related complaints after intraoperative damage of nerve fibers with pain immediately after surgery, the onset of chronic pain as a consequence of the FBR is typically more than 1 year after hernia repair.

In the postretrieval study, most explants from all the patients with chronic pain in their medical history, indicate nerve fibers and fascicles in the interface of the mesh [23]. Today, immunohistochemical stains allow the detection of even the smallest nerve structures that are mainly found in or around the foreign body granuloma. Due to the nature of the granuloma as a chronic inflammation, it may be speculated that these nerve structures are irritated by the inflammation and cause the sensation of pain. In some cases real traumatic

neuroma can be found at the interface of the mesh–recipient tissues, an indicator of the mechanical destruction of the nerve by the mesh (FIGURE 5B).

In total, all mesh modifications with small pores reveal unacceptably high rates of chronic pain in the retrieval study, in particular, all heavyweight PP meshes (TABLES 3 & 4). Vypro, a lightweight large pore-constructed mesh, demonstrates a dramatically reduced surface area compared with all common mesh modifications on the market. In combination with a favorable foreign body reaction, the small surface area leads to a minimum of nerve irritation and destruction.

Infection

Infection is the third major complication after mesh implantation [12]. Due to the results of the retrieval study, all mesh modifications seem to have similar infection rates. Multifilament mesh constructions as well as microporous ePTFE patches reveal no higher rates of infection as the reason for explantation. Furthermore, scanning electron microscopy studies indicate that colonies of bacteria including biofilm-forming colonies of *Staphylococcus epidermidis* from skin, persisting at the surface of the polymer fibers may be responsible for late infection months or, in rare instances, years after the initial operation (FIGURE 5C).

Fistula & adhesion formation

Fistula and adhesion formation belong to the most serious complications after mesh repair [64,65]. In particular, after intraperitoneal mesh application, adhesions and fistulas are mainly observed in the heavyweight small pore PP mesh group, however, they have also been observed following extraperitoneal mesh implantation [66]. ePTFE appears to have favorable biologic behavior; therefore, GoreTex® mesh modifications have currently been the first choice in all intraperitoneal techniques (IPOM) for incisional hernia repair. However, in the last few years a number of special mesh modifications have been introduced to the market for intraperitoneal hernia repair which seem to have some considerable advantages compared with ePTFE patches. These new mesh modifications mainly work due to different types of films and surface modifications to prevent adhesion of the intestines (e.g., Proceed® or Parietene Composite®) or at least with new antiadhesive polymers like PVDF (DynaMesh® Ipom). Beside enhanced anti-adhesive properties, the generation of new IPOM meshes fulfils all the criteria of modern lightweight meshes with large pores. In particular, the flexibility of the IPOM mesh is of importance in consideration of large defect areas in incisional hernia repair.

Calcification & degradation

Degradation of surgical meshes is rare [23]. Mostly, calcifications are observed after long-term implantation, especially in heavyweight small pore PP meshes as well as in microporous ePTFE (FIGURE 5D). Calcifications are probably due to small porous or even microporous mesh modifications because until now, calcifying depositions have not been observed in large porous constructions. It may be speculated that particularly the small pores disturb local metabolism and substrate exchange leading to a bradytrophic area with increased tendency to calcificate.

Real degradation of the mesh fibers is mainly observed in PET meshes after long-term implantation (FIGURE 5E). Incorporated PET can be degraded hydrolytically, finally resulting in an increased brittleness of the polymer with a loss of the mechanical features. Even ePTFE reveals an increased fragility after long-term implantation. In some explants, small fragments phagocytized by local macrophages were observed (FIGURE 5F).

Handling characteristics

Handling characteristics of lightweight meshes have been improved over the last few years. In particular, the first lightweight large porous mesh, Vypro, seemed to most surgeons to be too soft and smooth for a safe, comfortable and quick hernia repair. Lightweight meshes of the second generation present more stable textile structures or are combined with nonabsorbable polymers to adopt mesh features exactly to the requirements in hernia surgery.

The new generation: lightweight & large porous meshes

Vypro® & Vypro II®

The concept of lightweight large porous meshes for hernia repair was first realized in 1998 with the introduction of Vypro and later Vypro II® by Ethicon, Germany. These meshes represent the first attempt to create a mesh to meet the physiological demands. The amount of remaining material was reduced to approximately 30% of common heavyweight meshes (Vypro 25 g/cm^2 vs. Prolene® 80–85 g/cm^2, TABLE 2) and the pore size was increased by up to 500–600% (Vypro 3–5 mm vs. Prolene® <1 mm, TABLE 2). The nonabsorbable part is composed of multifilament PP combined with an absorbable part made of Vicryl® (PG 910), which is nearly doubled in Vypro II. (Vypro: PP 27g/m^2 and PG 910 27g/m^2; Vypro II: PP 35g/m^2 and PG 910 45g/m^2). The Vicryl® part will be absorbed within the first 6 weeks after implantation and has been added to the nonabsorbable PP to ensure appropriate handling characteristics for the surgeon.

Generally, the construction of Vypro is calculated to augment the abdominal wall and is not designed for complete abdominal wall replacement in large inguinal or incisional hernias. In larger hernias without the possibility to close the fascia Vypro II or another lightweight mesh with a tensile strength of more than 32 N/cm should be used.

First clinical trials confirm the expected superiority of the lightweight large porous mesh concept concerning quality of life after hernia repair [25].

Polypropylene

Most manufactures have added to their range of PP heavyweight small porous mesh modifications, a lightweight large porous adaptation. There are also, numerous monofilament PP meshes on the market, which fulfill all of the criteria for a flexible lightweight mesh with reduced material. An older member

of this group is the Parietene® mesh, a brand new member is the Dynamesh®. In particular, the Dynamesh is matched to the physiologic values with reference to pulling forces and flexibility of the abdominal wall. The textile structure of the warp-knitted mesh generates excellent handling characteristics. All meshes in this group are produced of fibers reduced in diameter and pores of more than 2 mm compared with the heavyweight PP group.

Biocompatibility of the new generation of lightweight PP meshes in experimental studies is acceptable with a significantly decreased FBR and only a minor fibrotic reaction around the PP mesh fibers after long-term implantation in rats (FIGURE 6A). However, clinical trials have yet to confirm the promising preclinical results [43].

TiMesh® light & extra light

TiMesh® light (35 g/m^2) and TiMesh® extra-light (16 g/m^2) represent newer members in the lightweight large porous mesh family. The special feature of these meshes is a surface modification with titanium, which is bound to the PP surface. The basic mesh is a monofilament PP mesh with an average diameter of 67 µm of each single PP fiber and pores of more than 1 mm.

Both mesh modifications were announced as a revolution on the mesh market and have the best biocompatibility possible. Indeed, the titanium-modified meshes exhibit a significantly increased biocompatibility compared with conventional heavyweight small porous meshes [43], however, if the biocompatibility of both titanium meshes is compared with simple lightweight large porous PP meshes without surface modification, the biocompatibility is equal. Basically, titanium modification of the PP surface has no significant effect on FBR in soft tissue contact. This phenomenon has independently been described by the authors' group (Hernia, in press; FIGURE 6B) and by Lehle and colleagues in 2004 [67]. Another important disadvantage of the TiMesh extra-light is a tensile strength of 12 N/cm, a value significantly lower than the calculated minimum of 16 N/cm.

UltraPro®

UltraPro® represents the newest member in the lightweight large porous mesh group. The mesh is constructed of a monofilament lightweight large porous PP mesh with pores of more than 3 mm. An absorbable Monocryl® (polyglecaprone 25) component is added to improve handling characteristics and to optimize implantation and increased tensile strength in the first weeks of the repair.

Monocryl (polyglecaprone 25) is a monofilament derived from a segmented copolymer of ε-caprolactone and glycolide. This complex polymeric system contains soft segments of a random copolymer of ε-caprolactone and glycolide, which provide good handling characteristics and hard segments of polyglycolide that provide high strength. Both hard and soft segments are combined in the same polymeric chain. Evaluating the toxicity potential of Monocryl sutures, no genotoxic, cytotoxic, teratogenic, irritating or allergic effects were found. As suture material it was introduced in 1995 and since then it demonstrated many preferable qualities including a significantly lowered tissue reaction in the early phases of wound healing compared with polyglactine 910 (Vicryl). Monocryl is essentially absorbed without increased cellularity, inflammatory and fibrotic reaction within 84–140 days (FIGURE 6C–F). Interestingly, the supplement of PP with Monocryl leads to significantly decreased FBR compared with simple lightweight large porous PP meshes with identical textile structure; an effect still under investigation. Overall, the Monocryl-PP-composite UltraPro is currently the member of the lightweight large porous mesh family with the lowest FBR and optimized handling. The first clinical studies produced encouraging results to move forward with this mesh concept [68].

Expert opinion

The lightweight large porous mesh concept is one of the most important developments in hernia surgery of the last decade. Mesh modifications of this group represent implants for hernia repair with an optimum of biocompatibility. The new lightweight large porous mesh generation should reveal significant advantages in the field of patient comfort and chronic pain.

More important new data indicate hernias (in general and recurrent hernias in particular) to be a disease of the connective tissues and the ECM. These findings explain why meshes cannot protect the patients completely from recurrence and tell us that we have to learn more about basic pathophysiologic processes of hernia formation. These data will be essential for future mesh modifications and to define populations at risk.

Five-year view

The next 5-year interval in hernia research will give further insight into the advantages or disadvantages of both mesh concepts. Important ongoing clinical studies including multicenter trails will be finished and provide corresponding data.

Furthermore, other nonflat mesh modifications such as plugs or whole systems for hernia repair will be rebuilt with large porous textile structures.

The next generation in hernia meshes will be a bioactive implant. These meshes of the third generation (behind the heavyweight meshes of the first and the lightweight meshes of the second generation) will probably consist of an optimized lightweight large porous mesh construction with chemical and biologic surface and polymer modifications which directly influence hernia development or recurrence. The next 5 years will finish the lightweight mesh period and will introduce a new epoch in hernia and mesh research with the formation of interdisciplinary research groups including basic scientists in biology, polymer chemistry and tissue engineering, as well as pathologists and surgeons. Only these groups will be able to illuminate the complex pathophysiology of hernias and use newest technologies to create the bioactive mesh of tomorrow.

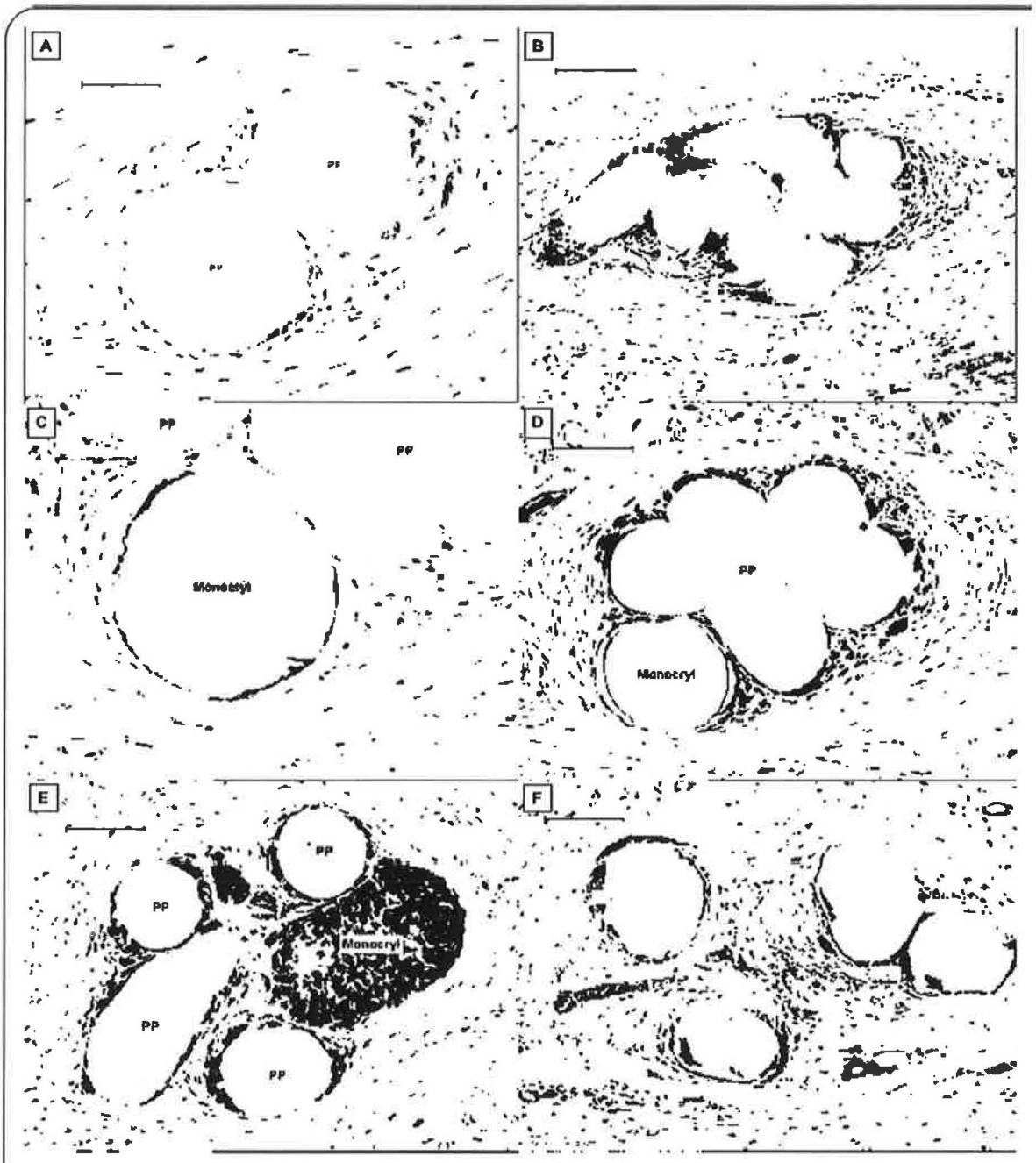

Figure 6. Members of the lightweight and large porous mesh family. (A) Lightweight and large porous PP mesh without surface modification 182 days post implantation in Whiter rats with a minor FBR and fibrotic tissue reaction around the mesh fibers (hematoxylin and eosin, 200×). **(B)** TiMesh® light 182 days after implantation in the same experimental setting; note the still persisting foreign body reaction which is at least equal to that of unmodified polypropylene (hematoxylin and eosin; 100x). **(C)** UltraPro® after 42 days; note the polypropylene and Monocryl® composite (hematoxylin and eosin, 200×). **(D)** Macrophage response on the interface of UltraPro 42 days after implantation with a reduced macrophage response to the Monocryl part (CD68, 100×). **(E)** UltraPro 84 days after implantation; the Monocryl part is absorbed by macrophages, but without increased inflammatory reaction and fibrosis (CD68, 100x). **(F)** UltraPro 182 days after implantation; remaining PP fibers with a remaining granuloma thickness of few µm (hematoxylin and eosin, 100×).

Key issues

- Lightweight large porous meshes indicate newer mesh modifications with main features such as optimized biocompatibility and adoption of the textile structure to physiologic values of the abdominal wall. In particular, mechanical characteristics such as tensile strength and flexibility of mesh and abdominal wall have been the focus of interest during the development of these meshes.
- The textile structure in general is large porous. The large porous construction reveals a significantly improved integration of the mesh into recipient tissues. In lightweight and large porous meshes a significantly decreased foreign body reaction can be observed. The reduced foreign body reaction correlates with decreased rates of connective tissue formation, shrinkage and bridging.
- A postretrieval study of explanted meshes that failed after hernia repair demonstrate that mesh-related complications are rare. However, mesh-related complications might be serious and severe such as fistulas, adhesions, infection and, in particular, chronic pain. Overall, lightweight meshes with large pores seem to have less serious complications, confirmed by the postretrieval study and first clinical studies.
- Recurrence is the most frequently observed complication in hernia surgery. Beside technical faults during operation, alterations of the extracellular matrix play a decisive role in the formation of long-term recurrences. The type of mesh used for the hernia repair plays no or only a minor role in cases of biologic recurrence.
- Future strategies to decrease the rate of biologic recurrences will be the introduction of bioactive meshes.

References

1 Usher F. Hernia repair with Marlex mesh. *Arch. Surg.* 84, 325–328 (1962).

2 Usher F, Cogan J, Lowry T. A new technique for the repair of inguinal and incisional hernias. *Arch. Surg.* 81, 847–854 (1960).

3 Usher F, Fries J, Ochsner J, Tuttle LJ. Marlex mesh, a new plastic mesh for replacing tissue defects: clinical studies. *Arch. Surg.* 138–145 (1959).

4 Bay-Nielsen M, Kehlet H, Strand L *et al.* Quality assessment of 26,304 herniorrhaphies in Denmark: a prospective nationwide study. *Lancet* 358, 1124–1128 (2001).

5 Cassar K, Munro A. Surgical treatment of incisional hernia. *Br. J. Surg.* 89, 534–545 (2002).

6 Macintyre IM, Miles WF. Critical appraisal and current position of laparoscopic hernia repair. *J. R. Coll. Surg. Edinb.* 40, 331–336 (1995).

7 McCormack K, Scott NW, Go PM, Ross S, Grant AM. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst. Rev.* CD001785 (2003).

8 Scott NW, McCormack K, Graham P *et al.* Open mesh versus nonmesh for repair of femoral and inguinal hernia. *Cochrane Database Syst. Rev.* CD002197 (2002).

9 Seid AS, Amos E. Entrapment neuropathy in laparoscopic herniorrhaphy. *Surg. Endosc.* 8, 1050–1053 (1994).

10 Haapaniemi S, Nilsson E. Recurrence and pain three years after groin hernia repair. Validation of postal questionnaire and selective physical examination as a method of follow-up. *Eur. J. Surg.* 168, 22–28 (2002).

11 Bower S, Moore BB, Weiss SM. Neuralgia after inguinal hernia repair. *Am. Surg.* 62, 664–667 (1996).

12 Leber GE, Garb JL, Alexander AI, Reed WP. Long-term complications associated with prosthetic repair of incisional hernias. *Arch. Surg.* 133, 378–382 (1998).

13 Usher FC. The repair of incisional and inguinal hernias. *Surg. Gynecol. Obstet.* 131, 525–530 (1970).

14 Amid PK, Shulman AG, Lichtenstein IL. The Lichtenstein Herniotomy Procedure. *Chirurg* 65, 54–58 (1994).

15 Klinge U, Klosterhalfen B, Conze J *et al.* A modified mesh for hernia repair adapted to abdominal wall physiology. *Eur. J. Surg.* 164, 951–960 (1998).

16 Klinge U, Conze J, Klosterhalfen B *et al.* Alteration of abdominal wall mechanics after mesh implanation. Experimental alteration of mesh stability. *Langenbecks Archiv. Fur. Chirurgie* 381, 323–332 (1996).

17 Klinge U, Junge K, Stumpf M *et al.* Functional and morphological evaluation of a low-weight, monofilament polypropylene mesh for hernia repair. *J. Biomed. Mater. Res.* 63, 129–136 (2002).

18 Klosterhalfen B, Klinge U, Henze U *et al.* Morphological correlation of the functional mechanics of the abdominal wall after mesh implantation. *Langenbecks Archiv. Fur. Chirurgie* 382, 87–94 (1997).

19 Klinge U, Conze J, Limberg W *et al.* Pathophysiology of the abdominal wall. *Chirurg* 67, 229–233 (1996).

20 Junge K, Klinge U, Prescher A *et al.* Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants. *Hernia* 5, 113–118 (2001).

21 Klinge U, Müller M, Brücker C, Schumpelick V. Application of three dimensional stereography to assess abdominal wall mobility. *Hernia* 2, 11–14 (1998).

22 Klinge U, Prescher A, Klosterhalfen B, Schumpelick V. Origin and pathophysiology of abdominal wall defects. *Chirurg* 68, 293–303 (1997).

23 Klosterhalfen B, Klinge U, Rosch R, Junge K. Long-term inertness of meshes. In: *Meshes: Benefits and Risks.* Schumpelick V, Nyhus L (Eds.). Springer-Verlag, Berlin, Germany (2003).

24 Welty G, Klinge U, Klosterhalfen B, Kasperk R, Schumpelick V. Functional impairment and complaints following incisional hernia repair with different polypropylene meshes. *Hernia* 5, 142–147 (2001).

25 Post S, Weiss B, Willer M, Neufang T, Lorenz D. Randomized clinical trial of lightweight composite mesh for Lichtenstein inguinal hernia repair. *Br. J. Surg.* 91, 44–48 (2004).

26 Langer C, Neufang T, Kley C, Liersch T, Becker H. Central mesh recurrence after incisional hernia repair with Marlex – are the meshes strong enough? *Hernia* 5, 164–167 (2001).

27 Anderson JM, Miller KM. Biomaterial biocompatibility and the macrophage. *Biomaterials* 5, 5–10 (1984).

28 Bhardwaj RS, Henze U, Klein B *et al.* Monocyte–biomaterial interaction inducing phenotypic dynamics of monocytes: a possible role of monocyte subsets in biocompatibility. *J. Mater. Sci. Mater. Med.* 8, 737–742 (1997).

29 Beets G, van Mameren H, Go P. Long-term foreign body reaction to preperitoneal polypropylene mesh in the pig. *Hernia* 2, 153–155 (1998).

30 Buscaroli S, Stea S, Arciola CR *et al.* Theoxidative burst in the determination of immune response to synthetic materials. *G. Chir.* 11, 144–146 (1990).

31 Klosterhalfen B, Junge K, Hermanns B, Klinge U. Influence of implantation interval on the long-term biocompatibility of surgical mesh. *Br. J. Surg.* 89, 1043–1048 (2002).

32 Klosterhalfen B, Klinge U, Hermanns B, Schumpelick V. Pathology of traditional surgical nets for hernia repair after long-term implantation in humans. *Chirurg* 71, 43–51 (2000).

33 Bellon JM, Bujan J, Contreras LA, Carrera San Martin A, Jurado F. Comparison of a new type of polytetrafluoroethylene patch (Mycro Mesh) and polypropylene prosthesis (Marlex) for repair of abdominal wall defects. *J. Am. Coll. Surg.* 183, 11–18 (1996).

34 Klinge U, Klosterhalfen B, Ottinger AP, Junge K, Schumpelick V. PVDF as a new polymer for the construction of surgical meshes. *Biomaterials* 23, 3487–3493 (2002).

35 Laroche G, Marois Y, Guidoin R *et al.* Polyvinylidene fluoride (PVDF) as a biomaterial: from polymeric raw material to monofilament vascular suture. *J. Biomed. Mater. Res.* 29, 1525–1536 (1995).

36 Laroche G, Marois Y, Schwarz E *et al.* Polyvinylidene fluoride monofilament sutures: can they be used safely for long-term anastomoses in the thoracic aorta? *Artif. Organs* 19, 1190–1199 (1995).

37 Mary C, Marois Y, King M *et al.* Comparison of the *in vivo* behavior of polyvinylidenfluoride and polypropylene sutures in vascular surgery. *ASAIO J.* 44, 199–206 (1998).

38 Urban E, King MW, Guidoin R *et al.* Why make monofilament sutures out of polyvinylidene fluoride? *ASAIO J.* 40, 145–156 (1994).

39 Klosterhalfen B, Klinge U, Schumpelick V. Functional and morphological evaluation of different polypropylene-mesh modifications for abdominal wall repair. *Biomaterials* 19, 2235–2246 (1998).

40 Schachtrupp A, Klinge U, Junge K *et al.* Individual inflammatory response of human blood monocytes to mesh biomaterials. *Br. J. Surg.* 90, 114–120 (2003).

41 Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V. Shrinking of polypropylene mesh *in vivo*: an experimental study in dogs. *Eur. J. Surg.* 164, 965–969 (1998).

42 Schumpelick V, Arlt G, Schlachetzki A, Klosterhalfen B. Chronic inguinal pain following TAPP. A case of mesh shrinkage. *Chirurg* 68, 1297–1300 (1997).

43 Scheidbach H, Tamme C, Tannapfel A, Lippert H, Kockerling F. *In vivo* studies comparing the biocompatibility of various polypropylene meshes and their handling properties during endoscopic total extraperitoneal (TEP) patchplasty: an experimental study in pigs. *Surg. Endosc.* 18, 211–220 (2004).

44 Conze J, Rosch R, Klinge U *et al.* Polypropylene in the intra-abdominal position: influence of pore size and surface area. *Hernia* 8, (2004). In Press.

45 Conze J, Prescher A, Kisielinski K, Klinge U, Schumpelick V. Technical consideration for subxiphoidal incisional hernia repair. *Hernia* 8 (2004). In Press.

46 Sollman SM. Anchorage overlapping repair of incisional hernia. *J. R. Coll. Surg. Edinb.* 34, 140–142 (1989).

47 Klinge U, Klosterhalfen B, Birkenhauer V *et al.* Impact of polymer pore size on the interface scar formation in a rat model. *J. Surg. Res.* 103, 208–214 (2002).

48 Flum DR, Horvath K, Koepsell T. Have outcomes of incisional hernia repair improved with time? A population-based analysis. *Ann. Surg.* 237, 129–135 (2003).

49 Bellon JM, Bujan J, Honduvilla NG *et al.* Study of biochemical substrate and role of metalloproteinases in fascia transversalis from hernial processes. *Eur. J. Clin. Invest.* 27, 510–516 (1997).

50 Friedman DW, Boyd CD, Norton P *et al.* Increases in Type III collagen gene expression and protein synthesis in patients with inguinal hernias. *Ann. Surg.* 218, 754–760 (1993).

51 Junge K, Klinge U, Klosterhalfen B *et al.* Influence of mesh materials on collagen deposition in a rat model. *J. Invest. Surg.* 15, 319–328 (2002).

52 Klinge U, Si ZY, Zheng H *et al.* Collagen I/III and matrix metalloproteinases (MMP) 1 and 13 in the fascia of patients with incisional hernias. *J. Invest. Surg.* 14, 47–54 (2001).

53 Zheng H, Si Z, Kasperk R *et al.* Recurrent inguinal hernia: disease of the collagen matrix? *World J. Surg.* 26, 401–408 (2002).

54 Si Z, Bhardwaj R, Rosch R *et al.* Impaired balance of Type I and Type III procollagen mRNA in cultured fibroblasts of patients with incisional hernia. *Surgery* 131, 324–331 (2002).

55 Read R. Metabolic factors contributing to herniation. *Hernia* 2, 51–55 (1998).

56 Pans A, Pierard GE, Albert A, Desaye C. Biomechanical assessment of the transversalis fascia and rectus abdominis aponeurosis in inguinal herniation – preliminary results. *Hernia* 1, 27–30 (1997).

57 Pans A, Albert A, Lapiere CM, Nusgens B. Biochemical study of collagen in adult groin hernias. *J. Surg. Res.* 95, 107–113 (2001).

58 Beighton P. Heritable disorders of connective tissue. In: *The Ehlers-Danlos syndrome. 5th Edition.* Beighton P (Ed.). Mosby, St Louis, USA, 189–251 (1993).

59 Chang EG. When to use mesh in inguinal hernia repair. *Mil. Med.* 156, 364–366 (1991).

60 Ansaloni L, Catena F, D'Alessandro L. Prospective randomized, double-blind, controlled trial comparing Lichtenstein's repair of inguinal hernia with polypropylene mesh versus Surgisis gold soft-tissue graft: preliminary results. *Acta Biomed. Ateneo. Parmense* 74(Suppl. 2), 10–14 (2003).

61 Bay-Nielsen M, Perkins FM, Kehlet H. Pain and functional impairment 1 year after inguinal herniorrhaphy: a nationwide questionnaire study. *Ann. Surg.* 233, 1–7 (2001).

62 Gillion J, Fagniez P. Chronic pain and cutaneous sensory changes after inguinal hernia repair: comparison between open and laparoscopic techniques. *Hernia* 3, (1999).

63 Kumar S, Wilson RG, Nixon SJ, Macintyre IM. Chronic pain after laparoscopic and open mesh repair of groin hernia. *Br. J. Surg.* 89, 1476–1479 (2002).

64 Bingener J, Kazantsev GB, Chopra S, Schwesinger WH. Adhesion formation after laparoscopic ventral incisional hernia repair with polypropylene mesh: a study using abdominal ultrasound. *JSLS* 8, 127–131 (2004).

65 Miller K, Junger W. Ileocutaneous fistula formation following laparoscopic polypropylene mesh hernia repair. *Surg. Endosc.* 11, 772–773 (1997).

66 Farmer L, Ayoub M, Warejcka D *et al.* Adhesion formation after intraperitoneal and extraperitoneal implantation of polypropylene mesh. *Am. Surg.* 64, 144–146 (1998).

67 Lehle K, Lohn S, Reinerth GG *et al.* Cytological evaluation of the tissue-implant reaction associated with subcutaneous implantation of polymers coated with titaniumcarboxonitride *in vivo*. *Biomaterials* 25, 5457–5466 (2004).

68 Holzheimer RG. First results of Lichtenstein hernia repair with Ultrapro-mesh as cost saving procedure-quality control combined with a modified quality of life questionnaire (SF-36) in a series of ambulatory operated patients. *Eur. J. Med. Res.* 9, 323–327 (2004).

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