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'The Ideal Mesh?'

Uwe Klinge[a] Joon-Keun Park[b] Bernd Klosterhalfen[c]

[a]Department for General, Visceral and Transplant Surgery, University Hospital of the RWTH Aachen, Aachen, [b]Clinic for Nephrology and Hypertensiology, Medical School Hannover, Hannover, and [c]Institute for Pathology, Düren Hospital, Düren, Germany

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Abstract
Currently, more than 200 different textile constructions, so-called 'meshes', are available for use world-wide in the more than 20 million operations performed annually for the reinforcement of tissues. As any reintervention at the mesh-tissue compound is a surgical challenge, sometimes resulting in almost untreatable defects, huge efforts are being made to improve the biological and functional performance of the meshes. Based on numerous experimental and clinical studies in the past 20 years, our understanding of them has improved markedly. This includes the biomechanical aspects and the histopathological evaluation of the recipient tissue. Sufficiently large pores as well as structural stability in case of mechanical strain have been identified to be crucial to reduce excessive inflammation and fibrosis. Furthermore, large pores prevent bridging of the foreign body reaction through the pore and thereby help to reduce clinical adverse events as erosion, shrinkage or pain. However, with regard to the many different indications for meshes, there will never be one single ideal mesh for all purposes. To achieve an optimal performance, every construction should be designed according to the specific functional requirements, charging the surgeon to identify the best mesh for his purpose.

Textiles in Surgery

Textile implants, so-called 'meshes', are currently widely used for the reinforcement of anatomical structures in the abdominal wall, the pelvic floor, the diaphragm area or the thoracic wall. It is estimated that about 20 million textile prosthetic devices are used worldwide per year [1]. In the late 1950s, Usher [2] showed in dogs that textile structures can help to cover large defects of the abdominal or thoracic wall. Subsequently, these implants were used in humans, initially to close complex hernias, usually by placing a large piece of mesh underneath the hernia gap. In the mid-1980s, the implantation of textile meshes in the groin became the most popular standard for groin hernia repair. The placement of meshes 'tension-free' underneath the external aponeurosis is still named the Lichtenstein procedure in honour of I.L. Lichtenstein, A.G. Shulman and P.K. Amid, who first had the idea and then developed the surgical procedure as it is used till today, largely unchanged [3]. With the upcoming laparoscopic techniques in the 1990s, placement of meshes for the treatment of groin hernia became feasible by using laparoscopy, either via the abdominal cavity as TAPP (transabdominal preperitoneal) or preperitoneal as a TEP (totally extraperitoneal) procedure. Traditional suture repair has been reserved for young patients with small primary hernias. The indication for use of meshes is still expanding, and today meshes are recom-

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Uwe Klinge
Surgical Department, University Hospital of the RWTH Aachen
Pauwelsstrasse 30
DE–52074 Aachen (Germany)
E-Mail uklinge@ukaachen.de

mended in guidelines as the general standard for hernia repair [4].

After two decades of mesh use, it is clear that this technique can help to reduce the manifestation of recurrences [5]. Furthermore, particularly in the case of a recurrence, the laparoscopic approach is faster than the open redo procedure and may have the advantage of reducing the incidence of postoperative chronic pain. Epidemiological data indicate that meshes often only delay the manifestation of a recurrence, however, and may not in fact decrease the life long risk for entire populations, with epidemiological databases showing a constancy of recurrence rates for most countries [6]. So the introduction of meshes has not eliminated the problem of recurrent hernia. Correspondingly, it is still under debate whether or not textiles should be used as first choice for all type of hernias. However, the reinforcement of tissue by extended overlapping textiles has become an undisputed option, in particular if suture repair has already failed or for patients at an increased risk for recurrence.

This discussion is influenced by the quality of the implanted material with its impact on the risk-benefit balance of meshes. The lower the risks related to the use of meshes, the greater the indication for this use. Meanwhile, the incidence of complications related to the mesh material – as opposed to an inadequate surgical technique or a patient's compromised immune system – are so low that clinical trials fail to come up with reliable results. Postmarket surveillance of medical devices currently uses registries as these detect even rare side effects that manifest with a long delay [7].

As any reintervention after mesh implantation is a technical challenge for surgeons, enormous attempts are being made to improve our understanding of the biological reaction to meshes and to find constructions which can help to further reduce adverse side effects. The pioneers of mesh repair used the structures they found on the market and did not consider the impact of the material on outcome, but in the mid-1990s the first textile structures were designed specifically for use in the abdominal wall, adapting the physicomechanical properties of the textile to the physiological requirements [8].

In the face of the various procedures for which meshes are currently used, it becomes increasingly evident that the assumption of one ideal mesh, fit for all purposes and for all defects, is an illusion. Instead, many different mechanical and functional requirements have to be considered, among them the distinct tissue response depending on the anatomical location, and the cellular activation due to variations of the immunological defense capability of patients for their response to stress. All these aspects contribute to the overall performance of the implant.

Impact of Textile Properties of Meshes on the Biological Response

In the past two decades, we have learned from numerous experimental and clinical studies (in vitro and in vivo) that every mesh is recognized by the tissue as a foreign body. As it is obviously not possible for the mesh to mimic all the properties of the local tissue, it thus disturbs the physiological regenerative capacity of this tissue and tends to healing by filling the defect with scar tissue. The inappropriate biomechanical properties of a device with its subsequent tissue reaction can be related to a number of adverse side effects, ranging from:

- excessive scar formation
- formation of a chronic wound with intense inflammation
- erosion of surrounding tissues
- chronic pain due to the entrapment of nerves in a scar-mesh compound
- early surgical site infection or delayed infection by reactivation of biofilm-forming bacteria that were attached to the implant
- migration of the implant due to inadequate elasticity
- perforation into bowels or bladder.

For identification of the impact of the material on the tissue response to the foreign body, precise characterization of the device is essential, at least of all aspects considered to be relevant for the outcome. It is still open to discussion, however, which aspects are relevant and how to measure them.

Today, expanded polytetrafluorethylene (ePTFE), polypropylene (PP), polyethylene terephthalate/polyester (PET) or polyvinylidenfluoride (PVDF) are the main nonabsorbable polymers used. However, the polymer seems to be far less important than the textile structure for the subsequent tissue reaction [9, 10]. While textile constructions reveal huge variations in tensile strength and stretchability, the physicomechanical characterization of a textile is, unfortunately, not so simple [11]. Most of the textiles show considerable anisotropy because of the way the meshes are manufactured. This is caused by the fibers mostly running parallel as they come out of the machine. Correspondingly, most of the meshes have a limited deformation when stressed in the direction of these (warp) fibers, whereas perpendicular strain leads to

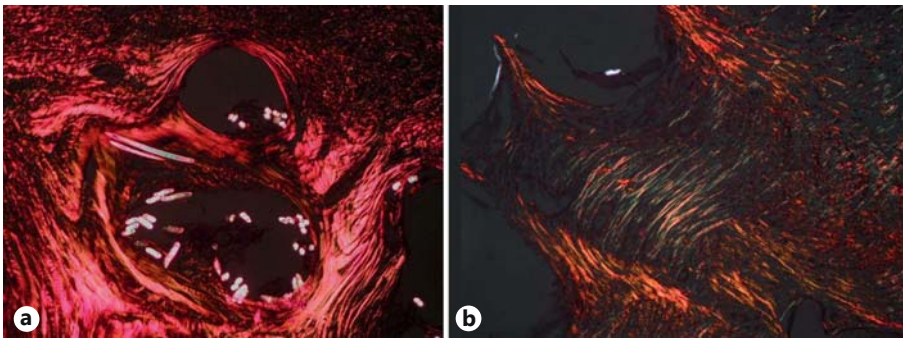

Fig. 1. Sirius red staining of scar at the interface of explanted human meshes [16]. Red reflects mature, highly cross-linked and stable collagen type I, whereas green represents immature collagen type III. **a** Scar of a patient with late bacterial infection and local fibrosis with mainly type I collagen. **b** Scar of a patient with repeated recurrences and formation of instable type III collagen around the mesh.

a substantial elongation of the mesh device. This capacity to stretch is a consequence of the lengthening of the pores accompanied by the consecutive narrowing of the width of the mesh. So the level of anisotropy is largely influenced by the type of textile binding between the filaments. However, the existence of anisotropic properties hinders any clear experimental characterization of the mesh biomechanics, and tends to inconsistencies [12]. Different uniaxial or multiaxial measurements have been attempted, but ultimately the many reports present a mixture of incomparable results presenting pressures (N/m^2), forces (N) or Pascal's wall tension (N/cm). The last of these seems to be best suited for a comparison of meshes and tissues, as it does not include the thickness of the layers, which usually is not known. Depending on the theoretical model applied, a minimum of 16–32 N/cm for the appropriate tensile strength of meshes is considered adequate for the reinforcement of the abdominal wall [13].

The weight of the material is regarded an insufficient characteristic because it does not reflect differences in the specific weights of polymers. Furthermore, films, micropore fleece structures or meshes comprising large pores and thick filaments, all displaying markedly different tissue reactions [14], can have similar weights.

Surface hydrophilicity is assumed to influence the local attraction of proteins and cells; however, reliable values of surface hydrophilicity for fibers and textiles are rare. Already in 1962, Vroman [15] showed how difficult it is to control the surface-protein interaction, and there have not been substantial improvements since then.

Preclinical in vivo testing of textiles in animal models has its limitations when making a comparison with humans, not only because of size or anatomy, more because of the lack of the diseases and comorbidities that occur in humans that can markedly influence the outcome after an intervention. Our own Sirius red staining of scars close to meshes has clearly shown that human patients suffering from recurrences demonstrate an impaired scar quality with a predominance of collagen type III, whereas scars of other patients consists mainly of collagen type I (fig. 1). In the subgroup of patients with mesh explantation due to recurrences, about 2 out of 3 showed a defective wound healing with an impaired ratio of collagen type I/type III; this is hardly considered in any animal experiment.

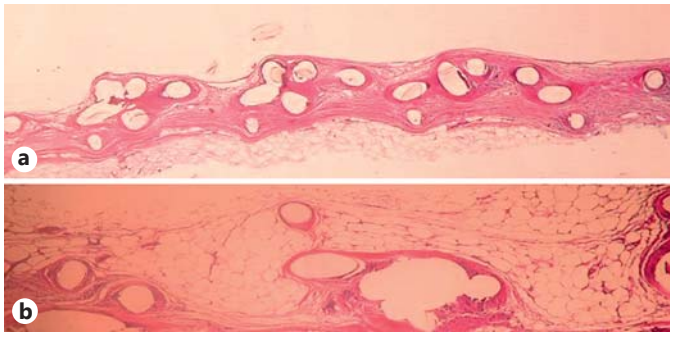

Fig. 2. HE staining of a small-pore mesh with bridging of the scar throughout the entire pore (**a**) and of a large-pore mesh without bridging (**b**).

Histopathological analysis of explanted meshes always reveals some scarring reaction after incorporation into tissues as a result of the surgical trauma during implantation. Whereas in the case of large interfilament distances the pores can be filled with local physiological tissues like fat, in the case of small pores, the gap in between the filaments is usually completely filled with inflammatory infiltrate or a dense fibrotic scar, a phenomenon called 'bridging' (fig. 2).

The minimum distance required in order to avoid bridging has been measured to be >1 mm for polypropylene and >0.6 mm for PVDF (due to its less intense foreign body reaction) [17]. With an algorithm that in a 2-dimensional image fits spheres to the pores, only the area of

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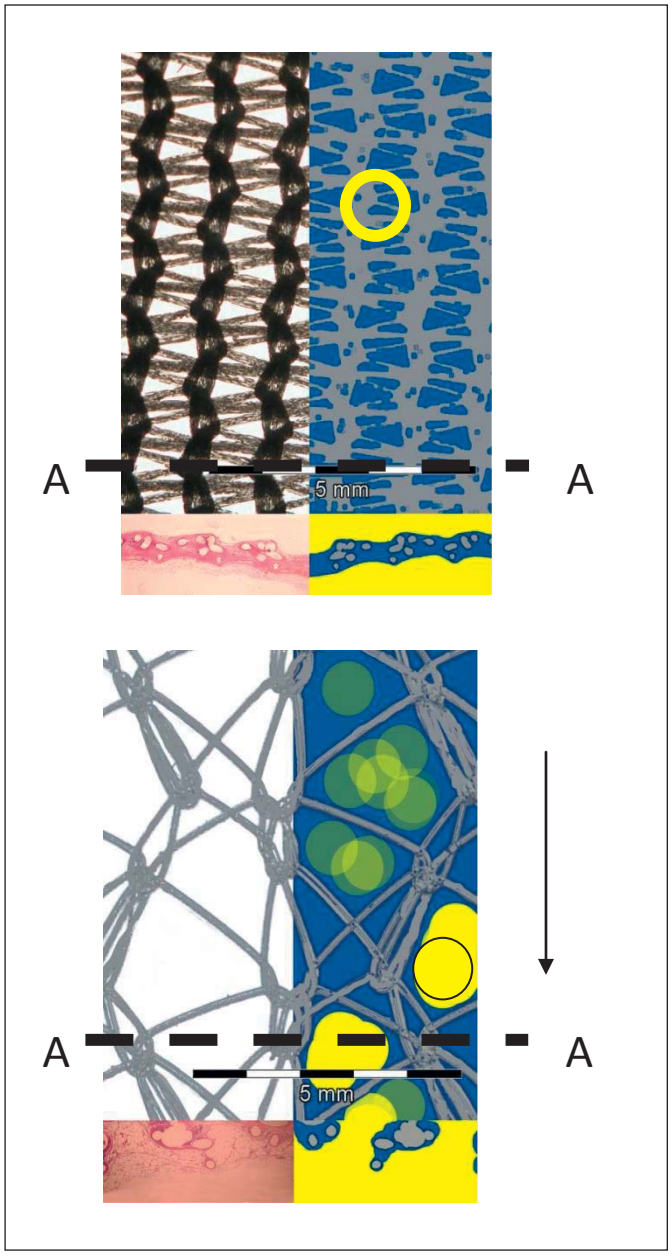

Fig. 3. Small-pore polypropylene mesh with zero effective porosity as there is no pore able to include a sphere with 1 mm in diameter (A). Large-pore PVDF mesh with effective porosity of 42%, area of bridging-free pore is estimated by iterative placement of spheres with a diameter that has been proven to avoid bridging [17].

nonbridging pores can be measured. In relation to the total area of the mesh, this is summarized as 'effective porosity' (fig. 3) [18].

The effective porosity has been found to be more important than other textile characteristics in estimating

Table 1. Classification of mesh materials based on porosity [19]

Class I: Large-pore meshes with a low risk for bridging, defined by textile porosity >50% and effective porosity >0%
1a) monofilament
1b) multifilament
1c) mixed structure or polymer
Class II: Small-pore meshes with a high risk for bridging, defined by textile porosity <50% and effective porosity of 0%
2a) monofilament
2b) multifilament
2c) mixed structure or polymer
Class III: Porous mesh with special features in addition to the pure textile construction, e.g. to prevent adhesions
Class IV: Film-like mesh without porosity, sub-micronic pore size or secondarily excised pores
Class V: Complex textiles difficult to uniformly characterize, either preshaped, preformed or 3-dimensional
Class VI: Tissue-derived biologicals
6a) non-cross-linked
6b) cross-linked
6c) special features

biocompatibility. Correspondingly, the several hundreds of different textile devices on the market have been grouped according to this criterium (table 1) [19]. With the focus on bridging/not bridging, this revised classification may predict the performance of textile implants better than the former classification by Amid [20], which mainly addressed the risk for infection and bacterial adherence and classified any pores of >75 μm as 'large'.

Cell and Tissue Response to Textile Implants

The complexity of cellular and tissue response to meshes with intense interaction between various immune-competent cells and the local extracellular matrix of resident tissues means all in vitro investigations using cell cultures have limitations. Correspondingly, our current knowledge of the foreign body reaction is derived from animal studies (with their natural limitations) and from the analysis of retrieval studies. In the latter, the focus on explanted materials was based on a selection of bad cases, focusing on a small subset of a cohort, so the studies do not reflect true incidences. However, despite these limitations and based on more than 4,000 explanted mesh samples from humans, we can state that all meshes induce a foreign body reaction forming a granuloma around the filaments. Intensity of inflammation

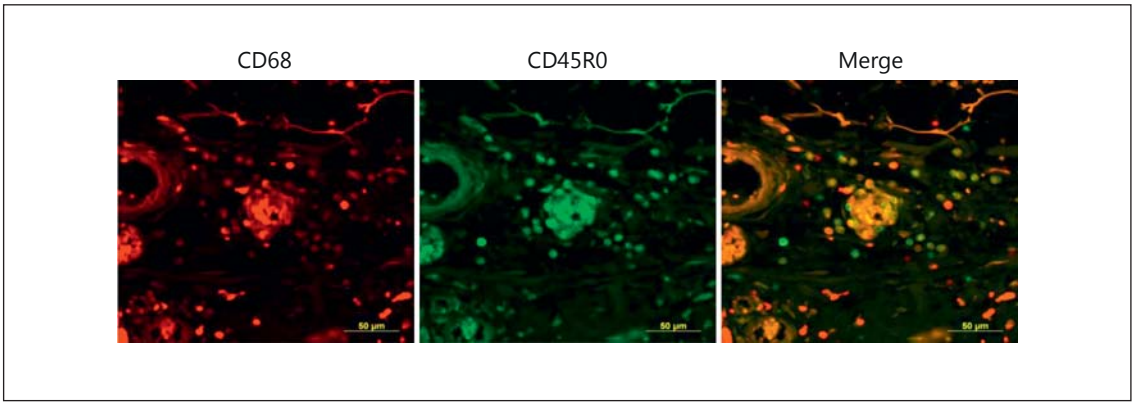

Fig. 4. Immunofluorescence double staining of the perifilamentary infiltrate for CD68 (red) and CD45R0 (green). Immunofluorescence staining was performed using the following primary antibodies: rabbit anti-human CD68 (Santa Cruz Biotechnology, Santa Cruz, Calif., USA), mouse anti-human CD45R0 (clone: UCHL1, Dako, Hamburg, Germany). For fluorescent visualization of bound primary antibodies, sections were further incubated with following secondary antibodies: donkey anti-rabbit Alexa Fluor 555 and donkey anti-mouse Alexa Fluor 488 (Life Technologies, Darmstadt, Germany).

and fibrosis can vary markedly, depending on mesh porosity or local bacterial contamination. Interestingly, we have to consider considerable interindividual variations with more or less inflammation even in quite similar constellations. In general, however, and corresponding with animal studies, large-pore constructions usually show less inflammation, fibrosis, bridging or calcification than small-pore meshes. Three-dimensional plugs always show an accumulation of material due to folding. Not surprisingly, this performance is similar to that of small-pore structures [9].

Even years after implantation of a mesh, the foreign body granuloma around the fibers can still be detected, with an inner inflammatory infiltrate and an outer fibrotic capsule. The infiltrate often consists of foreign body giant cells close to the polymer surface. Next to it, lots of macrophages and some lymphocytes or granulocytes can be seen, but also many other mononuclear cells of dubious origin. Our own attempts to characterize this infiltrate revealed numerous cells that express CD45R0 on the surface with only partial coexpression of the marker for macrophages, CD68 (fig. 4).

Correspondingly, a considerable part of this infiltrate may consist of pluripotent fibrocytes, first described by Bucala et al. [21] in 1994. In 2011, Thevenot et al. [22] demonstrated that within 2 weeks after implantation, there is an accumulation of fibrocytes around implants. Our findings on explanted human meshes suggest further that the persistence of fibrocytes may play a crucial role in chronic reactions [23].

Apart from the insight provided into the tissue response to the textile implants, the analysis of the retrieved explants confirmed that at least ePTFE, PET and PP all develop signs of degradation, cracking of the surface or even fragmentation, underlining that inert behavior of these so-called permanent materials should no longer be expected.

Considering both the persistence of the chronic foreign body reaction and the reduced stretchability of scar tissue, the aim for any design of modern textile structures is the reduction of inflammation and fibrosis, favoring integration into local tissues with the least disturbance. Today, this aim can best be achieved by large-pore structures. However, as pores may collapse in cases of tensile stress, in any anatomical structure coming under mechanical strain (e.g. the pelvic floor and the diaphragm) there should be sufficient structural stability in order to preserve these large pores even when stretching forces are applied.

Any inadequate mesh design with locally enhanced inflammatory activity will increase the risk for mesh-related adverse side effects and may compromise the clinical outcome by, for example, bacterial infection, fibrotic immurement, chronic pain, restricted mobility, mesh migration cutting through the tissue or adhesions when placed within the abdominal wall cavity.

How to Select the Most Suitable Mesh?

As the ultimate mesh for the surgical consumer may never come into existence, we may have to consider the following aspects to help us find the ideal for our specific purpose.

(1) A film-like barrier can help to protect adhesions when the mesh is placed within the abdominal cavity, avoiding any direct contact of polypropylene to the bowel but requiring permanent fixation, whereas pore constructions permit tissue ingrowth and require less durable fixation. Large-pore constructions seem to be superior with regard to the induced intensity of inflammation and fibrosis.

(2) If tension-free conditions cannot be guaranteed, structural stability is necessary to prevent collapse of pores when stretched.

(3) Though there are some coated meshes on the market, current evidence of bioactive functionality is low but may come up in the future.

(4) Fixation of the mesh can be achieved by suture, glue or tacks, whereas glue needs pores, and a film needs permanent fixation. However, with fixation, the immediate functional stress to the prosthesis has to be considered. For many indications, physiological fibrin and tissue ingrowth alone provide sufficient fixation (e.g. TEP).

(5) Three-dimensional constructions may support the easy placement of a device, but with the disadvantage of reduced porosity. As 3-dimensional constructions with sufficiently large pores offer the option for tissue regeneration, these may be a valuable future option.

(6) As the development of a long-term complication can never be completely excluded, a postoperative visualization of the textile can help to avoid unnecessary revisions. If indicated, the addition of ferro particles to the polymer fibers allows depiction on MRI with sufficient contrast to adjacent tissues [24].

(7) As even the best implant is not as good as healthy tissue, the indication to use an alloplastic prosthesis always has to be restrictive, and is of course influenced by the risk profile of the device as well as of the patient. The surgeon ultimately has to provide an individual risk-benefit assessment.

(8) The incidence of complications from permanent implants accumulates over time; consequently, the age of the patient has an impact on the risk-benefit balance.

(9) As most of the device-related complications with comparably rare incidences are not reported within clinical studies, individual experiences may be as valuable as the published literature.

(10) In any case, all patients with an implant should be monitored and recorded in a personal register which some of the public registries can use, providing a highly valuable set of variables for adequate quality control [7, 25].

Last but not least, the cost is relevant … but this is another story as costs are unpredictably affected by the local regulations of insurance and health systems. Subsequent costs for treating possible late-onset complications have to also be considered, making the length of surveillance also a factor.

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