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Effect of biomaterial design criteria on the performance of surgical meshes for abdominal hernia repair: a pre-clinical evaluation in a chronic rat model

Gabriela Voskerician · Judy Jin · Michael F. White · Christina P. Williams · Michael J. Rosen

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Abstract Despite the recognized advantage of surgical meshes in abdominal hernia repair, reports of long term complications after implantation are increasing. 25 chronic hernia rats underwent incisional repair ($n = 5$/mesh group) with compressed poly(tetra-fluoro-ethylene) (cPTFE), expanded poly(tetra-fluoro-ethylene) (ePTFE), polypropylene (PP), poly(ethylene-terephtalate) + collagen (PET + C), and porcine intestinal submucosa (SIS). At 30 days, the extent and strength of intra-abdominal adhesions was evaluated, along with tissue-mesh integration, material shrinkage, and inflammatory response. The extent and tenacity of adhesions were reduced in PET + C and SIS, while tissue contraction was largely reduced in the presence of cPTFE. The tissue integration was not affected by composition or material construction. The host tissue response was elevated and arrested in a chronic imflammatory phase in the presence of PET + C and SIS, and resolved in the case of cPTFE. The different composition and material construction did not affect significantly the overall performance of the evaluated surgical meshes, apart from PP.

1 Introduction

Incisional hernias develop in up to 13% of all laparotomies [1]. Large abdominal wall defects are associated with 25–52% recurrence rates upon primary repair [1]. The implementation of a synthetic mesh tension-free repair has been shown to minimize the recurrence rates associated with the repair of large abdominal defects, yet it continues to be a challenge [1, 2]. Patients in this category are often obese, have a history of previous operations, and suffer from a range of comorbidities that render the management of hernia repair difficult [2]. Advanced abdominal wall pathologies such as poor or loss of musculature and impossibility of peritoneal containment of the herniated visceral mass further affect clinical management of hernia repair [2–4].

The function of synthetic meshes is to provide either mechanical closure to the defect (sublay technique) and/or induce a strong scar tissue that incorporates the mesh within the surrounding environment [5]. However, the placement of a synthetic mesh during hernia repair leads to short as well as long term clinical complications including seroma or infection development, mesh shrinking and migration, visceral erosions, adhesions, and chronic pain [6, 7]. These complications have been linked to specific mesh-related composition and design parameters responsible for inducing in some cases a persistent and active inflammatory response, irregular or low formation of scar tissue leading to insufficient mesh integration in the reparative tissue area, and over-engineered biomechanical properties contributing to long term stiffness [5].

Supported by the clinical finding outlined above along with strict Food and Drug Administration (FDA) guidelines for safety and efficacy, the performance of the ideal mesh should not be altered by the tissue environment nor produce a foreign body reaction. The ideal synthetic mesh should be chemically inert and noncarcinogenic, nonallergenic; capable of rendering the necessary mechanical support to the surrounding environment; acting as a

G. Voskerician (✉) · M. F. White
Proxy Biomedical Limited, Spiddal, Co, Galway, Ireland
e-mail: gxv4@case.edu; gabriela.voskerician@case.edu

J. Jin · C. P. Williams · M. J. Rosen
Department of Surgery, Case School of Medicine, Case Hernia Institute, University Hospitals Case Medical Center, Cleveland, OH, USA

suitable template for tissue remodeling; and maintaining its inherent compositional and structural characteristics post-sterilization [2, 3, 8]. None of the clinically used meshes incorporate all the parameters associated with the construct and performance of an ideal mesh.

Therefore, the aim of this study was to investigate the pre-clinical role of composition and construction parameters on the biocompatibility and the performance of surgical meshes in a chronic hernia rodent model. The surgical mesh variants evaluated spanned from synthetic to biologic, incorporating different chemistries, fabrication methods, filament type, weight, and pore size. Evaluations focused on clinically relevant aspects including extent and tenacity of adhesions, mesh shrinkage, and host tissue response. Further, a chronic hernia model was created to more closely resemble the clinical pathology facing the surgeon during hernia repair and follow-up management.

2 Materials and methods

Female Sprague–Dawley rats (Charles River Laboratory, Wilmington, MA) weighing between 225 to 250 g were acclimated and housed under standard conditions. All animal care and operative procedures were performed in accordance with regulations from the Institutional Animal Care and Use Committee. Six rats were assigned to each mesh group that included compressed PTFE (cPTFE, MotifMESH, Proxy Biomedical Incorporated, Galway, Ireland), expanded PTFE (ePTFE, DualMesh, W.L.Gore & Associates, Flagstaff, AZ), polypropylene (PP, Prolene, Ethicon, Cincinnati, OH), polyethylene-terephtalate + collagen (PET + C, Parietex Composite, Covidien, Norwalk, CT), and small intestine submuscosa (SIS, Surgisis, Cook Medical Inc, Bloomington, IN) (Tables 1, 2; Fig. 1) [2, 9–11].

2.1 Hernia model

A hernia model was adapted from an established protocol. After the rat had been properly anesthesized using rodent cocktail (ketamine, xylazine, acepremazine) and prepped with betadine solution, a 2 × 4 cm skin flap was raised through the avascular prefascial plane. A 3 cm midline laparotomy incision was then made, and the procedure completed with skin closure only. After 28 days, the rats all develop midline ventral hernias with intact hernia sac and a mean hernia defect size of 1.5 × 2.5 cm.

2.2 Hernia repair

At the second surgery, the skin flap incision was identified and the prefascial plane re-entered. The hernia sac was dissected free from the skin flap, and it was excised to the hernia edge. Each hernia defect was measured on two perpendicular axes to determine the overall shape and dimensions of the repair material. Then, an intraperitoneal underlay repair was performed, where the mesh was placed between the contents of the abdominal cavity and the abdominal wall, using a 0.5 cm overlap of each mesh with the respective fascial edge of the abdominal tissue. The dimensions of each mesh at the time of the repair were recorded. The mesh was anchored at eight equidistant points using 4–0 Prolene sutures. Finally, the skin incision was closed with 4–0 Nylon suture material (Monosoft, US Surgical, Norwalk, CT). All surgical procedures were conducted under aseptic conditions.

2.3 Postoperative care and euthanasia

Rats were housed one per cage. Following recovery from anesthesia, the animals were given food and water ad libitum. During the survival time, the animals were observed daily for evidence of wound infection or wound breakdown.

Table 1 Characteristics of commercially available meshes for abdominal repair surgery

Material composition	Mesh construction	Pore size (μm)	Thickness (mm)	Aerial density (kg/m^2)	Surface area	Product
cPTFE	Macroporous, non-woven	2350	0.15	0.19	Low	MotifMesh Soft Tissue Patch
ePTFE	Nano porous/closed, dual sided	22	1.0–2.0	0.32[a]	High	DualMesh
PP	Macroporous, monofilament	640–920	0.5	0.085	Moderate	Prolene
Polyethylene-terephtalate + collagen hydrogel	Macroporous composite	1500	0.4	Not available	High	Parietex Composite
Small intestinal submucosa	Nanoporous, heterogenous	0.2–0.5	1.0–2.0	Not available	High	Surgisis

[a] *Note*: overall aerial density of the dual design construct

Table 2 Mechanical properties of biomedical polymer films and biologics used as materials in mesh fabrication for abdominal repair surgery

Chemical composition	Water absorption (%)	Tensile strength (MPa)	Elongation at break (%)	Degradation mechanism
PTFE	0.01–0.05	15–40	250–550	Oxidation by host
PP	0.01–0.035	21–40	100–300	Oxidation by host
Polyethylene-terephtalate	0.06–0.3	42–80	50–500	Hydrolysis, oxidation/ oxidation by host
Small intestinal submucosa	2.5	0.5–6	15	Oxidation by host, enzymatic

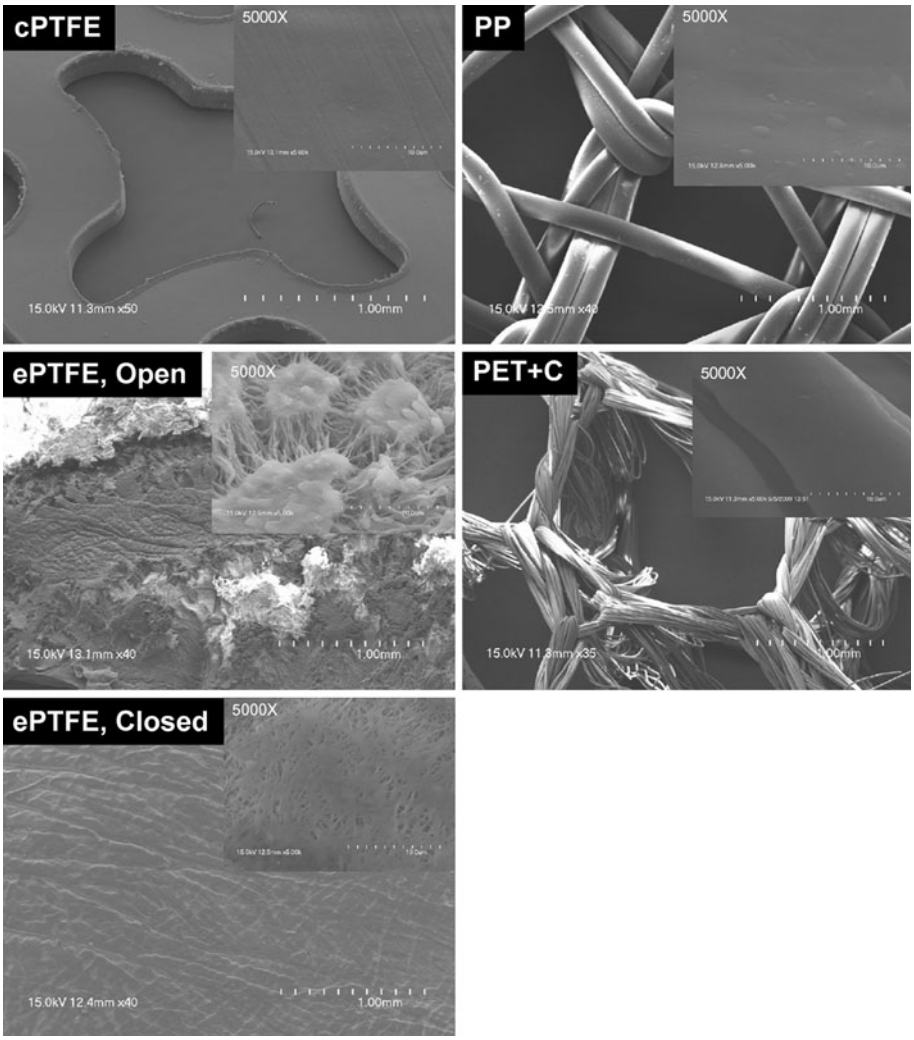

Fig. 1 Material construction of commercially available meshes. * Note: SIS was not available for examination by Scanning Electron Microscopy

The animals were euthanized 30 days following surgical treatment of hernia using a carbon dioxide chamber. The skin incision was then re-opened and the series of analyses described below was performed.

2.4 Necropsy and histological evaluation

Mesh measurements, adhesion assessment, and tissue integration evaluations were performed at the time of necropsy. The mesh size measured at necropsy was compared to its original size to calculate overall mesh shrinkage. The type of tissue adherent onto the mesh (i.e. omentum, intestines or liver) was recorded, along with a qualitative estimation of adhesions coverage (% surface area coverage). The qualitative estimation of adhesion coverage was performed through visual inspection by the same surgeon throughout the entire length of the study. A quantitative morphometric analysis of % surface area coverage was precluded by the small size of the repair site and care in avoiding the manipulation of adhesions.

Finally, quantitative mechanical analysis on the tenacity of intestinal adhesions and the strength of mesh-native abdominal wall integration were performed.

The quantitative mechanical analysis was performed using a hand-held tensiometer (Toriemon FGC B series, NICEC-SHIMPO Corp., Japan). The instrument recorded a force value (Newtons) every time intestinal adhesions were pulled away from the mesh surface (tenacity of adhesions) or every time each mesh was pulled away from the surrounding overlapping native abdominal tissue (tissue integration). For the latter case, testing was conducted after the original suture knots were removed.

Tissue specimens obtained at necropsy that included the mesh and the adjacent abdominal wall, were preserved in 10% buffered formaldehyde (Fisher Scientific, Fair Lawn, NJ). The Hematoxylin and Eosin (H&E) and Masson's TriChrome staining process and specimen imaging followed previously described protocols to evaluate collagen deposition and evidence of residual inflammatory infiltrates present (GV PAPER 2003). Histological grading was performed as follows: 0 = no, 1 = minimal, 2 = mild, 3 = moderate, 4 = extensive alterations in comparison to tissues of native rats [12].

2.5 Statistical analysis

Statistical analysis was performed using the R software. Comparisons between continuous variables were done using the student's *t*-test. For categorical values, Fisher's exact test was used. A P value of less than 0.05 was considered statistically significant.

3 Results

3.1 Gross evaluation

All animals survived the study period without any complications. There was no wound infection or wound breakdown noted during the survival period. At the time of necropsy, no hernia recurrence was evident within any of the mesh group. However, four of the six animals in the SIS group presented frank pus between the skin flap and the mesh itself. Further, one animal in the PET + C mesh group developed a significant seroma; approximately 20 ml of clear fluid was aspirated above the mesh.

3.2 Extent and tenacity of adhesions

PET + C and SIS mesh groups presented only omental adhesions, while PP, ePTFE, and cPTFE displayed adhesions to omentum, bowel, and liver. The percentage of mesh covered by adhesions ranged from 18 to 54%, with cPTFE having the highest adhesion coverage (PET + C 18 ± 22%, PP 22 ± 24%, ePTFE 30 ± 27%, SIS 53 ± 52%, and cPTFE 54 ± 24%, ANOVA $P = 0.15$). The adhesion tenacity was higher in the cPTFE mesh group compared to the other meshes (cPTFE 12 N, PP 8 N, SIS 5 N, ePTFE 5 N, PET + C 4 N, ANOVA $P = 0.003$).

3.3 Mesh contraction and abdominal wall integration

Comparisons of contraction among mesh groups as a result of the fibrous encapsulation, identified SIS and ePTFE as undergoing significant in vivo changes compared PP, PET + C or cPTFE (SIS 55 ± 16%, ePTFE 50 ± 4%, cPTFE 20 ± 17%, PET + C 18 ± 20%, PP 15 ± 10%; ANOVA $P = 0.0004$, Fig. 2). Tissue integration force, however, was not significantly different among the five mesh groups (PET + C 16 ± 6 N, cPTFE 15 ± 9 N, SIS 14 ± 6 N, PP 13 ± 4 N, ePTFE 8 N ± 8, ANOVA $P = 0.30$).

3.4 Histological evaluation

The evaluation of the host response to the presence of the surgical meshes used for repair determined that cPTFE induced a significantly reduced inflammatory and wound healing response compared to the other materials (ePTFE $P = 0.014$, PET + C $P = 0.0001$, PP = 0.0054, and SIS $P = 0.0001$, respectively), while ePTFE and PP displayed a similar inflammatory response ($P = 0.36$) (Figs. 3, 4).

4 Discussion

The long term biocompatibility for alloplastic materials has been succinctly described by CDRH (Center for Devices and Radiological Health) as "the ability of an implant to

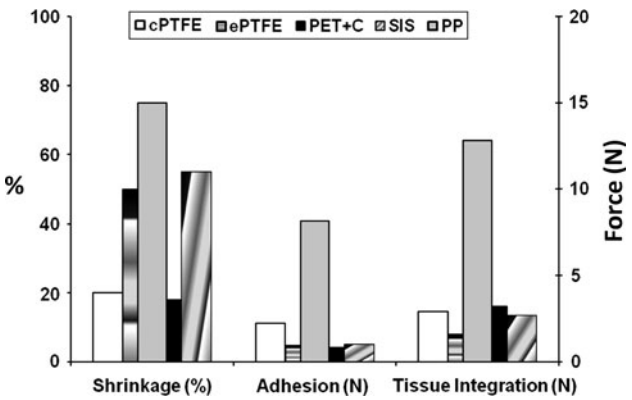

Fig. 2 Evaluation of material shrinkage (%), intra-abdominal adhesion (N), and tissue integration (N)

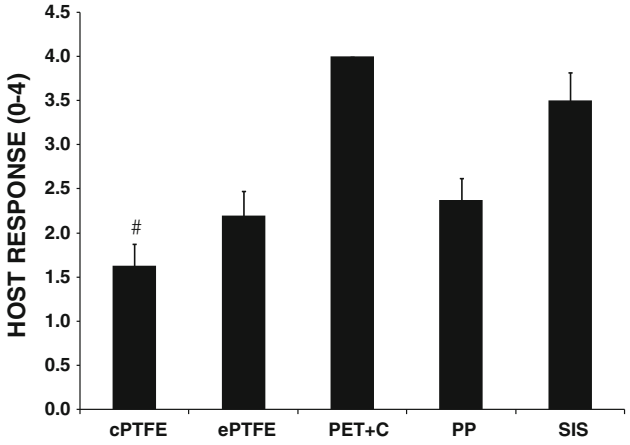

Fig. 3 Histometric evaluation of the host tissue response to the presence of repair surgical meshes

fulfill its predetermined function, achieving a high level of tissue incorporation without exercising any undesired or systemic side-effects" [6, 13]. As interpreted by Weyhe et al., this definition implies that the implant should exercise its intended function in the short as well as the long term, undergo a well studied and understood wound healing process, and provoke no local or systemic complications [6]. Such approach led to a complete overhaul and restructuration of composition and engineering design parameters for surgical meshes. In this context, the mesh weight has emerged as a critical factor shifting the mesh design towards lighter materials, a standard that is clinically recognized today. Yet, review of the clinical literature revealed that lighter meshes, such as Vypro II®, have been found to induce enhanced tissue contraction (shrinkage) than a heavier weight control, Atrium® [6].

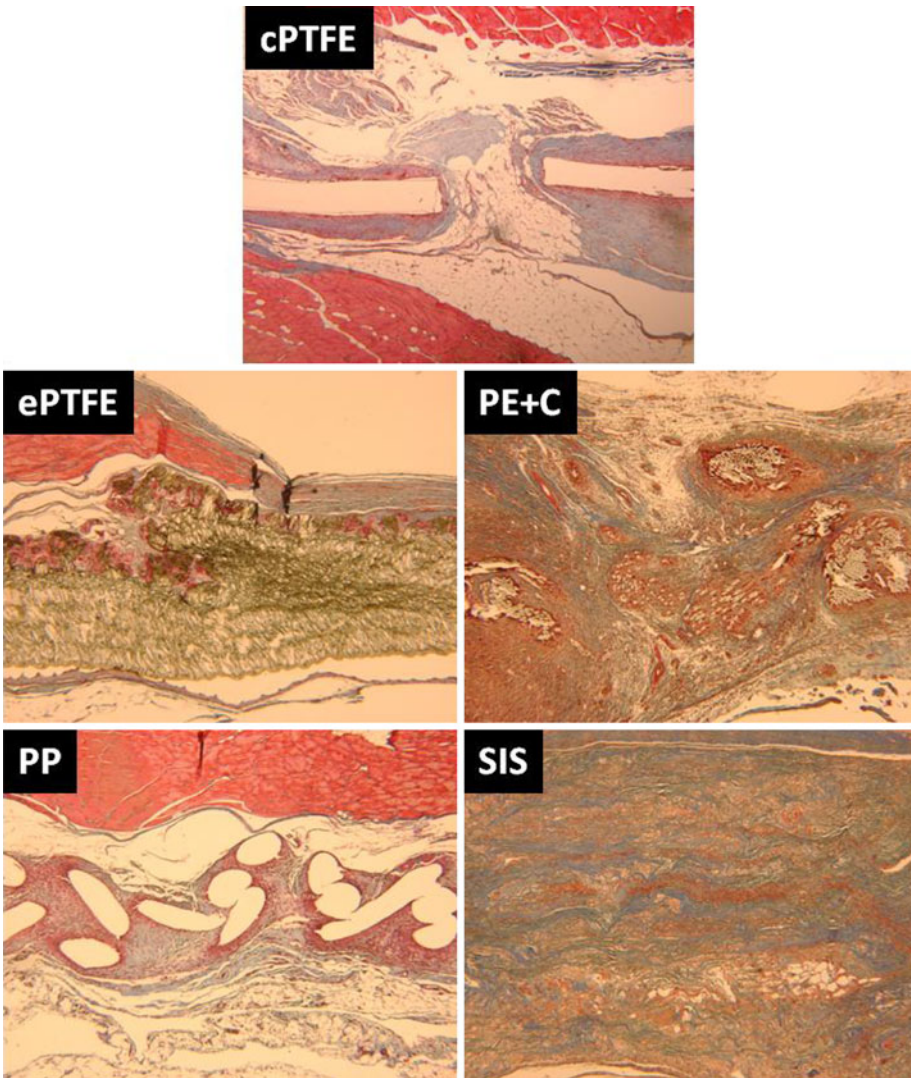

Fig. 4 Host tissue response to the presence of repair surgical meshes (Masson's TriChrome, 4×)

The compounded role of various parameters within a surgical mesh design leads to its overall performance. However, the discrete effect of each individual parameter can only be inferred, and often it is abused in data reporting, if appropriate mesh controls are not concomitantly evaluated or available for evaluation. In this reporting, the role of mesh composition and engineering design parameters including weight, pore size, and filament type are first explained in the context of individual design parameter, then related to the overall pre-clinical recorded response.

4.1 Chemical composition

The use of polymers is essential to the fabrication of medical devices, including meshes for abdominal repair surgery. Such polymers may be derived from natural sources or as a result of synthetic processes. Natural derived polymers such as collagen have evolved past the simple extraction of the active collagen polymer to tissue scaffold structures exemplified in this study by SIS. However, the naturally sourced polymers are sometimes eclipsed by the seemingly endless variety of synthetic polymers that are available today. Among those, hydrophobic materials such as PTFE and PP compete against more polar (hydrophilic) materials such as PET (Table 2) [11]. The chemical composition of a polymer will affect its mechanical properties and in vivo stability (Table 2). While materials such as PP and PTFE will not undergo hydrolytic degradation, PET, a polyester, will. Further, PET is also susceptible to oxidative degradation due to its ester groups, enhanced by a supplementary degradation mechanism common to all polymers, the direct oxidation by the host. The latter degradation mechanism is the result of host generated molecular species culminating with a foreign body reaction characterized by a continuous process of frustrated phagocytosis by the foreign body giant cells [12, 14]. In particular specific to SIS is the process of enzymatic degradation of the collagen scaffold by local collagenases (Table 2). The extent and severity of the degradation mechanism will play a significant role in the in vivo long term modulation of mechanical properties specific to each material. Thus, PP and PTFE may present an in vivo long term stability superior than that of PET + C or SIS. Further, histometric evaluation employed in this study identified SIS as inducing the most significant host tissue response among all material groups, clearly not resolved 30 days post-operatively (Figs. 3, 4). Pathologic examination of the harvested sections suggests a chronic and vigorous inflammatory and wound healing response mounted by the body against the material itself rather than a successful healing process. Further longer term evaluation will be necessary to determine the potential implications for clinical outcomes.

4.2 Weight

Traditional synthetic meshes have been classified into heavy weight or lightweight depending on whether their weight is equal to or greater than 80–90 g/m^2 or less than this value [15, 16]. The rationale for developing a lighter weight mesh is to introduce less material in situ, which has been equated with a reduction in the host tissue response as well as less fibrosis. One aspect of mesh weight that is sometimes neglected is its implant size. Weyhe et al. commented on the gradually less relevant impact of mesh weight as its implant size increases [6]. In the present study, the size of the repair averaged 2.4 × 3.5 cm^2, equivalent to a large hernia in a clinical setting. While characterized by lower aerial density compared to cPTFE, PP presented a less satisfactory host tissue response. Considering that both materials are accepted as hydrophobic, such observation supports Weyhe's suggestion regarding the diminished relevance of aerial density with increased defect size.

4.3 Pore size

Following the past three decades of continuous clinical evaluation of surgical meshes, it has been recognized that to ensure good tissue integration of the material, pores should be in excess of 75–100 μm in size, largely because it was found that this size reduces in particular the incidence and persistence of infection [17]. Recent studies further suggested that only meshes with pore sizes greater than 1,000 μm foster a physiologic wound healing response rather than the traditional fibrous encapsulation [18]. A number of groups have further supported the correlation between large pore size and better wound healing/tissue integration by observing that larger pore meshes led to less overall fibrous encapsulation followed by tissue contraction than meshes with small pores [16, 19]. Further, employing immunohistochemical analyses of harvested tissues, Pasqual et al. reported on the disparity between early deposition of collagen type I and type III between large pore versus small pore meshes. The predominant presence of type III collagen around the large pores mesh fibers led to a better tissue development and incorporation compared to small pore meshes [16]. This study supports the findings by Pasqual et al. identifying cPTFE as performing significantly better in regard to tissue wound healing than meshes of lesser pore size (Table 1).

5 Conclusions

Material design parameters such as chemical composition, weight, pore size, and filament structure represent critical

parameters employed in surgical mesh design. The right balance between composition and material construction of surgical meshes can lead to similar performance in the field. This study supports such hypothesis by demonstrating that the different composition and material construction of the evaluated meshes did not affect significantly the overall performance of each surgical mesh (extent and tenacity of adhesions, tissue integration, and foreign body reaction) apart from PP.

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