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Early biocompatibility of crosslinked and non-crosslinked biologic meshes in a porcine model of ventral hernia repair

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Abstract

Purpose—Biologic meshes have unique physical properties as a result of manufacturing techniques such as decellularization, crosslinking, and sterilization. The purpose of this study is to directly compare the biocompatibility profiles of five different biologic meshes, AlloDerm® (non-crosslinked human dermal matrix), PeriGuard® (crosslinked bovine pericardium), Permacol® (crosslinked porcine dermal matrix), Strattice® (non-crosslinked porcine dermal matrix), and Veritas® (non-crosslinked bovine pericardium), using a porcine model of ventral hernia repair.

Methods—Full-thickness fascial defects were created in 20 Yucatan minipigs and repaired with the retromuscular placement of biologic mesh 3 weeks later. Animals were euthanized at 1 month

and the repair sites were subjected to tensile testing and histologic analysis. Samples of unimplanted (de novo) meshes and native porcine abdominal wall were also analyzed for their mechanical properties.

Results—There were no significant differences in the bio-mechanical characteristics between any of the mesh-repaired sites at 1 month postimplantation or between the native porcine abdominal wall without implanted mesh and the mesh-repaired sites ($P > 0.05$ for all comparisons). Histologically, non-crosslinked materials exhibited greater cellular infiltration, extracellular matrix (ECM) deposition, and neovascularization compared to crosslinked meshes.

Conclusions—While crosslinking differentiates biologic meshes with regard to cellular infiltration, ECM deposition, scaffold degradation, and neovascularization, the integrity and strength of the repair site at 1 month is not significantly impacted by crosslinking or by the de novo strength/stiffness of the mesh.

Keywords

Biologic mesh; Crosslinking; Ventral hernia repair; Tensile strength; Remodeling

Introduction

Incisional hernias are responsible for a significant amount of wound-related morbidity in general surgery. Ventral incisional hernia formation is a prevalent problem as it arises in up to 20% of patients who have had previous laparotomy. Recurrence after primary ventral hernia repair has been reported to be in excess of 60% [1], especially when the loss of abdominal domain creates inadequate autogenous tissue to create a tension-free repair. Synthetic textile meshes have revolutionized hernia surgery, reducing recurrence rates to 0–24% [1–3]. As such, synthetic meshes are utilized to restore the integrity of the abdominal wall. Repair techniques include securing the prosthetic in the retroperitoneal or intraperitoneal space. Rare complications of mesh erosion and fistulization have been reported with the use of polypropylene mesh [4–6]. However, mesh infection is a more relevant concern for complex ventral incisional hernia repair. Biologic mesh is an alternative material for use in a compromised surgical field [7–9].

Biologic meshes are grafts harvested from human dermis or animal dermis, pericardium, or intestinal submucosa, which are vigorously processed to remove cells and immunogenic moieties, leaving behind the extracellular matrix (ECM) as a scaffold into which host cells and vessels can repopulate after implantation. In general, biologic meshes are believed to have superior biocompatibility to synthetic meshes, as they are less prone to chronic inflammatory responses [10] and are more resistant to harboring bacteria if implanted in a contaminated field [3, 7, 8, 11–13]. Furthermore, some biologic meshes are chemically crosslinked to render the collagen more resistant to degradation in vivo. This step is believed to augment the strength and longevity of these materials while providing the benefits of a biologic scaffold [10, 14–16]. Some crosslinked biologic products, however, have been shown to incite more inflammation than polypropylene [10, 17]. Despite the clinical use of crosslinked biologic mesh, it is poorly understood what role chemical crosslinking plays in the remodeling of these materials and the integrity of the tissue-graft repair site.

The purpose of the current study is to compare the biomechanical properties and histologic remodeling profiles of five selected biologic meshes using a porcine model of ventral hernia repair. We hypothesize that there will be detectable differences in both the physical integrity and histologic response to crosslinked versus non-crosslinked meshes after 1 month in vivo.

Materials and methods

This study was conducted under a protocol approved by the Washington University School of Medicine Animal Studies Committee. Twenty female Yucatan minipigs were used for this study. The animals were housed, fed, and handled according to the Guide for the Care and Use of Laboratory Animals [18] and standard protocols on file with the Washington University Division of Comparative Medicine. Strict sterile conditions were maintained intraoperatively. Biologic meshes utilized in this study included: AlloDerm® (LifeCell Corporation, Branchburg, NJ, non-crosslinked human dermis), PeriGuard® (Synovis Surgical Innovations, St. Paul, MN, crosslinked bovine pericardium), Permacol® (Covidien, Mansfield, MA, crosslinked porcine dermis), Strattice® (LifeCell Corporation, Branchburg, NJ, non-crosslinked porcine dermis), and Veritas® (Synovis Surgical Innovations, St. Paul, MN, non-crosslinked bovine pericardium). A model of ventral hernia repair was utilized by creating bilateral abdominal wall defects in the Yucatan minipigs and repairing these defects with a preperitoneal technique 21 days after hernia creation, as described previously [19].

The manufacturer's "Instructions for Use" were followed for the handling and manipulation of the biologic grafts. The preperitoneal repair was performed by opening the previously created abdominal wall defects and dissecting down to the underlying peritoneum, and the biologic grafts were positioned bilaterally in the preperitoneal/retromuscular space. Grafts were oriented with the long edge (10 cm) running axially and the short edge (8 cm) running transversely, and were secured with eight circumferential transfascial interrupted sutures of #0 Prolene placed approximately 3 cm apart and at least 1 cm from the graft edge (Fig. 1). An overlap of 2–3 cm was provided circumferentially between the graft–abdominal wall interface. The hernia sac was closed with interrupted #0 PDS to eliminate excess dead space. All incisions were closed with a double layer of interrupted 3–0 PDS suture and sealed with cyanoacrylate-based dermal glue. The postoperative care was similar to that of the hernia creations.

After a survival of 1 month, animals were sedated with intramuscular telazol (4 mg/kg), xylazine (2 mg/kg), and ketamine (2 mg/kg). Euthanasia was then performed by the administration of IV pentobarbital (>100 mg/kg) or by the administration of IV potassium chloride (> 100 mg/kg IV) under anesthesia. Following euthanasia, the abdomen was opened longitudinally along the midline, and the mesh samples were visually inspected for in situ appearance. The abdominal wall was harvested en bloc from the animal and trimmed to one muscle layer of thickness in order for specimens to fit into grips for tensile testing. The peritonealized transversus abdominis muscle layer was used for all specimens. As the borders of the implanted meshes were illdefined due to their placement in the preperitoneal plane and as a result of remodeling over time, we utilized the center of each repair site to ensure that the biologic mesh was uniformly included in all specimens. The biologic mesh itself was not dissected out of the abdominal wall for testing. Instead, the specimens consisted of the entire repair site, including both the mesh and the associated abdominal wall tissue as one composite specimen. A 4 × 4-cm specimen of the repair site was recovered, and a 1 × 4-cm strip was reserved for histologic testing, leaving the remaining 3 × 4-cm piece of repair site composite (i.e., mesh + abdominal wall tissue) for tensile testing.

Tensiometry was conducted using an Instron Series 5542 Universal Testing System (Instron, Norwood, MA). Each specimen was oriented vertically, with each end secured inside the grips (Fig. 2) and tested to failure at a rate of 0.42 mm/s (1 inch/min). The maximum load sustained by the specimen was recorded in Newtons (N), and the tensile strength per unit width was calculated by dividing the maximum load sustained by the material by the width of the specimen (N/cm). The approximate stiffness (N/mm) was calculated from the slope of the force-vs-displacement curve in the linear region of the curve. Eight specimens were

tested for each type of implanted mesh ($n = 8$). Specimens of porcine abdominal wall away from the hernia repair sites ($n = 10$) as well as time zero (de novo) specimens of each type of mesh ($n = 8$) were tested in an identical fashion to compare the biomechanical properties of the meshes pre- and postimplantation.

For histologic analysis, a 1×1 -cm piece of mesh–tissue composite was embedded in paraffin. Thin sections were stained with H&E and analyzed under light microscopy at 40, 100, and 200 $\times$ magnification by a veterinary pathologist. Five to ten non-overlapping fields per specimen were evaluated at 100 $\times$ magnification and graded for cellular infiltration, cell types present, ECM deposition, scaffold degradation, fibrous encapsulation, and neovascularization according to a scale adapted from Valentin et al. [20] and published previously [19]. Higher scores on this scale represent more favorable outcomes with respect to graft remodeling; greater cellular infiltration, deposition of ECM, scaffold degradation, and neovascularization with low levels of inflammation and fibrous encapsulation conferring the highest scores. A composite histologic score was also calculated for each sample by taking the average of the scores in each of the six subcategories mentioned above.

Statistical analysis

Data was analyzed by a one-way analysis of variance (ANOVA), followed by a Fisher's least significant difference (LSD) post-test to determine whether significant differences were observed. A P -value of <0.05 was considered to be statistically significant. The data are presented as the mean $\pm$ standard error of the mean (SEM).

Results

Maximum loads sustained during uniaxial tensile testing of de novo biologic meshes were as follows: AlloDerm®, 253.0 ± 15.2 N; PeriGuard®, 169.5 ± 18.3 N; Permacol®, 317.2 ± 23.6 N; Strattice®, 385.1 ± 28.3 N; and Veritas®, 89.6 ± 9.7 N (Fig. 3a). The tensile strength per unit width (N/cm) of each material was calculated by dividing the maximum load sustained by the specimen by the width of the specimen. The tensile strength per unit width (N/cm) were as follows: AlloDerm®, 84.3 ± 5.1 N/cm; PeriGuard®, 56.5 ± 6.1 N/cm; Permacol®, 105.7 ± 7.9 N/cm; Strattice®, 128.4 ± 9.4 N/cm; and Veritas®, 29.9 ± 3.2 N/cm (Fig. 3b). Significant differences were detected between the five mesh types at time zero ($P < 0.01$ for all comparisons) for both maximum load sustained (N) and tensile strength per unit width (N/cm). De novo Strattice® was stronger than de novo Permacol®, which was stronger than de novo AlloDerm®, which was stronger than de novo PeriGuard®, and stronger than de novo Veritas®.

The stiffness of de novo biologic meshes was calculated as the slope of the force-vs-displacement curve in the linear region of the curve, and the results were as follows: AlloDerm®, 18.2 ± 1.3 N/mm; PeriGuard®, 34.8 ± 2.7 N/mm; Permacol®, 58.3 ± 4.0 N/mm; Strattice®, 58.3 ± 7.3 N/mm; and Veritas®, 10.0 ± 1.3 N/mm (Fig. 3c). Significant differences were detected between the five mesh types at time zero ($P < 0.05$ for all comparisons), except between Strattice® and Permacol® ($P = 0.985$). De novo Strattice® was similar in stiffness to de novo Permacol® and greater than de novo PeriGuard®, which was stiffer than de novo AlloDerm® and de novo Veritas®.

All de novo meshes except Veritas® were significantly stronger and stiffer at time zero compared to their corresponding repair sites after 1 month of implantation ($P < 0.001$ for all comparisons). Veritas® was significantly stronger at time zero compared to the repair sites at 1 month, but the stiffness values at 0 and 1 month were statistically equivalent ($P = 0.0569$), with a general trend of greater stiffness de novo.

The maximum loads sustained during the uniaxial tensile testing of native porcine abdominal wall and repair sites 1 month after hernia repair were as follows: native porcine abdominal wall, 16.8 ± 1.8 N; AlloDerm®, 37.1 ± 5.7 N; PeriGuard®, 40.9 ± 7.2 N; Permacol®, 35.6 ± 3.5 N; Strattice®, 47.0 ± 5.0 N; and Veritas®, 29.9 ± 3.0 N (Fig. 3a). The tensile strength per unitwidth (N/cm) of each material was calculated by dividing the maximum load sustained by the specimen by the width of the specimen. The results were as follows: native porcine abdominal wall, 5.6 ± 0.6 N/cm; AlloDerm®, 12.4 ± 1.9 N/cm; PeriGuard®, 13.6 ± 2.4 N/cm; Permacol®, 11.9 ± 1.2 N/cm; Strattice®, 15.7 ± 1.7 N/cm; and Veritas®, 10.0 ± 1.0 N/cm (Fig. 3b). There were no significant differences between the five mesh-repaired sites after 1 month of implantation ($P > 0.05$ for all comparisons) for either maximum load sustained (N) or tensile strength per unit width (N/cm). In addition, no significant differences were detected between the maximum load and/or tensile strength of native porcine abdominal compared to any of the mesh-repaired sites postimplantation ($P > 0.05$ for all comparisons).

Stiffness values, calculated in the linear region of the slope of the force-vs-displacement curve were as follows: native porcine abdominal wall, 1.1 ± 0.2 N/mm; AlloDerm®, 3.6 ± 0.5 N/mm; PeriGuard®, 5.8 ± 0.9 N/mm; Permacol®, 5.8 ± 0.9 N/mm; Strattice®, 3.0 ± 0.5 N/mm; and Veritas®, 2.6 ± 0.4 N/mm (Fig. 3c). No statistical difference was observed between the five mesh-repaired sites after 1 month in vivo ($P > 0.05$ for all comparisons). In addition, no significant differences were detected between the stiffness of the native porcine abdominal wall and any of the mesh-repaired sites after 1 month ($P > 0.05$ for all comparisons).

Histologic analysis of the repair sites revealed that after 1 month in vivo, all three non-crosslinked products (AlloDerm®, Strattice®, and Veritas®) scored significantly higher with regard to cellular infiltration, ECM deposition, and neovascularization compared to both crosslinked meshes ($P < 0.05$ for all comparisons, Fig. 4). Veritas® and AlloDerm® also scored significantly higher than the crosslinked meshes for scaffold degradation. In terms of fibrous encapsulation, Veritas® exhibited the least encapsulation ($P < 0.001$ all comparisons), thereby, achieving the highest score in this category. PeriGuard® was less encapsulated than Permacol® and Strattice® ($P < 0.04$), with Strattice® demonstrating the highest level of encapsulation of all the meshes in this study (highest encapsulation = lowest score, $P < 0.004$). With regard to the cell types present, PeriGuard® demonstrated significantly fewer inflammatory cells and more fibroblasts compared to AlloDerm® ($P = 0.009$). All other comparisons of inflammatory cell types did not reach statistical significance ($P > 0.05$). Evidence of inflammation was observed by basophilic staining on H&E stained specimens, and ECM deposition and fibroblast infiltration by eosinophilic staining (Fig. 5). Combining scores in all six categories is a strong indicator of the overall remodeling process and resulted in a “composite” score for each mesh type (Fig. 6). Non-crosslinked matrices scored significantly higher overall (i.e., had more favorable remodeling characteristics) than the crosslinked materials. In addition, Veritas® scored significantly higher than the other two non-crosslinked matrices, AlloDerm® and Strattice®. $P = 0.000$.

Discussion

An ideal mesh for ventral hernia repair would provide long-term structural integrity, optimal integration at the implantation site, and resistance to bacterial colonization. A material with all of these characteristics has not yet been developed. Although 14 commercially available biologic meshes are in clinical use, relatively few comparative short- or long-term clinical outcomes studies on biologic meshes, and virtually no studies directly comparing biologics against each other, have been published. This study represents the first of its kind to directly

compare the biomechanical and histologic characteristics of biologic meshes in a porcine model of ventral hernia repair.

It is anticipated that a biologic mesh with a very high de novo tensile strength would augment the strength of the abdominal wall, resulting in a repair site with greater tensile strength than the native abdominal wall itself. However, these biomechanical testing results demonstrate that the strength of the native porcine abdominal wall 1 month after hernia repair was not augmented by any of the biologic meshes, even in the case of the strongest de novo materials such as Permacol® and Stratattice®. Furthermore, even though very large differences were detected between the de novo tensile strengths of the five materials, all of them eventually resulted in equivalent repair site strengths 1 month after hernia repair. Thus, it appears that there is little or no relationship between de novo strength and strength of the repair site after 1 month.

It was also expected that the de novo stiffness of the biologic mesh materials could potentially influence the stiffness of the repair site and the overall comfort of the repair. In general terms, stiffness is a measure of the force that a material can withstand as it is deformed or stretched. Materials with greater stiffness are better able to resist deformation and could resist bulging as a clinical outcome after ventral hernia repair. It is also possible, however, that materials which are too stiff (i.e., stiffer than the native abdominal wall) would hinder physiologic movement or cause discomfort in areas that require mobility during respiration, bending, or stretching. Thus, the stiffness of each repair site was compared to the stiffness of the corresponding de novo mesh, as well as to the native porcine abdominal wall without mesh. No significant differences were detected between the stiffness of the native porcine abdominal wall and any of the mesh-repaired sites, despite the very large differences observed between the de novo stiffness of the five types of mesh. Thus, it appears that there is very little relationship between the de novo stiffness of the mesh and the stiffness of the repair site, even for the stiffest de novo materials such as Permacol® and Stratattice®. In addition, materials with the lowest de novo stiffness values such as AlloDerm® and Veritas® did not result in any gross visible bulging at the repair site or evidence of reherniation.

It should be noted, however, that the stiffness of collagenous materials such as the biologic meshes evaluated here is dependent upon the strain at which the stiffness value is measured. In the initial low-strain region of the curve, viscoelastic materials such as collagen behave differently compared to near the maximum load/high-strain region. The “stiffness” values reported here are taken from the linear region near the maximum load and, thus, represent the relative stiffness of the five biologic meshes at high strain and more intense physical activity. In this study, AlloDerm® exhibited greater stiffness than Veritas® at time zero ($P=0.0353$) when measured in the high-strain region. At low strain, corresponding to most daily activities, the greater intrinsic elasticity of dermis materials such as AlloDerm® would likely be more apparent compared to materials comprised of the naturally “stiffer” pericardium, such as Veritas®.

Histologic analyses revealed that two of the non-cross-linked materials (AlloDerm® and Veritas®) exhibited more favorable remodeling characteristics overall (i.e., higher composite scores) compared to both crosslinked meshes (PeriGuard® and Permacol®) after 1 month. In addition, Veritas® scored the highest for the composite remodeling score of all of the non-crosslinked materials evaluated. It is important to note that this overall “composite” score represents six important histologic features of remodeling that influence the body's response to these materials. True remodeling requires a balance between degradation of the original scaffold and the deposition of new tissue and blood vessels. In this study, the subcategory of “scaffold degradation” is defined as a lack of ability to detect

the original scaffold material. When observed together with evidence of cellular infiltration, ECM deposition, and neovascularization, scaffold degradation can be interpreted as strong evidence of remodeling. However, scaffold degradation without the key components of ECM deposition and neovascularization does not represent true remodeling of the repair site and could be detrimental to the success of the ventral hernia repair.

In the individual subcategories, non-crosslinked AlloDerm®, Strattice®, and Veritas® all exhibited greater cellular infiltration, ECM deposition, and neovascularization compared to the crosslinked meshes (PeriGuard® and Permacol®), suggesting that crosslinking may slow cellular infiltration and neotissue development in the early postoperative period. In addition, Veritas® exhibited the least amount of fibrous encapsulation of all five materials, suggesting that it elicits the least foreign body response of all of the materials evaluated. Interestingly, with regard to scaffold degradation and encapsulation scores, Strattice®, though not crosslinked, scored similarly to the crosslinked materials.

Overall, the data suggest that, while crosslinking differentiates biologic meshes with regard to cellular infiltration, ECM deposition, scaffold degradation, and neovascularization, the integrity and strength of the repair site are not significantly impacted by whether or not the material has been crosslinked. Part of the rationale for crosslinking materials is that it renders the mesh more resistant to degradation once implanted. While less scaffold degradation was observed for both of the crosslinked materials evaluated here, we did not observe a significant impact on the strength/stiffness of the repair site.

It is unclear from this short-term data if any of the examined biologic meshes have superior biocompatibility for ventral incisional hernia repair due to the wide variation in clinical scenarios and biological response of individual patients. Additional, perhaps unpredictable, responses will be witnessed clinically for crosslinked and non-crosslinked materials or differences based on the type/source of tissue, method of decellularization, and sterilization process. A goal of ongoing research is to characterize optimal source tissue types, as well as manufacturing and/or crosslinking steps, to allow surgeons to match the physicomachanical properties of a biologic mesh to patient-specific clinical scenarios. Further research also needs to be completed in order to objectively evaluate the biocompatibility profiles of biologic meshes over longer periods of time to better define how the remodeling process evolves with time. Thus, the early results are presented here, and the data at longer implantation times (i.e., 6 and 12 months) will be presented in a subsequent publication.

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Fig. 1. Diagram of mesh placement in the porcine preperitoneal incisional hernia repair. Biologic mesh (8 × 10 cm) was implanted in the preperitoneal plane, secured by eight trans fascial sutures, centered under the 4-cm hernia defect

Fig. 2. Uniaxial tensile testing. The mesh–tissue specimen is secured into grips and pulled apart at a constant displacement (0.42 mm/s). The maximum load (N), tensile strength (N/cm), and stiffness (N/mm) are recorded for each specimen

Fig. 3.

a Maximum load, **b** tensile strength per unit width, and **c** stiffness of de novo mesh ($t = 0$ months) compared to native abdominal wall without implanted mesh and to mesh–tissue composites after 1 month in vivo

Fig. 4. Histologic scoring of all meshes after 1 month in vivo by subcategory: **a** cellular infiltration, **b** cell types present, **c** extracellular matrix (ECM) deposition, **d** scaffold degradation, **e** fibrous encapsulation, **f** neovascularization. Higher scores represent more favorable outcomes with regard to graft remodeling

Fig. 5. H&E photomicrographs of biologic meshes after 1 month in vivo. Non-crosslinked meshes, *top row*: **a** Veritas®, **b** AlloDerm®, **c** Strattice®. Crosslinked meshes, *bottom row*: **d** Permacol®, **e** PeriGuard®. Basophilic (*blue*) staining represents inflammatory infiltrate and eosinophilic (*pink*) staining represents collagen and ECM deposition

Fig. 6.
Histologic scoring of all meshes after 1 month in vivo; composite scores