INTRODUCTION

Biomaterials derived from processed extracellular matrix, commonly referred to as “biologic or bioprosthetic meshes,” are widely used in clinical surgical practice. Their uses include tissue repair and reinforcement in implant-based breast reconstruction, hernia repair, tendon augmentation, dural repair, and wound healing. Following implantation, these materials exhibit different properties from one another, and from the numerous antecedent synthetic mesh materials. However, many surgeons will simply substitute bioprosthetic meshes for synthetic meshes, using the same surgical repair techniques established and optimized for synthetic mesh, but with varied outcomes.

This tenant is especially true in hernia repair. Whereas some synthetic and bioprosthetic materials have demonstrated clear success in reinforcement of hernia repairs, others have been associated with high rates of hernia re-
The SurgiMend (Integra LifeSciences) was adhering peripherally were not. This is consistent with the wall in areas of injury or suture placement, regions extending to the peritoneal surface of the anterior abdominal wall in previous observations. A lack of foreign body reaction to 'scarring into place' following a well-characterized foreign body encapsulation response. A lack of foreign body reaction to SurgiMend (Integra LifeSciences) has been demonstrated previously.

The goal of this study is to improve our understanding of bioprosthetic material behavior following implantation to optimize surgical techniques and outcomes. For example, most hernia repairs fail at the musculotendinous junction, which changes over time as the materials remodel at that interface following implantation. From previous human clinical and animal model experience, we suspect that adherence and revascularization between SurgiMend (Integra LifeSciences) and surrounding tissues are linked to local apposition with each other and/or association with injured healing areas. We hypothesize that in the absence of a classic foreign body response, adherence, revascularization, and cell repopulation are modulated by localized injury and tissue apposition. To test these variables, a novel intra-abdominal implant (IAI) model was created and characterized.

**METHODS**

**IAI Model and Study Design**

The IAI model is not a hernia repair but rather consists of 2 cm × 2 cm² of material implanted intra-abdominally, lateral to a midline incision (Fig. 2). A total of 4 conditions were investigated: (1) limited mesh apposition versus (2) tight mesh apposition; and (3) uninjured versus (4) injured peritoneum (Fig. 2). Mesh apposition was controlled using prolene sutures: 1 central suture for limited apposition or 4 corner sutures for tight apposition, against the anterior abdominal wall. Injury was performed by surgical abrasion of the peritoneal lining. A single, 5-week time point was investigated for each condition. Acellular neonatal bovine dermis (SurgiMend 2.0; Integra Life Sciences, NJ) or a control polypropylene mesh (Prolene; Ethicon, Sommerville, NJ) was implanted. Conditions were repeated in replicates of 5 for SurgiMend (Integra LifeSciences) and 3 for the Prolene (Ethicon) control.

**Animals**

Adult, male, Sprague-Dawley rats were obtained from Charles River Laboratories (Wilmington, MA) weighing between 245 and 300 g. A total of 16 animals were used in this study. Two identical implants were placed per animal, in a pairwise comparison of injured versus uninjured abdominal wall, using the surgical techniques outlined below. Following surgery, animals were housed in individual cages, monitored daily, and fed ad libitum.

**Surgical Techniques**

Each animal was anesthetized with isoflurane. The animal was placed supine, its abdomen shaved, and prepped in povidone iodine. A ventral midline incision was made, and skin flaps were elevated laterally to expose the myofascial abdominal wall. A 4-cm incision was made through the linea alba to enter the peritoneum. On one side of each animal, a 2 cm × 2 cm² was marked and the peritoneal lining was sharply abraded. The contralateral side was left uninjured. Two squares of hydrated mesh were inserted and sutured to the areas of abrasion or noninjury. Sutures (40 Prolene; Ethicon, Sommer-
ville, NJ) were placed in either the center or the 4 corners of each implanted mesh. Sutures were placed transmyofascially through a partial thickness of the SurgiMend (Integra Lifesciences), with knots tied on the subcutaneous plane, to minimize exposure of the suture to the intraperitoneal contents. The midline abdominal muscle and skin were closed in layers with interrupted prolene suture and skin staples, respectively. Skin staples were removed after 7 days.

**Tissue Harvest**

Five weeks after implantation, animals were euthanized and the implant sites were photographed. Each implant was characterized as either adherent or nonadherent to the peritoneal surface, based on the percentage of the implant surface that could not easily be lifted from the abdominal wall. Categories of adherence included the following: less than 25%, between 25% and 75%, and greater than 75%. The composite of implant, muscle, and skin was lastly excised and placed into 10% buffered formalin for histological analysis.

**Histology**

After 1 week of fixation in 10% buffered formalin, specimens were bisected diagonally. The specimens were placed into cassettes, dehydrated, paraffin embedded, sectioned 5 microns thick, and stained with hematoxylin and eosin.

**Statistics**

Results were analyzed by contingency tables using two-tailed Fisher’s exact test because the sample sizes were small (N ≤ 5). Differences between categorical variables were considered significant if \( P < 0.05 \). Calculations were performed using statistical analysis tools provided by InSilico (Hamburg, Germany).

**RESULTS**

**Adherence with Synthetic Mesh**

Synthetic mesh implanted against the peritoneal surface was explanted at 5 weeks, and the results were summarized in Table 1. In a majority of the explants, regardless of the condition, the synthetic mesh was adherent to the abdominal wall in >75% of the total surface area. With limited apposition, some areas of the synthetic mesh had curled away from the abdominal wall and were instead adherent to other internal organs (Fig. 3). Scar tissue had grown through the large pores of the Prolene (Ethicon) mesh, encapsulating the implant (Fig. 3). With tight apposition, the synthetic mesh was not only adherent to the abdominal wall but also often embedded within the muscle itself (Fig. 4). Adhesions to the omentum and bowel were routinely observed with synthetic mesh, but not with bioprosthetic mesh (Table 1).

| Table 1. Summary of Adherent Area and Bowel Adhesions with Bioprosthetic or Synthetic Mesh |
|-----------------------------------------------|-------------|------------|-------------|-------------|-------------|-------------|
| Adherent Area (%)                            | Uninjured   | Synth1etic | Bioprosthetic | Synthetic | Injured     | Synthetic | Injured |
| Limited apposition to anterior abdominal wall |             |            |              |            |             |           |         |
| <25                                           | 5           | 0          | 1            | 0          | 0           | 1          | 0       |
| 25–75                                         | 0           | 2          | 4            | 1          |             |           |         |
| >75                                           | 0           | 1          | <0.001       | 0          | 2           | 0.018     |         |
| Tight apposition to anterior abdominal wall   | <25         | 5          | 0            | 1          | 0           | 3          | 4       |
| <25                                           | 0           | 0          | 0            | 1          | 0           | 0          | 1       |
| 25–75                                         | 0           | 0          | <0.001       | 0          | 0           | >0.99     |         |
| >75                                           | 0           | 3          |              | 4          | 3           |           |         |
| Bowel and/or omentum adhesions               | Yes/no     | 0/10       | 6/0          | <0.001     | 0/10        | 6/0       | <0.001  |
Adherence with Bioprosthetic Mesh

The implanted bioprosthetic mesh was explanted at 5 weeks, and the results were summarized in Table 1. Without injury to the peritoneum, adherence of the bioprosthetic to the abdominal wall was focused at the sutures. In limited apposition, an area of attachment and vascularization originated from the center (Fig. 5); with tight apposition, this attachment/vascularization occurred in the corner regions (Fig. 6). Histologically, a classic foreign body inflammatory response was noted, often extending into the muscle, and encapsulating the synthetic plastic fibers of the mesh: limited apposition, no injury (B, C), and limited apposition, with injury (E, F). No bowel or omental adhesions were observed to the bioprosthetic mesh, and this was statistically significant when compared with synthetic mesh (Table 1). These results are summarized graphically in Figure 2.

Histology

At the 5-week time point investigated, the Prolene (Ethicon) mesh was associated with an inflammatory response consistent with classic foreign body encapsulation (Figs. 3, 4). The mesh was surrounded by fibrous connective tissue including loose collagen fibers, inflammatory cells (macrophages, foreign body giant cells), and fibroblasts. The bioprosthetic mesh, regardless of condition, was repopulated with host vasculature and cells, predominantly fibroblasts but less frequently macrophages, mast cells, and other inflammatory cells (Figs. 5, 6). Cell density and capillary/blood vessel deposition were grossly noted, but not quantitated. In the uninjured conditions, cell density appeared qualitatively greater in regions closer to the suture(s) and lesser in areas distant from them. Capillaries and blood vessels were present through the entire 2 mm thickness of the implant, but more sparse or absent in regions farther from the suture at this time point. With injury, the matrix was tightly apposed to the abdominal wall, but without histological evidence of a strong inflammatory response or foreign body encapsulation response. Qualitatively, the density of cells and blood vessels within the SurgiMend (Integra LifeSciences) appeared greater with peritoneal injury. In the injured, limited apposition condition, the peritoneum regenerated at the periphery up to the region of mesh adherence, and at this interface, mesothelial cells continued around to...
cover the exposed surface of the SurgiMend (Integra LifeSciences). In injured, tight apposition conditions, the mesothelial lining also covered the exposed surface of the SurgiMend (Integra LifeSciences).

DISCUSSION

Most hernia repairs fail at the musculotendinous junction, which changes over time as materials remodel at that interface following implantation. The goal of this study was to understand the behavior of bioprosthetic meshes so that we may modify surgical techniques to improve patient outcomes. Toward this end, an IAI model was employed to compare SurgiMend (Integra LifeSciences), a bioprosthetic mesh, to Prolene (Ethicon), a permanent synthetic mesh. The results demonstrate several important findings.

First, the amount of adherence of this bioprosthetic mesh to the abdominal wall is facilitated by injury of the mesothelial lining. Limited injury occurs with suture placement and is more extensive with surgical abrasion. Without injury or suture placement, adhesion between the bioprosthetic mesh and the peritoneal lining or visceral contents should not occur. In contrast, synthetic mesh will adhere irrespective of injury or suture placement, and results in foreign body encapsulation under all conditions.

Second, adherence of both bioprosthetic and synthetic meshes is strongly associated with tissue apposition. Even with mesothelial lining injury, the bioprosthetic mesh was nonadherent across the entire surface of the implant if the implant was not maintained in tight tissue apposition. The peritoneal mesothelial lining will repair itself from its cut edges, underneath a nonadherent mesh. This results in a central region in which the matrix adheres to the abdominal wall, and a peripheral region where it does not. Interestingly, the SurgiMend (Integra LifeSciences) may have also prevented bowel from adhering to these injured areas, until such time that repair of the injured areas could occur. In contrast, the synthetic mesh was encapsulated and strongly adherent to any tissue maintained in apposition, including uninjured peritoneum and in some cases bowel or omentum.

Third, revascularization originates from areas of injury with bioprosthetic mesh. The source blood vessels were seen specifically near areas of suture placement and extending outward within the SurgiMend (Integra LifeSciences) in the uninjured series. In the injured series, vascularization was less focused but did include the entirety of the adherent portions. Continued angiogenesis toward the periphery occurred even in cases with limited injury and apposition. It is unclear at this time if inherent

Fig. 4. Synthetic mesh with tight apposition was adherent to the abdominal wall and often embedded into the abdominal muscle regardless of injury: tight apposition, no injury (A), and tight apposition, with injury (D). Histologically, a classic foreign body inflammatory response was noted, extending into the muscle, and encapsulating the synthetic plastic fibers of the mesh: tight apposition, no injury (B, C), and tight apposition, with injury (E, F). Black squares in images B and E are magnified and shown in images C and F, respectively. Scale bars = 2.5 mm in B and E, 500 µm in E and F.
signaling with the SurgiMend (Integra LifeSciences) contributes to this neovascularization, but will be the focus of future studies. In contrast, the foreign body response to the synthetic mesh was present throughout the implant and demonstrated scar formation consistent with this classic injury response.

The inflammatory and wound healing responses associated with SurgiMend seem fundamentally different from those of Prolene (Ethicon) mesh. However, it is unclear if these responses can be extrapolated to other bioprosthetic and synthetic materials. Additional questions arise from these data, including (1) Which cell types are specifically involved and are they host tissue specific? (2) How do these results affect the surgical application of these materials and ultimately the clinical results? (3) Are there ways to utilize these principles to modify or improve surgical techniques to get desired outcomes? (4) How are these materials “remodeled” after implantation, and to what effect on clinical outcomes? The animal model used in this study can easily be adapted for these studies and are now ongoing.

Several limitations of this study exist as well. Neonatal bovine dermis was the source material for this study, but other materials are commonly used in hernia repair. SurgiMend (Integra LifeSciences) is known to exhibit greater mechanical strength compared to adult porcine dermal matrices, but its comparative revascularization and remodeling characteristics remain less well defined. Also, the mechanisms of bioprosthetic mesh adherence to host tissue, the signals that govern and coordinate host cell infiltration, and the eventual remodeling that ensues remain unknown. Further studies are currently in progress to help answer these questions. Also, the factors that govern tissue healing in rats may differ from humans, and immediate extrapolation to human surgical procedures may be premature.

Taken together, these results suggest that, depending on the location of the implanted bioprosthetic mesh, important differences may exist in the biology of hernia repair. Well-described techniques for hernia repair include placing mesh as an onlay, as an inlay (within the rectus sheath and/or preperitoneal plane), and as

Fig. 5. Bioprosthetic mesh in limited apposition without injury (A) was adherent only in an area adjacent to the suture. Revascularization originated from this location of injury as well. With injury and limited apposition, the area of attachment extended laterally, but did not extend all the way to the edges (D), suggesting a competition between repair of the peritoneal lining and host tissue ingrowth from the muscle. Histologically, the bioprosthetic was repopulated with host cells, but without indications of a classic foreign body response, including a lack of foreign body giant cells or encapsulation: limited apposition, no injury (B, C), and limited apposition, with injury (E, F). In areas remaining in contact, the muscle is directly against the bioprosthetic without encapsulation or significant inflammation. Black squares in images B and E are magnified and shown in images C and F, respectively. Scale bars = 2.5 mm in B and E, 500 µm in E and F.
an underlay within the peritoneum. If an onlay or inlay is used, limited suture apposition of the bioprosthetic mesh may be sufficient for vascularization due to the large raw surface area present (although the mechanical properties and surgical tenants of hernia repair may still require additional suturing). If an underlay is used, increased rate and extent of vascularization may occur if additional suturing is performed, and/or the peritoneal lining is denuded where the bioprosthetic mesh is in contact with the abdominal wall. Such techniques may allow the bioprosthetic mesh to integrate and vascularize more quickly, which in turn may increase resistance to infection, important in patients who are at higher risk for such a complication. The strength of the hernia repair may also be increased faster and to a greater degree, and less dependent on the sutures placed at the musculotendinous junction, with faster/greater adherence of the mesh to the myofascial abdominal wall. Seroma formation may also be reduced with greater adherence of the mesh to the abdominal wall, decreased dead space, and less inflammatory response. It should be stated, however, that increasing the rate of vascularization and adherence of a mesh has unknown effects.

**Fig. 6.** Bioprosthetic mesh in tight apposition with uninjured (A) and injured (D) abdominal muscle. Adherence is limited to the perisuture area without injury (A), but the bioprosthetic is totally adherence across the surface with in tight apposition with injured muscle (D). Histologically, the bioprosthetic was repopulated with host cells, but without indications of a classic foreign body response, including a lack of foreign body giant cells or encapsulation: tight apposition, no injury (B, C), and tight apposition, with injury (E, F). In areas remaining in contact with injured muscle, the muscle is directly against the bioprosthetic without encapsulation or significant inflammation. Black squares in images B and E are magnified and shown in images C and F, respectively. Scale bars = 2.5 mm in B and E, 500 μm in E and F.

**Video Graphic 1.** See video, Supplemental Digital Content 5, which displays a demonstration of one animal demonstrating the condition of bioprosthetic mesh in tight apposition to uninjured and injured abdominal muscle. Bioprosthetic adherence is limited to the perisuture area without injury to the peritoneum but adherent across the surface in tight apposition with peritoneal abrasion. This video is available in the “Related Videos” section of the Full-Text article on PRSGlobalOpen.com or available at http://links.lww.com/PRSGO/A699.
on its long-term remodeling and longevity of the matrix itself. It is important that future studies are designed to further characterize these properties.

The history and clinical experience with synthetic mesh materials are extensive and have defined a set of expectations for behavior upon implantation. For the surgeon accustomed to using synthetic meshes in hernia repair, using a bioprosthetic mesh may require an additional change in techniques than the simple substitution of materials itself. In addition to patient conditions and comorbidities, the inherent biology of the matrix and its possible effects on clinical outcomes needs to be considered. Adherence, neovascularization, and ultimately remodeling of the bioprosthetic matrix will be affected by several additional variables that need to be considered: whether or not the bioprosthetic is in tight apposition to injured, activated capillaries, whether the mesothelial surfaces are intact or violated, and possibly the distance from an invading blood supply. In conclusion, the results of this study demonstrate clear differences in these variables between bioprosthetic and synthetic mesh materials and highlight the need for further applied research to help surgeons both select appropriate mesh materials, and to apply these materials in the most appropriate manner to achieve quality clinical outcomes for their patients.

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