Biologic and Absorbable Prosthetic: When, Why, and Where Are We Going

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Introduction

The need for tissue reinforcement in hernia repair was recognized as early as the 1800s and was finally realized in the advent of synthetic mesh in 1958 with the introduction of polyethylene mesh by Usher [1]. The benefit of using mesh to repair ventral hernias has been well established [2]. The principle of mesh repair hernia surgery is to reinforce native tissues and provide a scaffold for the cellular and vascular ingrowth and deposition of proteins necessary to integrate the mesh into host tissues. Tissue deposition and ingrowth occurs over the surface of the mesh, allowing distribution of the lateralizing forces of the abdominal wall over the entire area rather than at isolated points of fixation. This has helped significantly decrease hernia recurrence [3].

Synthetic mesh has become a routine part of hernia repair when used for fascial reinforcement. Improved outcomes, with regard to reduction in hernia recurrence, and low rates of wound complication and mesh infection are well documented with use in the appropriate setting [4–6]. However, the use of nonabsorbable synthetic mesh in high-risk patients comes with increased risk and is often warned against by mesh manufacturers. Complications such as wound infections, hernia recurrence, visceral erosion that can result in enterocutaneous fistulae, and chronic mesh infection are possible and significantly more so in high-risk patients [7–9]. The Ventral Hernia Working Group (VHWG) warns surgeons against using nonabsorbable synthetic mesh in the presence of contamination. Prosthetic materials may act as a reservoir for bacteria, biofilm creation, and inhibited clearance of infection by the

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immune system; this in turn leads to chronic infection, inflammation, pain, wound dehiscence, draining sinuses, cellulitis, abscesses, and hernia recurrence. Risk factors for mesh infection and explantation include obesity (high body mass index), chronic obstructive pulmonary disease, prior surgical site infection, longer operative time, enterotomy, or enterocutaneous fistula [10].

Nonpermanent materials for abdominal wall reinforcement can provide an alternative in high-risk patients. In theory, biologic and absorbable synthetic meshes provide mechanical support and reinforcement as well as a temporary scaffold for cellular infiltration during the early critical period in wound healing. Hernia repair with these products should be accompanied by primary closure of overlying fascia whenever possible. As there are many absorbable synthetic and biologic meshes currently on the market, the aim of this chapter is to describe the most commonly used products and existing data. The financial burden of complex hernia repair is significant; defining the value of different meshes is the critical factor determining the continued ability to provide optimal surgical care to these patients.

Biologic Mesh

Biologic meshes, first introduced in the late 1990s, are derived from decellularized, collagen-rich tissues from cadavers and animals. Biologics have been shown to have a lower rate of infection ($p < 0.00001$) and a similar rate of recurrence compared to synthetic meshes, supporting the use of biologic meshes in high-risk patients [8]. Biologic grafts are generally derived from human, porcine, and bovine tissue. Grafts are further divided into categories of cross-linked and non-cross-linked meshes; cross-linked meshes appear to be more stable against degradation but have reduced vascularization and tissue integration. Cross-linked meshes act more like synthetics and are more prone to infection and possible explantation [2, 11, 12]. Infection of non-cross-linked tissue-derived grafts appears to result in accelerated degradation of the collagen scaffold, which can take place before sufficient healing has occurred and has led to concerns regarding hernia recurrence [13]. Despite this, non-cross-linked meshes have been considered an option as they may be less likely to harbor contamination by supporting rapid neovascularization and may decrease the risk of postoperative complications [14]. Furthermore, several publications have suggested a benefit to biologic mesh in complex cases, but there is currently no Level 1 evidence supporting the decision to use either synthetic or biologic in these patients [3–7, 9, 14–17].

Biologic grafts often require specific storage, transport, or pretreatment protocols to preserve the integrity and function of the product. Given that these must be harvested and processed from human or animal tissues and subsequently undergo various methods of sterilization and packaging, variability of the different products is inevitable, and new data are emerging that better characterize the variation in biologic grafts [18]. Biologic meshes are not FDA approved for use in contaminated settings, although this has become their most advocated and prevalent application. These meshes have succeeded in filling a gap in the options available for abdominal wall closure and reconstruction in high-risk patients and have made one-stage repair

Table 6.1 Market available biologic mesh

	Strattice™	XenMatrix™	FlexHD®	Permacol™
Manufacturer	LifeCell Corporation	C.R. Bard, Inc./ Davol Inc.	Ethicon, Inc.	Medtronic Corporation
Cross-linked	Non-cross-linked	Non-cross-linked	Non-cross-linked	Cross-linked
Species	Porcine dermis	Porcine dermis	Human dermis	Porcine dermis
Thickness (mm)	1.76 ± 0.012	1.95 ± 0.012	1.15 ± 0.043	0.91 ± 0.008
Tear resistance (N) [24]	>20 N	>20 N	>20 N	≤20 N
Approximate cost per cm^2 (20×30 cm^2) (USD)	$20–30	$20–30	>$30	$20–30
Registered clinical trials	NCT01987700 NCT01083472 NCT02587403 NCT02121743	NCT02587403 NCT01305486 NCT02691962 NCT02228889	NCT01987700 NCT03145337 NCT02372305	NCT01268514 NCT01644695 NCT02703662

possible, thus improving the chance that of avoiding multiple laparotomies [19]. Although high recurrence rates and cost are often attributed to biologics, supportive studies such as Garvey et al.'s recently reported a hernia recurrence of 8.3% at 5 years in high-risk patients who underwent mesh-reinforced abdominal wall reconstruction with acellular dermal matrix [20]. In that study, human acellular dermal matrix was an independent risk factor for recurrence and porcine performed significantly better [20]. A summary of the most commonly used biologic mesh grafts is included in Table 6.1.

Strattice™

Strattice Reconstructive Tissue Matrix (LifeCell Corporation, Branchburg, NJ) is a non-cross-linked acellular porcine dermal matrix. The manufacturer has published some details of their processing technique and results using 0.25% trypsin and 0.1% sodium dodecyl sulfate prior to incubation in 0.25% trypsin, followed by 560 units/l dispase at 25 °C. According to the manufacturer, evaluation of this tissue processing technique demonstrated "most of the original type I collagen" [21]. Histologic biopsies at 1 month, 6 months, and 36 months demonstrate rapid neovascularization and preserved extracellular matrix for collagen deposition and minimal foreign body reaction. Furthermore, when compared to two other biologic grafts in a nonhuman primate mode, this process resulted in Strattice™ having less susceptibility to collagenase degradation, improved stability, and less inflammatory response when compared to its competitors [22]. Strattice™ has been extensively studied in humans, and the recent publications by Garvey and Huntington show promising results and recurrence under 10% in high-risk patients [18, 20].

XenMatrix™

XenMatrix™ surgical graft (C.R. Bard, Inc. [Davol], Warwick, RI, USA) is a non-cross-linked porcine dermal scaffold with an added antibacterial coat of minocycline and rifampin. According to the manufacturer, their process results in an increased pore size in the tissue scaffold, which may improve cell adhesion and infiltration [23]. In vitro performance data have demonstrated XenMatrix™ to have equivalent or higher suture retention strength, tear resistance, and tensile strength and integrity [24]. A study from Baker et al. examined 74 patients undergoing ventral hernia repair with XenMatrix™AB. They included patients with modified VHWG grade 1 17.6%, grade 2 66.2%, and grade 3 14.9% and reported a surgical site infection rate of 6.8% [25]. They reported a hernia recurrence rate of 5.4% within their 6-month follow-up period.

FlexHD®

FlexHD® Structural Acellular Hydrated Dermis (Ethicon, Inc., Somerville, NJ, USA) is an acellular human dermal matrix derived from donated allograft skin that is processed by the Musculoskeletal Transplant Foundation. Using a rabbit model, the company demonstrated less degradation and better tissue integration of their AHDM compared to APDM at 4 and 20 weeks [26]. With regard to recurrence, FlexHD® has been compared to AlloDerm™ (LifeCell Corporation, Branchburg, NJ). The reported hernia recurrence was 31% in the FlexHD® group and 100% in the AlloDerm™ group. While this is a remarkable difference, it has not been reproduced, and other head-to-head studies have shown recurrence rates of 37% with FlexHD® and 35% with AlloDerm™ [18].

Permacol™

Permacol™ (Medtronic Corporation, Minneapolis, MN) is a cross-linked acellular porcine dermis. According to the manufacturer, the cross-linking process improves the stability of the dermal matrix and allows Permacol to be stored at room temperature. The implant also has greater longevity when compared non-cross-linked mesh [27]. Clinical experience is mixed; however, in a study of 270 patients undergoing ventral hernia repair with either Permacol™ or Strattice™ mesh, the Permacol™ group had a higher rate of postoperative wound infections compared to Strattice™ (21 vs. 5%, $p < 0.01$) and overall complications (28 vs. 13%, $p < 0.05$) including seroma/hematoma and dehiscence [28]. Patients were statistically similar between Strattice™ and Permacol™ groups; however more patients with Strattice™ had clean wound classification (45%) than in Permacol™ group (26%, $p < 0.01$). Within the Permacol™ group, there was a significant difference in overall complication rate between patients with infected and clean wound classifications (55 vs. 35%, $p < 0.05$). A similar hernia recurrence rate was noted between Permacol™ and

Strattice™ groups regardless of patient differences in prior mesh repair, obesity, or technique of mesh repair (reinforcement after primary closure versus fascial bridge).

Currently more than 200 meshes are on the market in the USA, but there have been few direct comparison studies of various biologic meshes [11, 19]. Furthermore, existing studies have been small or have compared meshes in a pairwise fashion, such as Strattice™ versus Permacol™ [19], AlloDerm™ versus Permacol™ [29], AlloDerm™, Permacol™, Surgisis [14], and SurgiMend versus FlexHD® [30]. While others have not demonstrated reproducible results, Huntington et al. examined 223 abdominal wall reconstructions in high-risk patients. Of the five most commonly utilized biologic meshes (AlloDerm™, AlloMax™, FlexHD®, Strattice™, and XenMatrix™), Strattice™ had the lowest hernia recurrence rate of 14.7% ($p < 0.001$) over an 18-month follow-up period [18]. A multivariate analysis controlling for confounding factors including patient comorbidities, hernia size, and intraoperative techniques (e.g., fascial bridge) demonstrated significantly higher odds of hernia recurrence with AlloMax™ (odds ratio [OR] 3.4), FlexHD® (OR 2.9), and XenMatrix™ (OR 7.8) compared to Strattice as a reference. After controlling for patient comorbidities and intraoperative factors, XenMatrix™ was the most expensive biologic mesh with adjusted cost of $59,122 after multivariate analysis compared to AlloMax™, the least expensive at $22,304 [18].

Absorbable Synthetic Mesh

Recently, there has been an increase in interest in absorbable synthetic meshes. These meshes are laminar from absorbable synthetic polymers and have been in clinical use for many years as suture and orthopedic fixation devices [2, 15]. One can change the composition and alter compliance, elasticity, fracture, strength, and rate of absorption and degradation. Compared to tissue-derived products, they have the added advantage of homogeneity, predictability, and limited size constraints. Furthermore, there are comparatively few mandatory storage, transport, or pretreatment requirements to preserve the integrity and function of these products. The most significant advantage of these meshes compared to tissue-derived meshes, however, may be a substantial reduction in cost, as much as 66% by one estimate [31].

Through modification of the micro- and macrostructure and composition of materials, the physical properties of the final implant can be manipulated according to the application, including tensile strength, stiffness, and rate of biodegradation. A summary of the most commonly used absorbable synthetic mesh grafts is included in Table 6.2.

The most common components of absorbable synthetic meshes are polyglycolic acid, polylactic acid, and trimethylene carbonate. Polyglycolic acid (PGA), or polyglycolide, is a semicrystalline hydrophilic polymer rapidly degraded in vivo primarily by hydrolysis into glycolic acid monomers, which are in turn oxidized by the citric acid cycle into CO_2 and water, followed by urinary excretion [15]. To improve its hydrolytic stability, it is frequently copolymerized with other polymers. Polylactic acid (PLA) is derived from lactic acid. It is absorbed significantly slower than PGA

Table 6.2 Market available absorbable synthetic mesh

	Vicryl	Gore Bio-A	PHASIX™	TIGR® Matrix
Manufacturer	Ethicon, Inc.	W.L. Gore & Assoc., Inc.	C.R. Bard, Inc./ Davol Inc.	Novus Scientific
Fiber	92% PGY 8% PLLA	67% PGA 33% TMC	P4HB	1. Primary matrix: PGA:PLA:TMC 2. Secondary matrix: PLLA:TMC
Mechanism of degradation	Hydrolysis	Hydrolysis	Hydrolysis	Hydrolysis
Maintains mechanical strength	14 days		12–26 weeks	6 months
Complete resorption	2–3 months	6 months	12–18 months	3 years
Approximate cost (20 ×30 cm^2) (USD)		$4400	$6775 (20 × 25 cm^2)	$4000

and adds mechanical strength when used in combination with less crystalline polymers such as PGA. PLA undergoes degradation to lactic acid through a process similar to PGA [15, 32]. Trimethylene carbonate (TMC, also polytrimethylene carbonate [PTMC]) is a comparatively elastic polymer that is degraded enzymatically through surface erosion and a macrophage-mediated mechanism. Its common use for biosynthetic hernia mesh is as a copolymer with other substances to increase elasticity of the final compound [15, 16, 33].

Phasix is composed of poly-4-hydryoxybutyrate (P4HB) which is produced by *Escherichia coli* K12 via transgenic fermentation techniques. Therefore, it is free from heavy metal residues from catalysts used during their synthesis. Degradation of P4HB in vivo occurs through surface erosion, and then hydrolysis into 4-hydroxybutyrate (4HB) like PGA and PLA is ultimately metabolized by the citric acid cycle into CO_2 and water. Its properties vary based on orientation of its fibers, but like TMC, P4HB is generally pliable and not prone to fracture [17, 34].

Recognition of the final degradation products of these implants is critical to their safety and overall biocompatibility and is therefore known in detail; end byproducts are typically eliminated through known pathways or are otherwise already present in the in vivo setting. However, the effect of pathogenic bacteria in the infected wound on the physical properties of these materials is less understood, including the effects of bacterial adherence, bacterial enzyme activity, and the altered wound pH.

Our knowledge of the inflammatory processes central to wound healing and mesh biocompatibility is growing. While some inflammation is necessary for wound healing and mesh integration, excessive or prolonged cytokine-mediated inflammation can lead to undesired pathologic effects such as mesh encapsulation or accelerated

degradation. Much investigation remains regarding the precise pathways that define successful mesh integration and fascial reinforcement. For absorbable synthetic products in particular, macrophage activity is central to mesh degradation both for hydrolysis and enzymatic activity; the net effect of the inflammatory response on the properties of the mesh with regard to rate of resorption in the presence of pathogenic bacteria and the associated immune response is a yet unanswered question. Both PGA and PLA are known to substantially increase the acidity of the wound bed upon degradation to their respective monomers, with unknown effects on wound healing [35]; changes in the local pH resulting from polymer degradation can in turn exponentially accelerate the rate of hydrolysis and absorption of mesh [15]. Additionally, PGA has been found to produce a nonspecific foreign body reaction in a small percentage of cases in orthopedic rod implants, resulting in chronic sinus formation [36]. Notwithstanding, although they bear mention, the ultimate clinical significance of these observations remains unclear, since materials derived from these polymers have been in widespread practical use since the 1960s.

Clinical studies are ongoing, and the volume of published data currently available on use in hernia repair for most of these is relatively small. However, we will review four most common types of absorbable synthetic meshes currently in use: Vicryl®, Gore Bio-A®, TIGR®, and P4HB meshes.

Vicryl®

The first absorbable synthetic meshes with widespread use for abdominal wall repair were predominantly polyglycolic acid based. Absorbable mesh used in temporary abdominal closure was first described by Levasseur et al. in 1979 [37]. It soon became an accepted method for fascial closure in contaminated fields where a hernia was already present or when the abdominal wall required gross debridement, such as in closure for necrotizing fasciitis, burns, and after infected mesh removal [38]. Vicryl® (polyglactin 910, PGA(92%):PLLA(8%)), Ethicon, Inc., Somerville, NJ, USA) is representative of this class of materials and is the absorbable synthetic mesh for which the greatest amount of data is available [39]. Vicryl® mesh has a tensile half-life of 2 weeks and is completely absorbed by 4 weeks. Its most commonly reported application in abdominal wall repair is as a damage control measure for temporary abdominal closure as a bridge to an eventual definitive repair, either by serial tightening with delayed primary closure of the fascia or by allowing the wound to granulate with subsequent skin grafting [40]. Recent data suggests it has the same adhesion-producing properties as non-coated synthetic meshes and may increase the inflammatory response while not resulting in any added wound strength [41–43]. A recent randomized control trial between polyglactin mesh placement and intra-abdominal wound vacuum-assisted closure found that both had similar rates of closure (26% vs. 31%, respectively) [44]. Vicryl mesh has been associated with high enterocutaneous fistula rates [45].

Gore Bio-A®

Gore® Bio-A® Tissue Reinforcement (Bio-A®, W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) is a laminar absorbable synthetic mesh composed of a 67% PGA/ 33% TMC copolymer, constructed as a 1.3-mm-thick nonwoven three-dimensional web. Bio-A® is degraded by hydrolysis and enzymatic processes over 6 months. The composition is very similar to Maxon™ (Covidien Inc., Norwalk, CT, USA), and SureTac™ (Smith & Nephew Endoscopy, Andover, MA, USA) used for bone fixation, and is the same material used for Seamguard® (W. L. Gore & Associates, Inc., Flagstaff, AZ, USA). Other applications include treatment of perianal fistulas, [34, 46] paraesophageal hiatal hernia repair, [47, 48] and pelvic floor reconstruction [49]. In vitro evaluation indicates that Bio-A® stimulates significantly less chemotactic pro-inflammatory cytokine production (IL-1β, IL-6, IL-8, VEGF) than two out of three different human dermis-derived biologic meshes and the least absolute production overall [50]. Another study that evaluated neoperitoneum formation found that Bio-A® stimulated less in vitro mesothelial cover, greater macrophage production, and less neoperitoneum production than Tutomesh® or Strattice™, with greater biodegradation than Strattice™ at 90 days post-implantation [51]. Using a rabbit model, Bio-A® showed more type I collagen deposition at 30 days and at a time point significantly earlier than FlexHD®, Strattice®, or Permacol™, with significantly greater fibroblast and vascular ingrowth up to 180 days [52]. Other data indicate that mRNA expression of both type I and III collagen appears to peak significantly earlier in than Strattice® and Tutomesh® [53].

The COBRA (Complex Open Bioabsorbable Reconstruction of the Abdominal Wall) study is a prospective, multicenter trial to evaluate the use of Bio-A® for reinforcement of midline fascial closure in complex ventral hernias with contaminated or clean-contaminated surgical fields. One hundred four patients underwent hernia repair with a single sheet of absorbable synthetic mesh. They reported a wound infection rate of 20%, none of which required implant removal [54]. Hernia recurrence was 17% with 24 months of follow-up. Interestingly, with retrorectus mesh placement, the recurrence rate decreased to 13% [54].

TIGR®

TIGR® Matrix Surgical Mesh (Novus Scientific, Uppsala, Sweden), a dual-filament absorbable synthetic mesh system knitted from two fibers of different composition and rates of degradation, has been commercially available since 2010. The more rapidly absorbed fiber is a copolymer of PGA, PLA, and TMC and accounts for 40% of the composite product. This set of fibers loses tensile strength after 2 weeks, and complete resorption occurs by 4 months. The second polymer is a copolymer of PLA and TMC and makes up the remaining 60% of the mesh by weight, loses tensile strength at 9 months, and is resorbed by 3 years. TIGR® mesh is therefore designed to maintain its maximal tensile strength through 6 months post-implantation with complete degradation by 3 years [55, 56].

Clinical data on TIGR® mesh are available on the company website reveals. A study by Ramshaw et al. demonstrates early results on the use of TIGR® versus biologic mesh for abdominal wall reconstruction in 39 patients. They found equal or better mesh-related and overall outcomes (recurrence, 13% vs. 19%) and over 70% cost savings at a mean follow-up of 12 months [57]. Most recently, a Swedish group reported on a prospective pilot study of 40 primary inguinal hernias undergoing Lichtenstein repairs using TIGR® Matrix with long-term follow-up [58]. In their study, a 22.8% recurrence was noted at 36 months.

P4HB

P4HB was initially investigated experimentally in vitro and in vivo for use in engineered vascular conduits and heart valves [59–62]. It first became commercially available for clinical use in 2007 as surgical suture, with FDA clearance for P4HB absorbable synthetic mesh following shortly thereafter. PHASIX® is not recommended for use in patients with known allergies to tetracycline or kanamycin, and safety and effectiveness for use in children has yet to be established. Currently several P4HB mesh products are available for use in hernia repair, including PHASIX™ Mesh (C.R. Bard, Inc. [Davol], Warwick, RI, USA), PHASIX™ Plug and Patch for groin hernias, TephaFLEX® light mesh (Tepha, Inc., Lexington MA, USA), and Tornier® Surgical Mesh (Tornier, Inc., Edina, MN, USA). Deeken et al. used a porcine preperitoneal bridging hernia model to further investigate the pre- and post-implantation characteristics, of PHASIX mesh and P4HB plug over 52 weeks after removal of the peritoneum to assess the characteristics of the repair alone [63]. Both PHASIX® and P4HB plug had significantly greater burst strength compared to native abdominal wall, and between 6 and 52 weeks, neither showed a significant decline in burst strength, changes in stiffness, or evidence of hernia or diastasis, despite the bridging nature of the repair. The inflammatory response was judged to be mild with mild to moderate granulation and vascularization [63]. Wormer et al. compared 160 (50.2%) patients with prophylactic onlay mesh to 159 (49.8%) patients who did not receive mesh when undergoing DIEP reconstruction [62]. Wormer et al. were able to demonstrate a smaller bulge rate in bilateral DIEP patients with a mean follow-up of 16.4 months [64]. Currently, there is an ongoing prospective interventional trial with an accrual of 112 patients undergoing ventral hernia repair with PHASIX.

Hybrid Mesh

In attempts to join biologic and synthetic meshes, potentially capturing the most desirable characteristics of each, a new category of mesh has emerged. Hybrid meshes include Synecor™ (W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) and Zenapro™ (Cook Medical Inc., Winston-Salem, NC, USA).

Synecor is designed for intraperitoneal use and marketed for use bridging fascial defects and as a replacement for biologic mesh in complex patients. It is comprised

of a combination of layered materials. These include Bio-A™ on the parietal surface, a macroporous knit monofilament PTFE in the middle, and an absorbable and a PGA/TMC nonporous film on the visceral surface.

Zenapro™ is comprised of acellular porcine small intestinal submucosa layered around a core of ultralightweight polypropylene mesh. It is FDA approved for hernia repair. However, like each mesh described previously, it is not approved for use in a contaminated field.

There are no clinical data on either product, but ongoing trials are in effect. Long-term data and definition of appropriate settings for use of hybrid meshes need to be further evaluated.

Conclusion

Abdominal wall reconstruction and hernia repair in high-risk patients remain an area of intense research. Mesh infections are costly complications, dramatically exceeding the up-front expense of any implant in the final calculation, with an unquestionably negative impact on patient quality of life. Understanding the value of mesh repair, impact of complications, and patient quality of life is fundamental. Guidelines should be based on comparative trials and long-term clinical data. As new meshes enter the market, large databases such as the AHSQC will be essential in obtaining long-term follow-up, defining techniques and minimizing complications.

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