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Design strategies and applications of biomaterials and devices for Hernia repair

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ABSTRACT

Hernia repair is one of the most commonly performed surgical procedures worldwide, with a multi-billion dollar global market. Implant design remains a critical challenge for the successful repair and prevention of recurrent hernias, and despite significant progress, there is no ideal mesh for every surgery. This review summarizes the evolution of prostheses design toward successful hernia repair beginning with a description of the anatomy of the disease and the classifications of hernias. Next, the major milestones in implant design are discussed. Commonly encountered complications and strategies to minimize these adverse effects are described, followed by a thorough description of the implant characteristics necessary for successful repair. Finally, available implants are categorized and their advantages and limitations are elucidated, including non-absorbable and absorbable (synthetic and biologically derived) prostheses, composite prostheses, and coated prostheses. This review not only summarizes the state of the art in hernia repair, but also suggests future research directions toward improved hernia repair utilizing novel materials and fabrication methods.

Contents

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1. Introduction

1.1. The clinical relevance of Hernia repair

Hernia repair is among the most common surgical procedures performed worldwide, with approximately 20 million procedures performed annually [1]. Furthermore, the increasing prevalence of abdominal surgeries as well as co-morbidities including obesity has led to an increased risk of hernia development and recurrence [2]. Of the 4 million laparotomies conducted each year in the US alone, up to 800,000 of these patients will later develop complications in the form of incisional hernias [3]. Due to the overwhelming presence of this disease and related, post-operative conditions, the Global Hernia Repair Devices and Consumables Market is estimated to reach $6.1 billion by the year 2020 [4].

1.2. Anatomy and physiology of the Hernia

Hernias can present in a variety of different ways depending on their anatomical location as well as any predisposing factors. In general terms, a hernia is classified as the protrusion of organs through an opening in the cavity that is intended to contain them [5]. The most common hernias are inguinal, ventral, incisional, femoral, umbilical, hiatal, and epigastric [6]. Of the aforementioned, inguinal hernias are the most frequent, accounting for nearly two-thirds of all abdominal wall hernia procedures [7]. Inguinal herniation consists of abdominal contents protruding through a defect in the musculature of the groin [8]. The inguinal region is especially vulnerable to herniation as a result of particular anatomical features involving several layers of fascia and ligamentous tissue coming together in a tight space. Outside of inguinal, almost all other hernias of the abdominal wall can be categorized under ventral hernias, with incisional and congenital being the two main sub-classifications. Incisional herniation can occur as abdominal contents protrude through defects created in the musculature from previous surgical procedures or localized trauma [9]. On the other hand, defects formed in the abdominal wall from birth that lead to herniation can be classified as congenital.

At the level of the rectus superior to the umbilicus the abdominal wall consists of multiple layers: skin, subcutaneous fat and Scarpa's fascia, anterior fascia (anterior rectus sheath), muscle (rectus abdominis), posterior fascia (posterior rectus sheath), preperitoneal fat and peritoneum. The exact layers of the abdominal wall differ depending on the exact location (medial to lateral, or above and below the umbilicus) [10]. Collagenous connective tissue, as is found in the dermis layer of the skin, also appears in several layers throughout the abdominal wall, such as the subcutaneous fascia, transversalis fascia, and the pre-peritoneal layer [11]. The structural integrity of the abdominal wall is provided primarily by the integrated neuromuscular fascia of the transversus abdominis, internal and external obliques, and the rectus abdominis. These muscle groups impart the abdomen with sufficient mechanical strength and elasticity to withstand the pressures generated within the cavity by the internal organs [11]. The peritoneum, which covers both the abdominal wall and the internal organs contained within, enables the organs to move within the abdomen without detaching [11]. A detailed rendering of the abdominal wall and its components is shown below (Fig. 1).

Abdominal hernias develop due to areas of structurally compromised tissues within the abdominal wall. In most cases, hernias occur when damage is sustained to the inner four layers of the abdominal wall, although this is location-dependent (for instance, in the midline a hernia develops when only the midline fascia, or linea alba, is damaged). Excessive damage and loss of musculature within the wall is replaced with scar and connective tissues, which are unable to withstand the pressures exerted within the cavity [11]. Normal everyday actions including laughing, lifting, coughing and standing can significantly increase the intra-abdominal pressure exerted on the abdominal wall. In patients with compromised abdominal wall structure, a substantial increase in intra-abdominal pressure is enough to tear or bulge the abdomen, resulting in a hernia [11]. Additionally, herniation can result from several pathological conditions, such as congenital birth defects of the abdominal wall as well as excessively high intra-abdominal pressure as a result of obesity, ascites, straining due to benign prostatic hypertrophy or constipation, pregnancy and pulmonary diseases in conjunction with chronic coughing [12].

2. The evolution of Hernia repair

2.1. Suture repair

As early as the 1800s, the adverse effects inguinal hernias presented to their patients were recognized and understood. It became

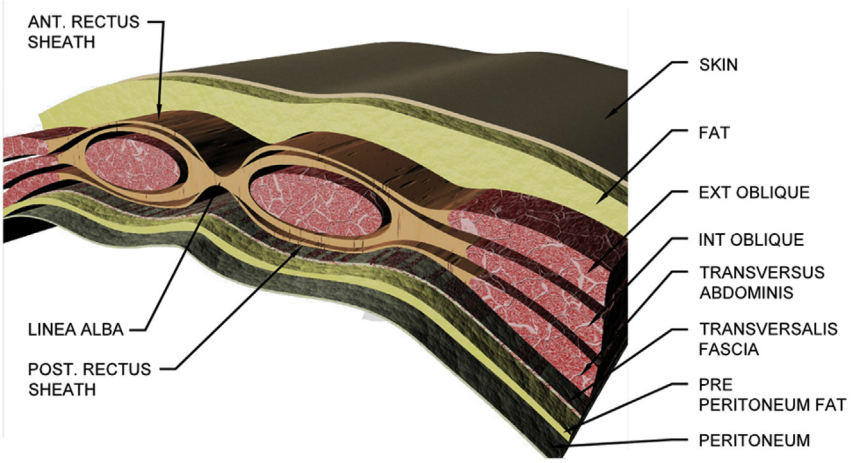

Fig. 1. Detailed rendering of the human abdominal wall with subsequent components.

increasingly apparent to early surgeons, such as Billroth, that the need for an artificial prosthetic capable of replicating the "density and toughness of fascia and tendon" was necessary in order to effectively cure hernia symptoms [13]. Prior to the introduction of novel biomaterials, suture repair, comprising multiple techniques such as Bassini's for inguinal hernias, was the most common method of abdominal hernia repair.

Bassini's technique utilized musculo-aponeurotic repair in order to close abdominal wall defects using sutures under tension [14]. Additional, commonly used suture techniques include simple fascial closure, Mayo with overlap of fascial edges, internal retention sutures, "keel" procedure and the Nuttall procedure [15]. Bassini began his work with silk sutures, transitioning to silver in order to introduce bactericidal properties [16]. Although suture repair can be successful, these techniques suffer from high reoccurrence rates [14].

2.2. Introduction of Hernia meshes

According to George and Ellis, suture repair techniques are fundamentally flawed in that they subject afflicted tissues to unneeded tension, resulting in ischemia, suture cut-out and overall repair failure [17]. Metal sutures began to be reinforced with silver coils by Phelps and later with stainless steel meshes by Babcock. Stainless steel remained the most effective metal; however, its rigid material properties resulted in patient abdominal stiffness, discomfort, sinus formation and fibrotic response [16].

2.3. Mersilene (Ethicon)

In response to the biologically unacceptable performance of metal prosthetics, plastics became the main area of focus for abdominal wall repair in the late 1950s [16]. Dacron, marketed by Ethicon under the trade name Mersilene, became the first nonmetallic, polyester material to be used for abdominal wall prosthesis by Wolstenholme. Stoppa and colleagues utilized large Dacron prostheses, six to ten times larger than the hernia defect, in the pre-peritoneal space to repair abdominal wall defects without the use of sutures. Due to the significant overlap of the Dacron fabric, this method relied on the intra-abdominal pressure and the subsequent tissue in-growth for fixation of the prosthesis [18]. Although Dacron polyester meshes were the first non-metallic prostheses to be used for abdominal hernia repair, a transition to polypropylene based materials occurred as they were believed to be more resistant to infection and tissue adhesion [16].

2.4. Marlex (Bard)

In 1958, Francis Usher introduced the world's first polyethylene mesh [13]. The Marlex mesh was comprised of monofilament high density polyethylene which was woven using hot-melt extrusion [19]. Usher was particularly interested in Marlex because it was strong, inert, non-wettable, and it resisted fragmentation when manipulated. Furthermore, the Marlex mesh provided a pliable alternative to previous, rigid metal prostheses, which lead to reduced patient discomfort and pain [18]. Usher optimized mesh design parameters such as thickness, porosity, stretch-ability and tensile strength and reported that 20% of surgeons were using this prosthesis for abdominal wall repair. In 1962, Usher introduced an improved version of the Marlex mesh marketed by C.R Bard made from polypropylene [16]. The mesh improvements unveiled by Usher and colleagues provided surgeons with substantially expanded treatment options for tension-free abdominal wall hernia repair [20]. Plastic meshes made it possible for surgeons to repair hernias by bridging tissue gaps rather than subjecting them to high tension suture closures, resulting in a decrease in reoccurrences [18].

2.5. ePTFE

In 1963, expanded polytetrafluoroethylene (ePTFE), was discovered by Sumitoma Electric Industries of Japan. A processed version of PTFE, commonly referred to as Teflon, ePTFE differed in that it contained a highly uniform, continuous fibrous porous structure with greatly enhanced mechanical strength. W.L Gore refined this process and in 1983 developed the Gore-Tex Soft Tissue Patch (STP), which was used clinically as a hernia repair prosthesis [18]. The Gore-Tex STP patch was stronger, with suture retention strength equivalent to Marlex (Bard), Prolene (Ethicon) and Mersilene (Ethicon) meshes [21]. Due to the inert nature of the material, The Gore-Tex soft tissue patch became especially useful in intra-peritoneal hernia mesh placement. In contrast to polypropylene, ePTFE meshes placed intra-abdominally produce less inflammatory response and form fewer adhesions to the internal viscera [16]. Koehler and colleagues performed intraabdominal hernia repairs using a ePTFE Dual Mesh (Gore) and found that of 65 patients, 59 (91%) presented no or very thin avascular visceral adhesions 14 days after implantation [22].

3. Prostheses for Hernia repair: necessity and complications

Surgical hernia repair studies performed on large groups of

patients indicate that the use of prosthetic meshes can result in a 50% reduction in recurrence risk for ventral hernias [23]. With regards to incisional hernias, which occur due to compromised musculature resulting from previous abdominal surgeries, the use of mesh prosthetics for repair can decrease the risk of reoccurrence 24 times [24]. The benefits mesh prostheses present to abdominal wall hernia repair are overwhelming. Surgeons continue to search for ideal materials and methods that can further improve patient outcomes [25].

The goal of surgical mesh prostheses for hernia repair is to fortify and replace localized tissue defects in an effort to stabilize the abdominal wall for long term relief of symptoms [26]. Since the introduction of mesh prosthetics in the 1950s, several variations and adjustments in design have been presented in hopes of developing an "ideal" prosthetic. In reality, the use of a single mesh design capable of functioning effectively in all scenarios is unrealistic. Surgical repair requirements vary depending on the type of hernia along with several other parameters such as defect size and applied surgical technique [26]. In general terms, mesh prostheses should possess good handling properties, induce a desired host response, integrate with surrounding tissues and demonstrate sufficient mechanical properties for abdominal wall stabilization [27,28]. Moreover, when examining materials and prostheses for abdominal wall repair, surgeons must take into account several additional physiological considerations to better understand the suitability of the implant.

3.1. Cyto-compatibility/foreign body response

According to Williams, " the single most important factor that distinguishes a biomaterial from any other material is its ability to exist in contact with tissues of the human body without causing an unacceptable degree of harm to that body" [29]. Materials used for abdominal wall repair must remain biologically inert and resist rejection [30]. Biomaterials used for mesh prostheses can prompt adverse inflammatory foreign body responses (FBR) including fibrosis, calcification, thrombosis, infection, as well as granuloma, fistula and seroma formation [31,32]. Commonly used mesh prosthetic materials, such as polypropylene (PP), polyethyleneterephthalate (PET), and ePTFE, produce varying FBRs due to differing physiochemical properties on the surface of the implant [31]. Alternatively, biologically derived meshes are capable of displaying diminished FBR, particularly in the long term, due to their improved integration with neo-tissue and the presence of bioactive signals and growth factors within the bio-derived materials [33]. Moreover, researchers have deduced relationships between prosthesis design and host response that may act to counter some of the adverse reactions produced from the materials inherent chemical properties. For example, larger mesh pore sizes have been shown to yield significantly less FBR and fibrosis of localized tissues when compared to meshes with small pore sizes [34]. Recently, there has been substantial focus on the development of technical improvements to mesh design in order to improve local integration of prostheses by host tissues [24].

3.2. Collagen composition

Mesh prostheses implanted in the body can modify the naturally occurring collagen compositions found in the abdominal wall. The normal conversion of Type I collagen from immature Type III collagen is delayed in the presence of foreign bodies such as surgical meshes. The increase in Type III collagen could alter the mechanisms responsible for the deposition of Type I collagen, resulting in localized tissues with significantly decreased mechanical stability [35,36]. A reduction in Type I to Type III collagen ratio also has considerable implications for the recurrence of hernias [37]. Junge and colleagues found that the Type I/III collagen ratio in patients requiring ex-plantation of prosthesis due to recurrence was significantly lower (1.3 ± 0.7) compared to those experiencing chronic pain (3.4 ± 1.2) or infection (2.9 ± 1.6). These results indicate the dependence of abdominal wall mechanical stability on collagen composition [37].

3.3. Resistance to adhesion/fistula formation

An important property of mesh prosthetics is their ability to infiltrate host abdominal wall tissues in order to create a strong and secure repair. Unfortunately, due to the porous nature of most prosthetic meshes, interaction with undesired tissues is possible as can be seen with the adherence of meshes to the bowel [13]. Ideal mesh based prostheses for abdominal wall hernias will provide fascial defect repair capabilities, integrate into surrounding tissues by allowing tissue in-growth, and inhibit the formation of abdominal tissue adhesions to the mesh surface [38]. Abdominal adhesions are estimated to occur in 90% of all abdominal wall repair procedures and involve irregular fibrous strands that attach between tissues and organs within the abdominal cavity and the prosthesis [39]. The adhesions formed within the abdominal cavity progress to the formation of collagen dense extra-cellular matrix (ECM) which effectively closes the gap between internal viscera and prosthetic [33]. The occurrence of adhesions in hernia repair is predicated around the introduction of foreign bodies to injured peritoneal surfaces within the abdominal cavity [8,40,41]. The formation of adhesion sites within the abdominal cavity can cause chronic abdominal pain, bowel obstructions and perforations, enterocutaneous fistulae, as well as migration of prosthesis, and is responsible for 15–20% of female infertility cases [12,28,33,38,42–44]. Design and construction parameters of biomaterial prostheses can influence the development of adhesions as well as the production of neoperitoneum, which is formed between the material and visceral peritoneum [28].

3.4. Resistance to infection

The implantation of prosthetics within an abdominal wound can lead to the appropriation of necrotic debris and slime-producing bacteria resulting in surgical infection [27]. The use of mesh prosthesis in open ventral hernia repair can result in infection rates as high as 18%. Patients presenting with abdominal wall infections are generally treated by removing the prosthetic, requiring the patient to undergo further surgery [45]. Infections occur as a result of the infiltration and proliferation of bacteria within the pores of the prosthetic [13]. Such infections are considered to be the main cause of incisional hernia formation in patients that have undergone previous abdominal surgery [46]. The design of a mesh plays a critical role in the propagation of wound infections in patients requiring the use of prostheses for abdominal wall repair [30]. Macroporous meshes containing pore sizes greater than 75 μm have been shown to produce less infection when compared to microporous counterparts. Multifilament meshes designed with pores smaller than 10 μm allow for the infiltration of bacteria while preventing macrophages from entering to combat the infection.

3.5. Seroma/hematoma formation

A common complication resulting from the use of mesh prostheses for abdominal wall hernia repair is the formation of a seroma or hematoma. Seromas and hematomas develop as a result of the host inflammatory response to a foreign body and are defined by fluid build-ups in the subcutaneous space containing serous fluid or blood, respectively [13,47]. The production of fluid pockets around

a prosthesis can create dead space between material and host tissue, inhibiting the host tissues' ability to infiltrate and secure the prosthesis successfully. Meshes designed to facilitate rapid fibrinous fixation to host tissues are able to minimize dead space between prosthesis and native tissues, thereby minimizing the formation of seromas [13,30].

4. Prostheses for hernia repair: ideal material and design properties

The design and construction parameters of surgical meshes can greatly alter the behavior of the prosthetic itself and should be fully understood before making appropriate selections for repair. Although several design parameters exist, most commercially available meshes can be generally categorized according to filament constitution (mono vs. multifilament), pore size (macro vs micro), and weight (light vs. heavy). Although one design may present clear advantages over another, it is difficult to pin-point a single product that contains all of the properties of an ideal mesh [48]. For example, a microporous mesh may provide better resistance to adhesions, but would fail to prevent infections as effectively as macroporous meshes [34]. No single ideal mesh exists, as is evident from the large variety of mesh materials and designs in today's market [35]. In order for surgeons to provide the best possible outcomes for their patients, they must first understand the biomechanical and compositional properties of the mesh designs available to choose from.

4.1. Pore size

The porosity of a prosthesis refers to the ratio of open to solid space with respect to volume, area, or weight. The porosity of an artificial prosthesis plays an extremely important role in the overall performance of the implant as it is directly proportional to the degree of host tissue incorporation [49]. Amid classified the most frequently used materials for hernia surgery into four different types based on their pore sizes (Table 1) [13]. Type I meshes, containing pores larger than 75 μm, allow for more profound infiltration of macrophages, blood vessels, and collagen. Additionally, Type I meshes permit increased soft tissue in-growth and are more flexible than microporous meshes due to the inhibition of granuloma bridging [50]. Although the formation of granulomas is expected around the fibers of a mesh, bridging occurs when granulomas become confluent with one another and encapsulate the entire mesh [35,51]. Studies suggest that meshes containing pores larger than 1 mm are able to promote adequate wound healing while reducing the presence of dense scar tissue formed from granuloma bridging [24,52]. Furthermore, as a result of host penetration, meshes constructed using large pores appear to promote increased vascularization and collagen deposition [53]. In concurrence with these findings, studies have shown that the use of large pore meshes in non-contaminated environments can also counteract the presence of infections and seromas [54,55]. Along with erosion and migration into the GI tract, a fundamental disadvantage associated with the use of macroporous meshes is the risk of adhesion to internal viscera [13,56–58].

Recently, some manufacturers have begun developing composite meshes, which combine materials in order to utilize the advantages of each. Composite meshes generally require implantation in a particular orientation in order to utilize the full benefit of the design [59]. A composite mesh designed with ideal porosities for both the viscera and parietal regions would contain a macroporous surface exposed to the parietal side to allow tissue ingrowth, and a microporous surface in contact with the internal organs to prevent the formation of adhesions [56,59].

Table 1
Categories of prosthetic pore size [27].

Very Large pore	>2,000 μm
Large Pore	1000–2000 μm
Medium Pore	600–1000 μm
Small Pore	100–600 μm
Microporous (Foil)	<100 μm

4.2. Weight

A previous lack of understanding regarding the biomechanical nature of intraabdominal forces led to a generation of mesh prosthetics which were over-engineered and contained too much foreign material. These "heavyweight" meshes led to chronic pain, a loss of abdominal wall compliance and mesh shrinkage. More recently, improved mesh prosthetics have been designed containing significantly less material while still providing sufficient mechanical strength to repair abdominal wall defects [60,61]. In today's market, synthetic meshes are categorized as either being heavyweight, lightweight or medium weight (Table 2) [59]. These terms can sometimes be difficult to interpret due to vague descriptions and a lack of consensus provided in literature [26]. Fundamentally, the three groups are different in terms of several physical properties such as thickness, weight, ultimate tensile strength and modulus of elasticity [60].

Lightweight meshes generally contain larger pore sizes (>1 mm), thinner filaments, improved elasticity (25–35%), smaller surface areas, a decrease in overall weight/foreign material and shrink less in physiological conditions compared to their heavyweight counterparts [26,31,51]. Such properties allow lightweight meshes to inhibit the formation of dense scar tissue while still maintaining sufficient mechanical strength. As a result, the repaired abdominal wall is able to maintain its flexibility and functions as a dynamic system in spite of the foreign prosthesis [62].

In contrast, heavyweight prosthetics have thick polymer fibers, small pores, high tensile strength and increased surface area [31]. Consequently, heavyweight meshes are associated with intensified adverse effects including profound foreign body response, chronic pain, fibrosis, as well as the formation of adhesions, fistulae and scar tissue [31,51,63]. In summary, the use of lightweight prosthetics for hernia repair appears to be far more beneficial in reducing long-term complications such as chronic pain, inflammatory reaction and fibrous formation [64]. These results suggest that the biological response associated with lightweight meshes is significantly more favorable compared to heavyweight meshes [65].

4.3. Filament structure

Prosthetic meshes used for hernia repair are developed from various polymers in either a mono or multi-filament extrusion [50]. An ideal mesh design would include the following properties: resistance to infection, molecular permeability, pliability and mechanical functionality. Monofilament polypropylene meshes adequately satisfy the aforementioned requirements and are the

Table 2
Categories of prosthetic density [27].

Heavyweight	>90 g/m^2
Medium weight	50–90 g/m^2
Lightweight	35–50 g/m^2
Ultra-lightweight	<35 g/m^2

most commonly used prosthetics for inguinal hernia repair [66]. Multifilament meshes, which consist of several braided fibers, are associated with an increased risk of infection, granuloma formation and sinus tract formation, and promote increased inflammatory response. The risk of infection is a prominent phenomenon in multifilament meshes as a result of small (~10 μm) interstices produced in-between braided fibers. Interestingly, the small gaps are large enough for the infiltration of bacteria, but too small for the penetration of neutrophil and macrophage cells which are responsible for eliminating the bacteria [30,32,66,67]. Although infection is theoretically possible with any mesh, infections occurring from monofilament meshes generally do not require immediate ex-plantations, as is the case with multifilament prosthetics. Furthermore, studies performed by Klinge and colleagues demonstrated a significant increase in the adherence of *Staphylococcus aureus* bacteria to multifilament meshes for all concentrations of bacteria when compared to monofilament equivalents [68]. Although multifilament meshes have been reported to be more pliable than lightweight monofilament prosthetics, manufactures are developing a new generation of meshes containing partially absorbable filaments which provide additional handling properties [48,61]. An important property of mesh fabrics is the method in which they are processed. Knitted meshes are commonly more porous and flexible; however, they lack the mechanical strength of woven meshes due to a decrease in filament density [69]. Additionally, the mechanical properties of knitted and woven meshes can differ depending on the spatial orientation, a concept that will be discussed in the mechanical properties section.

4.4. Mechanical strength/elasticity

The human abdominal wall is composed of a laminar structure, containing several sheet-like muscles and tendinous fibers oriented in various directions [70]. The lateral forces produced from contraction of the oblique and transverse muscles are significantly greater than the stresses generated in longitudinal directions. Thus, the abdominal wall appears to be inherently ridged in the horizontal direction while remaining naturally elastic in the vertical [70–72]. The proper repair of abdominal wall hernias is dependent upon the design of a prosthetic capable of mimicking the biomechanical nature of the native tissues. Studies conducted by Cobb and associates suggest the highest intraabdominal pressure in humans is generated during coughing and jumping. These values correspond to a peak intraabdominal pressure of 171 mmHg [73]. These values can be converted to mean tensile strength using Laplace's Law, which relates tension, diameter, pressure and wall thickness. Therefore, it can be concluded that the maximum theoretical tensile strength per unit width that prosthetic meshes must withstand for successful repair of large and small hernias is 32 N/cm and 16 N/cm, respectively [31,35,72,74–76]. First generation heavyweight meshes were crudely over-engineered, containing too much foreign material providing unnecessarily large tensile strengths of nearly 100 N/cm [35,51]. In today's market, all available mesh prosthetics, including lightweight meshes, possess the structural integrity to meet the mechanical needs for physiological repair [31,62,75–77].

Along with possessing required mechanical strength to provide sufficient repair, prosthetic meshes should be capable of mimicking the natural distensibility of the abdominal wall. Junge and associates determined the mean vertical elasticity of the abdominal wall at 16 N was 23 ± 7% for males (15%–37% range), and 32 ± 17% for females (12%–69% range). The elasticities in the horizontal direction at 16 N were, 15 ± 5% for the males (9%–23% range), and 17 ± 5% for females (7%–24% range). In general, mean elasticities were determined to be between 11% and 32% in all directions (horizontal, vertical, and oblique) at a force of 16 N [78]. Heavy meshes used for hernia repair that do not account for the natural pliability of surrounding tissues will result in severe restriction of the mobility of the abdominal wall which can lead to discomfort and pain [78–81]. Heavyweight meshes generally present elasticities in the range of 4%–16%, while lightweight counterparts can be as high as 20%–35% [31], [78]. Current and next generation mesh design concepts are transitioning towards lighter and more elastic prostheses, which are capable of mimicking the physiological environment. Understanding the design properties and characteristics of modern hernia meshes can allow surgeons to better predict their functions *in vivo.*

5. Biomaterials for hernia meshes

Over the last several decades, the use of mesh prosthetics has become an ordinary practice in most countries and is the preferred course of treatment for hernia repair. Since the original metal prosthesis introduced in the early 1900s by Witzel and Goepel, progressive development of new materials and methods for hernia repair has occurred [16]. Although the use of mesh prostheses has become the gold standard due to a prominent decrease in reoccurrence rates when compared to primary suture repair, the potentially problematic physiological interactions present between prosthetic and host tissue cannot be ignored [82]. The introduction of a non-native prosthetic material into the human body is quickly followed by a systematic foreign body response activated by the host's immune system. Consequently, the resultant FBR associated with hernia repair can manifest into severe problems such as seroma formation, mesh shrinkage or encapsulation, tissue degradation and chronic pain [33]. At present, the most common treatment options for hernia repair involve the use of prosthetic biomaterials (absorbable, non-absorbable, composite, coated, impregnated), xenografts and allografts [10]. This section aims to outline and categorize the currently available options for prostheses that physicians have at their disposal.

5.1. Non-absorbable prostheses

Commonly used synthetic non-absorbable biomaterials such as polypropylene (PP) (Table 3), polyethylene terephthalate (PET or polyester) (Table 4), and expanded poly-tetrafluoroethylene (ePTFE) (Table 5) are the fundamental pillars of most hernia prostheses used today. Since its inception in the early 1960s, polypropylene has remained the most commonly used synthetic biomaterial for hernia repair [51]. Although all of the aforementioned materials are readily available in a clinical setting as a result of their alleged biocompatibility and inertness, some studies suggest these materials may activate certain histopathological processes and immune reactions upon implantation [33].

A key advantage in using polypropylene meshes for hernia repair is the ability of host tissue to infiltrate and integrate into the prosthesis. However, PP's propensity to form adhesions with visceral organs and tissues remains one of its major weaknesses. On the other hand, ePTFE meshes are advantageous in preventing visceral adhesions, though they lack the ability to promote sufficient parietal host tissue in-growth [83]. Lastly, PET meshes are valuable due to their superior histological properties, strong tissue in-growth and conformity to the abdominal wall [48].

PET meshes appear to be more cytocompatible than PP, presenting with a less profound foreign body and inflammatory reaction [31,32]. However, long term stability and susceptibility to infection remain pressing concerns regarding the use of pure polyester meshes as hernia repair prostheses [48].

Table 3
Common polypropylene Hernia meshes.

Product name®	Pore size (mm)	Weight (g/m^2)	Filament structure
Prolene (Ethicon)	0.8–1.6 [35,146]	105–108 [61,146]	Monofilament [31]
Parietene (Covidien)	1.0–1.6 [147]	78 [147]	Monofilament [72]
Parietene Light (Sofradim)	1.5 [148]–1.7 [149]	38 [149]	Monofilament [150]
Serapren (Serag-Wiessner)	0.08–0.1 [146]	116 [146]	Multifilament + Monofilament [146,151]
Surgipro (United States Surgical)	0.8 [35]	110 [61]	Monofilament + multifilament [66,72]
Marlex (Bard)	0.46 [52]	95 [61]	Monofilament [31]
BardSoft (Bard)	2.5 [149]	44 [149]	Monofilament [152]
Prolite (Atrium)	0.8 [153]	85 [153] –90 [61]	Monofilament [61]
Atrium (Atrium)	0.8 [154]	92 [154]	Monofilament [31]
Trelex (Meadox)	0.35–0.6 [153]	95 [153]	Monofilament [51]
Optilene (B-Braun)	1.0 [149]	36 –48 [149,155]	Monofilament [150]

Table 4
Polyethylene terephthalate (PET) Mesh.

Product name®	Pore size (mm)	Weight(g/m^2)	Filament structure
Mersilene (Ethicon)	1 [156]	33–40 [35,156]	Multifilament [31]
Parietex (Covidien) [147]	1.0–1.6	38	Multifilament

Table 5
ePTFE and PTFE meshes.

Product name®	Pore size (mm)	Weight(g/m^2)	Filament structure
DualMesh (Gore)	0.003/0.022 μm [157]	320 [158]	Foil [31]
Soft Tissue Patch (Gore)	1.3 [159]	Heavyweight [35]	Nonwoven [159]
MycroMesh (Gore)	0.025/0.3 [159]	Heavyweight [35]	2 mm perforations [160]

5.2. Absorbable prostheses

Fully absorbable meshes were designed to create prosthetic devices that were capable of serving their intended function while minimizing the amount of foreign material left over for the body to contend with. In principle, these designs are capable of alleviating the intense foreign body and immune response that is seen with non-absorbable meshes [33]. The most commonly used absorbable meshes are reviewed below (Table 6). Overall, the use of absorbable meshes for hernia repair presents several advantages over conventional, permanent prostheses. Most notably, permanent meshes can act as vessels for the proliferation of bacteria, which increases the risk of infections post implantation [13]. As a result, non-absorbable meshes may be problematic in pre-contaminated environments [84]. Furthermore, studies suggest that the use of non-absorbable meshes in children can hamper normal tissue growth [85]. Finally, non-absorbable meshes are associated with increased risk of fistula formation, chronic pain and a general restriction of physical movement [85,86].

5.3. Biologically derived prostheses

Biologically derived mesh prostheses have been largely developed for open abdomen conditions presenting contamination or a high risk of contamination [51]. Fundamentally, biological prostheses are extracellular matrices obtained from decellularized living tissues that are designed to function as active scaffolds, allowing native cells to populate the mesh in order to activate the remodeling process [27,33]. Unlike synthetic prosthetic meshes, biological materials used for hernia repair can become highly vascularized over time. As a result, these materials promote host collagen deposition and tissue in growth as they slowly degrade. The end result is the formation of functional neo-tissue, which provides strength and integrity to localized defect sites [33,48]. Biological prostheses can be classified according to their origin: xenogenic (animal) (Table 7) or allogenic (cadaveric acellular dermal matrices) (Table 8) [33].

In addition to the matrices derived from acellular dermal and small intestine submucosa tissues, researchers are also developing Acellular Bladder Matrices (ABM). Eberli and associates are developing collagen based layered biomaterials from porcine bladder submucosa, known as the lamina propria. Both single and quadruple layer ABM have demonstrated exceptional biocompatibility with marked influx of fibroblast and lymphocyte cells over time [87]. Researchers have also fabricated mesh prostheses using silk proteins isolated from both worms and spiders. Silk derived from worms has been shown to produce various immune responses and is considered to be less biocompatible than spider silk due to a lack of natural lubricant coatings [88,89].

Overall, biologically derived prostheses for hernia repair are advantageous in that they contain a dense network of collagen as well as several bioactive signals and growth factors. These cues, which include, proteoglycan, elastin and hyaluronan, along with the physical construct of the matrix itself can promote impressive tissue remodeling and wound healing in hernia patients [33].

6. Composite & combination prostheses

The long-term mechanical stability concerns associated with fully absorbable meshes have prompted a new generation of composite prostheses to emerge, combining non-absorbable materials with absorbable ones. As a result, composite meshes demonstrate the mechanical handling properties of conventional permanent polymers such as PP and PET, while reducing the overall mesh weight through the use of absorbable fibers integrated within the mesh construct [27].

Combination meshes utilize the advantages of multiple materials to create an orientationally dependent prosthesis [51]. Similar to composite meshes, the goal of combination meshes is to create prostheses capable of being successfully implanted laparoscopically into the intraperitoneal space. In order to promote tissue ingrowth while simultaneously attenuating intestinal adhesion/fistula formation, combination meshes are constructed with different surface materials for the parietal (abdominal wall) and

Table 6
Common absorbable meshes.

Product	Material	Design	Pros	Cons
Dexon (Davis & Geck) Safil (B-Braun)	Poly (glycolic) acid (PGA)	Multifilament [161]	• Anti-bacterial degradation productions allow for use in contaminated environments [84] • Induces minimal inflammatory response with moderate fibrosis [161] • Resistance to adhesion formation [48]	• Rapid mesh degradation resulting in mechanically unstable collagen formation leading to high reoccurrence rates [33,48,84]
Vicryl (Ethicon)	Polyglactin 910 (92% glycolide, 8% lactide [33]	Multifilament and woven [162] 0.5 mm pore size and 50 g/m^2 weight [85]	• Improved mechanical stability compared to purely PGA meshes with introduction of PLA [33] • Able to maintain mechanical stability of non-absorbable prosthesis up to 3 weeks post implantation [163]	• Although improved from PGA, mechanical tensile strength was not sufficient over prolonged time period [163] • Stimulate inflammatory response and formation of scar tissue [85] • Loss of mechanical stability after 6 months in saline [85]
Polylactide Mesh(Ethicon) [85]	Polylactide (95% Lactide, 5% glycolide	Multifilament with pores 0.2–1.4 mm in size and weight of 50 g/m^2	• Further improved mechanical properties with 50% retention of tensile strength after 9 months (functional assessment) • Improved seam tearing retention over Polyglactin • Decreased rate of seroma compared to Polyglactin • Decreased connective tissue formation inflammation response compared to Polyglactin.	• Activate the formation of foreign body granuloma and giant cells • Although mechanical stability is improved, long term studies testing Polylactide meshes ability to prevent incisional herniation and adhesion formation.
TIGR (Novus Scientific) [164,165]	Fast degrading: PLGA-PTMC poly (trimethylene carbonate). Slow Degrading: PLA-PTMC	Macroporous, multifilament mesh knitted 2 resorbable filaments, a slow and fast degrading fiber	• Long term (6 month) resorbable nature preserves mechanical function better than competitor resorbable meshes made from PGA, PLA or polyglactin. • Collagen deposition more similar to native connective tissue • Enhanced tissue integration • After degradation, mesh is replaced with newly formed collagen matrix, with increased ratio of type I/III collagen.	• Studies were not conducted on patients with collagen deficiencies • Potential mechanical load bearing issues after mesh has fully degraded are present
GORE BIOA (Gore)[33,166,167]	PGA - PTMC	Electrospun membranes of PGA-PTMC copolymer	• Interconnected fibers created from electrospinning optimize tissue in-growth. • Able to resist infection • Suggested reports indicate the BIOA may be beneficial to use in contaminated environments	• Long term mechanical strength is questioned due to degradation of materials.
Phasix (Bard) [168]	Poly(4-hydroxybutyrate) (P4HB)	Knitted Monofilament Weight: 182 g/m^2 Pore Size: 0.0004 in^2	• Mesh provides short term support that is comparable to permanent meshes. • Provides absorbable scaffold allowing abdominal wall to remodel and regenerate overtime. • Resistant to infection due to monofilament mesh design. • Mesh is made from natural polymer unlike other absorbable meshes. Metabolic byproducts of degradation are far less acidic than glycolic and lactic acid	• Long degradation time (>72 weeks in male Yucatan swine). • Typical issues of bulk erosion materials for long-term implantation. • Limited information regarding the long-term in vivo host responses.

visceral (intestinal) side [48]. Outlined below are the most commonly used composite and combination meshes (Table 9).

7. Coated prostheses

In an effort to further mitigate the foreign body response seen with most modern prostheses, manufacturers have begun functionalizing the surfaces of common mesh prosthetics with biological, chemical, and physical treatments [33]. Due to increasing demand for intraperitoneal mesh placement, coated meshes have been modified accordingly in order promote adequate tissue integration, while minimizing the formation of adhesions. The most commonly used mesh coatings are reviewed below (Table 10).

In addition to the modifications outlined above, meshes are being coated with various alternative substrates in order to improve their bio-functionality. Wolf and Faulk demonstrated an attenuated foreign body and inflammatory response in polypropylene meshes coated with extra-cellular matrix (ECM) hydrogels derived from porcine dermis or urinary bladder. The studies conducted showed that the use of ECM coated meshes resulted in an increase in the M2/M1 macrophage population ratio, which is responsible for tissue remodeling rather than inflammation [90,91].

Table 7
Common xenogenic meshes.

Meshes constructed from small intestine submucosa (SIS)		
Product	Design	Comments
Surgisis (Cook Surgical) [163,169]	Constructed using four layers of acellular SIS tissue. Mostly acceular, however occasional fibroblast and endothelial cells may remain within construct	Supports new vessel growth and acts as scaffold for remodeling of localized tissues. May decrease risk of infection in contaminated environments
Fortagen (Organogenesis) [170]	Matrix is crosslinked with 1-ethyl-3 (3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (rectocele repair)	Crosslinking may disrupt tissue integration and remodeling. Material may be perceived as foreign due to crosslinking.
Meshes Derived from Acellular Porcine Derma Tissue		
Product	Design	Comments
Permacol (Covidien)	Chemically crosslinking using hexamethylene diisocyanate (HMDI) to delay degradation of collagen fibers and improve prosthesis stability [33,171]	Low antigenicity, little inflammatory reaction, resistant to adhesion formation. Promising integration and neovascularization with host tissues [172]
Collamend (Davol)	Chemically crosslinking using carbodiimide hydrochloride (EDAC) to delay degradation of collagen fibers and improve prosthesis stability [33,173]	Has been shown to produce less mechanical failure and infection compared to Permacol. Collamend and Permacol both produced poor tissue integration due to the crosslinked components of their design [173]
Strattice (Life Cell) [174]	Porcine dermis matrix without any chemical crosslinking	Mechanical instability compared to crosslinked meshes. Demonstrated revascularization, cell repopulation, and cell migration in post-implantation
XenMatrix (Brennen Medical) [175]	Non-crosslinked porcine dermal matrix	Facilitates tissue ingrowth and remodeling. Minimizes encapsulation and fibrotic tissue formation. Available in very large sizes and does not require tissue reconstitution.
Meshes Derived from Acellular Porcine Liver Tissue		
Miromesh (Miromatrix Medical) [176]	Non-crosslinked porcine liver matrix	Facilitates tissue ingrowth and remodeling, including vascularization. Minimizes fibrotic tissue formation. Matrix replicates natural tissue organization.

Table 8
Common allogenic meshes.

Product	Comments
AlloDerm (LifeCell) [177,178]	Especially useful in the prevention of inflammation, encapsulation, and infection for defects being treated in contaminated conditions.
FlexHD (Ethicon) [179]	A possible drawback of acellular human dermal matrices is that fact that the material being used has already been functionally used by a donor, making trauma and other comorbid conditions a possibility.
AlloMax (Davol) [180]	Mesh has been shown to promote increased infiltration of vascular endothelial growth factor and interleukin 8 compared to other acellular dermal matrices.

Additionally, Chen and associates revealed that plasma treated PTFE surfaces, which become less hydrophobic, were more favorable for cell attachment, decreased encapsulation and attenuated inflammatory responses [92]. Udpa et al. determined that polypropylene meshes coated with chitosan encourage the ingrowth of skeletal muscle, which can decrease the risk of mesh erosion. Moreover, chitosan coated meshes produced minimal inflammatory responses due to a lack of neutrophil activation [93]. Finally, substantial work is currently being done involving the coating of various drugs within mesh architecture. Brandt and Klinge found that coating PVDF meshes with hydrocortisone and spironolactone can protect the prosthesis from a host inflammatory response [94]. Garcia et al. are working on developing polymer systems capable of loading non-steroidal anti-inflammatory drugs (NSAIDs) within polypropylene films in order establish devices capable of drug release into localized tissues [95].

8. Design of citrate-based elastomers promising for Hernia repair

Soft tissue engineering has previously been limited by the mismatch of the physical, particularly mechanical, properties of commonly used thermoset materials such as PLA, PLGA and PCL with the native extracellular matrix (ECM) [96]. This mechanical mismatch prompts inflammation and scar formation, limiting the integration of the implanted material with the host tissue. While materials such as these have formed the cornerstone of tissue engineering, a new generation of biomaterial design must take into consideration the native ECM structure towards improving clinical outcomes. Inspired by the three-dimensional crosslinked ECM network, composed of collagen, glycosaminoglycans and elastin, our group has developed a family of citrate-based elastomers (CBEs) capable of mimicking the mechanical properties and structural integrity of ECM [96]. The mechanical properties, functionality and degradation rate of these elastomers can be readily tuned via modulation of the crosslinking degree, allowing them to be adapted for a number of applications including hernia repair.

Citric acid, long known for its role in the Kreb's cycle, is a natural metabolic product that is nontoxic, inexpensive and readily available. The presence of three carboxylic acids and one hydroxyl group on each citrate molecule imparts multifunctionality to CBEs. Citrate can readily form ester bonds with diol and polyol monomers via a simple and cost-effective polycondensation reaction without the need for catalysts, while the various pendant groups of the citrate molecule can be partially preserved during the initial reaction for modification with biomolecules or other functional moieties as well as used to form a 3D network via post-polymerization crosslinking. The modification potential inherent in CBEs has led to a wide

Table 9
Common composite meshes.

Product name	Material	Design	Function
Ventralight ST (Bard) (ventralight ST + behavior of new composite)	Polypropylene (PP), Sodium Hyaluronate (HA), Carboxymethylcellulose (CMC), Polyethylene glycol(PEG), Poly glycolic acid (PGA)	Monofilament PP fiber. Knitted with PGA fiber coated with HA, CMC, and PEG hydrogel.	Minimize adhesion formation by placing PGA coated side towards viscera
Composix (Bard) Dulex (Bard)	PP, ePTFE (evaluation of adhesion formation)	Macroporous PP on parietal side Microporous ePTFE on visceral side3 (evaluation of adhesion) Lightweight mesh (which mesh for)	Macroporous PP surface is designed to optimize tissue ingrowth. Microporous ePTFE is hydrophobic and intended to resist tissue adhesions functioning as an antiadhesive barrier. (evaluation of adhesion)
Vypro II (Ethicon) (partially absorbable meshes)	PP, Polyglactin 910 (92% glycolide, 8% lactide)	3.4 mm pore size Multifilament	Utilize PP mechanical stability while decreasing mesh weight by integrating absorbable filament
UltraPro (Ethicon)	PP, Polyglecaprone 25 (PGA copolymerized with polycaprolactone(PCL))	Monofilament PP mesh supplemented with monofilament polyglecaprone 25 (Monocryl). Weight ~49.6 g/m^2 (Influence of polyglecaprone) >3 mm pore size (which mesh for repair)	Provide partially absorbable mesh constructed of monofilament structure in order to decrease risk of infection (influence of polyglecaprone)
Dynamesh IPOM (FEG Textiltechnik)	PP, Polyvinylidene fluoride (PVDF) (which mesh for)	Monofilament PP on the parietal side (mech properties of) Monofilament PVDF on the visceral side(Mech prop of) Pore size ranges from 1 to 2 mm (which mesh for repair)	PVDF is especially effective in minimizing the foreign body response (which mesh for) Sufficient incorporation and prevention of adhesions (prevention of parastomal)
Prevadh (Covidien) (adhesion prevention after myo)	Porcine Collagen, Polyethylene glycol, Glycerol, Lyophilized collagen	Dual sided membrane. Containing nonporous porcine collagen, polyethylene glycol, and glycerol on visceral side. Porous, lyophilized porcine collagen on parietal side.	Prevadh is highly hydrophilic and quickly transforms into hydrogel post implantation. Effective in decreasing inflammation and minimizing adhesion formation,
Parietex (Sofradim)	Polyester (PET), collagen type I, Polyethylene glycol (PEG), Glycerol	Double layer mesh with PET on parietal side and hydrophilic collagen membrane on visceral PET pore size: 700 μm	The PET parietal side is intended to promote tissue infiltration while the hydrophilic collagen membrane minimizes adhesion formation.
SurgiWarp (MAST BioSurgery) (comparison of three separate)	PP 70:30 poly(L-lactide-co-D,L-L lactide) (PLA)	Monofilament PP Macroporous Containing a PLA adhesion barrier	PLA, which is intended to minimize adhesion formation, is more mechanical stable than most other adhesion barriers used.

variety of functional polymers.

Biomaterial implant design must take into consideration a variety of interactions between host and material including blood/material interactions and implant induced oxidative stress as well as surgically introduced infection. Both the intrinsic properties and incorporated functional groups of CBEs have demonstrated significant attenuation of these adverse occurrences. The hemacompatibilty of poly(octamethylene citrate) (POC) was demonstrated in early studies, displaying decreased platelet adhesion versus PLGA and ePTFE [97]. POC coating of vascular grafts resulted in significant reductions of thrombogenicity and inflammation [98,99]. Further modification of POC with heparin resulted in an even greater reduction of whole blood clot mass and platelet adhesion [100]. These results clearly demonstrate the improved blood/material interactions of CBEs.

In biomaterial induced inflammation, cytokines and chemokines generate reactive oxygen species that impair normal cellular function via DNA, protein and lipid damage [96]. Poly (diol citrates) have intrinsic antioxidant properties that can be significantly enhanced through the incorporation of ascorbic acid (a common antioxidant vitamin) or nitric oxide to form poly(octamethylene citrate −co- ascorbate) (POCA) and diazeniumdiolated POC (POC-DA) capable of providing extended antioxidant protection throughout the course of degradation in the case of the former and for up to one week in the case of the latter [101,102]. The incorporation of these antioxidant moieties can greatly diminish oxidative stress mediated tissue damage *in vivo*.

Significant efforts have been made both clinically and in material design to limit post-implantation infections. Citric acid is a highly germicidal compound, imparting CBEs with intrinsic antimicrobial potential via the lowering of intracellular and cell membrane pH and possible metal ion chelation within cell membranes as a result of citrate release during degradation, causing bacterial cell damage and death [96]. The intrinsic antimicrobial potential of CBEs can be supplemented by functionalization with quaternary ammonium salts (QAS) and 10-undecylenic acid (UA), or incorporation of antibiotics, sodium metaperiodate, or silver nitrate [103–107]. Previous research has demonstrated the effectiveness of these polymers against common bacteria including *Staphylococcus aureus* and *Escherichia coli*.

The physical and mechanical properties and hydrophilic/hydrophobic balance of CBEs can also be readily modified via diol or acid selection. Incorporating unsaturated monomers such as maleic acid or alkyne and azide containing diols allows additional crosslinking through free radical or click reactions respectively [108–110]. The addition of click chemistry to CBEs results in increased mechanical strength and an additional route to the incorporation of functional side groups. Additionally, the mechanical properties of CBEs can also be improved by adding urethane bonds through incorporation of hexamethylene diisocyanate (HDI) to form crosslinked urethane doped elastomers (CUPEs) [111,112]. Partially or fully replacing aliphatic diols with water soluble poly(ethylene glycol) (PEG) imparts CBEs with water solubility, which in combination with double bond containing monomers

Table 10
Common coated meshes.

Product	Materials	Design	Coating function
Sepramesh (Genzyme) [83,181]	PP Coating: HA/CMC	Monofilament PP knitted mesh (6 mm pore) coated on visceral side with Seprafilm Adhesion Barrier, consisting of HA/CMC	HA/CMC has been clinically proven to limit visceral adhesions PP layer remains in contact with parietal tissue to promote infiltration
Proceed (Ethicon) [182,183]	PP, Polydioxanone, Coating: Oxidized regenerated cellulose (ORC)	PP encapsulated with polydioxanone parietal layer. ORC coated on visceral layer	Mesh is design to promote tissue in growth on the parietal side and resist adhesion formation on the ORC coated side
Physiomesh (Ethicon) [5,184]	PP, polydioxanone Coated: Monocryl polyglecaprone 25	Monofilament PP mesh Coated with Monocryl on the peritoneal and subcutaneous sides. Polydioxone film binds coating to mesh	Mesh is coated to resist adhesion formation with visceral tissues and decrease seroma development
TiMesh (PFM Medical) [33,185]	PP Coating: plasma activated chemical vapor deposition of atomic Titanium	Monofilament PP Coated with 30 μm Titanium layer Available in: 16 g/m^2, 35 g/m^2, 65 g/m^2 all with pore sizes >1 mm	The titanium coating increases the mesh hydrophilicity, which enhances contact with soft tissues
TiO_2 (BioCer) [185]	PP Coating: Titanium Dioxide	Monofilament PP Pore Size: 3.0 mm Weight: 45 g/m^2 PP filament are coated with titanium dioxide	Titanium coating allows for less post-operative pain, lower analgesic consumption, and quicker return to everyday movement
Glucamesh (Genzyme) [186,187]	PP Coating: beta-D-glucan	Microporous PP Weight: 55 g/m^2 3% beta-glucan coating	Beta-glucans extracted from oats have been shown to be effective promotors of wound healing and tissue integration
C-Qur (Atrium) [35,188]	PP Coating: Omega 3 fatty acid	Monofilament PP Weight: 50 g/m^2 Pore size: >1 mm	The use of omega 3 fatty acid complexes as coatings on meshes has shown a decrease in adhesion formation as well as an attenuated inflammatory response
Zenapro (Cook Medical) [189]	PP Coating: porcine SIS	Lightweight macroporous PP coated with 8 ply porcine SIS	The biologic SIS coating may shield the synthetic PP from infection while allowing eventual replacement with native tissue, incorporating the synthetic component into the surrounding tissue. Could be used to diminish the risk of fistulization and infection.

facilitates *in situ* crosslinking. *In situ* crosslinkable CBE formulations including poly((ethylene glycol) maleate citrate) (PEGMC) have been utilized as void filling materials as well as potential drug or cell delivery systems [113–117].

The introduction of dopamine, a catechol containing biomolecule similar to the catechol containing amino acid DOPA that imparts mussels with excellent wet surface adhesion, to PEG containing CBEs resulted in the development of injectable citrate-based mussel-inspired bioadhesives (iCMBAs). iCMBAs display a wet tissue adhesion strength 2.5–8.0 times stronger than gold standard fibrin glue and their hydrolytically liable ester bonds make them completely biodegradable [118]. The incorporation of antifungal 10-undecylenic acid into the polymer and sodium periodate or silver nitrate mediated free radical crosslinking imparts iCMBAs with antimicrobial properties [109]. This combined with the ability to deliver water soluble drugs or biomolecules makes iCMBAs an attractive alternative to clinically utilized adhesives for suture less wound closure post-surgery.

Biodegradable fluorescent materials have been a major research focus for theranostic healthcare and *in vivo* imaging [96]. Previous efforts have focused on the incorporation of organic dyes or quantum dots through encapsulation or conjugation; however, these systems suffer from the minimal photobleaching resistance of organic dyes and the potential toxicity of quantum dots. The incorporation of essential amino acids into CBEs imparts fluorescence, resulting in the synthesis of biodegradable photoluminescent polymers (BPLPs). In contrast to previous aromatic fluorescent polymers or organic dyes, BPLPs remain fully biodegradable and display elastic properties [119,120]. BPLPs display quantum yields of up to 62.3%, low photobleaching and tunable fluorescence depending on amino acid selection [121,122]. BPLPs are also capable of initiating ring opening polymerization of lactone monomers, resulting in the development of biodegradable photoluminescent polylactide (BPLP-PLA) [123]. BPLP-PLAs display tunable and strong fluorescence, with quantum yields of up to 51% [123]. Incorporation of BPLPs and BPLP-PLA into tissue engineering systems allows for non-invasive *in vivo* imaging as well as degradation tracking.

Given the advantages of CBEs in tunable elastomeric mechanical properties, hemacompatibility, biocompatibility, antimicrobial and antioxidative potential as well as the above demonstrated degree of potential functionality, the incorporation of CBE coatings to hernia meshes is expected to result in improved clinical outcomes. As a demonstration of the ability to coat meshes with CBEs, BPLP was coated on non-degradable PP meshes, resulting in an even coating that can improve tissue/material interactions (Fig. 2). Incorporation of BPLP also adds potential imaging *in vivo* and with the incorporation of drugs or growth factors could actively aid in the regeneration process. Additional coatings of CBEs such as POC, POCA, or antimicrobial UA and silver containing elastomers could impart the favorable properties of these biodegradable materials to existing or developed hernia meshes. The development of CBEs expands the repertoire of available biomaterials as coatings and adhesives for non-degradable hernia meshes or even in the fabrication of fully degradable scaffolds for hernia repair and regeneration.

9. Future perspectives for hernia repair

To date, significant progress has been achieved in the design of materials for hernia repair; however, as outlined above, multiple

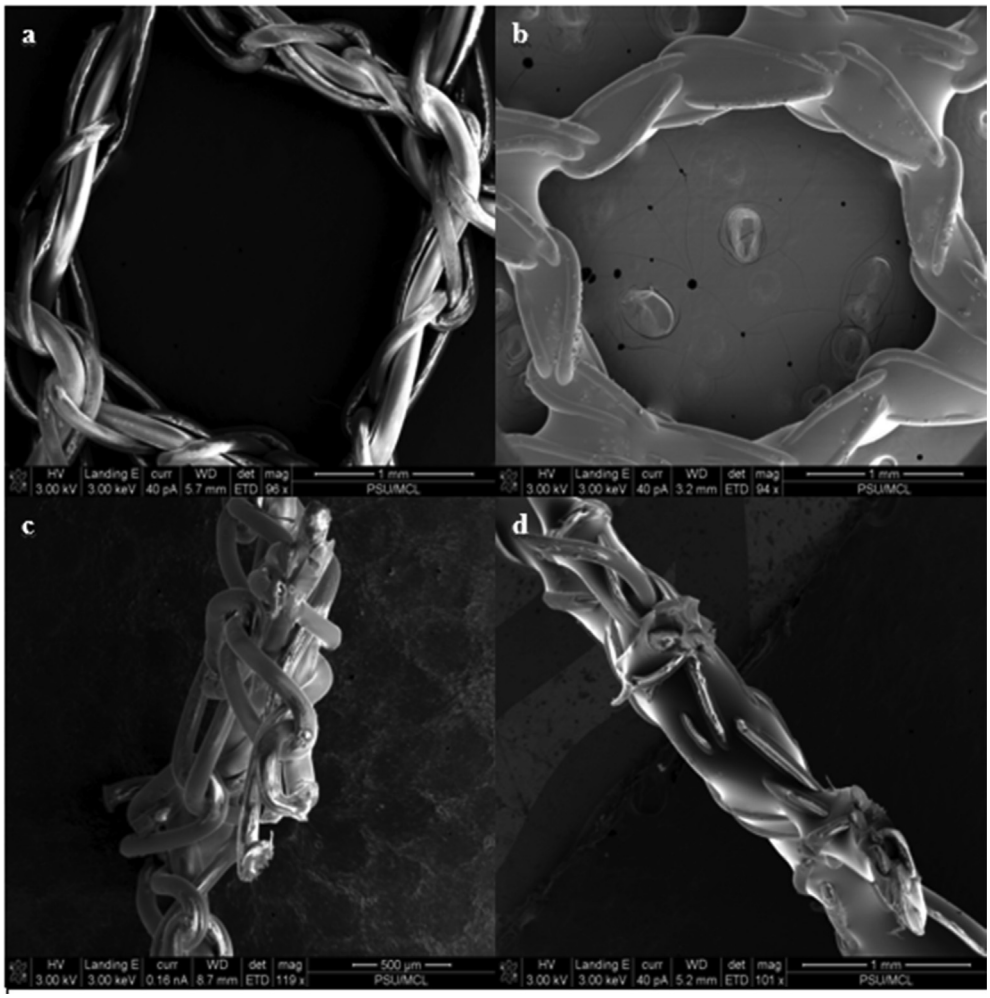

Fig. 2. Poylpropylene (PP) hernia mesh before (A) and after (B) coating with BPLP. Cross sections of PP hernia mesh before (C) and after (D) coating with BPLP.

and significant challenges remain. Critical among these are limiting the acute and chronic foreign body response to the implanted material, preventing/controlling post-operative infection, promoting tissue ingrowth and vascularization, and achieving physiologically relevant mechanical properties.

In recent years, biomaterials research has undergone a paradigm shift from creating largely passive scaffolds, designed to provide mechanical and structural stability while having minimal positive effect on tissue growth, to "active" materials, capable of influencing and directing tissue regeneration via the incorporation of drugs, cells, or materials with favorable intrinsic properties within the scaffold. Additionally, with the advent of additive manufacturing and other fabrication techniques, there is significant drive toward the generation of custom, patient specific implants.

Despite these trends, hernia repair remains largely dependent on non-degradable materials designed as one size fits all patches with minimal to no ability to actively encourage tissue regeneration. Future research will focus on the incorporation of new technologies and of new materials toward solving these remaining challenges and improving patient outcomes.

9.1. Absorbable surface coatings and meshes

The use of non-absorbable implant materials has long been associated with significant instances of chronic inflammation and foreign body response leading to impaired tissue regeneration and in extreme cases the necessity for surgical removal of the implant. The permanent presence of a foreign material will also typically lead to fibrous and scar tissue formation, resulting in a non-physiological replacement tissue whose mechanical and physical properties do not match those desired. Additionally, the mismatch of mechanical properties of most non-degradable mesh materials can combine with scar tissue to create areas of discomfort and limited mobility. Consequently, a major focus of biomaterials research is the replacement of permanent or semi-permanent implants, such as metals and non-absorbable plastics, with fully degradable counterparts.

Currently, non-absorbable materials are most common in hernia repair; however, several absorbable materials, based upon synthetic polymers including PLA and PGA or bio-derived materials, such as chitosan, collagen and dermal extracellular matrix (ECM) are currently being tested [124–126]. These materials allow complete replacement with mature neo-tissue and in the case of bio-derived materials significantly improve tissue ingrowth and foreign body response. However, fully absorbable implants are often limited by insufficient mechanical properties, prompting research into absorbable coatings on clinically utilized meshes designed to improve the tissue/implant interface as well as incorporate drugs and growth factors [127–129]. Polypropylene meshes have been coated with materials including Poly(ethylene glycol) (PEG), chitosan, and porcine extracellular matrix [127–129]. Among these coatings, ECM is the most promising, with ECM coated heavy-weight meshes displaying a foreign body response and tissue remodeling resembling a light-weight mesh [127,130].

Given these and other results, it is clear that absorbable coatings are capable of improving mesh biocompatibility while also allowing drug and growth factor incorporation and will thus be a major focus in the future, while the development of more mechanically robust materials will also remain a major focus toward creating viable, fully absorbable meshes.

9.2. Drug eluting meshes

The presence of post-operative infection is a major concern in hernia repair, preventing wound healing and necessitating additional surgeries. Currently, reported rates of mesh infection are as high as 10% [131,132]. These rates vary widely based on mesh type, technique, location of the mesh, and wound class (clean, clean/contaminated, contaminated, and dirty/infected). The occurrence of infection in laparoscopic placement is typically much lower than in open placement procedures, while microporous, multifilament, heavy-weight meshes suffer from a higher rate of infection than their low-weight, monofilament counterparts [13,133,134]. The ability to deliver drugs locally from implants, reducing the off-target effects and drug degradation/elimination inherent in systemic delivery, will improve the effectiveness of treating potential infection. Many surgeons presoak synthetic mesh in antibiotic solution prior to implantation. Sadava et al. looked at the presence of biofilm on 4 different types of mesh (composite multifilament polyester, multifilament polyester, composite monofilament polypropylene, and monofilament polypropylene) that were either soaked in saline or a vancomycin solution after 30 days of implantation in a rat model [135]. They found that meshes soaked in vancomycin prior to implantation had a much higher rate of clearance in all types of mesh examined. Yurko et al. bound various antimicrobial peptides (Lysozyme, human beta defensin, human cathelicidin, and lysostaphin) to polypropylene mesh and measured the antimicrobial action in a suspension of *s. aureus* [136]. They found that mesh impregnated with lysostaphin had superior antimicrobial activity. Gore Dualmesh Plus Biomaterial (WL Gore & Associates, Flagstaff, AZ) is an ePTFE mesh that is coated with silver carbonate and chlorhexidine diacetate. In one study comparing bacterial adherence on Dualmesh Plus with numerous other commercially available meshes, the Dualmesh Plus was the only mesh that had no identifiable bacteria after a one hour incubation period in a bacterial bath [137]. Additionally, biodegradable meshes and mesh coatings incorporating silver as well as antibiotic drugs including ciprofloxacin, ampicillin, and vancomycin have shown effectiveness over extended time periods in the inhibition of infection *in vitro* and *in vivo* [128,129,138–140].

The incorporation of growth factors to improve tissue regeneration is also of critical importance given the inability or limited ability of most materials used in hernia repair (with the exception of ECM) to promote tissue growth. Incorporation of bFGF in a collagen scaffold and bFGF, TGF-B and IGF-1 in a PCL fiber coated PP mesh resulted in accelerated collagen and myofibril integration as well as increased mechanical strength in the case of the former and increased mechanical strength due to tissue growth and integration in the case of the latter [125,141]. From these studies, it is clear that incorporation of drugs and growth factors to improve tissue regeneration and prevent infection will be critical to improving hernia repair.

9.3. Stem cell pre-seeding and encapsulation

Although adequate, acellular implants often take significant time to cellularize, increasing healing time. Pre-seeding of scaffolds with stem cells, particularly autologous populations, has the potential to accelerate the healing process. Seeding of mesenchymal stem cells within both synthetic Ultrapro, Vicryl and Marlex meshes as well as dermal ECM scaffolds resulted in a viable cell population capable of implantation [142,143]. ECM scaffolds in particular displayed angiogenesis, complete defect repair, and improved mechanical properties over their acellular counterparts *in vivo* [142]. In the future, absorbable coatings or scaffolds could be used to encapsulate stem cells prior to implantation. Such meshes, alone or combined with local delivery of encapsulated growth factors, could significantly decrease healing time.

9.4. Custom and anisotropic meshes fabricated with additive manufacturing

Current hernia meshes are typically one dimensional and have limited customizability for specific wound requirements. Additionally, current meshes display isotropic mechanical and physical properties that fail to replicate the anisotropic nature of the abdominal musculature and the forces generated in the abdominal area. Meshes capable of better replicating the wound area and mechanical environment could potentially reduce implant failure and improve integration and healing.

Anisotropic mechanical and swelling properties have previously been achieved utilizing electrospinning with multiple fiber alignments as well as 3D printing of materials with anisotropic swelling characteristics to create controlled mechanics and complex 3D shapes [144,145]. Additive manufacturing techniques such as 3D printing are capable of fabricating mesh structures as well as plugs and other 3 dimensional constructs that could conform to the individual patient. 3D printing is also capable of incorporating multiple materials and porosities into a single scaffold in a highly controlled manner. Utilizing 3D printing, scaffolds can be designed with varying pore structures, fiber orientations, and material properties, imparting mechanical anisotropy. Integrating computer modeling and diagnostic imaging, custom implants could be generated that conform to the patients' specific anatomical requirements.

In the future, hernia repair will incorporate not only scaffolding but active elements such as drugs, growth factors, and cells capable of improving and accelerating the healing process. Novel materials will lead to improved host response and material integration, while improved manufacturing will result in custom implants capable of better mimicking the native tissue in terms of mechanics. Non-degradable mesh implants will be replaced by partially or fully absorbable scaffolds capable of attenuating foreign body response and infection while promoting tissue ingrowth and maturation, leading to improved patient outcomes.

10. Conclusion

The importance of the surgical repair of hernias has been recognized since the 19th century. From the earliest surgical techniques, utilizing metal sutures, hernia repair has evolved to include a variety of surgical strategies and mesh implants. Despite the availability of multiple products clinically, implants continue to suffer from multiple limitations, and there is no ideal mesh capable of preventing adverse effects. Multiple design characteristics, including material, pore size, filament structure and mesh weight are critical to the success of the implant. Non-absorbable meshes, composed of materials such as polypropylene and ePTFE, display improved host response compared to the earlier metal implants; however, they still suffer from adhesions, mechanical mismatch and potential scar tissue formation. Absorbable materials, whether synthetic, such as polycaprolactone, or bio-derived, elicit even more favorable immune responses and are replaced by natural tissue over time. Combination meshes, composed of both non-

absorbable and absorbable components, combine the advantages of multiple materials and morphologies to minimize adhesions, infections and other complications, while coated implants provide the opportunity for local delivery of growth factors and drugs.

As discussed above, the choice of material is critical to success in hernia repair, necessitating the development of novel materials or coatings. Ideally, fully biodegradable hernia meshes possessing improved host interactions will become commonplace in the future; however, this requires the development of new materials capable of maintaining the required mechanical strength during degradation and promoting tissue ingrowth. Alternatively, the use of biodegradable coatings comprising citrate based elastomers or other biocompatible polymers should be further investigated to improve outcomes where non-absorbable meshes are used. These coatings could also be used as wells for drugs, growth factors, or other active molecules as well as enabling imaging. Despite a long history of advancement, significant challenges remain, and the development of novel materials and designs remains critical to improving patient outcomes in the future.

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