

BIOLOGICALLY RELEVANT PROPERTIES AND IN VIVO CONSIDERATIONS OF  
SYNTHETIC MESH MATERIALS USED IN ABDOMINAL HERNIA REPAIR

By

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A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelor's Degree  
with Honors in

Molecular and Cellular biology

THE UNIVERSITY OF ARIZONA

M A Y 2 0 1 6

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## ***Abstract***

The perpetual evolution and development of meshes for abdominal hernia repair have made the determination of a single optimal mesh material a constant challenge. A significant number of research teams have evaluated the important properties of a surgical mesh as they relate to the prevalence of complications and recurrence, and a multitude of clinical trials have compared the efficacy of two or more meshes in an attempt to reveal a potential standard. This literature review will evaluate the properties of synthetic meshes used for hernia repair, and aim to illuminate those which should be considered when choosing an optimal mesh.

The results of clinical trials of the last 5 years will also be compiled for convenience. The trials included in this review comprise those which appointed mesh type (or mesh system) as the primary variable. Most of these trials were comparative (2 or more meshes), and a few evaluated the performance of a single mesh. Clinical trials such as those evaluating fixation technique, surgical technique, prophylactic use and other topics not relevant to the efficacy of the mesh itself were excluded. The conceptual design of a novel absorbable block polymer triggered by small molecule localization will also be explored.

## ***Background on Surgical Options for Hernia Repair***

The advent of synthetic polymers for hernia repair in the 1940s ushered in a new age of surgical technology and methodology. Prior to the 1930s, a decade which marked a turning point in hernia repair due to the arrival of synthetic, biocompatible polymers, hernias indicative of surgical intervention were solely treated using open, tension repairs – named after the tension they create on either side of the sutured defect. Some of these methods, such as the Shouldice technique<sup>1</sup> and McVay/Cooper's Ligament repair<sup>2</sup>, two types of open herniorrhaphy, are still used in a minority of inguinal hernia repairs today and involve herniotomy and suturing to reinforce affected anatomical structures. The Shouldice technique is the most common non-mesh surgical repair. Alternatively, some open, suture based repairs, such as the Bassini method<sup>2</sup>, are no longer practiced (except in some developing medical communities) due to comparative inferiority with competing methods, but are historically significant. Tension-free suture based methods such as the Desarda and Guarnieri techniques are less common due to their relative novelty, and do not put tension on surrounding tissues - a limitation which has been linked to increased postoperative pain.<sup>3</sup> The most common technique used for inguinal hernia repair today is the Lichtenstein repair, which is an open, mesh-based, tension-free hernioplasty. The use of mesh to reinforce the abdominal wall revolutionized hernia repair and significantly lowered recurrence and complication rates when compared to traditional non-mesh herniorrhaphies.<sup>4</sup>

Laparoscopic hernia repair was first described in the 1970s and has been observed to minimize postoperative pain and expedite the recovery process.<sup>5</sup> However, due to the precision required in this operation to compete with the recurrence and complication rates of open repair (Lichtenstein), it is usually not recommended unless performed by an experienced surgeon.<sup>6</sup> There are three main types of laparoscopic inguinal hernia repair: intraperitoneal onlay mesh (IPOM), transabdominal preperitoneal (TAPP) and totally extraperitoneal (TEP). IPOM has lost popularity due to higher rates of recurrence and complications such as bowel strangulation.<sup>7</sup> Although recurrence and complication rates, recovery time and postoperative pain can be reduced with laparoscopic repair in the hands of the right surgeon, open hernioplasty is considered the “gold standard” because most general surgeons lack the experience to produce these results.<sup>8</sup> Open repair not only requires less expertise, but is also cheaper and can be performed more quickly. Ideally, surgically treated hernia outcomes would be optimized if repairs were performed laparoscopically by an experienced surgeon, as laparoscopic repairs produce substantially fewer complications than open repairs.<sup>9</sup> However, logistical limitations popularize open hernioplasty despite increased postoperative pain and longer recovery.

### ***Introduction to Mesh Associated Morbidity Factors***

In the United States alone, over 1 million hernia repairs are performed each year.<sup>10</sup> Historically, inguinal hernias are by far the most prevalent type of abdominal wall hernia at a frequency of about 71%, followed distantly by umbilical hernias (14%) and epigastric hernias (7%).<sup>11</sup> Chronic pain and foreign body sensation are common complications reported in a significant number of cases, and present a complex problem for patients suffering from hernias pertaining to quality of life following surgical intervention. The high complication rate following traditional herniorrhaphy encouraged the design of non-absorbable biocompatible meshes following the invention of unreactive polymers in the mid 1900s. Since then, the market for surgical mesh has steadily grown into a multi-billion dollar industry, supporting the creation of dozens of variations of mesh composed of several substances including polypropylene (PP), polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), polyvinylidene fluoride (PVDF), absorbable block polymers and even biologics usually composed of porcine or bovine intestinal submucosa. These biologics are expensive and find utility in contaminated fields where synthetic polymers cannot be used. Recurrence rates and complications of the aforementioned mesh-based surgical techniques can vary greatly depending on several characteristics of the mesh itself, including pore size, molecular weight, composition, tensile strength, elasticity, contraction, fiber organization, absorptivity, and fiber coating. The presence of the mesh encourages tissue ingrowth and an acute foreign body reaction which will reinforce the abdominal wall through neovascularization, deposition of extracellular matrix (i.e. collagen) and formation of local scar tissue. The chemical properties of each mesh material imparts unique advantages

and disadvantages, which will be discussed throughout this paper, and causes the implant to interact differently with surrounding tissues.<sup>12</sup>

Despite drastic improvements in the outcomes of patients following surgical hernia repair as a result of widespread adoption of mesh-based intervention, complications such as chronic pain, ejaculation disorders, mesh migration, bowel obstruction, foreign body sensation, infection, adhesion, erosion, meshoma, fistula and general discomfort continue to be an issue. In recent years, mesh manufacturing companies have enhanced existing mesh designs by lowering weight, increasing pore size, creating composite meshes and incorporating coatings which are thought to prevent adhesion to, and erosion of, visceral organs in cases where the mesh is fixed on the innermost surface of the abdominal wall. Currently, there is no single mesh design that has demonstrated total superiority over all competing meshes in its limitation of common complications and subsequent quality of life. The search for an ideal mesh that embodies the strengths of each of its counterparts without compromise continues to gain momentum.

In recognition of the continuing effort to develop improved implants for hernia repair, the next section of this review will explore the relevant components of a biocompatible mesh, and their relationship to the complications that arise from hernioplasty.

### ***Mesh Properties Affecting Biocompatibility and Foreign Body Reaction***

Many studies have targeted meshes used in abdominal wall repair for efficacy analysis. Depending on the mesh chosen, different intensities of acute foreign body reaction can be achieved, resulting in varying levels of tissue integration and formation.<sup>13</sup> The search for an ideal mesh is underway, and seeks to incorporate optimal mesh properties in a cost-effective manner while minimizing aforementioned complications. This section of the paper will focus on mesh properties and their role in reinforcing the abdominal wall.

### **Composition and Chemical Reactivity**

Meshes most commonly used to repair abdominal wall hernias are composed of polypropylene, polyethylene terephthalate or expanded polytetrafluoroethylene. Polyvinylidene fluoride is a relatively new material that has been shown to decrease chronic inflammatory reactions, but has not yet reached the same popularity as the more tried and true materials. Non-expanded PTFE is also becoming more common in the making of macroporous, lightweight meshes.

The thermoplastic polymer polypropylene is a relatively inert substance. However, the exposed carbon backbone of polypropylene leaves the hydrocarbon vulnerable to oxidative damage which can lead

to degradation in the long term. Although minimal, these structural abnormalities (stress cracks) lead to a reduction in mechanical strength. The ester moieties of PET make the molecule susceptible to hydrolysis, which can also result in a reduction in tensile strength and abdominal support. PET has also been observed to fail *in vivo*.<sup>14</sup> The fluorine molecules surrounding the carbon backbone of ePTFE make it the most inert material, which minimizes degradation due to oxidative physiologic conditions, but high molecular weight and small pore size of ePTFE have certain contextual disadvantages which will be discussed in the following sub-sections. PTFE has the same chemical properties, but allows for differing physical properties owing to its macroporous, lightweight construction.

PP, PET and ePTFE represent the majority of meshes used in hernioplasty, and all 3 have demonstrated a lack of long-term inertness due to oxidative damage (PP) or an increase in chronic inflammation and contraction due to surface scar tissue formation (PET and ePTFE).<sup>15</sup>

PVDF is another fluoropolymer that is highly unreactive and lighter weight than PTFE (as it contains 1 fluorine per carbon on average compared to ePTFE's 2). Therefore, PVDF retains a similar level of inertness while also imparting the benefits of having a lower weight. PVDF was developed in recognition of many of the weaknesses found in preceding polymers, and has demonstrated reduced degradation and induction of chronic inflammatory response, less scar tissue formation and lower adhesion formation.<sup>16</sup>

Mesh composition has also been observed to induce variable macrophage responses depending on the material used; PTFE demonstrates an augmented macrophage response when compared to PP.<sup>17</sup>

### **Pore Size and Shape**

Pore size is directly correlative to level of tissue integration. Meshes are generally characterized as either macroporous (>75 $\mu$ m) or microporous (<75 $\mu$ m). Larger pores (>1.5mm) facilitate greater ingrowth which ultimately allows for stronger reinforcement of the abdominal wall.<sup>18</sup> Polypropylene, PVDF, PET and non-expanded PTFE meshes can be designed with large or small macroporous specifications, whereas the thermomechanical expansion technique used to synthesize ePTFE limits the substance to small pores on the order of microns. Therefore, ePTFE is resistant to tissue integration and is more often seen encapsulated by fibrous tissue *in vivo*.

Increasing pore size, and pore shapes with a larger number of vertices (i.e. hexagons vs diamonds) have been shown to increase mechanical strength of ingrown tissue in a porcine model, while mesh density had no effect.<sup>19</sup> In polypropylene, a large macroporous mesh design (3mm) reduced granuloma formation despite similar intensities of foreign body reaction compared to 1mm and .5mm meshes.<sup>20</sup> In addition to stimulating stronger tissue ingrowth, larger pore meshes seem to encourage more efficient mRNA

translation, since collagen deposition is higher despite lower levels of mRNA when compared to microporous meshes like ePTFE.<sup>17</sup>

### **Mesh Weight (Density)**

Pore size, mesh material and fiber organization are usually indicative of the weight of a mesh. Meshes can be classified as either lightweight (<50 g/m<sup>2</sup>), medium weight (50-80 g/m<sup>2</sup>), heavy weight (>80 g/m<sup>2</sup>) or ultra-lightweight if density is below 35 g/m<sup>2</sup>.<sup>17</sup> The smaller the pore size and denser the fibers, the heavier the mesh will be. The chemical structure of the mesh also plays a role in weight. Although not as relevant to tissue integration, the weight of the mesh is closely associated with chronic pain and foreign body sensation.<sup>21</sup>

Before the late 1990's, a robust, rigid mesh design was favored because it was thought that maximizing mesh density and strength would impart the greatest level of support to abdominal wall defects. High rates of recurrence following hernioplasty and other complications such as chronic pain and foreign body sensation prompted a transition to lighter weight meshes. This reduction in weight sacrificed tensile strength, but led to greater flexibility and elasticity, less irritation of the implant site (foreign body reaction) and therefore lower inflammation and scar tissue formation, and reduced foreign body sensation and other mesh weight-associated morbidity factors. Since large pore meshes typically have less mass per unit area, they are usually categorized as lightweight meshes. A study performed by Weyhe et al. showed a greater inflammatory and fibrotic response in a microporous lightweight PP mesh than a macroporous heavyweight PP mesh, demonstrating that the porosity of the mesh may be more closely associated with foreign body reaction, and that lower weight doesn't necessarily indicate a lesser biological response.<sup>22</sup>

With the shift to lightweight meshes originated the ideology that the ideal mesh should closely imitate the dynamic movements, anisotropy and biomechanical properties of the abdominal wall so as to avoid chronic inflammation and restriction of movement, thereby reducing complications and recurrence.<sup>23</sup> Mesh density is a determinant of mechanical factors such as maximum load, stiffness and deflection at maximum load.<sup>24</sup> Although the inherent qualities of the mesh that are naturally linked to mesh weight (e.g., pore size and tensile strength) impact a variety of potential complications, the primary factors associated with weight are numbness, foreign body sensation, pain and discomfort.

It should be noted that higher rates of recurrence have been documented in the use of lightweight monofilament polypropylene mesh for incisional hernia repair, likely due to mechanical failure.<sup>25</sup> According to a study performed by Cobb et al, unlike medium and heavyweight polypropylene meshes, lightweight meshes exhibit a significant reduction in burst strength and stiffness 5 months post-

implantation.<sup>26</sup> Although the magnitude of the reduced burst strength still exceeds that of normal abdominal tissue, there is cause for concern that this transition may lead to recurrence in some cases.

### **Contraction (Shrinkage)**

Contraction, or shrinkage of the mesh in vivo, has been linked to pore size, mesh composition and mesh localization. Although the cause is not entirely understood, shrinkage is thought to be associated with the physical properties of the mesh material that provide variable levels of resistance to tissue contraction brought about by chronic inflammation and healing.<sup>27</sup> A lack of resistance to tissue contraction causes mesh contraction. Contraction has been linked to recurrence and chronic pain. Although highly debated, ePTFE in particular has become well known as the mesh material most prone to shrinkage. Studies evaluating ePTFE shrinkage range from 7.6% shrinkage to as much as 50.8% (the average being  $38\pm 6\%$ ).<sup>28</sup> Similar discrepancies have been observed among other macroporous meshes due to a wide range of factors including experimental technique, animal model used, mesh placement and mesh time in vivo. This has made the determination of shrinkage by mesh material difficult to ascertain, but the general consensus remains that shrinkage of PTFE (expanded or non-expanded) is significantly greater than that of other mesh materials.<sup>29,30</sup> Multiple studies have concluded that pore size in macroporous materials is inversely correlated with shrinkage, while a supportive 3D structure and minimal mesh elongation at 50N also seem to contribute to low shrinkage.<sup>18,20</sup>

### **Fiber Organization**

Mesh knit pattern and filament arrangement (i.e., multifilament vs monofilament) dictate the combinations by which filamentous polymers can be arranged into a mesh framework. Both influence mesh density and weight, as well as possible pore sizes and shapes. These characteristics impart intrinsic qualities of contractility, elasticity, flexibility and strength unique to each mesh design. In addition to considerations regarding complications and recurrence that have already been discussed, multifilament vs. monofilament meshes have different implications regarding bacterial adherence and infection, and foreign body reaction.

One study by Blatnik et al. showed that unprotected monofilament meshes clear a significantly larger percentage of MRSA contaminants than do multifilament, barrier, or laminar antimicrobial impregnated meshes.<sup>31</sup> According to Sanders et al, decreasing fiber diameter, monofilament meshes, larger pores, and silver chlorhexidine coating (but not titanium) all reduce bacterial adherence.<sup>32</sup> Meshes adhering to the advantages of decreased prosthetic load and effective coatings should be considered for use in patients susceptible to infection.

Another study demonstrated a reduced foreign body reaction in a monofilament PP mesh compared to a multifilament mesh, indicated by a reduction in mRNA expression of inflammatory cytokines and matrix metalloproteinases (MMP).<sup>33</sup> The same study also showed that monofilament PET mesh induces a significant reduction in expression of tumor necrosis factor and MMPs 3 and 9 compared to a monofilament PP mesh. These results are supported by a 1996 porcine study which observed a greater foreign body reaction following implantation of Surgipro (multifilament) as opposed to Prolene (monofilament) by method of quantifying multi-nucleated giant cells where the mesh is exposed to tissues.<sup>34</sup>

### **Tensile Strength**

The mechanically appropriate mesh should mimic the flexibility and elasticity of surrounding tissues, but not sacrifice tensile strength to the extent that the maximum burst pressure of the mesh is less than that of the intraabdominal pressure generated during high exertion activities such as coughing (about 170mmHg).<sup>35</sup> A study by Anurov et al demonstrated that if the biomechanical properties, such as tensile strength, of the fascia to be repaired are not closely paralleled in the mesh implant, deformation of the mesh, biomechanical impairment or recurrence at the edge of the mesh may occur.<sup>36</sup> Therefore, there is no single mesh that can impart the ideal properties for every circumstance. The surgeon should take into consideration the location of the defect and probable strength, elasticity and other mechanical properties of the patient's surrounding tissues when selecting a mesh that will maximize recovery.

### **Complete Absorptivity**

Several mesh materials on the market such as polyglycolic acid can be completely absorbed by the body. Depending on the polymer(s) used, a mesh may be completely reabsorbed by the body in as quickly as a few months, up to several years. This innovation initially generated much promise for the advancement of mesh-based hernia repair as several advantages emerge when compared to permanent counterparts, such as reduction of the likelihood that the patient will develop certain complications such as fistula, erosion, bleeding, chronic pain, foreign body sensation and adhesion (which can lead to obstructive disorders in the bowel or reproductive tract). A 1986 study by Dayton et al reports that polyglycolide may limit some complications like infection more effectively than permanent meshes, and claims that a significantly higher recurrence rate has been recognized in some absorbable meshes.<sup>37</sup> According to these findings, an absorbable mesh could be an appropriate alternative in the event of contamination or infection as a temporary support until a permanent implant can be introduced. However, a 2015 review of infection in mesh implants concluded that absorbable meshes are actually more prone to bacterial colonization and biofilm formation than permanent meshes, and suggests that new meshes with prophylactic properties may be more effective where infection is a concern.<sup>38</sup>



Several recent long-term clinical human studies evaluating the long-term outcome of absorbable prosthetics have found that recurrence is a substantial concern; although patients with absorbable implants who do not experience recurrence report complications such as pain and foreign body sensation at a lower rate than patients who receive permanent implants, the risk of recurrence in absorbable prosthetics is often too great to justify their implementation.<sup>39</sup> The relatively new field of absorbable meshes demonstrates great potential for the reduction of many complications common to hernia repair, but their use will not be widespread so long as the reduction in frequency of these complications is negated by the more than reasonable increase in the number of recurrences. Furthermore, although resorption time-frames have been determined in animal models for some absorbable meshes (TIGR Matrix) as a result of autopsies and explantations, these findings have yet to be confirmed in a human model, as MRIs are unable to differentiate between mesh and new tissue.<sup>40</sup> The development of new non-invasive radiological techniques, such as amide proton transfer MRI, have shown promise in differentiating mesh from surrounding tissues in vitro post-implantation.<sup>41</sup>

In the process of compiling this review, no studies were found that evaluated mesh related complications in the very long term (on the order of decades). The longer a permanent mesh is in vivo, the more it is exposed to the degrading effects of the body. Eventually, this environmental stress could lead to a renewed inflammatory response, chronic pain and foreign body sensation. The field of completely absorbable meshes seems to reserve much potential for further development, and it may be useful to design a mesh polymer with the chemical potential to expose absorbable moieties when activated by external stimulus such as radiation or a small molecule – essentially, a permanent mesh made absorbable upon activation. This would allow for a mesh to be safely and non-invasively removed should a complication arise much later on, while also limiting recurrence to the level of any effective permanent mesh. In this way, a mesh can provide all of the benefits of a permanent mesh, and should a complication arise at any point, the mesh can be stimulated to be reabsorbed. Because of this property, surgeons would no longer be forced to weigh the patient's risk of recurrence against the likelihood of developing other mesh-related complications, and the appeal of eliminating the foreign material from the body as soon as possible.

### **Fiber Coating and Partially Absorbable Meshes**

There is an array of modified polymers on the market which have incorporated fiber coatings, such as metals (titanium), nano fibers, omega fatty acids, extracellular matrix (ECM) hydrogel, polyglycolide, MONOCRYL (polyglactone), sodium hyaluronate, carboxymethylcellulose, collagen and trimethylenecarbonate among several others that enhance the ability of the mesh to prevent complications and recurrence by minimizing adhesive interactions of the mesh with viscerally oriented

tissues. For example, ECM hydrogels have been shown to decrease inflammatory response (decreased macrophage recruitment) as well as collagen deposition (scar tissue) compared to a traditional polypropylene mesh.<sup>42</sup> A study on Wistar rats demonstrated that collagen-coated polyester mesh led to minimal visceral adhesion when placed intraperitoneally (10% of the surface involved with adhesion occurring on uncoated edges), whereas 80% of the surface of the polypropylene mesh was involved with adhesion.<sup>43</sup>

A 2013 publication by Schreinemacher compared adhesion formation between various meshes with coatings including collagen, omega-3 fatty acids and carboxymethylcellulose and hyaluronic acid. This study found that the adherence of all coated meshes was significantly less than that of the uncoated polypropylene control, and that Sepramesh IP (cellulose and hyaluronic acid) had the lowest adhesion score compared to several other meshes ( $p < 0.05$ ). The omega-3 fatty acid coated mesh had the lowest abdominal wall strength of incorporation ( $p < 0.05$ ).<sup>44</sup> According to another study by Schreinemacher et al in 2009, all absorbable coatings in the study (except for polyglactone) developed significant increases in adhesion formation when the coatings began to degrade.<sup>45</sup> The denuded fibers then proceeded to incorporate tissue from the visceral side. This finding is inconsistent with data from some other studies at a follow up time of 30 days. Baptista et al. showed that adhesions start to develop as a result of inflammation following mesh (polypropylene) placement within 1 day and progress up to 7 days, at which point a new layer of mesothelial cells is protective against further adhesion formation.<sup>46</sup> Generally, day 7 and day 30 are thought to represent different phases of wound healing; at day 7 the inflammatory phase is thought to have ended, and the proliferative phase begun. The 30 day mark on the other hand is thought to separate the proliferative phase from the remodeling phase, at which point changes in adhesions are minimal.<sup>47</sup> However, these standards were generalized on the basis of observations made in studies focusing on polypropylene, and may not be transferrable to other types of mesh or polypropylene meshes with coatings. Comparing data between the 2 similar studies by Schreinemacher et al. reveals an interesting characteristic of meshes with coatings on the visceral surface; the 2009 study reports 'percent of mesh covered with adhesion' values of 20 and 19 for C-Qur and Parietex Composite after 90 days, respectively, whereas the 2013 publication reports values of 38 and 59 after only 30 days. In both cases, meshes were placed intraperitoneally by laparotomy. This finding is more in line with the theory that adhesions seem to diminish following the initial tissue incorporation phase provoked by inflammation and degradation of the absorbable coating.<sup>48</sup> However, changes in the adhesions observed by Schreinemacher clearly occur after the 30 day mark, at which point changes are supposed to be minimal due to protective mesothelial cells and neoperitoneum, and continue decreasing in severity as is evidenced by the 90 day follow-up values. It should be noted from histological evaluations performed in these studies that, in macroscopic evaluations where an increase in adhesions from day 7 to day 30 is observed, a prolonged

inflammatory response is also apparent. This finding suggests that inflammation-inducing properties of some meshes as a result of their coating may extend the inflammatory period, thereby inaccurately causing a mesh to appear ineffective in relation to adhesion prevention. Longer follow up of these meshes (Parietex Composite, C-Qur and Proceed) is necessary to better characterize their true performance.

Another characteristic of absorbable coatings is that they may impair tissue incorporation with the abdominal wall when the coating possesses anti-inflammatory properties (the anti-inflammatory properties of O3FA reduce visceral adhesion formation, but also prevent the mesh from becoming incorporated into the abdominal wall).<sup>45</sup>

Although previous studies have claimed that titanized meshes improve biocompatibility and mitigate complications following hernia repair, they often failed to eliminate the possibility that the performance of titanized meshes is actually attributable to other properties of the mesh (such as weight and pore size) and not the titanium itself. A 2004 study by Junge et al recognized this issue and eliminated other causative variables by evaluating the biocompatibility of the same polypropylene mesh with and without titanization, and concluded that no significant improvement in biocompatibility was detected in the titanium coated mesh.<sup>49</sup>

One interesting material that has demonstrated a sophisticated approach to maximizing biocompatibility is electro-spun poly- $\epsilon$ -caprolactone (PCL) nanofibers prepared in thrombocyte rich solution (TRS). These nanofibers provide a scaffold for an underlying fiber (such as polypropylene), and the adhered thrombocytes have been shown to promote adhesion, viability, growth, proliferation and metabolic activity of mouse fibroblasts in vitro.<sup>50</sup> Further studies in animal models are necessary to investigate if these fibroblast-coated PCL fibers promote long-term tissue integration, an optimal foreign body reaction and improved clinical outcomes compared to competing coatings and absorbable meshes.

According to Emans et al., a non-degradable hydrophilic copolymer coating (NVP/BMA) may find use in preventing adhesions following hernia repair.<sup>51</sup> NVP/BMA coated polypropylene showed a significantly reduced adhesion score at 30 days follow up compared to Proceed (ORC and polydioxanone coated PP) and Prolene (PP). Further follow up is needed to better evaluate the adhesive tendencies of NVP/BMA.

To summarize, fiber coatings are useful in preventing short-term adhesion formation. Absorbable coatings that lack anti-inflammatory properties may be degraded in a matter of weeks due to a chronic inflammatory response, leaving exposed fibers susceptible to adhesion. However, in an effective coated mesh, by the time the coating is absorbed, the inflammatory period will have ended and the coating will have been replaced by anti-adhesive mesothelial cells. Some meshes with absorbable coatings on the

parietal side have been shown to incorporate insufficiently with the abdominal wall, which can lead to complications like migration, meshoma or shrinkage; however, incorporation in the referenced study (even of the polypropylene control mesh known for good parietal tissue integration) may have been poor due to a lack of acute injury, the identity of underlying tissue or the fact that only 2 sutures were used and potential anchoring sites were minimal.<sup>45</sup> Most coatings have been found to reduce adhesion formation regardless of their chemical properties (with the exception of some coatings such as polyglecaprone, titanium and polydioxanone which perform more poorly when compared to O3FA). The identity of the coating may modulate inflammatory response in different ways, but the presence of a barrier itself seems to be the most important factor when considering adhesion reduction, especially in the first post-operative week.<sup>44,45</sup> However, perhaps due to the short-lived nature of absorbable coatings in particular, grafts with absorbable films, such as polyglecaprone coated polypropylene, have not been implicated in improving complication or recurrence rates, or quality of life in relation to standard lightweight polypropylene meshes.<sup>52</sup> A coating may be used effectively if it promotes strong parietal incorporation through inflammatory mediation, and protects the visceral surface long enough to avoid adhesion formation that is believed to occur during the inflammatory phase of wound repair.

### **Composite Meshes**

As the progression of mesh research and technology move us closer to the ideal implant, composite meshes have emerged as a clear front-runner due to their ability to accommodate the different expectations of the visceral and parietal surfaces. The visceral surface of the mesh must be impregnable to deeper tissues such as omentum and visceral organs, while the parietal surface must encourage integration of native tissue without exacerbating the ongoing inflammatory reaction, thereby interfering with normal development of the fibrosis. As a whole, the mesh should exhibit biocompatible properties that control inflammation and prevent bacterial invasion while minimizing the likelihood that the patient will develop complications such as pain or foreign body sensation. This can be accomplished by maintaining optimal weight, pore size and mechanical properties that match surrounding tissues.

A 2003 study evaluated the performance of Composix (a composite mesh with polypropylene and ePTFE components) in 95 patients who underwent abdominal incisional hernia repair, and recorded a recurrence rate of only 2% - a significant improvement over the recurrence rate of traditional polypropylene meshes (about 10%).<sup>53</sup> Lannitti et al compared an ePTFE/PP composite mesh to an ePTFE graft for open ventral hernia repair and found that neither differed significantly on the visceral side, but that the composite mesh had substantially improved tissue ingrowth on the parietal side (where polypropylene was localized).<sup>54</sup> A larger multicenter study of composite mesh in 455 subjects found a recurrence rate of 1%, a complication rate of 9% (with 5 subjects requiring reoperation), and infection occurred in 1.3% of patients.<sup>55</sup> Other studies

report similar findings of low recurrence and infection rates, low to moderate complication rates, short hospital stay (mean less than 1 day) and a general improvement in post-operative patient comfort compared to patients who underwent open ventral hernia repair without a composite mesh.<sup>56</sup> Other composite meshes such as Ventralex (parietal:PP, visceral:hydrogel coated PGA) have been evaluated alongside Parietex (parietal:monofilament PET, visceral:collagen film) and the Proceed Ventral Patch (alternating layers of polypropylene (parietal) and absorbable oxidized regenerated cellulose (visceral) encapsulated by an absorbable polydioxanone film).<sup>48</sup> In this study, Proceed led to the development of significantly more adhesion up to 6 months when compared to Parietex, whereas Parietex and Ventralex performed comparably. Type III collagen was also lower in the presence of Proceed, and macrophage response was more pronounced in Proceed and Ventralex after 2 weeks, and Proceed only after 6 months.

### *Conclusion*

Although the sheer number of mesh properties that seem to play a role in postoperative outcomes, quality of life and ease of use make the task of choosing a mesh very daunting, the discussion above should serve to benefit in the making of this decision. Currently, there are over 100 different mesh materials on the market, and if the varying designs and application of each material are considered, there are substantially more than that. In reality, there is no single mesh that is 'ideal' for every unique case. In order to maximize the benefit to the patient, the ideal mesh should depend on the nature of the injury and the biomechanical properties of relevant tissues. The general consensus, according to the trials in table 1, suggests that a lightweight, macroporous, monofilament, composite design is optimal. This configuration reduces the likelihood of pain, foreign body sensation and discomfort (the most common 'significant' findings in table 1). The larger pore size of the mesh is thought to mitigate contraction and subsequent pain and discomfort, and allows for adequate tissue integration of the parietal surface. Monofilament meshes reduce the chance of infection, and a composite mesh (if placed intra-abdominally) contains specialized properties depending on the contact surface to promote integration, or inhibit inflammation and adhesion. However, many of these studies fail to eliminate confounding variables as a result of comparing meshes with several differing characteristics. For example, comparing a titanized lightweight, large pore mesh to a heavyweight, small pore mesh fails to confine causality to a single locus. Furthermore, due to factors such as varying skill among surgeons across studies, surgical technique, available surgical equipment, and study design, it is usually not conclusive or reliable to compare mesh performance between studies.

Many of the refinements being made in contemporary meshes seem to have a negligible impact on outcome in the cases of some surgeons, which suggests that some factors only play a role in improving

outcomes when the surgeon lacks experience or proficiency in a certain technique. In one large study in table 1, there were no significant differences between cases performed by the same surgeon where patients received a small pore heavyweight mesh, or a large pore lightweight mesh. Therefore, considering the current hernia mesh standard brought about by decades of improvement, experience, expertise and surgical technique may now play a more significant role than choosing between several meshes which are all capable of producing a desirable outcome if used correctly.

After considering these observations, it becomes apparent that several methods of future research should be considered so as to better define the true cause of current rates of morbidity among patients who have undergone hernia repair. Future research, whether analyzing outcomes of hernia repair on the basis of mesh type, surgical technique, surgeon experience or any other focus, should ensure that each test group is controlled, and that in every instance only 1 variable is changing. Proficiency in this area would greatly reduce the current struggle in identifying which properties of a mesh are relevant, and alleviate the constant influx of seemingly inconsistent results. Until more conclusive research is undertaken, it will not be possible to further rationalize which materials and techniques will produce the best outcome in the field of hernia repair.

*Comparative Clinical Trials in the last 10 Years*

Author	Year	Number of Subjects	Meshes Compared	Significant Findings	Non-Significant Findings	Notes
Demetrashvili et al. <sup>57</sup>	2014	198	Prolene (PL), Ultrapro (UP)	Foreign Body Sensation (UP)	Infection, hematoma, seroma, recurrence, hospital stay, sick leave, chronic pain, primary complication	None
Chatzimavroudis et al. <sup>58,59</sup>	2014	50	Prolene (PL), Parietene ProGrip (PPG)	None	Pain, Seroma, Hematoma, infection, recurrence	Authors claim that absence of pain in lichteinstein repair could be a result of nerve preservation by surgeons skilled in the technique. Self-fixating Parietene could potentially reduce pain when repair is performed by less experienced surgeons. Operation time is lower with PPG.
Nikkolo et al. <sup>60</sup>	2015	145	Optilene LP (OLP), Parietex ProGrip (PTP)	Foreign body sensation (OLP), social functioning quality of life domain (OLP)	Chronic pain, 7 of 8 additional quality of life domains	Limitations are stated as: nerve preservation unknown in OLP group, meshes are made of different materials. Self-gripping mesh may have

						increased foreign body sensation due to unabsorbed microgrips at 6 months.
Hirose et al. <sup>61</sup>	2013	182	Ultrapro Plug (UPP), PerFix (PF)	Foreign body sensation (UPP)	Chronic pain, numbness, pulling sensation, discomfort, impaired physical activity	None
Sanders et al. <sup>62</sup>	2014	557	Parietene Light (PTL), Parietex ProGrip (PTP)	Pain at 1 week (PTP)	Seroma, hematoma, infection, recurrence, length of hospital stay	Resection of the iliohypogastric nerve was observed to significantly mitigate postoperative pain at all follow up points compared to preservation. Operating time with PTP was significantly less.
Yasdankhah et al. <sup>63</sup>	2012	110	Lightweight Dynamesh (LD), heavyweight Dynamesh (HD)	Foreign body sensation (LD), numbness (LD), limitation of vigorous activity (HD)	Hematoma, recurrence, discomfort, pain, most types of activity limitation	None
Jorgensen et al. <sup>64</sup>	2013	334	Parietene Light (PTL), Parietene ProGrip (PPG)	Groin discomfort at 1 month (PTL)	Hematoma/seroma, infection, readmission, pain, numbness, recurrence	The study did not allow for the evaluation of early postoperative symptoms. These findings challenge the theory that fixation technique has a significant impact on outcomes.



Rickert et al. <sup>52</sup>	2012	80	Optilene Mesh Elastic (OME), UltraPro (UP)	None	Quality of life measured by SF-36 score, infection, hematoma, seroma, pain, recurrence, all other complications	First randomized trial assessing quality of life following incisional hernia repair
Canonico et al. <sup>65</sup>	2013	80	Prolene (PL), Evolution P3EM (EP)	Pain intensity at 1 month (PL), analgesics (PL)	Hematoma, ecchymosis, other complications	Meshes were fixated using human fibrin glue (HFG). The study recognizes limitations of only providing data for up to a 1 month follow up.
Moreno-Egea et al. <sup>66</sup>	2013	102	TiMesh light (TML), Parietex Medium Weight (PTM)	Pain at 1 month (TML), return to normal activity (TML),	Pain at 1 week, 6 months and 1 year, postoperative morbidity, hospital stay, intraoperative morbidity, recurrence	The study acknowledges that bias could have influenced the results due to the open nature of the study.
Fumagalli Romario et al. <sup>67</sup>	2013	96	Polyester/polylactic acid self-gripping mesh (SGM), polypropylene/polyglycaprone mesh (PPP)	None	Recurrence, chronic pain, hospital stay	The study does not disclose the manufacturers are trademarked names of the meshes used. The authors recommend that cost and tissue trauma be taken into consideration when choosing between either of these meshes for TAPP hernioplasty.

Kingsnorth et al. <sup>68</sup>	2012	302	Parietex ProGrip (PTP), Parietene Light (PTL)	Pain at discharge and 1 week (PTP), infection (PTP)	Recurrence, hematoma, seroma, chronic pain at 1 and 3 months	
Sadowski et al. <sup>69</sup>	2011	78	Heavyweight Polypropylene (HPP), Polyester (PE)	Catching, pulling, tugging or tearing at 3 months follow up (HPP)	Chronic pain, most abnormal sensations, numbness, physical limitation, and recurrence at 2 weeks and 3 months follow up	The authors claim that, as a result of funding limitations, the sample size of the study was not large enough to detect small but potentially significant differences between the test groups. The authors did not detail the brand of the specific meshes that were used.
Nikkolo et al. <sup>70</sup>	2012	116	Premilene Mesh (PM), Optilene LP (OLP)	None	Pain in the groin at the 3 years, foreign body sensation, recurrence	According to this study, severe preoperative pain was associated with the development of chronic pain at follow up.
Nikkolo et al. <sup>71</sup>	2014	134	UltraPro (UP), Optilene LP (OLP)	None	Pain in the groin up to 6 months, foreign body sensation (p=.052), quality of life at 6 months, hematoma, seroma	The authors of this study concluded that pore size was not associated with short term pain. The macroporous mesh also demonstrated a trend toward a stronger foreign body reaction (a finding for which the authors were unable to identify a reason).
Pierides et al. <sup>72</sup>	2012	394	Parietene ProGrip/Parietene	None	Hematoma, infection bleeding, pain, sick	The goal of this study was to evaluate any postoperative disparities between a

			Light (PPG/PTL), Prolene (PL)		leave, aspiration, and recurrence, physical limitation, scrotal swelling and sensory loss at 1 year	self-fixating mesh and a sutured mesh. The only significant difference was increased operating time with the sutured mesh.
Bury, Smietanski <sup>73</sup>	2012	356	Prolene (PL), UltraPro (UP)	None	Pain and recurrence at 5 years.	The study found no difference at 5 year follow up between the heavyweight polypropylene mesh and the polypropylene/poliglecaprone composite mesh.
Mutter et al. <sup>74</sup>	2012	95	PerFix Plug (PFP), 4DDOME Implant (4D)	Evolution of postoperative pain and discomfort at 180 days (4D), evolution of pain at 180 days by VAS score (4D), SF36 survey pain score at day 30 (PFP) and health core at day 180 (PFP).	Pain evolution and discomfort at 1, 8, 30 and 360 days, hematoma, seroma, infection, hospital stay, recurrence and all other SF36 variables	The study is limited in its evaluation of recurrence and long-term follow-up by a small study population. The authors also disclose involvement with the design of one of the meshes evaluated in the study (4DDOME).
Bittner et al. <sup>75</sup>	2011	150	Prolene (PL), TiMesh Extra Light (TMEL)	Seroma formation (TMEL)	Pain sensation and pain intensity at 4 weeks, 6 months and	The study concluded that extra lightweight mesh does not play a significant role in chronic pain

					1 year, foreign body sensation, and impairment of physical activities	reduction, but may improve early postoperative discomfort.
Lionetti et al. <sup>76</sup>	2012	148	UltraPro (UP), Prolene (PL)	VAS score (Postoperative pain) at 6h, 12h, 24h and 7 days (UP), return to daily activity and work (UP), chronic pain at 6 months (UP) and operating time (UP).	Hematoma and urinary retention	The study concludes that lightweight mesh fixated with fibrin glue reduces postoperative pain and hospital stay, which offsets the increased cost when compared to Lichtenstein repair.
Bittner et al. <sup>77</sup>	2011	600	Prolene (PL), Premilene LP (PLP), Ultrapro (UP), TiMesh TC Light (TTCL)	Presence and severity of impairment of physical activity at 4 weeks (PLP, UP, TTCL)	Seroma, foreign body sensation, analgesia consumption, surgical complications, recurrence, presence and severity of impairment of physical activity at early post op, 6 months and 1 year,	Although there were no significant differences between the groups relative to pain, there was a tendency toward greater pain in the heavyweight group. The authors conclude that although pain and discomfort may be reduced with material-reduced meshes in the short term, there is no difference between these meshes at 1 year.

					and pain at early post op, 4 weeks, 6 months and 1 year	
Magnusson et al. <sup>78</sup>	2012	309	Polypropylene (not specified), Ultrapro Hernia System (UHS), Prolene Hernia System (PHS)	None	All perioperative findings, complications, VAS pain scores up to 1 year, and quality of life scores using the SF-36 survey.	Despite a lack of significant findings, the authors still recommend Lichtenstein repair (polypropylene) to the Ultrapro and Prolene Hernia Repair systems because of improved cost, and the lack of a need to explore the pre-peritoneal space which could complicate the possibility of laparoscopic repair.
Silvestre et al. <sup>79</sup>	2011	30	Prolene (PL), Ultrapro (UP)	Mesh shrinkage (UP)	None	Both meshes shrank significantly by 30 days compared to their respective areas at implantation, but Prolene (heavyweight) showed a higher tendency toward shrinkage compared to Ultrapro (lightweight). The study acknowledges the limitations of a small sample size.
Paajanen et al. <sup>80</sup>	2013	312	Premilene Mesh (PM), Premilene LP (PLP), Vypro II (VP II)	None	Recurrence, reoperation, foreign body sensation and analgesic use at 2 and	All operations were performed by the same surgeon, and the only variable was mesh material. The authors conclude that mesh material has little

					5 years, and pain before the operation, at 30 days, 1 year, 2 years and 5 years.	bearing, at least in circumstances involving Lichtenstein hernioplasty performed by an experienced surgeon, and further studies must be performed to compare these meshes as they relate to quality of life and cost effectiveness.
Pierides and Vironen. <sup>81</sup>	2011	299	Prolene Hernia System (PHS), Surgipro (SP)	Sensory dysfunction of the skin total (PHS), sensory dysfunction without pain (PHS).	Recurrence, patient satisfaction, pain, pain medication, foreign body sensation, discomfort.	The authors state that the cause of the sensory function discrepancy are unknown. Lichtenstein repair with Surgipro seems to have a disadvantage compared with the Prolene Hernia System due to sensory dysfunction.
Smietanski et al. <sup>82</sup>	2011	182	Surgimesh WN (SWN), Prolene (PL)	Redness or edema (SWN), VAS score at 7 days (SWN).	Perioperative nerve injury, hematoma, analgesic consumption, urine retention, infection, pain (preoperative up to 60 months), VAS score (preoperative, 1st day and 3 <sup>rd</sup> month), and recurrence at 12 and 60 months.	The authors recommend the use of Surgimesh WN over Prolene on the grounds that postoperative pain is slightly improved according to the VAS score at 7 days.

\*Mesh in parentheses for ‘significant complications’ is the mesh with the significantly lower value. Significance defined as  $p < .05$ .

### Non-Comparative Clinical Trials in the Last 10 Years

Author	Year of Publication	Number of Subjects	Mesh	Findings	Notes
Sommer et al. <sup>83</sup>	2013	181	Dynamesh	6% reoperation rate due to mesh-related complications. 19% of patients reported moderate to severe pain.	According to this study, other studies on Dynamesh have reported reoperation rates of 0-21%.
Berrevoet et al. <sup>84</sup>	2013	235	Rebound Shield Mesh (RSM)	1% recurrence rate, 5% of patients complained of chronic pain (VAS score > 3) at 3 months.	High tensile strength nitinol ring surrounding patch maintains original shape. Recurrences and intense pain linked to x-ray findings of incorrect placement of mesh. Study limited by lack of a control and statistical analysis, and short follow up period. Mesh placed by TIPP technique.
Champault et al. <sup>85</sup>	2011	186	Adhesix	Significant decrease in patient reported mild and moderate pain evidenced by decreased VAS scores from preoperative evaluation to 1 week, 1 month and 3 month follow ups. 89.3% reported no pain at 3 months. Numbness and discomfort were reduced in all VAS score subgroups at 3 month follow up, while all quality of life domains improved significantly. No recurrences,	Longer follow up is required to properly evaluate recurrence rate. Overall, this mesh exhibited better outcomes than meshes fixated with fibrin sealant.

				infections or re-interventions occurred. 2.6% developed hematoma or seroma, 1.3% developed ecchymosis.	
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