Review Article

A review of available experimental evidence on the use of prosthetic material in diaphragmatic hernia repair

ABSTRACT

Aim: The benefits of prosthetic material in hiatal hernia repair have been well documented. However, the associated risks are substantial and they are related to the technique, but also the choice of material. Experimental data are invaluable to understand and evaluate the interaction of different meshes with the host tissue. The purpose of this article is to summarize the available experimental evidence in the repair of hiatal hernias with the use of prosthetic materials in animal models.

Methods: A review of the literature from January 1990 to December 2014 was carried out for articles presenting experimental data on hiatal hernia repair.

Results: After discarding non relevant articles, 35 articles were identified. A variety of synthetic and absorbable materials were studied. Review of the available studies showed that synthetic materials have greater mechanical strength, however biological/absorbable materials have a tendency for better integration in host tissue.

Conclusions: Experimental data are essential in order to fully appreciate the process of repair of a hiatal hernia with a prosthetic material. The articles reviewed provide insight into the properties of different prosthetic materials. However, there were large variations in their quality and the methods used. Data from animal studies are an excellent way of evaluating the multitude of materials that have recently become available. Good quality, comparative animal studies are essential in an effort to further improve outcomes for patients who undergo hiatal hernia repair.

Keywords: hiatal, diaphragmatic, mesh, animal, experimental, review

1. INTRODUCTION

The introduction of laparoscopic techniques in hiatal hernia repair resulted in a significant increase in the number of annually performed anti-reflux procedures in less than a decade [1]. There are now randomized trials supporting the use of surgical management as a first-line treatment in selected patients [2]. In some patient subgroups, however, such as the patients with a large paraesophageal hernia, recurrence rates can reach 42% [3]. Recurrence usually occurs after disruption of the crural closure and as the tissues being approximated are frequently attenuated and sutured under tension [4].

In an effort to overcome these limitations, selective mesh use has been reported since the 1970s. In the first large series of patients published, Carlson et al were able to achieve excellent results with polypropylene repair, without any clinical recurrences in long term follow up [5]. A number of clinical trials have since established the efficacy of prosthetic mesh in preventing recurrence in the hiatus [6], however, the emergence of relatively few, but in some cases devastating, complications such as mesh erosion, highlight the need for further research [7].

As new materials are continuously being developed it is important for surgeons to make an informed decision on which material to use. Animal studies are essential in evaluating the interaction between the different prosthetic materials and the host tissue and their relative safety and efficacy in hiatal hernia repair. We have performed a literature review in order to examine the contribution of the available experimental evidence towards selecting the optimal prosthetic material and surgical technique in mesh repair of diaphragmatic hernia.

2. MATERIAL AND METHODS

We searched for articles on diaphragmatic hernia repair meeting the criteria outlined below and analyzed them for specific outcomes using the PRISMA guidelines.

2.1 ELIGIBILITY CRITERIA

1) Type of study: Experimental animal (in vivo) study of repair of hiatal/paraesophageal or congenital diaphragmatic hernia using prosthetic material (mesh). Models of congenital diaphragmatic hernia were included in this review, because, although the mesh was not placed in the hiatus in these models, they can be considered orthotopic models, usually involving creation of a hernia by excision of part of the left hemidiaphragm, mimicking conditions like those found in a giant paraesophageal hernia (large defect, attenuation of muscular tissue).
2) Language: English
3) Publication year: 1990-2014

2.2 *LITERATURE SEARCH STRATEGY*

Studies were identified by searching the PubMed/Medline and Scopus databases. The following key words were used as search strings: hiatal, diaphragmatic, mesh, animal, experimental.

Potentially relevant articles were identified by the title and abstract and full papers were obtained and assessed in detail by two of the authors prior to their inclusion in the review. The reference list for each article was also screened to identify further relevant publications.

2.3 *Study selection*

Eligibility assessment was performed independently by 2 reviewers. Disagreements between reviewers were resolved by consensus.

2.4 *Data extraction*

Data collection and analysis were carried out independently by 2 researchers. Studies were classified into two experimental model groups which investigated mesh repair of either hiatal or congenital diaphragmatic hernia. Articles were reviewed for a number of variables examining their design (number and type of animals, mesh implantation time, use of comparative/control group, biomechanical/histopathological analysis) and the technique used (Mesh type and shape, fixation type, surgical technique).

Study results were specifically assessed for findings relevant to controversial topics in diaphragmatic hernia repair with prosthetic mesh (Table 1).

Table 1: Controversial topics in hiatal hernia repair with prosthetic mesh

1. Mesh shape	
2. Mesh type	a. Infection potential
	b. Handling characteristics
	c. Durability of repair
	d. Adhesion potential, tissue incorporation, fibrosis/stenosis potential
	f. Migration/erosion potential
3. Fixation method	
4. Sutured vs tension-free hiatoplasty	

3. RESULTS

3.1 *Literature search*

Our search strategy initially returned 924 studies which we evaluated based on title and abstract and we selected 21 articles based on our inclusion criteria. The full text of these articles was downloaded and another 9 studies were obtained from their reference lists. After excluding 2 articles studying hiatal hernia repair in the context of fetal tissue engineering, 28 articles were assessed in detail (Figure 1).

3.2 *Study design*

Large animals (swine, dogs) were used in most studies. The number of animals in each study was small (6-36 animals). Implantation time ranged from 2 weeks to 12 months (Table 2). A majority of studies included a comparison or control group and histopathological analysis, however only a few studies used endoscopic or radiological assessment or biomechanical analysis.

3.3 *Mesh characteristics and surgical technique*

A variety of meshes were evaluated, including conventional (polypropylene, polytetrafluoroethylene - PTFE) and newer (polypropylene/ polyglactin 910 - PP-PG, poly(lactic-co-glycolic acid) - PLGA) synthetic materials, biologically derived materials such as bovine pericardium and newer biologic meshes (Small intestinal submucosa - SIS, acellular dermal matrix - Alloderm). Most authors used a rectangular piece of mesh, but circular and U-shaped meshes were also used. The surgical technique used in most studies was mesh fixation in the hiatus using an open technique, with or without excision of part of the left hemidiaphragm, while in two studies an endoscopic approach was utilized: laparoscopic creation of a defect in the left hemidiaphragm and repair in one study and thoracoscopic creation of a paraesophageal hernia and subsequent laparoscopic repair in another. Finally, mesh fixation was achieved with sutures in most cases, while a few of the authors used biological adhesives, such as fibrin glue (Table 3).

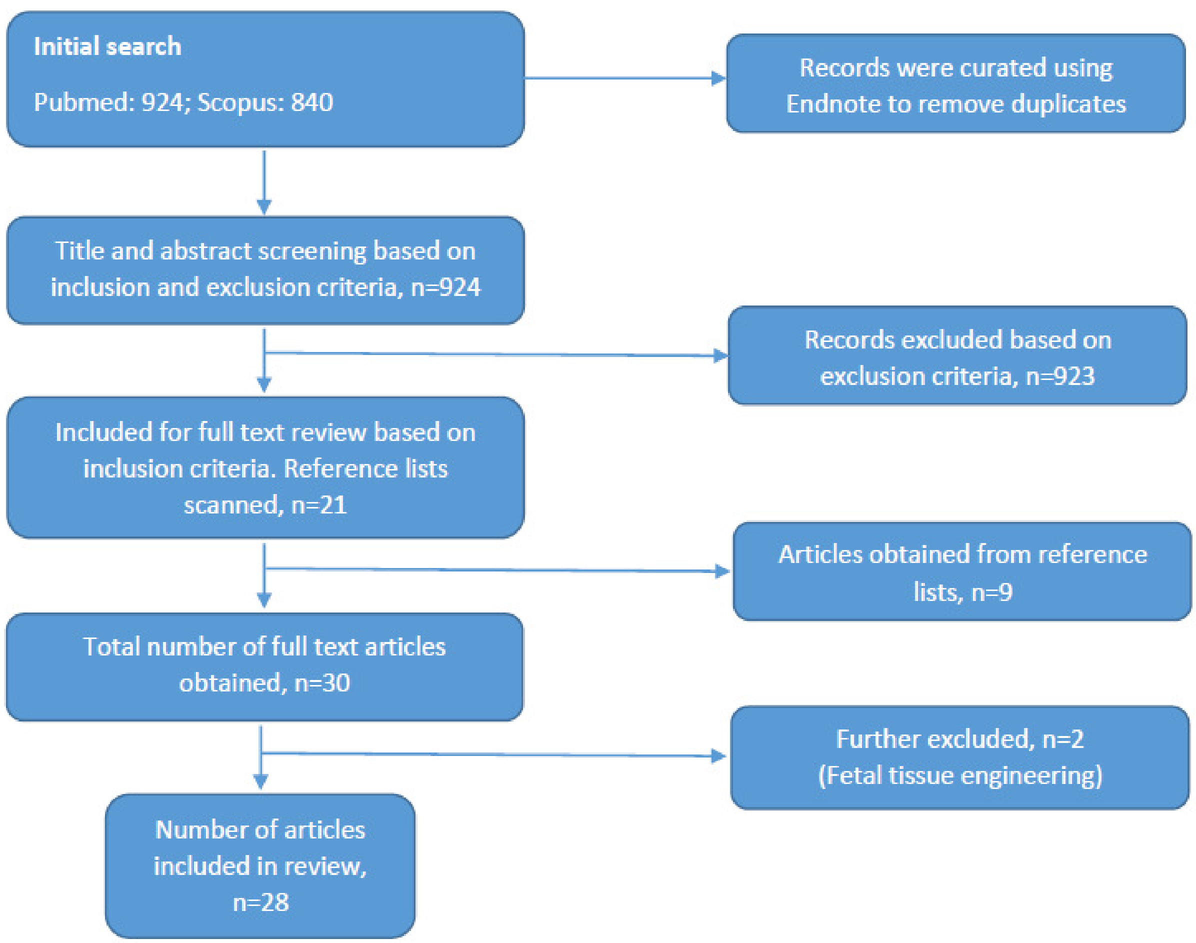

Figure 1: Flow diagram of literature search

3.4 *Results of individual studies*

3.4.1 Mesh shape

Although circular, rectangular and U-shaped meshes were used, no study directly compared meshes of different shapes. In a study of polypropylene meshes of a circular shape fixed by sutures in a rabbit model, the meshes had usually moved from their implantation bed and had eroded into the esophagus [16]. However, in another study a circular polypropylene mesh was fixed in place using fibrin glue in a swine experimental model and in this case the authors reached conflicting results as they found the meshes stayed in position and their inner edge had retracted evenly from the esophagus [14].

3.4.2 Mesh type

3.4.2.1 Infection potential

No study on mesh use in contaminated fields has been carried out.

3.4.2.2 Handling characteristics

The handling characteristics of each mess i.e. the ease of its use in laparoscopic surgery was not addressed in any study.

3.4.2.3 Durability of repair

Most of the studies discussed showed that the mesh repair remained successful during the observation period. SIS was shown to have equivalent strength to PTFE when applied on the diaphragm [27, 32], although it was not as strong as polypropylene meshes [25, 26]. In another study comparing two forms of SIS mesh in a dog model, the first comprised of 4-ply and the other from 8-ply, the thicker version was shown to be stronger, while both showed more strength than native diaphragmatic tissue [28]. Fascia lata was also shown to be equivalent to PTFE in mechanical strength [29].

3.4.2.4 Adhesion potential, tissue incorporation, fibrosis/stenosis potential

Polypropylene mesh consistently caused formation of strong adhesions [25, 26], which were less pronounced with low-weight polypropylene [9]. Dualmesh showed less extensive adhesions than polypropylene [17], while Surgisis showed less adhesions than PTFE in two studies [11, 32], but dense adhesions comparable to polypropylene in another [25].

Table 2: Design of experimental studies in diaphragmatic hernia repair

	Author	Pub year	Animal type	N	Implantation time	Comparative/ control group	Biomechanical analysis	Histopathological analysis	Endoscopic/ radiological assessment
					Hiatal hernia repair models				
1	Muller-Stich [8]	2014	Swine	24	8 weeks	✓		✓	
2	Senft [9]	2014	Swine	24	8 weeks	✓			
3	Krpata [10]	2012	Swine	20	30 days				
4	Vereczkei [11]	2012	Dogs	3	1/3/6 months	✓		✓	
5	Jenkins [12]	2011	Swine	32	2 weeks				
6	Fortelny [13]	2010	Swine	7	4 weeks			✓	
7	Muller-Stich [14]	2008	Swine	9	6 weeks			✓	
8	Otto [15]	2008	Rabbits	20	3 months	✓		✓	
9	Jansen [16]	2007	Rabbits	20	3 months	✓	✓		✓
10	Smith [17]	2007	Swine	18	3/28 weeks	✓		✓	
11	Desai [18]	2006	Dogs	6	12 months			✓	✓
					Congenital diaphragmatic hernia repair models				
12	Brouwer [19]	2013	Lambs	7	6 months	✓		✓	
13	Zhao [20]	2013	Rats	52	1, 2, 4, and 6 months	✓		✓	
14	Brouwer [21]	2013	Rats	36	12 weeks	✓		✓	
15	Brouwer [22]	2013	Rats	36	2/12 weeks	✓		✓	
16	Brouwer [23]	2013	Rats	25	2/4/8/12/24 weeks	✓		✓	
17	Gonzalez [24]	2011	Swine	20	6 months	✓		✓	
18	Bohm [25]	2010	Rabbits	33	4 months	✓		✓	
19	Bohm [26]	2010	Rabbits	33	4 months	✓	✓		
20	Urita [27]	2008	Rats	24	1-3 months				
21	Sandovalb [28]	2006	Dogs	11	6 months	✓	✓	✓	

22	Suzuki [29]	2002	Dogs	24	15/30 days			
23	Upadhyaya [30]	2001	rat	8	3 weeks	✓	✓	✓
24	Steinau [31]	2000	pigs	24	3/6 months	✓	✓	✓
25	Lantis II [32]	2000	Rabbits	32	6/12 weeks	✓	✓	✓
26	Kimber [33]	2000	Lambs	12	1,3,6 months	✓	✓	
27	Dalla Vecchia[34]	1999	Rats	87	2 weeks - 4 months	✓		✓
28	Lally [35]	1993	Rats	37	400 gr	✓		✓

Mesh shrinkage was shown to be around 50-70% of original size for polypropylene [9, 14, 16], while the percentage of shrinkage was more for the low-weight mesh [9]. When PTFE, polyester and polypropylene were compared, PTFE showed considerably more shrinkage [8].

Bohm et al compared two synthetic polypropylene meshes (Ultrapro, Proceed) to Surgisis in a rabbit model [25, 26]. Inflammatory reaction at the border of the mesh was more pronounced with Proceed, followed by Ultrapro and Surgisis. On the other hand Surgisis and Ultrapro showed better tissue regeneration compared to Proceed. Collagen maturation was slower for Surgisis compared to the synthetic meshes. A composite polypropylene mesh was compared to a conventional polypropylene mesh and the composite mesh showed better integration and reduced inflammatory response, which could be associated with a lower risk of erosion and postsurgical dysphagia [16]. Histological examination and cross-polarization microscopy showed differences in cell proliferation rate, apoptosis and collagen I/III ratio, which were statistically significant and show better tissue integration for the composite mesh [15, 16] Another study showed excellent integration, for a titanium-polypropylene mesh [13].

Polytetrafluoroethylene (ePTFE/ Dualmesh) was evaluated and caused the formation of minimal adhesions except in segments of the mesh where folding exposed its superior surface. There were no erosions or migration noted. Microscopic evaluation showed only an unstable capsule encompassing the mesh underlining the importance of a stable fixation [17, 24, 33].

Biologically-derived materials were evaluated in several studies. The authors reported complete mesh replacement by fibrovascular scar tissue with SIS mesh, with significant muscular regeneration, without any erosion in surrounding hollow viscera [18]. The 8-ply SIS mesh shows a slower rate of degradation compared to the 4-ply, which can in turn lead to better integration into host tissue [28]. SIS shows equivalent capillary ingrowth to Alloderm (acellular human cadaveric dermis), but a higher level of thinning [34]. When compared to PTFE, SIS shows better integration [11], more collagen deposition and skeletal muscle regeneration and neovascularization [24]. Finally, fascia lata showed superior integration and capillary ingrowth to ePTFE [29] and, in a separate study, excellent tissue integration and neovascularization, along with a mild to moderate inflammatory reaction [11].

3.4.2.5 Migration/erosion potential

The level of migration and the extent of foreign body reaction were higher when a conventional polypropylene mesh was used compared to a composite one [15, 16]. The part of the mesh close to the diaphragm showed less mechanical stability compared to the one close to the esophagus. In a comparative study of PTFE and SIS in a pig model of congenital diaphragmatic hernia repair, the authors were able to demonstrate PTFE has a poorer integration into host tissue compared to SIS and tends to migrate and fold [24].

3.4.3 Fixation method (sutures/tacks/glue)

Biologically compatible adhesives like fibrin glue and polyethylene glycol were used with no evidence of migration, no evidence of any adverse effect to the incorporation of the mesh and equivalent strength to suture fixation. Krpata et al used an acellular porcine dermal matrix and compared fibrin sealant to fixation with sutures [10]. Meshes fixed with fibrin glue showed no folding, while there was minimal folding in the control group. Esophagograms did not exhibit any signs of strictures. The authors used a “peel” test to compare the force needed to separate the mesh from the crura and found no difference between the two techniques, whilst the introduction of glue between the crura and the mesh did not result in a significantly different cellular response. Use of fibrin sealant resulted in a significant reduction in operative time. Jenkins et al compared two biological adhesives and found both equally effective in mesh fixation [12].

3.4.4 Sutured or tension free hiatoplasty

In reviewing the available published studies we did not find any study comparing sutured to tension-free hiatoplasty.

4. DISCUSSION

There are a number of controversial points regarding the best surgical technique in hiatal and paraesophageal hernia surgery [36], the most controversial of which concerns the placement of mesh in the oesophageal hiatus [37-39]. There are reports of a significant reduction in recurrence rates when mesh is used in the surgical repair of hiatal hernia [40, 41]. On the other hand, the surgical community is now conscious that there are important drawbacks in the form of mesh-related complications, reports of which were scarce for two decades and have now begun to appear in the literature [7, 42, 43]. A mesh placed in the diaphragm is subjected to the constant movements of breathing, which are likely to affect its incorporation to the host tissue. Therefore, although there are multiple articles available studying mesh use in animal models for a variety of indications, it is important to evaluate results from animal models of diaphragmatic hernia repair.

Our literature review showed that there were large variations in the quality of experimental studies, only a few of which incorporated histopathological, biomechanical, endoscopic and radiological assessment. The number of animals was small and the implantation time was limited. The surgical technique used in most cases is a disadvantage, since

Table 3: Mesh characteristics and surgical technique

	Mesh type	Mesh shape	Surgical technique	Fixation method
		Hiatal hernia repair models		
1 [8]	PP/ PET/ PTFE	Circular	Open hiatoplasty and placement of patch in the oesophageal hiatus	Fibrin glue
2 [9]	heavyweight small-porous/heavyweight large-porous/lightweight large-porous PP	Circular	Open hiatoplasty and placement of patch in the oesophageal hiatus	Fibrin glue
3 [10]	acellular porcine dermal matrix	U shaped	Laparoscopic hiatal hernia repair	Sutures/Fibrin sealant
4 [11]	Pericardial and fascia lata patches	Rectangle	3x3 cm patches fixed on muscular part of diaphragm	Polypropylene 3/0
5 [12]	SIS	U shaped	Laparoscopic placement of patch in oesophageal hiatus	Fibrin glue/ polyethylene glycol
6 [13]	Titanium polypropylene mesh	Keyhole	Open placement of the patch without prior hiatoplasty	Fibrin glue
7 [14]	Heavy-weight polypropylene	Circular	Open hiatoplasty and placement of patch in the oesophageal hiatus	Fibrin glue
8 [15]	PP/ PP–polyglecaprone 25 composite	Circular	Open hiatoplasty and placement of patch in the oesophageal hiatus	Polypropylene 6/0
9 [16]	PP/ PP–polyglecaprone 25 composite	Circular	Open hiatoplasty and placement of patch in the oesophageal hiatus	Polypropylene 6/0

10 [17]	DualMesh	U shaped	Open transabdominal excision of left hemidiaphragm and open placement of patch in the oesophageal hiatus without prior hiatoplasty	Interrupted ePTFE
11 [18]	SIS	U shaped	Thoracoscopic creation of diaphragmatic hernia and subsequent laparoscopic repair, with hiatoplasty and placement of patch	Interrupted 2/0 polyester
		Congenital diaphragmatic hernia repair models		
12 [19]	Collagen-Vicryl	Rectangle	Posterolateral 3x1.5 cm diaphragmatic defect	Running 4/0 prolene
13 [20]	poly(ε-caprolactone) and collagen type I	Rectangle	Excision of 70% of the left hemi-diaphragm (approximately 2-3 cm2)	Interrupted 6/0 Prolene
14 [21]	Dual layered collagenous scaffolds	Rectangle	12 mm diameter right diaphragm defect	Interrupted 6/0 Prolene
15 [22]	Cross-linked collagenous scaffolds	Rectangle	12 mm diameter right diaphragm defect	Interrupted 6/0 Prolene/ interrupted 5/0 Vicryl
16 [23]	Cross-linked collagenous scaffolds	Rectangle	Excision of 1/3 of the right hemidiaphragm	Interrupted 6/0 Prolene
17 [24]	SIS, ePTFE	Rectangle	Excision of the left hemidiaphragm	Running 3/0 prolene
18 [25]	SIS, PP plus Polyglecaprone-25, and PP plus polydioxanone and cellulose plus Tachosil	Rectangle	A defect of 1cm in diameter was made into the lateral left diaphragm at the interface of tendon and muscle	Running 5/0 Prolene
19 [26]	SIS, PP plus Polyglecaprone-25, and PP plus polydioxanone and cellulose plus Tachosil	Rectangle	A defect of 1cm in diameter was made into the lateral left diaphragm at the interface of tendon and muscle	Running 5/0 Prolene
20 [27]	PLGA - collagen mesh	Rectangle	Open transabdominal left hemidiaphgragm excision and repair	N/A
21 [28]	SIS	Rectangle	Open transabdominal left central hemidiaphragm excision and repair	N/A
22 [29]	Autologous fascia lata/ ePTFE	Rectangle	Left thoracotomy, left hemidiaphragm excision and repair	N/A
23 [30]	Integra	Rectangle	Open excision of left hemidiaphragm and patch repair	Interrupted 6/0 Vicryl
24 [31]	lyophilized dura/ transverse abdominal bovine pericardial serosa	Rectangle	Open excision of left hemidiaphragm and patch repair	Polypropylene 3-0
25 [32]	SIS/ PTFE	Rectangle	Open transabdominal left hemidiaphragm excision and repair	N/A
26 [33]	PTFE/ fluoropolymer-coated PET	Rectangle	Laparoscopic creation of 2x2 cm defect in left hemidiaphragm and repair	3-0 braided polyester
27 [34]	SIS/AlloDerm	Rectangle	Open transabdominal left central hemidiaphragm excision and repair	N/A
28 [35]	ePTFE/oxidized cellulose/polyglactin 910	Rectangle	Excision of the left hemidiaphragm followed by repair with a patch	Running 4-0 silk.

SIS: small intestinal submucosa; PTFE: polytetrafluoroethylene; PP: polypropylene; PLGA: poly(lactic-co-glycolic acid); PET: polyester

neither the creation of a hiatal hernia nor minimally invasive techniques were used, although similar experimental models have been described as in the article by Desai et al, where a study incorporating the creation of a diaphragmatic hernia and its subsequent repair using laparoscopy is presented, in a model closely resembling the current clinical practice and enabling the surgeon to appreciate the handling characteristics of each mesh [18]. Finally, due to the heterogeneity of the studies quantitative analysis of the results was not possible.

We evaluated studies regarding specific topics and a number of these were not addressed at all (infection potential, handling characteristics, sutured/ tension free hiatoplasty), while there was limited data on the impact of mesh shape and the migration/erosion potential and durability of each mesh.

A test of the durability of the hiatoplasty should ideally compare biological/bioabsorbable prostheses to materials like polypropylene or PTFE, the efficacy of which has been demonstrated in randomized trials [40, 41]. Biological meshes made from small intestinal submucosa have been shown to reduce recurrence rates in a randomized trial with short-term follow-up [44] and can also be used as a control to evaluate newer biological materials. The ability of the mesh to prevent recurrence can be investigated at autopsy or radiologically. However, new recurrences have been known to occur for a long time after surgery. Indeed, long term observation of the patients in the previously mentioned trial showed no benefit in recurrence rates with SIS mesh [45]. The practical limitations of observation time in animal studies lead authors to perform biomechanical evaluation of mesh materials to evaluate the durability of the repair. Results confirm the better results obtained clinically with polypropylene compared to biologics, but are surprising since PTFE was weaker than expected [40].

Most of the authors focused on the potential of adhesion formation, biocompatibility and tissue integration of each mesh and adequate experimental data on several materials is available. The safety profile of each material i.e. its potential to adhere to and erode into viscera, to cause extended fibrosis resulting in oesophageal stenosis, or to migrate from its position is the most pressing issue, since it is the reason mesh-augmented hiatoplasty is not widely used in clinical practice. Polypropylene meshes showed good integration, but also caused significant adhesions. Experimental studies will be very useful for the comparison of the new generation lightweight meshes, so as to evaluate their advantages compared with standard polypropylene meshes. PTFE resulted in less adhesions, but poor integration with the host tissue. SIS mesh showed an excellent safety profile in experimental studies. These results are in accordance with those obtained from clinical trials including a prospective randomized trial [44] but a marked fibrous response was observed in a previous comparative experimental study, published in abstract form, where significant esophageal stenosis was shown [46]. This finding is significant since esophageal stenosis have been reported in clinical series of patients operated on with SIS mesh [7].

The method used to fix the prosthesis to the crura presents a problem since laparoscopic suturing is challenging and time consuming (and potentially risky for the inexperienced) and use of tacks, although fast and effective, places large vessels and the heart at risk of serious injury with potentially catastrophic results [47]. The stability of the mesh depends on both the fixation method but also the material itself and the strength of its incorporation. T-peel testing is an elegant method of quantifying the strength of mesh incorporation [10]. Directly observing the tendency of the mesh to migrate and cause adhesions is tempting, however results must be interpreted with caution; failure of known complications to emerge in these studies could be caused by the relatively short observation time (erosions occur up to nine years after surgery) [7], but could also be interpreted to a lesser extent as proof of the importance of surgical technique (i.e. to strengthen the argument that the reported complications are not inherent in the mesh type but rather are a result of inadequate surgical technique). Indeed, there was a striking difference in mesh migration of polypropylene mesh in the article by Fortelny et al compared to the study of Jansen et al [13, 16]; the difference in the ratio of thickness between the mesh and the tissues of the two different animal models was offered as an explanation.

The introduction of the new collagen-based biomaterials and the preliminary encouraging results from their use raised great expectations for improved outcomes. The biomaterials from porcine small intestinal submucosa and porcine or human acellular dermis are already widely used in clinical practice (they were being used in 1/3 of all mesh-augmented diaphragmatic hernia repairs a few years ago [48]) and experimental data are invaluable to further our understanding of their incorporation in host tissue. Fascia lata has been used as a prosthetic material in the hiatus during the 1970s with mixed results, showing efficacy but also some complications [49]. It is, however, in our opinion a very interesting material because it is the only easily obtainable strong autologous patch and has been shown to possess strength equal to PTFE and better incorporation on the diaphragm [28]. Although, the reviewed articles study most of the types of meshes currently in clinical use, new biological and bioabsorbable materials are being introduced in clinical practice without any available published experimental data [49, 50].

There is an ever growing need for experimental studies, which should also be well-designed in order to also tackle ethical concerns with regards to animal sacrifice. Studies on mesh-augmented hiatoplasty should include a laparoscopic animal model, biomechanical evaluation and histopathological evaluation of no less than two different biomaterials at the very minimum. In the absence of good quality clinical trials, which are invariably difficult to put together due to the relatively small number of patients, good quality, comparative animal studies are essential in order to identify the mesh with the best safety/efficacy profile, determine the optimal shape and fixation method and enable surgeons to make an inform decision on the merits of using mesh in hiatal hernia repair.

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