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Review Article

Development of Bio-artificial Esophageal Tissue Engineering Utilization for Circumferential Lesion Transplantation: A Narrative Review

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Abstract

The esophagus is the gastrointestinal tract's primary organ that transfers bolus into the stomach with peristaltic motion. Therefore, its lesions cause a significant disturbance in the nutrition and digestive system. Esophageal disease treatment sometimes requires surgical procedures that involve removal and circumferential full-thickness replacement. Unlike other organs, the esophagus has a limited regeneration ability and cannot be transplanted from donors. There are various methods of restoring the esophageal continuity; however, they are associated with certain flaws that lead to a non-functional recovery. As an exponentially growing science, tissue engineering has become a leading technique for the development of tissue replacement to repair damaged esophageal segments. Scaffold plays a significant role in the process of tissue engineering, as it acts as a template for the regeneration of growing tissue. A variety of scaffolds have been studied to replace the esophagus. Due to the many tissue quality challenges, the results are still inadequate and need to be improved. The success of esophageal tissue regeneration will finally depend on the scaffold's capability to mimic natural tissue properties and provide a qualified environment for regeneration. Thereby, scaffold fabrication techniques are fundamental. This article reviews the recent developments in esophageal tissue engineering for the treatment of circumferential lesions based on scaffold biomaterial engineering approaches.

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Keywords ● Tissue engineering ● Esophagus ● Stem cells ● Biocompatible materials ● Tissue scaffolds ● Regeneration

What's Known

- Several works have been done on esophageal tissue engineering, but a comprehensive review of recent works that focuses on full-thickness replacement has been missing.

What's New

- This article is a comprehensive review of the work done for natural and synthetic materials used in esophageal tissue engineering in recent years, which has not been presented so far.
- The present article reviewed the new works done in esophageal tissue engineering with a focus on full-thickness replacements.

Introduction

The esophagus, or gullet, is a muscular tube in the vertebrate body that connects the pharynx to the stomach. Transferring bolus into the stomach is the dominant role of the esophagus in the digestive system. The esophagus in humans can be divided into three regions: cervical, thoracic, and abdominal. The cervical muscle belongs to the category of skeletal muscles, while the thoracic muscle is a smooth muscle.[1] Similar to the other gastrointestinal tract components, the esophagus wall consists of four layers, namely the mucosa, submucosa, muscularis propia, and adventitia layers. Blood vessels, nervous system fibers, and esophageal glands are mostly located on the submucosa layer. The mucosa layer covers the inner wall of the esophagus. The mucosa layer cells in the proximal region are squamous epithelial cells, and in the distal region where the esophagus attaches to the stomach, they are columnar epithelial cells.[2] Accordingly, it can be said that the esophagus is one of the primary organs of the gastrointestinal tract, and its lesions cause a significant disturbance in the nutrition and digestive system. Although the esophageal function is the transfer of food by peristaltic movements, its ailment causes serious gastrointestinal problems and decreases the quality of life.

Esophageal diseases are increasing yearly. Hence, it is necessary to devise a comprehensive plan and find suitable treatments. Accordingly, considering the rapid advancement of science and the integration of various disciplines aiming to advance modern medical treatments and achieve high levels of tissue engineering technology, appropriate therapeutic solutions can be proposed, as they have been for other organ lesions. To create an adequately engineered tissue with the natural human esophagus' properties, in addition to choosing the right scaffolding method, it is also necessary to use proper polymer structures and materials that have appropriate characteristics, such as mechanical strength, biocompatibility, biodegradability, and elasticity. Besides, the selection of appropriate biological factors and components, such as growth factors, cytokines, differentiated cells, or stem cells, is also required to obtain a suitable engineered tissue that stimulates and promotes regeneration in the human body.[2]

This review aims to discuss the advancements in tissue-engineered esophageal fabrications. Furthermore, this study evaluates various techniques utilized to advance proper tissue replacement, and the challenges we face in clinical practice. The esophageal tissue engineering process is briefly illustrated in figure 1.

Anatomy and Histology

The esophagus is a muscular tube-shaped organ with a 20-25 cm length and an approximately 2 cm diameter. It is divided into three main parts: cervical, thoracic, and abdominal.[3]

The esophageal tube starts within the 6th cervical vertebrae and ends at the junction with the stomach at the 11th thoracic vertebrae level. The cervical segment is about 5 cm, which continues unto a 17-18 cm thoracic part. After crossing the diaphragm, it reaches the abdominal part, which is about 2-3 cm in length.[4]

The length of the esophagus depends on age, sex, and physical characteristics. For instance, in newborns, this organ's proximal and distal ends are typically one or two vertebrae higher than in adults, and it extends to lower vertebrates by age.[5] Mucosa, sub-mucosa, muscular externa and adventitia are the main layers of this organ.

The mucosa is a non-keratinized stratified squamous epithelium, which coats the inner surface of the esophageal wall. Lamina propria and lamina muscularis mucosa are the next subsections of mucosa beneath the epithelium. Loose connective tissue is the major component

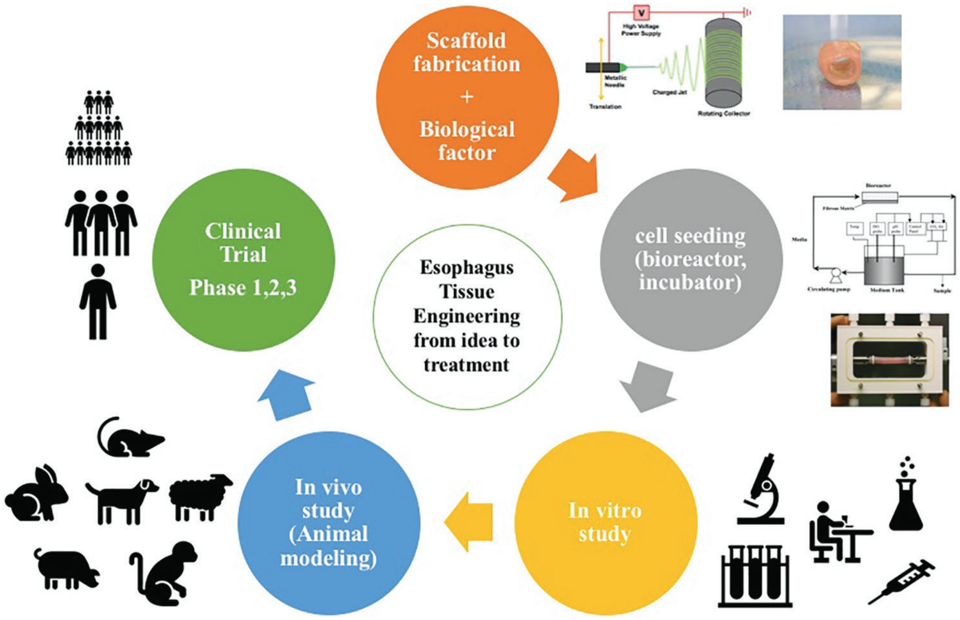

Figure 1: The diagram shows the esophagus tissue engineering trend

of lamina propria. Smooth muscle tissue and elastic fibers make the muscular subsection of the mucosa. The “Z line” is the point, where the non-keratinized stratified squamous epithelium of the mucosa attaches to the simple columnar epithelium in the cardia of the stomach.[5]

The sub-mucosa is an elastic and collagenous layer formed mainly by dense, irregular connective tissue, containing veins, lymphatics, and Meissner plexus.[5] The muscularis propria layer consists of longitudinal (outer part) and circular (inner) muscle fibers. The longitudinal fibers originate from the posterior portion of the cricoid cartilage and develop a triangle called the “Lamier triangle”, surrounded by the longitudinal muscle fibers laterally and the cricopharyngeal muscle superiorly. The Killian triangle is another anatomic hallmark that is located in this region. Inferior constrictor muscles of the pharynx and the cricopharyngeus muscle form the limiting borders of this triangle. Longitudinal muscle fibers are collected laterally in the upper portion of the esophagus, but these fibers expand and cover all surfaces at the lower sides and make a more potent layer in the lower third part of the esophagus. Circular muscle fibers are a thinner and medial layer relative to longitudinal fibers. These fibers are not circular within different esophagus segments, but they become circular at the lower parts. Despite their irregular formation, their regular pattern makes the entire muscle layer act as a shutter-like apparatus. Sometimes, following a sudden increase in luminal pressure, spontaneous perforation occurs in the lowermost parts, including the entire esophageal wall. Striated muscles are the dominant upper esophageal muscular layer, the lower parts, consisting of mainly smooth muscle fibers. Changing the muscular layers of different segments is associated with a transition zone, including striated and smooth muscle fibers.[5]

Adventitia

The adventitia is a loose connective tissue surrounding most of the esophagus and is the outer layer of the organ. This loose layer facilitates the spread of infections and the creation of tumors in the esophagus.[5]

Esophageal Arteries

The blood supply of the esophagus is mainly provided by the inferior thyroid artery, aorta, and left gastric artery, which supplies the cervical, thoracic, and abdominal segments, respectively. Since esophageal arterial blood flow is rich enough for anastomosis, any unwanted dissection can cause life-threatening bleeding in the esophagus.[6, 7]

Esophageal Veins

The venous system starts to develop from the submucosa layer, and after passing the outer layers, drains into the inferior thyroid, azygos, and left gastric vein along with cervical, thoracic, and abdominal segments, respectively. The esophageal venous plexus also acts as a venous outflow for the drainage of other veins, including short gastric veins, splenic vein, left gastroepiploic vein, and branches of an inferior phrenic vein.[6, 8]

Sphincters

The upper esophageal sphincter (UES) and the lower esophageal sphincter (LES) are the two main proximal and distal boundaries of the esophagus.[9] The function of these two sphincters is to close the entries of the esophagus. However, they do not have the exact anatomical features of other sphincters.[10] Although UES is a striated muscle, it is not under voluntary control, and the opening is resulted from a swallowing signal.[11]

The LES, also called the gastroesophageal sphincter, controls the lower part of the esophagus at the gastroesophageal junction.[12] Some of its functions are presented here.

Swallowing Using Peristaltic Motion

After swallowing, food and fluids pass through the pharynx and esophagus, one of the first parts of the alimentary tract.[10] The swallowing process begins with a backward movement of the epiglottitis and simultaneous UES relaxation, leading to the food and fluids passing the bolus through the esophagus. The downward movement of food results from a rhythmic and regular contraction and relaxation of the different parts of the esophagus.[10]

Prohibiting Gastric Acid Reflux

Gastric acid is the main secreting component of the stomach, consisting of hydrochloric acid (HCl) and potassium and sodium salts, which correlate with food ingestion. The normal pressure of LES prevents the backflow of the gastric ingredients, protecting the esophageal mucosa. The lower crura of the diaphragm is another compensatory component that helps decrease the reflux of acid and the acute angle of His.[10]

Prevalent Esophageal Diseases and Current Treatments

Esophageal lesions can be divided into two categories: congenital lesions and lesions occurring throughout life due to various factors. In recent years, around 500,000 people globally have gotten malignant esophageal cancer each year. Although the rate of human malignant cancers of other organs, in most cases, has either been kept fixed or decreased, esophageal cancer has increased by about 140% in the last 10 years.[13, 14]

Even though esophageal cancer is more common in adults, other diseases, such as esophageal atresia, are seen in infants and newborns. Depending on the geographic region, in every 2500 to 5000 newborns, one infant gets esophageal atresia.[15, 16] Because of this congenital defect, the newborn's esophagus is closed, and he/she will be unable to swallow and digest fluids and milk; therefore, surgery is required. One of the most common types of atresia is the tracheoesophageal fistula (TOF), in which a part of the esophagus is connected to the trachea.[17] In this type of disease, not only the ability to drink milk is disturbed, but also breathing becomes difficult. Therefore, on the first day following birth, an initial surgery is required to split the trachea from the esophagus in order to reduce breathing problems. The life condition will be stabilized, but the problem of esophageal atresia will persist.[18, 19] Several methods have been suggested and performed to treat esophageal atresia, but a thoroughly efficient method has not been developed yet. The first reports of successful surgeries are from the 1940s. Since then, various surgical techniques have been developed and optimized,[17] leading to an increase in the success of these surgeries by a rate of over 95%.[20] Despite these improvements, neonates have a lower quality of life after surgery. Several factors may be involved, such as anastomosis leakage, stenosis, gastric reflux, dysfunction, and inadequate esophageal motility. Hence, these factors cause frequent referrals to the hospital, and various surgical and non-surgical treatments are needed. Among different esophageal atresia types, long-term esophageal atresia (LGOA) is the most complicated, and consequently, the most difficult to treat. Therefore, esophageal connectivity is not achieved with one surgery alone and requires multiple steps. One of the usual strategies for these patients is to have a gastrostomy performed on their stomach on the first day following birth, helping them stay alive and grow. During the treatment, which can take weeks up to months, patients cannot stay at home and require hospitalization. They should also be admitted to the intensive care unit (ICU), since multiple discharges would be accumulated in the upper esophagus, causing the risk of respiratory complications. Therefore, these substances should be routinely exhaled through a suction tube. When the normal growth of the esophagus is not sufficient, a technique is suggested to stretch the two sides of the esophagus, reducing the distance, and then, connecting them with surgery. This is one of the newest methods currently being implemented.[17]

Other methods, such as gastric transposition or colon replacement, have been suggested and are currently performed by surgeons.[21, 22] Esophagectomy is the primary part of these different procedures, which tries to maintain the uniformity of the esophagus[23] by replacing the missed portion with plastic[24] and synthetic constructs.[25, 26] One of the approved treatment options is known as an esophageal replacement with gastric tube.[27-33] However, utilizing other alternatives, including aortic autografts[34] and prosthetic constructs[26, 35, 36] has been a standard method of the last decades. The promotion of surgical techniques and instruments such as stents[37-40] has allowed for the progress of valuable methods for restoring esophageal continuity and functionality. These procedures include the omental wrapping of the esophagus,[41-43] gastric pull-up,[44-48] colonic interpositions,[49-51] and deltopectoral,[52-54] and pectoralis major[55-58] myocutaneous flaps. Nevertheless, all of these various practices are still associated with considerable complications and mortality. The main problem with conventional esophagectomy treatments is the appropriate replacement of esophageal lesions.[59, 60]

It is currently impossible to build a human esophagus based on the existing knowledge. Spontaneous reconstruction and repair of the esophagus following injury do not occur for more than a specified length within the body, and the body cannot regenerate the entirety of esophageal tissues. Moreover, due to the lack of an adequate vascular network in those areas, a repair cannot occur.[61-64] Due to the stated therapeutic limitations, there is a strong need for a suitable esophagus substitute. The conduit or construct for the esophagus should have the ability to transfer food and fluids from the mouth to the stomach without leakage, perforation, or rupture, while also having the appropriate mechanical and structural characteristics similar to those of the natural esophagus. The stress and strain of the esophagus wall in the human body undergo up to about 1 MPa and 175% change in pressure and length, respectively, which are significant.[65, 66] Hence, the esophagus must be able to tolerate this expansion. Despite substantial advances in stem cell therapy and tissue engineering of the skeletal muscle systems and the ability to prepare 3D multi cells culture, there is no significant progress achieved in the field of multilayer tissue engineering of the internal organs of the gastrointestinal tract until now.[67-69] Developing an appropriate tissue-engineered product *in vitro* and implementing the tissue *in vivo* is the main challenge we face, mostly due to struggles in creating large perfused scaffolds that implement oxygen, nutrients, and waste products' proper diffusion. These challenges are tough when the organ candidate for regeneration has distinct spatial structural characteristics.[67] A new option for *in vitro* research is the use of bioreactors to simulate *in vivo* biological states. Numerous works have been done on acellular matrix materials used in bioreactors to improve esophageal healing.[70, 71] However, efforts need to be continued to stimulate esophageal regeneration and attachment of the cell population to the scaffold.[72-74] The *in vivo* scope and the use of endogenous signaling stimulation by mesenchymal stem cells (MSCs) have been addressed in further bioreactor works. Pre-clinical trials have been performed on these cells, some of which have reached clinical trials,[75-77] and no adverse effect has been reported in the healing stages. Another benefit to using MSCs is their availability; they can be easily obtained from autologous sources.[78] Although clinical data suggest that MSCs are safe to use, their effect on esophageal repair is still unclear. Recent work on esophageal tissue engineering involves the utilization of synthetic materials with a cylindrical structure.[79-81] Although these materials provide appropriate mechanical support for the structure, they cannot stimulate regeneration *in vivo* by themselves. Recent works have focused on combining these materials with biological factors to construct hybrid scaffolds.[82-84] Substances of biological origin have a higher ability to simulate natural tissue compositions and properties than synthetic materials, and hence, they have been studied for esophageal repair in several works.[85, 86] However, their combination with synthetic materials and biological factors has been recently considered due to their benefits. Since about 150 years ago, there have been many ways to replace cancerous esophageal tissues, perhaps the simplest and the most practical one is the use of a rubber tube.[87]

Recently, scientists have been using surgical polymers like Dacron and Marlex alone or coupling with silicone to develop synthetic grafts.[80-82] The postoperative survival rate in an animal model (canine) was reported to be 44% for one year and 25% for six years. Reconstruction of the mucosa and sub-mucosa layers was observed due to anastomosis of the scaffold with normal esophageal tissue, but no muscle tissue was formed. In another work on pigs, using nitinol and silicone, about 60% of the constriction occurred in the specimens, and it resembled the animal specimen (dog) of the mucosa and sub-mucosa; however, the muscle layer was not formed.[88] These studies are strong evidence that synthetic materials, despite being able to provide the appropriate strength and mechanical properties, are not capable of stimulating and completely reconstructing the organ. In another experience, a poly-glycolic acid-adsorbed polymeric scaffold with an amniotic membrane was used, and a muscle layer was formed during the reconstruction process.[89] It was found that adding specific cells, along with several growth factors, to the polymeric scaffold can greatly enhance the repair and reconstruction. Scaffold design parameters are also important; for example, the effect of different porosities of esophageal scaffolds on cell migration, adhesion, and their proliferation has been studied.[90] Another critical parameter is the scaffold degradation rate in the biological environment of the body. Studies on scaffold degradation rate and tissue regeneration rate have reported that if the scaffold degradation rate exceeds the tissue regeneration rate, the mechanical strength of the structure will be lost, and the structure will collapse. On the other hand, if the degradation rate is below the regeneration rate, blockage builds up, and it is not repaired properly.[91-93] As mentioned earlier, recent attempts have been made to utilize biological components with scaffolds; in this area, extracellular matrix (ECM) proteins such as collagen have been used along with scaffold polymers to improve esophageal remodeling.[94-96]

Collagen and polymeric scaffolds have also been used as composite scaffolds in esophageal epithelial cells.[97-99] Another important issue related to the scaffold is the processing method. Various researchers have used electro-spinning to create esophageal scaffolds. Electro-spinning is a new and evolving method, which can create filament structures with nanometer diameters.[100] This is a major advantage to this method, which has thus far produced numerous scaffolds for the esophagus using polymeric materials that can be soluble. However, the major problem is the lack of adequate mechanical strength in the scaffolds produced by electro-spinning. Therefore, other techniques have been proposed to be used or combined with electro-spinning to enhance the scaffold strength.[101-103]

Clinical Importance of Circumferential Lesions

Various types of esophagus diseases have become known since 200 years ago.[104]

This paper tries to focus on the full-thickness breakdown, which engages all layers. Fistulae and leaks are the primary consequence of full-thickness defects. Esophagectomy is a common cause of full-thickness defects, which is performed following malignant and benign conditions. These surgeries require implementing colon or stomach segments to keep the lumen's uniformity. These interventions can lead to major morbidities, followed by a low quality of life. Due to the limited ability of the esophagus in regenerating its tissues, these injuries can cause refractory strictures, leaks, and fistulae. Attempts at transplanting the cadaveric esophagus have failed.[104] Eventually, regenerating the esophagus would be optimal for these patients.

Moreover, common esophagus diseases, such as adenocarcinoma, squamous cell carcinoma, caustic ingestion, and congenital disorders, can also cause full-thickness defects. Adenocarcinoma and squamous cell carcinoma have engaged about 50,000 and 400,000 people in the world each year, respectively.[105] Esophageal atresia is a common congenital disease, which affects every one in 3000 infants.[106-108] About 5000 cases of caustic ingestion have been reported in the US annually. It can cause a severe injury to the esophagus and the stomach and depending on the burn degree, it can affect even all layers of the esophagus.[109]

Stenosis

Four points in the esophagus have the potential for stricture. In cases of swallowing a corrosive substance or a solid object, damage to one of the points mentioned in the following is more probable. The compression of the esophagus by surrounding structures causes these constrictions. Acute stricture can also be considered as a full-thickness defect. These constrictions include:[9]

- At the proximal part of the esophagus, where the pharynx connects to the esophagus, behind the cricoid cartilage
- Where the aortic arch crosses the esophagus in the superior mediastinum
- Where the left main bronchus compresses the esophagus in the posterior mediastinum
- The esophageal hiatus where travels across the diaphragm in the posterior mediastinum

Esophageal Cancer

An annual rate of about 400,000 deaths associated with esophageal cancer has been estimated,[110] which makes it the sixth leading cause of death due to cancer worldwide.[111] Esophageal cancer is divided into two main types; I) Squamous cell carcinoma (SCC), which occurs in the esophageal squamous cells (SCC is more commonly seen in China and Iran).[112-117] II) Adenocarcinoma, which occurs in the esophageal columnar cells or its glands. Adenocarcinoma is more common in developed countries, especially in patients with Barrett's esophagus. It also mainly affects the cuboidal cells.[118] No symptoms may manifest in the early stages of the disease. With the progression of the disease, obstruction, difficulty in swallowing, and finally, weight loss may appear. Staging of the cancer is based on the invasion of the tumor into the esophageal wall, the number of affected lymph nodes, and the occurrence of metastases to different parts of the body. Radiotherapy and chemotherapy are often needed for the management of this disease. Moreover, a partial or full-thickness surgical removal of the esophagus may be performed.[118]

Esophageal Atresia

Esophageal atresia (EA) is the most common congenital atresia of the GI system. In neonates with EA, the upper and lower esophagi are not connected, which results in the esophagus having two separate parts. Therefore, food can't pass to the stomach. Besides, affected babies sometimes have difficulty breathing. This condition is often accompanied by a tracheoesophageal fistula, a congenital defect in which a part of the esophagus is connected to the trachea or windpipe. In some children, the missing part of the esophagus is so large that the ends cannot be easily connected with surgery. This condition is known as long-gap *esophagus atresia*. Without a functioning esophagus, it is impossible to receive enough nutrition through the mouth. Babies with EA are also more prone to infections such as pneumonia and conditions such as acid reflux.[118]

Caustic Ingestion

Caustics and corrosives cause tissue injury through a chemical reaction. In contrast with children in whom ingestion is usually accidental, caustic ingestion in adults occurs on purpose and usually after suicidal attempts. The majority (68 %) of cases worldwide involve children due to the unintentional ingestion of caustic chemicals.[118]

Discussion

Biomaterials can be acquired from nature or synthesized in the laboratory using a distinctive chemical approach consisting of metal, polymer, or ceramic components. Biomaterials have their own advantages. For instance, one of the advantages of biologically derived biomaterials for esophageal repair over synthetic ones is their ability to incorporate an extracellular matrix, which may improve regeneration.[119-121] Concisely, alterations in different regeneration and management stages of inflammation and scar tissue formation are caused by properly-configured biologic scaffolds. The biomaterial-host collaboration helps this process through complex factors. These include both host-related factors, including age, immune system, stem cell populations, and total health state, and biomaterial-related factors, including source and composition,[122-125] efficiency of the biomaterial process,[126, 127] post-processing modifications such as crosslinking and solubilization,[128-134] age of the source animal,[135] and surface topography.[136, 137]

To assess the usefulness of biomaterial-mediated esophageal repair, biologic scaffolds have been used in several large animal model studies. In early investigations, porcine-derived acellular small intestinal sub-mucosa (SIS) and urinary bladder matrix (UBM) were utilized for the reconstruction of patchy defects in a dog model.[138] Defects measuring 5 cm in length and encircling either 40% or 50% of the esophageal circumference, or even the entire circumference, were reconstructed using these materials. The stricture was formed within 45 days of implantation by the scaffolds used to repair the full-circumference segmental defects. As for stricture formation during a full-thickness full-circumference defect repair, later studies demonstrated the need for a native (i.e., host) tissue component for adequate esophageal reconstruction without stricture formation. In these investigations, the repair of esophageal defects enclosing different parts of the esophageal circumference was carried out by UBM-ECM.

Full-circumference full-thickness defects, full circumference mucosa resections, and full-thickness defects with 30% intact muscularis externa constituted the treatment groups. In addition, the reinforcement of surgical anastomoses of the esophagus was carried out by biologic scaffolds in a dog model.[138] Afterward, the endoscopic implementation of biologic scaffolds was considered for mucosa repair performed after endoscopic mucosa resection in the dogs. Biologically-made biomaterials have also been investigated in small animal models. The objectives of small animal studies, unlike large animal models, include determining the mechanisms of tissue reconstruction, screening large numbers of potential therapies, and optimizing treatment options through the systematic advancement of design specifications. For instance, a murine model of esophageal reconstruction with chimeric mice has been utilized, which constitutively expressed green fluorescent protein in the bone marrow.[139, 140]

Similar research used gastric acellular matrix in a rat model for repairing the esophageal patch defects formed in the abdominal esophagus.[141] In the mentioned study, no stenosis or dilation was observed in the implant site, when the rats were sacrificed one week to 18 months after the implantation. At the two week mark, regeneration in the entire fabrication with keratinized stratified squamous epithelium was observed. However, the muscle layer or lamina muscularis mucosa was not restored.

Limited success has been achieved using various synthetic biomaterials for esophageal repair in different studies. Combining a synthetic biomechanical properties of materials with the biocompatible features of biologic materials as hybrid fabrications, usually as a coating agent, is becoming increasingly popular in regenerative medicine,[142-144] and this has been investigated for esophageal repair. Collagen-coated Vicryl tubes have also been used to replace complete esophageal segments within the thoracic esophagus.[145] Initial results showed prosthetic leakage secondary to acid reflux and digestion of the construct, which resulted in mediastinitis within days following the implantation. Increased material resistance due to the crosslinking of the constructs with glutaraldehyde was the main observed complication; however, stenosis was observed in the animals at an average of 11 days postoperatively, and histologically, substantial granulation tissue and scar formation were observed. Collagen, in addition to being used for coating Vicryl tubes, has also been utilized to coat silicone stents.[93, 146] In these experiments, they used collagen-coated silicone tubes to replace 5 cm esophageal segmental defects in dogs. At weekly intervals ranging from two to four weeks, the endoscopic removal of the inner silicone stents was performed. When stent removal was carried out at the two to three weeks mark, stricture formation and incapability to swallow were reported. However, at the four weeks mark, a regenerated esophagus with stratified flattened epithelial, striated muscle, and esophageal glands was observed in the dogs. Despite the use of various synthetic materials for the reconstruction of esophageal defects, certain difficulties had emerged, such as having to obtain the proper mechanical strength; on the other hand, stricture formation,

Table 1: Synthetic biomaterials used for a circumferential esophageal replacement since 2013

Biomaterial	Cell	*In vivo/in vitro*	Year	Fabrication
PCL-Gelatin[147]	-	*In vitro*	2013	Electro-spinning
PLGA-PCL[148]	Epithelial and smooth muscle cells	*In vitro*	2015	Electro-spinning
Pluronic F127-PCL[149]	Human esophageal fibroblasts	*In vitro*	2018	Electro-hydrodynamic jetting
PCL-SF[150]	Epithelial and smooth muscle cells	*In vivo* (rat)	2015	Electro-spinning
PU-PCL[151]	MSC	*In vivo* (rat)	2019	3D printed and electro-spinning
Poly(L-lactide-co-ε-caprolactone) (PLC)[152]	-	*In vitro*	2016	Melt-drawing method
PU[153]	Esophageal mucosa cells	*In vivo* (pig)	2018	Electro-spinning
Polyamide-6[154]	AD-MSC and BMD-MSC	*In vitro*	2019	Electro-spinning
PU[155]	MSC	*In vivo* (pig)	2018	Electro-spinning-bioreactor
PCL[156]	MSC	*In vivo* (rabbit)	2016	3D printing
PCL[157]	Mucosa and Muscular cell	*In vitro*	2020	3D Bio-printing
PCL and PU[158]	ADSC	*In vivo(rat)*	2020	Electro-spinning-3D printing

PCL: Polycaprolactone; PLGA: Poly Lactic-co-Glycolic Acid; PU: Polyurethane; MSC: Mesenchymal stem cell; ADSC: Adipose-derived stem cell; BMD: Bone marrow-derived

inflammation, foreign body reaction, and leakage were observed as complications. Some recent works using synthetic biomaterial for full-thickness esophagus replacement are presented in table 1.

Conclusion

As a proximal part of the alimentary tract, the esophagus is a complex organ containing multiple tissue layers that cannot regenerate. In recent years, esophageal tissue engineering has become a pioneering specialty for the treatment of esophagus diseases. Despite the different available approaches and the achieved advancements, a gold standard for fully efficient tissue-engineered esophageal fabrication is not yet defined. Various numbers of scaffolds, ranging from non-biodegradable stents to bioactive matrices, have been investigated for esophagus reconstruction, a goal that is now followed by making multi-layered scaffolds that imitate the behavior of different layers of the natural esophagus. The results are still not favorable due to many challenges relating to tissue quality, which requires improvement. The success of esophageal tissue regeneration will finally depend on the capability of the scaffold to resemble natural tissue properties and yield a qualified environment for regeneration. This emphasizes the importance of the scaffold design and fabrication technique.

Authors' Contribution

M.H, M.H.I, Y.G, and A.A.A: Contributed to initial plan; M.H: Contributed to drafting the manuscript; M.H, H.H, Y.G: Contributed to data acquisition; M.H, H.H, and Y.G: Contributed to drafting the manuscript; M.H.I and A.A.A: contributed to the critical revision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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