

## Emerging biomaterials and technologies for advancing surgical meshes

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## **Abstract**

Surgical meshes play a significant role in the treatment of various medical conditions, such as hernias, pelvic floor issues, guided bone regeneration, wound healing, etc. To date, commercial surgical meshes are typically made of non-absorbable synthetic polymers, notably polypropylene and polytetrafluoroethylene, which are associated with postoperative complications, like infections. Biological meshes, based on native tissues, have been employed to overcome such complications, though mechanical strength has been a main disadvantage. The right balance in mechanical and biological performances has been achieved by the advent of bioresorbable meshes. Despite improvements, recurrence of clinical complications associated with surgical meshes raises significant concerns regarding the technical adequacy of current materials and designs, pointing to a crucial need for further development. To this end, current research focuses on the design of meshes capable of biomimicking native tissue and facilitating the healing process without post-operative complications. Researchers are actively investigating novel bioresorbable materials, both synthetic and natural biopolymers, while also exploring the performance of therapeutic agents, surface modification methods and advanced manufacturing technologies such as 4D printing. This review seeks to evaluate emerging biomaterials and technologies for enhancing the performance and clinical applicability of the next-generation surgical meshes.

## **Keywords:**

Surgical meshes, clinical complications, biopolymers, hydrogels, 4D printing, hernia, bone regeneration, wound healing

## **1. Introduction**

Surgical meshes have been used in various applications. The first meshes were clinically used for the treatment of hernia conditions in 1950s. A tension-free reconstruction of the injured tissue was the great achievement in hernia surgery using surgical meshes that resulted in better outcomes both in terms of tissue integration and consequent repair [1]. In 1970s, the improvements in the treatment of hernia were reported for the management of pelvic floor dysfunctions (PFDs) such as pelvic organ prolapse (POP) by using surgical meshes [2]. Thus far, surgical meshes were manufactured using mainly nonabsorbable materials, especially for hernia and PFDs. They have been developed as an alternative to biological patches to overcome clinical complications, such as the possibility to develop infections and low mechanical properties [3]. However, nonabsorbable materials increased the risk of postoperative infection of the meshes, most commonly in hernia [3], PFDs [2], breast reconstruction [4], and guided bone regeneration (GBR) [1, 5]. Furthermore, nonabsorbable meshes resulted in permanent foreign body reactions, leading to inflammations, excessive fibrosis, and even enterocutaneous fistula. Although most of those meshes provide sufficient mechanical strength, they can impair tissue growth [6].

Biological meshes/patches were introduced to reduce the risk of infections associated with synthetic nonabsorbable meshes [7]. These are composed of an extracellular matrix (ECM) that is derived from collagen rich tissues [8]. Biological implants become vascularized over time, resulting in the deposition of host collagen that provides integrity as the strength of the mesh dissipates over time [9]. However, the toxic host reaction to the biologic mesh is a significant disadvantage. A higher rate of reactions is likely attributed to the biologic properties of the mesh stimulating an immunologic response. Another disadvantage of biological meshes is their high cost [8, 10]. An alternative to biological meshes might be the use of a slowly resorbable synthetic mesh, which aims to combine benefits of both synthetic (no early degradation after implantation)

and biological meshes (the “remodelling” aspects and better tolerance in case of contamination) [11].

Bioresorbable surgical meshes are temporary implants which can be slowly degraded or replaced by healing tissue and integrated within the body’s innate repair mechanisms. The term "bioresorbable" is reserved for those polymeric systems which can degrade into low molecular weight compounds which are involved normally in metabolic pathways, or which can be, at least, eliminated from the body through natural pathways [12]. Bioresorption reflects the total elimination of the initial foreign material and of the degradation by-products (low molecular weight compounds) with no residual material remaining [13]. Consequently, this avoids the need for further surgical procedures to remove the implants or scaffolds [14, 15]. Bioresorbable meshes maintain mechanical strength for a pre-determined period. These implants will gradually resorb, allowing regeneration of connective tissue. In this way, this new generation of materials is different from the available quickly absorbing polyglactin mesh (Vicryl mesh; Johnson & Johnson) [11].

Over the last decade, many different bioresorbable meshes have been designed and developed using natural, synthetic and composite biomaterials. there is an increasing trend in tissue engineering to use naturally occurring macromolecules as a starting material to prepare scaffolds for tissue remodelling such as hydrogels and meshes, since such materials are well tolerated and have an inherent bioactivity including promotion of cell proliferation and adhesion [16]. This is the result of the intrinsic properties of biodegradable hydrogels, the most significant being degradation, bioadhesion, bioactivity, transport, controlled release of drug and bioactive molecules, and mechanical properties [17]. In particular, the biodegradation of hydrogels is based on a number of mechanisms, such as hydrolysis, proteolysis, or environmental triggers. The

desired hydrogel bioresorbability can be achieved by designing the material with a controlled number of degradable crosslinks in the polymer network. This feature of hydrogels allows researchers to design anti-adhesive or drug-eluting mesh-hydrogel composites to prevent some serious complications in clinical studies, especially for hernia repair. Furthermore, hydrogel-mesh composites have been recently advanced by adopting 4D biofabrication methods, which employ programmable shape-transformations of preliminary 3D constructs, using smart hydrogels that respond to external stimuli such as pH, temperature, and magnetic fields to achieve desired morphology [18].

Current research efforts focus on providing potential solutions that range from the formulation of novel biomaterials to new biofabrication techniques that could ameliorate existent shortcomings in clinical use of surgical meshes. The aim of this review is to provide an overview of the emerging biomaterials and technologies for enhancing the preclinical and clinical performance of advanced surgical meshes.

## 2. Ideal surgical mesh and regulations

The continuous developments in the field and the appearance of novel materials have declared fundamentals for designing the “ideal” mesh. An early study highlighted, that surgical meshes must be inert, resistant to infections and other side-effect, adequate mechanical stability and non-carcinogenic [19]. In the past two decades, other aspects have occurred, like the need of cost-effectivity, shape memory effect, flexibility and easy handling [20], also, the use of lightweight materials are encouraged [20, 21]. **Table 1** describes the properties of an ideal surgical mesh according to its application.

**Table 1.** Properties of an ideal surgical mesh.

Properties	Description
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Biocompatibility [19, 22]	The mesh material should be biologically compatible to minimize the risk of adverse reactions or inflammation. In addition, the mesh should be easily sterilized to prevent postoperative infections
Tensile properties and stiffening behavior [23]	Sufficient tensile strength is crucial to withstand the forces exerted on the mesh and provide structural support. Furthermore, the mesh should have some degree of compliance to adapt to the surrounding tissue and prevent stiffness or discomfort.
Pore size and structure [24]	Optimal pore size and geometry promote tissue ingrowth and vascularization while preventing complications such as adhesions.
Surface bioactivity and anti-adhesion (if applicable) [22]	Coatings with bioactive substances can enhance tissue integration, reduce inflammation, and prevent infection. Coatings that resist tissue adhesion can reduce the risk of postoperative complications, such as adhesions between organs.
Biodegradability [24]	In some applications, a biodegradable mesh that degrades over time may be preferred, especially if long-term structural support is not necessary.
Postoperative visualization [22]	The mesh should be visible on imaging studies (such as X-rays, MRI or CT scans) to allow for postoperative assessment.
Ease of handling and placement [20, 22]	The mesh should be easy to handle and manipulate during surgery, conforming to the anatomical site.

In 2017, the FDA Center for Devices and Radiological Health (CDRH) published its top ten regulatory science priorities for medical devices, including using “big data” for regulatory decision-making, modernized biocompatibility evaluation, computational modelling technologies, precision medicine and biomarkers [25, 26]. As per the code of the US Food and Drug Administration, surgical mesh is identified as “*a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are*

*metallic and polymeric mesh for hernia repair and acetabular and cement restrictor mesh used during orthopaedic surgery”.*

The European Union (EU) Medical Device Regulation (MDR) came into force in May 2017, which applies to implantable and long-term surgically invasive devices (> 30 days). These are primarily implants in the orthopaedic, dental, ophthalmic, and cardiovascular fields and soft tissue implants such as those used in plastic surgery. Breast implants and surgical meshes are classified as class III devices under Rule 8. The US Food and Drug Administration (FDA) approved the first urogynaecological mesh only 20 years ago [27]. Due to safety concerns, the FDA withdrew some vaginal mesh products for stress urinary incontinence (SUI) and pelvic organ prolapse (POP) from 2011 to 2019 [27]. Also, some countries like New Zealand and Australia discontinued the application of Pelvic floor dysfunction (PFD) meshes. 3D-printed meshes have gained attention in the last decade due to their better surgical results. In 2017, the US FDA issued guidelines that included information on materials, design, printing methods, post-processing, and validation [1].

### **3. Biomaterials for bioresorbable meshes**

Bioresorbable polymers can be classified into naturally occurring and synthetic materials. Natural materials derive from animals or plants, including the decellularized extracellular matrix (dECM) obtained from allografts and xenografts, and cover a wide range of organic materials such as polysaccharides (hyaluronic acid, chondroitin sulphate, heparin, dextran, alginate, cellulose, chitin, and chitosan), and polypeptides (collagen, gelatin, silk fibroin, albumin, elastin, and keratin) [28, 29]. Natural biomaterials are highly biocompatible and have a favourable pro-remodelling host immune response<sup>[30]</sup>. However, they exhibit great variability owing to their biological source, and are often not suitable for load-bearing applications due to limited physical and mechanical stability [31]. These drawbacks can be compensated by synthetic polymers, which are materials of

great interest in the medical field [32]. Synthetic biomaterials offer several advantages over traditional natural materials, including the possibility of being precisely and consistently manufactured with minimal variability. They have better controlled physical and mechanical properties that can be easily tuned, but biocompatibility is a major concern since cells may have difficulty attaching and growing, and they might elicit a pro-inflammatory response in the host [33]. An increasing number of studies have been therefore carried out to exploit the advantages of both classes of biomaterials, either by improving the mechanical properties and shape stability of natural biomaterials or by developing processes to modify the surface and bulk properties of synthetic biomaterials to enhance their biocompatibility [34, 35].

In 1959, Francis Usher introduced the initial synthetic mesh composed of polypropylene for hernia repair applications. Subsequently, there was a burgeoning progress of mesh technology, that led to extensive biophysical and clinical investigations aiming at discovering the perfect mesh. Through the utilization of synthetic, natural, and composite biomaterials, many different resorbable meshes have been developed [36, 37]. The majority of bioresorbable meshes consist of biodegradable synthetic polymers, such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic) (PLGA) copolymer. These absorbable materials undergo degradation, and their degradation rate must align with the duration required for tissue regeneration. However, the regenerated tissue following resorption of the mesh material does not possess adequate strength to combat hernia recurrence [3, 38, 39]. Despite their initial popularity, PGA meshes are no longer employed due to their rapid degradation. As a result, there has been a notable emergence of biosynthetic polymers that show complete biodegradation over a mid- to long-term period for hernia repair applications in the recent few years. The main aim of developing novel biomaterials is to diminish the foreign body reaction within the host and facilitate tissue regeneration [40]. Since

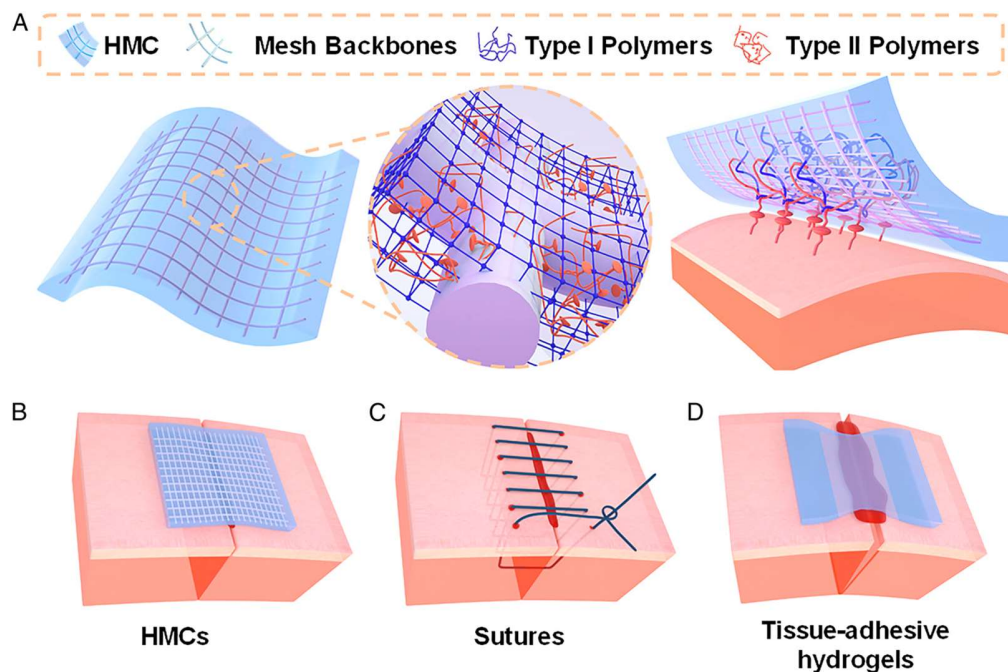


PLA degrades slower than PGA, PLGA was employed in the development of several commercial meshes, such as POLYGLACTIN 910 (Vicryl™, Ethicon) [41]. However, PLA-based meshes also present complications such as foreign body granuloma and giant cell formation [42](Serrano-Aroca & Pous-Serrano, 2021). Biodegradable Gore® BIO-A mesh was developed by copolymerisation of 67% of PGA and 33% of trimethylene carbonate (TMC). These scaffolds have demonstrated notably long-term prevention of hernia recurrence and superior tissue integration when compared to biological matrices such as Strattice™ and Veritas®, as well as the natural abdominal wall [43, 44]. Another fully absorbable material in the field is TGR™ (Matrix Surgical Mesh), which comprises two types of synthetic fibres (co-polymer glycolide-lactide trimethylene carbonate/lactide and trimethyl carbonate) with a multifilament structure [40]. While preclinical experience with this material appears satisfactory, its clinical confirmation is still pending [45, 46].

Various natural bioresorbable materials are used in surgical mesh development. Biosynthetic resorbable meshes encompass materials based on silk fibroin, gelatin, polyhydroxyalkanoates, and plant fibre-based materials. Notably, insect-based protein-based products like silk fibroin extracted from silkworms, specifically *Bombyx mori*, have garnered attention due to their exceptional mechanical properties and resorption time of up to 2 years, positioning them as potential competitors to biological matrices [47, 48]. Combination approaches involving electrospun silk fibroin (SF) and other materials with excellent biological properties, such as poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), have been explored to produce hybrid scaffolds that demonstrate high efficiency and biocompatibility for repairing abdominal wall defects [49, 50]. Bioresorbable meshes based on bacterial poly(4-hydroxybutyrate) (P4HB) have been developed, such as Phasix™. This type of mesh is a fully resorbable monofilament scaffold designed for rapid tissue incorporation. It has demonstrated *in vitro* and *in vivo* degradation while

maintaining 80% and 18% greater strength than the native abdominal wall at 8 and 72 weeks post-implantation, respectively, despite significant biopolymer degradation [51]. Although clinical trials are limited, the application of this material in ventral hernia repair has shown no recurrences after two years [52]; however, a recurrence rate of 9% for inguinal hernia repair was observed at 18 months post-implantation [53].

Unique material properties tailored for specific biomedical applications can be obtained by modulating biomaterial chemistry and synthesizing composites made of a combination of natural and synthetic materials [54-56]. The benefits of this approach include shorter operative time, decreased technical difficulty in tissue repair, and the ability to mimic the *in vivo* microenvironment better to stimulate normal tissue or organ development [57]. Gao and co-workers have provided an interesting example of how the combination of natural and synthetic polymers with a specific design can improve the properties of a biomaterial [58]. The authors proposed a design called hydrogel–mesh composites (HMCs) which broadens the function of surgical meshes by adding one important property: strong tissue adhesion (**Figure 1**). They demonstrated that HMCs form strong and swell-resistant adhesion with various tissues under physiological environments, as well as on tissues under high pressure or great tension. Finding a balance between the fabrication method and biomaterial selection, to match the properties between the scaffold and the target tissue, will be key to the field of tissue engineering in the future.



**Figure 1.** Design and potential advantage of a hydrogel–mesh composite (HMC). (A) Schematic of the HMC. In the HMC, the hydrogel and the surgical mesh form topological entanglement. The hydrogel has long polymer chains of two types: Type I polymers form a covalent network, and type II polymers carry functional groups for adhesion to a tissue. When an HMC contacts a tissue, the hydrogel and tissue adhere through complementary functional groups. Wound closure using three materials: (B) HMC, (C) suture, and (D) tissue-adhesive hydrogel. Reproduced with permission from Ref [58].

Resorbable polymer meshes are widely available on the market, but several preclinical *in vitro* and *in vivo* experiments had to precede commercialization. The experimental studies aiming to analyse degradation profile of polymeric meshes in preclinical settings guarantee the safety and improve the understanding of the degradation phenomenon of meshes under *in vivo* conditions leading to better clinical application [59-61]. Several preclinical studies on different animal models (rabbit, sheep, rats, minipigs, pigs, vervets) were performed on commercially available synthetic resorbable meshes like TIGR<sup>®</sup> Surgical Matrix Mesh, GORE<sup>®</sup> BIO-A<sup>®</sup>, and Phasix<sup>™</sup> and showed promising results as site for cell proliferation. Furthermore, when clinically applied for hernia treatment they showed positive short- and medium-term outcomes [11, 62].

#### **4. Surface modification in anti-adhesive meshes**

Tissue adhesion and fibrosis can be one of the significant complications during wound healing via surgical meshes; hence, the anti-adhesion functionality is a primary challenge in mesh preparation, particularly for polypropylene (PP) meshes, which are widely used by clinicians. For abdominal wall reconstruction, anti-adhesive properties prevent the formation of adhesions between the mesh and abdominal organs, decreasing the risk of bowel obstructions, chronic pain, and other complications. Efforts to address this issue and develop antiadhesive properties in mesh materials continue to be a central focus in research and development. The main concept behind antiadhesion mesh development is to effectively restrict fibrosis, recognizing its close association with adhesion formation in hernia regions [63].

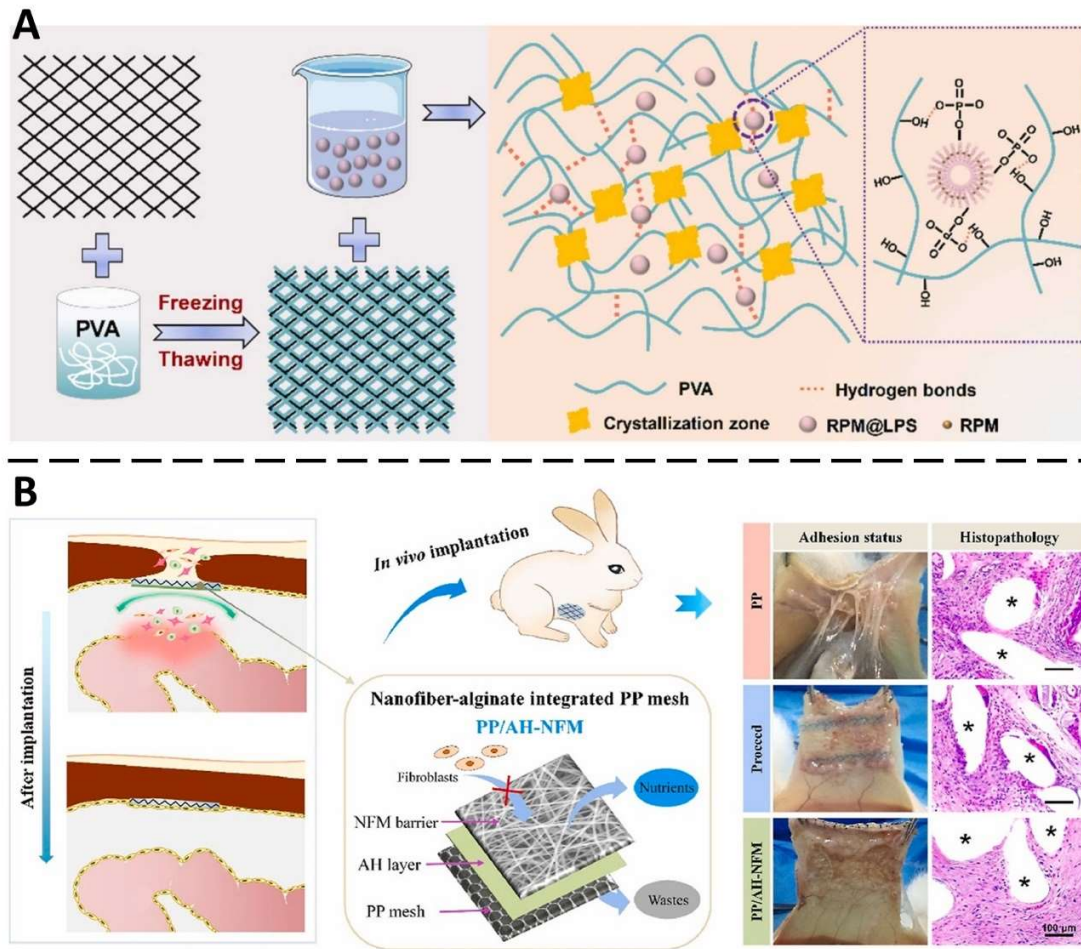
Research studies have demonstrated that materials like chitosan (CS), hyaluronic acid (HA), and absorbable oxidized regenerated cellulose (ORC) possess antiadhesion properties. As a result, many antiadhesion treatments are applied to meshes by using those antiadhesion agents [64-66]. Among the antiadhesion products certified by FDA, the Interceed® produced by J&J, is prepared from ORC [67]. In 2018, Lai *et al.* [65] modified bacterial cellulose using TEMPO (2,2,6,6-tetramethylpyperidine-1-oxyl) to enhance its properties while retaining its favourable tensile properties and elastic modulus. Their findings demonstrated that modified cellulose exhibited preferential adsorption of bovine serum albumin, resulting in improved secretion of type I collagen, inhibition of fibroblast proliferation, and subsequent reduction of adhesion [65]. Alongside the application of antiadhesion agents, the antiadhesion membrane serves as a physical barrier, effectively isolating the surgical site from adjacent organs or tissues. *In-vivo* biocompatibility evaluation of polyethylene glycol (PEG) hydrogels hybridized with hyaluronan was performed after intramuscular and subcutaneous administration to a mice model. Histologic

and hematological parameters analysed at varying time intervals (7, 14, and 21 days) including the hematopoietic system showed promising outcome on hyaluronic acid release during hydrogel degradation [68]. The study used the pig model, and conventional laparotomy pelvic surgery was performed after histopathological evaluation. It was observed that resorbable hyaluronic acid reduces laparotomy pelvic surgery-induced adhesion [69].

Most of commercial surgical meshes are inert without groups to react with the grafted compounds, particularly for hernia repair applications. Hence, plasma treatment is employed to activate the inert surface of the mesh for functionalisation. For instance, oxygen plasma activation was employed to treat a PP mesh, followed by the grafting of polyvinyl alcohol (PVA) onto the mesh with the assistance of hydrogen peroxide [70]. Subsequently, the PP-g-PVA mesh was implanted into mice. Remarkably, adhesion was only observed in small corners, constituting less than 2% of the total area, while the remaining region exhibited a remarkably smooth surface [70]. Most recently, an antiadhesive PP mesh was developed with PVA hydrogel and liposomes drug delivery system (**Figure 2A**) [71]. First, the PVA hydrogel coating was prepared by a freezing-thawing process; then, rapamycin (RPM)-loaded liposomes (LPS) were immobilized in the PVA hydrogel. Findings showed the hydrogel coating was stable on PP mesh at 37 °C for 30 days. The optimal antiadhesive composite mesh showed a slighter inflammation response and remarkably looser fibrous tissue surrounded the PP filaments as compared to the native PP [71].

Electrospun nanofibrous membranes possess the ability to mimic the ECM structure and effectively modulate cellular behaviour. Unlike knitted structures, these membranes offer distinct structural characteristics that can cater to specific performance needs on each side [72]. By incorporating a nanofiber-based layer, physical isolation can be achieved between organs or tissues and the mesh. This isolation prevents fibroblast adhesion and proliferation between these entities,

consequently mitigating the risks of bridging and organ adhesion [63]. (PLGA/CS nanofibers were electrospun on PP mesh and then the antiadhesion effects of PLGA/CS nanofibers were studied [66]. The peritoneal adhesion score of the PP/PLGA-CS30 mesh was 59% lower than that of the pure PP mesh [66]. Aydemir Sezer *et al.* [73] developed an antiadhesion PP hernia mesh by incorporating micrometre-sized particles of absorbable ORC and PCL using the electrospinning technique. The mesh retained its mechanical properties, while the inclusion of PCL facilitated controlled degradation, reducing acidity, and improving biocompatibility. Animal experiments demonstrated that the antiadhesion performance depended on the concentration of ORC, suggesting that a combination of ORC with a more efficient antiadhesion polymer could enhance the effectiveness of the composite mesh [73]. Recently, nanofiber membranes (NFM) composed of PLGA and polycaprolactone (PCL) showed a good physical barrier for abdominal wall hernia repair [74, 75]. An adhesive composite hernia mesh was prepared by integration of PP substrate with a alginate hydrogel (AH) layer containing a NFM barrier (**Figure 2B**) [74]. *In vivo* experiments on rabbits indicated that incorporating AH-assistant NFM into the PP prostheses significantly reduced visceral adhesion and enhanced mesh integration into nearby tissues from the abdominal wall [74].



**Figure 2.** Antiadhesion surgical meshes. **(A)** The schematic illustration of the drug-loaded hydrophilic hydrogel coating RPM@LPS/PVA. Reproduced with permission from Ref [71]. **(B)** Schematic illustration of showing the strategy to endow PP mesh with a barrier composed of a nanofiber membrane (NFM) and alginate hydrogel (AH) layer for preventing adhesion formation in abdominal wall hernia repairs in rabbit model. Reproduced with permission from Ref [74].

In clinical practice, it is more often a combination of the physical antiadhesive layer and the regulation of biochemical agents that can ultimately boost the antiadhesion effect. The strategy of combining hydrogel and dopamine to functionalise the mesh has been considered by researchers in order to remodel the ECM via the hydrogel and solve the problems of poor adhesion of hydrogel to tissue by dopamine. Dual-functional layer membranes/meshes have been developed to optimize the performance of each function. For example, Shokrollahi *et al.* [76] fabricated a novel

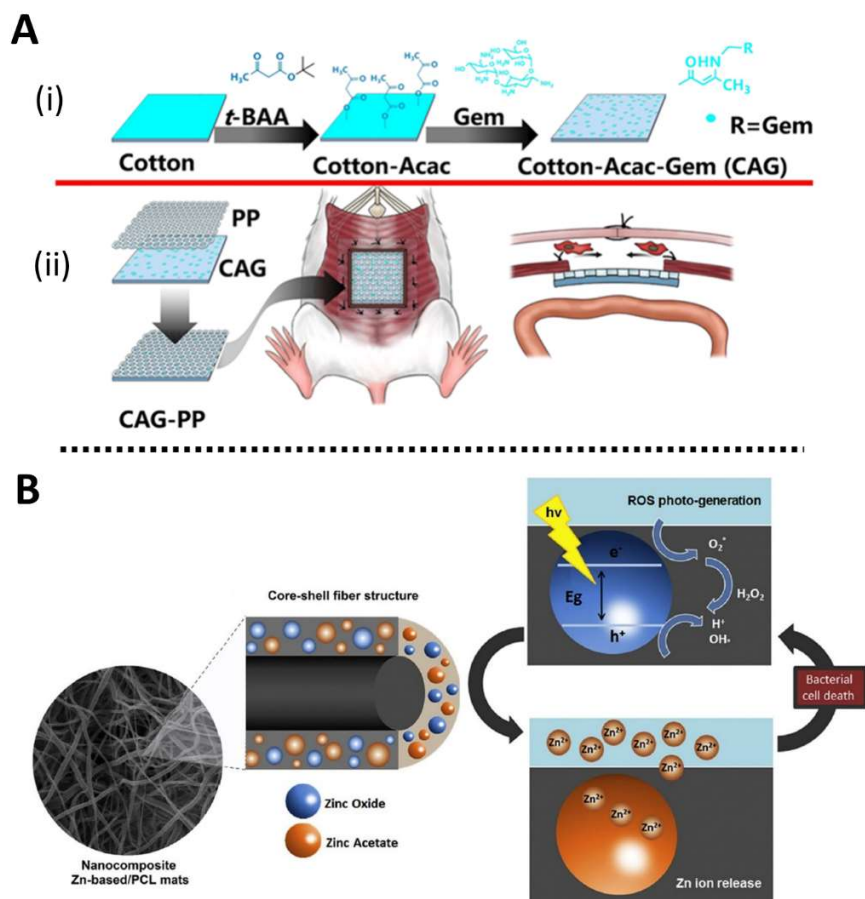
bifunctional PP mesh, the back of which was coated with PCL nanofibers with antiadhesion and antibacterial function; the PCL nanofibers were treated with a mussel-derived L-DOPA binder.

## **5. Drug-eluting bioresorbable meshes**

Resorbable hydrogels are engineered to deliver the drug locally for extended periods and are capable of being combined with surgical meshes resulting in significantly better and more effective materials called hydrogel–mesh composites (HMCs) [58]. Novel surgical meshes with drugs loaded into the mesh structure have attracted much attention in the field of regenerative medicine. The incorporation of antibacterial drug/coating is underway to address the current clinical issue of inflammation and infection [77]. Antibiotics have been highly employed for bacteria-specific treatment, including rifampicin, fluoroquinolones (e.g. ofloxacin, ciprofloxacin, levofloxacin), metronidazole, gentamicin, etc [78]. The application of carboxymethylcellulose gel loaded with chlorhexidine was developed to study the antibacterial effect at the defect area *in vivo*. This showed that antibacterial gel-coated PP meshes can inhibit bacterial adhesion to the mesh surface and have no impact on wound repair [79]. Reinbold *et al.* [80] utilised rifampicin in hernia management by fabricating rifampicin-loaded PLGA microspheres used for coating the surgical mesh. The microspheres-coated meshes showed a controlled release profile of rifampicin over 60 days and an antibacterial activity over 30 days. The antibacterial effect of an ofloxacin/PCL-coated PP mesh was studied for hernia repair applications [81]. The mesh successfully achieved a controlled antibiotic release profile with no mechanical failure (i.e. burst) over 4 days. From the antibacterial analysis of *E. coli*, the inhibition zone diameter of 39 mm indicates a potent antibacterial activity [81]. In another work, minocycline-loaded chitosan nanoparticles have been incorporated into a collagen/chitosan membrane. *In vitro* drug release tests showed that the antibiotic release was sustained for up to 7 days, with an initial burst release [82]. The woven cotton fabric was modified



with gentamicin (Gem) *via* the enamine bonds and combined with a commercial PP mesh to serve as a two-layer composite mesh for abdominal wall defect repair (**Figure 3A**) [83]. The obtained mesh showed antibacterial properties against *E. coli* and *S. aureus* with a bactericidal rate of over 99.99%. The two-layer composite mesh indicated great biocompatibility and satisfactory anti-infective properties in abdominal wall defect repair in a rat model [83]. Loading growth factors and other biological molecules can improve hosting and colonization of stem cells on hernia meshes [1]. The electrospun PLLA mesh loaded with bFGF was studied to inhibit inflammatory reactions to enhance wound healing [84]. The loaded mesh promoted fibroblast growth, increased collagen expression, and regulated immune-related cytokines [77, 84].



**Figure 3.** (A) Schematic illustration of the preparation of antibacterial cotton fabric (Cotton-Acac-Gem) (i) and combination with polypropylene (PP) tissue mesh for abdominal wall defect repair (ii). Reproduced with permission from Ref [83]. (B) Zn-loaded PCL coaxial fibres and their antibacterial mechanisms, which are releasing of  $\text{Zn}^{2+}$  ions and photocatalytic reactive oxygen species generation (ROS) generation. Reproduced with permission from Ref [85].

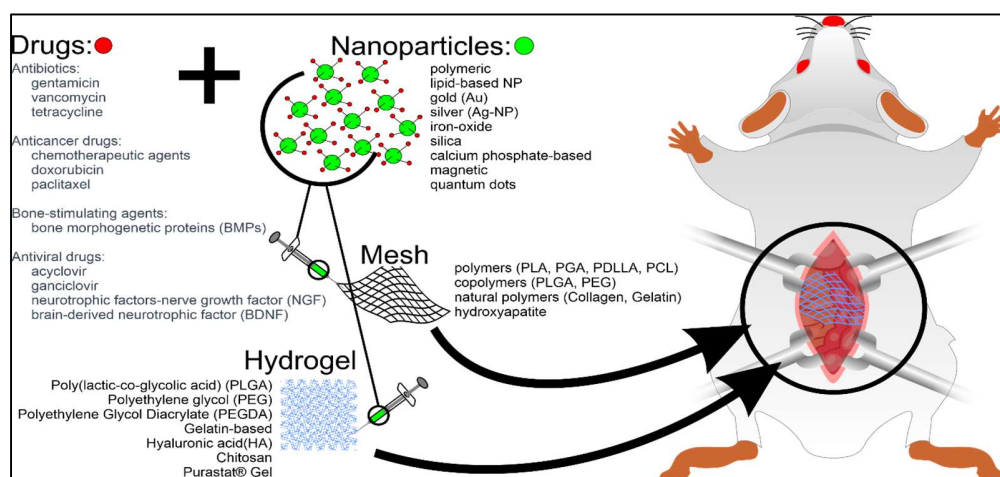
Natural-based antimicrobial molecules have been also used in advanced hernia mesh to achieve a better integration of the mesh with the surrounding tissue and with less cytotoxic side effects [1]. For example, Mancuso *et al.* prepared an antibacterial PCL fibrous mesh for soft tissue regeneration by layer-by-layer deposition of Manuka honey. The incorporation of Manuka honey into the fibrous mesh did not change the physicochemical feature of the implant, while the layer-by-layer functionalization showed a concentration-dependent antimicrobial activity against *S. aureus*, *E. coli* and *P. aeruginosa* with good cytocompatibility for fibroblast and endothelial cells [86].

Metal and metal oxide nanoparticles (MNPs) can also be used as therapeutic agents and loaded into surgical meshes with/without hydrogel incorporation. Muwaffak *et al.* showed the antibacterial properties of MNPs-loaded PCL mesh by studying the efficacy of silver-loaded (Ag-loaded), zinc-loaded (Zn-loaded) and copper-loaded (Cu-loaded) meshes. They reported higher activity of Ag and Cu against *S. aureus* [87]. Recently, a non-electrospun bioactive 3D nanofibrous hybrid micromesh consisting of PLA nanofibrous microspheres (NF-MS) loaded with didecyldimethylammonium bromide (DDAB)-modified zinc oxide nanoparticles (D-nZnO) (**Figure 4A**) demonstrated significant antibacterial, regenerative, and haemostatic functionalities, of value in diverse biomedical applications including wound healing [88].

In another work, an antibacterial wound mat was fabricated by coaxial electrospinning to prepare PCL (core) loaded with Zn nanoparticles ((shell) (**Figure 3B**) [85]. Antibacterial tests carried out

against *S. aureus* and *E. coli*, indicating that mats possess two main antibacterial mechanisms, release of  $\text{Zn}^{2+}$  ions and generation of photocatalytic reactive oxygen species which together allowed inhibition of planktonic and biofilm bacterial growth and improvement of the mats antibacterial properties [85]. Beside Zn nanoparticles, the positive antimicrobial effects of silver nanoparticles have long been known and used in clinical chemistry. Sobczak–Kupiec *et al.* attached silver nanoparticles (Ag-NP) by microwave irradiation to polymeric matrix poly(acrylic acid) and gelatin-based polymer/hydroxyapatite composite to assess the possible decomposition changes of the material due to silver supplementation, and found greater degradation behaviour for samples containing 4% to 5% hydroxyapatite in artificial saliva and simulating body fluid which should be considered during device development and estimation of degradation time.[89]

**Figure 4** illustrates the roles of different biomaterials, nanoparticles, and therapeutic agents in the structure of a bioresorbable mesh used for wound healing on a pre-clinical mouse model.



**Figure 4** Schematic representation depicting the roles of different biomaterials, nanoparticles, and therapeutic agents in the structure of a bioresorbable mesh used for wound healing on a pre-clinical mouse model.

## 6. Advanced technologies in bioresorbable meshes

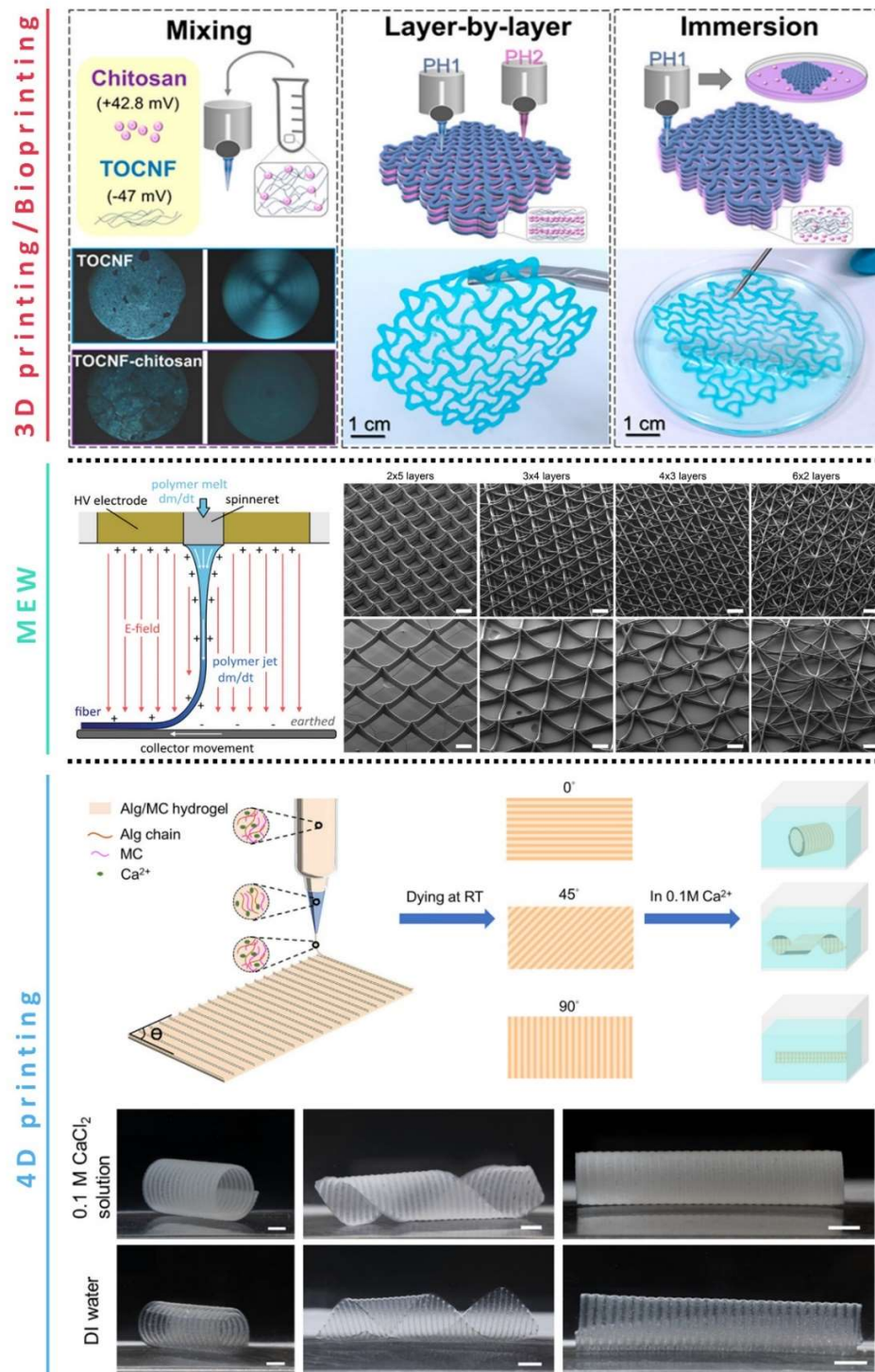
Surgical meshes, like PP mesh, are traditionally produced by fibre extrusion, melt-spinning, and wet-spinning; however, several different technologies have been investigated to fabricate bioresorbable hernia meshes in the last decade. Electrospinning is one of the emerging fabrication technologies for bioresorbable surgical meshes [90]. Electrospinning involves applying an electric field to create material fibres in nanoscale diameter. This method allows for the production of meshes with a high surface-to-volume ratio with the ability to incorporate drugs or bioactive agents into the fibres [91, 92]. Recently, an electrospun composite ibuprofen-loaded (PEG/PCL) nanofibrous membrane (NFM) has been fabricated to prevent abdominal adhesions in hernia repair. The optimal membrane (PCL/25PEG-6%) created a barrier between the abdominal wall and surrounding tissues, without interrupting mass transfer and normal wound healing and showed a sustainable drug profile release ( $\approx 80\%$ ) within 14 days [93].

3D printing, also known as additive manufacturing, is another emerging technique that offers unique advantages in terms of mesh properties and customization. This technology allows to create complex mesh structures with precise control over composition, pore size and geometric shapes of meshes. In addition, the biological compounds such as ECM proteins, cells and drugs can be used in 3D printing to create innovative devices and living biologically active tissue constructs [94]. For instance, the drug distribution in the mesh can be achieved by incorporating drug-loaded filaments or microspheres into the mesh structure in predetermined locations. This concept, known as bioprinting, has great potential for regenerative hernia repairs [95]. For instance, PCL meshes were 3D-printed with two different pore sizes containing sodium alginate-encapsulated gentamicin [96]. The antibacterial activity of these devices was assessed *in vitro*. The drug-loaded meshes showed good antibacterial activity *in vitro* against *E. coli*, as well as mild inflammation and early tissue repair of the abdominal wall in a rat model. However, adhesions to the mesh limited its

intraperitoneal applicability [96]. Bioabsorbable PLA containing gentamicin was 3D-printed to assess antibacterial characteristics against *S. aureus* and *E. coli*. The results showed the feasibility of incorporation of drugs into the 3D printed meshes, without losing the antibacterial effectiveness [97]. 3D printing via single or multi-head extrusion was employed to fabricate layer-by-layer (LbL) meshes based on (TEMPO)-oxidized cellulose nanofibrils (TOCNF) and chitosan (**Figure 5**) [98]. 3D-printed nanocellulose mesh was immersed in the chitosan polymer solution to obtain chitosan-sorbed nanocellulose mesh. The excellent biocompatibility and non-cytotoxicity toward human monocyte/macrophages and controllable shrinkage upon solvent exchange make the cellular meshes appropriate for use as biomedical implants [98]. Recently, an innovative bioinspired micromesh-integrated 3D-printed hydrogel construct was developed as an antibacterial/regenerative bilayer scaffold for treating diabetic wounds [99]. A hyaluronan/chitosan ink was used to fabricate a bilayer construct composed of an upper dense hydrogel layer topping a lower regenerative/antibacterial layer with hierarchical porosity achieved by incorporating PLA nanofibrous micromeshes embedded with nano D-nZnO, developed earlier [100]. The scaffold afforded 95% wound-closure, infection control, regulation of three healing-associated biomarkers and skin regeneration in 14 days.

Melt electrowriting (MEW) and 4D printing are two advanced biofabrication technologies that have the potential to revolutionize hernia mesh production by introducing innovative designs, adaptability and controlled properties. MEW has been recently used to gain a precise and continuous deposition of microfibrous structures. MEW is typically based on applying a voltage to generate a stable molten fluid jet and drawing out a single fibre onto a pre-determined path [72]. In hernia mesh production, MEW offers two main advantages, extrusion of ultrafine fibres and fabrication of complex mesh designs with specific pore sizes, orientations, and patterns, which can

optimize the mechanical performance and match patient-specific anatomical requirements [101](Saidy et al., 2022). Examples of MEW mesh with different architectures are presented in **Figure 5** [102, 103]. Recently, Ren *et al.* [104] fabricated degradable PCL/PEG composite meshes with MEW. Two PCL/PEG mesh groups: 90:10 and 75:25 (PCL: PEG, wt%) were fabricated and characterized for their degradation rate and mechanical properties, with PCL meshes used as a control. The antibacterial properties of the meshes were elicited by coating them with azithromycin. Results indicated that the PCL/PEG meshes with antibiotic coating will be effective after about 2 weeks of drug release and the mesh will be supporting cell (hMSC) attachment and proliferation [104].



**Figure 5.** Examples of advanced technologies in bioresorbable meshes. **3D printing/Bioprinting:** Schematics of the three approaches used to develop 3D printed mesh structures from nanocellulose (TOCNF) and chitosan, including mixing the components before printing; the mixture was evaluated by *in situ* imaging of TOCNF and TOCNF-chitosan mixture under rheology tests at low

( $0.15\text{ s}^{-1}$ ) and high ( $700\text{ s}^{-1}$ ) shear rates; Double printheads (PH1 containing TOCNF and PH2 containing chitosan) were used to deposit multilayers; 3D printed nanocellulose mesh was immersed in the chitosan polymer solution to obtain chitosan-sorbed nanocellulose mesh. Reproduced with permission from Ref [98]. **MEW (melt electrowritten)**: A schematic of a stable molten fluid jet that is direct-written onto a substrate onto a pre-determined path; SEM images of the 8 MEW mesh with different laydown patterns. Scale bars are  $100\text{ }\mu\text{m}$ . Reproduced with permission from Ref [102, 103]. **4D printing**: illustration of 4D printing for fabrication of patterned alginate/methylcellulose (Alg/MC) hydrogels and their 3D deformations on immersion in  $0.1\text{ M CaCl}_2$  solution. Reproduced with permission from Ref [105].

The next generation of additive manufacturing is so-called 4D printing, which adds an extra dimension of time-dependent shape transformation to 3D printed geometries. This emerging technology seeks to resolve the limitations of 3D-printed structures to mimic the dynamics of living tissues by introducing “time” as a new parameter [106]. In 4D printing, the smart biomaterials respond to physicochemical or biochemical stimuli (e.g., temperature, pressure, presence of molecules, pH), resulting in shape changes or functional transformations over time [107]. Hence, 4D printing offers the potential to create meshes with adaptive properties and enhanced functionality in hernia mesh applications. Stimuli-responsive biomaterials could be used to prepare pioneer meshes with the ability to progressively adapt and respond to changes in the host-tissue environment, enhancing tissue generation and implant compliance [95]. Printable alginate/methylcellulose (Alg/MC) hydrogels were 4D printed into the 2D meshes, which were encoded with anisotropic stiffness and swelling properties by tailoring the network density gradients vertical to the orientation of the patterned strips (**Figure 5**) [105]. The dynamic deformations of the printed Alg/MC hydrogels into helix structures or rolling structures, depending on the orientation of the patterned strips, occurred after immersion in a calcium chloride solution ( $0.1\text{ M}$ ) [105]. Lanzalaco *et al.* [108] investigated the 4D behaviour of a substrate of knitted fibres of isotactic polypropylene (iPP) mesh with a coating of thermosensitive poly(N-



isopropylacrylamide-coN,N'-methylene bis(acrylamide) (PNIPAAm-co-MBA) hydrogel when subjected to cycles of increase/decrease temperature and by considering different mesh configurations and humidity conditions. The presence of the iPP mesh and the distribution of the gel surrounding the PP threads, affect both the PNIPAAm gel expansion/contraction as well as the time of folding/unfolding response. In addition, PP-g-PNIPAAm meshes indicate an improvement in the bursting strength of 16% with respect to the uncoated mesh, suggesting a strongest and adaptable system after implantation [108].

## **7. Clinical applications of bioresorbable meshes**

Resorbable polymer meshes applications have the great benefit of tissue support for the critical time period when it is needed, or even stimulate tissue regeneration and proliferation. In the end, they get completely broken down and dissolved avoiding long term complications, such as foreign body reactions, scarring or occlusion. The resorption time varies based on the material used. Clinically, the most frequently used bioresorbable polymer materials are: PLLA bioresorbable by hydrolyzation and complete metabolism of lactic acid at physiologic temperature with average 60% reduction by 18 months; polydioxanone (PDX) bioresorption varies from few weeks to 12 months; PCL undergoes degradation over 24 months; porcine collagen degradation ranges between 2 weeks to 3-4 months; PGA can be resorbed within a month and P4HB over 1–5. years [109, 110].

### **6.1. Hernia repair applications**

Hernia occurs when a part of an organ moves through a weakened muscle into a different body segment, which could be an inherited or acquired condition, and the classification is based on the localization of the disorder. In hiatus hernia (HH), a part of the stomach is moved to the mediastinum via the weakened diaphragm. Protrusion of intestinal or fat tissue due to abdominal

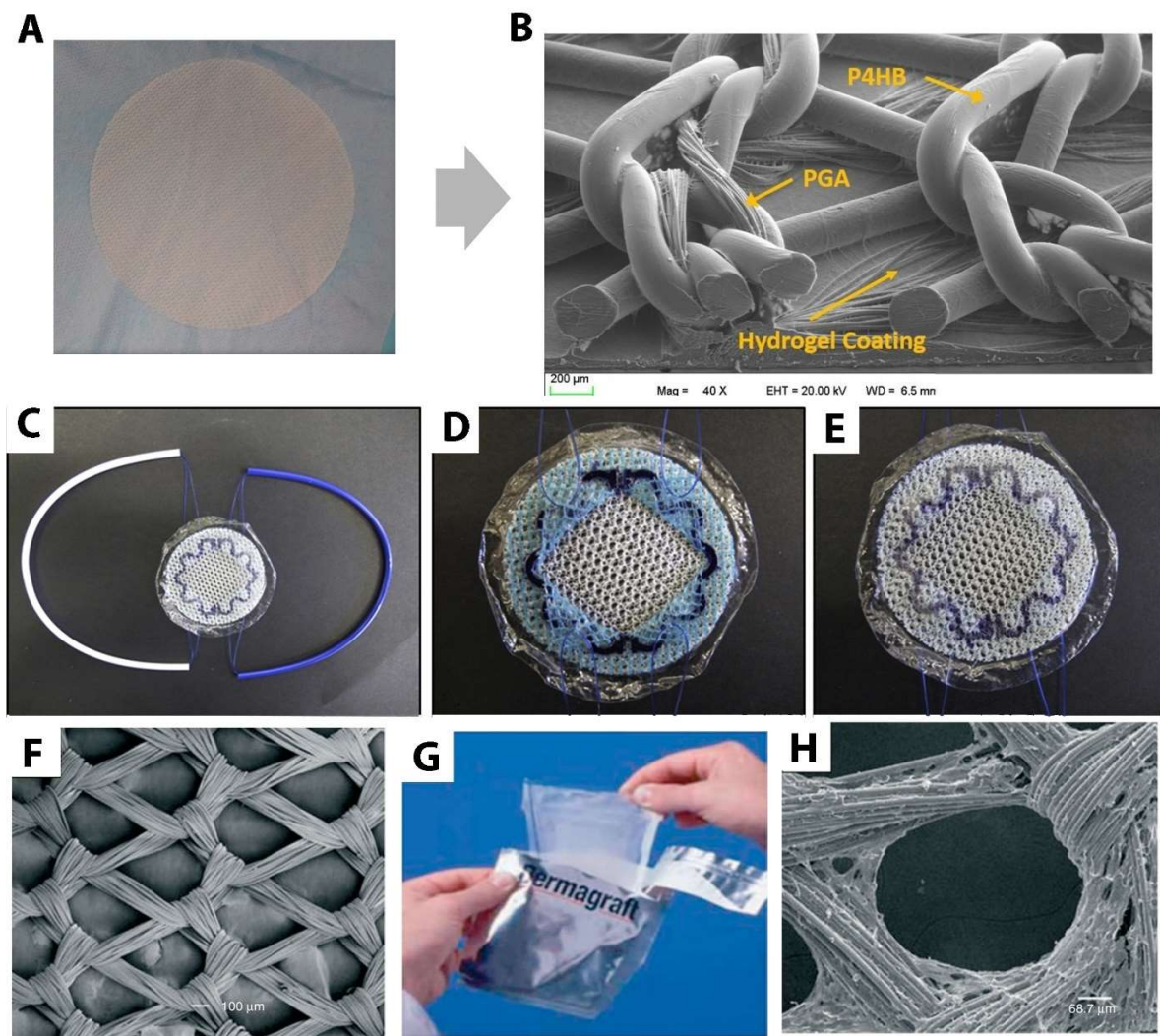
wall weakness results in different types of abdominal hernia including inguinal hernia when intestinal tissue is squeezed through the lower abdominal wall [111]. The standard treatment of hernia is surgical, with mesh reinforcement to release the pressure on the tissues and decrease the complication rate [112]. Originally used permanent synthetic meshes were made of PP or PTFE. Despite favourable mechanical properties, synthetic meshes have been associated with serious complications [113-115]. PTFE have a good profile for adhesion risk but a high risk of infection; however, PP meshes are durable and have a low infection risk, but they show limited little flexibility and a high adhesion risk [116]. This led to the use of partly or completely bioresorbable polymers such as PGA, P4HB, or different polymer blends [113-115].

OviTex<sup>®</sup>, an FDA approved ovine polymer-reinforced bioscaffold with PP or PGA, was successfully tested on 25 primary or recurrent HH repair. The results indicated successful relief of symptoms, no perioperative complications or recurrence of HH during the relatively short follow up period; no.[117] The operation technique of HH highly depends on the size of the lesion. For instance, treatment of a large HH (>5 cm) with a bioresorbable mesh (Gore Bio A<sup>®</sup>) made of PGA/trimethylene carbonate with an estimated resorption time of 6 months was found superior regarding recurrence (in the first 2 years) vs. non-mesh treatment [118]. Although a similar recurrence rate was noted in five years, an earlier failure rate was observed in the non-mesh group at 12 months.

Recently, a novel Phasix<sup>™</sup> mesh (**Figure 6A and B**) made of P4HB scaffold with PGA and hydrogel barrier was tested in the repair of large and complicated hernia r with either laparoscopic or robotic surgery technique resulted in excellent clinical outcomes including absence of migration, stenosis, recurrence or dysphagia in 30 patients [119-121]. In 2018, Renard *et al.* compared the use of resorbable synthetic (Vicryl<sup>®</sup>) and biological () meshes to treat infected

incisional hernia and found Strattice® superior to Vicryl in terms of early and late postoperative infections.[122] Later, slowly resorbable biosynthetic meshes made of P4HB (Phasix™) with a slower breakdown profile and capable of inducing cell proliferation showed to be effective tools to treat infected incisional hernias avoiding chronic infection or mesh removal within one year follow up in 29 patients.[113]

As a next generation of the meshes, a hybrid PTFE and PGA/trimethylene carbonate scaffold (Synecor™), selected to enhance mechanical strength and stimulate tissue proliferation and vascularization, respectively, was tested on 35 ventral hernia patients [123]. During the 2 years follow up, no recurrency took place and infection rate was in line with previous data. In addition, patients reported satisfaction with significant improvement especially regarding self – esteem, relief of pain and discomfort with only one patient needed reoperation. Accordingly, the new hybrid mesh Synecor™ was considered safe and effective [123]. Parietex™ composite ventral patch is made of polyester with absorbable collagen, PEG, and glycerol. The patch has a fixation system composed of four monofilament polyester flaps. Two removable handles complete the device. This fixation system and the three-dimensional reinforcement material are assembled with absorbable PGLA expanders as shown in **Figure 6C-E** [124]. The Parietex™ composite ventral patch has been successfully used with low recurrence rate in different types of hernia in 48 patients [125]. A recent meta-analysis involving the comparison of synthetic, biologic, or bioabsorbable use of meshes for complicated ventral hernia cases reported similar results. Recurrence rate and infection was lowest in case of the bioresorbable meshes, with similar seroma rates compared to the other two meshes implying effectiveness of bioresorbable meshes [115].



**Figure 6.** (A) PHASIX Mesh comprised of a fully resorbable polymer (poly-4-hydroxybutyrate, P4HB) monofilament knitted into a flat sheet configuration. Reproduced with permission from Ref [120]. (B) Scanning electron micrograph (SEM) of Phasix™ ST Mesh (40× magnification; scale bar = 200 µm). Phasix™ ST Mesh is comprised of fully resorbable poly-4-hydroxybutyrate (P4HB) fibers co-knitted with polyglycolic acid (PGA) and coated with a resorbable hydrogel layer on the visceral side of the mesh. The hydrogel layer is comprised of sodium hyaluronate (HA), carboxymethylcellulose (CMC), and polyethylene glycol (PEG). Reproduced with permission from Ref [121]. (C) Peritoneal surface of Parietex™ showing two positioning loops attached to four flaps composed of polyester monofilament. (D) Parietex™, subcutaneous side. (E) Parietex™, peritoneal side. Reproduced with permission from Ref [124]. (F) Polyglactin mesh, (G) Dermagraft as received from a pack, (H) dermal fibroblasts cultured on polyglactin mesh. Reproduced with permission from Ref [126].

## **6.2. Gynecological applications**

Following abdominal or pelvic surgery the appearance of pelvic adhesion is a very frequent complication occurring in around 95% of patients following pelvic surgery and resulting in chronic pain, altered organ motility or even bowel obstruction [127].

The application of surgical mesh in gynecological applications, especially transvaginal mesh for pelvic organ prolapse (POP) and stress urinary incontinence (SUI), has been associated with safety concerns for women [128]. The transvaginal meshes were reclassified from moderate-risk class II devices to high-risk class III devices in 2016, meaning the 510(k) process can no longer be used for mesh products to gain market access. That reclassification resulted in a sharp decrease of using transvaginal mesh for POP repair surgery [129]. The observation and assessment of the surgeries confirmed the high level of risks with respect to the benefits; therefore, the FDA ordered mesh manufacturers to stop selling and distributing surgical meshes intended for transvaginal repair of anterior prolapse (cystocele) on April 16, 2019 [130]. In addition, the Therapeutic Goods Administration (TGA) cancelled the approval of urogynaecological meshes for POP repair surgery (through the vagina) and SUI repair surgery (single incision mini-slings) in November 2017 [131]. Several attempts were made to develop anti-adhesive membranes, such as CoSeal<sup>®</sup> which is a resorbable hydrogel made of two different synthetic PEG. Crosslinking of the two polymers upon ejection from a syringe result in the formation of a barrier capable of inhibiting adhesion in the acute and subacute period, getting completely resorbed within a month [127].

CoSeal<sup>®</sup> was successfully tested in preclinical models and a randomized controlled clinical trial on myomectomy patients and proved to be safe and effective by significantly decreasing adhesion both in high and lower risk patients without any notable complication or adverse event [127].

Different types of implants and meshes have been also tested during sarcocolepopexy surgery, the treatment of for example vaginal prolapse, to decrease the operation-caused complications such as recurrence or infection [132]. A partially resorbable graft composed of PP and polyglactone showed mechanically good results without significant complications. However, the composite PP graft was withdrawn shortly after introduction to clinical practice, leading to the use of non-resorbable polyvinylidene fluoride in sarcocolepopexy. The polymer showed similar results as far as anatomical success, patient satisfaction or complication rate are concerned [132].

### **6.3. Wound healing**

Acute skin lesions as burns or chronic lesions like ulcers are common disorders, severely affecting the quality of life. Even with modern absorbent wound dressing materials (e.g. alginate), the definite treatment and success rate is still limited especially in case of infected ulcers (e.g. in diabetic patients). This may lead to systemic complications and even life-threatening septic states. Several preclinical trials aimed to develop partly or completely resorbable wound healing polymer-based hydrogels with promising results and development of next generation drug or stimulating factor eluting meshes [133, 134]. The most frequently used polymers are HA, collagen, and PLGA exhibiting a controlled degradation profile synergizing with epithelization (skin healing) and PEG which induces proliferation and collagen precipitation. Other polymers include PCL with excellent structural properties but limited capacity against microorganisms. Polymers lacking antimicrobial activity are therefore frequently combined with silver nanoparticles to induce matrix proliferation in an antimicrobial environment or even sericin derived from moth or spider combined collagen with great resorption and antimicrobial effects in preclinical trials for burn injuries [134, 135]. Several commercially available and approved polymer appliances are proved to be effective in wound healing, such as resorbable collagen matrix (Hyalomatrix®) successfully used in burn

injuries. Furthermore, a knitted Polyglactin (PLGA) mesh, as typically shown in **Figure 6F**, was cultured with human neonatal fibroblasts leading to the development of one commercial product of cryopreserved Dermagraft® (Advanced Tissue Sciences) (**Figure 6G**) [126]. The knitted PLGA meshes support homogenous cell distribution and withstand the cell contractile force (**Figure 6H**) [126]. Dermagraft® was successfully applied extensively on chronic ulcers with good clinical healing results without complications [1, 134, 136, 137].

#### **6.4. Dentistry applications**

In dental care, there are several conditions where guided bone regeneration (GBR) is indicated, in order to provide the necessary amount and quality of bone tissue for implantology.[138, 139] Membranes in the GBR procedure serve as a cell-occlusive barrier, which prevents the regeneration of epithelial and connective tissues in the wound, maintaining a space for the migration of pluripotent and osteogenic cells [138, 140, 141]. Two main types of resorbable polymer meshes and membranes are employed in dentistry: the group of collagens as natural polymers, and the group of synthetic polyesters. **Figure 7A** shows the application of GBR in surgical procedures. Following a treatment plan for extraction, the defect site is debrided, and the bone is perforated (**Figure 7A(i)**) by the surgeon prior to implantation of the bone graft and membrane. Dental bone graft is placed in the void socket to promote bone growth (**Figure 7A(ii)**) while the barrier membrane is implanted sub gingivally over the alveolar ridge to protect the bone growth within the socket and prevent gingival ingrowth (**Figure 7A(iii)**). Finally, the tissue closure is performed when applicable (**Figure 87A(iv)**) [5].

In the 2010's, Jung et. al have examined the clinical outcome of 265 dental implants, involving 72 patients. In the study, the researchers aimed to compare the practical efficacy of resorbable and non-resorbable membranes. All the patients received deproteinized bovine bone

mineral (DBBM) in combination either with a collagen) or an expanded polytetrafluoroethylene non-resorbable (e-PTFE) membrane and confirmed that both resorbable and non-resorbable membrane systems are safe, reliable, predictable and have a long survival rate (91.9% and 92.5%, respectively) during the median follow up-time of 12.5 years [142].

The effectiveness of collagen membranes was enhanced when used in combination with a bone graft [143]. **Figure 7B** illustrates the clinical benefit (9 months postoperative) of using bone grafting material (BioOss) and a membrane (AlloDerm® GBR) to treat a class I ridge defect. The patient experienced significant hard and soft tissue growth [143]. In another study, CelGro™ (Orthocell Ltd.), a type I collagen bilayer membrane, was employed in a clinical study for a total of 16 dental implants, which were placed in 10 participants receiving GBR. The results showed that Celgro™ restores bone defect with no complications or adverse events [144]. A recent study has compared collagen-based membranes with synthetic PLA resorbable membranes during the dental implantation process and showed no clinically significant change in facial bone thickness reduction implying that synthetic and resorbable polymer membranes can be equally used supporting aesthetic implantology.[145] Interestingly, ridge augmentation treatment extended with PRF or dehydrated human amnion-chorion membranes has no different clinically visible effect on vital bone formation or augmentation compared to traditional collagen membrane, however it caused a slight pain reduction in patients undergone lateral ridge augmentation, followed by mandibular ramus block harvesting [146-148].

### **6.5. Maxillofacial surgery**

Facial bones could be damaged by injuries, trauma, tumour, infection and also can be affected by congenital anomalies [149]. Results regarding the reconstruction methods of facial bones has a

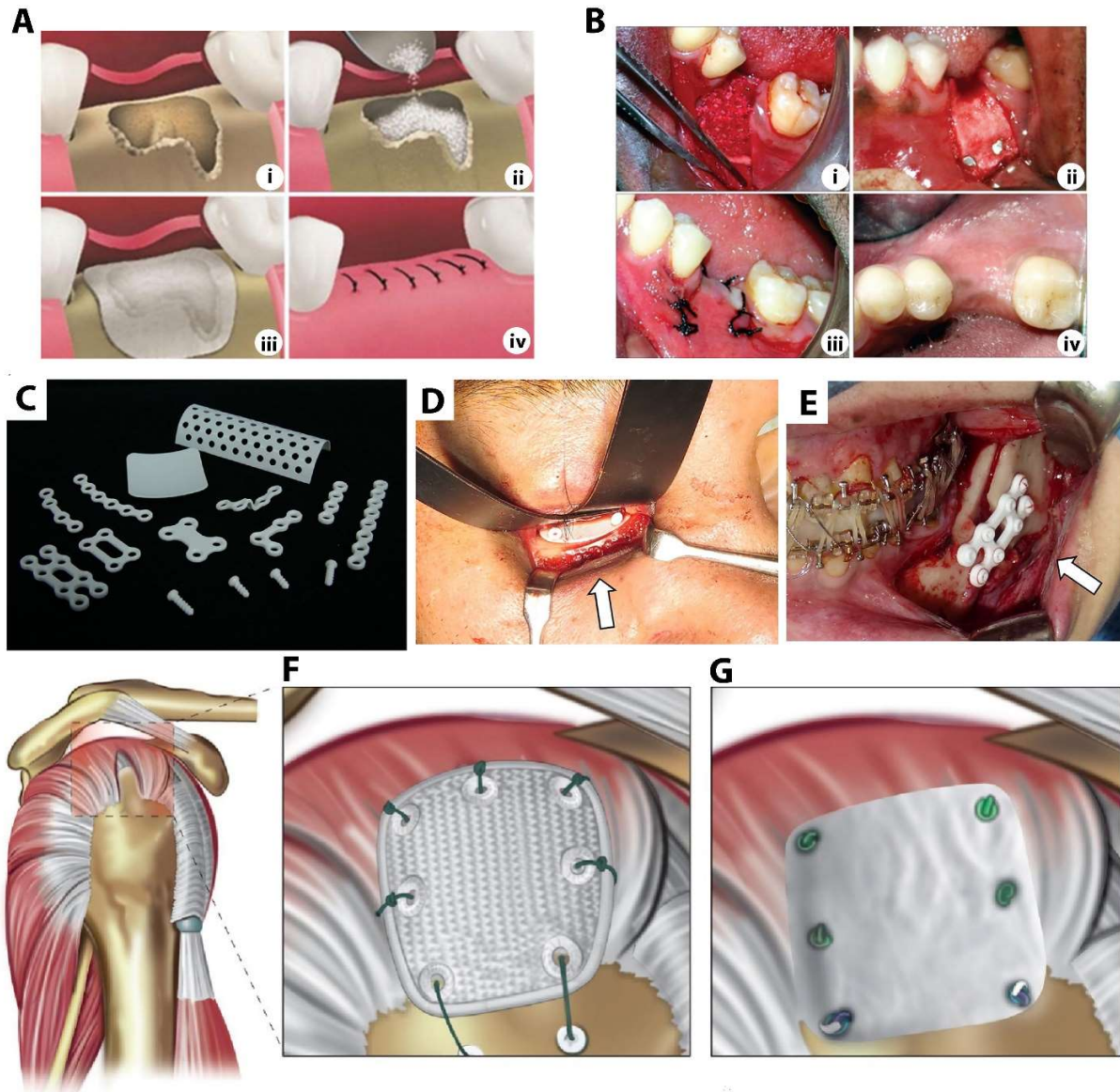


wide and well described literature, and it must be noted, that surgical techniques and materials strongly depend on the actual deformity, origin of bone defect and characteristics of patients.[149] In 2005, an early study investigated the use of resorbable membranes in the treatment of unilateral cleft palate in 15 participants divided to three different treatment groups: autogenous iliac bone graft (ABG) alone; expanded polytetrafluoroethylene (ePTF; Gore-Tex™) membrane implanted alone; while the third group was treated with a resorbable PLA/PGA membrane, combined with ABG [150]. Guided bone regeneration has been found successful both with membranes and with standalone ABG however, the authors reported significantly better results with combined techniques following the radiological evaluation [150].

Biodegradable polymers can also be mixed with hydroxyapatite (HA). The use of a composite product (Osteotrans MX®) composed of un-sintered PLLA/HA can support fracture stabilization and re-ossification with minimal complications (**Figure 7C-E**) [151]. Because they are osteoconductive and biodegradable, the u-HA/PLLA nanocomposites can be used for complete replacement by bony tissue in addition to the advantages of early functional improvements [152]. The same research group investigated the complications related to PLLA/PGA copolymer plate and mesh systems used in maxillofacial surgery. In total, 87 patients have been involved in the retrospective study which concluded that PLLA/PGA is a useful material for maxillofacial osteosynthesis, with good healing process and rapid resorption however, it must be noted that plate thickness was associated with the risk of exposed plates as a complication, therefore right diameter selection is essential [153]. Among 147 patients with midfacial trauma or dentofacial deformity as complication plate exposure was 7.4%, infection was 2.4% and plate breakage was 0.7%, respectively, when PLLA/PGA meshes and plates have been used for reconstruction also

interestingly, authors concluded that female sex and the greater number of plates are risk factors for perioperative complications [154].

Not only synthetic, but natural polymer based membranes can be used in the treatment of intra-bony defects in the maxillofacial region [155]. With the participation of 18 patients, resorbable collagen membranes have been used to treat mandibular defects, based on HA grafting, supported with the addition of PRP and significant bone density growth has been observed on the radiography images in the 1<sup>st</sup> and 6<sup>th</sup> month after treatment [155]. Interestingly, a previous research work concluded that using collagen membrane is disadvantageous, compared to the addition of  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) because of the decreased bone regeneration, which is in agreement with the findings related to guided bone regeneration (GBR) in dental applications, in comparison with titanium implants [156, 157]. To overcome these challenges, a novel technique and material has been introduced in 2017. The method used a resorbable polymeric thermo-reversible gel, as a space-maintain approach, with similar indication and goal as described at GBR with resorbable membranes [158]. The resorbable polymeric thermo-reversible gel manufactured from a specific mixture of poloxamers dissolved in water (predominantly poloxamer 407) [158]. After examining the results of the 11 patients participating in the study, new bone formation has been reported between 54% to 60%, without the appearance of fibrous tissue. Radiographic evaluation showed more than 10 mm height of new bone in all cases, after 6 month-follow up. Based on the clinical outcomes, cost-effectivity and simplicity of the technique, it is considered as one of the best techniques for the maxillary sinus elevation procedure [158].



**Figure 7.** (A) General step-by-step procedural diagram for a GBR/GTR procedure. Treatment begins with a tooth extraction or tooth loss (i), bone graft placement (ii), barrier membrane placement for compartmentalization of tissues (iii), and closure (when applicable/possible) (iv). Reproduced with permission from Ref [5]. (B) Visual diagram of a class I ridge defect procedure. Patient Seibert class I ridge defect was treated with BioOSS bone graft (i) and an AlloDerm® GBR membrane (ii), secured with silk sutures (iii) for ridge restoration and augmentation, with significant hard and soft tissue growth at 9 months postoperative (iv). Reproduced with permission from Ref [143]. (C-E) Maxillofacial osteosynthesis system using third-generation bioactive/bioresorbable materials (Osteotrans MX®); (D) Bioresorbable sheet and tack fixation for right orbital reconstruction in a case with naso-orbito-ethmoidal (midfacial) fractures using the SuperFIXORB-MX® (OsteotransMS®) system (E) Bioresorbable plate osteosynthesis of advancement mandibular BSSRO using the SuperFIXORB-MX® (OsteotransMS®) system in orthognathic surgery. Reproduced with permission from Ref [151]. Application of commercial mesh and patch in tendon-to-bone interface repair: (F) Pitch-Patch graft is designed for

reinforcement of the rotator cuff as a non-absorbable graft, sutured via multiple sutures directly to rotator cuff tissue. The designed suture holes in Pitch-Patch resist suture cut-through. (G) CelGro™ for augment repair of rotator cuff tears. Torn tendon must be trimmed and anchored with sutures back into healthy bone prior placing the CelGro™. Then, CelGro™ can be trimmed to size and placed over the repair site to promote tendon healing. Reproduced with permission from Ref [47].

## **6.6. Other clinical applications of resorbable meshes**

Beside the well documented clinical trials related to dental and maxillofacial applications, meshes consisting of natural or synthetic polymers have other clinical tissue regeneration applications, such as breast surgery, nerve, and tendon repair. Tissue stretches and concomitant unpleasant appearance and dissatisfaction is a common complication of breast implant surgery. This led to the use of resorbable meshes in soft tissue augmentation like gradually resorbing P4HB based GalaFlex® or the slower resorption PDX, both proved to be safe and efficiently maintained the mechanical strength and increased patient satisfaction without notable complications, malposition or ptosis [159, 160].

Peripheral nerve injuries are common on upper extremities resulting in motor or sensory loss and consequently, limited daily activities. Nerve repair is performed with microsutures or if the nerve defect is extensive, nerve grafts could be used with limited effectivity and persistent loss of function. To overcome this problem, resorbable materials were used in these injuries, ensuring the induction of regeneration process, but absent by the time it could interrupt the normal healing [161]. Based on preclinical results, PHB was used in ulnar and/or median nerve injury patients and found to be safe with very few complications and at least as effective as the conventional treatment since considerable improvement was seen in some sensory, motor and overall functional assessments in the PHB patients compared to epineural suture treatment recipients [161]. Furthermore, several bioresorbable nerve conduits (such as: polyglycolic mesh – Neurotube,

porcine collagen – Rovelnerve etc.) have received the FDA or CE approval and showed impressive sensory outcome (75% of the cases were rated as good to excellent) following reconstruction of the resorbable polymers [162].

Tendons play a significant role in transmitting loads between musculoskeletal tissues. The repair of injured tendons typically involves biocompatible materials and surgical reparative techniques using a commercially available artificial tendon being the most common clinical treatment. Tendon scaffolds can be based on absorbable and non-absorbable materials [72]. Poly-Tape mesh (Neoligaments Ltd., UK) is manufactured by weaving the non-absorbable polyethylene terephthalate (PET) fibres and particularly used for rotator cuff tears (RCTs) repair (**Figure 7F**). While the open woven structure of Poly-Tape supports space for tissue ingrowth, the parallel fibres provide high strength (average tensile strength for the medium and larger patches are over 400 N and 550 N, respectively) [47]. On the other hand, natural resorbable biomaterials have resulted in better biological outcomes. Recently, CelGro™ (Orthocell Ltd.), a type I collagen bilayer membrane, has been used in a clinical study to regenerate RCTs, indicating that the membrane is promising for induction of tendogenesis into the healing areas of tendon and tendon-bone interfaces (**Figure 7G**) [47, 163]. However, this scaffold is not recommended as a structural graft because of low tensile strength (average ultimate tensile strength of  $0.35 \pm 0.06$  MPa; failure force of  $5.4 \pm 0.38$  N) in some specific tendon repair applications [47].

## **8. Conclusion and future perspectives**

With the rapid development of polymer material science, resorbable meshes and hydrogels gained attention in clinical studies. Before clinical adaptation, the preclinical safety and feasibility studies are essential and inevitable. The main benefits of resorbable materials are the avoidable second surgery for the removal of the implant and the long-term inflammatory reactions initiated by the

permanent inserts along with the lack of systemic effects. Evading the second surgery also causes less discomfort to the patient, and it can potentially decrease the economic burden; however, it must be noted that resorbable polymer meshes and plates are more expensive compared to non-resorbable devices. Using resorbable polymer meshes and plates are favourable in paediatric cases, exceptionally in cranio-maxillofacial reconstruction procedures. In clinical applications, it is observed that resorbable polymer devices are well-visible on radiographic images, and they do not produce artefacts. The majority of the studies conclude that none of resorbable or non-resorbable meshes are superior, both types can result in excellent clinical outcomes, and their application must be considered based on several factors, including the medical history and overall status of the immune system of the patient, origin of the disease and the nature of tissue defect.

In the last few years, the use of resorbable polymers has progressively increased in soft and hard tissue applications with impressive results. However, most of the studies were performed on a small sample size, with relatively short follow up periods. Consequently, large, multicenter studies are needed to assess the real benefits and long-term effects of the implantable resorbable devices, with a special focus on materials enhanced with bioactive supplements.

The progressive demand for bioresorbable meshes with optimal functionality and behaviour at interfacial tissues has led to the constant development and improvement of biomaterials constantly. Hydrogel barriers, drug-loaded surface coatings, nanofibrous mats and modifications with nanoparticles have come up with very promising outcomes in *in vivo* animal models of the mesh. Despite many efforts in this field, there is no ideal bioresorbable hernia mesh with a minimal recurrence rate, post-infection, and tissue adhesion. Thus, current studies focus on developing novel bioresorbable meshes to address the main complications in clinical studies, mostly biocompatibility, enhanced mechanical performance, anti-adhesion, and infection prevention. The

next generation of the mesh will be based on novel prosthetic biomaterials that are fully resorbable in the long-term facilitating tissue regeneration and combating infection in the surgical site through controlling the release of drugs after implantation. Surface modification of the resorbable meshes to achieve anti-adhesion features should be investigated using more efficient nanoparticles, hydrogels, or therapeutics. Smart or stimuli-responsive biomaterials should receive more attention for tissue regeneration. By incorporating stimuli-responsive biomaterials, 4D-printed surgical meshes can be designed to change geometry over time. Such advancements will enable the mesh to dynamically adapt to the surrounding tissues post-implantation, improving tissue integration, reducing the risk of mesh displacement, and reinforcing abdominal walls. Furthermore, the incorporation of “time” factor to the MEW scaffolds by using shape memory biopolymers can unlock new capabilities and features in hernia mesh applications. MEW enables the fabrication of microfibrinous meshes with precise control over structure and drug delivery, while 4D printing offers shape-changing adaptability to the mesh. These technologies have the potential to upgrade tissue regeneration procedures fundamentally by offering functionalised, personalised, and biocompatible bioresorbable meshes, which enhance patient outcomes and long-term success rates. In addition, the combination of appropriate surgical procedures and optimal meshes based on the specific requirements of the patients can overcome the current treatment complications. Furthermore, the outcomes on large animal models are essential to evaluate the complete biofunctionality of the advanced bioresorbable mesh before clinical phase studies. Finally, the complexity of advanced bio-fabrication techniques and biomaterials with the integration of therapeutic agents will not only be technically challenging but also needs specific consideration of regulatory approval pathways.

## Acknowledgments

This publication was supported by the project MEBioSys with reg. no. CZ.02.01.01/00/22\_008/0004634, co-funded by the ERDF as part of the MŠMT.

## Conflict of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Minghao Zheng is consultant to Orthocell Ltd and hold stock in the company.

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