



## Review article

# Emerging materials and technologies for advancing bioresorbable 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, and wound healing. To date, commercial surgical meshes are typically made of non-absorbable synthetic polymers, notably polypropylene and polytetrafluoroethylene, which are associated with postoperative complications, such as 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 advanced bioresorbable materials, both synthetic polymers 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.

## Statement of significance

In the ever-transforming landscape of regenerative medicine, the embracing of engineered bioabsorbable surgical meshes stands as a key milestone in addressing persistent challenges and complications associated with existing treatments. The urgency to move beyond conventional non-absorbable meshes, fraught with post-surgery complications, emphasises the necessity of using advanced biomaterials for engineered tissue regeneration.

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This review critically examines the growing field of absorbable surgical meshes, considering their potential to transform clinical practice. By strategically combining mechanical strength with bioresorbable characteristics, these innovative meshes hold the promise of mitigating complications and improving patient outcomes across diverse medical applications. As we navigate the complexities of modern medicine, this exploration of engineered absorbable meshes emerges as a promising approach, offering an overall perspective on biomaterials, technologies, and strategies adopted to redefine the future of surgical meshes.

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## 1. Introduction

Surgical meshes have been used in various applications. The first meshes were clinically used for the treatment of hernia conditions in the 1950s. A tension-free reconstruction of the injured tissue was a significant achievement in hernia surgery using surgical meshes that resulted in better outcomes both in terms of tissue integration and consequent repair [1]. In the 1970s, 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]. To date, surgical meshes have been manufactured using nonabsorbable materials, especially for hernia and PFDs.

Non-absorbable meshes were developed in the latter half of the 20th century to replace metal meshes such as silver wire braided meshes which were abandoned for stiffness and unfavorable outcomes [3]. Non-absorbable meshes possess the required mechanical properties, are easily shaped intraoperatively, and exhibit long-term structural stability [4]. They are intended to remain in the body permanently but may undergo some degradation over time [5]. The most common applications of these types of mesh include breast reconstruction [6], hernia [7] and PFD [8]. Non-absorbable meshes (permanent meshes) are mainly composed of either expanded polytetrafluoroethylene (ePTFE) or polypropylene (PP) [9]. Those meshes show good mechanical properties overall, where tensile strength exceeds the physiological requirements; however, Food and Drug Administration (FDA) reports show that increased inflammation, pain, and infection rates are associated with the application of non-absorbable meshes [9,10]. For instance, PP mesh has been noted to undergo some degradation *in vivo*, typically due to oxidation. This degradation results in changes in mechanical strength and appearance of surface cracks, which weaken the material further [11]. Additionally, the undesirable oxidation and degradation may cause significant activation of inflammatory cytokines and infiltration of immune cells at the implantation site [12]. On the other hand, ePTFE is considered a hydrophobic, inert and chemically stable mesh, which allows for resistance to enzymatic attacks during the foreign body response. However, chronic inflammation and remarkable shrinkage are associated with the use of ePTFE mesh [11,13]. Various approaches have been employed to improve their biocompatibility by either changing the functional physical properties such as porosity to improve cell infiltration or coating with more biocompatible materials that act as barriers to the synthetic mesh material coming into direct contact with the local target tissue [14]. These are designed to reduce local inflammatory/immune responses thereby reducing the chances of complications. Literature information indicated that coating PP meshes with biomaterials such as collagen [15], fibrin [16], and extracellular matrix (ECM) [17] or mesenchymal stem cells [18] enhanced their biocompatibility and reduced the inflammatory response. Surface hydrophilization of PP meshes with titanium treatment (e.g., TiLOOP® pfm medical) also reduced chronic pain and immune response [19,20]. Polymers applied to PP meshes either

by simple surface deposition [21,22] or chemical grafting [23] reduced tissue adhesion and conferred various desirable effects. On the other hand, poor clinical outcomes have been associated with some coated PP meshes such as ETHICON PHYSIOMESH™ having a laminated layer of poliglecaprone 25 and C-Qur (Atrium) mesh coated with omega-3 fatty acid because of a higher hernia recurrence and reoperation rate compared to similar products. Indeed, the mesh antiadhesive properties of C-Qur (Atrium) decline over time leading to dense abdominal adhesions necessitating mesh explantation [24–26].

Despite relevant biocompatibility enhancement, challenges in nano-absorbable surgical meshes have not been completely resolved as they are still associated with a risk of postoperative infection, pain, fistulation and need for explantation in contaminated settings [1,27,28]. This led to the evolving of biological mesh products in the first decade of the century, e.g. Strattice™ RTM, Permacol™, AlloDerm™, etc., with expected reduced rates of infection and other shortcomings associated with permanent meshes [29].

Biological meshes/patches were introduced to reduce the risk of infections associated with synthetic non-absorbable meshes [29]. These are composed of an ECM that is derived from collagen-rich tissues [30]. 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 [31]. However, undesirable host reaction to the biologic mesh is a significant disadvantage [10,29]. A higher rate of reactions is attributed to the biologic properties of the mesh, such as the source animal's DNA, stimulating an immunologic response [32]. In a study reporting adverse effects associated with various surgical meshes for hernia repair, biologic meshes (from human or animal collagen) elicited higher foreign body reactions compared to synthetic and composite meshes [10]. In another report, both Strattice™ (porcine, non-cross-linked tissue matrix) and Tutomesh® (bovine, collagen I membrane) were associated with an acute, short-term inflammatory response as a macrophage-foreign-body reaction around mesh filaments [29]. Another disadvantage of biological meshes is their high cost [10,30]. The evidence base supporting the use of biological mesh is currently too limited to support routine clinical use, restricting it to mostly niche applications. Current evidence increasingly supports reconsidering synthetic mesh as the prosthesis of choice for elective open ventral hernia repair even in contaminated cases [33].

The key takeaway from the pre-clinical and clinical studies focusing on non-absorbable and biological surgical meshes is that not every innovation transfers to improved patient care or better clinical outcomes. The limitations and failures of the developments highlighted the importance of proper materials selection and the need of appropriate surgical techniques. Nevertheless, such failures may guide the development of future generations of prostheses with greater efficacy. Assuming appropriate surgical technique and mesh placement, flaws have generally involved long-term interactions of the prosthesis system (base / surface modification materials / fixation tool), its architecture and manufactur-

ing method, and the host tissues and organs [13]. Improvements require collaborative efforts between surgeons, material scientists and biomedical engineers to optimize the mesh composition and structural design. Moreover, the evidence base needs to be improved in future studies via a standard approach for the description of mesh type and exact placement, and consistent monitoring of the intervention regarding recurrence rate, infection, and seroma to enable reliable assessment and reproducibility of clinical outcomes. The evidence base may also be improved by testing the efficacy of the mesh in randomized trials and the inclusion of more high-risk patient cases to establish the limits of indication [34]. From a regulatory perspective, sufficiently rigorous requirements to demonstrate the safety of the prosthesis must be satisfied to gain clearance.

In the quest for more reliable implants for use inside the peritoneal cavity, bioresorbable meshes evolved as a slowly resorbable synthetic mesh, combining the benefits of both synthetic (no early degradation after implantation) and biological meshes (the “remodeling” aspects and better tolerance in case of contamination) [35]. Bioresorbable surgical meshes are temporary implants that 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 that can degrade into low molecular weight compounds that are involved normally in metabolic pathways, or which can be, at least, eliminated from the body through natural pathways [36]. 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 [37]. Consequently, this avoids the need for further surgical procedures to remove the implants or scaffolds [38,39]. 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) [35].

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 remodeling such as hydrogels and meshes, since such materials are well tolerated and have an inherent bioactivity including promotion of cell proliferation and adhesion [40]. 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 [41]. 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 [42].

Current research efforts focus on providing potential solutions that range from the formulation of multi-functional 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 emerging biomaterials and technolo-

gies for enhancing the preclinical and clinical performance of advanced surgical meshes.

## 2. Ideal surgical mesh and regulations

Although the “ideal” mesh has not been developed yet, the continuous developments in the field and the appearance of advanced materials have created the basis for designing the optimal mesh. An early study highlighted that surgical meshes must be inert, resistant to infections and other side-effects, adequate mechanical stability and non-carcinogenic [43]. In the past two decades, other aspects have occurred, like the need for cost-effectiveness, shape memory effect, flexibility and easy handling [44]. In addition, the use of lightweight materials is encouraged [44,45]. Table 1 describes the properties of an ideal surgical mesh according to its application.

As the field of implantable meshes is rapidly developing, which is fundamental for contemporary personalized and advanced medical solutions, there is an international regulation for these solutions based on the United States (US) FDA and European Union (EU) Medical Device Regulation (MDR), which strictly regulate and control the new device applications taking safety as primarily aim during implementation. 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 [49,50]. As per the code of the US FDA, 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 orthopedic surgery” [51].

The EU 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 orthopedic, dental, ophthalmic, and cardiovascular fields as well as 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 FDA approved the first urogynecological mesh only 20 years ago [8]. Due to safety concerns, the FDA withdrew some vaginal mesh products for stress urinary incontinence (SUI) and POP from 2011 to 2019 [8]. In addition, some countries such as New Zealand, the United Kingdom and Australia discontinued the application of PFD meshes. These withdrawals were in response to various complications following mesh implantation including infection, pain, discomfort and erosion into the vagina and in some cases, some patients had to undergo follow-up surgery [52]. Both 3D-printed and 3D bioprinted meshes have gained attention in the last decade due to their better surgical results with the latter approach able to design and print different types of matrices based on biocompatible polymers and biomaterials as well as the ability to embed bioactives such as cells and proteins [1,53]. For example, Dewey and co-workers reported that incorporating 3D-printed bone mesh improved the behavior of mineralized collagen scaffolds in terms of their mechanical and osteogenic performance [54]. The scaffolds were designed for the reconstruction of craniofacial bone defects caused by different factors including cancer treatments, congenital abnormalities and trauma. Ren et al. [55] fabricated a resorbable mesh with antibacterial properties and controlled degradation rates via 3D printing of polycaprolactone/polyethylene glycol-based matrices, to overcome problems associated with the traditional PP-based meshes. In 2017, the US FDA issued guidelines that included information on materials, design, printing methods, post-processing, and validation [1].

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

Properties	Description
Biocompatibility [43,46]	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 [47]	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 [48]	Optimal pore size and geometry promote tissue ingrowth and vascularization while preventing complications such as adhesions.
Surface bioactivity and anti-adhesion (if applicable) [46]	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 [48]	In some applications, a biodegradable mesh that degrades over time may be preferred, especially if long-term structural support is not necessary.
Postoperative visualization [46]	The mesh should be visible on imaging studies (such as X-rays, magnetic resonance imaging (MRI) or computer tomography (CT) scans) to enable postoperative assessment.
Ease of handling and placement [44,46]	The mesh should be easy to handle and manipulate during surgery, conforming to the anatomical site.

### 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 (HA), chondroitin sulphate, heparin, dextran, alginate, cellulose, chitin, and chitosan-(CS)], and polypeptides (collagen, gelatin, silk fibroin, albumin, elastin, and keratin) [56,57]. Natural biomaterials are highly biocompatible and have a favorable pro-remodeling host immune response [58]. 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 [59]. These drawbacks can be compensated by synthetic polymers, which are materials of great interest in the medical field [14]. Synthetic biomaterials offer several advantages over traditional natural materials, including the possibility of being precisely and consistently manufactured with minimal variability due to the controlled physical and mechanical properties that can be easily tuned. However, biocompatibility is a major concern since cells may have difficulty attaching and growing, and consequently might elicit a pro-inflammatory response in the host [60]. An increasing number of studies have therefore been 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 [61,62].

In 1959, Francis Usher introduced the initial synthetic mesh composed of PP for hernia repair applications. Subsequently, there was a burgeoning progress of mesh technology, which 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 [63,64]. The majority of bioresorbable meshes consist of biodegradable synthetic polymers, such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic) (PLGA; a copolymer of PLA and PGA). It is important to emphasize that these absorbable materials undergo degradation, and their degradation rate must align with the duration required for tissue regeneration, since after degradation, the tissue support is diminished, therefore the application must be carefully considered to avoid complications or lesion recurrence [65–67]. Despite their initial popularity, PGA meshes are no longer employed due to their

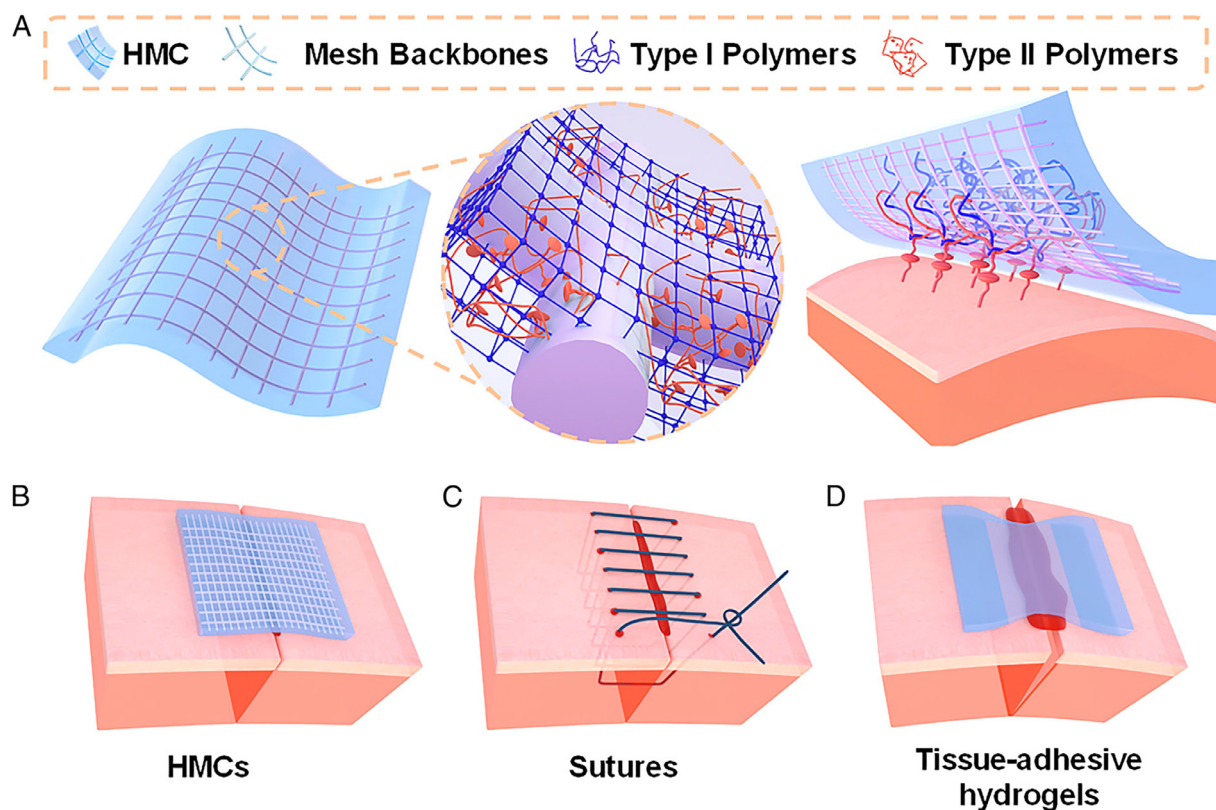
rapid degradation. As a result, there has been a notable emergence of biosynthetic polymers that show complete biodegradation over a mid- to long-term period for surgical applications.

The main aim of developing biomaterials is to diminish the foreign body reaction within the host and facilitate tissue regeneration [68]. PLGA was employed in the production of several commercial meshes, such as POLYGLACTIN 910 (Vicryl™, Ethicon) [13]. Despite the better degradation rate, PLA-based meshes still present complications such as foreign body granuloma and giant cell formation [69]. Biodegradable Gore® BIO-A mesh was developed by copolymerization of 67 % of PGA and 33 % of trimethylene carbonate (TMC), and in preclinical and clinical studies showed promising results in mechanical endurance and tissue integration. Another fully absorbable material in the field is TGR™ (Matrix Surgical Mesh; Novus Scientific Ltd., Singapore), which comprises two types of synthetic fibers (co-polymer glycolide-lactide TMC/lactide and TMC) with a multifilament structure, with satisfactory preclinical and limited clinical results [68,70,71].

Various natural bioresorbable materials are used in surgical mesh development. Biosynthetic resorbable meshes encompass materials based on silk fibroin (SF), gelatin, collagen, polyhydroxyalkanoates, and plant fiber-based materials. Notably, insect-based protein products such as SF 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 [72,73]. Combination approaches involving electrospun SF and other materials with high biocompatibility, such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate), have been explored to produce hybrid scaffolds that demonstrate high efficiency and biocompatibility according to the *in vitro* and *in vivo* studies [74,75]. The increased resistance to surgical site infections associated with bacterial poly(4-hydroxybutyrate) (P4HB) surgical meshes has made this material of extreme interest in hernia repair procedures. Bioresorbable meshes based on P4HB (Phasix™, BD Bard, Rhode Island, USA) were engineered to maintain structural integrity long enough to allow for tissue ingrowth but also completely degrading to avoid the complications associated with permanent mesh materials.

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 [76–78]. 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 [79]. Gao and





**Fig. 1.** Design and potential advantage of an HMC. (A) Schematic of the HMC. In the HMC, the hydrogel and the surgical mesh (polyethylene terephthalate) form topological entanglement. The hydrogel has long polymer chains of two types: Type I polymers (poly(N-isopropylacrylamide)) form a covalent network, and type II polymers (CS) carry functional groups (amino 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 [80]. Copyright 2021 National Academy of Sciences.

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 [80]. 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 (Fig. 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.

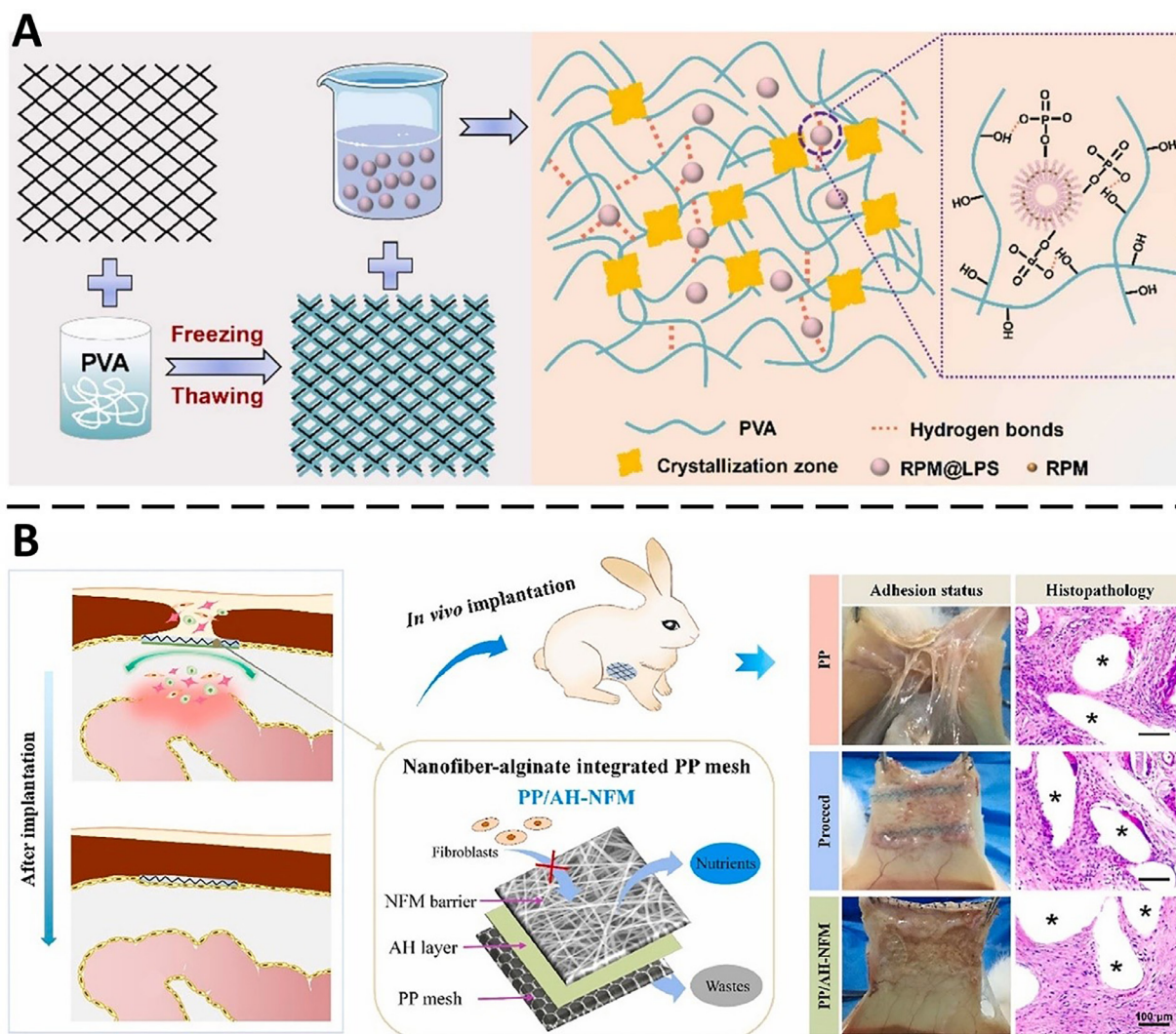
Resorbable polymer meshes are widely available on the market, but several preclinical *in vitro* and *in vivo* experiments had to precede commercialization. The experimental studies aiming to analyze degradation profiles of polymeric meshes in preclinical settings guarantee the safety and improve the understanding of the degradation phenomenon of meshes under *in vivo* conditions leading to better clinical application [81–83]. Several preclinical studies on different animal models (rabbit, sheep, rats, minipigs, pigs, vervets) were performed on commercially available synthetic resorbable meshes like GORE BIO-A® and Phasix™ and showed promising results as sites for cell proliferation [35,84].

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

Tissue adhesion and fibrosis can be a major complication during wound healing via surgical meshes; hence, the anti-adhesion functionality is a primary challenge in mesh preparation, particularly for PP meshes, which are widely used by clinicians. For ab-

dominal 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 [85].

Research studies have demonstrated that materials such as CS, 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 [86–88]. Among the antiadhesion products certified by the FDA, Interceed® produced by J&J, is prepared from ORC [89]. In 2018, Lai et al. [87] modified bacterial cellulose using TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to enhance its properties while retaining its favorable 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 [87]. 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 HA was performed after intramuscular and subcutaneous administration to a mice model. Histologic and hematological parameters analyzed at varying time intervals (7, 14, and 21 days) including the hematopoietic system showed promising outcomes on HA release during hydrogel degradation [90]. The study used the pig model, and conventional



**Fig. 2.** Antiadhesion surgical meshes. **(A)** The schematic illustration of the drug-loaded hydrophilic hydrogel coating RPM@LPS/PVA. Reproduced with permission from Ref [95]. Copyright 2023, with permission from Elsevier. **(B)** Schematic illustration showing the strategy to endow PP mesh with a barrier composed of a NFM and AH layers for preventing adhesion formation in abdominal wall hernia repairs in rabbit model. Reproduced with permission from Ref [98]. Copyright 2022, with permission from Elsevier.

laparotomy pelvic surgery was performed after histopathological evaluation and concluded that resorbable HA reduces laparotomy pelvic surgery-induced adhesion [91].

Most of the commercial surgical meshes are inert without groups to react with the grafted compounds, particularly for hernia repair applications. Hence, plasma treatment, using oxygen or argon gas, is employed to activate the inert surface of the mesh for functionalization [92,93]. 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 [94]. Subsequently, the PP-g-PVA mesh was implanted into mice [94]. 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 [94]. Most recently, an antiadhesive PP mesh was developed with PVA hydrogel and liposomes (LPS) drug delivery system (Fig. 2A) [95]. First, the PVA hydrogel coating was prepared by a freezing-thawing process; then, rapamycin (RPM)-loaded LPS were immobilized in the PVA hydrogel. Findings showed that the hydrogel coating was stable on PP mesh at 37 °C for 30 days. The optimal antiadhesive composite mesh showed a slighter inflammation re-

sponse and remarkably looser fibrous tissue surrounding the PP filaments as compared to the native PP through *in vivo* experiments [95].

Electrospun nanofibrous membranes possess the ability to mimic the ECM structure and effectively modulate cellular behavior. Unlike knitted structures, these membranes offer distinct structural characteristics that can cater to specific performance needs on each side [96]. 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 [85]. PLGA and chitosan (PLGA/CS) nanofibers were electrospun on PP mesh and then the antiadhesion effects of PLGA/CS nanofibers were evaluated in pre-clinical studies [88]. The peritoneal adhesion score of the PP/PLGA-CS30 mesh (containing 30 % chitosan) was 59 % lower than that of the pure PP mesh [88]. Aydemir Sezer et al. [97] developed an antiadhesion PP hernia mesh by incorporating micrometer-sized particles of absorbable ORC and PCL using the electrospinning technique. PP/PCL-ORC20 mesh (PCL/ORC coated PP mesh with 20 % ORC) showed the best tensile properties (ultimate strength: ~30 MPa,



modulus: ~42 MPa, elongation at break: ~112 %) among the samples, 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 [97]. Recently, nanofiber membranes (NFM) composed of PLGA and PCL acted as a good physical barrier *in vitro* [98,99]. An adhesive composite hernia mesh was prepared by integration of PP substrate with an alginate hydrogel (AH) layer containing a NFM barrier (Fig. 2B) [98]. *In vivo* experiments on rabbits indicated that incorporating AH-assisted NFM into the PP prostheses significantly reduced visceral adhesion and enhanced mesh integration into nearby tissues from the abdominal wall [98].

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 functionalize the mesh has been considered by researchers in order to remodel the ECM via the hydrogel and overcome the problem of poor adhesion of hydrogel to tissue by dopamine or l-3,4-dihydroxyphenylalanine (L-DOPA; a chemical precursor to dopamine) [100,101]. For instance, dual-functional layer membranes/meshes have been developed to optimize the performance of each function, such as a bifunctional two-sided PP mesh, in which one side was coated with PCL nanofibers with antiadhesion and antibacterial functions; and on the other side, the PCL nanofibers were treated with a mussel-derived l-DOPA binder [100].

In addition to problems with adhesion when implanted *in vivo*, synthetic meshes will typically result in a foreign body response by the body's defence system, with various consequences including scar tissue formation, degradation of local tissue with resultant inflammation, chronic pain and discomfort at the site of application [102]. This is particularly common with hernia meshes, the majority of which are made of PP. Therefore several efforts have been made to functionalize the surface of synthetic meshes (surface coating) using various approaches including nanoparticle-based matrices [103]; biocompatible polymers such as polyester, collagen, PLGA, polyvinyl pyrrolidone, PVA, CS and cellulose-based polymers [104–106], as well as using bioinspired materials naturally present in the body such as platelet-rich plasma (PRP) [107]. Furthermore, these surface coatings also serve as vehicles for local delivery of therapeutic agents such as growth factors, [1] antibiotics [108] and antimicrobial agents [109].

In a recent study, Yu et al. [110] employed a warp-knitting approach to fabricate hernia meshes made from PP and coated them with CS and alginate solutions to impart hydrophilic properties to the meshes. The resulting surface-coated meshes were characterized for surface morphology (SEM and AFM) and wettability (contact angle goniometry), cell attachment (ectomesenchymal stem cells derived from male Sprague-Dawley rats), cell viability and proliferation of the ectomesenchymal stem cells. Their results showed that the PP mesh coated with CS and alginate showed improved cytocompatibility and reduced side effects which facilitated cell attachment and proliferation for rapid healing compared to the plain meshes.

In a similar study, Seraphim et al. [111] designed bioinspired coatings to bioactivate PP meshes. The coatings were based on methacryloyl gelatin and methacryloyl mucin hydrogels with or without PRP supplementation. The successful coating was confirmed by FTIR spectroscopy, homogeneity of the coating and stability in a simulated biological matrix by SEM and micro-computed tomography CT and biological cell assays showed that the hydrogel coatings could stimulate and modulate fibroblast activity on the meshes.

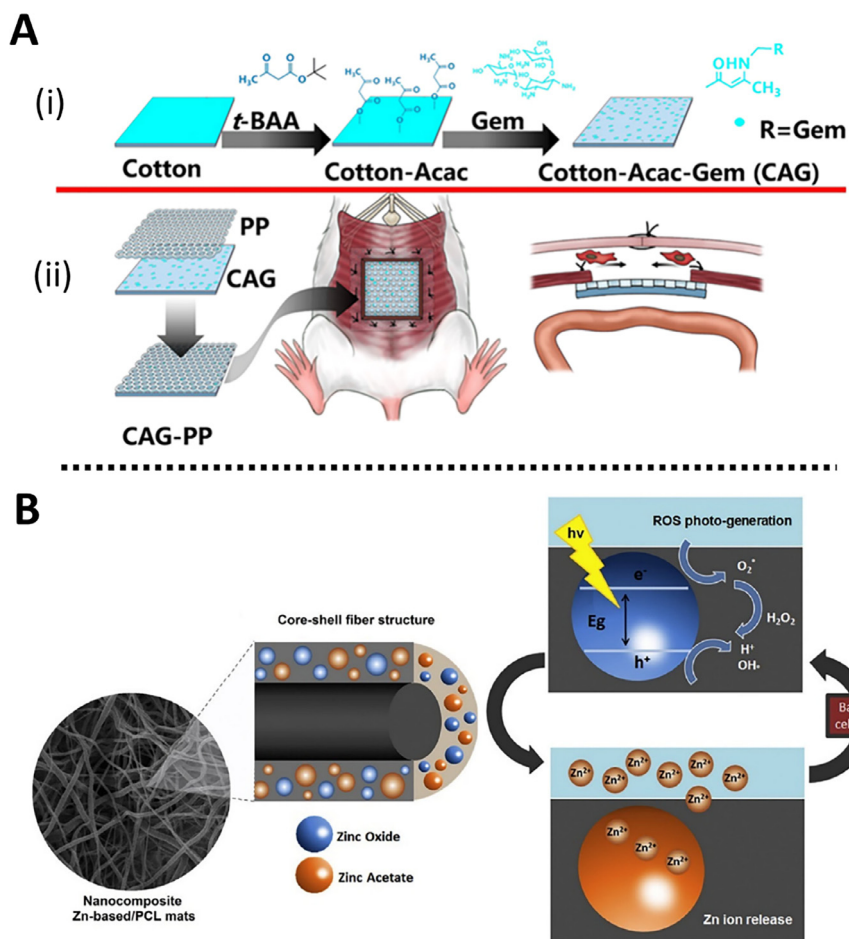
## 5. Drug-eluting bioresorbable meshes

Resorbable hydrogels are engineered to deliver the drug locally for extended periods and are capable of being HMCs resulting in significantly better and more effective meshes [80]. Advanced 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 [9]. Antibiotics have been highly employed for bacteria-specific treatment, including rifampicin, fluoroquinolones (e.g. ofloxacin, ciprofloxacin, levofloxacin), metronidazole, gentamicin (Gem), etc. [112]. The application of carboxymethylcellulose (CMC) 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 [113]. Reinbold et al. [114] utilized 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 [115]. 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 indicated a potent antibacterial activity [115]. In another study, minocycline-loaded CS nanoparticles were incorporated into a collagen/CS membrane. *In vitro* drug release tests showed that the antibiotic release was sustained for up to 7 days, with an initial burst release [116]. The woven cotton fabric was modified with 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 (Fig. 3A) [117]. 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 [117]. Loading growth factors and other biological molecules can improve the hosting and colonization of stem cells on hernia meshes and inhibit inflammatory reactions to enhance wound healing [1,9,118].

Natural-based antimicrobial molecules have also been 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, which 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 *in vitro* cytocompatibility for fibroblast and endothelial cells [120].

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* [121]. Recently, a non-electrospun bioactive 3D nanofibrous hybrid micromesh consisting of PLA nanofibrous microspheres loaded with didecyldimethylammonium bromide-modified zinc oxide nanoparticles (D-nZnO) demonstrated significant antibacterial, regenerative, and hemostatic functionalities through *in vitro* assays [122].

In another study, an antibacterial wound mat was fabricated by coaxial electrospinning to prepare PCL (core) loaded with Zn nanoparticles (shell) (Fig. 3B) [119]. Antibacterial tests were car-



**Fig. 3.** (A) Schematic illustration of the preparation of antibacterial cotton fabric (Cotton-Acac-Gem) (i) and combination with PP tissue mesh for abdominal wall defect repair (ii). t-BAA: tert-Butyl acetoacetate; Cotton-Acac: cotton transestericified with acetoacetyl groups; Gem: gentamicin; CAG: Cotton-Acac-Gem. Reproduced with permission from Ref [117]. Copyright 2020 American Chemical Society. (B) Zn-loaded PCL coaxial fibers and their antibacterial mechanisms, which are releasing  $Zn^{2+}$  ions and photocatalytic reactive oxygen species (ROS) generation. Reproduced with permission from Ref [119]. Copyright 2018, with permission from Elsevier.

ried out against *S. aureus* and *E. coli*, indicating that mats possess two main antibacterial mechanisms; release of  $Zn^{2+}$  ions and generation of photocatalytic ROS which together allowed inhibition of planktonic and bacterial biofilm growth and improvement of the mats' antibacterial properties [119]. Besides Zn nanoparticles, the positive antimicrobial effects of silver nanoparticles (Ag-NP) have long been known and used in clinical chemistry. Sobczak-Kupiec et al. attached Ag-NP by microwave irradiation to polymeric matrix poly(acrylic acid) and gelatin-based polymer/hydroxyapatite (HAP) composite to assess the possible decomposition changes of the material due to silver supplementation, and found greater degradation behavior for samples containing 4 % to 5 % HAP in artificial saliva and simulating body fluid, influencing the antimicrobial functionality and release profile of the nanoparticles [123]. Fig. 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.

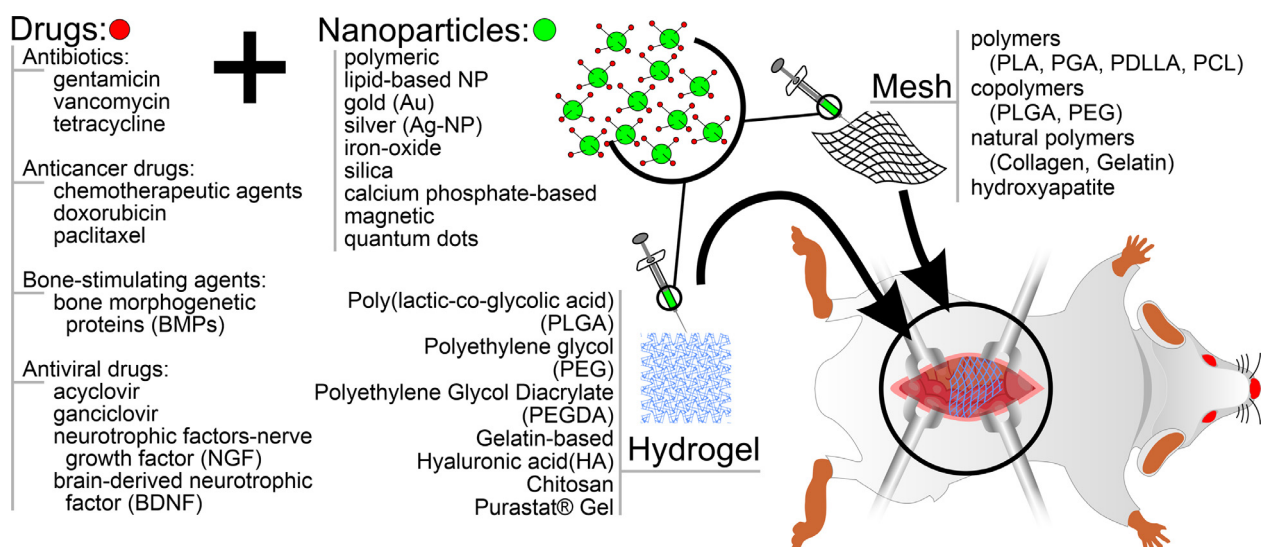
## 6. Advanced technologies in bioresorbable meshes

Surgical meshes, like PP mesh, are traditionally produced by fiber 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 [124]. Electrospinning involves applying an electric field to

create material fibers 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 fibers [125,126]. Recently, an electrospun composite ibuprofen-loaded (PEG/PCL) NFM has been fabricated aiming to be used in hernia repair and to prevent abdominal adhesions. In the *in vivo* animal study, the optimal membrane (PCL/25PEG-6 %) created a barrier between the abdominal wall and surrounding tissues, exhibited normal wound healing without interrupting mass transfer and showed a sustainable drug release profile ( $\approx 80$  %) within 14 days [127].

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 the creation of complex mesh structures with precise control over the composition, pore size and geometric shapes of meshes. In addition, 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 [128]. For instance, drug distribution in the mesh can be achieved by incorporating drug-loaded filaments or microspheres into the mesh structure at predetermined locations. This concept, known as bioprinting, has great potential for regenerative hernia repairs [129]. For instance, PCL meshes were 3D-printed with two different pore sizes containing sodium alginate-encapsulated Gem [130]. The antibacterial activity of these devices was assessed *in vitro*. The drug-loaded meshes





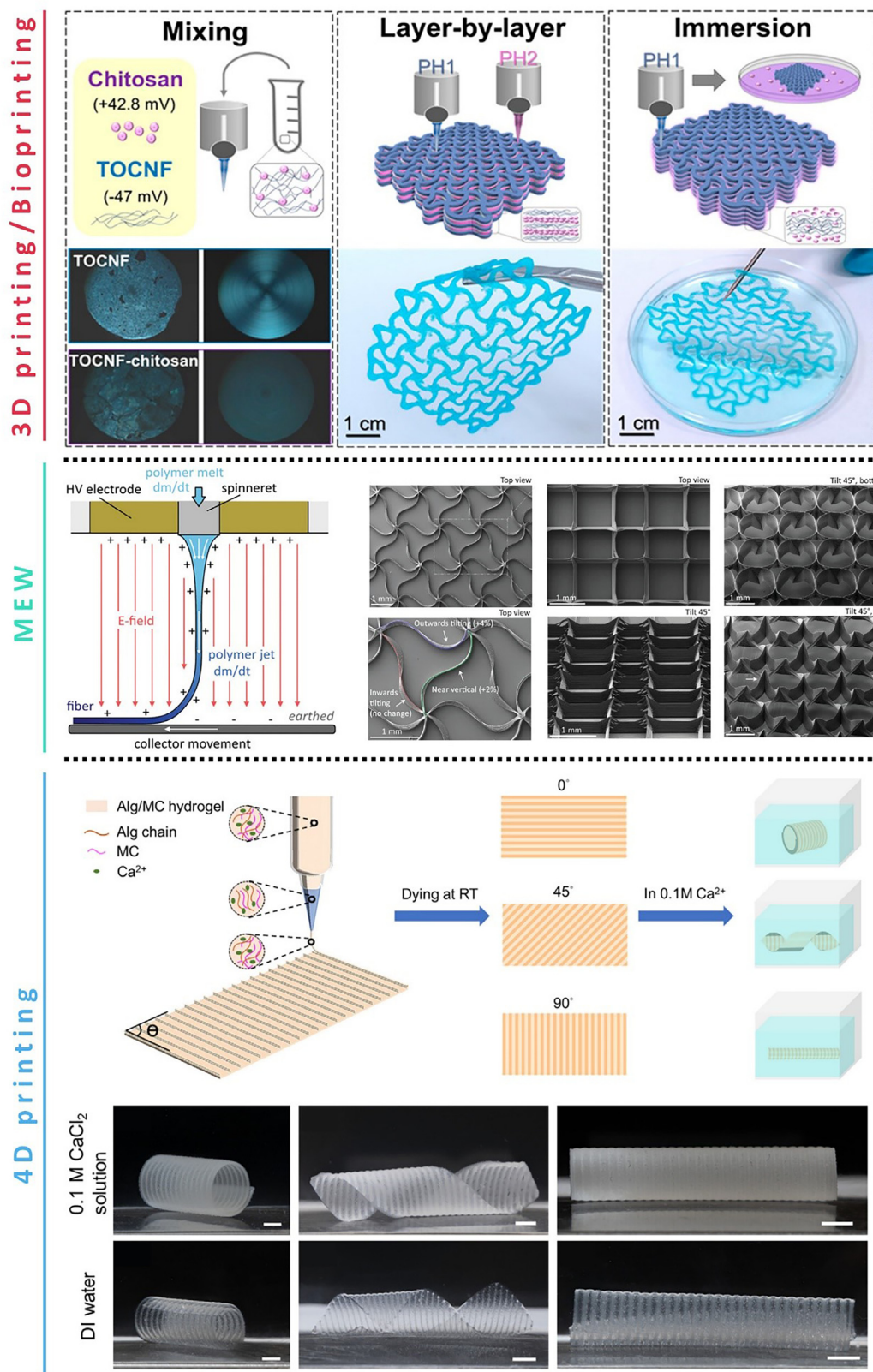
**Fig. 4.** Schematic representation depicting the roles of different biomaterials, nanoparticles, and therapeutic agents in the structure of a bioresorbable mesh used for wound healing on a pre-clinical mouse model.

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 [130]. Bioabsorbable PLA containing Gem was 3D-printed to assess antibacterial characteristics against *S. aureus* and *E. coli*. The results showed the feasibility of incorporating drugs into the 3D printed meshes, without losing the antibacterial effectiveness [131]. 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 CS (Fig. 5) [53]. 3D-printed nanocellulose mesh was immersed in the CS polymer solution to obtain CS-sorbed nanocellulose mesh. The non-cytotoxicity toward human monocyte/macrophages and controllable shrinkage upon solvent exchange make the cellular meshes appropriate for use as biomedical implants [53]. Recently, an innovative bioinspired micromesh-integrated 3D-printed hydrogel construct was developed as an antibacterial/regenerative bilayer scaffold for treating diabetic wounds [132]. A HA/CS ink was used to fabricate a bilayer construct composed of an upper dense hydrogel layer on top of a lower regenerative/antibacterial layer with hierarchical porosity achieved by incorporating PLA nanofibrous micromeshes embedded with nano D-nZnO, developed earlier [122]. The scaffold afforded 95 % wound-closure, infection control, regulation of three healing-associated biomarkers and skin regeneration in rats in 14 days.

Melt electrowriting (MEW) and 4D printing are two advanced biofabrication technologies that have the potential to revolutionize surgical mesh production by introducing innovative designs, adaptability and controlled properties. MEW has been recently used to gain a precise and continuous deposition of microfibrillar structures. The technique is typically based on applying a voltage to generate a stable molten fluid jet and drawing out a single fiber onto a pre-determined path [96]. In surgical mesh production, MEW offers two main advantages, extrusion of ultrafine fibers and fabrication of complex mesh designs with specific pore sizes, orientations, and patterns, which can optimize mechanical performance and match patient-specific anatomical requirements [133]. Examples of MEW mesh with different architectures are presented in Fig. 5 [134,135]. Recently, Ren et al. [136] fabricated degradable PCL/PEG composite meshes using 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. *In vitro* studies indicated that the PCL/PEG meshes with antibiotic coating will be effective after about 2 weeks of drug release and the mesh can support human mesenchymal stem cell attachment and proliferation [136].

The next generation of additive manufacturing known as 4D-printing, 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 [138]. 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 [139]. Hence, 4D-printing offers the potential to create meshes with adaptive properties and enhanced functionality in surgical 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 [129]. Printable 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 vertically to the orientation of the patterned strips (Fig. 5) [137]. The dynamic deformations of the printed Alg/MC hydrogels into helix or rolling structures, depending on the orientation of the patterned strips, occurred after immersion in a calcium chloride solution (0.1 M) [137]. Lanzalaco et al. [140] investigated the 4D behavior of a substrate of knitted fibers of isotactic PP (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 affected both the PNIPAAm gel expansion/contraction as well as the time of folding/unfolding response. In addition, PP-g-PNIPAAm meshes indicated an improvement in the bursting strength of 16 % with respect to the uncoated mesh, suggesting a very strong and adaptable system after implantation [140].



**Fig. 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 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 [53]. Copyright 2021 The Authors. **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 3 MEW meshes with different patterns and printing path amplitudes. Scale bars are 1 mm. Reproduced with permission from Ref [134,135]. Copyright 2019 The Authors. Copyright 2020 The Authors. **4D printing:** illustration of 4D printing for fabrication of patterned alginate/methylcellulose (Alg/MC) hydrogels and their 3D deformations on immersion in 0.1 M CaCl<sub>2</sub> solution. Reproduced with permission from Ref [137]. Copyright 2021 The Author(s).

## 7. Clinical applications of bioresorbable meshes

Surgical meshes were first and widely introduced for hernia repair applications in clinical practice however, as technology improved, other clinical fields got involved including cardiovascular interventions, gynecology, dentistry, dermatology and orthopedics. Resorbable polymer mesh applications have the great benefit of tissue support for the critical time period when it is needed or even stimulate tissue regeneration and proliferation. Eventually, they get completely broken down and dissolved, avoiding long-term complications, such as foreign body reactions, scarring or occlusion. The resorption time of bioresorbable meshes varies based on the type of polymer used and the construct design and porosity. With known degradation mechanisms, the chemistry, molar mass, and crystallinity of degradable polymers can be tuned to realize the combination of mechanical properties and degradation rates required for diverse clinical needs. Clinically, the most frequently used bioresorbable polymer materials are: PLLA bioresorbable by hydrolysis and complete metabolism of lactic acid at physiologic temperature with an average 60 % reduction by 18 months; polydioxanone (PDO) bioresorption varies from a few weeks to 12 months; PCL undergoes degradation over 24 months; porcine collagen enzymatic degradation ranges between 2 weeks to 3–4 months; PGA can be resorbed within a month and P4HB over 12 months [141,142].

The time typically required for supported healing depends on the clinical scenario and the physicochemical and structural characteristics of the prosthesis including porosity and topographical cues. For instance, a hernia mesh needs to remain in place until tissue integration is complete which usually takes around 2–3 weeks after surgery, but the mesh can take longer to completely dissolve [143]. In wound healing applications, an electrospun hybrid-scale fiber matrix (Restrata®) composed of two synthetic biocompatible and biodegradable polymers polyglactin 910 and PDO and possessing a structure of varying fiber diameters with high porosity was approved for the healing of different types of wounds. The FDA-approved fibrous matrix undergoes resorption at a rate ideally matching the process of new tissue formation and acute wound healing over the course of 2–3 weeks, on average [144,145]. For the treatment of chronic wounds of varying etiologies in patients with different demographics, the matrix-supported treatment was required for 12–21 weeks for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) [146–148], eight weeks for post-Mohs wounds [149], eleven weeks for hematomas and complex pressure ulcers [150,151] and 23 weeks for augmented flap reconstruction of complex pressure ulcers [152]. Table 2 shows the properties of the clinically used bioresorbable surgical meshes, patches and plates along with their clinical outcomes.

### 7.1. 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 hiatal 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 [174]. The standard treatment of hernia is surgical, with mesh reinforcement to release the pressure on the tissues and decrease the complication rate [175].

OviTex®, an FDA-approved ovine polymer-reinforced bioscaffold with PP or PGA, was used in an open complex abdominal wall reconstruction (CAWR) for fifty-five patients in the Netherlands [176]. None of the patients with a surgical site infection that made direct

contact with the mesh needed mesh explantation for persistent infection involving the mesh. Hence, the reinforced mesh can withstand infectious complications and provide acceptable mid-term recurrence rates. However, longer follow-up data from prospective studies are required to determine further risk of hernia recurrence in that study [176]. In another study, a PP-reinforced tissue matrix (OviTex®) was successfully tested on 25 primary or recurrent HH repair patients. The results indicated successful relief of symptoms, no perioperative complications or recurrence of HH during the relatively short follow-up period [163]. 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®) made of PGA/TMC with an estimated resorption time of 6 months was found superior regarding recurrence (in the first 2 years) vs. non-mesh treatment [177]. Although a similar recurrence rate was noted in five years, an earlier failure rate was observed in the non-mesh group at 12 months. Low recurrence rate and complication-free recovery were demonstrated in a small study treating paraesophageal HH with Gore Bio-A® [159]. Furthermore, Bio-A® proved to be effective in long-term recurrence in the treatment of contaminated ventral hernia, where an increased risk for post-operative infection is present [160]. TIGR™ is a synthetic surgical mesh, made of two different synthetic resorbable fibers containing a distinct proportion of glycolide, lactide and TMC, resulting in a longer absorption time [70]. Although the initial results for uncomplicated inguinal repair were encouraging, in the case of complicated hernias, the recurrence and complication rates were high, leading to FDA recall. In 2018, Renard *et al.* compared the use of resorbable synthetic (Vicryl®) and biological (Strattice®) meshes to treat infected incisional hernia and found Strattice® superior to Vicryl in terms of early and late postoperative infections [158].

Recently, a slowly resorbable biosynthetic Phasix™ mesh (Fig. 6A and B) made of P4HB scaffold with PGA and hydrogel barrier was tested in the repair of large and complicated HH with either laparoscopic or robotic surgery technique resulted in promising clinical outcomes including absence of migration, stenosis, recurrence or dysphagia in 30 patients [178–181]. Furthermore, this mesh was shown to be safe and effective in high-risk incisional hernia patients during a five-year follow-up [162].

As a next generation of the meshes, a hybrid PTFE and PGA/TMC scaffold (Synecor™), selected to enhance mechanical strength and stimulate tissue proliferation and vascularization, respectively, was tested on 35 ventral hernia patients [166]. During the two-year follow-up, no recurrence occurred and the infection rate was in line with previous data. In addition, patients reported satisfaction with significant improvement, especially regarding self-esteem, and relief of pain and discomfort with only one patient needing re-operation. Based on a recent trial involving 157 patients, Synecor™ was proven safe and effective in inguinal hernia repair considering the recurrence and complication rates together with patient-reported pain [167]. 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 and two removable handles complete the device. This fixation system and the three-dimensional reinforcement material are assembled with absorbable PGLA expanders as shown in Fig. 6C–E [182]. The Parietex™ composite ventral patch has been successfully used with a low recurrence rate in different types of hernia in 48 patients and effectivity could be further induced by implementing Parietex™ composite mesh overlaid by an aponeurotic graft in large incisional hernia repairs [164,165]. A recent meta-analysis involving the comparison of synthetic, biologic, or bioabsorbable meshes for complicated ventral hernia cases reported similar results. Recurrence rate and infection were lowest in the case of the bioresorbable meshes, with similar seroma rates compared to the other two meshes implying the effectiveness of bioresorbable



**Table 2**

The characteristics of the clinically used bioresorbable surgical meshes, patches and plates along with their clinical outcomes.

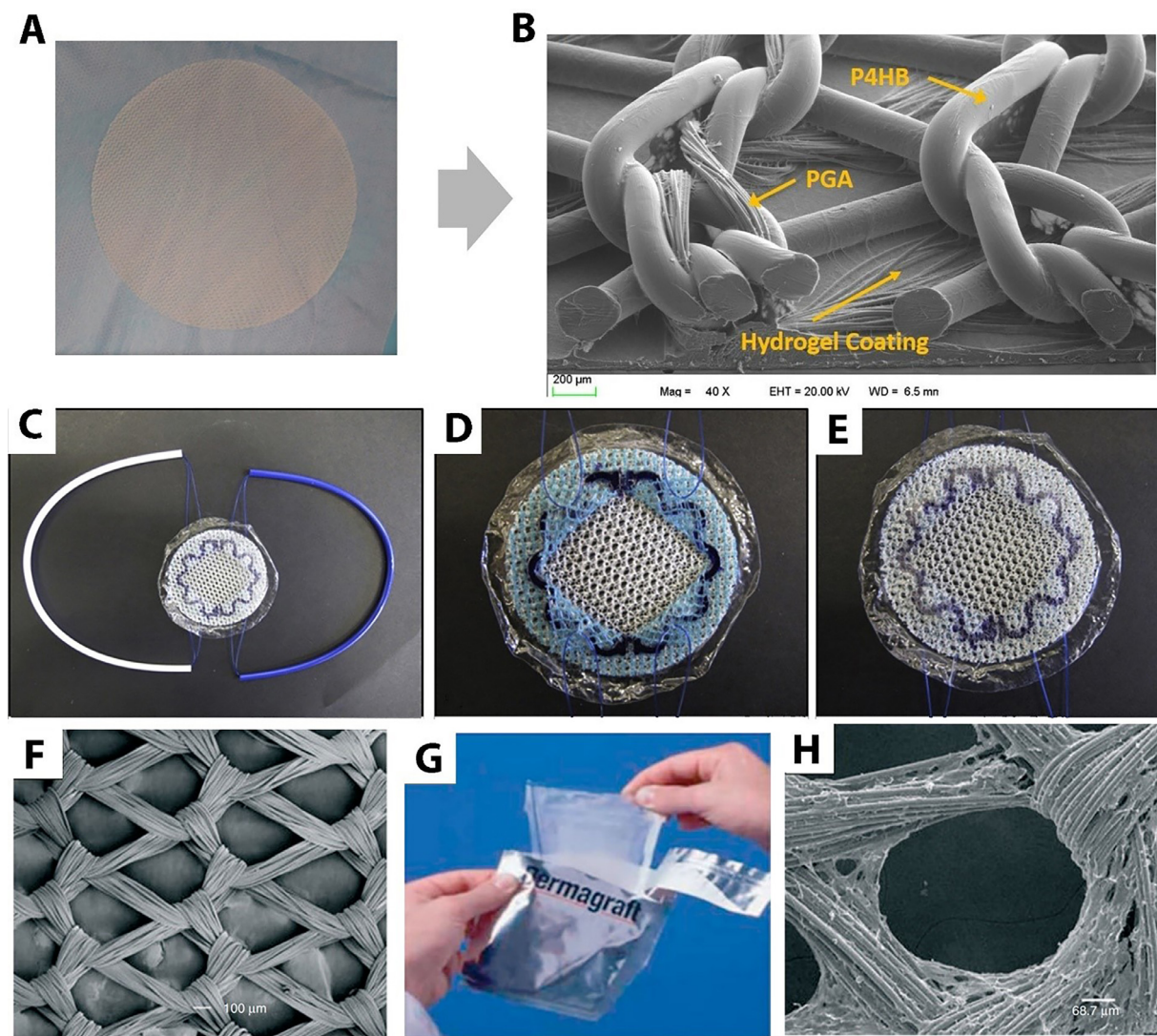
Name of the base biomaterial	Brand name	Pore size**	Resorption time	Clinical applications, <i>in vivo</i> studies
PGA	Neoveil™ Sheet	NA (nonwoven)	3 weeks	Reducing pancreas-related complications after minimally invasive surgery for gastric cancer [153]
PLA	3D-printed mesh	3 mm	1–2 years	Biocompatible mesh with efficient elasticity and tensile strength for hernia repair [154]
	Guidor®	combination of layers with different pore sizes	1 year	GBR in dentistry improves soft tissue mass in ridge preservation [155]
PDO	DuraSorb™	>1 mm	6–8 months	Successful soft tissue reinforcement e.g. in revisional breast surgery [156]
PCL	TnR Nasal Mesh; T&R Biofab Co., Ltd, Siheung, Korea)	500 µm	20 months	Corrective rhinoplasty, with good effectivity and no side effects [157]
PLGA	POLYGLACTIN 910 (Vicryl™)	2 mm	3 months	Biological mesh is superior in the surgical treatment of infected incisional hernia with a similar recurrence rate [158]
67 % PGA + 33 % TMC	Gore® BIO-A® (W. L. Gore & Associates Inc., USA)	1–3 mm	6 months	Low recurrence and no complications in the treatment of large hiatal hernia, large paraesophageal hiatal hernia, and contaminated ventral hernia [28,159,160]
glycolide + lactide + TMC P4HB	TIGR™* (Novus Scientific Ltd., Singapore) Phasix™	1–1.5 mm	26 months	Safe and effective in inguinal hernia repair [70]
		0.5–1 mm	12–18 months	Efficient and safe in case of complicated hiatal hernia and ventral hernia repair in high-risk patients [161,162]
bovine collagen + PLGA	OviTex® (TELA Bio Inc., Malvern, USA)	50–300 µm	10–12 months	Safe and effective in primary or recurrent hiatal hernia treatment [163]
polyester + collagen + PEG + glycerol	Parietex™*	1.5–1.8 mm	>18 months	Promising results were shown in different types of hernia, but safety concerns were raised [164,165]
PTFE + PGA/TMC	Gore® Synecor® (W. L. Gore & Associates Inc., USA)	1–3 mm	6–7 months	Successful in ventral and inguinal hernia repair (based on recurrence rate, complications and patients feedback) [166,167]
Synthetic PEG	CoSeal®* (Angiotech Pharmaceuticals, Inc., Canada)	NA	5–7 days	Early studies on myomectomy patients showed good results, but safety concerns were raised [168]
PLGA + fibroblasts	Dermagraft® (Organogenesis, Canton, USA)	0.5–1 mm	20–30 days	In combination with standard treatment proved to be significantly better in chronic foot ulcer treatment [169,170]
Collagen	CelGro™ (Orthocell Ltd., Murdoch, Australia)	0.5–1 mm	4 months	Successful GBR in dentistry [171]
PLLA + HA	Osteotrans MX® (TEIJIN Medical Corp., Osaka, Japan)	100–500 µm	3–5.5 years	Maxillofacial bone replacement [172]
PLLA/PGA bioresorbable osteosynthetic plate	RapidSorb® 85:15 (DePuy Synthes CMF, West Chester, USA) Lactosorb® 82:18 (Lorenz Surgical, Jacksonville, USA)	50–300 µm	12–18 months	Plate systems were used in maxillofacial surgery. Both of the systems are effective and have low complication rate, however, Lactosorb® was linked to a higher incidence of complications vs. RapidSorb® [173]

\* FDA recall.

\*\* The pore sizes are based on the factory and publication data, however, might vary depending on the application of the mesh.

meshes [28]. Furthermore, Phasix™ has demonstrated the ability to maintain 80 % and 18 % greater strength than the native abdominal wall at 8 and 72 weeks post-implantation, respectively, despite significant biopolymer degradation [183]. However, the ability of P4HB to promote the expression of the antimicrobial peptide (AMP) cathelicidin LL-37 in macrophages [184] makes this type of

surgical mesh capable of decreasing the incidence of post-operative surgical site infection when compared with other surgical meshes [185,185]. Although clinical trials are limited, the application of this material in ventral hernia repair has shown good outcomes with an effective reduction of hernia recurrence rate [186–188]. Quality of life improvements were noted with no recurrences af-



**Fig. 6.** (A) PHASIX Mesh comprised of a fully resorbable, P4HB monofilament knitted into a flat sheet configuration. Reproduced with permission from Ref [179]. Copyright 2013 Corey R. Deeken and Brent D. Matthews. (B) SEM of Phasix™ ST Mesh (40× magnification; scale bar = 200 μm). Phasix™ ST Mesh is comprised of fully resorbable 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 HA, CMC, and PEG. Reproduced with permission from Ref [180]. Copyright 2022 Becton Dickinson (BD). (C) 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 [182]. Copyright 2015, with permission from Elsevier. (F) Polyglactin mesh, (G) Dermagraft as received from a pack, (H) dermal fibroblasts cultured on polyglactin mesh. Reproduced with permission from Ref [190]. Copyright 2010 John Wiley & Sons, Inc.

ter two years [189] despite a recurrence rate of 9 % for inguinal hernia repair observed at 18 months post-implantation [161]. A more recent five-year hernia repair follow-up of Phasix™ mesh in high-risk patients demonstrated a recurrence rate of 15.9 %, low pain scores, and no mesh-related complications or reoperations for chronic pain, confirming the potential of this biomaterial to prepare meshes for hernia repair [188]. Despite the promising results, Parietex™ was withdrawn in 2018 from FDA approval due to safety concerns in the case of parastomal hernia repair.

## 7.2. 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 [168]. The application of surgical mesh in gynecological applications, especially transvaginal mesh for POP and SUI, has been associated with safety concerns for women [191]. The transvaginal meshes were reclassi-

fied 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 in using transvaginal mesh for POP repair surgery [192]. 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 [193]. In addition, the Therapeutic Goods Administration (TGA) cancelled the approval of urogynecological meshes for POP repair surgery (through the vagina) and SUI repair surgery (single incision mini-slings) in November 2017 [194].

Several attempts were made to develop anti-adhesive membranes, such as CoSeal® which is a resorbable hydrogel made of two different synthetic PEGs. Crosslinking of the two polymers upon ejection from a syringe results in the formation of a barrier capable of inhibiting adhesion in the acute and subacute periods, getting completely resorbed within a month [168].

CoSeal® 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 [168]. Regardless of the positive early clinical data, FDA approval was withdrawn due to the potentially incomplete dissolution of PEG and its inappropriate effect on tissue integration led to safety concerns [195].

Different types of implants and meshes have tested during sarco-colpopexy surgery, for example in the treatment of vaginal prolapse, to decrease the operation-caused complications such as recurrence or infection [196]. A partially resorbable graft composed of PP and polyglycaprone showed mechanically good results without significant complications. However, the composite PP graft was withdrawn shortly after its introduction to clinical practice, leading to the use of non-resorbable polyvinylidene fluoride in sarco-colpopexy. The polymer showed similar results as far as anatomical success, patient satisfaction or complication rate are concerned [196].

### 7.3. Wound healing

Acute skin lesions such as burns or chronic lesions such as 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 the 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 the development of next-generation drugs or stimulating factor eluting meshes [197,198]. The most frequently used polymers are HA, collagen, and PLGA exhibiting a controlled degradation profile synergizing with epithelialization (skin healing) and PEG which induces proliferation and collagen precipitation. Other polymers include PCL with high structural properties but limited capacity against microorganisms. Polymers lacking antimicrobial activity are therefore frequently combined with Ag-NP to induce matrix proliferation in an antimicrobial environment or even sericin derived from a moth or spider combined with collagen to achieve improved resorption and antimicrobial effects in preclinical trials for burn injuries [198,199]. Several commercially available and approved polymer appliances have proved to be effective in wound healing, such as resorbable HA matrix (Hyalomatrix®) successfully used in burn injuries. Furthermore, a knitted PLGA mesh, as typically shown in Fig. 6F, was cultured with human neonatal fibroblasts leading to the development of one commercial product of cryopreserved Dermagraft® (Advanced Tissue Sciences) (Fig. 6G) [190]. The knitted PLGA meshes support homogenous cell distribution and withstand the cell contractile force (Fig. 6H) [190]. Dermagraft® was successfully applied extensively on chronic ulcers with good clinical healing results without complications [1,169,198,200].

Generally, acute wounds tend to heal within 3 weeks while chronic wounds tend to persist for a minimum of 3 months from the time of injury. A matrix with optimal handling properties and a rate of resorption ideally matched to the process of new tissue formation and wound healing [200]. Once applied to a wound, the matrix supports cellular infiltration, new tissue formation, and wound healing while progressively resorbing into the tissue over the course of 2 weeks, on average. [201].

### 7.4. Dentistry applications

In dental care, there are several conditions where GBR is indicated, in order to provide the necessary amount and quality of

bone tissue for implantology [202,203]. 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 [202,204,205]. 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. Fig. 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 (Fig. 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 (Fig. 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 (Fig. 7A(iii)). Finally, the tissue closure is performed when applicable (Fig. 7A(iv)) [206].

In the 2010s, Jung et al. 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 PTFE (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 [207].

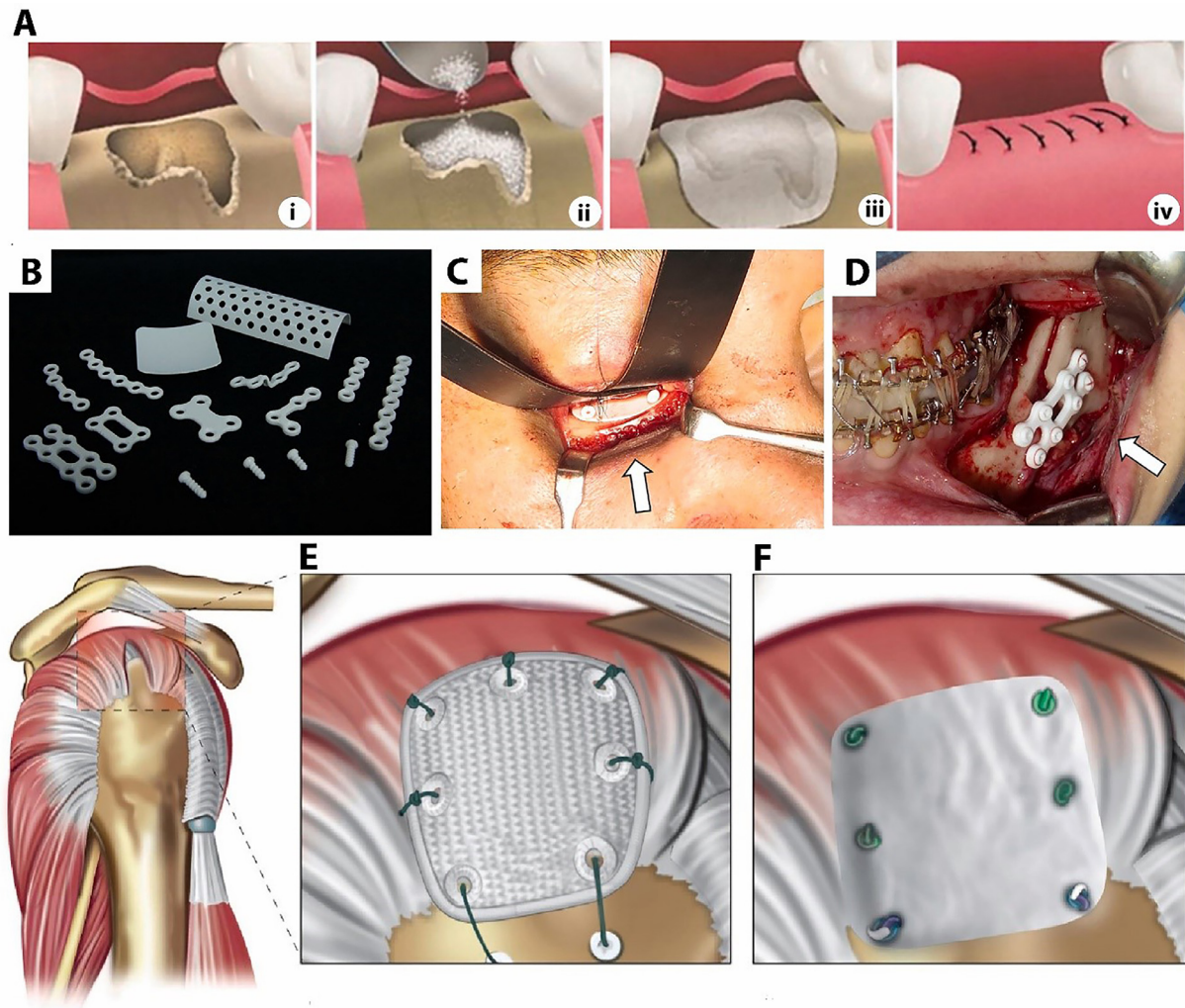
The effectiveness of collagen membranes was enhanced when used in combination with a bone graft [208]. A promising clinical outcome (9 months postoperative) was observed for using bone grafting material (BioOss) and a membrane (AlloDerm® GBR) to treat a class I ridge defect. The patient experienced significant hard and soft tissue growth [208]. 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 defects with no complications or adverse events [171]. A recent study 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 to support aesthetic implantology [209]. Furthermore, in a small study, PLA-based membrane proved to be effective in ridge preservation for soft tissue regeneration [155]. Interestingly, ridge augmentation treatment extended with platelet-rich factor or dehydrated human amnion-chorion membranes did not have a significantly different clinically visible effect on vital bone formation or augmentation compared to traditional collagen membranes. However, it caused a slight pain reduction in patients who had undergone lateral ridge augmentation, followed by mandibular ramus block harvesting [210–212].

### 7.5. Maxillofacial surgery

Facial bones could be damaged by injuries, trauma, tumor, and infection and can also be affected by congenital anomalies [213]. Results regarding the reconstruction methods of facial bones has a widely 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 [213].

In 2005, an early study investigated the use of resorbable membranes in the treatment of unilateral cleft palate in 15 participants divided into three different treatment groups: autogenous iliac bone graft (ABG) alone; ePTFE; (Gore-Tex™) membrane implanted alone; while the third group was treated with a resorbable PLA/PGA membrane, combined with ABG [214]. GBR has been found successful both with membranes and with stan-





**Fig. 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 [206]. Copyright 2018 Rodriguez IA. (B) Maxillofacial osteosynthesis system using third-generation bioactive/bioresorbable materials (Osteotrans MX®); (C) Bioresorbable sheet and tack fixation for right orbital reconstruction in a case with naso-orbito-ethmoidal (midfacial) fractures using the SuperFIXORB-MX® (OsteotransMS®) system (D) Bioresorbable plate osteosynthesis of advancement mandibular BSSRO using the SuperFIXORB-MX® (OsteotransMS®) system in orthognathic surgery. Reproduced with permission from Ref [172]. Copyright 2018, with permission from Elsevier. Application of commercial mesh and patch in tendon-to-bone interface repair: (E) 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. (F) CelGro™ for augment repair of rotator cuff tears. Torn tendon must be trimmed and anchored with sutures back into healthy bone before 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 [72]. Copyright 2022 The Authors.

dalone ABG, however, the authors reported significantly better results with combined techniques following radiological evaluation [214]. Subsequently, 3D-printed PCL meshes were successfully implemented for rhinoplasty patients supporting cartilage repair and airway opening during healing time, without considerable side effects [157].

Biodegradable polymers can also be mixed with HAP. The use of a composite product (Osteotrans MX®) composed of unsintered HAP (u-HAP)/PLLA can support fracture stabilization and re-ossification with minimal complications (Fig. 7B–D) [172]. Because they are osteoconductive and biodegradable, the u-HAP/PLLA nanocomposites can be used for complete replacement by bony tissue in addition to the advantages of early functional improvements [215]. The same research group investigated the complications related to PLLA/PGA copolymer plate and mesh systems used in maxillofacial surgery. In total, 87 patients were involved in the retrospective study which concluded that PLLA/PGA is a useful material for maxillofacial osteosynthesis, with a 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 [173]. 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 %, when PLLA/PGA meshes and plates were used for reconstruction. Furthermore, also interestingly, the authors concluded that female sex and the greater number of plates are risk factors for perioperative complications [216].

Not only synthetic but natural polymer-based membranes can be used in the treatment of intra-bony defects in the maxillofacial region [217]. With the participation of 18 patients, resorbable collagen membranes have been used to treat mandibular defects, based on HAP grafting, supported with the addition of PRP and significant bone density growth was observed on the radiography images in the 1st and 6th month after treatment [217]. Interestingly, a previous research work concluded that using collagen membrane is disadvantageous, compared to the addition of  $\beta$ -tricalcium phos-

phate because of the decreased bone regeneration, which corroborates findings related to GBR in dental applications, in comparison with titanium implants [218,219]. To overcome these challenges, a new technique and material was introduced in 2017. The method used a resorbable polymeric thermo-reversible gel, as a space-maintain approach, with a similar indication and goal as described for GBR with resorbable membranes [220]. The resorbable polymeric thermo-reversible gel was manufactured from a specific mixture of poloxamers dissolved in water (predominantly poloxamer 407) [220]. After examining the results of the 11 patients participating in the study, new bone formation was 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 a six-month follow-up. Based on the clinical outcomes, cost-effectiveness and simplicity of the technique, it is considered one of the best techniques for the maxillary sinus elevation procedure [220].

### 7.6. Other clinical applications of resorbable meshes

Besides 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 such as 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 [156,221].

Peripheral nerve injuries are common on the 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 effectiveness and persistent loss of function. To overcome this problem, resorbable materials were used in these injuries, ensuring the induction of the regeneration process, but absent by the time it could interrupt normal healing [222]. Based on preclinical results, poly[(R)-3-hydroxybutyrate (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 [222]. Furthermore, several bioresorbable nerve conduits such as polyglycolic mesh – Neurotube, porcine collagen – Rovolnerve etc., have received FDA or CE approval and showed impressive sensory outcomes (75 % of the cases were rated as good to excellent) following reconstruction of the resorbable polymers [223].

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 [96]. Poly-Tape mesh (Neoligaments Ltd., UK) is manufactured by weaving the non-absorbable polyethylene terephthalate (PET) fibers and is particularly used for rotator cuff tears (RCTs) repair (Fig. 7E). While the open woven structure of Poly-Tape supports space for tissue ingrowth, the parallel fibers provide high strength (average tensile strength for the medium and larger patches are over 400 N and 550 N, respectively) [72]. On the other hand, natural resorbable biomaterials have resulted in better biological outcomes. Recently, CelGro™ (Orthocell Ltd.), a type I collagen bilayer membrane, was 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 (Fig. 7F) [72,224]. However, this scaffold is not recommended as a structural graft because of the 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 [72].

## 8. Conclusion and future perspectives

With the rapid development of polymer material science, resorbable meshes have gained attention in clinical studies. Before clinical adaptation, 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. Avoiding 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. Nevertheless, the cost of resorbable meshes usually outvalues the burden of mesh failure associated with the high rate of non-resorbable mesh removal and morbidity, mainly due to prosthesis infection. Indeed, material biocompatibility is a key factor guiding successful mesh implantation. Using resorbable polymer meshes and plates is favorable in pediatric cases, especially in cranio-maxillofacial reconstruction procedures. In clinical applications, resorbable polymer devices provide better visibility on radiographic images, and they do not produce artefacts.

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 implantable resorbable devices, with a special focus on materials enhanced with bioactive supplements. Such studies would expectedly provide enough data essential for better consolidated decision making in the clinical setting. Surgeons can make more informed decisions for mesh selection based on the obtained knowledge of mesh material, construct weight as well as the patient's medical history, the overall status of the immune system, the origin of the disease and the nature of tissue defect.

The progressive demand for bioresorbable meshes with optimal functionality and behavior in interfacial tissues has led to the constant development and improvement of biomaterials. Hydrogel barriers, drug-loaded surface coatings, nanofibrous mats and modifications with nanoparticles have produced very promising outcomes *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 multi-functional 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 advanced prosthetic biomaterials that are fully resorbable in the long term facilitating tissue regeneration and combating infection at 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 therapeutically active agents. 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 the “time” factor to 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 improve tissue regeneration procedures fundamentally by offering functionalized, personalized, 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 need specific consideration of regulatory approval pathways.

### Declaration of competing interest

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

### CRediT authorship contribution statement

**Behzad Shiroud Heidari:** Writing – review & editing, Writing – original draft. **Jagan Mohan Dodda:** Writing – review & editing, Writing – original draft, Conceptualization. **Labiba K. El-Khordagui:** Writing – review & editing. **Maria Letizia Focarete:** Writing – original draft. **Peter Maroti:** Writing – original draft. **Luca Toth:** Writing – original draft. **Serafina Pacilio:** Writing – original draft. **Salma E. El-Habashy:** Writing – review & editing. **Joshua Boateng:** Writing – original draft. **Ovidio Catanzano:** Writing – original draft. **Nitin Sahai:** Writing – original draft. **Lingjun Mou:** Writing – original draft. **Minghao Zheng:** Writing – review & editing.

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### Data availability

The data described in the article are available at <https://zenodo.org/records/10656703>. We would appreciate if other researchers could benefit from our literature and results. This will foster discussions and collaboration among scientists worldwide.

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