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Enhancing biomaterial performance: the advantages and applications of Collagen coating

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Abstract: Collagen, the primary structural protein in the extracellular matrix, has gained significant attention as a surface modification agent for biomaterials due to its exceptional biocompatibility, bioactivity, and ability to promote cellular adhesion and proliferation. Collagen coatings enhance the integration of synthetic and natural biomaterials with biological tissues, making them highly relevant in biomedical engineering, regenerative medicine, and implantable medical devices. This review explores the mechanisms by which collagen coatings improve biomaterial properties, including their role in modulating surface chemistry, hydrophilicity, and cellular interactions. Furthermore, we discuss various coating techniques, such as adsorption, covalent binding, and electrospinning, and their implications for optimizing material performance in biomedical applications. The advantages of collagen coatings in orthopedic, dental, and cardiovascular implants, as well as wound healing and drug delivery systems, are also examined. By highlighting the potential of collagen-functionalized surfaces, this article provides insight into the future directions of biomaterial innovation aimed at improving patient outcomes and medical device efficacy.

1 Introduction

Biomaterials play a fundamental role in modern medicine, particularly in applications such as prosthetics, implants, and tissue engineering scaffolds [1,2]. However, many biomaterials, including metals (e.g., titanium and stainless steel), ceramics (e.g., hydroxyapatite), and polymers (e.g., polylactic acid and polyethylene glycol), lack the inherent bioactivity necessary for optimal integration with biological tissues [3]. A major challenge in biomaterial science is developing surfaces that support cell adhesion, proliferation, and tissue regeneration while preventing immune rejection or fibrotic encapsulation [4,5].

Collagen, as the most abundant structural protein in the ECM, provides a bioactive and biocompatible surface modification strategy that enhances cell-material interactions (Figure 1). The presence of integrin-binding sites (e.g., RGD sequences) within collagen allows for direct interaction with cell surface receptors, promoting cytoskeletal organization, cell migration, and differentiation. Furthermore, collagen coatings influence hydrophilicity, charge distribution, and protein adsorption, factors that collectively impact material performance in vivo [6,7].

The use of collagen coatings has been explored across multiple disciplines, including orthopedic and dental implantology, cardiovascular stents, wound healing, and controlled drug delivery (Table 1). Despite its numerous advantages, several challenges remain in terms of long-term stability, degradation kinetics, and large-scale manufacturing. This review provides a comprehensive analysis of collagen coating methodologies, their impact on biomaterial properties, and their biomedical applications [8]. Harnett et al. calculated the surface energy of various tissue culture substrates (polystyrene, silicon, silicon dioxide, and indium tin oxide) before and after coating with adhesion molecules (collagen, fibronectin, poly-l-ornithine, and poly-d-lysine) to assess their hydrophobicity. Wetting experiments with culture media and saline revealed that fibronectin consistently created the most hydrophobic surface, while the hydrophilicity of other coatings depended on the underlying substrate, providing insights relevant to cell manipulation and biomedical research [9].

Nagai et al. in their study examined the effect of collagen coating on titanium implants by evaluating the initial attachment of human gingival fibroblasts and their morphological changes using SEM. Results showed that collagen coating enhanced cell attachment and promoted the formation of lamellipodia and filopodia, suggesting its potential to improve peri-implant soft tissue integration [4].

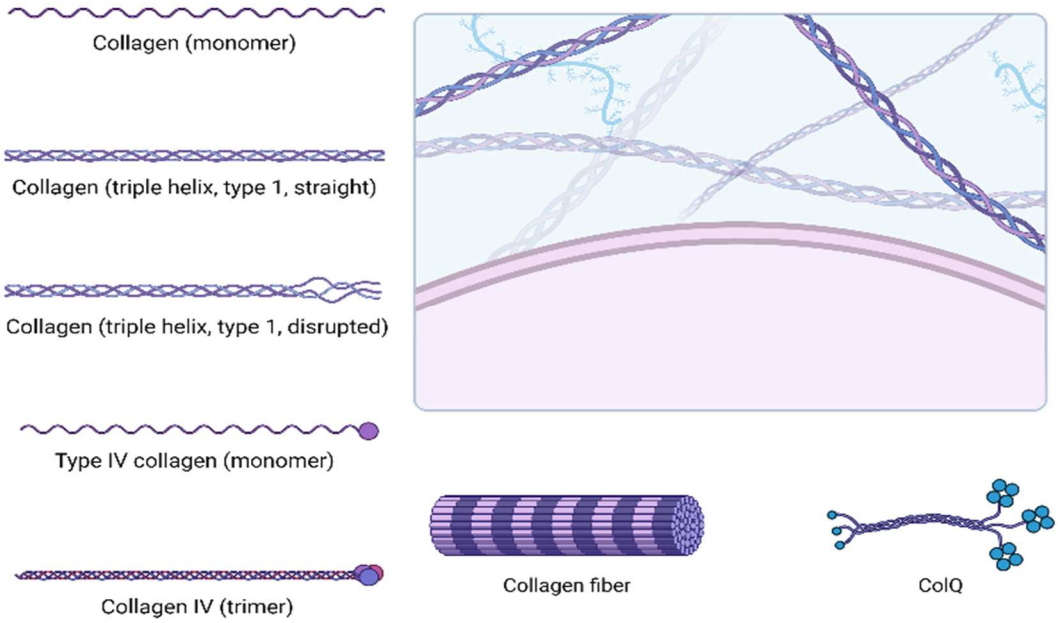

Figure 1 Different collagen structures, including monomers, triple helices, collagen IV trimers, and collagen fibers, highlighting their organization and role in the extracellular matrix (created with Biorender.com)

Table 1 Uses of collagen coating [5,10,11,12]

Application Area	Coated material	Function
Orthopedic Implants	Titanium	Improves osseointegration
Dental Materials	Hydroxyapatite	Enhances bone bonding
Cardiovascular Stents	Metal stents	Reduces thrombogenicity
Wound Dressings	Hydrogel dressings	Accelerates tissue regeneration

2 Methods of Collagen coating

The effectiveness of collagen coatings in biomedical applications depends significantly on the method used for their deposition onto biomaterial surfaces (Table 2). Various techniques have been developed to improve the adhesion, stability, and bioactivity of collagen layers, each tailored to specific applications. The selection of a coating method influences the long-term performance of the biomaterial, as it determines not only the mechanical and chemical stability of the collagen layer but also its ability to support cellular interactions [13,14].

Table 2 Methods of collagen coating [15-17]

Coating Method	Advantages	Limitations
Adsorption	Simple, cost-effective, preserves collagen structure	Weak adhesion, prone to desorption
Covalent Binding	Strong adhesion, long-term stability, bioactive sites remain functional	May alter collagen bioactivity, requires chemical modifications
Electrospinning	Mimics ECM, high porosity, supports cell growth	Complex fabrication, requires specialized equipment
Layer-by-Layer (LbL)	Tunable thickness, controlled release properties	Time-consuming, requires multiple processing steps

2.1 Adsorption method

The adsorption method is based on the spontaneous adhesion of collagen molecules onto the surface of biomaterials through non-covalent interactions, including:

- **Electrostatic forces** – Arise due to charge differences between collagen and the substrate surface.
- **Hydrophobic interactions** – Collagen adsorption is often influenced by the hydrophobicity of the biomaterial.
- **Hydrogen bonding** – Occurs between functional groups on the biomaterial and collagen molecules.
- **Van der Waals forces** – Weak interactions that contribute to molecular adhesion.

This method is widely used due to its simplicity, cost-effectiveness, and ability to preserve collagen's native structure. It is particularly effective for polymers and metallic biomaterials, where collagen can adhere passively without requiring chemical modification [17,18].

The primary advantage of adsorption is its **ease of application and preservation of collagen's native structure,** as the process does not involve harsh chemical modifications that could alter its bioactivity. This method is highly suitable for **metallic, polymeric, and ceramic biomaterials** used in orthopedic and dental implants. Additionally, it allows for **rapid processing and cost-effective production,** making it an attractive option for large-scale applications. Jacquermat et al. study investigated the supramolecular organization of collagen adsorbed on polystyrene under varying adsorption durations and drying conditions using AFM, XPS, radioassays, and wetting measurements. Results showed that collagen adsorption plateaued after 5 hours, forming a dense felt-like layer, with slow drying causing reorganization due to dewetting, while fast drying led to a more stable structure [14].

Despite its simplicity, adsorption suffers from **poor long-term stability**, as collagen layers are prone to desorption when exposed to bodily fluids and competitive protein interactions. This instability is particularly problematic in dynamic environments, such as **vascular implants**, where fluid shear forces can rapidly remove the adsorbed collagen layer. To improve adhesion, surface pre-treatment methods such as **plasma treatment, oxidation, or polyelectrolyte layering** are often employed to increase the affinity of collagen for the biomaterial [19].

2.2 Covalent binding

Covalent binding methods offer a more stable alternative to adsorption by chemically attaching collagen molecules to the biomaterial surface. This process involves the formation of permanent chemical bonds between collagen's functional groups (such as amine or carboxyl groups) and reactive sites on the biomaterial. Covalent immobilization is widely employed in applications requiring long-term bioactivity and resistance to enzymatic degradation, such as load-bearing implants and cardiovascular grafts [20,21].

Yang et al. modified poly(L-lactic acid) (PLLA) by covalently grafting collagen via gamma irradiation with poly(acrylic acid) as a coupling agent, achieving a dose-dependent grafting yield exceeding 7% at 21 kGy. Characterization by XPS, swelling experiments, and immunostaining confirmed successful collagen attachment, crosslinking, and retention of biologically active binding sites, demonstrating the potential of this method for enhancing scaffold biocompatibility in tissue engineering [22].

2.2.1 Crosslinking strategies for Covalent binding

Several chemical crosslinking strategies have been developed to achieve covalent binding of collagen to biomaterials:

- **Glutaraldehyde Crosslinking:** This approach involves the reaction between aldehyde groups and primary amines on collagen and biomaterial surfaces, forming Schiff base linkages. While highly effective, residual glutaraldehyde can be cytotoxic, necessitating additional washing or neutralization steps.
- **Carbodiimide Chemistry (EDC/NHS):** This method activates carboxyl groups on collagen, allowing their reaction with amine-containing biomaterials to form stable amide bonds. This technique is more biocompatible than glutaraldehyde crosslinking and retains collagen's bioactivity.
- **Diisocyanate Crosslinking:** This strategy forms urethane linkages between hydroxyl or amine groups of collagen and biomaterials, commonly used for polymeric scaffolds [23].

Covalent immobilization significantly improves coating stability, durability, and mechanical resilience, making it ideal for implants and scaffolds that must maintain bioactivity over long periods. However, excessive crosslinking can reduce the natural flexibility and bioactivity of collagen, potentially altering its ability to interact with cells. To mitigate this, dual crosslinking strategies that combine synthetic and enzymatic crosslinkers (e.g., genipin) are being explored [24].

Myles et al. study developed a method to covalently couple adhesion peptides containing the arginine-glycine-aspartic acid (RGD) sequence to type I collagen monomers before fibrillogenesis, using a heterobifunctional coupling agent to form stable bonds. The modified collagen retained similar microstructure and gelation properties as unmodified collagen, while enhancing cell adhesion in a dose-dependent manner, demonstrating its potential for controlled cell localization in tissue engineering applications [16].

2.3 Electrospinning

Electrospinning is a versatile technique that allows for the deposition of collagen nanofibers onto biomaterial surfaces, creating a highly structured, biomimetic coating that closely resembles the extracellular matrix (ECM). This process involves applying a high-voltage electric field to a collagen solution, which causes the formation of ultrafine fibers that are collected onto a substrate. The resulting coatings exhibit high porosity, controlled fiber orientation, and tunable mechanical properties, making electrospinning particularly useful for tissue engineering, wound healing, and scaffold fabrication [25].

Dupont-Gillian's study developed a strategy to create nanoscale polymer surface architectures by adsorbing

collagen onto PMMA, drying it at different rates, and then spin-coating PMMA solutions over it. The resulting surfaces, analyzed by AFM and XPS, showed that collagen layers influenced PMMA dissolution and redeposition, enabling the formation of controlled surface topographies with pits or cavities depending on drying conditions and PMMA concentration [15].

3 Discussion

The findings presented in this review highlight the critical role of collagen coatings in enhancing biomaterial performance across various biomedical applications. By modifying surface chemistry, hydrophilicity, and bioactivity, collagen coatings improve cellular interactions, thereby promoting adhesion, proliferation, and integration with biological tissues. These effects are particularly beneficial in implantology, tissue engineering, and regenerative medicine, where successful biomaterial integration is paramount [26,27].

One of the most significant advantages of collagen coatings is their ability to enhance cell adhesion through integrin-mediated interactions. Studies demonstrate that the presence of collagen coatings on metallic and polymeric substrates leads to increased cellular attachment and spreading, as observed in titanium implants for dental and orthopedic applications. The formation of lamellipodia and filopodia on collagen-coated surfaces further indicates improved cytoskeletal organization and migration potential, factors that are crucial for tissue regeneration [7,21].

Additionally, collagen coatings influence biomaterial hydrophilicity, which plays a vital role in protein adsorption and cellular response. Hydrophilic surfaces are generally more favorable for cell attachment, and collagen's ability to modulate this property provides a strategic advantage in designing biomaterials tailored for specific applications. However, variations in collagen layer stability across different coating techniques present a challenge. Adsorbed collagen layers, while simple and cost-effective, often lack long-term stability due to weak non-covalent interactions, which may lead to desorption under physiological conditions. Conversely, covalent immobilization offers greater durability but may require additional processing steps to preserve collagen's bioactivity and structural integrity [28,29].

Despite the numerous advantages, some challenges remain. The long-term stability, degradation kinetics, and cost-effectiveness of collagen coatings require further investigation to optimize their clinical translation. Additionally, batch-to-batch variability in collagen sources and differences in coating methodologies can impact reproducibility, necessitating standardized protocols for biomedical applications [13,30].

4 Conclusion

Collagen coatings have emerged as a powerful strategy for enhancing the bioactivity and biocompatibility of biomaterials across various biomedical applications. By promoting cell adhesion, proliferation, and integration with biological tissues, collagen-functionalized surfaces play a critical role in improving the performance of orthopedic implants, dental materials, cardiovascular devices, wound dressings, and drug delivery systems. The selection of an appropriate coating technique—whether adsorption, covalent binding, or electrospinning—significantly influences the stability, functionality, and long-term efficacy of collagen coatings [5].

Despite their numerous advantages, challenges such as coating degradation, variability in collagen sources, and large-scale manufacturing constraints must be addressed to optimize clinical translation. Future research should focus on refining coating methodologies, developing crosslinking strategies that balance stability with bioactivity, and exploring novel biomaterial-collagen composites for advanced regenerative medicine applications. By continuing to innovate in this field, collagen coatings hold immense potential to improve patient outcomes, enhance medical device performance, and contribute to the next generation of biomaterial development [7,17].

While collagen is a widely used biopolymer for surface modification, other polymers such as chitosan, alginate, polyethylene glycol (PEG), and polylactic acid (PLA) have also been explored for their bioactive properties. These polymers offer unique advantages, including antibacterial effects, controlled degradation rates, and tunable mechanical properties, making them suitable alternatives or complementary materials to collagen in biomedical applications [31,32].

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