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用于糖尿病伤口治疗的水凝胶研究进展

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摘　要:糖尿病伤口是糖尿病的常见并发症,具有发病机制复杂、伤口易感染难愈合等特点。为了清除感染、缓解伤口炎症和防止坏死,多种功能性水凝胶被成功研制并作为伤口敷料用于消除病原体感染,根据功能不同,水凝胶可分为抗菌水凝胶、抗炎水凝胶及多功能水凝胶。其中,根据作用原理不同,抗菌水凝胶又包括固有抗菌水凝胶、负载抗菌剂水凝胶及触发式抗菌水凝胶。水凝胶在糖尿病伤口的治疗取得了一定的进展,但其仍然存在如成本过高、吸水性不足等问题,有待进一步完善。该文系统总结了功能性水凝胶应用于糖尿病伤口的研究进展,可为糖尿病伤口的临床治疗提供新思路。

关键词:糖尿病伤口;伤口敷料;水凝胶;抗菌水凝胶;抗炎水凝胶;多功能水凝胶

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The research progress of hydrogels for diabetic wound treatment

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Abstract: Diabetic wounds are common complications of diabetes, characterized by complex pathogenesis, susceptibility to infection, and difficulty in healing. To eliminate pathogenic infections, alleviate wound inflammation, and prevent necrosis, various functional hydrogels have been successfully developed as wound dressings. Based on their different functions, hydrogels can be categorized into antibacterial ones, anti-inflammatory ones, and multifunctional ones. Among them, antibacterial hydrogels can be further divided into intrinsic antibacterial ones, drug-loaded antibacterial ones, and triggerable antibacterial ones, depending on their mechanisms of action. While hydrogels have made progress in the treatment of diabetic wounds, there are still some to-be-improved issues such as high cost, and insufficient water absorption. This article systematically summarizes the research progress of functional hydrogels applied to diabetic wounds, aiming to provide new ideas for the clinical treatment of diabetic wounds.

Key words: diabetic wound; wound dressing; hydrogels; antibacterial hydrogel; anti-inflammatory hydrogel; multifunctional hydrogel

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0 引 言

糖尿病伤口是指在糖尿病患者身体上出现的难以愈合或缓慢愈合的创伤。糖尿病伤口是糖尿病并发症之一,通常由于长期高血糖水平引起的血管、神经和免疫系统的损害而导致[1]。糖尿病伤口可能在皮肤上、足部或其他部位产生,严重时可导致溃烂、感染、坏疽,甚至需要截肢[2]。

糖尿病伤口的形成与多种因素密切相关。首先,长期高血糖水平可引起糖尿病患者的局部血管损伤,导致血液循环不良,氧气和营养物质供应不足,从而影响伤口的愈合[3]。其次,神经损伤会导致糖尿病患者对伤口的疼痛和感觉减弱,使其无法及时发现和处理伤口,从而增加感染的风险[4-5]。此外,免疫系统功能受损使糖尿病患者更容易受到感染,从而伤口难以愈合[6]。

伤口敷料主要包括水凝胶[7-8]、纤维敷料[9-12]、泡沫敷料[13-14]等。理想的伤口敷料应具有以下优势:a)组织相容性良好;b)保湿性好,能保持伤口的湿润环境;c)有足够的物理和机械强度,保持其完整性;d)具有促细胞黏附、增殖和分化的功能。水凝胶是一类高度水合的聚合物网络,具有细胞友好的水环境、良好的生物相容性,以及可调控的机械性能等优势。在生物材料领域,水凝胶被作为伤口敷料得到广泛研究与应用,包括药物递送、伤口敷料、微组织等[15]。目前,基于水凝胶的伤口敷料在糖尿病伤口应用中取得了显著进展。相较于传统敷料,水凝胶的优势在于:a)有益于精准控制伤口的湿润度,减少细菌滋生和感染风险;b)由于可控的机械性能,水凝胶可减少伤口撕裂和疼痛;c)水凝胶的可控降解性使其能根据伤口的大小或深度调控吸收和保护能力,减少频繁更换敷料对伤口的损伤,增强伤口实时检测便捷性;d)水凝胶材料易与其他材料或药物复合,赋予更多的扩展性。尽管如此,水凝胶还是面临着成本较高、吸水能力不足、不适用于大面积伤口等问题。

本文概述了可用于糖尿病伤口治疗的功能性水凝胶的最新研究进展。功能性水凝胶可以针对糖尿病伤口特点促进糖尿病伤口愈合。基于不同的功能,水凝胶可分为抗菌水凝胶、抗炎水凝胶及多功能水凝胶。

1 抗菌水凝胶在糖尿病伤口的应用研究

糖尿病伤口环境的性质导致伤口感染的几率很高,这也导致了细菌感染成为阻碍糖尿病患者伤口愈合的主要因素[16]。除了抗生素之外,目前已开发出了多种现代抗菌方法,如无机抗菌纳米粒子、抗菌阳离子多肽、光动力疗法(Photodynamic therapy, PDT)、光热疗法(Photothermal therapy, PTT)等。将这些方法与水凝胶应用相结合,可以显著提高治疗效果。根据水凝胶发挥抗菌作用原理不同,抗菌水凝胶可分为三类:a)负载抗菌剂水凝胶;b)固有抗菌水凝胶;c)触发式抗菌水凝胶。

1.1 负载抗菌剂水凝胶

水凝胶作为广泛应用的药物载体具有独特的优点,高度吸水性和可调控的释放速率使其能够有效稳定药物,实现持续而精确的药物释放,从而提高治疗效果并减少副作用[17]。并且,水凝胶材料的网格结构和易修饰性使其可携带多种不同类型的药物、生长因子或生物活性物质(表1),实现组合治疗或针对多个治疗目标。

表1 水凝胶中不同抗菌成分分类

抗菌剂分类	抗菌成分	抗菌种类
抗生素	环丙沙星[18]、莫西沙星[19]、庆大霉素[20]	革兰氏阴性菌
	氨苄西林[21]、四环素[22]、多西环素[23]、阿莫西林[24]	革兰氏阳性菌,革兰氏阴性菌
金属离子	Ca^{2+}[25-26]、Cu^{2+}[26-27]、Ag^{+}[28]、Fe^{3+}[29]、Zn^{2+}[25,30-31]	金黄色葡萄球菌,大肠埃希菌
金属纳米颗粒	Ag NPs[32-35]、ZnO NPs[25,36-37]、Cu NPs[38-39]、Au NPs[40]	金黄色葡萄球菌,大肠埃希菌
天然提取物及抗菌肽	单宁酸[17,41]、丝素蛋白[42]、姜黄素[43]、芦荟大黄素[44]、虫草素[45]、抗菌肽[46-47]	金黄色葡萄球菌,大肠埃希菌

从表1可见,抗生素仍然是目前临床上最常使用的抗菌手段,将抗生素搭载到水凝胶上可以使得抗生素仅在局部发挥作用,降低抗生素用量,提高生物相容性。根据报道,大量抗生素被封装在水凝胶中以制备成抗菌伤口敷料,包括环丙沙星[18]、氨苄西林[21]、四环素[22]等。但是,抗生素的过度使用导致耐药细菌数量增加。

金属离子如 Ag^{+}、Cu^{2+} 和 Zn^{2+} 是众所周知的抗菌剂,并已普遍应用于伤口的治疗[48]。Li等[25]将 Ca^{2+} 和 Zn^{2+} 搭载到海藻酸钠水凝胶上,能够抑

制细菌生长并促进伤口愈合。利用无机金属制备而成的纳米颗粒(Nanoparticles, NPs)合成技术不断进步,使得将抗菌纳米颗粒加入水凝胶中用于伤口愈合称为可能。在各种金属 NPs 中,Ag NPs 和 ZnO NPs 的应用范围最广。Xie 等[32]所研发出的含有 Ag NPs 的壳聚糖基水凝胶具有更好的机械性能和抗菌性能。Khorasani 等[36]所制备的水凝胶中 ZnO NPs 表现出广谱抗菌能力,可改善伤口愈合。

除此之外,一些天然提取物如生物碱、类黄酮、萜类化合物等都被广泛研究并作为抗菌材料搭载到水凝胶上[17]。Jing 等[42]发现由丝素蛋白和单宁酸制备的杂化水凝胶可以抑制细菌活性,并促进伤口愈合。抗菌肽(Antimicrobial peptides, AMPs)也是一类天然产生的蛋白质分子,具有广谱的抗菌活性,可以对抗多种细菌、病毒和真菌[49]。天然抗菌肽通常具有较好的生物相容性,减少对人体的不良影响[46]。Hou 等[46]制备的 GC/EPL 冷冻凝胶由于搭载了乙二醇壳聚糖(GC)和 e-聚赖氨酸(EPL)抗菌肽,表现出了优异的抗菌功效,可以显著加快伤口愈合。Lin 等[47]将 AMP Tet213 固定在水凝胶上,对包括 MRSA 在内的多种细菌表现出了抗菌活性。

1.2　固有抗菌水凝胶

固有抗菌水凝胶是一类具有天然或固有的抗菌活性的水凝胶材料,其抗菌性能不依赖于外部添加的抗菌剂。固有抗菌水凝胶通过材料本身的特性来实现对细菌的抑制和消除,从而在伤口治疗和感染防治中发挥重要作用,因此固有抗菌水凝胶具有持久抗菌性、长久有效性并降低对组织的细胞毒性等优点。Chi 等[50]利用具有天然抗菌特性的壳聚糖制备的水凝胶微针敷料显著促进伤口愈合,这是由于壳聚糖能与细菌细胞壁和细胞膜上的阴离子基团相互作用并破坏生物膜。Chen 等[51]利用希夫碱反应将氧化魔芋葡甘聚糖(Konjac glucomannan, KGM)和壳聚糖反应形成水凝胶,该种水凝胶对金黄色葡萄球菌(革兰氏阳性菌)和大肠埃希菌(革兰氏阴性菌)具有优异的抗菌活性,杀灭效率分别为 96%和 98%。Hoque 等[52]利用阳离子壳聚糖衍生物 N-(2-羟丙基)-3-三甲基壳聚糖氯化铵(Hydroxypropyltrimethylammonium chloride chitosan, HTCC)和生物黏附聚合物聚葡聚糖醛原位开发而成的水凝胶可以通过破坏细菌膜来灭活包括耐甲氧西林金黄色葡萄球菌(Methicillin-resistant Staphylococcus aureus, MRSA)在内的细菌,并且对伤口愈合也有促进作用。

与负载抗菌剂水凝胶相比,固有抗菌水凝胶不仅避免了细菌耐药性,还可减少由于药物释放或药效衰减后更换水凝胶导致的伤口损伤风险[53]。并且固有抗菌水凝胶普遍具备较强的抗菌广谱性。例如 Kito 等[54]利用抗菌肽 α-聚赖氨酸(Alpha-poly-l-lysine, PLL)制备水凝胶,并发现其可诱导革兰氏阴性菌和革兰氏阳性菌死亡。然而,固有抗菌水凝胶导致细菌膜破裂裂解的机制并不完全明确,伤口微环境(如湿度、pH 值、活性因子等)是否改变固有抗菌水凝胶的拓扑结构、机械性能、黏附性能等物理化学性质以调节其抗菌效果仍有待研究。

1.3　触发式抗菌水凝胶

触发式抗菌水凝胶是一种智能型水凝胶,它能够在受到特定刺激时释放抗菌物质,并有效抑制细菌的生长和扩散。触发式抗菌水凝胶具有较高的选择性及广谱抗菌活性。触发式抗菌水凝胶的刺激类型主要包括光照、温度、pH 值、化学物质、生物分子等。鉴于修复急性期的 pH 值较低,研究者们开发出了一些在酸性 pH 值下增强释放的水凝胶。例如,在酸性条件下通过降低单宁酸与金属离子之间的配位来制备单宁酸释放的抗菌抗炎水凝胶[55]。

光照作为触发式抗菌水凝胶主要的触发方式,包括 PTT 和 PDT 两种。PTT 是一种通过近红外(700～1100 nm)辐射光热剂产生伤口局部高温的热疗抗菌手段。Liu 等[56]将没食子酸修饰的银(GA-Ag)纳米颗粒嵌入水凝胶的网络结构中,作为光热剂的 GA-Ag 纳米颗粒在 808 nm 的近红外辐射帮助下赋予水凝胶快速有效的抗菌活性。Zhao 等[57]所开发水凝胶通过儿茶酚－Fe^{3+} 发挥协同作用,使水凝胶具有良好的光热灭菌活性。

与 PTT 不同,PDT 主要依靠辐照光敏剂后 ROS 的产生。根据光敏剂的不同,所产生的 ROS 包括单线态氧、羟基自由基等,它们具有强氧化活性,从而对细胞造成氧化损伤。Mao 等[58]开发的 Ag/Ag@AgCl 水凝胶暴露于模拟可见光后,增强了 ZnO 的光催化和抗菌活性,95 min 内杀死 95.98%的大肠埃希菌和 49.20%的金黄色葡萄球菌。

2　抗炎水凝胶在糖尿病伤口的应用研究

糖尿病伤口组织在炎症期的初始阶段产生各种促炎细胞因子和趋化因子,导致中性粒细胞和巨噬细胞在受伤部位浸润。中度炎症有助于去除坏死组织,杀死局部细菌并促进伤口愈合。然而,过度的炎

症浸润会干扰正常的愈合事件,如胶原蛋白沉积、血管生成和肉芽组织形成。因此,必须将伤口中的炎症精确调节到适合促进伤口愈合并且避免阻碍伤口愈合的水平。抗炎水凝胶通常从以下两种途径对炎症进行改善:a)促进巨噬细胞由M1(促炎型)向M2(抗炎型)转化;b)促进螯合趋化因子,清除活性氧。

2.1 用于促进巨噬细胞由M1向M2转化的抗炎水凝胶

早期炎症型(M1)巨噬细胞积累和过度炎症是糖尿病伤口中常见的问题,这会导致糖尿病伤口修复受到阻滞。因此,具有免疫调节能力的水凝胶在糖尿病伤口愈合的临床实践中具有很大的前景[59]。Saleh等[60]研发的负载有miR-223 5p模拟物(miR-223*)的水凝胶,其中miR-223*可控制伤口愈合过程中的巨噬细胞向抗炎(M2)表型极化,这改善了伤口愈合过程中的过度炎症反应。Yang等[61]制备的透明质酸基水凝胶,其中引入的芍药苷(paeoniflorin)能显著促进巨噬细胞从M1到M2的极化,这一结果伴随着炎症、血管生成、再上皮化和胶原沉积的改善。此外,近年来无添加剂的水凝胶逐渐成为热点,科研人员通过修饰水凝胶材料或调控水凝胶的机械性能、拓扑结构等调控水凝胶的生物功能。Qian等[62]开发了一种具有内在免疫调节特性的新型甘草酸(Glycyrrhizic acid, GA)杂化水凝胶,该水凝胶可以调节炎症微环境中的巨噬细胞反应,并避免使用任何添加剂,以促进糖尿病伤口的快速愈合。

2.2 可用于螯合趋化因子,清除活性氧的抗炎水凝胶

伤口中过多的活性氧(Reactive oxygen species, ROS)和趋化因子都会导致炎症细胞的过度浸润,炎症反应加深。Zhang等[63]研发的杂化水凝胶具有高吸水性(聚丙烯酸)和抗氧化特性(聚酯酰胺),使其能够吸收渗出物并与之相互作用,从而清除ROS。葡聚糖具有出色的保水能力,可作为ROS的温和清除剂,并减少血小板过度活化[64]。Qiu等[65]利用羧基甜菜碱葡聚糖和磺基甜菜碱葡聚糖构建了基于两性离子葡聚糖的水凝胶,该水凝胶具有出色的抗氧化能力,并且相比于商业化伤口敷料具有更好的促进伤口愈合能力。Lohmann等[66]定制了一种基于肝素衍生物的模块化水凝胶,有效螯合炎症趋化因子IL-8、巨噬细胞炎症蛋白-1和单核细胞化学引诱蛋白-1,抑制了人单核细胞和中性粒细胞的迁移。

3 多功能水凝胶在糖尿病伤口的应用研究

糖尿病伤口的愈合过程复杂多变,因此在不同阶段有不同需求。例如,在炎症阶段需要抗氧化功能;在组织重塑阶段需要促进细胞增殖和分化;在整个伤口愈合阶段,需要提供一定浓度的氧气[67]。目前,市面上一种名为Mepilex(莫尔博尔)的多功能水凝胶,具有渗出液吸收和防止伤口感染的功能,适用于糖尿病多种伤口类型。

Li等[68]设计了一种由鸟苷、2-甲酰基苯硼酸和腐胺组成的鸟苷四联体水凝胶能有效清除金黄色葡萄球菌及铜绿假单胞菌,并且降低伤口周围葡萄糖浓度,从而结合抗菌和缓解伤口微环境功能,显著促进糖尿病伤口愈合。Yin等[69]开发了一种基于镁有机框架的多功能微针贴片,可实现糖尿病患者的透皮给药和联合治疗,该凝胶通过释放Mg和没食子酸可以诱导细胞迁移,清除活性氧,促进胶原沉积,并促进血管生成。Zhou等[70]研发了一种抗三明治结构光电子水凝胶,可以有效清除MRSA,促进新生血管生成,以及降低炎症反应。Yang等[71]开发了一种基于单宁酸(Tannic acid, TA)的水凝胶创可贴,该水凝胶具有优异的耐湿黏附性和器官止血性,优异的抗炎、抗菌和抗氧化性能,并且可有效促进糖尿病小鼠皮肤切口和缺损的恢复。Di Luca等[72]利用明胶—姜黄素偶联物和聚乙二醇二甲基丙烯酸酯进行聚合所得到的水凝胶具有抗氧化能力,并且有效抑制MRSA的增殖。Chen等[73]开发了一种由乙二醇壳聚糖和新型可生物降解希夫基交联剂双官能团聚氨酯制备一种多功能冷冻凝胶生物材料,具有抗菌活性和生物降解性,可以有效促进慢性糖尿病伤口愈合。

4 结论与展望

与正常伤口愈合相比,糖尿病引起的伤口愈合过程更为复杂,自我条件环境更为不利,长期暴露在外界环境中会大大增加感染的几率。同时,慢性期持续的炎症环境和高血糖造成的血管屏障,大大延缓了伤口的愈合。而在过去的几十年中,水凝胶已成为最具竞争力的伤口敷料候选材料,并且在伤口敷料的应用中呈逐年增加的趋势。本文综述了水凝胶在糖尿病伤口愈合过程中的作用,展示了水凝胶在糖尿病伤口中的应用潜力。

近年来糖尿病伤口水凝胶正朝抗菌、抗炎和多功能化的方向发展,不同负载型和非负载型水凝胶

的抗菌、抗炎机制不断被揭示与深化。传统抗生素引起的细菌耐药问题饱受诟病,因而如今的水凝胶逐步发生从抗生素递送到其他抗菌物质递送的转变,如金属和金属纳米颗粒、阳离子、抗菌肽、天然产物中的抗菌成分递送。水凝胶也出现了抗菌策略的转变,如光热、光动力抗菌和多功能协同抗菌策略等。

同时,水凝胶在抗炎、调控伤口免疫微环境、促血管化等方向也不断被研究。但伤口的炎症水平是动态的,巨噬细胞的表型根据伤口微环境而变化,目前的敷料缺乏精确调节巨噬细胞表型以达到可预测的理想结果的能力。伤口修复过程通常是复杂、动态的,例如,在伤口愈合的炎症噬菌体期间控制炎症很重要,但在伤口修复的其他时期则没有必要。此外,伤口敷料中装载的细胞、细胞因子和功能成分通常仅在特定时间需要,而在其他时间,它们甚至可能发挥相反的效果。因此,响应型材料和炎症响应激活的水凝胶可能成为突破伤口环境动态调控的研究新思路。得益于近年来许多复合多功能水凝胶的出现,针对复杂伤口修复的多功能水凝胶具有极大的发展潜力。通过将抗炎、抗菌、伤口微环境调控功能与内源或外源响应功能结合,未来水凝胶在糖尿病伤口治疗的发展方向包括智能化和个性化治疗、创新的药物载体、生物材料整合、纳米技术的应用、个体化医疗和更多的临床研究验证。这些发展方向旨在提高治疗效果、减轻患者痛苦,并为糖尿病患者的伤口管理提供更先进的解决方案。

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