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抗炎性水凝胶对糖尿病创面愈合的研究进展

王秀娟[1]，李　毅[2*]

[1]青海大学临床医学院，青海　西宁
[2]青海大学附属医院烧伤整形外科，青海　西宁

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摘　要

糖尿病可导致多种并发症，由于高血糖、高水平的氧化应激和炎症以及易受感染等不利因素导致糖尿病慢性伤口难以愈合甚至恶化。如糖尿病足、糖尿病溃疡创面等这是糖尿病患者死亡的重要原因之一。与正常伤口相比，糖尿病创面难愈合的因素最重要的是巨噬细胞的活化失调，M1不能及时转化为M2，炎症期延长，炎症因子过度表达，阻碍转化成M2抗炎的状态，降低抗炎因子的活性，这就使得糖尿病创面炎症表达过高，不能通过自愈能让创面愈合。目前水凝胶已成为伤口敷料研究的热点材料。水凝胶能提供一个最佳的伤口水分水平的控制，因为它能够吸收多余的液体从伤口或释放水分的需要。水凝胶由于含水量高、生物相容性好、传递药物等优点，与纱布等传统敷料相比，水凝胶敷料可以提供有利于伤口愈合的湿润环境。水凝胶敷料还具有优异的组织粘附、抗菌能力、抗氧化和炎症调节作用等，在伤口敷料中具有广阔的前景。本文基于水凝胶材料的特点和糖尿病慢性创面的微环境，总结了近年来新型抗炎性水凝胶敷料治疗糖尿病慢性创面的研究进展，并探讨了目前水凝胶敷料的缺点和展望，让糖尿病伤口的个性化管理和治疗成为可能。

关键词

糖尿病创面，巨噬细胞的活化，抗炎水凝胶

Research Progress of Anti-Inflammatory Hydrogels on Diabetic Wound Healing

Xiujuan Wang[1], Yi Li[2*]

[1]School of Clinical Medicine, Qinghai University, Xining Qinghai
[2]Department of Burn Plastic Surgery, Affiliated Hospital of Qinghai University, Xining Qinghai

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*通讯作者。

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Abstract

Diabetes can lead to a variety of complications, due to high blood sugar, high levels of oxidative stress and inflammation, as well as susceptibility to infection and other. adverse factors that make diabetic chronic wounds difficult to heal or even worsen. Such as chronic wounds, diabetic feet, diabetic ulcer wounds, etc. This is one of the important causes of death in diabetic patients. Compared with normal wounds, the most important factor that makes diabetic wounds difficult to heal is the dysactivation of macrophages, M1 cannot be converted into M2 in time, and the overexpression of inflammatory factors prevents the transformation into anti-inflammatory factors. As a result, the inflammatory expression of diabetic wounds is too high, and the wound cannot be healed through self-healing. At present, hydrogels have become a hot material in wound dressing research. Compared with traditional dressings such as gauze, hydrogel dressings can provide a moist environment conducive to wound healing due to their high water content, good biocompatibility and drug delivery. Hydrogel dressings also have excellent tissue adhesion, antibacterial ability, anti-oxidation and inflammation regulation, etc., and have broad prospects in wound dressings. Based on the characteristics of hydrogel materials and the microenvironment of diabetic chronic wounds, this paper summarizes the research progress of new anti-inflammatory hydrogel dressings for the treatment of diabetic chronic wounds in recent years, and discusses the shortcomings and prospects of current hydrogel dressings, so as to make personalized management and treatment of diabetic wounds possible.

Keywords

Diabetes Wound, Activation of Macrophages, Anti-Inflammatory Hydrogel

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1. 糖尿病创面

1.1. 糖尿病创面发病机制

全球成人(20~79 岁)糖尿病患者为 2.85 亿人，到 2030 年将增加到 4.39 亿人。随着全球 2 型糖尿病患病率的急剧上升，慢性、难愈合或不愈合的糖尿病伤口和溃疡的病例预计会增加[1]。糖尿病会导致多种并发症如慢性创面，糖尿病创面是糖尿病常见的严重并发症。由于治疗过程差，花费高和死亡率高，糖尿病伤口的治疗和护理已成为一个全球性的挑战[2]。糖尿病性高血糖会导致多种全身并发症，引起一系列在伤口微环境中表现出来的局部病理，包括慢性炎症、血管生成失调、缺氧诱导的氧化应激、神经病变、晚期糖基化终产物和神经肽信号受损，对患者生活和社会医疗系统均造成较大的负担[1] [3] [4]。伤口愈合通常经过一般阶段，如止血、炎症、增殖、上皮化和组织重塑。许多慢性伤口在愈合过程中不能完成所有这些阶段[2] [5]。而在糖尿病伤口中，导致了各个阶段的功能失调，使创面难愈合[6] [7]。正常的伤口愈合过程是由成纤维细胞、内皮细胞、吞噬细胞和血小板协调的协调重塑过程，由一系列生长因子控制。在与糖尿病相关的伤口中，这些协调过程是功能失调的[8]。在患有糖尿病不愈合伤口的患者中，伤口单核细胞衍生的巨噬细胞可塑性控制炎症的发生和消退，这对正常愈合至关重要，然而，在糖尿病中，炎症的消退无法发生[9]。由于四个阶段的损伤和延长，伤口愈合过程减慢甚至停滞，通常，内皮细胞功能障碍和微循环障碍经常发生在糖尿病患者中，这会导致血管生成过程受损，这一过程发生在增殖

阶段的开始[10]。糖尿病通过影响这些过程的一种或多种生物学机制导致伤口愈合受损[11]。

1.2. 糖尿病创面难愈合的因素

糖尿病伤口难愈合的因素包括细菌感染、巨噬细胞功能障碍、促炎细胞因子过多、活性氧水平高和持续缺氧等。糖尿病创面的这种微环境可导致足够的血管生成和巨噬细胞功能障碍，生成因子的平衡被打破，从而进一步延缓创面愈合。伤口修复在炎症阶段停滞不前，因此无法进行正常的伤口愈合过程，从而导致慢性伤口[12]。具体来说，控制促炎表型－抗炎表型的进展是确保从炎症阶段到愈合阶段转换的关键步骤[1] [13] [14]。这种炎症反应包括巨噬细胞的积累，巨噬细胞是愈合的重要因素，因为单核细胞/巨噬细胞的消耗会导致上皮再生延迟、胶原沉积减少、血管生成受损和细胞增殖减少[15]。巨噬细胞的极化高度依赖于伤口微环境，在愈合过程中是动态的，从而影响巨噬细胞的表型和功能。不良因素，如高血糖和细菌感染，阻碍促炎巨噬细胞的极化(M1)到抗炎巨噬细胞(M2)。然后，伤口仍处于炎症期，损害上皮再生、胶原沉积和血管生成，并阻碍伤口进入修复阶段。因此，如何促进持续性促炎巨噬细胞(M1)在伤口中成为一个极其紧迫的问题[16]。许多慢性创面由于局部组织缺血或缺血再灌注损伤而不能愈合，随着高压氧被使用，能增加氧气供应和促进愈合方面是有效的。组织水平的氧气可用性对伤口愈合至关重要[17]。大多数糖尿病伤口是慢性的，以缺氧为特征。在缺血肢体缺氧环境下，细胞存活受到限制，血管供应中断和慢性炎症引起的慢性缺氧阻碍了伤口愈合过程，因此改善伤口组织氧合以支持糖尿病足损伤组织的修复至关重要[18]。对于难以愈合的糖尿病创面，细菌感染、炎症因子的过度表达是关键因素，因此伤口治疗的关键是最大限度地提高伤口愈合率，减少细菌负担。由于感染和截肢的风险很高，干预措施的时机至关重要[19]。

2. 巨噬细胞的活化炎症因子

在糖尿病慢性伤口中，不易愈合原因主要是伤口愈合炎症期的失调，这种失调可能会进一步导致伤口无法愈合，并增加感染的风险[1] [13] [14]。巨噬细胞在伤口愈合中起着核心的作用，从抑制炎症到清除细胞碎片和协调组织修复。巨噬细胞是关键的免疫细胞，首先到达损伤部位，清除碎片和病原体。然后，它们分泌的细胞因子和生长因子招募并激活成纤维细胞，这对组织修复和疤痕形成至关重要。巨噬细胞在组织中具有不同的功能，取决于局部环境和其他系统因素。伤口愈合是一个复杂的动态过程，经历了止血、炎症、增殖和重塑等不同阶段。在伤口中，巨噬细胞沿一个谱存在，其中侵袭性促炎或“M1”表型有助于组织炎症和杀菌活性，促愈合或“M2”表型促进炎症减少、生长因子分泌和组织修复。在糖尿病伤口中，促炎到抗炎的巨噬细胞表型开关受损，导致慢性炎症和伤口愈合延迟。M1 巨噬细胞具有高水平的促炎分子，产生大量的促炎细胞因子和趋化因子，如肿瘤坏死因子-a (TNF-a)、白细胞介素-1b (IL-1b)和基质金属蛋白酶 9 (MMP9)，以促进炎症的进展和清除坏死组织和细胞碎片。在接下来的阶段，经典活化的 M1 表型逐渐向交替活化的 M2 表型倾斜，巨噬细胞表型从 M1 促炎型向 M2 抗炎(促愈合)型转换的严格调控有助于修复过程的顺利进行，M2 巨噬细胞释放生长因子，如肝细胞生长因子(HGF)和胰岛素样生长因子 1 (IGF-1)，分泌细胞因子和其他因子(如 TGF-β1 和 VEGF)来协调修复过程，并促进细胞增殖、伤口修复和组织重塑[6] [20] [21]。最佳的伤口愈合依赖于高度调控的 M2 巨噬细胞反应。M2 巨噬细胞反应不足会导致伤口愈合受损[22]。由于巨噬细胞反应失调与糖尿病伤口愈合受损有关，因此巨噬细胞被认为是改善伤口愈合的治疗靶点[23]。

3. 抗炎性水凝胶

3.1. 水凝胶的性能

水凝胶由于其优异的生化和机械性能，在伤口敷料领域显示出诱人的优势[24]。水凝胶是一类具有三

维网状结构的凝胶，有利于形成一个促进适当再生的环境，作为再生和愈合过程的框架，具有良好的保湿性能和渗透性，可促进自溶清创和物质交换，还可以过度吸收伤口渗出物，限制了伤口附近微生物的生长。是开发糖尿病慢性伤口最理想的敷料选择。水凝胶模拟细胞外基质的自然环境，为细胞增殖提供合适的环境[25] [26]。水凝胶是药物输送系统中很有吸引力的载体，可以将药物输送到靶点并以可控的速率释放[27]。为了实现具有理想治疗特性的理想药物输送系统，水凝胶已被广泛尝试。水凝胶独特的物理化学和生物学特性，以及它们巨大的多样性，共同引起了人们对这些聚合物材料作为治疗剂输送系统的优秀候选者的极大关注[28]。目前使用的水凝胶通常是通过添加化学或分子物质或优化机械性能来改性的。根据慢性伤口的不同需要，已经生产出具有抗炎、抗氧化、促血管生成、抗菌、降糖、热敏甚至多功能特性的水凝胶[29]。具有固有抗菌活性的水凝胶具有预防感染、吸收伤口液和气体交换等优点，制备一种具有抗菌活性的水凝胶来促进慢性糖尿病创面愈合是非常必要和有前景的[30]。

3.2. 抗菌性水凝胶伤口敷料对糖尿病慢性创面的作用

功能性水凝胶是一种很有前途的伤口治疗材料，因为它具有可调节的肿胀速率和吸收伤口渗出物的能力，可以使伤口与外界隔离以防止感染[29]。Chenggui Wang 等人开发了一种可注射、自愈和抗菌多肽为基础的 FHE 水凝胶(F127/OHA-EPL)，FHE@exo 水凝胶结果显示提高了糖尿病全层皮肤创面的愈合效率，其特点是创面愈合率提高，血管生成速度加快，创面内再上皮形成和胶原沉积加快[30]。He Zhao 利用聚乙烯醇(PVA)与活性氧反应连接剂交联制备了一种清除活性氧的水凝胶。通过降低创面周围 ROS 水平，上调 M2 型巨噬细胞，促进创面愈合[31]。熊勇等人制备了一种新型原位注射 HA@MnO2 引入/FGF-2/EXOS 水凝胶以改善糖尿病伤口愈合。通过简单的局部注射，就能够形成覆盖伤口的保护屏障，提供快速止血和长期抗菌保护[32]。赵赫等人开发了一种基于 PVA 的水凝胶，通过 ROS 反应连接物交联，并同时加载抗生素莫匹罗辛和生长因子 GM-CSF，以促进组织再生。在创面微环境中，该水凝胶能够通过下调促炎细胞因子，上调 M2 型巨噬细胞，促进血管生成和胶原蛋白的产生，清除创面中 ROS，促进创面愈合[14]。陈蔡宇等人把壳聚糖 DF-PU 水凝胶作为伤口敷料，发现低温水凝胶可以吸收多余的伤口渗出液，保留有益的生长因子，促进损伤组织的恢复，促进伤口愈合[33]。朱卫东等人发现 GelMA/SFMA/MSN-RES/PDEVs 水凝胶降低促炎因子 TNF-α 和 iNOS 的表达，增加抗炎因子 TGF-β1 和 Arg-1 的表达，促进血管生成，加速伤口愈合[34]。齐旭等人开发了 AuPt@melanin 掺入(GHM3)水凝胶敷料，GHM3 破坏了 ROS 炎症级联循环并下调了 M1/M2 巨噬细胞的比例，以促进高效的热疗增强局部葡萄糖消耗和 ROS 清除，从而改善了糖尿病大鼠背侧皮肤和 DFU 伤口的治疗结果[35]。

4. 总结

糖尿病创面血管生成受损导致血流量减少，成纤维细胞、角质形成细胞等向伤口部位的迁移减少，导致再上皮化减少、基质形成受损、生长因子表达降低，以及 M1/M2 巨噬细胞比率增加等，限制创面的增殖和重塑过程，导致组织修复延迟。长期高血糖和慢性炎症会导致氧化应激增加，这会进一步损害伤口愈合，导致皮肤细胞功能障碍和损伤。以上创面修复异常的相关途径或许可以成为治疗糖尿病创面的靶点，比如降低血糖、减少高血糖诱导的氧化应激、改善创面微环境；促进巨噬细胞 M2 极化、修复受损的免疫细胞、恢复成纤维细胞正常功能；去除创面生物膜、恢复创面生物多样；神经修复和再生等。此外，有研究表明，抗炎性水凝胶参与糖尿病创面愈合中重要细胞的降低炎症因子生成，极大地能使创面愈合率提高，上调 M2 型巨噬细胞，促进血管生成和胶原蛋白的产生，清除创面中 ROS，促进创面愈合[14]。糖尿病患者的伤口愈合能够有序、快速地完成。对抗炎性水凝胶的进一步研究可能为未来治疗糖尿病伤口提供一种方法。

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