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糖尿病伤口愈合的未来：揭示间充质干细胞和外泌体治疗的潜力

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摘 要

糖尿病(DM)是一个重大的公共卫生问题，是世界范围内最具挑战性的医疗条件之一。严重的并发症使DM更加复杂。糖尿病性伤口就是其中一种并发症。糖尿病患者患糖尿病足溃疡(DFU)的风险较高。由于常规治疗的无效，截肢的增长、发病率和死亡率已经被认识到。间充质干细胞(MSCs)能显著促进伤口愈合，但是，干细胞治疗也存在一些风险。外泌体治疗是糖尿病伤口的一种新的治疗选择，已显示出良好的效果。然而，一种更先进的形式——使用外泌体的无细胞疗法已经出现。这种升级版的干细胞疗法提供了更好的疗效，并消除了癌症进展的风险。外泌体疗法从多个角度促进伤口愈合，不像传统方法主要依靠身体的自我修复能力，只提供伤口保护。因此，外泌体疗法有可能有效地取代传统疗法。然而，需要进一步的研究来区分治疗的最佳干细胞类型，确保其安全性，建立适当的剂量，并确定最佳的管理路径。本研究的重点是目前关于糖尿病创面溃疡的文献，其治疗方法，以及间充质干细胞和外泌体治疗DFU的潜力。

关键词

糖尿病，间充质干细胞，外泌体

The Future of Diabetic Wound Healing: Revealing the Potential of Mesenchymal Stem Cells and Exosome Therapy

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Abstract

Diabetes mellitus (DM) is a major public health problem and one of the most challenging medical conditions worldwide. DM is further complicated by serious complications. Diabetic wounds are one such complication. People with diabetes are at higher risk for diabetic foot ulcers (DFU). The increase in amputations, morbidity, and mortality due to the ineffectiveness of conventional treatment has been recognized. Mesenchymal stem cells (MSCs) can significantly promote wound healing, however, there are some risks associated with stem cell therapy. Exosome therapy is a new treatment option for diabetic wounds and has shown good results. However, a more advanced form of cell-free therapy using exosomes has emerged. This upgraded version of stem cell therapy offers better efficacy and eliminates the risk of cancer progression. Exosome therapy promotes wound healing from multiple angles, unlike traditional methods that rely primarily on the body's ability to repair itself and only provide wound protection. Therefore, exosome therapy has the potential to effectively replace traditional therapies. However, further research is needed to distinguish the optimal stem cell type for treatment, ensure its safety, establish appropriate dosages, and determine the best path of administration. This study focused on the current literature on diabetic wound ulcers, their therapeutic approaches, and the potential of mesenchymal stem cells and exosomes to treat DFU.

Keywords

Diabetes, Mesenchymal Stem Cells, Exosome

1. 引言

近几十年来，经济显著增长，饮食习惯也发生了变化。因此，糖尿病患者的数量有所增加[1] [2]。流行病学计算预测，到 2045 年，这一数字将达到约 7 亿[3]。此外，糖尿病的治疗和护理给患者和社会带来了巨大的经济负担[4] [5]。糖尿病主要通过并发症造成很多伤害。最重要的并发症之一是糖尿病伤口，众所周知，糖尿病患者非常容易发生足部溃疡[6]。据统计，该病每年消耗 20%~40%的医疗资源[7]。约 15%的糖尿病患者有 DFU 并发症，而这种情况导致约 84%的下肢截肢[8]。糖尿病足溃疡的预后往往较差，死亡率也不容乐观(其 5 年总生存率降低 60%) [9] [10]。然而，DFU 的愈合可以通过几个因素来预测，其中一些因素可以修改。例如，更好地控制糖尿病，神经病变的治疗和溃疡的早期处理可以改善愈合过程。因此，患者的诊断和及时的治疗措施对于提高其愈合机会至关重要[6]。糖尿病引起的足部溃疡有几种传统治疗方法，如卸掉伤口、伤口敷料以提供湿润的伤口环境、清创、使用抗生素和手术干预。干细胞移植近年来在包括 DFU 在内的各种疾病的治疗中发挥了重要作用。先前的研究表明，MSCs 可以显著促进伤口愈合[6]。此外，在多项研究中，外泌体治疗作为 DFUs 的一种新的治疗选择已显示出令人满意的结果[11]。调节受体细胞和管理巨噬细胞、内皮细胞(ECs)和成纤维细胞之间的细胞串扰是由间充质干细胞衍生的外泌体通过遗传物质和转录因子运输完成的。更重要的是，与单独的干细胞治疗相比，它具有更低的癌症风险，使其成为糖尿病伤口治疗的更安全的选择[11]。因此，它已成为糖尿病伤口愈合的热门选

择。本文综述了间充质干细胞和外泌体治疗 DFU 的研究进展。

2. 糖尿病足部溃疡的发病机制和特点

糖尿病足部溃疡的病因和进展是复杂的，受多种内在和外在因素的影响。考虑到这两个方面对于实现提出这一问题的负责任机制至关重要。神经病变 DFU 病例的神经病变引起感觉和运动神经损伤。同样，自主神经系统也可能受损。因此，可能会增加下肢皮肤溃疡、肌肉萎缩和运动功能障碍的风险[12] [13]。此外，神经病变引起的汗腺分泌异常会导致皮肤过热，增加足部溃疡的危险。感觉和运动神经病变合并可导致足部压力过大，最终导致溃疡难以愈合[14]。以动脉粥样硬化为主的血管病变血管病变可引起内皮损伤、炎症和血液高凝。因此，它促进了动脉粥样硬化病变的形成[15] [16]。这种血管病变是 DFU、截肢和死亡的潜在因素[17]。动脉粥样硬化斑块破裂可导致动脉血栓形成，导致下肢缺血，形成 DFUs [18]。

伤口感染

由于血液供应不良和神经损伤，糖尿病患者可发生糖尿病足感染。这些慢性感染可能由多种微生物引起，如真菌白色念珠菌[19]。此外，持续性疾病与免疫细胞紊乱有关，损害了抗性特征[20]。许多生长因子也被确定在发展糖尿病及其并发症中起关键作用。在这些升高的因子中，血管内皮生长因子(VEGF)已被证明是一个更有效的因子。在糖尿病溃疡患者中，丙二醛(MDA)和肿瘤坏死因子 α (TNF-α)水平显著升高，这可能是可溶性 VEGF1 分泌所必需的。这些因素导致伤口愈合和血管化受损[21] [22]。如上所述，这些也是糖尿病患者溃疡发展的主要原因。此外，除了这些因素外，其他因素被认为是导致 dfu 预后不良的主要原因。糖尿病患者与伤口愈合不良相关的其他健康问题被很好地评估如下：高血糖会损害血管，导致血液流动不畅。糖尿病患者也可能有周围血管疾病和神经病变，这使得发现伤口具有挑战性。糖尿病伤口的特点是过度炎症，血管生长减少，皮肤细胞运动受损，细胞生长减少。这些变化会使伤口更难愈合，并增加并发症的风险，如感染、伤口不愈合和慢性伤口不愈合[23]。另一方面，血管生成不足是糖尿病创面愈合不良的主要因素之一。这是由于缺乏必要的原产因子，这可能是由巨噬细胞引起的[24]。此外，糖尿病创面抗血管生成因子增加，毛细血管成熟因子减少。这种成熟因素的延迟可能导致愈合过程不良，增加伤口成为慢性或复发的风险[25]。此外，糖化血红蛋白(HbA1c)衡量糖尿病患者的长期血糖控制。研究表明，高 HbA1c 水平与伤口愈合不良之间存在很强的相关性。最近的一项回顾性研究发现，糖化血红蛋白(HbA1c)水平在 7.8%及以上的糖尿病患者发生术后伤口并发症的风险最高，包括愈合不良。因此，美国糖尿病协会建议糖尿病患者将 HbA1c 水平维持在 7%以下，以降低此类并发症的发生风险[26]。

3. 溃疡与非溃疡创面愈合的差异

常规创面愈合过程主要分为四个阶段：止血、炎症、增殖和重塑[14]。当损伤发生时，由于血小板活化，止血过程被激活。因此，与损伤相关的因素开始释放。释放这些因子后，局部巨噬细胞激活并释放损伤相关分子模式(DAMPs)。因此，前淋巴细胞中性粒细胞(pmn)开始炎症期[27]。在整个感染过程中，被称为趋化因子的特定信号蛋白，如 C-X-C 基元趋化因子 12 (CXCL12)被释放，促进巨噬细胞从 M1 (炎症状态)转化为 M2 (非炎症状态)。然后，M2 巨噬细胞释放非炎性细胞因子，促进组织愈合和重组。随着愈合的继续，细胞因子刺激角质形成细胞促进上皮组织的更新。最终，这一过程涉及免疫细胞和组织修复机制，如前所述，导致伤口愈合[28] [29]。高血糖，慢性炎症，微循环，缺氧，感觉神经病变，受损的血液供应是破坏这四个阶段和途径的影响因素，最终导致愈合延迟。高血糖对晚期糖基化终产物(AGEs)的形成至关重要，AGEs 通过阻止巨噬细胞从 M1 向 M2 的转变而影响免疫细胞功能和细胞因子水平[30]。炎症是糖尿病足并发症发生的重要因素。糖尿病患者血糖水平升高会激活促炎途径，释放肿瘤坏死因子-α 和白细胞介素-6 等细胞因子。这些细胞因子促进炎症并吸引免疫细胞到受影响的组织。慢性炎症状态

观察到糖尿病足有几个不良后果。它削弱了免疫系统有效抵抗感染的能力，并可能导致免疫细胞反应减弱，使机体难以控制感染[31]。慢性炎症导致组织损伤，导致纤维化，并进一步阻碍组织修复和再生。与标准组织愈合不同，糖尿病足溃疡表现出慢性促炎模式，炎症细胞因子水平较高。研究发现，血液中 IL-1β、单核细胞趋化蛋白-1 (MCP-1)和肿瘤坏死因子-α (TNF-α)等细胞因子的高水平与糖尿病足伤口愈合不良有关[32]。此外，在 2 型糖尿病中，参与炎症反应的免疫细胞巨噬细胞仍主要是促炎细胞，导致慢性炎症，随后是更多的组织损伤[33]。最近的研究表明，中性粒细胞，另一种类型的免疫细胞，也可能通过在愈合过程中产生中性粒细胞胞外陷阱(NETs)，对糖尿病伤口愈合产生不利影响。这些 NETs 是由一个称为“NETosis”的过程产生的，该过程涉及中性粒细胞分泌去密实的染色质来中和微生物。研究发现糖尿病患者的 net 相关生物标志物水平升高[34]。此外，高血糖或高血糖可以上调中性粒细胞 PAD4 的表达，促进 NETs 的产生，从而削弱伤口愈合。在糖尿病中，巨噬细胞表型改变不能促进组织修复，导致慢性伤口[35]。综上所述，慢性炎症可加重损伤，延长炎症反应，导致组织损伤。这可能导致各种器官和组织的功能受损和不利的重塑。修复途径的持续或异常激活是慢性炎症的潜在机制，慢性炎症可导致持续炎症和纤维化。分子研究的重点是慢性炎症的诱导、进展和解决。随着时间的推移，慢性纤维化会导致不良的组织重塑和功能受损[36]。血管疾病影响肢体血管，导致缺氧、氧化应激和伤口愈合障碍[37]。此外，糖尿病足神经病变阻碍了对恢复至关重要的神经肽的分泌，从而为糖尿病患者的伤口愈合过程增加了进一步的并发症。糖尿病患者伤口愈合过程中炎症期的延长会导致活性氧的过量产生，损害附近组织，减缓愈合过程[15]。糖尿病患者伤口中生长因子和细胞外基质成分的不平衡也会导致愈合受损，导致新鲜血管的产生和胶原蛋白的产生不足，而胶原蛋白是伤口适当愈合的重要成分。基质肌脂蛋白酶(matrix metalloproteinases, MMP)在糖尿病患者创面中的修饰表现可导致组织重构异常和创面愈合延迟[38]。总的来说，糖尿病创面愈合是一个复杂的过程，受多种因素的影响，对典型愈合级联的每个阶段都有显著影响。

4. 糖尿病足溃疡(DFU)的治疗

目前的策略包括几个措施。这些包括手术清创的局部伤口护理，敷料保持伤口湿润，卸载伤口，评估患者的血管健康状况，控制任何活动性感染，并保持合理的血糖控制。通过遵循 IWGDF 指南，临床医生可以帮助大多数足部溃疡患者痊愈[39]。清创过程通过帮助肉芽组织形成和再上皮化来促进伤口愈合。根据 IWGDF 指南，快速清创是最好的护理标准。它优于其他方法，如自溶、生物外科、水外科、化学或激光清创[40]。抗生素治疗的选择主要取决于微生物测试和抗生素耐药性的结果。建议在开始抗生素治疗前在清创期间进行深层组织培养。根据 IWGDF/IDSA 感染指南，治疗应首先使用经验性和广谱抗生素，针对常见的革兰氏阳性和革兰氏阴性细菌。应根据初始治疗的临床反应以及培养和敏感性试验的结果调整抗生素方案[41]。在糖尿病足溃疡(DFU)的护理过程中，定期进行外周动脉疾病(PAD)的筛查和血管评估是至关重要的[42]。IWGDF 提供的指南建议，符合以下任何标准的患者应接受紧急血管介入治疗：踝关节压力小于 50 mmHg，足趾压力小于 30 mmHg，踝关节肱指数小于 0.4，或经皮氧压小于 25 mmHg [43]。此外，卸载足部和处理任何畸形对于预防和治疗 DFU 至关重要。减压对于治疗由机械应力增加引起的足部溃疡是必不可少的。根据 IWGDF 卸载指南，神经性足底溃疡的首选治疗方法是不可拆卸的膝高卸载装置[44]。在某些情况下，截肢可能是必要的，尽管尽了最大的努力来挽救脚。由于近端截肢会导致活动过程中更多的能量消耗[45]，因此更可取的截肢是远端截肢。此外，优化血糖控制作为以人为中心的护理，或在必要时通过临床医生开具胰岛素来控制血糖是必不可少的[46]。为了管理糖尿病足溃疡，临床医生目前遵循 IWGDF (糖尿病足国际工作组)指南，这是一个基于证据的指南[40]。医学治疗和手术血流重建(血管内和开放)是 DFUs 的主要传统治疗方法[47]。然而，这些标准程序是低效的，特别是对于动脉狭窄和闭塞造成的足部缺血[48]。此外，在某些患有心脑血管疾病的患者中，进行动脉旁路介入治疗的

可能性变得不太可能，因此导致截肢的可能性大幅增加。一些先进和有效的治疗方法，包括基于细胞的治疗，已经建立了修复慢性伤口。干细胞改善了微环境，导致创面组织再生。因此，尽管两种治疗方法在 DFU 愈合中都存在一些缺陷，但干细胞治疗仍然更有益[1]。再生医学是一门以修复和替代受损组织和器官为中心的科学领域，利用干细胞的潜力或其他创新方法来实现其目标，称为再生医学。干细胞治疗已显示出积极的治疗效果，主要是由于旁分泌作用，而不是移植细胞的长期存活[49]。MSCs 具有独特的特性，可以改变免疫反应并促进再生，这使其成为增强糖尿病伤口组织修复和血管生成的一个有吸引力的选择[50]。利用间充质干细胞的旁分泌作用，可以调节伤口微环境中的炎症反应，加速愈合，降低慢性风险。此外，多种组织类型的再生，包括皮肤、血管和神经，是 MSCs 的分化潜能，促进全面的伤口修复[51]。两种类型的干细胞用于 DFU 治疗，包括自体和异体细胞[52]。

5. 外泌体在 DFU 中的作用机制

外泌体在细胞间转移各种颗粒(包括蛋白质、脂质和核酸)中起着至关重要的作用。此外，它们还参与多种生物过程，如免疫系统、纤维化和癌症进展[53] [54]。外泌体由不同类型的细胞分泌，如免疫细胞、血小板、癌细胞、上皮细胞和间充质细胞[55] [56]。研究表明外泌体可以通过多种机制促进慢性皮肤伤口的愈合过程。这些机制包括减少炎症反应，加速新组织和血管的发展，修复和替代受损细胞，以及减少疤痕形成。此外，先前的研究表明，外泌体表现出天然的物质运输特性，使它们能够在细胞之间转移各种重要的生物分子。此外，由于外泌体可以被分泌它们的细胞重新吸收并释放，它们的作用将被延长。它们的低免疫原性特性使它们能够以最小的副作用运输各种治疗药物[57]。间充质干细胞通过外泌体分泌的旁分泌机制使这种方法成为一种有价值的治疗方法。这些外泌体可能被功能化以有效治疗各种疾病[58]。

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