

## · 综 述 ·

## 牙周炎对糖尿病的影响及其作用机制的研究进展

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**[摘要]** 牙周炎与糖尿病具有双向促进作用。糖尿病作为全球高发的慢性代谢性疾病, 会显著升高牙周炎的患病风险并加速其进展。同时, 牙周炎作为一种常见的口腔感染性疾病, 也会提高糖尿病发病率, 加重血糖控制难度, 并促进心血管疾病、视网膜病变和肾病等糖尿病并发症的发生与发展。该文阐述了牙周炎对糖尿病发病风险、血糖控制难度及并发症等多方面影响, 分析了牙周炎影响糖尿病的可能机制, 旨在为合并牙周炎的糖尿病患者的防治提供新思路。

**[关键词]** 牙周炎; 糖尿病; 牙周致病菌; 胰岛素抵抗; 综述

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**Research progress on the impact of periodontitis on diabetes and its mechanisms**LI Yuxuan, GAO Zhi<sup>△</sup>

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**[Abstract]** Periodontitis and diabetes have a bidirectional promoting effect. As a globally prevalent chronic metabolic disorder, diabetes significantly increases the risk of periodontitis and accelerates its progression. Conversely, periodontitis, a common oral infectious disease, also raises the incidence rate of diabetes, exacerbates blood glucose control difficulties, and promotes the occurrence and progression of diabetic complications such as cardiovascular diseases, retinopathy, and nephropathy. This article elaborated on the multifaceted impacts of periodontitis on diabetes risk, blood glucose control, and complications, analyzed the potential mechanisms by which periodontitis influences diabetes, and aimed to provide new insights for the prevention and treatment of diabetic patients with periodontitis.

**[Key words]** Periodontitis; Diabetes; Periodontal pathogens; Insulin resistance; Review

糖尿病是一种以高血糖为特征的慢性代谢性疾病, 由胰岛素分泌缺陷或胰岛素作用障碍所引起。截至 2022 年, 全球约有 8.28 亿成年人患糖尿病, 其中我国占 1.48 亿, 位居全球第 2<sup>[1]</sup>。糖尿病的高血糖状态不仅能够导致糖尿病足<sup>[2]</sup>、视网膜病变<sup>[3]</sup>、糖尿病肾病<sup>[4]</sup>等多种并发症, 降低患者生活质量, 还会延缓创口愈合、提高感染的可能性, 从而增加死亡风险<sup>[5]</sup>。

牙周炎是牙周致病菌引起的慢性非特异性感染性疾病, 可引起牙龈红肿、牙周袋形成、牙槽骨吸收甚至牙齿松动脱落, 其是 35 岁以上人群牙齿丧失的主要原因之一<sup>[6]</sup>。《第 4 次全国口腔健康流行病学调查》显示, 我国约 90% 的成年人存在牙周状况不佳的情况, 其中重度牙周炎患者超过 30%<sup>[7]</sup>。牙周炎能够对包括糖尿病、动脉粥样硬化及慢性肾病等的多种全身系统性疾病的发生、发展产生不良影响<sup>[8-10]</sup>。牙周炎与糖尿病有着复杂的双向促进关系<sup>[11]</sup>。与非糖尿病患者相比, 患有糖尿病且血糖控制不佳的患者发生牙周炎的概率更高, 且病情进展更快、牙齿脱落风险

更高<sup>[12]</sup>。另一方面, 牙周炎不仅会增加患糖尿病的风险<sup>[11]</sup>, 而且被认为是血糖控制恶化的一个风险因素, 并可能增加糖尿病相关并发症的发生概率<sup>[13]</sup>。糖尿病病因复杂, 包括多种遗传因素和获得性危险因素。有证据表明, 牙周炎已经成为糖尿病发生和发展的一项重要危险因素<sup>[14]</sup>。然而牙周炎对糖尿病的作用机制目前尚缺少确切结论。本文就牙周炎对糖尿病的影响及相关机制进行综述。

**1 牙周炎促进糖尿病发生、发展**

**1.1 牙周炎增加糖尿病患病风险** 一项涵盖 803 项研究的 meta 分析显示, 牙周炎患者的糖尿病患病率为 13.1%, 显著高于非牙周炎人群的 9.6%<sup>[15]</sup>。牙周炎患者患糖尿病的概率较无牙周炎者增加 66%, 而严重牙周炎患者的风险更是前者的 2.31 倍<sup>[16]</sup>。一项为期 11 年的前瞻性队列研究表明, 牙周炎与糖化血红蛋白(HbA1c)水平长期升高存在显著关联<sup>[17]</sup>。这与中重度牙周炎能够显著升高前驱期糖尿病患病风险的结论一致<sup>[18]</sup>。

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**1.2 牙周炎对糖尿病并发症及死亡率的影响** 在糖尿病患者中,牙周炎不仅与心血管疾病、视网膜病变和肾脏疾病等多种并发症风险增加相关,还会导致死亡率上升。有研究表明,牙周炎与糖尿病并发症发生率密切相关,牙周炎合并糖尿病患者视网膜病变、神经性病变、心血管病变发生率显著高于无牙周炎的糖尿病患者<sup>[19-20]</sup>。牙周炎会加剧糖尿病并发症进展,其严重程度与糖尿病视网膜病变严重程度呈显著正相关<sup>[21]</sup>。牙周炎能提高糖尿病患者死亡率。与糖尿病患者相比,合并牙周炎的糖尿病患者 10 年内的全因死亡率、心血管死亡率及肾病死亡率更高<sup>[22-23]</sup>。

**1.3 牙周治疗对糖尿病的影响** 对糖尿病患者进行牙周非手术治疗,可有效控制血糖水平。若治疗效果能长期维持,则有机会减少糖尿病并发症,提高生活质量。龈下刮治等机械性牙周治疗可降低糖尿病患者 HbA1c、空腹血糖、C 反应蛋白、肿瘤坏死因子- $\alpha$  (TNF- $\alpha$ ) 等全身炎症标志物水平<sup>[24-26]</sup>。然而,牙周辅助治疗对 HbA1c 水平的影响作用尚存争议。有研究表明,使用抗生素或氯己定含漱辅助治疗牙周炎,并不能进一步降低患者 HbA1c 水平<sup>[25]</sup>。然而,也有研究显示,在龈下刮治中辅助使用甲硝唑或  $\alpha$ -硫辛酸,可使 HbA1c 水平降低约 2%<sup>[27]</sup>。

## 2 牙周炎促进糖尿病的作用机制

**2.1 系统性炎症反应的扩散** 健康人群患牙周炎会导致血清中促炎性细胞因子水平升高<sup>[28]</sup>。如牙周炎会导致局部炎症部位白细胞介素-1 $\beta$ (IL-1 $\beta$ )、TNF- $\alpha$ 、IL-6 等促炎性细胞因子水平显著升高,这些炎症因子通过牙周袋袋壁进入血液,导致全身系统慢性低度炎症状态。这种低度慢性炎症会对胰岛素信号通路造成损害,引起胰岛素抵抗和血糖控制失调<sup>[29-33]</sup>。而牙周治疗有助于抑制外周血巨噬细胞分泌 TNF,同时可降低血清中 C 反应蛋白和 E-选择素水平<sup>[34]</sup>。

**2.2 牙周炎对胰岛  $\beta$  细胞的作用** 作为胰岛素的主要来源, $\beta$  细胞对血糖的控制至关重要<sup>[35]</sup>。在健康状态下,胰岛  $\beta$  细胞的代偿性反应主要表现为胰岛素合成和分泌增加,旨在应对代谢升高的应激刺激,从而维持血糖稳定。当刺激持续增强时, $\beta$  细胞进入失代偿状态,其功能与胰岛素分泌能力逐步衰退,最终引发糖尿病。有研究显示,许多重度牙周炎患者常出现高胰岛素血症,这是  $\beta$  细胞的一种代偿性反应<sup>[36]</sup>。随着牙周炎的加重, $\beta$  细胞可能发生分化<sup>[36]</sup> 或凋亡<sup>[37]</sup>,进而使胰岛素分泌减少、空腹血糖水平升高。有研究表明,牙周炎致病菌牙龈卟啉单胞菌(*P. gingivalis*) 和齿垢密螺旋体(*T. denticola*) 混合培养得到的上清液可促进胰岛  $\beta$  细胞胰岛素的合成和分泌<sup>[38]</sup>,其机制包括两方面:(1)上调胰岛素基因 INS1 和 INS2 的转录水平,促进胰岛素的合成<sup>[38]</sup>; (2)通过激活  $\beta$  细胞中的免疫信号,促进胰岛素分泌。同时,该上清液可激活  $\beta$  细胞表面的 Toll 样受体(TLR),导致 IL-1 $\beta$ 、IL-6 等炎性细胞因子分泌<sup>[38-39]</sup>。

在牙周来源的毒力因子中,脂多糖是主要作用因

子之一。首先,脂多糖可通过上调胰岛  $\beta$  细胞 CD14 的表达,激活 TLR,同时借助核因子  $\kappa$ B(NF- $\kappa$ B) 通路刺激炎症因子纤溶酶原激活物抑制剂 1 的表达,进一步激活  $\beta$  细胞的丝裂原活化蛋白激酶(MAPK) 通路中的丝裂原活化蛋白激酶/细胞外信号调节激酶信号通路,从而促进胰岛素分泌<sup>[39-41]</sup>。其次,脂多糖还能刺激树突状细胞、巨噬细胞等固有免疫细胞分泌大量 IL-12<sup>[42]</sup>。IL-12 可降低  $\beta$  细胞中 Klotho 蛋白表达,抑制转录因子 PDX1 的活性,促进  $\beta$  细胞向  $\alpha$  细胞分化,从而加剧胰岛  $\beta$  细胞的胰岛素分泌功能障碍<sup>[43-44]</sup>。此外,*P. gingivalis* 分泌的牙龈蛋白酶和脂多糖可下调 B 淋巴细胞瘤-2 基因(Bcl-2) 表达,同时上调促凋亡蛋白 p53 和 Bcl-2 相关 X 蛋白表达,激活半胱氨酸蛋白酶-8(Caspase-8)、Caspase-9 和 Caspase-3 等,最终诱导胰岛  $\beta$  细胞凋亡。

**2.3 胰岛素抵抗** 胰岛素抵抗是 2 型糖尿病的核心特征,表现为肝脏、肌肉和脂肪等靶组织对胰岛素信号的敏感性降低,进而引发葡萄糖摄取缺陷,导致血糖水平升高<sup>[45-46]</sup>。牙周炎可诱发葡萄糖不耐受、高胰岛素血症和胰岛素抵抗<sup>[37-47]</sup>。*P. gingivalis* 等牙周致病菌可通过血液循环或促使宿主细胞分泌细胞外囊泡影响代谢组织,抑制胰岛素信号传导<sup>[48-49]</sup>。牙周炎患者血浆中细胞外囊泡通过抑制胰岛素信号通路关键蛋白[如蛋白激酶 B(Akt)、叉头转录因子 O 亚族 1 和糖原合酶激酶-3 $\beta$ ] 的磷酸化水平,下调葡萄糖转运蛋白 2(GLUT2) 的表达,从而显著削弱肝细胞对葡萄糖的摄取和利用能力<sup>[48]</sup>。牙周炎通过释放 TNF- $\alpha$ 、IL-6 等促炎性细胞因子,引发全身性低度炎症,干扰胰岛素信号通路,从而导致胰岛素敏感性下降<sup>[50-51]</sup>。

**2.4 牙周致病菌及其组分对糖尿病的影响** 牙周致病菌引起的菌群失调是牙周病的关键致病因素。同时,牙周致病菌能通过多种途径对糖尿病等全身系统性疾病造成影响。

**2.4.1 牙周致病菌直接进入血影响糖尿病** *P. gingivalis*、伴放线杆菌等牙周致病菌可通过牙周组织的破损或炎症进入血液循环,引发系统性炎症反应<sup>[52-53]</sup>。这种菌血症状态与糖尿病的发展相关<sup>[36]</sup>。进入血液的牙周致病菌及其毒力因子可激活巨噬细胞、中性粒细胞等免疫细胞,释放 IL-1 $\beta$ 、TNF- $\alpha$ 、IL-6 等促炎性细胞因子,进一步加剧胰岛素抵抗<sup>[29,52]</sup>。这些炎症因子通过干扰胰岛素信号通路,直接促进糖尿病的发生或恶化<sup>[54-55]</sup>。

*P. gingivalis* 等牙周病原体通过其表面成分脂多糖与宿主细胞膜上的 TLR4 结合,触发 NF- $\kappa$ B 和 MAPK 通路的持续激活。该过程可诱导 TNF- $\alpha$ 、IL-6、IL-1 $\beta$  和单核细胞趋化蛋白-1 等大量促炎性细胞因子释放,并增强氧化应激反应,具体表现为活性氧水平升高<sup>[56]</sup>。这些炎症因子与氧化应激产物协同作用于胰岛素信号通路的关键节点。首先,TNF- $\alpha$  和 IL-6 通过激活 c-Jun 氨基末端激酶和 I $\kappa$ B 激酶  $\beta$ ,促使胰岛

素受体底物-1(IRS-1)在丝氨酸位点发生磷酸化,导致其功能失活<sup>[57]</sup>。其次,IL-6 可诱导细胞因子信号传导抑制蛋白 3 表达,促进 IRS-1 的泛素化降解,从而削弱胰岛素信号传导<sup>[58-59]</sup>。由于 IRS-1 无法正常激活下游的磷脂酰肌醇 3-激酶/Akt 通路,导致 GLUT4 囊泡无法转位至细胞膜表面,最终造成胰岛素依赖组织的葡萄糖摄取障碍,具体表现为全身性胰岛素抵抗<sup>[60-62]</sup>。

**2.4.2 牙周致病菌通过口-肠轴影响糖尿病** 牙周致病菌可通过吞咽进入肠道,改变肠道菌群组成。有研究显示,*P. gingivalis* 可通过肠道微生物群的变化间接影响胰岛素抵抗<sup>[63]</sup>。在口服 *P. gingivalis* 的糖尿病小鼠肠道中可检测到 *P. gingivalis* 特异性肽段,提示其能在肠道定植<sup>[63]</sup>。这种定植可能通过竞争营养或改变肠道微环境,抑制苏黎世杆菌(*Turicibacter*)等益生菌生长<sup>[63-64]</sup>。同时,牙周致病菌引起的肠道菌群变化会抑制短链脂肪酸的生成,而短链脂肪酸具有抗炎、改善糖脂代谢和提高胰岛素敏感性的作用,其含量减少会削弱对宿主的多重保护作用<sup>[65-66]</sup>。

牙周致病菌的定植可破坏肠道紧密连接蛋白表达,增加肠黏膜通透性,导致细菌及其产物转移至血液循环,从而触发全身低度炎症<sup>[67-68]</sup>。*P. gingivalis* 和具核梭杆菌可通过抑制自噬通路或分泌毒素,导致闭锁小带蛋白、闭合蛋白-1 等紧密连接蛋白表达下调,从而使肠黏膜通透性增加。

### 3 小结与展望

糖尿病与牙周炎之间存在密切且复杂的双向促进关系。糖尿病作为全球高发的慢性代谢性疾病,会显著升高牙周炎的患病风险并加速其进展。另一方面,牙周炎作为一种常见的口腔感染性疾病,也会提高糖尿病发病率,加重血糖控制难度,并促进心血管疾病、视网膜病变和肾病等糖尿病并发症的发生与发展,其潜在机制主要包括系统性炎症反应的扩散、胰岛β细胞功能受损、胰岛素抵抗的加剧,以及牙周致病菌及其毒素通过血液、口肠轴等多种途径影响全身代谢和免疫应答。

牙周炎的控制对糖尿病的发生、发展具有积极作用。将牙周健康评估与牙周治疗系统地纳入糖尿病的综合管理方案中,通过多学科协作,可使牙周治疗成为控制全身炎症、改善血糖水平的有效辅助手段。未来的研究应侧重于探索精准的干预策略,如研发靶向牙周炎与糖尿病共病中关键炎症通路的新药,或基于微生物组学开发针对特定牙周菌群的微生态调节疗法。同时,寻找预测疾病风险的生物标志物与开展评估患者远期获益的大型长期研究,将是推动该领域最终实现精准医疗并积累高级别临床证据的关键。

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