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·综述·

牙周非手术治疗对糖尿病伴牙周炎患者血糖调控作用的研究进展

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【摘要】　牙周炎与糖尿病存在密切的双向关联，二者通过炎症因子交互及代谢紊乱等机制相互促进。研究表明，以龈下刮治及根面平整术（scaling and root planing，SRP）为核心的牙周非手术治疗（non-surgical periodontal therapy，NSPT）不仅可以有效治疗牙周炎，还可改善糖尿病患者的血糖控制及全身炎症状态。本文综述了不同NSPT方案（包括单纯SRP、抗菌药物辅助SRP、激光治疗辅助SRP等）对糖尿病伴牙周炎患者血糖控制的改善效果。SRP可以显著降低糖化血红蛋白（hemoglobin A1c，HbA1c）水平；而抗菌药物及激光治疗的辅助则能显著提高SRP的血糖改善疗效。同时，本文重点关注NSPT改善血糖控制的潜在调控机制，包括：炎症因子介导的JNK/IKKβ信号通路激活引起胰岛素抵抗；晚期糖基化终末产物（advanced glycation end products，AGEs）介导的RAGE-ROS/NF-κB信号通路调控引起胰岛β细胞功能障碍；肠道菌群失调介导的TLR4-MyD88/TRIF信号轴引发胰岛素抵抗；牙周致病菌鞭毛蛋白引起的胰岛素分泌障碍；以及牙周致病菌脂多糖（lipopolysaccharide，LPS）导致的Th17/Treg比例失衡及其下游STAT3/SOCS3信号通路对胰岛素信号传导的抑制作用，旨在为未来糖尿病伴牙周炎患者的靶向干预及协同治疗提供新的参考。尽管现有研究揭示了NSPT的临床疗效及部分机制，但仍存在以下问题：不同NSPT方案调控血糖的具体效应分子及信号通路网络尚未系统阐明，患者个体间疗效差异明显，以及辅助疗法额外获益的长期稳定性不明。未来研究需探索更多联合治疗方案实现多疗法协同增效、深入解析机制、识别关键靶点，推动糖尿病-牙周炎联合病变的精准管理。

【关键词】　牙周非手术治疗；　龈下刮治和根面平整；　牙周炎；　糖尿病；　激光治疗；　抗菌治疗；　糖代谢；　炎症因子；　NF-κB信号通路；　晚期糖基化终末产物
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Research progress on the impact of non-surgical periodontal therapy on glycemic control in diabetic patients with periodontitis

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【Abstract】　Periodontitis and diabetes have a close bidirectional relationship that is mutually exacerbated through mechanisms including inflammatory factor interplay and metabolic dysregulation. Research has shown that non-surgical periodontal therapy (NSPT), focused on scaling and root planing (SRP), effectively treats periodontitis, enhances glycemic control, and ameliorates systemic inflammation in diabetic patients. This review summarizes the glycemic improvement effects of diverse NSPT modalities (including SRP alone, SRP with adjunctive antimicrobials, and SRP with laser

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therapy) on patients with diabetes and periodontitis. SRP significantly reduces hemoglobin A1c (HbA1c) levels, while adjunctive antimicrobials and laser therapy considerably potentiate the glucose-lowering efficacy of SRP. Furthermore, we focus on elucidating the underlying regulatory mechanisms for NSPT-mediated glycemic control improvement, encompassing inflammation factor-mediated JNK/IKKβ pathway activation inducing insulin resistance; advanced glycation end products (AGEs)-triggered RAGE-ROS/NF-κB pathway dysregulation leading to pancreatic β-cell dysfunction; gut microbiota dysbiosis-driven TLR4-MyD88/TRIF signaling axis causing insulin resistance; flagellin from periodontal pathogens impairing insulin secretion; and lipopolysaccharide (LPS) of periodontal pathogens disrupting Th17/Treg balance with downstream STAT3/SOCS3 pathway inhibiting insulin signaling. These insights aim to provide novel references for targeted interventions and synergistic management of diabetes with periodontitis. Although current studies reveal potential benefits and partial mechanisms of NSPT, the following problems remain: unelucidated specific effector molecules and pathway networks for glycemic regulation by different NSPT regimens, significant interindividual variability in treatment response, and undetermined long-term stability of adjunctive therapy benefits. Future research should explore combined therapeutic strategies for synergistic efficacy, mechanistically dissect regulatory pathways, identify key targets, and advance precision management of diabetes - periodontitis comorbidities.

【Key words】 non-surgical periodontal therapy; scaling and root planing; periodontitis; diabetes mellitus; laser therapy; antimicrobial therapy; glucose metabolism; inflammatory cytokines; NF-κB signaling pathway; advanced glycation end products

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牙周炎是主要由牙菌斑引起的累及牙龈、牙槽骨等组织的多因素炎症性疾病[1],导致牙齿附着丧失[2],表现为牙周袋形成、牙槽骨吸收、牙齿松动或移位等[3]。流行病学调查显示,我国成年人牙周健康率仅为9.1%,35~44岁人群中牙周病患病率高达90.9%[4]。糖尿病以高血糖为特征,长期高血糖可引发心血管疾病、牙周炎等并发症[5]。据2021年全球糖尿病报告,全球糖尿病患者达5.37亿,中国患者约1.41亿,疾病负担持续居全球首位[6]。

近年来,牙周炎和糖尿病的双向关系引发关注。Chien等[7]研究显示,牙周炎患者的2型糖尿病(type 2 diabetes mellitus, T2DM)患病率显著高于健康者,而T2DM亦会增加牙周炎的发病风险(调整后风险比为1.99)。同时,牙周炎还会恶化T2DM患者的胰岛素抵抗并加重糖尿病并发症[8]。这种双向关系涉及多种因素。T2DM可通过炎性因子水平升高[5]、骨愈合过程受损和晚期糖基化终末产物(advanced glycation end products, AGEs)的产生增加等机制促进牙周组织破坏[9]。而牙周炎也可引起糖尿病病程的恶化及并发症的发生[10]。研究证实,牙周致病菌会导致患者糖化血红蛋白(Hemoglobin A1c, HbA1c)水平升高[11]并诱发葡萄糖耐量异常、胰岛素抵抗,直接加速糖尿病进展[12]。

研究表明,龈下刮治及根面平整(scaling and root planing, SRP)作为牙周非手术治疗(non-surgical periodontal therapy, NSPT)的核心,不仅能有效改善牙周状况,并显著降低糖尿病伴牙周炎患者的HbA1c水平,改善血糖控制[13-14]。然而,NSPT改善血糖控制的疗效及其作用机制尚未被系统阐明。现有综述多局限于NSPT改善糖尿病患者血糖控制的疗效论证,缺乏对于改善机制的深入探讨,本文则系统综述了不同NSPT方案(如单纯SRP、抗菌药物/激光辅助SRP)对糖尿病伴牙周炎患者血糖控制的改善效应,并重点解析其通过调控炎症因子网络、逆转菌群失调、改善胰岛素抵抗等通路影响血糖控制的潜在分子机制,以期为临床实施糖尿病-牙周炎联合病变的精准化联合治疗提供理论依据。本研究采用推荐分级的评价、制定与评估(grading of recommendations assessment, development and evaluation, GRADE)系统对HbA1c、空腹血糖(fasting plasma glucose, FPG)及炎症标志物等关键结局指标进行证据质量评估,

基于研究设计初始等级，综合偏倚风险、结果不一致性、证据间接性、结果不精确性及发表偏倚五维度进行证据质量等级调整（最终分为中、低、极低3级）。

1　牙周非手术治疗改善糖尿病伴牙周炎患者糖尿病相关指标的疗效

1.1　SRP对糖尿病伴牙周炎患者血糖控制和炎症改善的影响

SRP除了对牙周炎的治疗效果外，对糖尿病患者的血糖控制和炎症改善也有积极作用[15]。SRP可以改善T2DM伴牙周炎患者的血糖控制已逐渐成为共识[16]。Mauri-Obradors等[17]开展了一项为期6个月、基于90例患者的随机对照试验（randomized controlled trial，RCT），结果显示，与仅龈上洁治组相比，SRP 6个月后，糖尿病患者的牙周状况和HbA1c水平显著改善。一项纳入60例糖尿病伴牙周炎患者、随访6个月的RCT中，经过SRP后患者的HbA1c水平可显著下降0.52%[18]。一项纳入11个研究的Meta分析显示，SRP 6个月后，T2DM患者的HbA1c水平显著降低0.29%[19]。在炎症改善方面，一项为期12个月的观察性研究显示，T2DM伴牙周炎患者SRP后，局部炎症水平[白细胞介素-6（interleukin-6，IL-6）、肿瘤坏死因子-α（tumor necrosis factor-alpha，TNF-α）、IL-1β等]在12个月时呈显著下降，全身炎症水平在第3个月和第6个月的随访中也呈显著下降趋势，并且SEM分析显示SRP 12个月后，T2DM伴牙周炎患者全身炎症降低幅度显著大于非糖尿病牙周炎患者[20]。一项荟萃分析显示，糖尿病伴牙周炎患者SRP后，HbA1c水平显著下降了0.56%，C反应蛋白（C-reactive protein，CRP）水平则显著下降了1.89%[13]。为了深入研究SRP对糖尿病伴牙周炎患者的远期影响，D′Aiuto等[21]开展了一项为期12个月的RCT，共纳入264例患者，评估SRP与对照治疗（龈上洁治和抛光）对T2DM伴牙周炎患者的疗效差异。研究结果显示，在第2个月、6个月和12个月的随访中，SRP组HbA1c水平在12个月时显著低于对照治疗组，且敏感性分析显示SRP组的HbA1c水平呈持续降低趋势。此外，SRP组的FPG、CRP、TNF-α、血流介导扩张、肾小球滤过率均在不同时间点优于对照治疗组。该研究证实SRP不但可以改善T2DM患者的代谢控制，还可改善血管和肾功能、降低全身炎症。

胰岛素抵抗是T2DM发展的关键特征[22]，而已有研究发现胰岛素抵抗与牙周炎也密切相关[23]。因此SRP对T2DM伴牙周炎患者胰岛素抵抗的改善效果是值得关注的。Mammen等[24]通过C肽和稳态评估指数评估SRP对T2DM伴牙周炎患者胰岛素抵抗的作用，40例患者在第3个月时的随访结果显示，SRP组患者的C肽、胰岛素抵抗和胰岛素敏感性改善显著。但最近一项荟萃分析显示[25]，SRP对于T2DM伴牙周炎患者的胰岛素抵抗和β细胞功能的改善不明显，这与前面的结果互相矛盾。因此，针对SRP对胰岛素抵抗的影响的大型RCT是必要的。

GRADE证据质量总结：

①HbA1c降低：多项RCT[17-18, 21]和系统评价/Meta分析[13, 19]结果显示SRP显著降低T2DM伴牙周炎患者的HbA1c水平（0.39%-0.56%）。虽然部分研究存在随访时间或样本量的局限，但结果一致性高，效应量精确，证据质量等级中。

②全身炎症标志物降低（如CRP，TNF-α）：一项RCT[21]和一项Meta分析[13]研究显示SRP可以显著降低炎症标志物，但研究数量相对HbA1c较少，还有少量研究为观察性[20]，证据质量等级低。

③胰岛素抵抗改善：现有证据不一致。一项RCT[24]报告了改善显著，而一项更新的Meta分析[25]则未发现显著效果。研究数量少且结论相悖，证据质量等级极低。

1.2　抗菌药物辅助SRP对糖尿病伴牙周炎患者血糖控制的影响

现有证据表明，在牙周炎的治疗中辅助使用甲硝唑[26]、阿莫西林[26]、多西环素[27]等抗菌药物可以提高SRP疗效。但是，抗菌药物的辅助是否可以提高SRP对于T2DM伴牙周炎患者血糖控制的改善效果尚不明确。

有研究评估了甲硝唑和阿莫西林辅助SRP对T2DM伴牙周炎患者的影响，该RCT共包含58例患者，结果显示在第3个月、6个月和12个月的随访中，与安慰剂辅助SRP组相比，甲硝唑和阿莫西林辅助SRP（阿莫西林500 mg和甲硝唑400 mg，3次/d，持续14 d）并未显著改善HbA1c水平[28]。而在另一项相似研究中，Xu等[29]研究共招募了49例T2DM伴牙周炎患者，其中抗生素辅助SRP组为26例患者，该RCT调整了阿莫西林和甲硝唑（阿莫西林500 mg和甲硝唑200 mg，3次/d，连用7 d）的用量，随访3个月后，阿莫西林和甲硝唑辅助SRP组

和单纯SRP组患者的HbA1c水平均降低。两组研究的差异可能由以下原因导致：①受试者糖尿病水平存在差异。Xu等[29]研究中纳入的患者的T2DM诊断时间为2年以上，且HbA1c水平小于10%。而另一组研究中纳入患者的T2DM诊断时间为5年以上，HbA1c水平小于11%，该组中患者的糖尿病更加严重，血糖控制更差，因此血糖改善效果可能不明显。②高水平甲硝唑对肠道的影响。Miranda等[28]研究中甲硝唑的用量更高，用药时间也更长，已有研究[30]表明甲硝唑的使用会显著降低肠道短链脂肪酸（short chain fatty acids，SCFAs）水平。而SCFAs能够刺激胰高血糖素样肽（glucagonlike peptide-1，GLP-1）的分泌，GLP-1可以改善胰腺β细胞功能并诱导胰岛素表达增加，增强胰岛素敏感性[31-32]。因此甲硝唑的用量增加会使得肠道SCFAs减少，继而影响T2DM患者的血糖控制，使得两组试验结果存在差异。这提示不同剂量和用药时间的阿莫西林和甲硝唑辅助SRP可能会影响T2DM伴牙周炎患者的血糖控制改善效果。

除了甲硝唑以及阿莫西林，还有研究将其他抗菌药物辅助于T2DM伴牙周炎患者的SRP中。Bagde等[33]的RCT中使用了多西环素辅助SRP，第60天和90天时的随访显示多西环素辅助SRP组患者的HbA1c水平改善显著，且改善效果显著优于单纯SRP治疗。Komatsu等[34]评估了阿奇霉素辅助SRP的疗效，结果显示治疗6个月后，阿奇霉素辅助SRP组患者的HbA1c水平显著下降，且与单纯SRP组差异明显。

有研究发现在SRP中辅助使用甲硝唑和阿莫西林显著增加了不良反应（如腹泻、金属味）的发生率[35]，且在糖尿病患者群体中不良反应发生率更高。因此，使用抗菌药物时需要考虑其可能引发的副作用，此外还要警惕抗菌药物所引起的耐药性，因此，每位牙周医生在使用抗菌药物辅助SRP前要权衡使用抗菌药物的利弊[36]。

GRADE证据质量总结：

①甲硝唑/阿莫西林辅助SRP对HbA1c的影响：两项RCT比较了甲硝唑/阿莫西林辅助SRP与单纯SRP或安慰剂辅助的效果，研究结果不一致[28-29]。研究间存在剂量、疗程和患者基线特征的差异。样本量不足以检测组间差异，证据质量等级低。

②多西环素/阿奇霉素辅助SRP对HbA1c的影响：两项RCT报告了多西环素和阿奇霉素辅助SRP在特定时间点的改善效果显著优于单纯SRP[33-34]。然而，研究数量少、样本量有限，且缺乏独立重复验证，证据质量等级低。

1.3　激光治疗辅助SRP对糖尿病伴牙周炎患者血糖控制的影响

激光治疗是牙科治疗的一种创新治疗方法，凭借其促进牙周再生、止血作用强以及良好的组织切除和杀菌作用等优势被广泛应用于牙周炎治疗[37]。有研究将激光治疗辅助SRP应用于T2DM伴牙周炎患者的治疗中，以评估其是否可以提高SRP对血糖控制的改善效果。Zhang等[38]将Nd：YAG激光辅助SRP应用于T2DM伴牙周炎患者的治疗中，与SRP组相比，辅助激光组患者的FPG水平显著降低，但HbA1c水平未见明显改善。Feng等[39]对T2DM患者进行了Er：YAG激光辅助SRP的RCT，第3个月的随访结果显示与单纯SRP组相比，Er：YAG激光辅助SRP组T2DM患者的FPG水平显著降低。另有样本量为60例的RCT评估了二极管激光（diode laser，DL）辅助SRP对T2DM患者的影响，在治疗第3个月的随访时发现，与仅SRP组相比，DL辅助SRP组患者的HbA1c水平和IL-6等参数得到了显著改善[40]。Soi等[41]纳入44例T2DM伴牙周炎患者的RCT中，SRP后第6个月随访结果显示DL辅助SRP可以显著提高SRP对HbA1c水平的改善效果。Xie等[42]的荟萃分析表明，DL辅助SRP可显著改善T2DM伴牙周炎患者的HbA1c水平，并且与仅SRP相比，改善效果可显著提高0.27%。

GRADE证据质量总结：

激光辅助SRP对血糖指标（HbA1c，FPG）的影响：证据来源于4项RCT[38-41]和荟萃分析[42]，分别使用了不同类型的激光（Nd：YAG，Er：YAG，DL），研究结果存在不一致性，两项RCT报告FPG改善[38-39]，两项RCT和1项荟萃分析报告HbA1c水平改善[40-42]，也有一项研究报告HbA1c水平无改善[38]。各研究使用的激光参数（波长、功率、照射方式）差异大，导致间接性显著。所有RCT样本量小，随访时间相对短（3~6个月），导致研究结果可靠性有限。荟萃分析提示可能存在发表偏倚风险[42]，证据质量等级极低。

综上，SRP可有效改善T2DM伴牙周炎患者的血糖控制及全身炎症状态（表1），但对于胰岛素抵抗的改善作用存在争议，此外，抗菌药物或激光治疗辅助SRP的增效作用尚不确切，仍需进一步研

究。未来的研究需着力于：①开展大样本、长周期RCT，明确SRP对胰岛素抵抗的改善效果；②标准化辅助治疗方案（如抗菌药物种类/剂量、激光参数），并评估其长期安全性；③探索基于糖尿病病程及严重程度的个体化NSPT策略，以优化T2DM伴牙周炎的综合管理。

表1　牙周非手术治疗对糖尿病伴牙周炎患者血糖控制的改善效果

Table 1　The improvement effect of NSPT on glycemic control in diabetic patients with periodontitis

Treatment method	Glycemic/Inflammatory effects (Quality of evidence)	Research status & Key evidence
SRP	• Glycemic control: HbA1c ↓ 0.29% - 0.56%[13, 18-19], FPG ↓ [21] (Moderate) • Inflammatory status: TNF-α /IL-6 ↓ [20], CRP ↓ 1.89%[13] (Low) • Insulin resistance improvement[24] (Very low)	• Consensus efficacy (multiple meta-analyses) • RCT: Sustained HbA1c ↓ at 12 months[21] • Insulin resistance: Conflicting evidence
Antimicrobial-assisted SRP	• Metronidazole/Amoxicillin: Inconsistent HbA1c improvement[28-29] (Low) • Doxycycline: HbA1c ↓ > SRP alone[33] (Low) • Azithromycin: Significant HbA1c ↓ [34] (Low)	• Controversy: Dose/diabetes duration-dependent • High-dose metronidazole may attenuate effects (SCFA mechanism)[30-32] • Antimicrobial resistance risk
Laser-assisted SRP	• FPG consistently ↓ [38-39] (Very low) • Diode laser: HbA1c ↓ [40-42]/IL-6 ↓ [40] (Very low) • Nd: YAG/Er: YAG: Limited HbA1c improvement (Very low)	• Nd: YAG: FPG ↓ [38] • Er: YAG: FPG ↓ [39] • Diode laser: Optimal comprehensive effects[40-42]

Criteria for rating certainty of evidence: study limitations (risk of bias) ; inconsistency; indirectness; imprecision; publication bias. This study assessed the certainty of evidence for key outcomes (HbA1c, FPG, inflammatory markers) using the grading of recommendations assessment, development and evaluation(GRADE). The initial certainty level, based on study design, was adjusted considering five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (final levels: moderate, low, very low). SRP: scaling and root planing; Antimicrobial-assisted SRP: categorized by specific agents (metronidazole/amoxicillin, doxycycline, or azithromycin); Laser-assisted SRP: stratified by laser technology (Nd: YAG, Er: YAG, or diode). NSPT: non-surgical periodontal therapy; CRP: C-reactive protein; FPG: fasting plasma glucose; RCT: randomized controlled trial; SCFAs: short chain fatty acids; HbA1c: glycated hemoglobin; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6

2　牙周非手术治疗改善糖尿病伴牙周炎患者血糖控制可能涉及的信号通路

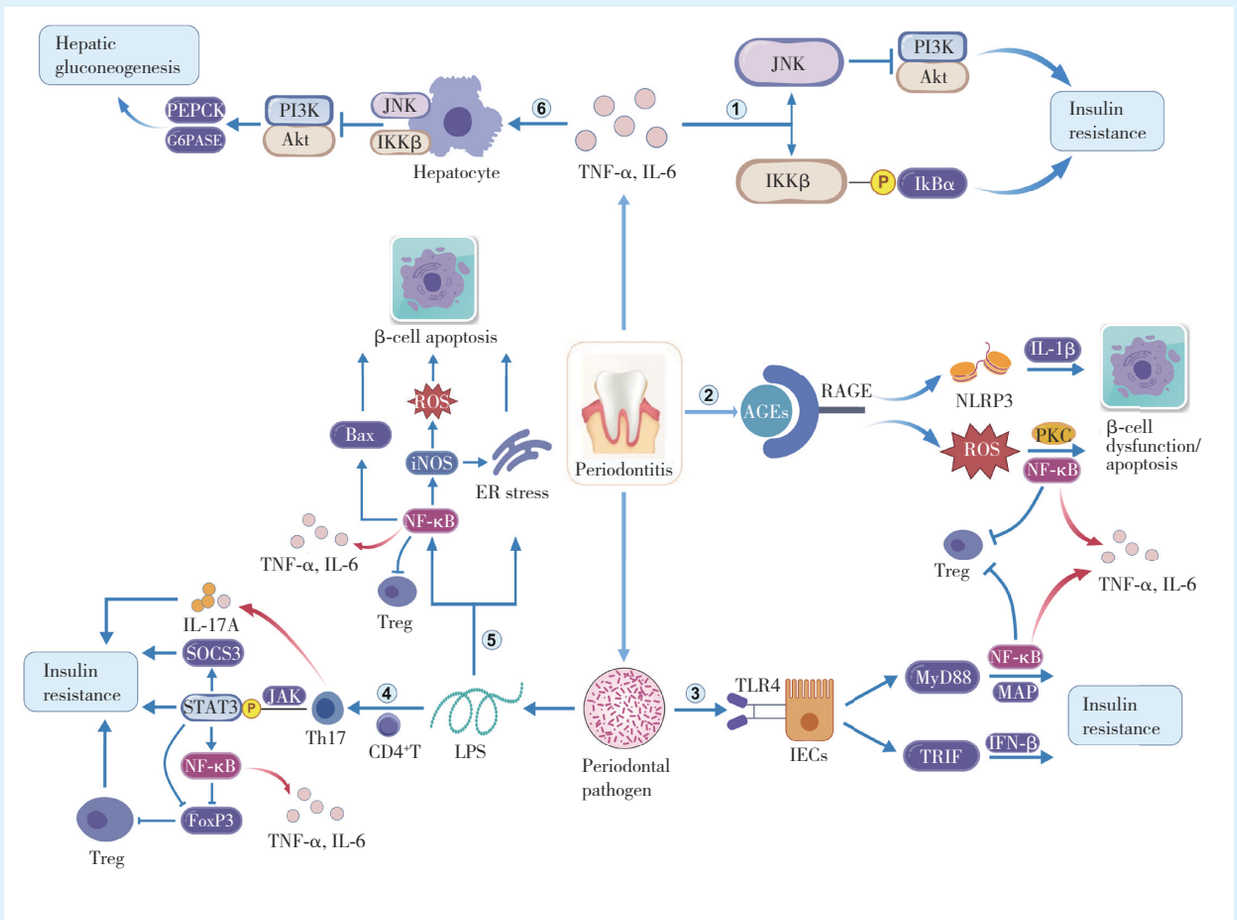
目前，牙周非手术治疗（NSPT）导致糖尿病患者HbA1c水平降低和血糖控制改善的确切机制尚未完全阐明，现有证据显示，NSPT对糖尿病代谢指标的调节作用可能涉及炎症因子网络调控[43]、胰岛素抵抗改善[44]等多重机制，其中局部炎症控制与全身代谢改善之间的动态平衡关系尤其值得关注（图1）。以下笔者将深入探讨NSPT改善糖尿病患者血糖控制的可能信号通路。

2.1　炎症因子介导的胰岛素抵抗改善（TNF-α/IL-6-JNK/IKKβ信号通路）

现有研究表明，NSPT可以显著降低糖尿病伴牙周炎患者的IL-6、TNF-α、IL-1β等炎症因子水平[20, 45-46]。在全身慢性炎症状态下，TNF-α被证实可诱导胰岛素抵抗[47]，而IL-6与胰岛素抵抗亦存在正相关关系[48]。此外，有证据表明针对糖尿病致病过程的抗炎治疗可以显著降低T2DM患者的FPG、HbA1c水平[49]。因此，NSPT可能通过改善炎症状态，进而改善糖尿病伴牙周炎患者的血糖控制。

牙周炎产生的炎症介质可以从牙周组织进入血液[50]。在牙周炎的病理进程中，以牙龈卟啉单胞菌为代表的牙周致病菌刺激大量TNF-α和IL-6等促炎因子释放[51]，从而加重了机体系统性炎症状态。进入血液循环的TNF-α和IL-6分别与其特异性受体结合，进而激活c-Jun N端激酶（c-Jun N-terminal kinase，JNK）和核因子κB抑制物激酶β（IκB kinaseβ，IKKβ）两条关键信号通路。

在JNK信号通路中，TNF-α结合胰岛素敏感组织（如骨骼肌、脂肪组织、肝脏等）细胞膜表面TNF受体后通过衔接蛋白TRADD以及丝氨酸/苏氨酸蛋白激酶1等[52]激活MAP激酶激酶激酶（mitogen-activated protein kinase kinase kinase，MAP3K）（如ASK1，凋亡信号调节激酶1等），随后级联激活MAP激酶激酶（mitogen-activated protein kinase kinasem，MAP2K）（如MKK4和MKK7），MAP2K磷酸化后激活JNK[53-54]。活化的JNK通过磷酸化胰岛素受体底物（insulin receptor substrate 1，IRS-1）的Ser307位点，抑制其与胰岛素受体的结合及酪氨酸



①TNF-α/IL-6-JNK/IKKβ pathway; ②AGEs-RAGE-ROS-NF-κB pathway; ③Periodontal pathogen-TLR4-MyD88/TRIF; ④LPS-Th17/Treg imbalance associated with STAT3/SOCS3 pathway; ⑤TLR4-NF-κB/ER stress-βcell apoptosis pathway; ⑥TNF-α/IL-6-FOXO1/PGC-1α-Hepatic gluconeogenesis pathway. JNK: c-Jun N-terminal kinase; IKKβ: IκB kinaseβ; PI3K: phosphoinositide 3-kinase; Akt: Ak strain transforming; IκBα: inhibitor of Nuclear Factor Kappa B Alpha; PEPCK: phosphoenolpyruvate carboxykinase; G6PASE: Glucose-6-phosphatase; AGEs: advanced glycation end products; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; NF-κB: nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; PKC: protein kinase C; TLR4: Toll-like receptor 4; IECs: intestinal epithelial cells; TRIF: TIR-domain-containing adapter-inducing interferon-β; MyD88: myeloid differentiation primary response 88; MAP: mitogen-activated protein; Treg: regulatory T cells; FoxP3: Forkhead box protein 3; STAT3: signal transducer and activator of transcription 3; SOCS3: suppressor of cytokine signaling 3; ER stress: endoplasmic reticulum stress; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; IL-17A: interleukin-17A; IFN-β: interferon-β; LPS: lipopolysaccharide; Th-17: t helper 17 cell; $CD4^+T$: CD4-positive t lymphocyte; iNOS: inducible nitric oxide synthase; Bax: b-cell lymphoma 2-associated x protein; JAK: janus kinase; IL-1β: interleukin-1β; FOXO1: forkhead box protein O1; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-Alpha

Figure 1　Mechanisms underlying the impact of periodontitis on glycemic control in diabetic patients

图1　牙周炎影响糖尿病患者血糖的相关机制

磷酸化，从而阻断磷脂酰肌醇3-激酶（phosphoinositide 3-kinase，PI3K）/蛋白激酶B（Ak strain transforming，Akt）信号通路的正常传导，降低葡萄糖转运蛋白4（Glucose transporter type 4，GLUT4）的表达，引发胰岛素抵抗[55-57]。

在IKKβ信号通路中，IL-6受体由配体结合亚基和信号转导亚基两部分组成，IL-6结合肝细胞、脂肪细胞、巨噬细胞等表面的IL-6受体后，配体结合亚基与信号转导亚基形成复合物，导致信号转导亚基的二聚化，然后通过酪氨酸激酶（janus kinase，JAK）/信号转导和转录激活因子3（signal transducer and activator of transcription 3，STAT3）信号[58]级联诱导IKKβ活化，进而磷酸化核因子κB抑制蛋白α（inhibitor of nuclear factor kappa-B alpha，IκBα）并促使其泛素化降解，最终导致核因子κB（nuclear factor kappa B，NF-κB）（p50/p65）二

聚体入核，上调TNF-α、IL-1β等促炎基因的表达，加剧炎症反应，促进胰岛素抵抗[59-60]。同时，活化的IKKβ还可通过诱导IL-23表达，进一步激活STAT3信号，形成炎症反应的恶性循环[61]。

NSPT显著降低了糖尿病伴牙周炎患者的IL-6、TNF-α、IL-1β等炎症因子水平[20-21]，可能通过间接抑制JNK和IKKβ信号通路，从而改善糖尿病患者的血糖控制。

2.2　AGEs-RAGE-ROS-NF-κB信号通路调控

高血糖是糖尿病的主要特征，持续的高血糖状态会促进AGEs的病理性蓄积[62]。此外，研究证实牙周炎患者的AGEs水平明显高于非牙周炎患者[63]，T2DM伴牙周炎患者体内高水平的AGEs与胰岛β细胞表面AGEs受体（receptor for advanced glycation end products，RAGE）结合后会触发级联病理反应：①激活NADPH氧化酶亚型（NOX2/NOX4），诱导活性氧（reactive oxygen species，ROS）大量生成[64]，通过激活IKKβ-NF-κB信号轴显著上调TNF-α、IL-6等促炎因子表达[65]；②ROS通过双重机制干扰胰岛素信号传导[66]，影响胰岛淀粉样蛋白多肽发生淀粉样变性，增加毒性胰岛淀粉样蛋白多肽的形成和聚集，从而导致胰岛β细胞损伤[67]，同时激活蛋白激酶C（protein kinase C，PKC），引起IRS-1酪氨酸磷酸化异常，促进IRS-1丝氨酸磷酸化，导致胰岛素受体信号传导缺陷[68-69]；③AGEs-RAGE互相作用通过上调NLRP3炎症小体表达，激活半胱氨酸天冬氨酸蛋白酶1介导的IL-1β成熟与释放，引发胰岛β细胞功能障碍及凋亡[70-71]。

牙周炎的组织破坏与免疫反应相关，宿主对感染微生物及其毒性产物的免疫应答会引发牙龈和牙周组织中免疫细胞（如中性粒细胞、巨噬细胞）的跨内皮迁移和激活。活化的中性粒细胞和巨噬细胞浸润炎症组织，吞噬病原体并释放ROS和促炎细胞因子[72]。过量的ROS进入体循环，可以促进血管内皮细胞线粒体内AGEs的形成与积累[73]。AGEs水平的增加会加剧全身氧化应激，进一步导致血糖负荷增加和循环性AGEs形成；此外，牙周致病菌还会利用唾液中的游离葡萄糖作为底物，上调甲基乙二醛（AGEs的前体）合酶的表达，进而促进甲基乙二醛的合成，进一步加剧氧化应激[74]。NSPT清除牙周致病菌后，可能通过降低循环AGEs水平，从而抑制RAGE信号通路过度活化所引起的胰岛素抵抗和胰岛β细胞功能障碍及凋亡，达到改善血糖控制的效果。

2.3　肠道菌群-TLR4-MyD88/TRIF信号通路调控

牙周致病菌可通过口腔-肠道途径发生异位定植，在肠道微环境中通过下调紧密连接蛋白的表达，破坏肠上皮细胞间连接复合体的完整性，从而导致肠道屏障功能障碍[75]。这些病原体可激活肠上皮细胞Toll样受体4（Toll-like receptor 4，TLR4），TLR4激活后分以下两条信号通路介导系统性代谢紊乱[76]。①髓样分化初级反应蛋白88（myeloid differentiation primary response 88，MyD88）依赖性信号通路：TLR4-MyD88信号级联激活IL-1受体相关激酶4，活化TNF受体相关因子6，导致转化生长因子β（transforming growth factor-beta，TGF-β）激活激酶1激活，进而诱导MAP激酶和NF-κB信号通路活化，促进IL-6、TNF-α等促炎因子的释放，引发全身性炎症反应[77-78]。②含TIR结构域的干扰素β诱导接头蛋白（TIR-domain-containing adaptor inducing interferon-beta，TRIF）依赖性信号通路：TLR4-TRIF信号通过激活TANK结合激酶1，磷酸化干扰素调节因子3，最终促进干扰素β异常表达，干扰脂肪组织、肝脏等细胞内IRS-1的酪氨酸磷酸化，从而加剧外周胰岛素抵抗[77，79-80]。

牙周致病菌的异位定植还会引起肠道菌群失调，导致肠道正常微生物群失衡[75]，肠道内兼性厌氧菌比例增加[81]，兼性厌氧菌的鞭毛蛋白可通过激活胰岛巨噬细胞上的Toll样受体5诱导促炎反应，从而抑制胰岛素基因表达、损害胰岛素原加工以及分泌过多应激诱导的胰岛素，最终导致胰岛β细胞衰竭[82]。此外，牙周致病菌在肠道微环境的异位定植所引发的肠道微环境生态失衡还会导致SCFAs生物合成受损，通过抑制G蛋白偶联受体（G protein-coupled receptor，GPR）41/43受体信号削弱肠L细胞GLP-1分泌功能，从而降低胰岛素分泌[83]。

除上述信号通路外，现有研究表明肠道菌群还可通过支链氨基酸代谢调控、胆汁酸转化、咪唑丙酸干扰等途径影响T2DM患者的血糖调节[84]。但鉴于这些途径与牙周致病菌的直接关联性证据尚不充分，故未进行详细分析。

NSPT通过清除牙周致病菌，可能减少其在肠道的定植，修复受损的肠道屏障功能，从而抑制TLR4信号通路的过度激活。此外，NSPT还可能通过调节肠道菌群失调，削弱鞭毛蛋白对胰岛β细胞衰竭的诱导作用，同时可能调节SCFAs-GPR信号

通路活性，改善GLP-1分泌受阻，最终调节血糖控制紊乱[85]。

2.4 Th17/Treg失衡与STAT3/SOCS3信号通路

在牙周炎的病理进程中，牙周致病菌的脂多糖（lipopolysaccharide，LPS）通过激活宿主树突状细胞表面的TLR4，刺激分泌IL-6和TGF-β[76]，然后分别通过$CD4^+$T细胞内的RORγt信号轴激活和磷酸化STAT3，驱动初始$CD4^+$T细胞向Th17亚群分化[86-87]。分化的Th17分泌大量IL-17A[86]，通过肝脏、脂肪等细胞内JAK2/STAT3信号通路磷酸化STAT3，进而上调促炎因子（IL-6、TNF-α）及NF-κB受体活化因子配体的表达，形成促炎-破骨细胞活化的恶性循环[88-89]。此外，分泌的大量IL-17A还可通过激活巨噬细胞分泌促炎细胞因子（TNF-α和IL-6）以及直接作用分化的脂肪细胞破坏胰岛素信号传导[90]。同时，磷酸化的STAT3可以直接与Smad家族成员3（SMAD family member 3，Smad3）相互作用，拮抗TGFβ信号传导[91]，而增加表达的NF-κB对Smad3活性也具有抑制作用[92]，二者通过抑制$CD4^+$T细胞内TGF-β/Smad3信号通路，下调叉头框蛋白P3（forkhead box protein 3，FoxP3）的表达，阻碍调节性T细胞（regulatory T cells，Treg）的分化成熟，Th17/Treg的平衡被破坏，导致免疫耐受失衡[93-94]。此外，STAT3的持续活化可诱导肝细胞中的细胞因子信号抑制因子3（suppressor of cytokine signaling，SOCS3）过表达，后者通过与IRS-1结合促进IRS-1的泛素化和降解，从而阻碍信号转导，降低胰岛素敏感性，直接干扰胰岛素信号转导[95-96]。

NSPT清除牙周致病菌后，会显著下降Th17的比例[97]，同时可能通过改善TGF-β/Smad3信号通路的活性抑制，调节Th17/Treg的失衡。这不仅会抑制STAT3的异常激活，还可能通过缓和IL-17A介导的胰岛素受体信号抑制以及削弱SOCS3对胰岛素信号通路的负调控作用改善糖尿病伴牙周炎患者的血糖控制。

2.5 β细胞凋亡与TLR4/内质网应激信号通路

牙周致病菌的毒力因子（如LPS、牙龈素）通过血液到达胰腺，会激活胰岛β细胞的TLR4/NF-κB[76]信号通路，诱导BCL2相关X蛋白（BCL2-associated x protein，Bax）/B细胞淋巴瘤2蛋白（B-Cell lymphoma 2，Bcl-2）凋亡通路失衡（Bax水平升高，Bcl-2水平降低）[98]，导致β细胞凋亡或转分化，减少胰岛素分泌；并且，激活的NF-κB可显著增加诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）的表达，致使β细胞内NO合成增加，过量产生的NO会导致ROS异常蓄积，最终引发β细胞氧化损伤及功能障碍[99-100]。同时，iNOS[100]和LPS[101]会触发β细胞内质网应激反应，激活蛋白激酶R样内质网激酶/真核翻译起始因子2α亚基/激活转录因子4信号轴，最终诱导C/EBP同源蛋白的异常表达，进一步加剧β细胞凋亡[102]。

NSPT后减少了LPS入血，有效降低外周血LPS浓度，可能通过抑制TLR4/内质网应激通路从而保护β细胞结构和功能完整性，维持机体正常的胰岛素分泌功能。

2.6 肝脏糖异生调控与FOXO1/PGC-1α信号通路

牙周炎微环境中升高的促炎因子（TNF-α、IL-6）会激活肝细胞JNK和IKKβ，特异性抑制IRS-1、IRS-2的酪氨酸磷酸化，阻断PI3K/Akt信号传导[103]。当Akt活性受到抑制时会导致叉头框蛋白O1（forkhead box protein O1，FOXO1）无法被磷酸化而滞留于细胞核内[104]，继而与过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator-activated receptor γ coactivator 1-α，PGC-1α）结合，上调磷酸烯醇式丙酮酸羧激酶和葡萄糖-6-磷酸酶的表达，从而增强肝脏糖异生代谢通路[105-106]。

NSPT有效降低循环炎症因子水平（TNF-α、IL-6）[107]后，可能通过抑制FOXO1/PGC-1α信号通路，从而改善患者的FPG水平异常。

上述信号通路不是独立运转的，各通路之间还存在密切的交互作用，共同调控血糖控制。牙周致病菌诱导产生的TNF-α和IL-6既可通过激活JNK/IKKβ信号通路直接诱导胰岛素抵抗，亦能在肝脏组织中驱动FOXO1/PGC-1α信号通路增强糖异生。此外，TNF-α、IL-6等炎症因子还可通过其他途径持续扩增：AGEs-RAGE信号通路经ROS激活NF-κB上调其表达；肠道TLR4-MyD88信号通路直接促进炎症因子释放；Th17分化后通过STAT3信号通路进一步刺激炎症因子生成，由此形成炎症级联的正反馈放大。在此调控网络中，NF-κB与ROS也作为重要枢纽介导多个通路互相作用：NF-κB不仅作为AGEs-RAGE和肠道菌群-TLR4信号通路的终末效应分子，还可被IL-6经IKKβ信号通路激活；而ROS作为AGEs-RAGE通路产物，既通过激活NF-κB放大炎症级联，又能直接损伤胰岛β细胞功能。这些信号通路通过器官间级联反应可逐

渐形成整体调控网络：肠道菌群失调经TLR4激活NF-κB，促进TNF-α/IL-6释放，激活肝脏JNK/IKKβ信号通路促进糖异生代谢；同时，激活的NF-κB与STAT3协同抑制TGF-β/Smad3信号通路，阻碍Treg分化，加剧全身炎症状态。NSPT通过清除牙周致病菌源头，同步阻断上述交互网络，最终实现炎症控制与血糖改善的协同效应。

3　小结与展望

综上，NSPT不仅能有效清除牙周致病菌生物膜、改善牙周临床指标，同时可显著降低血清CRP、IL-6等炎症因子水平，改善胰岛素抵抗状态，对糖尿病伴牙周炎患者的血糖调控具有积极意义。此外，越来越多的研究表明激光治疗、抗菌治疗等辅助SRP可以取得优于单一SRP的效果，这或许会为未来糖尿病伴牙周炎患者的NSPT带来新的启发。

然而，目前有关NSPT疗效的研究中存在样本量小[34]、随访时间短[29]、样本基线特征差异大[13]等局限性，并且多数研究局限于T2DM患者，缺乏对于1型糖尿病（type 1 diabetes mellitus，T1DM）患者的验证。因此，扩大样本量、优化实验设计以及纳入T1DM患者的NSPT效果试验对于研究结论的准确性是必要的。此外，虽然现有研究提示NSPT改善糖尿病伴牙周炎患者血糖控制的潜在机制可能涉及炎症因子调控、牙周致病菌群-代谢相互作用以及氧化应激介导的胰岛素抵抗等途径，但相关研究仍存在不足：①已有研究多基于牙周炎促进糖尿病进展的机制从而分析和推测NSPT改善血糖调控的可能机制，缺乏针对NSPT干预效应的动物实验及分子通路验证；②机制分析多聚焦于单一通路（如JNK/STAT3或TLR4/MyD88），缺乏对炎症-代谢-免疫网络的系统性解析；③未考虑个体的口腔菌群异质性对治疗响应的影响。

因此，未来的研究需首先明确牙周致病菌通过TLR4/NF-κB、AGEs-RAGE等通路影响胰岛β细胞功能及胰岛素信号传导的具体机制，进而拓展前文所提到的研究思路，系统展开相关研究，例如监测牙周组织及外周血免疫细胞的动态变化，揭示除Th17/Treg以外的其他免疫亚群如何响应NSPT并调控糖代谢；解析牙周致病菌经口腔-消化道途径迁移的规律及其对糖代谢的影响；探究牙周微生物代谢产物对胰岛β细胞功能的影响。明确NSPT改善糖尿病伴牙周炎患者血糖控制的具体机制将为研发调控糖代谢-炎症双通路的靶向药物提供理论依据。同时，在临床治疗中可以针对个体差异制定精准的个性化治疗方案，探索更多联合治疗方案实现多疗法协同增效，加强NSPT后的长期效果监测确保疗效的稳定性与持续性，建立内分泌-牙周联合诊疗体系以进一步提升糖尿病伴牙周炎患者的整体治疗水平。

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