病络理论视角下类风湿关节炎与牙周炎共病关系探析

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［摘要］ 类风湿关节炎（RA）与牙周炎（PD）共病的现象日益受到关注，均以慢性炎症、免疫失衡与进行性骨破坏为特征。现代研究证实PD是RA发病的重要危险因素，且二者共存时互相加重病情。然目前中医理论对此复杂共病关系尚缺乏系统解释。研究基于中医学“病络”理论，深入剖析RA与PD共病的内涵，提出“病络为枢、蕴毒蚀骨”为其核心中医病机。研究阐释PD作为“病络之始”，其病原体作为毒邪循络入节，通过分子模拟等机制诱发RA。RA与PD共病的动态病理演变过程：营卫倾移在微观层面的体现为免疫异常活化，导致络脉不荣；热毒循络引发络道亢变，使得病理性血管生成；最终于病络枢纽处蕴毒蚀骨，激活核因子κB受体活化因子配体（RANKL）/核因子κB受体活化因子（RANK）信号通路驱动的破骨细胞分化。该理论框架创新性地整合口腔微生物、免疫炎症及骨代谢等现代发现，为理解共病的复杂性提供整体动态新视角。鉴于现有牙周治疗对RA疗效存在局限及中医复方干预共病报道较少，依据病络理论，提出“以络统病、以药调络”的系统干预思路，提出“通络、清络、荣络”的中医策略。并列举治疗共病的潜在中药，未来应聚焦完善共病患者中医证候学特征，借助组学技术深入探索，为中医药应对多病共存状态提供理论依据与研究方向。

［关键词］ 类风湿关节炎；牙周炎；共病；病络
［中图分类号］ R259；R285；R289 ［文献标识码］ A ［文章编号］ 1005-9903（2026）10-0280-08
［doi］ 10.13422/j.cnki.syfjx.20251741
［网络出版地址］ https://link.cnki.net/urlid/11.3495.R.20250911.1142.005
［网络出版日期］ 2025-09-11 14:20:13 ［增强出版附件］ 内容详见http://www.syfjxzz.com或http://cnki.net

Analysis of Rheumatoid Arthritis and Periodontitis Multimorbidity from Perspective of Abnormal Collateral Theory

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［**Abstract**］ The multimorbidity of rheumatoid arthritis (RA) and periodontitis (PD) has drawn increasing attention, as both conditions are characterized by chronic inflammation, immune dysregulation, and progressive bone destruction. Modern research confirms that PD is a significant risk factor for RA development, and their coexistence mutually exacerbates disease progression. However, traditional Chinese medicine (TCM) currently lacks a systematic theoretical explanation for this complex multimorbid relationship. This study, based on the TCM theory of abnormal collateral, thoroughly examines the intrinsic connection between RA and PD multimorbidity, proposing "abnormal collateral as the pivot, with accumulated toxins eroding bone" as the core TCM pathogenesis. The research elucidates PD as the "origin of abnormal collateral", where its pathogens act as toxic factors that invade the joints through collaterals, triggering RA via mechanisms such as molecular mimicry. The dynamic pathological progression of

［收稿日期］ 2025-07-02
［基金项目］ 国家重点研发计划课题项目（2018YFC1707503）；国家中医针灸临床医学研究中心开放课题（NCRCOP2023015）；天津中医药大学教育教学改革研究项目（2023YJY036）；
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RA-PD multimorbidity can be described as follows: the displacement of Ying and Wei at the microscopic level manifests as immune hyperactivation, leading to collateral malnutrition; heat-toxins traversing collaterals induce collateral hyperactivity, resulting in pathological angiogenesis; ultimately, toxin accumulation at the pivotal abnormal collateral site erodes bone, activating the receptor activator of nuclear factor kappa-B ligand (RANKL)-receptor activator of nuclear factor kappa-B (RANK) signaling pathway-driven osteoclast differentiation. This theoretical framework innovatively integrates modern findings in oral microbiology, immune-inflammation, and bone metabolism, offering a holistic and dynamic perspective to understand the complexity of multimorbidity. Given the limited efficacy of current periodontal treatments for RA and the scarcity of reported TCM compound interventions for multimorbidity, the abnormal collateral theory proposes a systematic intervention strategy centered on "governing diseases through collaterals and regulating collaterals with herbs", along with TCM therapeutic principles such as "unblocking, clearing, and nourishing collaterals". Potential herbal treatments for multimorbidity are also highlighted. Future research should focus on refining TCM syndrome patterns in multimorbid patients and leveraging omics technologies for deeper exploration, thereby providing a theoretical foundation and research direction for TCM in addressing complex multimorbid conditions.

[**Keywords**] rheumatoid arthritis; periodontitis; multimorbidity; abnormal collateral

类风湿关节炎(RA)与牙周炎(PD)均为慢性炎症性疾病,分别以关节和牙周组织的进行性破坏为特征。RA主要表现为侵蚀性关节炎,可导致关节畸形甚至功能丧失[1];而PD则累及牙周支持组织(牙周韧带和牙槽骨),引发咀嚼障碍和牙齿过早缺失,甚至影响全身健康[2]。近年来,随着"多病共存"的生存状态逐渐受到重视[3],RA与PD的临床关联日益受到关注。文献表明,RA和牙周炎在临床上呈现出较高的共病率[4]。RA患者中中至重度牙周病的患病率高达75%,并且伴有更严重的牙周组织破坏[5]。荟萃分析显示,与健康人群相比,PD患者发生RA的风险同样增加(69%)[6]。值得注意的是,患有严重PD的RA患者往往表现出更高的疾病活动度[7],这一现象提示RA与PD可能存在相似的病理生理机制,其中包括慢性炎症状态、免疫失衡、破骨细胞活化和骨组织破坏等。更为关键的是,牙周状态直接影响RA的治疗效果。MOLLER等[8]发现同时患有严重牙周炎的RA患者,即使经过多轮合成或生物类抗风湿药物治疗,疗效仍显著低于牙周健康者。虽然非手术牙周治疗(如洁治、刮治等)可一定程度上改善RA病情,但仍存在无法彻底清除深牙周袋或复杂根面区域的菌斑,无法诱导骨再生和加重经济负担等问题[9]。因此针对RA合并PD的全身治疗,现有方案仍未满足的临床需求,而中医药因其多靶点调控炎症与免疫的独特优势,可为此类患者提供新的治疗选择。

病络理论是中医络病学说的重要组成部分[10],近年来在风湿免疫病领域逐渐受到关注[11]。现代研究多从瓜氨酸化、氨基甲酰化、口腔微生物和炎症反应等方向阐述RA与PD共病的机制[4]。中医方面从"痹症"和"牙宣"等方面解释RA与PD的临床表现,但缺乏从整体角度去看待共病问题的理论体系,难以深入揭示其共病状态下的病理过程。因此,本文拟从"病络"理论切入,将"病络"作为RA与PD共病的基本病机,探讨"病络为枢、蕴毒蚀骨"的中医病理过程,以期阐释RA合并PD的共病内涵,为中医药治疗复杂共病提供新思路。

1 络脉之本,病络之义

1.1 络脉之本 "络"首见于战国文字,《说文解字》释为"络,絡也",后引申为缠绕包裹,细微绵连之意。"络脉"的概念首次由《黄帝内经》提出,《灵枢》言:"经脉为里,支而横者为络",表明络脉为经脉的分支。络分大络、支络、细络等,络中充血,生理状态下充盈满溢[10]。《医门法律》指出络脉分布庞大,错综复杂的特点,"十二经生十二络,十二络生一百八十系络,系络生一百八十缠络,缠络生三万四千孙络"。《灵枢·经脉第十》曰:"经脉十二者,伏行分肉之间,深而不见……闷则急坐之也",描述了络脉的生理特征一为络浮表面常见可查,二为络横行于经脉所不及之处,三为经病以诊气口而知,视络脉可知络病。络脉的生理功能不外乎聚、流、通、化,能够通内外,遍周身,渗灌气血以荣养全身[12],《黄帝内经·灵枢·小针解》云:"节之交三百六十五会者,络脉之渗灌诸节者也"。络脉也是外邪深入、疾病演变之道,《黄帝内经·素问·皮部论篇》曰:"皮者,脉之部也,邪客于皮,则腠理开,开则邪入客于络脉"。因此,《黄帝内经·灵枢·经脉》所云:"经脉者,所以能决生死,处百病,调虚实,不可不通",强调了络脉通畅的重要性。

1.2 病络之义 病络出自《金匮要略》:"以由病络而涉于经,宜从治络血之法",指络脉一旦发生病变,邪气便可由此深入经脉,成为疾病发展的路径之一。病络不仅体现为络脉形态与功能的异常,更涵盖病势演变、病程变迁及病位更替的动态过程。络脉常则通,变则病,"病络"生则"络病"成[10],既是一种亚健康状态,也可以是一种疾病状态。《黄帝内经》记载了多种的病络表现形式为"血络、结络、盛络、横络、虚络"等[13]。病络为中医学中引起疾病或病证的基本病机,往往因邪气侵蚀或正虚而发,导致络脉充盈不足、形态异常和功能失调。《临证指南医案》云:"络中气血,寒热虚实,稍有留邪,皆能致病",说明病络具有留邪藏毒的特点。病络一旦形成,常呈现"易滞易瘀、易入难出、易积成形"的特点[14],使邪毒滞留难解,进而成为疾病演化的关键枢纽。因此,病络不仅是疾病发生与发展的病理基础,亦为辨证论治的重要依据。

2 共病源探

RA与PD病因相似,均为感受外邪,病起于局部。RA属中医"痹病"范畴,《素问·痹论》诉"风、寒、湿三气杂至,合而为痹也"。而PD在《诸病源候论》中亦载"头面有风,风气流入阳明之脉,与龈间血气相搏,故成肿"。

牙周炎或为RA之始动因素,过程为"毒入络脉,循络致

痹”。牙周炎属“牙宣”“齿痈”等范畴。热邪客于胃经，加风寒之邪外袭，循经上攻，久郁酿毒，灼伤龈肉。此“毒”包含牙周局部滋生的细菌及代谢产物等[15]。毒入络脉，内伏日久，形成“病络”。毒循络侵袭，随营卫之气波及他处，瘀阻关节，发为痹病。该病机恰与现代“黏膜起源假说”中PD诱发RA的机制相契合，即RA前期的免疫过程可以在关节症状出现多年之前发在关节外部位[16]，如肺、口腔和肠道黏膜的局部变化[17]。WENGNER等[18]提出受PD影响RA发病的“两次打击”模型：第1次是由牙周微环境中的细菌微生物引起，导致抗瓜氨酸化蛋白抗体（APCAs）产生的肽带的局部瓜氨酸化增加产生局部甚至全身抗体；第2次是针对蛋白表位阵列的自身抗体ACPAs水平和血液中促炎蛋白的不断增加，触发亚临床炎症，最终导致瓜氨酸化自身抗原的自我耐受性丧失，转变为临床表现的关节炎[19]。

2.1 源起齿龈 反复牙龈肿痛不仅是局部之患，更为络病之始。“齿为肾之余，龈为胃之络”，牙宣与经络密切相关，为胃经客热积久，外受邪风、寒凉相搏而成，《医宗金鉴》亦记载：“胃经客热风寒侵”。邪稽留于龈肉之内日久成毒，毒包括外来之细菌、病毒和内生之病理代谢产物等[15]。正如《素问·五常政大论》载：“夫毒者，皆五行标盛暴烈之气所为也”，《金匮要略心典》亦云：“毒者，邪气蕴蓄不解之谓”。局部反复热毒之邪久留龈络，“热毒上攻，宣露血出，齿龈肿痛不可忍”，气血壅滞，络伤血衄，病络生而络病成。PD常先于RA发病。荟萃分析显示，PD持续时间>5年的患者更有可能发生RA，并且发生RA的风险比普通人群高69%[6]。在RA的“临床前”阶段，PD和牙龈炎的患病率增加，同时存在口腔微生物丛紊乱[20-21]。牙龈卟啉单胞菌（*Porphyromonas gingivalis*）作为外来之毒，也是PD的关键致病菌，可在85.75%的慢性牙周炎患者中检出[22]。

2.2 循络入节 络病久而不解，毒循络入节致痹。局部牙龈反复炎症和屏障功能丧失使细菌及其毒力因子从黏膜移位到血液[23]。在滑膜组织中，RA的*P. gingivalis* DNA的阳性率高于健康人（33.3%∶5.9%）[24-25]。并且*P. gingivalis*被发现能够通过口腔分子模拟促进周身免疫耐受失衡，引发关节部位的免疫反应[18,26]。在最新2022年的大型队列中发现，RA患者中来源于*P. gingivalis*的瓜氨酸化*P. gingivalis*肽基精氨酸脱氨酶（CPP）3抗体水平升高，*P. gingivalis* CPP3与人类牙龈B细胞来源的瓜氨酸化肽之间存在交叉反应，并鉴定了来源于RA血液记忆B细胞的$CPP3^{+}$/$CCP2^{+}$克隆。因此在发炎的牙龈黏膜中，*P. gingivalis*衍生的瓜氨酸抗原的免疫力触发瓜氨酸耐受性的丧失，并且通过分子模拟机制促成RA患者中自身抗体的产生[27]。HONG等[28]发现具核梭杆菌（RA患者肠道中富集的口腔病原体）能够释放外膜囊泡，后者通过血液移位至关节并激活滑膜巨噬细胞，进而加重胶原诱导的关节炎。动物实验也证实*P. gingivalis*口腔感染能够导致血清阳性关节炎，并伴有全身炎症和骨侵蚀[29]。因此，齿龈之患为“病络之始”，关节之病乃“病络之延”，二者发病均源于络。

3 病络为枢，齿节同病

RA与PD的共病过程为素体络虚，复感外邪，营卫失调致卫气亢盛化火，营气衰少失濡，终致营卫倾移，气血失畅，络脉受损，导致疾病“虚实夹杂”。久病入络，邪毒乘虚内侵，热毒循络，生克制化失常，络道亢变，恣行无度，为毒邪由表及肌肉、经筋甚至骨提供通道。而关节若“久而不治，令人骨节蹉跌”，牙周则“日减腐颓久露根”，内外合邪，蕴热酿毒，侵蚀齿节。因此，二者共病以为“病络为枢，蕴毒蚀骨”为病机核心。

3.1 营卫倾移，络脉不荣 营卫倾移之论首见于《黄帝内经·素问·离合真邪论》载：“经言气之盛衰，左右倾移以上调下，以左调右……此皆荣卫之倾移，虚实之所生”，阐述了营卫倾移能够影响机体虚实和气血盛衰。《黄帝内经·素问·痹论篇》中叙述了营卫与风寒湿相合可致痹病：“营卫之气亦令人痹乎……逆其气则病，从其气则愈，不与风寒湿气合，故不为痹”。生理状态下，营卫相随，两气交感，和调内外以实现机体的基本运行；病理时，外邪趁袭而入，卫气抗邪，致营卫性质偏倾、分布改变[30]。此“营卫倾移”之态。

卫气凭其“慓悍滑利”之特性，迅即奋起抗邪，聚于病所而成实，《黄帝内经·灵枢·岁露论》亦言：“风府无常，卫气之所应”。RA与PD之局部病位肿痛实为“卫气抗邪”的外在表现。卫气过亢的微观表现为免疫细胞的异常活化，包括M1巨噬细胞极化和辅助性T细胞17（Th17）/调节性T细胞（Treg）比例失衡等[31-32]，导致局部炎症因子风暴，如白细胞介素（IL）-17A、IL-23、肿瘤坏死因子（TNF-α）、IL-1β等大量分泌，火热之邪内生[33]，正所谓“气有余便是火”。

与此同时，卫气亢盛无制失其“温分肉，充皮肤，肥腠理，司开阖”之常，反在脉内留滞逆行，克伐自身，致营气衰少。微观表现为免疫修复功能的下降和组织代谢环境趋于耗损失养。在缺氧的炎症条件下，RA与PD患者的Treg细胞表现出功能抑制甚至丧失[34-35]；而细胞能量代谢也会由氧化磷酸化转为糖酵解，能量利用效率下降，使成纤维细胞的表型转化为促炎和侵袭性表型，前者具有高度增殖，分泌促炎细胞因子的特点[36]，后者表达核因子κB受体活化因子配体（RANKL）和基质金属蛋白酶（MMPs），分别参与破骨细胞骨吸收和软骨降解[37]。牙龈成纤维细胞在PD中表现出类似滑膜成纤维细胞的持续炎症活化特征和骨吸收特性，如RANKL/骨保护素（OPG）比率上升[38-39]。

卫气过亢和营气衰少交织共致营卫倾移之象。营若不濡，络脉不荣，犹草木失溉，为病所乘，病络则生[40]。《素问·气穴论》云：“孙络三百六十五穴会……以通荣卫”，指出由络以通营卫。故营卫倾移，络脉失荣为共病之始。

3.2 络道亢变，热毒循络 RA与PD虽病位异处，但二者属络脉之病，为病络范畴，皆因《灵枢》言：“络脉者，病之所生也”。全身络脉纵横交织、遍布周身，构成疾病相互影响的枢纽[41]，其中一种疾病引起的全身炎症反应会加重或加速另一种疾病[42]。RA与PD共病之人，素体络虚，牙周致病菌及其毒力因子（如脂多糖）等“外来邪毒”乘虚侵袭，导致局部营卫失调。邪毒郁积于络，日久化热生毒，形成“热毒”。“热毒”不

仅囿于局部，还可循络远达，延至四肢关节，此即毒邪互通于络之象。现代研究证实了这一病理过程：RA合并PD者龈沟液中炎性因子TNF-α和IL-1β的平均水平高于PD患者[43]；共病患者血清中的骨桥蛋白、TNF受体1、TNF受体2和RANKL水平亦为RA或PD患者中最高[44]。与RA患者相比，共病患者血清中17/98的炎症标志物水平升高[45]。其中，MMP-8可能是毒邪循络互传，连接RA与PD的关键炎症因子。RA患者中MMP-8在唾液、龈沟和血液的中的水平均较高[46]，且MMP-8水平与牙周炎的严重程度呈正相关[47-48]。

热毒循络，持续损伤络脉，是络道亢变的始动因素[49]。正如《素问·六微旨大论》所言："亢则害，承乃制，制则生化，外列盛衰，害则败乱，生化大病"，"络道亢变"便据此提出。毒邪侵袭或内郁络道，正邪相争，络脉环境失稳，气机失常，生克之道逆乱，使络道恣行无度，结构多生变异，分布紊乱，增生无度。新生病络为毒邪由皮表、肌肉内侵至经筋甚至骨提供通道[50]。RA[51]与PD[52]共病的核心病理基础正是持续炎症与血管生成。在慢性缺氧与炎症微环境中，血管内皮生长因子（VEGF）和缺氧诱导因子-1α（HIF-1α）等关键促血管因子被激活，打破促血管因子与抑制因子的动态平衡，诱导病理血管生成[53]。新生的病理血管一方面为炎症部位输送氧和营养物质，并作为炎症细胞浸润和介质扩散的新通道促进炎症持续；另一方面由于其血管形态发育不全出现扩大和渗漏的现象导致血管灌流不足的缺氧，诱导促血管生成因子不断地转录，进一步促进血管生成[54]。关节肌骨超声显示，滑膜血流信号与RA疾病活动度呈正相关[55]。有研究发现PD患者唾液及牙龈组织中VEGF水平显著升高，并与牙龈血管密度呈正相关[56-57]。同样，牙周炎初期小鼠的牙周组织中H型血管的生成显著增加。*P. gingivalis*也能够诱导牙周组织的血管生成，其主要毒力因子脂多糖可刺激内皮细胞迁移和促进内皮管的形成[58]。

3.3 病络为枢，蕴毒蚀骨 RA和PD长期共存，互相加重的过程，体现出"病络为枢，蕴毒蚀骨"之病机特征。络伤日久，营血内不荣养，卫气外不御邪，邪久客虚处，使精血、津液变易，《三因极一病证方论》言："津液流润，营血之常，失常则为痰涎"。络脉结构细窄迂曲，易滞易瘀[14]，湿浊瘀阻日久相互搏结，痹而不通，蕴而化毒，致痹于节、蚀于齿。正如刘维教授所提出的"毒痹论"学术思想，毒为痹病反复发作、难以根治的核心病机[15]，该理论与RA与PD共病高度契合。

临床发现，RA可能是PD患者牙周组织破坏加剧的潜在原因，共病患者牙龈浆细胞分化水平及其诱导破骨样细胞分化能力均高于单纯PD患者[59]。此外，PD的持续存在也可能有助于RA相关自身抗体的产生。与单纯RA或PD患者相比，RA合并牙周炎患者的血清阳性率更高[60]，其中包括类风湿因子（RF）和ACPA水平的升高[45]，二者直接或间接与关节骨破坏相关[61]。微观层面，RA和PD自身免疫异常所产生的促炎细胞因子、炎性介质及免疫复合物等都属于毒，主要通过激活RANKL/核因子κB受体活化因子配体（RANK）信号轴驱动破骨细胞分化，导致关节与牙槽骨侵蚀。RA患者的滑膜和滑膜液中TNF-α、IL-6和IL-1水平升高，这些促炎因子与Th17细胞分泌IL-17、IL-21、IL-22等共同诱导滑膜成纤维细胞中的RANKL表达[37]。PD中Th17细胞浸润牙周组织，分泌的IL-17A也可刺激成纤维细胞、上皮细胞和内皮细胞产生RANKL、MMPs等，促进牙槽骨吸收[62]。除了刺激骨吸收外，炎症风暴还会抑制骨基质蛋白的表达并导致成骨细胞死亡，从而破坏骨形成[63]。固有免疫和适应免疫由细胞间细胞传递，这些过程均在全身络道中发生。从整体观念和动态视角下的免疫系统相互作用机制，有望为RA合并PD共病病理过程中相互作用的模式建立全新的生物学框架。

4 以络统病，以药调络

络以通为用，《景岳全书》中记载"脉络不通，皆由气血……诸如此者，皆能阻塞经络"，表明络脉气血运行不畅为络脉"不通则痛"的主要原因。叶天士在"络以通为用"的基础上提出"络病须治血"的治疗法则。共病患者因邪久入络而气血失常痰凝败瘀相杂酿毒，血瘀于络，治宜通络以活血。外邪侵袭，气郁化热灼络，故应循络而治，清络以凉血。患者因素体络虚，或病久毒损络脉，使得气虚则血行无力；血虚则气失所载，气机失常，皆可导致络脉瘀阻。《素问·举痛论》早有"血虚则痛"之训。络虚即为荣邪之处，因此宜荣络以通络补虚。故治共病应当兼顾通络、清络、荣络等法[64]。从病络视角中，部分具有共病潜力的中药总结见增强出版附加材料[65-97]。

5 结语

基于病络理论，本文阐述了PD是RA发病的危险因素，描述了2种疾病互相影响的复杂性和共病的病理特点。通过营卫倾移，络道亢变和蕴毒蚀骨的视角，深化了对RA合并PD共病过程中病络的内涵和认知，拓展了该理论在共病中的应用空间，提供了认识共病更具有系统性的崭新视角。虽临床关于治疗RA合并PD的报道较少，但依据病络学说和现代机制，依循"通络、清络和荣络"的治策，"以络统病、以药调络"的系统性干预思路，有望成为中医药应对慢性炎症性共病的新策略。目前亟需开展多中心，大规模临床研究，进一步探索共病患者的中医临床证候学特征描述和临床特点，目前虽无现成复方干预共病，但病络理论可作为组方指导思想，结合组学技术（转录组/代谢组）挖掘新的治络靶点与标志物，为病络理论指导下的中医治疗策略在不同患者群体中的疗效与安全性提供依据，为针对性开发特异性强的中药复方奠定基础。

［利益冲突］ 本文不存在任何利益冲突。

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