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·综述·

口腔疾病与抑郁症的关系

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【摘要】　口腔健康是身心健康的重要组成部分。口腔是与外界交流的渠道，具有表达紧张、悲观等情绪的功能。口腔疾病可引发抑郁情绪，抑郁症也可导致口腔疾病的恶化。作为人体微生物群落的重要组成部分，口腔微生态失衡可释放口腔病原微生物，通过循环、神经、免疫系统等途径，传递到大脑，对中枢神经系统的功能产生重大影响，导致下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal axis，HPA）轴失调，加重抑郁发展。同样，抑郁症患者口腔微生态的失衡，会加剧口腔疾病的发生。抑郁症与口腔疾病之间的关系并非孤立存在，而是相互影响、互为因果的复杂过程。为揭示两者之间的因果关系，并制定预防、治疗这两种疾病的共同策略，本文从口腔微生物角度探讨口腔疾病与抑郁症之间的互作机制：龋病、牙髓根尖周病和牙周病的发生与口腔内特定细菌的过度增殖密切相关，如变异链球菌、牙龈卟啉单胞菌、罗氏菌等，可通过不完整或受损的血脑屏障直接侵入大脑，激活促炎细胞因子，导致神经炎症，从而加重抑郁症状；口腔黏膜的炎症和溃疡由多种因素引起，包括感染、免疫异常等；由于抑郁症患者的免疫系统功能受损，这些炎症反应往往更为剧烈且难以控制；错𬌗畸形、三叉神经痛和颞下颌关节病等患者心理压力和免疫系统的变化，也会增加抑郁症的发生风险。未来需要探索抑郁症患者口腔微生态的治疗潜力，通过调整口腔微生态来改善抑郁症的症状和治疗效果，为抑郁症的预防和治疗提供新途径。

【关键词】　口腔疾病；　口腔健康；　抑郁症；　口腔微生态；　口腔病原微生物；　中枢神经系统；　免疫系统；　下丘脑-垂体-肾上腺轴；　互作机制

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Relationship between oral diseases and depression

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【Abstract】　Oral health is an integral component of overall well-being, with the oral cavity serving as a channel for external communication and expression of emotions such as stress and pessimism. Oral diseases can intensify feelings of depression, whereas depression can worsen oral health conditions. As a crucial part of the human microbiome, an imbalance in oral microbiota can release oral pathogenic microbes, which, through pathways including the circulation, nervous, and immune systems, can reach the brain and significantly affect the central nervous system. This can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, further intensifying the development of depression. Similarly, an imbalance in oral microbiota in individuals with depression can intensify the occurrence of oral diseases. The relationship between depression and oral diseases is not isolated but rather a complex interplay in which they mutually in-

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fluence and act as causative factors. To elucidate the causal relationship between oral diseases and depression and devise strategies for the prevention and treatment of both conditions, we explore the interaction mechanisms between oral diseases and depression from the perspective of oral microbiota. The occurrence of dental caries, periapical periodontitis, and periodontal diseases is closely associated with the excessive proliferation of specific bacteria in the oral cavity, such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum*. These bacteria can directly invade the brain through the compromised blood-brain barrier, activating pro-inflammatory cytokines and worsening depressive symptoms. Inflammatory conditions and ulcers in the oral mucosa are caused by various factors, including infection and immune abnormalities. Because of compromised immune function in individuals with depression, these inflammatory responses are often more severe and difficult to control. Malocclusion, trigeminal neuralgia, and temporomandibular joint disorders increase the risk of depression because of psychological stress and changes in the immune system. We also outline the diagnostic and therapeutic considerations for oral diseases in patients with depression, emphasizing the importance of early intervention for disease management. Future research will explore the therapeutic potential of oral microbiota in individuals with depression, with the aim to improve symptoms and treatment outcomes by adjusting oral microbiota, thus providing novel avenues for the prevention and treatment of depression.

【Key words】 oral diseases;　oral health;　depression;　oral microbiota;　oral pathogenic microorganisms;　central nervous system;　immune system;　hypothalamus-pituitary-adrenal axis;　interactions mechanism

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抑郁症是一种情绪障碍，其特征是失去感受快乐的能力或一直感到悲伤，并伴有日常功能缺陷，对人的感觉、思维方式和行为产生负面影响[1-2]。根据世界卫生组织（WHO）公布的数据，抑郁症位列全球第二大流行疾病，仅次于心血管疾病，超3亿人饱受困扰[2-4]。2010年以来，在中国，抑郁症是导致健康寿命损失年（years lived with disability，YLD）的第二大原因[3]。全球十大主要导致功能受损或劳动能力丧失的疾病，有五种属于精神疾病范畴，其中抑郁症名列第一[5]。抑郁症患者缺乏职业和社会角色功能，每年有一千万至两千万患者有自杀倾向，生活质量低下，治疗依从性低，为家庭及社会带来沉重的心理和经济负担。

1　抑郁症

抑郁症病因可由遗传、神经生化、神经内分泌异常、心理、社会等多因素造成[2, 6-8]。其中，遗传因素在抑郁症的发病中扮演重要角色，抑郁症患者的近亲罹患抑郁症的风险高于一般人群，约为2～10倍[2]。严重的躯体疾病和社会压力等因素损害患者的心理健康，也可导致抑郁症的发生[7]。此外，神经递质功能和内稳态失衡，可导致去甲肾上腺素、多巴胺、5-羟色胺等分泌异常，诱发抑郁症[6, 9]。研究表明，下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal，HPA）轴异常与抑郁症的病理生理变化高度相关[2, 9]。HPA轴是一个由荷尔蒙和神经通路组成的复杂网络，可调节人体对压力的反应。正常HPA轴活动会释放应激激素，如促肾上腺皮质激素释放激素（corticotropin releasing hormone，CRH）、促肾上腺皮质激素（adrenocorticotropic hormone，ACTH）和皮质醇等应对压力源[9-11]。然而，在抑郁症的患者中，中枢神经系统产生的炎症细胞因子会影响大脑区域（与情绪和奖励有关）的神经递质代谢，刺激CRH、ACTH和皮质醇的水平升高，导致HPA轴负反馈调节异常，从而产生抑郁[9]。

抑郁症与恶性肿瘤、内分泌疾病、心血管疾病以及神经系统疾病等内在原发性疾病之间存在双向关系[8, 10, 12-13]。例如，糖尿病患者长期的高血糖可能导致神经递质浓度变化，引发抑郁情绪。反之，抑郁症会引起免疫功能异常，当处于应激状态时，糖皮质激素分泌增加，降低葡萄糖利用，增加患糖尿病的风险[13]。肺癌、乳腺癌、前列腺癌、消化道癌、结直肠癌和胰腺癌也已被证实与抑郁症密切相关[12]。肿瘤和抗肿瘤治疗引起的炎性反应和细胞因子会诱发抑郁症。与此相反，长期抑郁情绪会对HPA轴产生慢性刺激[14-15]，皮质醇和肾上腺素分泌的不平衡，导致机体免疫功能紊乱和细胞因子释放增加，从而增加肿瘤进展的风险[9]。此外，抑郁症还与痴呆症、冠心病、帕金森病、癫痫、

疼痛、癌症、衰老、骨质疏松症和肠易激综合征等多种系统性疾病密切相关[12]。

抑郁症和口腔疾病作为两大危害公共健康的问题，同样存在双向关系。Cademartori等[16]利用Meta分析调查抑郁症与口腔疾病之间的关系，发现抑郁症与龋病、牙周病和牙齿缺失的风险呈正相关。如抑郁症患者的牙齿脱落几率是没有罹患抑郁症患者的1.31倍。随着抑郁症严重程度的增加，口腔感染性疾病（黏膜病、牙髓根尖周病、口腔异味）的发病率增加，这可能与抑郁症诱发体内生理变化有关，导致口腔疾病的患病率更高[17]。而口腔疾病，如错𬌗畸形、三叉神经痛、颞下颌关节病，也可促进抑郁症的发生发展[18]。颞下颌关节紊乱（temporomandibular joint disorders，TMD）可通过引起头痛、下巴疼痛、咀嚼困难和相关的心理障碍等，促使患者产生抑郁情绪[19]。需正颌手术的错𬌗畸形患者，影响正常进食、说话和社交能力，诱发抑郁症的产生[20]。口腔微生物作为人体微生物群落的关键成员，在口腔和全身疾病发展中发挥重要功能[1, 21-22]。在口腔疾病与抑郁症的相互影响中，口腔微生物也有着重要的作用。一方面，口腔微生物及其代谢物能够进入肠道，并迁移到受损的血脑屏障，导致神经炎症，促进抑郁症的发生发展[9, 11, 23]。另一方面，抑郁症患者中高浓度的皮质醇可通过唾液腺分泌进入口腔，对口腔健康和口腔微生物组产生影响[1, 24]，增加罹患龋齿和牙周病、口腔干燥综合症的风险。研究表明，抑郁症患者经常会主诉牙痛、牙周出血、咀嚼不适、口腔异味、口腔黏膜病、颞下颌关节病和三叉神经痛等，有些还会伴有牙齿缺失、缺损、错𬌗畸形等[25-27]。

2　与抑郁症发生相关的口腔颌面疾病

口腔微生物组的变化影响微生物组与宿主免疫系统之间的交流，导致唾液中的促炎沟通和皮质醇的增加，从而进一步加剧抑郁症。因此，了解口腔疾病与抑郁之间的关系对确定干预的早期目标和增进对机制的理解至关重要。

2.1　龋病

龋病作为影响全球多数人的慢性病，可能是导致人一生中牙齿脱落和其他并发症的主要病因[28]。Cademartori等[16]通过横断面研究2 000多名孕妇患龋齿与抑郁症状之间的关系，证实龋齿对抑郁症有直接影响，特别是在未经治疗的人群中，或成为抑郁症的独立危险因素，同时该团队通过龋病与抑郁症之间的Meta分析，发现抑郁症会增加成人和老年人患龋齿、牙齿脱落和无牙症的几率，且存在正相关性。研究表明，在未治疗龋病的抑郁症患者中，往往忽视预防性口腔卫生保健措施，增加牙齿脱落的风险[29]。

Li等[3]使用口腔微生物组最新全基因组关联研究（genome-wide association studies，GWAS）的摘要数据[30]，对285个唾液微生物群和309个舌背微生物群进行多基因风险评分（polygenic risk scores，PRSs），分析口腔微生物组与抑郁症之间的关系。研究发现，未分类的变异链球菌（*Streptococcus unclassified uSGB* 891）和罗氏菌（*Rothiamucilaginosa SGB* 3124）之间存在显著的相互作用，在患有龋病的抑郁症患者中，罗氏菌减少，变异链球菌增多，而后者是最主要的致龋菌，可通过血脑屏障不完整或受损的区域直接到达大脑，激活促炎细胞因子，导致神经炎症，加重抑郁[3]。Simpson等[1]发现，在皮质醇水平较高的抑郁症患者中，其口腔内放线菌明显降低。推测皮质醇水平的升高可导致HPA轴过度激活，从而加重抑郁。

2.2　牙髓根尖周病

由于未治疗的龋齿或牙髓炎可引起牙根尖周组织的急性或慢性炎症，导致牙齿根尖周围的牙槽骨破坏，牙龈组织发炎、肿胀和疼痛，并可能导致牙齿脱落[31]。牙龈卟啉单胞菌（*Porphyromonas-gingivalis*，*Pg.*）、具核梭杆菌在急性根尖周炎、牙髓根尖周感染中检出率很高，通过释放包括脂多糖（lipopolysaccharide，LPS）在内的毒力因子[32]，促进根尖周组织的免疫激活破坏，导致体循环中LPS水平升高，激活HPA轴，促进应激激素-皮质醇的释放，产生抑郁障碍[33]。Simpson等[1]通过收集66名参与者唾液样本进行皮质醇和C反应蛋白（C-reactive protein，CRP）检测，同时使用16S rRNA基因测序技术，分析参与者口腔微生物组变化，研究抑郁症与口腔微生物之间的关系，发现具核梭杆菌与抑郁症患者中的皮质醇水平呈正相关。另一方面，皮质醇也被证明可以抑制其他口腔细菌的生长[1]，如牙龈卟啉单胞菌。除了皮质醇之外，口腔中可能还存在其他神经内分泌关联[2, 6, 7, 23]，意味着或有其他激素（CRH、ACTH）、神经递质（去甲肾上腺素、脑内5羟色胺、多巴胺等）为连接口腔微生物与抑郁症之间的桥梁[34]。

2.3　牙周病

牙周致病微生物与抑郁症等精神疾病的病

因、病理生理学密切相关，可导致免疫系统失调。许多横断面流行病学研究表明[32]，牙周炎发病率与抑郁症发病率呈正相关。表明患有牙周炎的人更有可能患上抑郁症，但这种关联的因果关系和潜在机制尚不清楚。*Pg.*是造成牙周炎主要原因[32]。近年来，抑郁症患者中神经营养素缺乏假说受到了广泛关注[35]。该假设表明，减少神经营养因子（支持大脑中神经元生长和存活的蛋白质）会使大脑无法适应环境刺激，从而导致抑郁症的发作。*Pg.*的存在可能减少大脑中的神经营养因子，导致抑郁症的发展。此外，*Pg.*会产生LPS[36]，可导致促炎细胞因子的过度分泌，增加抑郁症的易感性。在患有牙周病的抑郁症患者中，与牙周健康紧密相关的奈氏放线菌、戈氏放线菌及普氏菌属，如中间普氏菌、产黑普氏菌、变黑普氏菌以及密螺旋体等均被发现[33]。

牙周炎若不及时治疗，会导致寄生菌滋生、口腔细菌产生毒素，从而引起口腔异味。牙周炎病变部位的细菌会分泌硫化物等气味物质，使口腔产生难闻味道。Simpson等[1]通过横断面研究发现，在抑郁症患者中具核梭杆菌、拟普雷沃菌和牙龈卟啉单胞菌检出率很高，是口臭和牙周病中最常见的几种菌属。这些病原菌通过血液或受损的血脑屏障区域直接进入大脑，还可通过促炎细胞因子间接影响中枢神经系统。促炎细胞因子激活内皮细胞中表达肿瘤坏死因子（tumor necrosis factor -α，TNF-α）和白细胞介素-1（interleukins-1，IL-1）的受体，将信号传递给激活小胶质细胞中的血管周围巨噬细胞，导致神经炎症[36]。

2.4　口腔黏膜病

复发性阿弗他溃疡（recurrent aphthae ulceration，RAU）、口腔扁平苔癣（oral lichen planus，OLP）以及灼口综合征（burning month syndrome，BMS）是最常见的口腔黏膜病[37-39]。口腔黏膜病因复杂，目前尚未明确，且存在明显的个体差异，病毒或细菌感染因素为主要原因，患者病损部位存在白色念珠菌、链球菌、幽门螺杆菌、腺病毒、巨细胞病毒、单纯疱疹病毒或乳头状病毒等，易导致感染[40]。免疫系统和神经内分泌紊乱易可造成黏膜病的发生[41]。

Suresh等[41]对18～49岁和50～77岁的人群进行了6个月的观察随访，发现RAU、OLP和BMS组的患者有不同程度的焦虑和抑郁症状，尤其是BMS组。焦虑、抑郁和心理压力与RAS和OLP症状之间存在高度相关性。免疫学模型表明，伴有黏膜病的抑郁症患者免疫系统会发生变化，从而影响口腔微生物组[38]。同样，患者体内炎症水平的增加会导致口腔病原微生物积聚[37]。免疫系统、病原微生物、口腔微生物组和心理健康之间可能存在复杂的相互作用[41]，了解互作机制可能是治疗抑郁症、口腔黏膜病患者的有效途径。

2.5　错𬌗畸形

错𬌗畸形是指在儿童生长发育阶段或成长过程中，由遗传、环境因素、外伤、替牙障碍、牙周病等原因引起，造成颌骨大小、形态和位置、上下颌之间的咬合关系、面部外形的异常[20]。错𬌗畸形的患者，尤其是需要正颌外科手术的患者，通常会因审美障碍、功能问题、口面部疼痛和慢性头痛而出现心理变化，内源性多巴胺能释放水平降低，加重抑郁症状[20]。

研究表明，需要正颌外科手术的患者中发生重度抑郁症的几率是正常人的5倍[20]。虽然正颌外科手术可适度改善患者心理和社会生活的质量，但其抑郁、焦虑和偏执加重，导致免疫系统持续被激活，促炎分子合成增加，HPA轴失调，释放应激激素，使唾液中皮质醇升高，造成口腔微生态失衡。然而，口腔微生物群的改变，可引起全身性炎症反应，造成C反应蛋白（C-reactive protein，CRP）升高。研究证实，抑郁症状与CRP水平升高有关，会加重抑郁障碍。因此抑郁症是该人群生活质量低下的主要因素，并严重影响患者的活力、社会方面和术后心理健康。

2.6　三叉神经痛

三叉神经痛（trigeminal neuralgia，TN）的特征是短暂、阵发性、电击样疼痛，持续数秒或数分钟。即使轻触口角、鼻翼、颊部和舌等区域，患者也会感到疼痛[42]。一项流行病学研究表明[43]，TN患者经常会感到焦虑、抑郁和睡眠不佳，周围神经的慢性损伤会导致行为异常，造成精神障碍，产生抑郁。长时间的神经疼痛会累积呼吸、心脑血管及消化系统，影响口腔微生态，使其失衡。口腔微生物群产生的代谢产物，通过不同途径输送到大脑，如循环系统、免疫系统和迷走神经，干扰中枢神经系统与口腔微生态的交流，造成抑郁。

2.7　颞下颌关节病

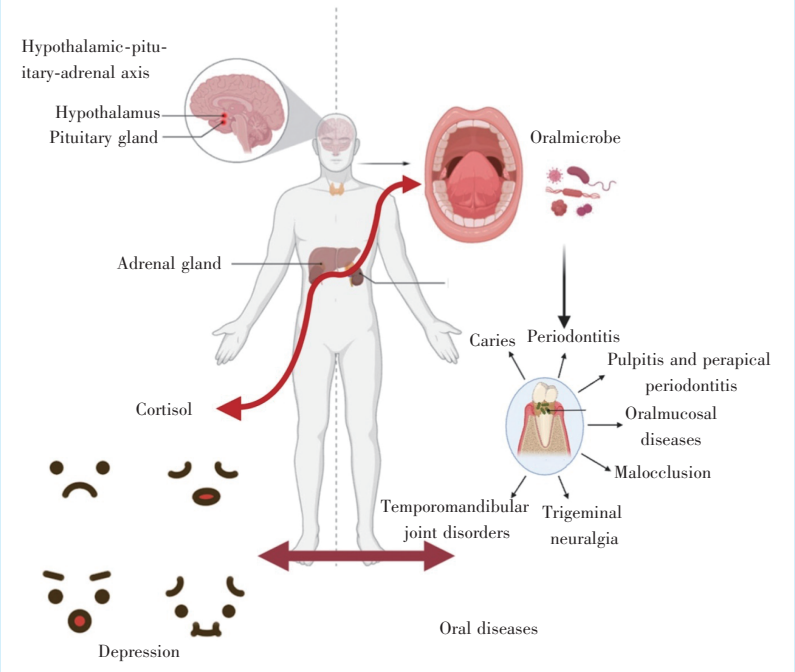
TMD是慢性疾病，临床表现为关节区疼痛、运动时关节弹响、下颌运动障碍等[18]。Sebastian等[18]发现，抑郁症常见于患有TMD的错𬌗畸形患

者，尤其是伴有肌筋膜疼痛时，作为一种持续的应激源，可调节白细胞介素6（interleukin-6，IL6）的表达，受易感遗传多态性的影响，导致抑郁症的产生。IL6是全身性炎症的重要介质，外周将这种炎症信号传递到大脑，促使中枢神经系统分泌促炎细胞因子，激活神经递质去甲肾上腺素、多巴胺和血清素的释放，干扰神经化学级联的调节，从而导致抑郁[44-45]。TMD功能性障碍往往与中枢致敏和痛觉放大有关，这种疼痛状况的病理生理机制尚不清楚。然而，疼痛感知的增强、大脑活动的改变、免疫和神经内分泌活动以及遗传易感性都可能参与其中。

3　小结与展望

口腔健康不仅是为了牙齿健康，还是个体健康和幸福的起点。口腔微生态与抑郁症发生发展紧密相关，口腔微生物群可通过神经、免疫和代谢等途径传递信号到大脑，这为靶向干预抑郁症提供新途径，此外，口腔微生态在抑郁症的发病机制中也发挥着重要作用（图1）。

临床方面，口腔微生态可作为抑郁症风险预测和诊断的生物标志物之一。对于患有口腔疾病的抑郁症患者，如龋病、牙周炎、牙髓根尖周病、口腔黏膜病、三叉神经痛、颞下颌关节病、错殆畸形等，需要在治疗口腔问题之前进行精神科会诊。根据口腔微生态的变化，识别出患有抑郁症风险的个体，开发个体化治疗方法，为早期干预抑郁症提供窗口，从而更好地提高患者的生活质量、延长预期寿命、降低医疗费用。未来需要更深入的研究来确定口腔微生态与抑郁症之间的因果关系，促进口腔医学和精神医学之间的跨学科合作。



Depression and oral diseases have a bidirectional relationship. An imbalance in the oral microbiome can lead to the release of oral pathogenic microorganisms, which, through pathways such as the circulation, nervous, and the immune systems, transmit to the brain, significantly affecting central nervous system function. This can lead to dysregulation of the hypothalamic-pituitary-adrenal axis, worsening the development of depression. Similarly, an imbalance in the oral microbiota of individuals with depression can intensify the occurrence of oral diseases

Figure 1　Relationship between depression and oral health

图1　抑郁症与口腔疾病的相互作用关系

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