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· 综述 ·

## 咬合紊乱导致的慢性应激对机体的影响

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**【摘要】** 咬合紊乱是上、下颌牙的静动态关系不协调的异常状态,临床中最常见的是因个别点的早接触而无法达到牙尖交错位或因咬合高点产生干扰的现象,可使牙周组织损伤、咀嚼功能下降、关节肌肉不适,甚至通过蓝斑-交感-肾上腺髓质系统和下丘脑-垂体-肾上腺轴的过度活化诱导血清皮质类固醇水平的升高导致机体慢性应激。本文就咬合紊乱导致的慢性应激对骨组织、颌颌系统、情绪及认知功能影响的相关研究进行了综述。研究表明,咬合紊乱不仅导致口腔局部的骨丢失、全身骨量的减少,对颌颌系统局部功能产生损害,在神经内分泌系统方面对机体的焦虑情绪、睡眠、认知功能及空间记忆能力亦有显著的负面作用。近年来对于咬合紊乱的关注呈上升趋势,早期发现并及时调整不协调的咬合关系已成为临床中不容忽视的问题。

**【关键词】** 咬合紊乱; 颌颌系统; 蓝斑-交感-肾上腺髓质系统; 下丘脑-垂体-肾上腺轴; 皮质类固醇; 慢性应激; 认知功能; 焦虑

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**Effects of chronic stress caused by occlusal disorder on the body** JIANG Jiayang, LI Baosheng, LI Yuyang, ZHANG Huiyan, JIN Zhuohua, OU Yanzhen, MENG Weiyang. Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling&School and Hospital of Stomatology, Jilin University, Changchun 130021, China

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**【Abstract】** Occlusal disorder is an abnormal condition in which the static and dynamic relations between the upper and lower teeth are not well aligned. The most common occlusal disorder in clinical practice is the inability to reach the intercusp position due to early contact of individual points or occlusal interference due to occlusal high points, which can lead to periodontal tissue damage, decreased masticatory function, temporomandibular joint and muscle discomfort; these results can occur through the overactivation of the locus coeruleus-sympathetic-adrenal medullary system and hypothalamic-pituitary-adrenal axis induce elevated serum corticosteroid levels, which leads to chronic stress in the body. This article reviews the effects of chronic stress caused by occlusal disorder on bone tissue, stomatognathic system, emotional health and cognitive function. It has been found that occlusal disorders not only result in the loss of bone in the oral cavity, the reduction of bone mass in the whole body and damage to the local function of the stomatognathic system but also negatively affect the body's anxiety, sleep, cognitive function and spatial memory ability as a result of the neuroendocrine changes. In recent years, concern about occlusal disorders has been on the rise. Early detection and timely adjustment of uncoordinated occlusion has become an issue that cannot be ignored in the clinic.

**【Key words】** occlusal disorder; stomatognathic system; locus coeruleus-sympathetic-adrenal medullary system; hypothalamic-pituitary-adrenal axis; corticosteroids; chronic stress; cognitive function; anxiety

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上下颌牙之间的接触现象称为咬合,咬合力主要由牙周本体感受器调节,可迅速辨别殆面12.5~160  $\mu\text{m}$  咬合高度的变化<sup>[1]</sup>,咬合信息的改变可通过牙周本体感受器传入中枢,反馈性引导咀嚼肌收缩变化,调整牙周组织和颞下颌关节承受的咬合力。当机体的适应能力降低,或受到修复、正畸等治疗因素影响时,可发生咬合的异常及咬合接触的不均匀,即咬合紊乱。咬合紊乱是上、下颌牙的静动态关系不协调的异常状态,临床中最常见的是因个别点的早接触而无法达到牙尖交错位,或因咬合高点产生的殆干扰的现象<sup>[2]</sup>,可使牙周组织损伤、咀嚼功能下降、关节肌肉不适,甚至引起机体的慢性应激<sup>[3]</sup>。

咬合紊乱通过蓝斑-交感-肾上腺髓质系统和下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)的过度活化及副交感神经的激活,导致应激激素水平的改变及应激性焦虑,从而对机体产生影响(示例图见本文OSID码)<sup>[4]</sup>。研究表明,咬合紊乱大鼠和慢性心理应激大鼠的血清糖皮质激素(corticosterone, CORT)浓度、5-羟色胺(5-hydroxytryptamine, 5-HT)及其受体5-HT<sub>2A</sub>R表达的显著变化,亦可表明咬合紊乱可通过HPA外周和中枢途径的焦虑促进因子发挥作用<sup>[5]</sup>。此外,由咬合紊乱引起的应激可诱导大鼠颌下腺脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达,使其促肾上腺皮质激素和CORT水平呈时间依赖性增加<sup>[6]</sup>。本文就咬合紊乱导致的慢性应激对机体的影响进行简要综述。

## 1 咬合紊乱对骨组织的影响

### 1.1 咬合紊乱导致全身骨量的减少

咬合紊乱可诱导小鼠模型中血清皮质类固醇水平升高从而降低骨骼的机械强度,最终导致骨量的减少。有研究者将小鼠口腔垂直方向增加0.5 mm的咬合高度诱发咬合紊乱7 d,在诱导后的第7 d血清皮质甾酮水平有显著升高,放射结果证实其第三腰椎和后肢长骨骨质减少。胫骨/股骨干骺端骨组织形态学分析评估发现骨形成显著抑制,骨吸收增加<sup>[7]</sup>。

### 1.2 咬合紊乱导致牙槽骨量的减少

除菌斑引起牙周组织破坏的炎症过程外,发生咬合紊乱时,机械应力或咬合力过大,可导致牙周组织的咬合创伤。咬合创伤是指由于超过功能适应的牙周电位力而导致支持性牙周组织发生的

损伤,影像学表现为牙槽硬板的丢失、牙周韧带间隙的扩大,甚至分叉区放射通透性增加、牙根吸收等骨组织丧失现象<sup>[8]</sup>。

创伤性咬合力不会导致牙龈炎、牙周袋、牙龈或临床附着水平衰退,但可加速已存在的牙周炎进展<sup>[9]</sup>。咬合创伤通过引起无菌炎症反应和骨吸收影响生物系统,咬合创伤可增强核因子受体激活剂- $\kappa\text{B}$ 配体(receptor activator of nuclear factor kappa-B ligand, RANKL)的表达最终直接或间接诱导骨吸收<sup>[8]</sup>。因此,在实现可预测的牙周或种植体骨再生过程中,无干扰的咬合接触的协调至关重要。

咬合过载是指通过早接触或侧向力从义齿传递到基牙或植入物的施加力,可导致结构损伤或生物损伤。由于种植体牙周韧带的缺失,其发生咬合过载引起的微动被认为是导致边缘骨丢失的一个重要因素,从而导致种植体周围炎的发生<sup>[10]</sup>。由于天然牙和种植体的生物学及物理学差异,使得研究种植体咬合紊乱具有一定的复杂性,伦理问题亦导致关于种植体咬合的研究有限。但咬合过载仍是造成种植体周围炎、种植修复体崩裂脱落及种植体结构破坏等生物力学并发症的主要原因<sup>[11]</sup>,因此种植修复体的结构设计、患者的咬合功能是不容忽视的重要因素。

## 2 咬合紊乱对口颌系统功能的影响

口颌系统由静态结构和动态结构组成,其和谐功能依赖于结构之间的平衡关系。咬合紊乱使咀嚼肌群持续收缩,短期内尚处于代偿阶段,长期则出现关节及肌肉损害<sup>[12]</sup>。

### 2.1 咀嚼肌损害

咬合垂直高度的增加或正颌手术后发生的咬合紊乱,初期可有咬肌纤维部分溶解,线粒体及糖原增多,线粒体空泡变性,核周间隙消失等显著改变。持续的咬合干扰可增强前扣带回皮质的突触传递,进而介导慢性咀嚼肌疼痛<sup>[13]</sup>。有研究通过消除咬合干扰平衡咬合力中心后,观察34名研究对象的肌电记录,结果显示:调整咬合关系可以减少牙周膜机械感受器的压迫,并间接地减少升颌肌的肌电活动,从而减轻肌肉相关的面部疼痛<sup>[14]</sup>。

### 2.2 颞下颌关节损害

Fernández等<sup>[12]</sup>,在慢性牙周炎的动物模型上,通过检测血浆皮质酮水平、相关酶的代谢活性等评价参数,发现慢性应激作为孤立因素,使大鼠翼内肌的氧化代谢、毛细血管密度和活性氧生成增

加;因此,慢性应激和咬合紊乱通过改变血管和翼内肌代谢的机制成为颞下颌关节疾病的病理生理学的危险因素,损伤口颌系统的功能。

### 3 咬合紊乱对情绪睡眠的影响

研究表明,口腔状况的改变会影响中枢神经系统的功能,如咬合紊乱可导致精神抑郁症、焦虑等情绪异常现象<sup>[15]</sup>。

#### 3.1 功能性咀嚼与慢性心理应激

功能性咀嚼可降低应激相关激素的表达,是一种有效应对应激的行为。咀嚼功能障碍也会导致BDNF的下调,从而导致神经前体细胞和功能神经元减少<sup>[16]</sup>。慢性应激状态可通过唾液皮质醇水平表示,通过收集28名受试者应力加载前、应力加载后、应力加载后10 min的唾液,测量并证实咀嚼可显著降低应激负荷后10 min唾液皮质醇水平的变化率,且唾液皮质醇水平的下降率与咀嚼次数呈负相关<sup>[17]</sup>。因此,适当的咀嚼及适宜的咬合力对慢性心理应激有一定的缓解作用。

#### 3.2 咬合紊乱与焦虑

咬合紊乱会产生慢性疼痛而引起焦虑,焦虑又会加重慢性疼痛发展。de Paiva Bertoli等<sup>[18]</sup>通过对巴西934名青少年统计学分析得出:咬合紊乱导致的颞下颌关节紊乱亦与焦虑密切相关。此外,体外实验表明焦虑可诱导大鼠磨牙症样活动,而抗焦虑药物可降低磨牙症样活动<sup>[19]</sup>。然而,产生焦虑相关的分子和细胞基础及其与咬合紊乱所致慢性疼痛相互作用的突触机制尚不清楚。

#### 3.3 咬合紊乱与睡眠

咬合紊乱可通过升高血清皮质类固醇水平进而对睡眠产生影响。咬合紊乱或咬合创伤可以改变睡眠期间大鼠的脑电图,主要影响深度睡眠并会降低睡眠质量<sup>[20]</sup>。改善成年夜磨牙患者的咬合力,可对其唾液皮质醇水平等应激指标、颞下颌关节症状、睡眠质量有积极影响。因此,夜间磨牙产生不良咬合力导致的长期慢性应激可通过改善咬合关系从而改善睡眠质量<sup>[21]</sup>。

### 4 咬合紊乱对认知功能的影响

咬合紊乱导致的慢性应激可增加血清皮质酮水平进而抑制海马神经发生,导致海马神经受损或凋亡增加,对认知功能及空间记忆能力造成损害<sup>[22]</sup>。

#### 4.1 咬合紊乱对海马体影响

咬合紊乱通过降低老年衰老加速倾向小鼠

(SAMP8)的糖皮质激素受体(glucocorticoid receptor, GR)和糖皮质激素受体信使核糖核酸(GRmRNA)的表达,削弱HPA反馈抑制,从而导致记忆障碍<sup>[23]</sup>。体外实验研究表明,母鼠咬合紊乱模型会显著抑制自身及后代海马齿状回新生细胞的增殖,导致认知学习功能障碍<sup>[24]</sup>。咬合紊乱持续的时间越长,海马CA3亚区神经元数量减少越多,空间学习能力受损越大<sup>[22]</sup>。咬合紊乱亦可导致杏仁核中强啡肽A水平的短暂增加,并特异性结合κ-阿片受体,从而暂时损害学习和记忆<sup>[15]</sup>。

有研究者使用蒙特利尔认知评估(MOCA-J)并根据994名70岁老人和968名80岁老人的残牙数量、牙周袋深度和最大咬合力评估口腔状况和功能,证实了认知功能与咬合力直接相关,咬合紊乱必然导致咬合力的改变,从而对认知功能产生负面影响<sup>[25]</sup>。临床队列研究表明,咀嚼效率和(或)功能性牙齿良好的人的认知功能也更好,可维持海马体的学习和记忆功能,因此,防止咬合紊乱引起海马体的衰减是非常重要的<sup>[26]</sup>。

#### 4.2 咬合紊乱与阿尔兹海默症

咬合紊乱引起的心理应激通过糖皮质激素信号可逆地导致大鼠模型中海马中淀粉样蛋白β(amyloid β, Aβ)的积累,成为阿尔兹海默症的风险因素。一项基于社区的老年队列研究证实,功能性牙齿和功能性咬合单元(尤其是前磨牙区)的缺失与认知功能障碍的增加有关,阿尔茨海默症患者的口腔失调和认知能力下降之间存在必然联系<sup>[27]</sup>。

### 5 小结

咬合紊乱作为导致机体慢性应激的重要因素,不仅危害口颌系统健康,加速牙周炎的进展,导致种植体修复并发症的发生,对机体认知功能、情绪及睡眠质量亦有着负面影响。目前认为广泛的预防性咬合调整存在一定的风险,但消除明显的咬合干扰可以减少短期症状,结合其他形式的治疗有助于取得积极的疗效已成为共识。咬合紊乱的发现及调整有着极其重要的意义。

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