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·综述·

骨关节炎软骨下骨的微结构改变

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摘要: 骨关节炎(OA)是老年人中常见疾病,在过去几十年中,软骨下骨组织结构的改变被认为在OA病因中起重要参与作用,软骨下骨微结构损伤将导致其加重。OA病理进程中可以在软骨下骨检测到一些微结构改变,包括微损伤,骨髓水肿样病变和骨囊肿等。关节软骨下骨的微结构改变与骨关节炎进展高度相关,软骨下骨微结构损伤将导致骨关节炎的加重保持软骨下骨的完整性可作为防治骨关节炎的方法之一。了解OA软骨下骨的微结构改变,阐明骨关节炎软骨下骨微结构损伤的发生机理及其与骨关节炎发生发展间关系,将有助于OA的诊断、预防和治疗。

关键词: 骨关节炎;软骨下骨;微损伤;骨髓水肿样病变;骨囊肿

Microstructural changes of the subchondral bone in osteoarthritis

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Abstract: Osteoarthritis (OA) is a common disease in elderly people. In the past decades, subchondral bone structure is believed to play an important role in the pathogenesis of OA. Subchondral bone microstructure damage may aggravate OA. During the progress of OA, subchondral bone microstructural changes are detected, including microdamage, bone marrow edema-like lesions, subchondral bone cysts, and so on. The change of subchondral bone microstructural is highly related with the development of OA. The damage of subchondral bone microstructural results in the severity of OA. Preservation of the integrity of subchondral bone is one of the prevention methods in OA. Understanding subchondral bone microstructural changes and the role of subchondral bone in osteoarthritis may help us to diagnosis, prevent, and treat OA.

Key words: Osteoarthritis; Subchondral bone; Microdamage; Bone marrow edema-like lesions; Subchondral bone cysts

在老年群体中骨关节炎(OA)是一种造成关节疼痛不适甚至残疾的多发疾病[1]。它的特点是关节软骨的破坏,软骨下骨的改变,骨赘生成,肌肉萎缩和滑膜的炎症[2]。虽然它长期被认为是关节软骨病变引起,但是越来越多的研究显示软骨下骨的微结构改变正在得到逐步重视[3]。软骨下骨的退化通常与关节软骨缺损相关连[4],软骨下骨硬化合并进展性软骨退化被广泛认为是骨关节炎重要标志[5]。其中一些微结构改变在软骨下骨中被检测到,包括微损伤,骨髓水肿样病变和骨囊肿[6]。

1 软骨下骨的结构和功能

软骨下骨在早、中、晚期都有显著微结构改变。尽管软骨下骨有很多种定义,但最常用的是钙化软骨深面的骨组织[6],即长骨的干骺端,可分为两部分[7]:软骨下骨骨板(皮质骨)和软骨下骨骨小梁(松质骨)。

软骨下骨骨板是一薄层皮质骨,处于钙化软骨深部,具有通透的管道结构和可渗透性。骨板的渗透性可将关节软骨和软骨下骨骨小梁之间连接起来,大量的动静脉、神经通过这些管道将分枝穿入钙化软骨[7]。管道的分布、形状和直径大小,不仅取

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决于患骨关节炎年龄、皮质骨板的厚度，还与关节传递给软骨和软骨下骨压力大小有关，因此多集中在关节承重大的区域；皮质骨骨板越厚的部位，管道就越细并形成树状网，在越薄的区域管道就会越宽而呈壶腹状[8]。

在正常关节，软骨下骨骨小梁起着重要的减震和支撑和为关节软骨提供营养和新陈代谢的作用[7]。在骨小梁间的骨髓腔中含血管、神经和骨髓组织细胞[9]。骨髓腔中大量的动静脉、神经通过软骨下骨和钙化软骨层到达软骨，从而将营养物质运送给软骨，并将代谢产物运走，形成良好的新陈代谢[10]，为软骨下骨和软骨之间的物质转运起重要作用。

关节软骨的非钙化部分与其深面的钙化部分，由“潮标（tidemark）相隔。“潮标”为这两种不同的软骨提供一个过渡地带，连续的胶原纤维穿过潮标，表明非钙化软骨和钙化软骨联系紧密。关节软骨与软骨下骨的之间形成一复合功能单位，即“骨软骨联合（osteochondral junction）[11]”。骨软骨联合包括非钙化软骨、潮标、钙化软骨和软骨下骨。其中任何一种组织改变都将影响到骨软骨联合其它部分的属性和功能。骨软骨联合中这些组织之间紧密的相互作用对于关节的承重相互影响[12]。在骨关节炎，因为关节软骨的损伤或缺损，传递到骨质上的载荷将明显增多，导致承受载荷更多的软骨下骨硬化。硬化的软骨下骨也能传递更多的负荷给表面的软骨，导致软骨的损伤和退行性变进一步加重[13]。尽管，软骨下骨和软骨之间的生物力学关系已经确定，但它们之间的生物化学作用仍然不是很清楚。软骨和软骨下骨的渗透性使其间能互相交流，有研究[8,14]显示，在软骨下骨重塑的时，由成骨细胞释放的前列腺素、白三烯和各种生长因子能到达表面的关节软骨，从而导致关节软骨释放炎症和破骨细胞的刺激因子，并增加骨关节炎中骨重塑，进而可能促使软骨下骨的退化[6]。

2 软骨下骨微结构的改变

软骨下骨组织结构的改变，在过去几十年被认为在骨关节炎病因中起重要参与作用，并且软骨下骨硬化已经成为骨关节炎的标志[15]。在骨关节炎进程的不同阶段，软骨下骨会发生不同的微结构改变，主要包括微损伤，骨髓水肿样病变和骨囊肿。

2.1 软骨下骨的微损伤

骨关节炎早期软骨下骨微损伤发生率极高[16]，微损伤是由于关节超负荷所导致的骨疲劳而引起，可表现出两种不同的形式：线性微损伤（linear microcrack）和弥漫性微损伤（diffuse damage）[17]。线性微损伤主要表现为短间隙的裂缝，而弥漫性微损伤主要表现为骨基质成簇的亚细微米级的微裂隙[18]。线性微损伤可触发骨重塑，因线性骨微损伤而继发的骨细胞损伤乃至骨细胞凋亡，可刺激破骨细胞性骨吸收和启动微损伤的修复[19]，有可能是线性微损伤触发骨重塑的机制之一；其次是为软骨和软骨下骨之间提供通道，合成、分解代谢的产物可以通过这样的通道进行交流。然而，相比于线性微裂隙，弥漫性微损伤有不同的生物力学反应。弥漫性微损伤不导致骨细胞凋亡，也不激活病灶骨重塑来清除和取代损伤的区域，这可能与缺少足够集中的损伤来诱导骨凋亡应答的启动有关[18]。最近有研究显示，弥漫性微损伤的修复不需要通过骨重塑，说明对于亚细微米级别的骨损伤有另外的修复机制，但仍不清楚[20]。

2.2 软骨下骨骨髓水肿样病变

在骨关节炎中、晚期，常可观测到骨髓水肿样变（Bone marrow edema-like lesions, BMELs）[21]。骨髓水肿样病变的病因尚不清楚。有研究显示，BMELs发生在软骨下骨硬化骨和松质骨之间的过渡区域[22]，BMELs代表这个区域的慢性应力损伤。关节应力的增加，关节软骨的损伤和修复的平衡被打破，导致骨损伤加重从而引起血管出血、纤维蛋白渗出和纤维组织增生[23]。如果重复的应力损伤可以被代偿，骨硬化的损伤区域就会增大而BMELs不会进展。然而，如果损伤大于修复，那过渡区域就会塌陷并不再修复从而形成BMELs[24]。骨关节炎软骨下骨骨髓水肿样病变的数量跟病人的疼痛成正比[25]。骨髓水肿样病变也被用来预测健康的、无症状的人群患骨关节炎的风险[26]。软骨病灶常发生在骨髓水肿样病变附近，且软骨的退变程度跟BMEL的信号强度是成正比的[27]。软骨下骨的骨髓水肿样病变跟骨囊肿也有紧密联系，骨髓水肿样变是骨囊肿形成前的病损，但不是每个水肿样变都会变成骨囊肿。在骨关节炎的病程中骨髓水肿样病变持续存在，并被认为是软骨结构退变的重要危险因子[28]。

2.3 软骨下骨囊肿

在中期、晚期骨关节炎的X线、MRI，常可以观测到软骨下骨中空洞的病灶，通常称之为软骨下骨囊肿（subchondral bone cysts，简称SBCs）。虽然对

软骨下骨骨囊肿的研究已有几十年，但这些病灶的病因和发病机理仍不清楚。有两种主要的假说解释软骨下骨囊肿起源：一种是“滑液入侵”理论[29]，认为因为骨软骨联合处的损伤缺口会导致关节滑液入侵到软骨下骨骨间隙，使得滑液渐渐增加并导致软骨下骨内压力增大外扩，形成软骨下骨囊肿；另一种是“骨挫伤”理论[30]，认为软骨下骨囊肿起源于软骨下骨坏死的病灶，坏死的病灶是由不正常的机械应力导致微裂隙、骨坏死，随后病灶骨吸收、滑液流入形成。在软骨下骨囊肿中，纤维组织增生，前列腺素E2等蛋白因子增多，可促使囊肿进一步增大[31]。软骨下骨的硬化和软骨下骨的囊肿形成相关联[32]，也许是因为软骨下骨囊肿周边骨形成增多，从而导致骨囊肿周围骨质硬化。一方面软骨下骨囊肿形成会使软骨下骨应力变化，使得正常软骨下骨应力集中并加重软骨下骨硬化；另一方面，骨硬化可以阻止骨囊肿进一步增大，最终形成了许多小的骨囊肿。有报道显示，骨关节炎患者的关节软骨下骨囊肿越多，病情将越严重，需施行关节置换的风险越高[33]。另外，也有报道显示，软骨下骨囊肿并不是骨关节炎一定会出现的放射学特征，更有可能与女性性别和膝内翻相关[34]。

关节软骨下骨的微结构改变与骨关节炎进展高度相关[35]；软骨下骨微结构损伤将导致骨关节炎的加重[36]；保持软骨下骨的完整性可作为防治骨关节炎的方法之一[37,38]。

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