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·综述·

纳米压痕技术在骨质疏松诊治中的研究进展

杨春宝 雷伟 吴子祥

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摘要：骨质疏松引起的最严重的并发症为骨质疏松性骨折，因此在骨质疏松病理过程中，骨生物力学具有举足轻重的作用。20世纪90年代，Oliver提出的纳米压痕技术（nanoindentation）成为研究材料微观力学特性的新技术。它不仅能够精确测量骨小梁细微结构的弹性模量、硬度，而且可以用于骨微观结构断裂韧性的检测。本文就近年来纳米压痕技术在骨质疏松症诊断治疗研究领域的应用作一综述。

关键词：纳米压痕；骨质疏松；微观力学；松质骨

Research progress of nanoindentation technique in diagnosis and treatment of osteoporosis *YANG Chunbao, LEI Wei, WU Zixiang.*
Department of Orthopedics, Xijing Hospital, the Fourth Military Medical University, Xi'an 710032, China
Corresponding author: WU Zixiang, Email: wuzixiang@fmmu.edu.cn

Abstract: Osteoporotic fracture is the most serious complication of osteoporosis. The biomechanical properties of the bone play an important role in the pathological process of osteoporosis. Since the nineties of the twentieth century, the nanoindentation technique introduced by Oliver has become popular in determining micro-mechanical properties of materials. It can not only measure the elastic modulus and hardness of trabecular bone, but also detect the fracture toughness in bone micro-architecture. This article reviews the recent application of nanoindentation technique in diagnosis and treatment of osteoporosis.

Key words: Nanoindentation; Osteoporosis; Micromechanics; Cancellous bone; Cortical bone

骨质疏松引起的最严重的并发症为骨质疏松性骨折，因此在骨质疏松病理过程中，骨生物力学具有举足轻重的作用。20世纪90年代，Oliver提出的纳米压痕技术（nanoindentation）成为研究材料微观力学特性的新技术。它不仅能够精确测量骨小梁细微结构的弹性模量、硬度，而且可以用于骨微结构断裂韧性的检测[1,2]。因此，近年来，国内外学者对骨质疏松的生物力学研究已从骨骼的宏观力学层面逐渐转向骨小梁水平的微观力学。本文就近年来纳米压痕技术在骨质疏松症诊断治疗研究领域的应用作一综述。

1 纳米压痕技术简介

根据测量目标的不同，纳米压痕仪配有不同类型的压头，如洛氏（Rockwell）压头、维氏（Vicker）压头、努氏（Knoop）压头以及玻氏（Berkovich）压头等（图1），其中最常使用的压头为维氏压头和玻氏压头。纳米压痕仪即是由这些压头针尖和试样表面组成的一个相互耦合的动力学系统，通过压头将力施加在被测材料上，使材料产生压痕即发生塑性变形，由电磁或静电驱动探针、电容式位移传感器记录载荷和压深，从而获得"载荷-位移"曲线，进而计算出其硬度值、弹性模量、屈服强度、塑性以及蠕变性能等多个参数。同时，检测器能够在微观尺度内，如沿骨小梁走行方向，连续测定"载荷-位移"曲线，进而计算出材料不同位置的力学性能。目前纳米压痕仪的工作压力范围在1 μN～500 mN，位移距离范围为1 nm～20 μm，分辨率可达到50 nN[3,4]。

2 纳米压痕技术在骨质疏松病理研究中的应用

2.1 纳米压痕技术在分析松质骨骨小梁微观力学

作者单位：710032 西安，第四军医大学西京医院全军骨科研究所
通讯作者：吴子祥，Email：wuzixiang@fmmu.edu.cn

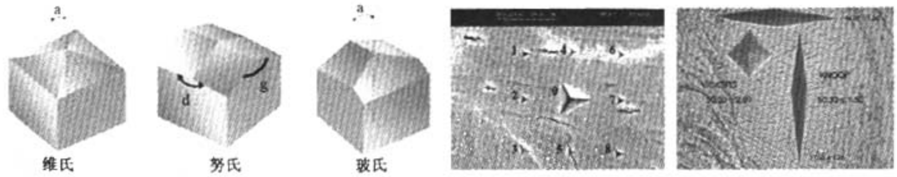

图1 纳米压痕仪的不同类型的压头

左图:各种压头的形状:维氏压头是两对面夹角为136°的金刚石正四棱锥(a=68°),努氏压头是金刚石四棱锥(棱夹角d=172.5°和g=130°),玻氏压头则是中心线与锥面之间夹角为65.03°的三棱锥;

中图:采用玻氏压头测量松质骨骨小梁硬度的扫描电镜图(摘自 Mullins LP, et al. Ann Biomed Eng, 2009);

右图:采用维氏和努氏压头测量皮质骨硬度的扫描电镜图片(摘自 Boivin G, et al. Bone, 2008)

特性中的应用

骨质疏松可导致骨宏观力学强度下降,进而引发骨折,其中又以松质骨丰富的部位受累最为严重,如脊柱、髋部及腕部等。以往研究认为,骨质疏松导致松质骨骨小梁稀疏、变细、数量减少引发力学强度下降是其骨折的主要原因。但对于骨质疏松病理过程中单个骨小梁力学特性的改变并不清楚。

2000年,Guo等[1]首次将纳米压痕技术应用于去势后大鼠的腰椎骨微观力学特性的变化。作者通过测量骨质疏松大鼠腰椎的松质骨骨小梁发现,在微观结构水平,骨小梁的弹性模量以及硬度并没有发生显著性改变。这提示尽管去势后骨质疏松大鼠的腰椎骨量丢失,骨小梁面积分数显著下降,但残余骨小梁的弹性模量和硬度特性却相对变化不大。Wang等[5]则对正常人群和存在椎体骨折的骨质疏松人群的髂骨松质骨进行了微观力学测定,并分析其与骨组织形态参数和骨矿参数之间的相关性。作者发现,在骨折组和正常骨质组中,骨小梁弹性模量和硬度并无显著性差别。但是,具有较高的单位骨表面积骨形成率(high or low bone formation rate per bone surface, BFR/BS),其弹性模量显著降低。并且,弹性模量和硬度与骨矿化程度无明显相关性。

为进一步研究骨小梁表面硬度分布规律,Brennan等[6]对正常绵羊和骨质疏松绵羊肱骨近端的松质骨骨小梁进行分析,发现不论是正常骨质还是骨质疏松骨质,其骨小梁的弹性模量和硬度均由表面向中央区域逐渐增加。即使是同一根骨小梁,其微观力学特性也有所不同。但与Guo等研究结果不同,Brennan发现正常羊骨质的弹性模量较去势后羊骨质增高,而尽管去势后骨质的生物力学强度下降,但两组之间的硬度没有显著的统计学差异。

为明确骨小梁微观力学性能的影响因素,Mulder等[7]采用MicroCT和纳米压痕技术对弹性模量、硬度、骨矿化程度和骨小梁刚性的之间的关系进行深入研究。通过对新生猪及胚胎猪的颌骨髁部松质骨进行了观察测量,结果发现,无论是骨矿化程度还是骨小梁刚性(stiffness),均是从骨小梁边缘向骨小梁中央逐渐增加。新生猪的骨小梁刚度显著高于胚胎猪,骨小梁矿化程度和弹性模量之间存在正相关性;但在矿化程度上,两者无显著性差别。这表明,矿化程度可能并不能显著影响骨小梁微观力学强度。此外,上述结果也提示,骨小梁结构在纳观尺度下也具有显著各向异性的特点。Hodgskinson等[8]的研究表明骨组织的弹性模量变化是由于骨钙含量的变化。骨钙含量和硬度有着很显著的正相关性,据此可推测弹性模量和硬度也是具有很显著的正相关性的。Norman等[9]在研究中证实骨组织中的弹性模量和硬度也有着显著的正相关性。从以上研究可推知,弹性模量、硬度、骨矿化程度和骨小梁刚性的之间是具有正相关性。

2.2 纳米压痕技术在分析皮质骨微观力学特性中的应用

与松质骨相比,尽管皮质骨受骨质疏松影响较小,但骨质疏松对皮质骨的影响仍不可忽视。Fratzl-Zelman等[10]对骨质疏松股骨颈骨折患者(74~92岁)和非股骨颈骨折患者(74~88岁)的股骨颈皮质骨(横截面)进行力学分析,并与骨钙含量进行相关性分析。通过比较股骨颈上方和下方皮质骨的弹性模量和硬度,发现靠近股骨距的下方皮质骨的弹性模量明显高于上方,其数值与骨质内钙含量显著相关。但是,骨折组的弹性模量和硬度与非骨折组无显著性差别。作者认为,由于股骨颈局部区域内骨转换率的差异[11],以及上下方皮质骨受不同的应力,导致股骨颈上方皮质矿化程度较下方区域降低,因此,力学强度也相应降低。但也有学者认为[12,13],矿化程度增加会导致微观尺度上骨强度和骨韧性的降低。

为了更好的了解皮质骨韧性概念,深入研究皮

质骨在微观情况下抵抗裂痕的产生及延伸的能力，以进一步评估骨质发生骨折的风险，Mullins 等[14,15]采用纳米压痕技术对皮质骨骨板、间骨板以及松质骨骨小梁微结构的抗裂痕能力进行比较。结果显示：随着压入载荷的增加，皮质骨和松质骨的裂痕长度逐渐增加。而且，在不同的载荷水平，松质骨的裂痕长度均显著高于皮质骨。皮质骨中，间骨板所产生的裂痕长度大于骨板，但无显著性差别。其原因在于间骨板的矿化程度高于骨板结构。这表明，松质骨的韧性明显低于皮质骨。实验结果也在一定程度上解释为什么松质骨更加容易发生骨折。

Hoc 和 Dong 等[16,17]通过对股骨干皮质骨微观力学性能进行研究，发现皮质骨的微观力学强度与松质骨一样具有极为显著的各向异性。国内蔡振兵等[18]也发现沿环骨板同心圆的半径方向测量不同位置上骨板的弹性模量。结果表明，随着压入部位从环骨板过渡到间骨板，其最大压入深度和残余深度均逐渐减小。位于内层的环骨板弹性模量与纳米硬度值明显小于外层骨板。这说明随着环骨板逐渐过渡到间骨板，骨组织的强度和抗疲劳性能逐渐增加。

3 纳米压痕技术在骨质疏松治疗中的应用

尽管很多药物对骨质疏松症都有相应的治疗作用，但是其降低骨折风险的机制各不相同，如提升骨矿含量，改善骨微观结构，增加骨矿化程度等。纳米压痕技术让研究者能够更加细致的区分不同药物的作用机理。

3.1 抑制骨吸收类药物：双膦酸盐类药物

Shahnazari 等[19]在大鼠骨质疏松模型上采用不同剂量的双膦酸盐进行为期 4 个月的治疗研究，结果发现两种剂量均能够提高骨量、增加骨强度，改善骨结构，但高剂量组增加更为明显。但是，作者发现两种剂量均不能改善骨质材料学性质，如骨质强度、弹性模量以及皮质骨韧性。Wang 等[20]则在狗骨质疏松模型上采用双膦酸盐类药物进行为期 1 年的治疗研究，结果发现其骨小梁硬度和弹性模量、刚性较空白对照组显著增加。Lane 等[2]则认为卵巢切除后，大鼠胫骨骨小梁纳米力学参数没有显著改变，并且应用抗骨质疏松药物治疗对骨质材料学性质无明显影响。作者认为原因可能在于骨转换率降低，导致骨重建速度减慢，使得骨质平均矿化程度有所降低。同时，由于骨为典型的各向异性材料，其材料学性质依赖各部位承受的载荷大小与方向，这就意味着即使是同一椎体，不同平面、不同走向骨小梁的材料特性必然会因受力的不同而出现差异。此外，有学者认为，双磷酸盐类药物有可能对骨材料学特性产生负面作用。Amanata 等[21]在大鼠股骨骨折模型中，采用纳米压痕技术分析唑来膦酸钠对骨折愈合的影响。结果发现，实验组骨痂的弹性模量和硬度与空白对照组并无显著性差别。因此，作者认为，双磷酸盐类药物并不会对骨折愈合期间的骨痂力学性能产生负面影响。

3.2 促进骨形成类药物：甲状旁腺素(PTH)等

Lane 等[2]研究了两种促进骨形成的药物：碱性成纤维细胞生长因子(bFGF)和甲状旁腺素(PTH)对去势后骨质疏松大鼠骨微观力学特性的影响。经过皮下注射 bFGF (1 mg/kg, 5 d/w)和 PTH (40 μg/kg, 5 d/w)4 个月后发现，大鼠胫骨近端松质骨骨小梁弹性模量和硬度两组之间并无显著性差别，并且与假手术组大鼠无明显差别。这些研究提示，上述两种药物可能并不能在微观层面改善骨小梁硬度等材料学属性，而是通过改善骨微观结构，增加骨量达到提高骨质强度的目的。Brennan 等[6]通过对不同药物对骨质力学性能的影响进行研究，也发现甲状旁腺素可影响骨微观结构，双膦酸盐(帕米膦酸钠)能够改变骨质的材料学特性，而雷洛昔芬则主要是增加皮质骨的刚性。

雷尼酸锶 (strontium ranelate) 是由法国 Servier 公司研制开发的新一代抗骨质疏松药物。它具有抑制骨吸收，促进骨形成的双重药理作用。临床研究表明，雷尼酸锶能够有效降低绝经后妇女的骨折风险。但是，它对骨微观力学强度的作用，目前尚不清楚。为研究雷尼酸锶对促进骨微观力学特性是否有积极作用，Ammann 等[22]将不同剂量(225, 450, 或 900 mg/kg)的雷尼酸锶口服给大鼠。结果发现，在整体力学层面，900 mg/(kg·d)组的腰椎较对照组具有更高的抗压强度；在微观力学层面，腰椎骨小梁的弹性模量、硬度和耗能也有显著性增加。这项研究证实，雷尼酸锶能够通过提高骨质量，增加骨力学强度，从而降低骨质疏松骨折的风险。

4 纳米压痕技术的局限性

虽然纳米压痕技术已经较广泛的应用于骨质疏松的诊断和治疗领域中，但该项技术依然存在一些局限性。首先，纳米压痕实验对标本及环境湿度的要求比较高，实验数值在干燥环境和生理环境下具有显著性差别，因此在进行测试时必须保证标本及

环境的实验条件一致[9,23]。同时,这也使得研究者难以对不同文献中的骨质弹性模量等微观力学参数进行横向比较,实验重复性较差。其次,尺寸效应对纳米压痕实验结果也有影响。尺寸效应通常是与压头形状相联系,不同压头形状也可导致测量结果的偏差[24]。在纳米压痕技术的数据处理方面,最常采用的是 Oliver-Pharr 方法[25]。它是建立在压针-样本间接触是纯弹性的前提下。在应用于生物材料时,材料的粘弹特性可能会影响结果的准确性。因此应采用相应的校正方法进行数据处理[24]。此外,材料表面粗糙度也是影响纳米压痕结果的因素之一[25-30]。在进行压痕前骨组织常需切片或磨光(通常薄至0.05 μm)[31-34],压痕深度的范围一般选定在能使材料表面粗糙度低于总穿透深度的10%的范围内,以减少实验偏差[35]。

纳米压痕技术是一种可直接测量骨微观力学特性的研究方法,在骨质疏松诊断治疗领域有着良好的发展前景。将纳米压痕技术引入到骨科疾病的诊断治疗中,能够为临床医师提供一个全新的视角,对疾病的病理变化、治疗效果有着更为深入的认识。

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纳米压痕技术在骨质疏松诊治中的研究进展

作者： 杨春宝， 雷伟， 吴子祥， YANG Chunbao， LEI Wei， WU Zixiang
作者单位： 第四军医大学西京医院全军骨科研究所,西安,710032
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