综　述

维生素D在假体周围感染防治中的应用研究进展

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[摘要]　假体周围感染(PJI)是关节置换术后的严重并发症，其防治面临巨大挑战。维生素D在钙磷代谢中发挥关键作用，同时具备免疫调节与抗菌活性：一方面可调节免疫反应，增强免疫细胞活性，促进抗菌肽生成，从而有效抵御病原菌入侵；另一方面可影响炎症因子的表达，改善假体周围组织微环境，降低PJI发生风险。临床前及临床研究发现，血清25-羟基维生素D[25(OH)D]<20 ng/ml与PJI的发生风险增加相关，靶向补充维生素D可降低关节置换术后感染率。但目前共病人群的精确剂量方案及患者特异性补充策略尚不明确。本文总结血清维生素D水平的判断标准及其与PJI发生的相关性，以期为维生素D及其相关试剂在PJI防治中的应用提供依据。

[关键词]　假体周围感染；维生素D；预防；治疗

Research advances in use of vitamin D for the prevention and treatment of periprosthetic joint infection

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[**Abstract**]　Periprosthetic joint infection (PJI), a severe complication following joint arthroplasty, poses significant challenges in prevention and management. Vitamin D plays a pivotal role in calcium-phosphate metabolism while demonstrating immunomodulatory functions and antimicrobial activity. Mechanistically, it regulates immune responses by enhancing phagocytic cell activity and promoting antimicrobial peptide production, thereby effectively combating pathogenic invasion. Moreover, vitamin D modulates inflammatory cytokine expression, improves the periprosthetic tissue microenvironment, and reduces PJI risk. Preclinical and clinical studies have revealed that serum 25-hydroxyvitamin D [25(OH)D] levels <20 ng/ml correlate with increased PJI incidence, whereas targeted vitamin D supplementation decreases postoperative infection rates. However, optimal dosing regimens for comorbid populations and patient-specific supplementation strategies remain undefined. This review summarizes the criteria for determining serum vitamin D levels and their correlation with the occurrence of PJI, in order to provide a basis for the application of vitamin D and related reagents in the prevention and treatment of PJI.

[**Key words**]　periprosthetic joint infection; vitamin D; prevention; treatment

假体周围感染(periprosthetic joint infection，PJI)　是全关节置换(total joint arthroplasty，TJA)术后的严

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重并发症，其预防和治疗是骨科医师面临的难点与挑战。维生素D具有多种免疫调节、抗炎、抗氧化和抗纤维化作用，是连接先天免疫与适应性免疫的关键因素，其在PJI防治方面的潜在价值也受到广泛关注[1-3]。据报道，TJA患者普遍存在维生素D不足的情况，其中近50%存在维生素D缺乏[4]。既往研究显示，维生素D缺乏与TJA术后感染的发生相关[5-7]。动物实验和临床研究均表明，补充维生素D有助于预防或缓解炎症和免疫介导的组织损伤，降低关节置换术后PJI的发生率[8-10]。因此，补充维生素D或可作为PJI防治环节的重要步骤。然而，目前并无统一推荐的血清维生素D水平判断标准，不同机构的判断标准存在差异。基于此，本文归纳总结血清维生素D水平的判断标准及其与PJI发生的相关性，以期为维生素D及其相关试剂在PJI防治中的应用提供依据。

1 维生素D的免疫调节作用

1.1 调节先天性免疫 维生素D在免疫系统中扮演着关键角色，作为连接先天性免疫与适应性免疫的桥梁，维生素D缺乏可能损害这两种免疫功能[11]。研究发现，1,25-二羟基维生素D[1,25-dihydroxyvitamin D，1,25$(OH)_2$D]不仅是调节多种信号通路基因表达的激素，且对骨矿物质密度、免疫功能和炎症反应具有显著影响[12-13]。维生素D缺乏的人类和动物感染风险的增加可能与巨噬细胞功能受损有关。某些免疫细胞如树突状细胞和活化的巨噬细胞中存在25-羟基维生素D-1α-羟化酶(cytochrome P450 family 27 subfamily B member 1，CYP27B1)，可将25-羟基维生素D[25-hydroxyvitamin D，25(OH)D]转化为1,25$(OH)_2$D[14]，表明维生素D可能通过影响免疫细胞的活化状态与功能表型，进而调节损伤部位的炎症反应。如在感染存在的情况下，病原体通过激活Toll样受体和诱导炎性细胞因子如γ干扰素(IFN-γ)的产生，促进活化的巨噬细胞和单核细胞中CYP27B1强表达，从而使25(OH)D转化为1,25$(OH)_2$D[15]。1,25$(OH)_2$D与细胞核中的维生素D受体(vitamin D receptor，VDR)结合，通过VDR-维甲酸X受体(RXR)异二聚体信号系统以自分泌方式增强巨噬细胞和单核细胞的抗菌活性[16]。这一过程促进了内源性抗菌肽Cathelicidin的生成，Cathelicidin是哺乳动物中广泛表达的阳离子抗菌肽，由12~80个氨基酸组成，通过形成离子通道和增加细胞膜通透性，直接杀死病原体或与内毒素结合增强机体的抗菌活性[17]。同时1,25$(OH)_2$D还能抑制单核细胞中Toll样受体的表达，减少T细胞产生的白细胞介素(IL)-2及单核细胞来源的IL-6、IL-17，从而调节炎症反应[18]。此外，1,25$(OH)_2$D通过调节抗原提呈细胞的分化功能，使细胞表面主要组织相容性复合体(major histocompatibility complex，MHC)II类的表达减少，通过抑制MHC II类分子转录激活因子(major histocompatibility complex class II transactivator，CIITA)活性，从而抑制促炎细胞因子IL-2的产生，促进抗炎细胞因子IL-10的产生，进而影响免疫应答的平衡[19]。

1.2 调节适应性免疫 维生素D作为关键的免疫调节剂，通过与免疫细胞(如T细胞、抗原提呈细胞)表面的VDR结合并激活下游信号通路，双向调控T细胞功能以抑制过度的炎症反应[20-21]。其作用机制为：一方面通过抑制Th1型促炎细胞因子[如IL-2、IFN-γ、肿瘤坏死因子(TNF)-α]的合成及分泌阻断促炎级联反应；另一方面通过促进Th2型抗炎细胞因子(如IL-4、IL-5、IL-10)生成及诱导调节性T细胞(Treg)分化建立免疫耐受环境[22-23]。基于上述双重机制，维生素D通过抑制IL-2、IL-12、IFN-γ等促炎因子分泌，同时上调IL-4、IL-5、IL-10等抗炎因子生成，最终实现对有害炎症反应和免疫过度激活的有效调控[16,23-25]。此外，Treg细胞($CD4^+$、$CD25^+$、$Foxp3^+$)是抑制免疫反应的主要T淋巴细胞亚群。维生素D可通过直接作用于Treg细胞前体细胞或间接调控相关信号通路[如转化生长因子-β(transforming growth factor-β，TGF-β)/Smad3通路]，促进*Foxp3*基因的表达，从而增加Treg细胞的产生[22,26]。免疫球蛋白样转录物3(ILT3)主要由树突状细胞等髓系细胞表达，通过抑制T细胞活化信号促进Treg细胞的分化，其表达可被1,25$(OH)_2$D通过VDR依赖的转录激活途径上调[22,27-28]。上述多种调节途径诱导的Treg细胞可通过产生IL-10和抑制Th17淋巴细胞的活性来维持抗炎环境[22,29]。

维生素D通过上调抑制细胞周期的p27蛋白表达，抑制B淋巴细胞的增殖，并通过诱导促凋亡分子(如Bax)表达或下调抗凋亡分子(如Bcl-2)表达导致免疫球蛋白产生减少、自身抗体分泌受抑制以及记忆性B细胞数量减少，最终诱导B淋巴细胞凋亡[20]。由于B淋巴细胞中的CYP27B1表达水平明显低于树突状细胞、巨噬细胞等髓系细胞，其无法自主合成1,25$(OH)_2$D，主要通过旁分泌方式摄取髓系细胞合成的外源性活性维生素D以参与免疫调节。1,25$(OH)_2$D可诱导树突状细胞表达IL-10，并通过上调共抑制分子(如PD-L1)增强树突状细胞对T细胞的抑制性信号转导，从而间接调控T细胞的功能[30-31]。综上，维生素D主要是通过抑制促炎细胞因子的产生和增加抗炎细胞因子的合成，从而调节组织炎症和氧化应激状态。

2 维生素D与PJI的相关性

PJI是翻修手术最常见的原因，因此深入探究PJI的危险因素对降低其发生率至关重要。研究发现，风湿性疾病、肥胖、低白蛋白血症、术前贫血、糖尿病、吸烟、酗酒以及类固醇用药史均是PJI的潜在危险因素，其中肥胖、吸烟、酗酒等属于可改变的危险因素[32-35]。此外，维生素D缺乏也是关节置换术后PJI的潜在可改变的危险因素[8,33-34,36]。TJA术后患者普遍存在维生素D缺乏，术前优化这些可改变危险因素，将有助于改善患者预后和降低医疗成本。

既往研究发现，维生素D水平较低的患者术后更易发生感染，且血清维生素D水平与围手术期炎症反应强度相关[37-42]。首先，维生素D缺乏增加了对炎症性疾病和自身免疫性疾病的易感性[43]。术前25(OH)D缺乏是手术部位感染的独立危险因素，其机制可能与免疫功能抑制、抗菌肽合成减少及炎症调控失衡相关[44-45]。其次，维生素D缺乏与多种外科手术术后感染风险增加相关，包括骨科植入物术、心脏手术和肝胆手术。在心脏手术[包括瓣膜手术、冠脉搭桥及左心室辅助装置(left ventricular assist device，LVAD)植入]中，术前25(OH)D缺乏(<20 ng/ml)与术后感染风险增加明显相关，且25(OH)D的严重缺乏状态(<10 ng/ml)与不良结局风险增加相关[40,46-48]。此外，一项多中心队列研究发现，肝移植术前25(OH)D <15 ng/ml的患者在术后6个月内感染的风险增加(*HR*=1.8，95%CI 1.2~2.7)[49]；另一项针对301例肝胆手术患者的前瞻性队列研究发现，术前25(OH)D <20 ng/ml的患者术后发生医院获得性感染(如手术部位感染、肺炎)风险明显增加(*OR*=2.5，95%CI 1.4~4.3)，且维生素D缺乏与感染严重程度呈剂量依赖性(维生素D每降低10 ng/ml，感染风险增加1.3倍)[50]。现有支持维生素D缺乏与TJA术后感染风险增加相关的证据详见表1[4,8,10,44]。有研究发现，维生素D缺乏与全膝关节置换术(total knee arthroplasty，TKA)后关节功能恢复不良相关，主要表现为关节翻修率增高和感染风险增加[51-54]。一项病例对照研究发现，维生素D水平较低与骨科感染风险增加存在关联，骨科住院患者中血清维生素D水平较高者感染发生率较低[7]。此外，另有研究发现，术前维生素D缺乏与关节置换术后PJI的发生密切相关[55]。Hegde等[33]发现，维生素D缺乏患者(<20 ng/ml)1年内PJI的发生风险增加了2倍。Zajonz等[56]发现，急性PJI患者的维生素D水平低于慢性PJI患者。然而，维生素D水平与PJI的发生风险呈U形关系，较高或较低水平均与PJI发生相关。一项纳入78例患者的回顾性研究发现，PJI的发生与较高的维生素D水平相关[57]。因此，未来仍需要多中心研究进一步探索PJI与维生素D水平的相关性。但目前多数研究证据仍支持血清维生素D水平低下是PJI的重要危险因素。

表1 不同研究类型的证据等级分类与方法学特征评估

Tab.1 Classification of evidence levels and methodological characteristics evaluation across different research types

代表性研究	样本量	研究类型	证据等级	主要优点	不足
Birinci等[10]	488	前瞻性队列研究	高(Ⅱ级)	标准化数据采集，控制混杂因素	耗时成本高，仍需长期随访
Bogunovic等[4]	723	回顾性队列研究	中(Ⅲ级)	快速获取大样本数据	偏倚风险高，混杂因素控制不足
Hegde等[8]	40	动物实验	低(Ⅳ级)	机制探索，控制变量严格	物种差异，剂量-效应不匹配
Abdehgah等[44]	300	横断面研究	低(Ⅳ级)	快速验证相关性	无法确定时序关系

证据等级参照牛津循证医学中心(OCEBM)分级系统

3 维生素D在PJI防治中的应用

维生素D具有免疫调节、抗炎、抗氧化及抗纤维化作用，可能参与多种免疫调节途径，有助于预防或缓解炎症及免疫介导的组织损伤[13,41,58]。研究表明，疾病进程中的衰老与炎症反应常与维生素D浓度降低并存，而维生素D缺乏可能进一步加剧氧化应激和免疫失调，形成恶性循环，这可能是在多种疾病中普遍观察到维生素D水平低下的关键机制[59]。维生素D可通过上调关节滑液中抗氧化酶的活性改善氧化应激状态，并通过抑制血小板活化因子释放或调节血小板-免疫细胞相互作用减轻血小板介导的炎症反应，进而减轻组织炎症损伤[60-61]。

随着关节置换等初级手术量的增加，PJI患者数量预计将同步增加[62]。大多数PJI发生于初次术后2年内，而需再次接受手术治疗的PJI患者术后1年病死率为4.2%，5年病死率高达21.2%[63]。因此，对PJI的综合管理仍然是骨科医师面临的巨大挑战。维生素D缺乏与PJI的发生风险增加相关，而术前补充维生素D似乎可降低PJI的发生率[64]。因此，通过术前筛选维生素D缺乏患者，骨科医师可通过优化其血清维生素D水平以降低PJI的发生率[6,65]。此外，越来越多的国际学术组织关注到维生素D的免疫调节作用，如骨科感染国际共识大会建议通过补充维

生素D增强患者免疫功能，以降低手术部位感染和PJI的发生风险[5]。PJI动物模型研究及临床研究同样证实，补充维生素D可明显降低术后PJI发生率[8,66]。

作为潜在的感染预防策略，补充维生素D是一种简单有效的方法[55]。通过增强免疫调节功能和抗炎作用，补充维生素D能够有效降低PJI的发生风险[5]。研究显示，血清维生素D水平较低与感染发生率较高之间存在相关性，预防性补充维生素D可改善患者预后[7]。基于此双重证据，未来可通过随机对照试验明确补充维生素D在临床实践中的有效性与安全性。因此，建议术前常规检查患者维生素D水平，如发现缺乏应及时补充[2]。一项基于全国人群的队列研究发现，维生素D的使用可降低与PJI相关的关节置换术后的翻修风险[67]。此外，一项纳入10项研究的Meta分析显示，其中6项研究提示补充维生素D可改善TKA术后关节功能恢复，减少不良事件的发生[53]。不良的营养状况与关节置换术后的感染发生率及病死率密切相关[68]。术前评估为识别高危个体提供了一个独特窗口，以便在选择关节置换术前对这些可改变风险进行优化。

4 血清维生素D缺乏的评估与治疗

4.1 维生素D缺乏的评估 血清25(OH)D的半衰期较长，是血液循环中浓度最高的维生素D代谢物，同时也是反映维生素D摄入和储存的可靠指标，因此目前国际普遍是通过测量血清25(OH)D的水平来评估机体的维生素D状态。但血清维生素D水平的判断标准至今尚未达成统一的国际共识，不同组织对维生素D缺乏的界定存在差异。值得注意的是，血清25(OH)D水平可能与维生素D的其他形式如维生素D_3、维生素D_2和1,25$(OH)_2$D等存在关联，但并非完全等同[69]。然而，低水平25(OH)D在健康人群和患有自身免疫性疾病或慢性炎症性疾病的人群中普遍存在，25(OH)D的水平未必能准确反映局部组织中1,25$(OH)_2$D的生物活性[59,70]。因此，对维生素D缺乏的评估标准值得更深层次的研究。Mangin等[59]提出，在基础和临床研究中同步检测25(OH)D和1,25$(OH)_2$D水平，相较单独测量25(OH)D更能全面反映维生素D的真实状况。目前，维生素D缺乏的诊断标准通常基于血清25(OH)D水平，具体阈值在不同研究和指南中存在差异。例如，一些研究将维生素D缺乏定义为血清25(OH)D水平<20 ng/ml，不足为21~29 ng/ml，充足则为≥30 ng/ml[71]。然而，当血清25(OH)D水平>150 ng/ml时，可能会出现维生素D中毒现象[72]。Herrick等[73]认为，维生素D缺乏为血清25(OH)D<12 ng/ml，不足为血清25(OH)D为12~19 ng/ml，充足则为血清25(OH)D为20~50 ng/ml。此外，维生素D委员会[59]、美国医学研究所(Institute of Medicine)[74]、内分泌学会(the Endocrine Society)[75]等机构也分别制定了各自的维生素D水平分类标准。尽管存在不同阈值的定义，但使用维生素D不足(<30 ng/ml)和缺乏(<20 ng/ml)这两个阈值时，维生素D缺乏在人群中普遍存在[76]。因此，在评估维生素D水平时，建议以血清25(OH)D为主要指标，并结合具体研究目的或目标人群参考相应指南的阈值标准。

4.2 维生素D缺乏的治疗 现有证据支持术前维生素D筛查与补充具有成本效益，可降低PJI发生风险并节约医疗资源。研究推荐对拟行TJA的患者行血清维生素D水平的常规筛查，对于缺乏患者建议将血清25(OH)D水平提升至≥30 ng/ml[36,53,77]。血清25(OH)D水平受多种宿主和环境因素的影响，包括年龄、性别、饮食、日晒、体力活动、体重、皮肤色素沉着及遗传等[73,78]。充足的25(OH)D水平与机体感染风险降低、免疫防御能力增强相关[79]。但血清25(OH)D的最佳免疫调节水平及对整体健康的最优阈值仍存在争议[80]。尽管维生素D缺乏与多种炎症性疾病相关，但至今尚未形成统一的治疗指南。主要问题在于维生素D的补充方式、剂量和形式等未具体说明，不同机构或组织推荐的治疗方案存在差异。内分泌学会建议根据年龄对人群进行分类，并在不同年龄组内对具有维生素D缺乏风险和确诊为维生素D缺乏的患者分组治疗[81]。最近的一项综述详细阐述了维生素D补充的基本原则，首先对具有低维生素D风险因素的患者血清25(OH)D水平进行分类，然后根据血清25(OH)D的不同水平对人群进行分层补充维生素D[82]。上述补充方案未明确说明维生素D的补充方式和形式。

鉴于维生素D代谢受到多种因素的影响，治疗应制定具体指导方案以确定特定疾病条件下维生素D所需水平的规范值，从而确保患者的治疗效果和安全性。最新的观点认为，一般人群应每日口服维生素D_3(胆钙化醇)作为维生素D补充的首选方法，每天补充2000 U维生素D被认为是预防和治疗成人维生素D缺乏症的安全有效剂量，但即使每日补充10 000 U时也没有安全问题[83-84]。活性维生素D类似物适用于甲状旁腺功能减退和严重肾、肝功能不全的患者；对于吸收不良综合征或维生素D抵抗状态患者，静脉注射维生素D可能更为有效[85]。然而，过量补充维生素D可导致多种并发症，如引发剂量依赖性的高钙血症与肌肉代谢紊乱，进而增加跌倒风险，甚至引起维生素D中毒。因此，应监测治疗过程中的维生素D水平以评估治疗的有效性和安全性。

5 总结与展望

PJI作为影响假体使用寿命的常见因素，其发生与促炎-抗炎机制失衡密切相关。维生素D在这一过程中扮演关键角色。TJA患者群体中血清维生素D普遍缺乏，且与PJI的发生有关。尽管多数研究支持PJI的发生与维生素D缺乏相关，但也有少量研究提示PJI的发生与血清维生素D水平较高相关[10,53,57,76]。此外，动物模型研究发现，补充维生素D可降低PJI的发生率，且临床研究也支持这一结论[8,36,67]。然而，目前维生素D补充的临床应用尚且欠规范、缺乏个性化，不同研究或指南共识的推荐方案也存在差异。

由于维生素D存在D_2/D_3代谢双路径，且25(OH)D与1,25$(OH)_2$D活性梯度存在差异；同时，其检测方法(如化学发光法高估D_3水平、质谱法因成本高而限制其普及)与临床判定阈值(内分泌学会定义血清25(OH)D充足标准为>30 ng/ml，而骨科学会定义为>20 ng/ml)尚未统一。上述因素共同导致血清总维生素D测定水平无法有效反映游离态活性维生素D的含量，从而无法反映组织局部特异性羟化酶的活性，也不能体现VDR受体多态性对维生素D功能的影响。因此常规检测数值难以准确表征其免疫调节、骨代谢调控等真实的生物效应，特别是在慢性炎症状态下可能产生充足/缺乏假象。

鉴于此，建议未来研究应根据不同临床条件下维生素D代谢变化的具体病理生理学特征，采取个体化的策略制定维生素D补充的规范；并且通过多中心、大样本的随机化研究进一步确定维生素D水平与PJI的关系及维生素D补充的剂量、形式、方式、服用时长及注意事项。此外，PJI的发生是多种不良因素共同导致的，尽管近期研究提示血清25(OH)D缺乏(<20 ng/ml)与PJI发生相关，但仍需要强调的是其仅为复杂病因网络中的单一环节，而非主导性驱动因子[10,54]。当前证据多源于单中心回顾性研究，其具体权重及因果关系需通过多中心大样本的前瞻性队列研究进一步阐明。鉴于维生素D的多重免疫调节和抗炎效应，建议对计划接受TJA的患者在术前常规检测其血清维生素D水平，并对维生素D不足的患者在术前及术后及时补充维生素D及其相关制剂，以降低PJI的发生风险。

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