[DOI]10.12016/j.issn.2096-1456.2019.04.001

· 专家论坛 ·

糖尿病患者口腔种植治疗研究现状

宋应亮，　张思佳

军事口腔医学国家重点实验室，国家口腔疾病临床医学研究中心，陕西省口腔生物工程技术研究中心，第四军医大学口腔医院种植科，陕西 西安（710032）

【作者简介】 宋应亮，现任空军军医大学（第四军医大学）口腔医学院种植科教授、主任医师、博士生导师，中华口腔医学会口腔种植专业委员会与口腔激光专业委员会副主任委员。研究方向为临床种植与相关风险因素，以及激光技术在口腔种植中的应用。自2010年以来，带领课题组已在本领域内发表论文65篇，其中SCI论文23篇。主译口腔种植修复专著《种植修复学-临床操作指南》1部，参编《口腔种植学》全国高等学校研究生规划教材编写，另参编专著5部（1部为副主编）。获国家发明专利2项，实用新型专利6项。承担国家自然科学基金面上项目3项。

【摘要】 2017年全世界有4.51亿（年龄18～99岁）糖尿病患者，预测至2035年这个数字将达5.92亿人，而糖尿病患者的一系列并发症常会导致其口腔相关的血管与骨组织病变，因此口腔种植科医生亟需了解糖尿病患者的临床特点以为其提供最佳的治疗方式。对于口腔种植医生而言，对血糖控制不良的糖尿病患者进行口腔种植治疗目前仍存在以下几项难题：① 糖尿病患者拔牙后牙槽窝愈合缓慢，常需辅以引导骨再生术，从而延长治疗周期，增加患者痛苦；② 糖尿病患者牙槽植骨后新骨生成率低；③ 糖尿病患者牙种植体取得有效骨结合所需时间长，效果差；④ 糖尿病患者牙种植体周围组织健康受血糖水平影响，维护不易。目前的研究认为，糖尿病患者当血糖水平得到很好控制时（HbA1c ≤ 6%），种植体的远期成功率是可预期的。本文将对糖尿病患者口腔种植治疗的研究现状进行述评，以期为临床提供参考。

【关键词】 口腔种植；　糖尿病；　骨代谢；　骨结合；　种植体成功率；　种植体周围疾病

【中图分类号】 R783.5　【文献标志码】 A　【文章编号】 2096-1456（2019）04-0205-07

【引用著录格式】 宋应亮，张思佳. 糖尿病患者口腔种植治疗研究现状[J]. 口腔疾病防治, 2019, 27(4): 205-211.

Current status of dental implantation therapy for diabetic patients

SONG Yingliang, ZHANG Sijia. State Key Laboratory of Military Stomatology & National Clinical Research Center for Oral Diseases&Shaanxi Engineering Research Center for Dental Materials and Advanced Manufacture, Department of Implant Dentistry, School of Stomatology, The Fourth Military Medical University, Xi'an 710032, China

Corresponding author: SONG Yingliang, Email: songyingliang@163.com, Tel: 0086-29-84776454

【Abstract】 In 2017, there were 451 million people (ages 18 to 99) with diabetes worldwide, and this number is expected to grow to 592 million by 2035. A series of complications in diabetic patients often leads to oral vascular and bone lesions. Therefore, dental implant doctors urgently need to understand the clinical characteristics of diabetes mellitus patients to provide the best treatment. For dental implant doctors, the following problems still exist in the treatment of diabetic patients with poor blood sugar control: ① alveolar fossa healing in diabetic patients is slow after extraction, and bone regeneration is often needed, which prolongs the treatment cycle and increases the pain of patients; ② the

【收稿日期】2018-10-31；【修回日期】2018-11-12

【基金项目】国家自然科学基金项目（81470775，81771107）

【通信作者】宋应亮，教授，博士，Email: songyingliang@163.com，Tel: 0086-29-84776454

rate of new bone formation in diabetic patients after alveolar bone grafting is slow; ③ it takes a long time for the body to achieve effective bone bonding after dental implantation in diabetic patients, and the outcomes are poor; ④ the health of the tissue around dental implants is affected by blood sugar level, which is difficult to maintain in diabetic patients. Current studies suggest that the long-term success rate of implants is predictable in diabetic patients when blood sugar levels are well controlled (HbA1c < 6%). This article will review the current research status of dental implantation therapy for diabetic patients to provide a reference for clinical practice.

【Key words】 Oral implantation; Diabetes; Bone metabolism; Bone union; Implant success rate; Periimplant disease

自上世纪60年代由Branemark教授发现“骨结合”现象以来，种植修复技术凭借其出色的生物学性能和理想的美学效果，已经成为广大医生和患者首选的缺牙修复方式。但对于糖尿病（diabetes mellitus，DM）患者，其在骨骼与血管系统的并发症常导致其拔牙创骨愈合减缓，引导骨再生术（guided bone regeneration，GBR）后新骨生成率低，种植体骨结合失败率高和种植体周围骨丧失加剧[1-3]。针对糖尿病缺牙患者的种植治疗已经成为本领域的研究热点。2017年全世界有4.51亿（年龄18～99岁）糖尿病患者[4]，预计至2035年该数字将超过5.92亿人[5]。与此同时，我国糖尿病发病率不断增加，目前已成为世界糖尿病患病人数第二大国家，因此，口腔种植医生亟需了解糖尿病缺牙患者的临床特征以为其提供相应的治疗。

糖尿病按照病因可以分为1型与2型糖尿病。其中1型是一种多基因自身免疫性疾病，其病因是由分泌胰岛素的胰腺β细胞被破坏进而导致的胰岛素分泌绝对不足[6]。1型糖尿病通常起源于免疫调节系统的异常，导致固有免疫系统活化，进而迅速并大量地产生自身反应性$CD4^+$、$CD8^+$ T淋巴细胞和B淋巴细胞，最终摧毁自身的胰岛素分泌β细胞[7]。而2型糖尿病是一种以高血糖和脂质代谢改变为特点的代谢紊乱性疾病，其病因是由于全部或部分失去功能的胰岛β细胞不能分泌足量的胰岛素来弥补自身不同程度的胰岛素抵抗[8]。而营养过剩，缺乏锻炼或肥胖均可导致胰岛素抵抗。代谢缺陷导致的2型糖尿病进一步发展表现为胰岛β细胞无法分泌足够与血液中较高的葡萄糖水平所匹配的胰岛素[9]。而这一切均可由以下因素引起：过度进食、胰高血糖素分泌增加、肠促胰岛素分泌减少、皮下扩张性脂肪组织损伤、脂肪组织炎、内源性葡萄糖增加和外周胰岛素抵抗的进行性发展[10]。慢性热量过剩是2型糖尿病发展的主要病因，尤其对于基因和表观遗传学中具有2型糖尿病高易感性的人群[11]。

目前，口腔种植修复技术已成为一种广泛应用的修复缺牙方法，糖尿病作为其相对禁忌证的资格已成为研究讨论的热点。由于越来越多的糖尿病患者要求进行种植修复治疗，就目前所掌握的资料来看，出于谨慎的态度将糖尿病列为种植修复治疗的相对禁忌证仍有必要，对于血糖水平控制较差（HbA1c ≥ 8%）的患者需要更加谨慎。当血糖水平得到很好控制时（HbA1c ≤ 6%），种植体的远期成功是可预测的，其并发症发生率与非糖尿病缺牙患者近似。本文将对糖尿病患者口腔种植治疗的研究现状进行述评。

1　糖尿病对骨代谢的影响

大量证据表明，糖尿病通过引起新陈代谢和内分泌紊乱进而影响骨质和骨量[12-14]。研究证实，糖尿病患者体内胰岛素的调节水平与骨髓来源间充质干细胞的活动水平相关[15]。目前，已经确定1型糖尿病患者的骨密度较正常人群下降[16]，降低的骨密度和由糖尿病引发的血管并发症均增加了骨折的风险[17]；而对于2型糖尿病患者，据目前大量的荟萃分析结果表明，其骨密度较正常值范围内未发生变化甚至有所增加[18]。尽管如此，2型糖尿病患者骨折风险还是较血糖正常人群高[19]，这个自相矛盾的现象可能是由于2型糖尿病患者身体其他并发症引起更多摔倒事故所导致。此外，新骨形成减少和骨质不良也被认为是其骨折风险更高的原因。在2型糖尿病动物模型上发现其骨骼机械强度下降，尽管其骨密度升高[20]。研究指出糖尿病患者种植体骨结合成功率低于健康患者人群，在他们身上能够观察到不完全和延缓的骨愈合，且新生骨呈现出不成熟的状态[21]。尽管如此，Khandelwal等[22]仍然在HbA1c ≥ 7%的患者口

内成功完成了种植修复治疗。

与此同时，骨代谢率的降低可能导致糖尿病患者骨骼的脆性增加。因骨代谢率降低，陈旧的骨无法被新骨取代，这就导致了骨骼的机械强度降低[23]。有相关的基础研究表明，糖尿病患者成骨细胞活动减少[24]。在1型糖尿病动物模型体内发现，伴随着骨代谢率的降低会出现骨矿化度降低，2型糖尿病大鼠模型也表现出降低的骨代谢率[25-26]。肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α），白介素-1β（interleukin-1β，IL-1β）和白介素-6（interleukin-6，IL-6）等细胞因子在炎症反应中扮演重要角色，但其在成骨分化过程中的具体作用还存在争议[27]，糖尿病可能通过过度的炎症反应导致促炎性细胞因子如IL-6，白介素-1β（interleukin-1β，IL-1β），基质金属蛋白酶（matrix metalloproteinases，MMPs）和TNF-α表达水平的改变来影响骨代谢[28-29]。在关于糖尿病对骨吸收影响的研究中，也有部分研究表明破骨细胞的活动增加[30]。

糖尿病患者常显示出骨折愈合的延迟，一项纳入477例糖尿病患者髋部骨折的研究报道指出，这些患者需要更长的住院时间来达到愈合[30]。在高脂高糖喂养的糖尿病大鼠体内发现，骨折后糖尿病大鼠骨痂明显较血糖正常的对照组小，且骨折愈合区内脂肪含量增高，影响骨折愈合的质量[31]，且在其早期软骨化骨过程中会发生软骨的吸收[32]。尽管严格控制血糖水平，口服伏格列波糖仍无法逆转糖尿病对骨代谢活动的影响[33]。

2　糖尿病患者骨结合的研究现状

目前，大量研究均认为控制不佳的血糖水平会对糖尿病患者牙槽骨骨质与骨量产生不良的影响[34-35]。因此，为了维护牙槽骨的健康，口腔种植医生应该对患者强调认真控制血糖的好处，指出高血糖会对种植治疗结果产生负面影响。血糖控制的好坏是判断糖尿病患者种植体远期成功的一个重要的参数[36]。

种植体骨结合过程包括周围骨的重塑，成骨细胞的迁移、增殖以及相关支持结缔组织的改建。糖尿病影响口腔种植体骨结合过程的作用机理还有待进一步研究，但血糖水平升高和胰岛素抵抗可能会对种植体周围骨的改建产生影响[37]。纤连蛋白与整合素α5β1均参与成骨细胞的粘附并在骨结合活动中扮演信号传导的角色。而糖尿病会通过干扰纤连蛋白与整合素α5β1的表达水平进而干扰种植体骨结合的过程[38]。此外，胰岛素治疗可以在大鼠体内正向调节种植体的骨结合水平[39]。

Hasegawa在2型糖尿病大鼠的胫骨远端植入种植体，术后8周取材发现，2型糖尿病大鼠体内的种植体表面含有大量软组织，软组织广泛穿插于新生的骨组织中，同时新生的骨组织连续性很差，种植体稳定性较差，而对照组大鼠体内的种植体表面骨组织连续性则较为完整[40]。

目前临床试验结果表明，糖尿病患者较非糖尿病患者其牙槽骨在受到损伤的情况下骨丧失风险有所增加[41]。种植体理想的骨结合是可以形成种植体与骨组织的直接接触，在分子水平上形成结合。然而在骨质疏松的情况下种植体形成骨结合的速度要较正常骨质减缓，而糖尿病患者大多都伴随着不同程度的骨质疏松。但也有研究指出，不同HbA1c水平的患者（≤6%、6.1%-8%、8.1%-10%、≥10%），种植体植入后1年的稳定性并无差异[42]。

严格控制的血糖水平可以减少患者微小血管并发症，与此同时，糖尿病患者体内与骨吸收代谢相关的血清和尿液中指标也显著减少，如骨钙素、吡啶啉和骨特异性碱性磷酸酶[43]。医生应对接受种植治疗的糖尿病患者反复强调血糖控制的必要性。

3　糖尿病对口腔种植体成功率的影响

糖尿病对患者口腔种植体成功率的影响具有争议[37，44-49]。糖尿病患者种植体成功率是否较非糖尿病患者低，目前尚无明确的结论。虽然考虑到高血糖对于牙槽骨的不利影响，但从实验室到临床研究还是不会给出一个完全一致的结论[50-51]。有研究指出，糖尿病患者在完成修复后第一年内显示出较对照患者更低的种植体成功率[52]。通过荟萃分析指出，糖尿病患者发生种植体边缘性骨缺损的比例更大[1，51]。系统性回顾研究指出，血糖控制较差的患者显示出更剧烈的种植体边缘骨吸收程度[53]。

目前，大量研究集中在证明糖尿病患者种植体成功率与非糖尿患者无区别，但是由于临床研究样本纳入标准的统一性及检查的全面性仍存在差异，以及动物实验的不全面性，因此对于糖尿病患者种植体成功率仍待进一步深入研究[42，54-58]。Tawil研究报告显示种植体存留率在非糖尿病人群

中与血糖控制良好的糖尿病缺牙患者之间(平均糖化血红蛋白值＜7%)没有显著性差异,整体植入存活率在非糖尿病人群和糖尿病人群中是相似的,分别为98.8%和97.2%[59]。在一项仅包括血糖水平控制不佳患者的研究中,尽管观察到一些并发症(软组织炎症、种植体旋转),但均达到98%的成功[22]。目前被广为接受的观点是血糖得到良好控制的糖尿病缺牙患者有着与非糖尿病缺牙患者相似的种植近期成功率。关于糖尿病患者年龄和患病时间是否会影响种植体成功率已经得到证实是无关的[42,60-61]。

然而,糖尿病患者血糖波动与骨结合显著相关。血糖波动通常是由于糖尿病患者血糖控制不当,其易在夜间出现低血糖,餐后出现高血糖,进而造成血糖波动频率较密集,幅度较大。研究表明血糖波动是糖尿病并发症的诱因,其会加速胰岛细胞凋亡[62]。刘乃彬等[63]研究显示过高的血糖波动较稳定持续性的高血糖对2型糖尿病大鼠种植体骨结合的影响更大。

随着种植技术理论的不断更新,即刻种植功能负载成为了可能。大量研究表明,即刻负载(轻受力)的种植体并不影响骨愈合的过程并可以取得良好的骨结合[64]。目前已有研究表明,对于血糖水平控制在正常范围内的2型糖尿病患者可以实现种植体的即刻负载[59]。

4　糖尿病与种植体周围疾病的关联

牙周炎是糖尿病口腔并发症的主要表现。糖尿病的基本病理变化包括胶原分解增加与合成减少、中性粒细胞功能降低、大血管与微小血管病变、免疫水平低下等,其会增加机体对牙周疾病的易感性,引起机体对牙周致病菌群抵抗力下降,进而加速并加重牙周组织的破坏[65]。研究显示糖尿病患者对牙周炎的易感性增加,由于血糖水平的稳态没有办法得到长时间维持,在患者免疫水平低下时其牙周组织更易发生感染,而种植体周围组织炎症也是种植早期失败的主要原因之一[14]。目前临床上最常见的糖尿病类型为2型糖尿病,其约占临床90%的病例[61]。由于2型糖尿病导致的病理变化,其发生牙周炎和失牙的几率更大。2型糖尿病可能会增加宿主对口腔菌群的炎症反应,这种反应可能会加剧牙周炎和牙龈炎易感人群的发病风险[66]。

糖尿病与种植体周围炎的关系仍存在争议[3,61,67-68]。对于不同文献中报道的种植体周围炎其本身就依据不同的诊断标准,因此很难断定糖尿病与种植体周围炎的确切联系。牙周病史对种植体周围炎具有更强的指示性,即使糖尿病患者的牙周病发病风险高于非糖尿病人群[69],但牙周病与种植体周围炎两者的具体联系仍需进一步的临床与实验室证据[70]。

Gomez-Moreno的前瞻性研究结果表明,糖尿病患者接受种植治疗后,HbA1c的升高会导致种植体周围出现更多的骨吸收[71]。在一项临床随机对照试验中,患者被按照HbA1c水平分为三组,其平均值分别为4.8%,6.1%和8.4%,研究发现HbA1c水平为8.4%的患者组其牙周状况与种植体周围软组织状况均较其余两组差[72]。在另一项临床随机对照实验中,两组患者的平均HbA1c分别为5%与4.5%,在完成口腔种植修复后一年观察期中,两组患者种植体成功率并无区别,但HbA1c 5%这一组的患者显示出更明显的种植体边缘骨吸收程度[73]。但在一项旨在评估糖尿病与种植体周围骨吸收的临床对照试验中,其结果指出糖尿病与种植体周围骨吸收程度关系较弱[74]。

研究表明,未经控制的糖尿病患者具有比血糖正常人群更高的牙菌斑指数[75]。种植体周围组织的炎症反应也与增多的牙菌斑呈正相关[76]。一项体外研究表明,在种植体表面粘附的细菌对种植体存留率和远期成功率有很大的影响,有效的牙周治疗、牙周炎症的缓解与糖化血红蛋白水平的降低呈正相关[77]。但在高脂高糖喂养的糖尿病大鼠体内发现,严重的胰岛素抵抗和紊乱的血糖水平会加速牙周炎的爆发[78]。因此,牙周疾病的控制和治疗应该是糖尿病缺牙患者治疗计划的一个重要的组成部分。之前大量动物实验研究指出血糖水平影响骨代谢与种植体骨结合[40]。考虑到糖尿病患者牙周病、伤口愈合不良和感染的风险上升,建议对糖尿病患者种植体周围组织进行严格的维护和关注[42,79]。有研究指出,含漱液的使用可以有效减少种植体周围黏膜炎的发生[80]。

依据美国糖尿病协会的标准认为HbA1c水平≤6.0%的患者为血糖水平控制较好的患者,而HbA1c水平＞8.0%被认为是控制较差。对于血糖控制较差的患者,建议医生持谨慎保守的治疗态度,将牙周维护与血糖水平监控结果作为种植体远期成功的参考标准之一[53]。

目前认为糖尿病患者存在拔牙创愈合缓慢,

种植体骨结合差，种植体周围骨吸收风险升高和种植体远期成功率降低等特点；当血糖水平得到很好控制时（HbA1c ≤ 6%），种植体的远期成功率是可预测的，其并发症发生率与非糖尿病人群近似。针对糖尿病缺牙患者口腔种植的相关临床远期研究结果，需要进一步研究。

致谢：

感谢团队成员吴春锋，王洪亮，孙道才，焦铁军，方开秀，许晓茹，刘向伟，谭乃文，王悦，丁峰，段彦盛，王蕾，陈旭涛，刘向东，乔桥等人的支持与帮助。

参考文献

[1] Chrcanovic BR, Albrektsson T, Wennerberg A. Diabetes and oral implant failure: a systematic review[J]. J Dent Res, 2014, 93(9): 859-867.

[2] De Araujo Nobre M, Malo P. Prevalence of periodontitis, dental caries, and peri-implant pathology and their relation with systemic status and smoking habits: Results of an open-cohort study with 22009 patients in a private rehabilitation center [J]. J Dent, 2017, 67: 36-42.

[3] Shi Q, Xu J, Huo N, et al. Does a higher glycemic level Lead to a higher rate of dental implant failure? A meta-analysis[J]. J Am Dent Assoc, 2016, 147(11): 875-881.

[4] Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045 [J]. Diabetes Res Clin Pract, 2018, 138: 271-281.

[5] Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035[J]. Diabetes Res Clin Pract, 2014, 103(2): 137-149.

[6] Padgett LE, Broniowska KA, Hansen PA, et al. The role of reactive oxygen species and proinflammatory cytokines in type 1 diabetes pathogenesis [J]. Ann N Y Acad Sci, 2013, 1281(1): 16-35.

[7] Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes[J]. Nature, 2010, 464 (7293): 1293-1300.

[8] Malone JI, Hansen BC. Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite?[J]. Pediatr Diabetes, 2019, 20 (1): 5-9.

[9] Lindekilde N, Pouwer F. More work is needed to better understand diabetes distress as a predictor of all-cause mortality in type 2 diabetes[J]. Diabetologia, 2018, 61(10): 2247-2248.

[10] Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management[J]. Lancet, 2011, 378(9786): 169-181.

[11] Janikiewicz J, Hanzelka K, Kozinski KA, et al. Islet beta-cell failure in type 2 diabetes - Within the network of toxic lipids[J]. Biochem Biophys Res Commun, 2015, 460(3): 491-496.

[12] Valkusz Z. Diabetes and osteoporosis[J]. Orvosi hetilap, 2011, 152 (29): 1161-1166.

[13] Wang QQ, Zhang BB, Xu YL, et al. The relationship between serum osteocalcin concentration and glucose metabolism in patients with type 2 diabetes mellitus[J]. Int J Endocrinol, 2013: 842598.

[14] King S, Klineberg I, Levinger I, et al. The effect of hyperglycaemia on osseointegration: a review of animal models of diabetes mellitus and Titanium implant placement[J]. Arch Osteoporos, 2016, 11(1): 29.

[15] Yan T, Venkat P, Chopp M, et al. Neurorestorative responses to delayed human mesenchymal stromal cells treatment of stroke in type 2 diabetic rats[J]. Stroke, 2016, 47(11): 2850-2858.

[16] Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women[J]. Osteoporos Int, 2006, 17(7): 1065-1077.

[17] Thong EP, Herath M, Weber DR, et al. Fracture risk in young and middle-aged adults with type 1 diabetes mellitus: a systematic review and meta-analysis[J]. Clin Endocrinol (Oxf), 2018, 89(3): 314-323.

[18] Larsson SC, Michaelsson K, Burgess S. Mendelian randomization in the bone field [J]. Bone, 2018.

[19] Ha M, Hu J, Petrini MA, et al. The effects of an educational self-efficacy intervention on osteoporosis prevention and diabetes self-management among adults with type 2 diabetes mellitus[J]. Biol Res Nurs, 2014, 16(4): 357-367.

[20] Tanaka H, Yamashita T, Yoneda M, et al. Characteristics of bone strength and metabolism in type 2 diabetic model Tsumura, Suzuki, Obese Diabetes mice [J]. Bone Rep, 2018, 9: 74-83.

[21] De Molon RS, Najarro JA, Morais-Camillo D, et al. Impact of diabetes mellitus and metabolic control on bone healing around osseointegrated implants: removal torque and histomorphometric analysis in rats[J]. Clin Oral Implants Res, 2013, 24(7): 831-837.

[22] Khandelwal N, Oates TW, Vargas AA, et al. Conventional SLA and chemically modified SLA implants in patients with poorly controlled type 2 Diabetes mellitus - a randomized controlled trial[J]. Clin Oral Implants Res, 2013, 24(1): 13-19.

[23] Seker A, Kara A, Camur S, et al. Comparison of mortality rates and functional results after transtibial and transfemoral amputations due to diabetes in elderly patients-a retrospective study[J]. Int J Surg, 2016, 33(A): 78-82.

[24] Khan MP, Singh AK, Joharapurkar AA, et al. Erratum. pathophysiological mechanism of bone loss in type 2 diabetes involves inverse regulation of osteoblast function by PGC-1alpha and skeletal muscle atrogenes: adipoR1 as a potential target for reversing Diabetes-Induced osteopenia.diabetes 2015; 64: 2 609-2623[J]. Diabetes, 2017, 66(12): 3142-3143.

[25] Williams GA, Callon KE, Watson M, et al. Skeletal phenotype of the leptin receptor-deficient db/db mouse[J]. J Bone Miner Res, 2011, 26(8): 1698-1709.

[26] Turner RT, Kalra SP, Wong CP, et al. Peripheral leptin regulates bone formation[J]. J Bone Miner Res, 2013, 28(1): 22-34.

[27] Wang Q, Li H, Xiao Y, et al. Locally controlled delivery of TNF alpha antibody from a novel glucose-sensitive scaffold enhances alveolar bone healing in diabetic conditions[J]. J Control Release,

2015, 206: 232-242.

[28] Akram Z, Abduljabbar T, Abu Hassan MI, et al. Cytokine profile in chronic periodontitis patients with and without obesity: a systematic review and Meta-Analysis[J]. Dis Markers, 2016: 4801418.

[29] Akram Z, Rahim ZH, Taiyeb-Ali TB, et al. Resistin as potential biomarker for chronic periodontitis: a systematic review and meta-analysis[J]. Arch Oral Biol, 2017, 73: 311-320.

[30] Norris R, Parker M. Diabetes mellitus and hip fracture: a study of 5966 cases[J]. Injury, 2011, 42(11): 1313-1316.

[31] Brown ML, Yukata K, Farnsworth CW, et al. Delayed fracture healing and increased callus adiposity in a C57BL/6J murine model of obesity-associated type 2 diabetes mellitus[J]. PLoS One, 2014, 9(6): e99656.

[32] Kayal RA, Tsatsas D, Bauer MA, et al. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity[J]. J Bone Miner Res, 2007, 22(4): 560-568.

[33] Hashiguchi C, Kawamoto SI, Kasai TA, et al. Influence of an antidiabetic drug on biomechanical and histological parameters around implants in type 2 diabetic rats[J]. Implant Dent, 2014, 23 (3): 264-269.

[34] Mohanty R, Sudan PS, Dharamsi AM, et al. Risk assessment in long-term survival rates of dental implants: a prospective clinical study[J]. J Contemp Dent Pract, 2018, 19(5): 587-590.

[35] Bell C, Bell RE. Immediate restoration of NobelActive implants placed into fresh extraction sites in the anterior maxilla[J]. J Oral Implantol, 2014, 40(4): 455-458.

[36] Alasqah MN, Alrabiah M, Al-Aali KA, et al. Peri-implant soft tissue status and crestal bone levels around adjacent implants placed in patients with and without type-2 diabetes mellitus: 6 years follow-up results[J]. Clin Implant Dent Relat Res, 2018, 20(4): 562-568.

[37] Kandasamy B, Kaur N, Tomar GK, et al. Long-term retrospective study based on implant success rate in patients with risk factor: 15-year follow-up[J]. J Contemp Dent Pract, 2018, 19(1): 90-93.

[38] Liu ZH, Zhou WJ, Tangl S, et al. Potential mechanism for osseointegration of dental implants in Zucker diabetic fatty rats[J]. Br J Oral Maxillofac Surg, 2015, 53(8): 748-753.

[39] Casap N, Nimri S, Ziv E, et al. Type 2 diabetes has minimal effect on osseointegration of Titanium implants in Psammomys obesus [J]. Clin Oral Implants Res, 2008, 19(5): 458-464.

[40] Hasegawa H, Ozawa S, Hashimoto K, et al. Type 2 diabetes impairs implant osseointegration capacity in rats[J]. Int J Oral Maxillofac Implants, 2008, 23(2): 237-246.

[41] Javed F, Al-Askar M, Al-Rasheed A, et al. Comparison of Self-Perceived oral health, periodontal inflammatory conditions and socioeconomic status in individuals with and without prediabetes[J]. Am J Med Sci, 2012, 344(2): 100-104.

[42] Oates J, Galloway P, Alexander PA, et al. The effects of elevated hemoglobin A(1c) in patients with type 2 diabetes mellitus on dental implants Survival and stability at one year[J]. J Am Dent Assoc, 2014, 145(12): 1218-1226.

[43] Capoglu I, Ozkan A, Ozkan B, et al. Bone turnover markers in patients with type 2 diabetes and their correlation with glycosylated haemoglobin levels[J]. J Int Med Res, 2008, 36(6): 1392-1398.

[44] Ormianer Z, Block J, Matalon S, et al. The effect of moderately controlled type 2 diabetes on dental implant survival and peri-implant bone loss: a long-term retrospective study[J]. Int J Oral Maxillofac Implants, 2018, 33(2): 389-394.

[45] Doll C, Hartwig S, Nack C, et al. Dramatic course of osteomyelitis in a patient treated with immediately placed dental implants suffering from uncontrolled diabetes: a case report[J]. Eur J Oral Implantol, 2015, 8(4): 405-410.

[46] Nobre MD, Malo P, Goncalves YA, et al. Outcome of dental implants in diabetic patients with and without cardiovascular disease: a 5-year post-loading retrospective study[J]. Eur J Oral Implantol, 2016, 9(1): 87-95.

[47] Esquivel-Upshaw J, Mehler A, Clark A, et al. Peri-implant complications for posterior endosteal implants[J]. Clin Oral Implants Res, 2015, 26(12): 1390-1396.

[48] Al-Sowygh ZH, Al-Kheraif AA, Akram ZA, et al. Peri-implant soft tissue inflammatory parameters and crestal bone loss among waterpipe (narghile) smokers and never-smokers with and without type 2 diabetes mellitus[J]. J Periodontol, 2018, 89(6): 645-652.

[49] Malo P, Nobre MD, Goncalves YA. Long-term outcome of implant rehabilitations in patients with systemic disorders and smoking habits: a retrospective clinical study[J]. Clin Implant Dent Relat Res, 2016, 18(4): 649-665.

[50] Reinwald S, Peterson RG, Allen MR, et al. Skeletal changes associated with the onset of type 2 diabetes in the ZDF and ZDSD rodent models[J]. Am J Physiol Endocrinol Metab, 2009, 296(4): e765-e774.

[51] Moraschini V, Barboza E, Peixoto GA. The impact of diabetes on dental implant failure: a systematic review and meta-analysis[J]. Int J Oral Maxillofac Surg, 2016, 45(10): 1237-1245.

[52] Annibali S, Pranno N, Cristalli MP, et al. Survival analysis of implant in patients with diabetes mellitus: a systematic review[J]. Implant Dent, 2016, 25(5): 663-674.

[53] Al Zahrani S, Al Mutairi A. Crestal bone loss around submerged and non-submerged dental implants in individuals with type-2 diabetes mellitus: a 7-year prospective clinical study [J]. Med Princ Pract, 2018: 000495111.

[54] Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks[J]. J Clin Periodontol, 2008, 35(8): 398-409.

[55] Dowell S, Oates TW, Robinson M. Implant success in People with type 2 diabetes mellitus with varying glycemic control-a pilot study [J]. J Am Dent Assoc, 2007, 138(3): 355-361.

[56] Erdogan O, Ucar Y, Tatli U, et al. A clinical prospective study on alveolar bone augmentation and dental implant success in patients with type 2 diabetes[J]. Clin Oral Implants Res, 2015, 26(11): 1267-1275.

[57] Ghiraldini B, Conte A, Casarin RC, et al. Influence of glycemic control on peri-implant bone healing: 12-month outcomes of local

release of bone-related factors and implant stabilization in type 2 diabetics[J]. Clin Implant Dent Relat Res, 2016, 18(4): 801-809.

[58] Alsaadi G, Quirynen M, Komárek A, et al. Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection[J]. J Clin Periodontol, 2007, 34(7): 610-617.

[59] Tawil G, Younan R, Azar P, et al. Conventional and advanced implant treatment in the type II diabetic patient: surgical protocol and long-term clinical results[J]. Int J Oral Maxillofac Implants, 2008, 23(4): 744-752.

[60] Schimmel M, Srinivasan M, Mckenna G, et al. Effect of advanced age and/or systemic medical conditions on dental implant survival: a systematic review and meta-analysis [J]. Clin Oral Implants Res, 2018, 29: 311-330.

[61] Eskow CC, Oates TW. Dental implant survival and complication rate over 2 years for individuals with poorly controlled type 2 diabetes mellitus[J]. Clin Implant Dent Relat Res, 2017, 19(3): 423-431.

[62] Shi XL, Ren YZ, Wu J. Intermittent high glucose enhances apoptosis in INS-1 cells[J]. Exp Diabetes Res, 2011: 754673.

[63] 刘乃彬, 焦铁军, 王洪亮, 等. 血糖波动对2型糖尿病大鼠种植体骨结合的影响[J]. 中华临床医师杂志, 2013, 7(5): 2073-2076.

[64] Quaranta A, Piattelli A, Scarano AA, et al. Light-microscopic evaluation of the dimensions of peri-implant mucosa around immediately loaded and submerged Titanium implants in monkeys[J]. J Periodontol, 2008, 79(9): 1697-1703.

[65] Anner R, Grossmann Y, Anner Y, et al. Smoking, diabetes mellitus, periodontitis, and supportive periodontal treatment as factors associated with dental implant survival: a long-term retrospective evaluation of patients followed for up to 10 years[J]. Implant Dent, 2010, 19(1): 57-64.

[66] Andriankaja OM, Barros SP, Moss K, et al. Levels of serum interleukin (IL)-6 and gingival crevicular fluid of IL-1 beta and prostaglandin E-2 among non-smoking subjects with gingivitis and type 2 diabetes[J]. J Periodontol, 2009, 80(2): 307-316.

[67] Daubert DM, Weinstein BF, Bordin S, et al. Prevalence and predictive factors for peri-implant disease and implant failure: a cross-sectional analysis[J]. J Periodontol, 2015, 86(3): 337-347.

[68] Brignardello-Petersen R. No evidence of higher rates of implant failure in People with controlled diabetes[J]. J Am Dent Assoc, 2017, 148(4): e5.

[69] Yadav R, Agrawal KK, Rao J, et al. Crestal bone loss under delayed loading of full thickness versus flapless surgically placed dental implants in controlled type 2 diabetic patients: a parallel group randomized clinical trial[J]. J Prosthodont, 2018, 27(7): 611-617.

[70] Marcantonio C, Nicoli LG, Marcantonio JE, et al. Prevalence and possible risk factors of peri-implantitis: a concept review[J]. J Contemp Dent Pract, 2015, 16(9): 750-757.

[71] Gomez-Moreno G, Aguilar-Salvatierra A, Rubio Roldan J, et al. Peri-implant evaluation in type 2 diabetes mellitus patients: a 3-year study[J]. Clin Oral Implants Res, 2015, 26(9): 1031-1035.

[72] Abduljabbar T, Al-Sahaly F, Al-Kathami MA, et al. Comparison of periodontal and peri-implant inflammatory parameters among patients with prediabetes, type 2 diabetes mellitus and non-diabetic controls[J]. Acta Odontol Scand, 2017, 75(5): 319-324.

[73] Al Amri MD, Abduljabbar TS. Comparison of clinical and radiographic status of platform-switched implants placed in patients with and without type 2 diabetes mellitus: a 24-month follow-up longitudinal study[J]. Clin Oral Implants Res, 2017, 28(2): 226-230.

[74] Pedro RE, De Carli JP, Linden MS, et al. Influence of age on factors associated with peri-implant bone loss after prosthetic rehabilitation over osseointegrated implants[J]. J Contemp Dent Pract, 2017, 18(1): 3-10.

[75] Javed F, Altamash M, Klinge B, et al. Periodontal conditions and oral symptoms in gutka-chewers with and without type 2 diabetes [J]. Acta Odontol Scand, 2008, 66(5): 268-273.

[76] Maximo MB, De Mendonca AC, Santos VR, et al. Short-term clinical and microbiological evaluations of peri-implant diseases before and after mechanical anti-infective therapies[J]. Clin Oral Implants Res, 2009, 20(1): 99-108.

[77] O´connell PA, Taba M, Nomizo A, et al. Effects of periodontal therapy on glycemic control and inflammatory markers[J]. J Periodontol, 2008, 79(5): 774-783.

[78] Watanabe K, Petro BJ, Shlimon AE. Effect of periodontitis on insulin resistance and the onset of type 2 diabetes mellitus in Zucker diabetic fatty rats[J]. J Periodontol, 2008, 79(7): 1208-1216.

[79] Oates TW, Huynh-Ba G, Vargas A, et al. A critical review of diabetes, glycemic control, and dental implant therapy[J]. Clin Oral Implants Res, 2013, 24(2): 117-127.

[80] Todkar R, Sheikh S, Byakod G, et al. Efficacy of chlorhexidine mouthrinses with and without alcohol-a clinical study[J]. Oral Health Prev Dent, 2012, 10(3): 291-296.

（编辑　罗燕鸿，曾曙光）