

移植肾受者的骨质疏松研究进展

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摘要: 骨质疏松症是肾移植患者常见的并发症之一,严重影响移植肾受者的生活质量,造成移植肾受者骨量减低的原因是多方面的,其中重要的原因之一就是激素的长期应用。由于肾移植患者须合用糖皮质激素及其他免疫抑制剂以控制症状,但其最佳剂量既可最大地控制患者病情,又可尽可能小地减少对肾移植受者骨量产生影响仍有待进一步地研究与统一。为了尽可能地改善移植肾受者的骨量以提高其生存质量,有多项研究资料表明,维生素 D 与磷酸盐类药物可能会改善肾移植受者的骨密度。

关键词: 骨质疏松;移植肾受者;骨密度;糖皮质激素;维生素 D;磷酸盐类药物

Research progress of osteoporosis in renal transplant recipients

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Abstract: Osteoporosis is a common complication in renal transplantation patients. It seriously affects the quality of life in renal allograft recipients. The cause of bone mass loss in graft recipients is various. One of the important reasons is the long-term application of hormones. Renal transplant patients have to be treated with corticosteroids and other immunosuppressive agents to control the symptoms. However, the optimal dose that not only can control the patient's condition, but also can reduce its influence to bone mass in renal transplant recipients, remains to be studied and integrated. A number of research data show that both vitamin D and bisphosphonates may improve the bone mineral density in the renal transplant recipients, resulting in improved bone mass and the quality of life in the renal allograft recipients.

Key words: Osteoporosis; Renal allograft recipients; Bone mineral density; Glucocorticoids; Vitamin D; Bisphosphonates

肾移植是肾衰竭患者有效的一种挽救生命的治疗方法,但尽管肾移植可以让患者的生命得以延续,但患者须长期服用免疫抑制剂以维持生命健康^[1],因此患者的身体状况必然会受到影响,其中主要的并发症之一就是会出现骨质疏松症^[2-3]。

1 肾移植后发生骨质疏松症须重视

儿童与成人移植肾患者均容易发生骨量减少与骨质疏松^[4],尤其在移植肾后的第一个半年到之后一年半的时间段里,骨量丢失的最快,移植肾患者在

术后 3 年以后,其骨密度趋于稳定^[5]。在移植肾后的半年里,腰椎部位的骨密度值下降 4%,股骨颈部位的骨密度值下降 3%^[6]。腰椎部位的骨量在肾移植术后多年的患者中是减少的^[7],慢性肾脏病患者发生骨折的危险度会增高^[8],移植肾受者发生骨折的危险性比正常人群高出 4 倍^[9],肾移植患者的骨量减少问题是必须得到重视的。

肾移植患者腰椎骨量每年约减少 1.7%,且男性与女性肾移植患者均减少^[10]。对于肾移植术后女性,尤其是绝经后女性患者,更应重视骨质疏松问题,应积极进行治疗^[11]。骨质疏松与骨折在肾移植术后患者中是很常见的,尤其是女性移植肾受

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者^[11]。

有研究表明,肾功能正常的移植者术后平均 7.5 年的患者,骨组织改变主要表现为骨吸收增加,而骨形成速度较慢,而且骨损伤在移植早期较严重,当移植龄大于 10 年后,骨形成与吸收则接近正常^[12]。移植肾受者若伴发了骨质疏松症,会严重影响其生活质量,因此须重视。

2 肾移植后发生骨质疏松症的原因分析

几乎每一个肾移植患者都经历了肾性骨病阶段,肾性骨病是由于慢性肾衰竭而导致 1, 25-(OH)₂-D₃ 缺乏和继发性甲状旁腺功能亢进而造成的。长期存在代谢性酸中毒、激素的常规服用及性激素相对缺乏都可以导致骨量减少^[13-14]。当患者接受肾移植后,常规应用糖皮质激素药物以控制移植肾受者的排斥反应而导致患者出现骨量的改变,使肾移植受者容易出现骨质疏松症^[15]。糖皮质激素对骨骼存在潜在的危害性作用,即使小剂量也可以导致服用者的骨量减低,甚至增加患者发生骨折的危险^[16]。

移植肾受者发生矿物质代谢及骨代谢紊乱的现象比较常见,主要表现为骨量的减少,最终导致骨转化降低的一系列疾病^[17]。在导致骨量减少的众多因素里,移植肾的排斥反应、慢性肾功能损伤、糖皮质激素的使用及其他类免疫抑制剂的使用是主要因素^[5, 18-19]。

糖皮质激素治疗可以导致骨量的减少^[20],主要是由于糖皮质激素诱导的成骨细胞与骨细胞的凋亡^[21-22]。肾移植术后患者停用糖皮质激素后,骨密度有所改善,可能与患者的肾基础功能状态与骨转化率有关^[23]。尽管糖皮质激素用量维持在低剂量,也会增加患者的骨折风险^[24]。

移植肾受者发生骨质疏松与骨折的风险比其他正常人群要高^[25]。移植肾受者接受糖皮质激素治疗与不接受糖皮质激素治疗的 2 组人群每年发生骨折的概率分别是 0.008% 与 0.0058%^[5]。与普通人群相比,移植肾受者发生骨折的危险性是正常人群的 4.5 倍^[26-27]。目前,移植肾受者怎样口服激素类药物以取得最佳效果仍待进一步的研究^[28]。

肾移植患者术后多服用他克莫司和环孢素,是一种钙调磷酸酶抑制剂,是移植肾受者最常用的免疫抑制剂。由于他克莫司用于治疗有相对较窄的安全范围,因此需定期检测其血药浓度。研究发现,血药浓度较高的患者相对于血药浓度较低的患者更容

易发生骨量减少^[29-30]。环孢素可能会影响破骨细胞的功能及骨矿物质的代谢,而逐渐出现移植后骨量的改变^[31]。而且移植肾受者多同时服用 2 种或 2 种以上的免疫抑制剂以控制病情^[32],因此移植肾受者是容易出现骨质疏松的。

在致使移植肾受者骨量改变的多个因素里,术后常规口服药物的治疗是主要因素。而且该类患者发生骨质疏松症时不容忽视的,因为一旦伴发骨折,患者的生活质量将受到较大的影响,因此需及时发现移植肾受者是否伴有骨质疏松症,并尽早采取措施改善患者骨量。

3 肾移植术后发生骨质疏松症的预防与治疗

肾移植术后患者须口服药物继续维持治疗,同时,鼓励患者进行适量的运动。医生及卫生保健系统都应应将锻炼纳入日常管理病人的范畴内。有氧运动可以降低心血管疾病的风险,减少骨质疏松症,并有利于减肥^[33]。

补钙与其他治疗方法相结合是防治骨质疏松症的一线疗法,但最近鉴于一项主要关于钙剂补充有可能的心血管不良效益调查结果的荟萃分析提出,针对骨质疏松症患者是否应该补充钙剂有了相应的争议^[34]。钙与维生素 D 补充的管理可能会增加循环中的钙与磷的总量,这会增加骨外沉积的危险。甚至可利用钙增加会降低血液中的 PTH,这会降低骨吸收,同时也会降低骨形成。肾功能降低的患者补钙会增加冠状动脉钙沉积可能性,此时补钙反而会增加危险^[35-36]。

降钙素具有抑制破骨细胞活性、减少骨丢失与增加骨形成等作用。对于因服用糖皮质激素出现的骨质疏松症病人,降钙素的疗效是肯定的,同时降钙素还有镇痛的作用^[37]。

依据 2010 年的 ACR 专家共识,若预期使用激素治疗将超过 3 个月的绝经期女性和 50 岁以上的男性患者,无论使用剂量大小及疗程长短均需给予双膦酸盐药物干预,除低危骨折人群预期激素 < 7.5 mg/d^[38] 外。而且在应用糖皮质激素药物后监测骨密度若出现骨量减低,即 T 值低于 -1,就应当给予抗骨质疏松药物治疗^[39]。但因糖皮质激素的应用导致的骨质疏松症的治疗,目前仍需要进一步研究^[22, 40]。

双膦酸盐类药物可以改善绝经后妇女的骨密度情况以及减少骨折的发生率,对服用激素导致的骨

量减少也有作用^[41-42]。阿仑膦酸钠治疗移植肾受者继发的骨质疏松有较好的效果^[43]。

维生素 D 与双膦酸盐类药物合用改善肾移植患者的骨量情况有较好的效果^[15, 44], 而特立帕肽的抗骨质疏松对于肾移植患者作用不明显^[45]。对于肾移植患者若能进行针对性的个体治疗骨质疏松方案, 男性或女性患者的骨密度均会有所改善, 并保持相对稳定^[46-47]。当移植肾受者接受阿仑膦酸钠治疗 1 年后, 腰椎和股骨颈部位的骨密度有所改善, 而在随访只服用骨化三醇的肾移植患者, 在 1 年里其骨密度没有明显改善^[47]。

对于移植肾受者明确诊断骨质疏松症的患者, 在接受治疗的同时, 应当根据病情变化或治疗方案的选择, 1 年复查 1 次骨密度或半年复查 1 次骨密度, 若条件允许建议患者每 3 个月复查一次骨标志物, 以观察其骨代谢情况, 更好地协助调整治疗方案^[48]。

4 结语

由于肾移植患者须合用糖皮质激素及其他免疫抑制剂以控制症状, 但其最佳剂量既可最大地控制患者病情, 又可尽可能小地减少对肾移植受者骨量产生影响仍有待进一步的研究与统一。对于改善移植肾受者的骨量的最佳药物及剂量仍有待进一步研究。

【参 考 文 献】

- [1] Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant* 2011, 11(3):450-462.
- [2] Julian BA, Laskow DA, Dubovsky J, et al. Rapid loss of vertebral mineral density after transplantation. *N Engl J Med*, 1991, 325: 544.
- [3] Gordon PL, Frassetto LA. Management of osteoporosis in CKD stages to 5. *Am J Kidney Dis*, 2010, 55(5):941.
- [4] el-Husseini AA, el-Agoudy AE, Wafa EW, et al. Bone mineral density in live related kidney transplant children and adolescents. *Int Urol Nephrol*, 2004, 36(1):95-100.
- [5] Grotz WH, Munding FA, Rasenack J, et al. Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. *Nephrol Dial Transplant*, 1995, 10(11):2096-2100.
- [6] Kodras K, Haas M. Effect of kidney transplantation on bone. *Eur J Clin Invest*, 2006, 36 (Suppl 2):63-75.
- [7] Brandenburg VM, Ketteler M, Fassbender WJ, et al. Development of lumbar bone mineral density in the late course after kidney transplantation. *Am J Kidney Dis*, 2002, 40(5):1066-1074.
- [8] Sprague S, Josephson M. Bone disease after kidney transplantation. *Semin Nephrol*, 2004, 24:82-90.
- [9] Grotz W, Munding F, Gugel B, et al. Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation*, 1994, 58(8):912-915.
- [10] Pichette V, Bonnardeaux A, Prudhomme L, et al. Long-Term Bone Loss in Kidney Transplant Recipients: A Cross-Sectional and Longitudinal Study. *Am J Kidney Dis*, 1996, 28(1):105-114.
- [11] Patel S, Kwan JT, McCloskey E, et al. Prevalence and Causes of Low Bone Density and Fractures in Kidney Transplant Patients. *J Bone Miner Res*, 2001, 16(10):1863-1870.
- [12] Carlini RG, Rojas E, Singer JR, et al. Bone disease in patients with long term renal transplantation and normal renal function. *Am J Kidney Dis*, 2000, 36(1):160-166.
- [13] 陈慧萍, 季大玺, 谢红娘, 等. 维持性血液透析患者骨组织学改变及计量分析. *肾脏病与透析肾移植杂志*, 2000, 9(2): 101-107.
Chen HP, Ji DX, Xie HN, et al. Analysis of bone structure changes and measurement in maintenance hemodialysis patients. *Chinese Journal of Nephrology Dialysis & Transplantation*, 2000, 9(2):101-107. (in Chinese)
- [14] 孙桂芳, 张宝霞. 慢性肾脏病矿物质和骨代谢异常治疗进展. *中外医疗*, 2010, 29:183-184.
Sun GF, Zhang BX. Advances in the treatment of mineral and bone metabolism disorders in chronic kidney disease. *China Foreign Medical Treatment*, 2010, 29:183-184. (in Chinese)
- [15] Mainra R, Elder G. Review article: Managing bone complications after kidney transplantation. *Nephrology (Carlton)*, 2009, 14(4):437-442.
- [16] TPV Staa, HGM Leufkens, L Abenham, et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res*, 2005, 20(8):1487-1494.
- [17] Kalantar-Zadeh K, Molnar MZ, Kovesdy CP, et al. Management of mineral and bone disorder after kidney transplantation. *Curr Opin Nephrol Hypertens*, 2012, 21(4):389-403.
- [18] Julian BA, Laskow DA, Dubovsky J, et al. Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med*, 1991, 325(8):544-550.
- [19] Casez JP, Lippuner K, Horber FF, et al. Changes in bone mineral density over 18 months following kidney transplantation: the respective roles of prednisone and parathyroid hormone. *Nephrol Dial Transplant*, 2002, 17(7):1318-1326.
- [20] Malluche HH, Monier-Faugere MC, Herberth J, et al. Bone disease after renal transplantation. *Nat Rev Nephrol*, 2010, 1(6):32-40.
- [21] Weinstein RS, Jilka RL, Parfitt AM, et al. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. *J Clin Invest*, 1998, 102(2):274-282.
- [22] 周晓, 孙伟, 隋晓杰, 等. 糖皮质激素引发骨质疏松或骨坏死等不良反应研究进展. *疑难病杂志*, 2015, 14(5):534-540.
Zhou X, Sun W, Sui XJ, et al. Research progress of adverse effects of glucocorticoid induced osteoporosis or bone necrosis.

- Chinese Journal of Difficult and Complicated Cases, 2015, 14 (5):534-540. (in Chinese)
- [23] Sambrook P, Birmingham J, Kempster S, et al. Corticosteroid effects on proximal femur bone loss. *J Bone Miner Res*, 1990, 5 (12): 1211.
- [24] Ing SW, Sinnott LT, Donepudi S, et al. Change in bone mineral density at one year following glucocorticoid withdrawal in kidney transplant recipients. *Clin Transplant*, 2011, 25 (2): E113-23.
- [25] van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int*, 2006, 79 (3):129-137.
- [26] Nikkel LE, Mohan S, Zhang A, et al. Reduced Fracture Risk With Early Corticosteroid Withdrawal After Kidney Transplant. *Am J Transplant*, 2012, 12 (3): 649-659.
- [27] Abbott KC, Oglesby RJ, Hypolite IO, et al. Hospitalizations for fractures after renal transplantation in the United States. *Ann Epidemiol*, 2001, 11: 450-457.
- [28] Vautour LM, Melton LJ 3rd, Clarke BL, et al. Long-term fracture risk following renal transplantation: A population-based study. *Osteoporos Int*, 2004, 15 (2): 160-167.
- [29] Thierry A, Mourad G, Büchler M, et al. Three-Year Outcomes in Kidney Transplant Patients Randomized to Steroid-Free Immunosuppression or Steroid Withdrawal, with Enteric-Coated Mycophenolate Sodium and Cyclosporine: The Infinity Study. *J Transplant*, 2014, 2014: 171898.
- [30] Luo L, Shi Y, Bai Y, et al. Impact of tacrolimus on bone metabolism after kidney transplantation. *Int Immunopharmacol*, 2012, 13 (1): 69-72.
- [31] Sun L, Peng Y, Zaidi N, et al. Evidence that calcineurin is required for the genesis of bone-resorbing osteoclasts. *Am J Physiol Renal Physiol*, 2007, 292 (1): 285-291.
- [32] 王英吉, 陈平. 移植后骨质疏松研究进展. *实用医院临床杂志*, 2014, 11 (1): 39-43.
Wang JY, Chen P. Research progress of osteoporosis after transplantation. *Practical Journal of Clinical Medicine*, 2014, 11 (1): 39-43. (in Chinese)
- [33] Gordon EJ, Prohaska T, Siminoff LA, et al. Needed: Tailored Exercise Regimens for Kidney Transplant Recipients. *Am J Kidney Dis*, 2005, 45 (4): 769-774.
- [34] Reid IR, Bolland MJ. Calcium risk-benefit updated - new WHI analyses. *Maturitas*, 2014, 77 (1): 1-3.
- [35] Park CY, Lee WH, Fleet JC, et al. Calcium and vitamin D intake maintained from preovariectomy independently affect calcium metabolism and bone properties in Sprague Dawley rats. *Osteoporos Int*, 2014, 25 (7): 1905-1915.
- [36] Karolina Paziana, Michael Pazianas. Calcium supplements controversy in osteoporosis: a physiological mechanism supporting cardiovascular adverse effects. *Endocrine*, 2015, 48 (3): 776-778.
- [37] 雷淑琴, 薛痕. 肾移植术后骨病. *现代预防医学*, 2008, 35 (15): 3034-3036.
Lei SQ, Xue H. Bone disease after renal transplantation. *Modern Preventive Medicine*, 2008, 35 (15): 3034-3036. (in Chinese)
- [38] Grossman JM, Cordo R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care (Hoboken)*, 2010, 62 (11): 1515-1526.
- [39] 吴现, 王国春, 周惠琼. 糖皮质激素诱导骨质疏松的诊治进展. *中日友好医院学报*, 2010, 24 (5): 307-310.
Wu X, Wang GC, Zhou HQ. Progress in the diagnosis and treatment of glucocorticoid induced osteoporosis. *Journal of China-Japan Friendship Hospital*, 2010, 24 (5): 307-310. (in Chinese)
- [40] Asano S, Suzuki A. Assessment of the treatment of glucocorticoid-induced osteoporosis. *Clin Calcium*, 2013, 23 (3): 401-408.
- [41] Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The alendronate phase III osteoporosis treatment study group. *New Engl J Med*, 1995, 333 (22): 1437-1443.
- [42] Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *New Engl J Med*, 1997, 337 (6): 382-387.
- [43] Okamoto M, Yamataka S, Yoshimoto W, et al. Masanori Okamoto, Shintaro Yamanaka. Alendronate as an Effective Treatment for Bone Loss and Vascular Calcification in Kidney Transplant Recipients. *J Transplant*, 2014, 2014: 269613.
- [44] Jeon HJ, Han M, Jeong JC, et al. Impact of Vitamin D, Bisphosphonate, and Combination Therapy on Bone Mineral Density in Kidney Transplant Patients. *Transplant Proc*, 2013, 45 (8): 2963-2967.
- [45] Cejka D, Benesch T, Krestan C, et al. Effect of Teriparatide on Early Bone Loss After Kidney Transplantation. *Am J Transplant*, 2008, 8 (9): 1864-1870.
- [46] Gordon PL, Frassetto LA. Management of osteoporosis in CKD stages 3 to 5. *Am J Kidney Dis*, 2010, 55 (5): 941-956.
- [47] Mainra R, Elder G. Individualized Therapy to Prevent Bone Mineral Density Loss after Kidney and Kidney-Pancreas Transplantation. *Clin J Am Soc Nephrol*, 2010, 5 (1): 117-124.
- [48] 张智海, 刘忠厚, 李娜, 等. 中国人骨质疏松症诊断标准专家共识 (第三稿·2014 版). *中国骨质疏松杂志*, 2014, 20 (9): 1007-1010.
Zhang ZH, Liu ZH, Li N, et al. Expert consensus on the diagnostic criteria of osteoporosis in the Chinese people (2014 release-Third Edition). *Chinese Journal of Osteoporosis*, 2014, 20 (9): 1007-1010. (in Chinese)

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