Published online www.wanfangdate.com.cn doi:10.3969/j.issn.1006-7108.2017.07.024

·综述·

铁蓄积、骨内血管与骨质疏松关系的研究进展

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中图分类号: R589.5 **文献标识码**: A **文章编号**: 1006-7108(2017)07-0954-05

摘要: 铁蓄积可能是骨质疏松症发生的独立危险因素,许多研究表明铁蓄积可导致骨质疏松症的发生。目前,骨内血管是骨质疏松研究的热点,骨中特殊的血管亚型偶联了骨形成与血管形成。那么,铁蓄积能否通过影响骨内特殊血管亚型,进而引起骨量下降?本文就铁蓄积与血管的关系作一综述,探讨铁与骨内血管调控骨代谢的潜在意义。

关键词: 骨质疏松;铁蓄积;骨内血管;骨代谢

Research advance in the relationship among iron accumulation, blood vessel in bone, and osteoporosis

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Abstract: Iron accumulation is an independent risk factor of osteoporosis. Basic research shows that iron accumulation leads to osteoporosis. Currently, microvasculature in bone becomes a hot topic in osteoporosis research. A special vessel subtype is found in skeletal system, coupling angiogenesis and osteogenesis. Whether iron accumulation could cause low BMD by decreasing the special vessel subtype of vessel? This paper reviews the relationship between iron accumulation and blood vessel, and explores its potential clinical significance.

Key words: Osteoporosis; Iron accumulation; Intraosseous vessel; Bone metabolism

铁蓄积对骨质疏松症的影响已得到了国内外学者的认可,铁蓄积通过氧化应激、Wnt/β-catenin 信号通路等途径,抑制骨形成,促进骨吸收[1-2]。骨质疏松与骨内血管的关系是近些年研究的热点,骨内存在一种特殊血管亚型,与骨形成相偶联,二者间偶联的机制可由 Notch 信号来解释,老年后骨形成与血管形成均下降,但可为专用药物所逆转[3-5]。既然骨质疏松与血管形成存在密切关联,那么,铁蓄积影响骨代谢是否通过调控骨内血管从而影响骨代谢呢?笔者对近 5 年"铁蓄积"与"骨质疏松"、"骨质疏松"与"骨内血管"及"铁蓄积"对"骨内血管"影响的相关文献作一综述。

1 铁蓄积的定义

临床上反映机体铁稳态的主要指标是血清铁蛋白[6]。当血清铁蛋白大于 1000 ug/L 时(血清铁蛋白正常值男性为 15 ~ 200 ug/L、女性为 12 ~ 150 ug/L),常被认为存在病理性铁过载;当血清铁蛋白大于正常值而小于 1000 ug/L 时,被认为存在铁蓄积。机体目前已知的排铁方式主要有排便、月经、皮肤等。铁蓄积常发生于绝经后女性,主要原因包括以下几点:①女性经月经排铁约 36 mg/年,一旦绝经,排铁减少,常发生铁蓄积;②雌激素下降至正常值 10%,血清铁蛋白水平可增加 2 ~ 3 倍[7]。Cho 等[8]对 1691 名绝经前女性和 1391 名绝经后女性进行临床相关数据分析,发现血清铁蛋白的增加

基金项目:国家自然科学基金(81572179);苏州市吴江区第一人民医院课题立项(院 201615);江苏省研究生创新计划(KYLX15_1227);苏州市科教兴卫青年项目(KJXW2015016);苏州科技计划项目(SYS201637)

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与绝经后女性代谢症候群有关，而与绝经前女性的状态无关。所以，围绝经期及绝经后期相关症状与疾病可能与血清铁蛋白水平升高存在相关性。

2 铁蓄积对骨质疏松的影响

2006年美国学者 Weinberg[9] 提出铁蓄积是骨质疏松的独立危险因素，铁蓄积能抑制成骨细胞的分化，干扰骨的再生与修复。2013年徐又佳等[10]在《中华医学杂志》发表专家论坛《铁与性激素关系在骨质疏松性别差异中的影响》；2015年徐又佳等[6,11]在《中华骨科杂志》分别发表述评及综述《重视绝经后骨质疏松性骨折及铁蓄积》和《铁蓄积与绝经后骨质疏松关系的研究进展》；2016年赵国阳等[12]分析临床相关数据认为输血相关铁蓄积的患者存在骨密度的降低，骨密度与体内铁蓄积的水平呈负相关。这一系列文章都说明铁蓄积与骨量下降、骨质疏松关系极其密切，是当今研究的热点，这一理念为骨质疏松相关疾病的防治提供了新的理论。笔者分别从细胞和临床病例方面作一总结。

2.1 铁蓄积对成骨细胞、破骨细胞及间充质干细胞的影响

Borriello 等[13] 提取人骨髓间充质干细胞（mesenchymal stem cells，MSCs）进行体外培养，应用铁剂干预，观察 MSCs 增殖、分化的情况，铁通过激活 MAPK 信号通路明显抑制 MSCs 向成骨细胞分化，并干扰基质矿化。Xie 等[14]通过提取小鼠股骨、胫骨骨髓细胞并进行体外培养，使用不同浓度外源性铁剂干预3～5 d后，观察到骨髓源性巨噬细胞向破骨细胞分化的程度增加，而去铁胺（deferoxamine，DFO）治疗后可部分抑制其分化作用。国内刘禄林[15]等报道 DFO 治疗后可缓解铁蓄积导致的破骨细胞增强和成骨细胞功能的抑制，从而提高骨密度、改善骨微结构。

Tsay 等[16]建立铁蓄积小鼠模型，铁蓄积后小鼠体内产生过量活性氧，造成骨量下降及骨显微结构的破坏，使用抗氧化剂后能部分改善骨量。Zhang 等[17]报道铁蓄积对小鼠骨髓微环境也产生不良影响，该团队构建铁蓄积小鼠模型，观察骨髓间充质干细胞的增殖及分化，证实铁蓄积后 MSCs 增殖能力下降，成骨/成脂分化失衡，应用抗氧化剂治疗可部分缓解骨髓细胞的受损程度。国内袁晔等[18]报道铁蓄积小鼠模型，骨髓内造血干细胞也受影响，该研究提示铁蓄积导致成骨相关指标明显受到抑制，而造血干细胞的数量及功能呈现增强现象，考虑可能与造血干细胞是破骨细胞的前体有关。Wang 等[19]报道铁蓄积小鼠增加了氧化应激的水平，在雌激素存在的情况下，铁蓄积对骨的影响较小，而雌激素一旦缺失（去势），铁蓄积通过促进破骨细胞的分化显著降低了骨量。国内王啸等[20]报道了一定浓度的高铁环境可升高活性氧水平，通过促进 p50-65 二聚体核易位，加速单核细胞 RAW264.7 向破骨细胞分化，骨量下降。

2.2 铁蓄积与临床患者相关性分析

国内张林林等[21]率先在本领域进行了临床相关研究，他们回顾性分析了76例绝经后髋部脆性骨折患者临床资料，结果显示绝经后髋部骨折患者的骨密度与血清铁蛋白相关。张伟等[22]对156例绝经后股骨颈骨折患者的股骨头进行骨铁含量测定，发现股骨颈脆性骨折患者骨铁含量随年龄增加而升高，且高龄女性骨小梁边缘和表面均有铁沉积，而年轻女性则未见。Li 等[23]在《Osteoporosis Int》发表综述，阐述了铁稳态在骨质疏松防治中具有潜在的临床作用。Chen 等[24]认为降低铁蓄积对绝经后骨质疏松防治具有重要的临床价值。韩国学者 Kim 等[25-26]对1729名体检人群股骨颈骨密度与血清铁蛋白进行分析发现二者呈负相关；该团队又对45岁以上693名女性进行股骨颈骨强度和血清铁蛋白结果分析发现，高血清铁蛋白与低股骨颈骨强度有关；因此他们认为铁蓄积可能是骨密度下降的独立危险因素。

3 骨内血管与骨形成的偶联关系

2014年德国学者 Kusumbe 等[3]通过对小鼠骨组织进行免疫荧光染色，发现在鼠类骨骼系统中存在一种新的毛细血管亚型，这种特殊的亚型血管表现为两种内皮细胞表面抗体共定位（CD31 和 Emcn），这种特殊的亚型血管之所以重要，是因为其周围伴随大量 Osterix 阳性染色的骨祖细胞，进一步分化为成骨细胞参与骨形成，二者的偶联关系主要存在于骨骺端及骨内膜区，而在骨干部位几乎不存在，这种现象可能与干骺端、骨膜下骨代谢活跃有关。所以，研究骨内特殊血管与骨形成之间的偶联具有潜在的临床意义。Ramasamy 等[5]进一步证明 Notch 信号通路参与了二者的偶联机制，在内皮细胞上特异性敲除 Notch 信号通路的相关基因，不仅骨量下降，形态变短，骨小梁稀疏，而且骨内特殊亚型血管也减少，应用外源性 Noggin（骨形态蛋白拮抗剂）可部分恢复骨量。同年，Xie 等[4]报道破骨细胞前体细胞分泌的血小板源性生长因子（PDGF-

BB)能诱导血管新生及骨形成,利用外源性 PDGF-BB 增加了骨内这种特殊的亚型血管并刺激了骨形成。为了强调上述发现,Kusumbe 等[27]在《Nature Medicine》上发表评述《破骨前体细胞可促进骨内血管新生与骨形成》。可见,骨内存在特殊亚型血管偶联了骨形成与血管形成,进一步研究其在骨代谢领域的作用具有重要的临床价值。

4 铁蓄积与血管形成

4.1 铁蓄积对组织器官血管形成的影响

张强等[28]报道在肿瘤的生长过程中铁能促进三阴性乳腺癌类血管的形成,三阴性乳腺癌细胞可通过自身变形形成类血管样结构,给肿瘤细胞提供营养,DFO 处理后能明显抑制类血管样管腔的形成。铁蓄积可增加心血管病的风险,引起血压升高,促进动脉粥样硬化形成,通过产生氧自由基对血管产生损伤,加重心力衰竭;过多铁蛋白是脑损伤过程中的危险因素之一,参与了自由基的形成,损伤血管内皮细胞,可引起脑卒中或再灌注损伤[29]。所以,铁水平的检测可作为动脉粥样硬化程度和预测脑梗死风险的重要指标。在肿瘤细胞代谢中铁蓄积可促进类血管腔形成,而在心血管及脑血管病的发病过程中,可产生血管损伤,加速了脑卒中、冠心病的发生。

4.2 铁蓄积对骨相关血管形成的影响

铁蓄积对骨的影响除了对破骨细胞、成骨细胞及骨髓相关细胞方面的作用以外,是否还存在其他方面的作用从而影响骨代谢呢?笔者查阅文献,作一总结。

Eckard 等[30]、Jian 等[31]通过体外细胞培养证实铁缺乏能稳定 HIF 信号通路,显著促进 VEGF 的分泌,增强血管形成;而铁蓄积则增加了氧化应激的水平并激活 MAPK 信号通路,抑制血管新生。Saghiri 等[32]发表综述评价多种元素(N、Fe、Se、P、Au 和 Ca)对血管形成的影响,体外实验表明铁蓄积干扰了 HIF 的稳定性,下调 HIF 相关信号通路基因的表达,导致 VEGF 水平下降,抑制血管形成。Farberg 等[33]通过对动物下颌骨进行延长实验,证实应用去铁胺能显著促进血管形成,加速骨再生。国内王亮等[34]首先在人的骨标本中发现 H 亚型血管的存在,并进一步探讨了骨质疏松患者的骨标本中 H 亚型血管的量较非骨质疏松明显减少,提示 H 亚型血管与骨密度存在密切偶联,那么,上述实验结果提示铁蓄积可通过抑制骨内血管形成来干扰骨形成,降低铁蓄积可缓解其对血管及骨形成的影响,这或许是铁蓄积干扰骨形成领域新的热点(图 1)。

图 1 铁蓄积通过影响骨内血管形成导致骨生成障碍

Fig. 1 Iron accumulation leads to osteogenesis disturbance by affecting the formation of blood vessels in the bone

5 小结

综上所述,临床上确实存在铁蓄积的患者,铁蓄积程度与年龄相关,常引起骨量下降。骨形成与血管形成的偶联是近年比较热点的话题,本文从二者的偶联现象、机制及相关干预等方面进行了系统总结,为临床相关问题的解决提出了新的思路。另外,笔者对铁蓄积影响血管的可能机制也进行了初步阐述,希望能引入铁蓄积对骨内血管方面的研究,为临床铁蓄积导致骨密度降低的机制提供新的思路。

【 参 考 文 献 】

[1] Jia P, Xu YJ, Zhang ZL, et al. Ferric ion could facilitate osteoclast differentiation and bone resorption through the production of reactive oxygen species. Journal of Orthopaedic Research, 2012, 30(11): 1843-1852.

[2] Zancan I, Bellesso S, Costa R, et al. Glucocerebrosidase deficiency in zebrafish affects primary bone ossification through increased oxidative stress and reduced Wnt/beta-catenin signaling. Human molecular genetics, 2015, 24(5): 1280-1294.

[3] Kusumbe AP, Ramasamy SK, Adams RH. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. Nature, 2014, 507(7492): 323-328.

[4] Xie H, Cui Z, Wang L, et al. PDGF-BB secreted by preosteoclasts induces angiogenesis during coupling with osteogenesis. Nature medicine, 2014, 20(11): 1270-1278.

[5] Ramasamy SK, Kusumbe AP, Wang L, et al. Endothelial Notch activity promotes angiogenesis and osteogenesis in bone. Nature, 2014, 507(7492): 376-80.

[6] 林华, 徐又佳. 重视绝经后骨质疏松性骨折及铁蓄积. 中华骨科杂志, 2015, 35(10): 981-982.
Lin H, Xu YJ. Pay attention to postmenopausal osteoporotic fracture and iron accumulation. Chin J Orthop, 2015, 35(10): 981-982. (in Chinese)

[7] Jian J, Pelle E, Huang X. Iron and menopause: does increased iron affect the health of postmenopausal women?. Antioxidants &

Redox Signaling, 2009, 11(12): 2939-2943.

[8] Cho GJ, Shin JH, Yi KW, et al. Serum ferritin levels are associated with metabolic syndrome in postmenopausal women but not in premenopausal women. Menopause, 2011, 18(10): 1120-1124.

[9] Weinberg ED. Iron loading: a risk factor for osteoporosis. Biometals, 2006, 19(6): 633-635.

[10] 徐又佳, Huang X. 铁与性激素关系在骨质疏松性别差异中的影响. 中华医学杂志, 2013, 93(48): 3809-3811.
Xu YJ, Huang X. Effects of iron and sex hormones on gender differences in osteoporosis. Natl Med J China, 2013, 93(48): 3809-3811. (in Chinese)

[11] 李光飞, 徐又佳. 铁蓄积与绝经后骨质疏松症关系的研究进展. 中华骨科杂志, 2015, 35(10): 1017-1021.
Li GF, Xu YJ. Research progress of relationship between iron accumulation and postmenopausal osteoporosis. Chin J Orthop, 2015, 35(10): 1017-1021. (in Chinese)

[12] 赵国阳, 狄东华, 庄琴, 等. 输血相关铁蓄积患者骨密度分析. 中国骨质疏松杂志 2016, 22(12): 1568-1572.
Zhao GY, Di DH, Zhuang Q, et al. Bone mineral density in patients withtransfusion-associated iron accumulation. Chin J Osteopor, 2016, 22(12): 1568-1572. (in Chinese)

[13] Borriello A, Caldarelli I, Speranza MC, et al. Iron overload enhances human mesenchymal stromal cell growth and hampers matrix calcification. Biochimica et biophysica acta, 2016, 1860(6): 1211-1223.

[14] Xie W, Lorenz S, Dolder S, Hofstetter W. Extracellular Iron is a Modulator of the Differentiation of Osteoclast Lineage Cells. Calcified tissue international, 2016, 98(3): 275-283.

[15] 刘禄林, 王啸, 李光飞, 等. 甲磺酸去铁胺治疗铁蓄积致骨量下降雄性小鼠的实验研究. 中国骨质疏松杂志, 2015, 21(1): 88-93.
Liu LL, Wang X, Li GF, et al. Effect of deferoxamine administration on the treatment of ironaccumulation-induced osteopenia in male mice. Chin J Osteopor, 2015, 21(1): 88-93. (in Chinese)

[16] Tsay J, Yang Z, Ross FP, et al. Bone loss caused by iron overload in a murine model: importance of oxidative stress. Blood, 2010, 116(14): 2582-2589.

[17] Zhang Y, Zhai W, Zhao M, et al. Effects of iron overload on the bone marrow microenvironment in mice. PloS One, 2015, 10(3): e0120219.

[18] 袁晔, 王亮, 曹彦, 等. 铁蓄积骨质疏松小鼠模型造血干细胞与骨代谢指标的相关性. 中华骨质疏松和骨矿盐疾病杂志, 2016, 9(3): 289-295.
Yuan Y, Wang L, Cao Y, et al. Correlation between hematopoietic stem cells and bone turnover markers in iron accumulation osteoporosis mouse model. Chin J Osteoporosis & Bone Miner Res, 2016, 9(3): 289-295. (in Chinese)

[19] Xiao W, Beibei F, Guangsi S, et al. Iron overload increases osteoclastogenesis and aggravates the effects of ovariectomy on bone mass. Journal of endocrinology, 2015, 226(3): 121-134.

[20] 王啸, 汪升, 陈斌, 等. 高铁环境对破骨细胞分化的影响及机制. 中华实验外科杂志, 2014, 31(11): 2512-2514.
Wang X, Wang S, Chen B, et al. Effects of high level of ferritin on osteoclasts differentiation. Chin J Exp Surg, 2014, 31(11): 2512-2514. (in Chinese)

[21] 张林林, 姜习凤, 艾红珍, 等. 绝经后髋部脆性骨折中铁过载指标与骨密度骨转换指标关系的研究. 中华外科杂志, 2013, 51(6): 518-521.
Zhang LL, Jiang XF, AI HZ, et al. Relationship of iron overload to bone mass density and bone turnover in postmenopansal women with fragility fractures of the hip. Chinese Journal of Surgery, 2013, 51(6): 518-521. (in Chinese)

[22] 张伟, 王兵, 张林林, 等. 绝经后股骨颈骨折股骨头骨铁含量、血清铁蛋白与骨密度相关性研究. 中华骨科杂志, 2014, 34(1): 39-47.
Zhang W, Wang B, Zhang LL, et al. Correlation between femoral head bone iron content, serum ferritin and bone mineral density of postmenopausal women with femoral neck fragility fracture. Chin J Orthop, 2014, 34(1): 39-47. (in Chinese)

[23] Li GF, Pan YZ, Sirois P, et al. Iron homeostasis in osteoporosis and its clinical implications. Osteoporosis International, 2012, 23(10): 2403-2408.

[24] Chen B, Li GF, Shen Y, et al. Reducing iron accumulation: A potential approach for the prevention and treatment of postmenopausal osteoporosis. Experimental and Therapeutic Medicine, 2015, 10(1): 7-11.

[25] Ahn SH, Lee S, Kim H, et al. Higher serum ferritin level and lower femur neck strength in women at the stage of bone loss (≥ 45 years of age): The Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV). Endocrine Research, 2016, 41(4): 334.

[26] Kim BJ, Ahn SH, Bae SJ, et al. Iron overload accelerates bone loss in healthy postmenopausal women and middle-aged men: a 3-year retrospective longitudinal study. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research, 2012, 27(11): 2279-2290.

[27] Kusumbe AP, Adams RH. Osteoclast progenitors promote bone vascularization and osteogenesis. Nature medicine, 2014, 20(11): 1238-1240.

[28] 张强, 史云湘, 史杪, 等. 铁对三阴性乳腺癌细胞体外血管生成拟态的影响. 基础医学与临床, 2016, 36(8): 1062-1067.
Zhang Q, Shi YX, Shi M, et al. The effect of iron on the vasculogenic mimicry in triple negative breast cancer cells in vitro. Basic & Clinical Medicine, 2016, 36(8): 1062-1067. (in Chinese)

[29] 高素玲, 刘国荣, 陈瑞英, 等. 进展性缺血性脑卒中患者血清铁蛋白测定的临床意义. 中华老年心脑血管病杂志, 2013, 15(2): 171-172.
Gao SL, Liu GR, Chen RY, et al. Measurement of serum ferritin level in patients with progressive ischemic stroke and its clinical significance. Chin J Geriatr Heart Brain Vesel Dis, 2013, 15(2): 171-172. (in Chinese)

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112.

[14] Brack AS, Conboy MJ, Roy S, et al. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science, 2007,317(5839): 807-810.

[15] Ruckh JM, Zhao JW, Shadrach JL, et al. Rejuvenation of regeneration in the aging central nervous system. Cell Stem Cell, 2012,10(1): 96-103.

[16] Baht GS, Silkstone D, Vi L, et al. Exposure to a youthful circulaton rejuvenates bone repair through modulation of beta-catenin. Nature Communications, 2015,6(2):7131.

[17] Sinha M, Jang YC, Juhyun OH, et al. Restoring Systemic GDF11 Levels Reverses Age-Related Dysfunction in Mouse Skeletal Muscle. Science, 2014,344(6184): 649-652.

[18] Scheib J. Impaired regeneration in aged nerves: Clearing out the old to make way for the new. Exp Neurol, 2016,284(Pt A):73-83.

[19] Kaiser J. Regenerative medicine. 'Rejuvenating' protein doubted. Science, 2015, 348(6237):849.

[20] Hilgard HR, Dalmasso AP, Martinez C, et al. Immune mechanisms in parabiosis intoxication. J Exp Med, 1964, 119(119): 567-579.

[21] Conboy MJ, Conboy IM, Rando TA. Heterochronic parabiosis: historical perspective and methodological considerations for studies of aging and longevity. Aging Cell, 2013,12(3): 525-530.

[22] Carlson ME, Hsu M, Conboy IM. Imbalance between pSmad3 and Notch induces CDK inhibitors in old muscle stem cells. Nature, 2008,454(7203): 528-539.

[23] Castellano JM, Mikael P, Li SB, et al. In vivo assessment of behavioral recovery and circulatory exchange in the peritoneal parabiosis model. Scientific Reports, 2016(6):29015.

[24] 郭宏伟,吴清玉,谢蜀生,等. 联体共生诱导大鼠心脏移植免疫耐受的实验研究. 中华器官移植杂志, 2004,25(4): 209-211.
Guo HW, Wu QY, Xie SS, et al. Parabiosis can lead the immune tolerance of the heart transplant of rat. Chinese Journal of Organ Transplantation, 2004,25(4):209-211. (in Chinese)

[25] 张春阳,史其新,李晨光,等. 联体共生诱导免疫耐受对大鼠肾功能的影响. 辽宁医学院学报,2009, 30(5): 403-404.
Zhang CY, Shi QX, Li CG, et al. The effect of the immune tolerance led by parabiosis on rat renal function. Liaoning Medical College Journal, 2009,30(5):403-404. (in Chinese)

[26] 冯楠. 联体共生模型对荷瘤小鼠肿瘤免疫的影响. 石家庄:河北医科大学,2015.
Feng N. The effect of parabiosis on the immune of tumor mice. Shijiazhuang: Hebei Medical University,2015. (in Chinese)

[27] Eggel A, Wyss-Coray T. A revival of parabiosis in biomedical research. Swiss Medical Weekly, 2014,144(144):w13914.

(收稿日期: 2016-12-13;修回日期:2017-01-05)

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[30] Eckard J, Dai J, Wu J, et al. Effects of cellular iron deficiency on the formation of vascular endothelial growth factor and angiogenesis. Iron deficiency and angiogenesis. Cancer cell international,2010,10(1): 28.

[31] Jian J, Yang Q, Dai J, et al. Effects of iron deficiency and iron overload on angiogenesis and oxidative stress-a potential dual role for iron in breast cancer. Free radical biology & medicine,2011, 50(7): 841-847.

[32] Saghiri MA, Asatourian A, Orangi J, et al. Functional role of inorganic trace elements in angiogenesis—Part I: N, Fe, Se, P, Au, and Ca. Critical reviews in oncology/hematology,2015,96 (1): 129-142.

[33] Farberg AS, Jing XL, Monson LA, et al. Deferoxamine reverses radiation induced hypovascularity during bone regeneration and repair in the murine mand ible. Bone, 2012,50(5): 1184-1187.

[34] 王亮,张鹏,姚喆,等. 骨组织 H 亚型血管在骨质疏松与非骨质疏松骨折患者中的表现. 中华骨科杂志,2016,36(20): 1327-1334.
Wang L, Zhang P, Yao Z, et al. Changes of H type microvessel in patients with osteoporotic and nonosteoporotic fractures in bone. Chin J Orthop,2016,36(20):1327-1334. (in Chinese)

(收稿日期: 2016-12-18;修回日期:2017-02-22)