中国骨质疏松杂志 2015 年 7 月第 21 卷第 7 期 Chin J Osteoporos, July 2015, Vol 21, No. 7
Published online www.wanfangdate.com.cn doi:10.3969/j.issn.1006-7108.2015.07.027

·综述·

关注系统性红斑狼疮继发性骨质疏松

严静霞 高丽霞* 靳洪涛
河北医科大学第二医院风湿免疫科,石家庄 050000

中图分类号:R593.24 **文献标识码**:A **文章编号**:1006-7108(2015)07-0888-06

摘要:系统性红斑狼疮(systemic lupus erythematosus,SLE)是多系统损害的自身免疫性疾病,糖皮质激素和免疫抑制剂是治疗的主要药物。SLE 的骨损害包括骨量减少、骨质疏松(osteoporosis, OP)、无菌性骨坏死和骨折,随着 SLE 生存期的延长,心血管并发症和 OP 成为影响患者生活质量和生存的主要因素,同时 OP 对于心血管的发病也有促进作用,是目前备受关注的并发症。OP 是一种以骨量减少和骨组织的细微结构破坏为特征的全身性疾病。关于 SLE 的骨质疏松也存在不少争议,主要集中在 OP 的发病率和骨质疏松与激素治疗关系两个方面。就 OP 发病率来讲,不同的研究得出的结论不同。SLE 的骨质疏松涉及多种机制包括炎性因素、免疫介导的因素、固有因素、代谢因素、药物因素和疾病本身的因素。SLE 相关的骨质疏松的治疗首先是治疗原发病,此外健康的生活方式包括钙剂和维生素 D 的补充也非常重要,对诊断骨质疏松的 SLE 患者应及时给予双膦酸盐治疗。

关键词:系统性红斑狼疮;骨质疏松;发病机制

Pay attention to the secondary osteoporosis in systemic lupus erythematosus

YAN Jingxia, GAO Lixia, JIN Hongtao
Department of Rheumatology, the Second Hospital of Hebei Medical University, Shijiazhuang 050000, China
Corresponding author: GAO Lixia, Email: songsongningning@126.com

Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease involving multisystem. Glucocorticoids and immune-suppressors are main drugs for the treatment. The bone damage of SLE includes osteopenia, osteoporosis (OP), aseptic osteonecrosis, and fractures. In recent years the survival of patients with SLE has increased markedly, and the complications of cardiovascular disease and OP become major factors affecting quality of life and death of the patients. OP can promote the onset of cardio-vascular disease, and it is the complication that we pay attention to. OP is a systemic disease characterized by bone loss and disruption of the microstructure. There are some debates about OP in SLE, mainly focusing on the incidence of OP and the relationship between OP and steroid treatment. For the incidence of OP, the conclusion is different from different study. The pathogenesis of OP in SLE includes chronic inflammation, immunological factors, traditional factors, metabolism factors, drug factors, and disease itself. Optimal treatment of the underlying SLE is the first step toward prevention of OP and fractures. Apart from that, a healthy lifestyle is important such as calcium and vitamin D supplementation. Bisphosphonates should be timely given for the SLE patients with osteoporosis.

Key words: Systemic lupus erythematosus; Osteoporosis; Pathogensis

系统性红斑狼疮(systemic lupus erythematosus, SLE)是自身免疫介导的以免疫性炎症为突出表现的弥漫性结缔组织病,血清中出现以抗核抗体为代表的多种自身抗体和多系统受累是 SLE 的主要特征。西方大多数研究发现,SLE 的发病率仍在增加,年发病率在 1-2/100 000[1],患病率在 20-200/100 000[2],亚太地区年发病率在 0.9-3.1/100 000,患病率在 4.3-45.3/100 000[3],我国的患病率约为 70-100/100 000。随着免疫学的进展,SLE 的生存率逐渐提高,5 年生存率达 60%~97%,10 年生存率达到 70%~94%[3],随着生存时间的延长,心血管疾病和骨质疏松等慢性并发症越来越成为影响 SLE 生活质量和生存率的主要因素。骨质疏松(osteoporosis, OP)是一种以骨量减少和骨组织的细微结构破坏为特征的全身性疾病,最终导致骨

基金项目:河北省科技厅科研计划项目(12277731)
* 通讯作者:高丽霞,Email:songsongningning@126.com

脆性增加和骨折,随着骨免疫概念的出现,OP 与 SLE 的关系越来越密切,但人们的重视不够,许多患者未得到积极的针对骨质疏松的治疗,本文对 SLE 继发 OP 的流行病学及影响因素进行综述。

1 流行病学

研究表明[3],SLE 可继发骨质疏松;但关于 OP 许多方面的报道也存在争议,主要集中在 OP 的发病率和骨质疏松与激素治疗的关系两个方面。就 OP 发病率来讲,不同的研究得出的结论不同,国外文献报道在 SLE 骨量减少发生率为 25% ~74%,OP 发生率 1.4% ~68%[4],国内报道绝经前 SLE 合并 OP 发生率估计在 4% ~31.9%,骨量减少在 16.9% ~39% 之间,而绝经后患者估计达 OP 范围者为 48% ~60.5%[5]。SLE 主要影响育龄期女性,男女发病比例为 1∶9,疾病本身和长期应用激素使绝经前女性腰椎和股骨颈骨密度(bone mineral density, BMD)降低,绝经前女性 SLE 骨量减少发生率 40%,OP 仅 5%[5-10]。在长期接受激素治疗的绝经后女性 OP, 特别是脊柱最常见,腰椎 OP 发生率可高达 48%[11,12]。对于男性,虽然有几篇相关报道,但仍然有争议。两个研究认为尽管使用激素治疗,男性 SLE 患者骨量并无减少,骨密度与患病时间,激素剂量疾病活动指数均没有相关性[13,14]。另外的研究则报道了不同的结论,Mok CC 的病例对照研究发现在 SLE 男性患者降低的 BMD 和低体重相对普遍,股骨颈和脊柱的 BMD 较正常健康对照组都明显下降,年龄、长期饮酒,低体重指数和大剂量激素的使用都与脊柱的 BMD 降低相关[15]。儿童发病的 SLE 骨量减少明显高于健康对照,尤其在腰椎和股骨颈部位[16,17],最近一项关于青少年 SLE 患者骨质量的横断研究与纵贯研究发现这些患者骨量减低不能赶上生长速度,导致骨峰值年龄时期的峰值骨量下降,是 OP 的高风险因素[18]。

2 SLE 骨质疏松的危险因素

SLE 的骨损害包括骨量减少、OP、无菌性骨坏死和骨折,OP 是目前应高度重视的并发症。SLE 骨丢失的原因是多方面的,包括:炎性因素、免疫介导的因素、传统因素、代谢因素、内分泌因素、药物因素和疾病本身的因素。

2.1 炎性因素

SLE 是一种免疫介导的炎性疾病,疾病本质是血管炎,在疾病过程中许多炎性细胞因子参与疾病的发生发展,例如白细胞介素(interleukin, IL) -1、IL-6、肿瘤坏死因子(tumor necrosis factor, TNF)-α 等在 SLE 患者中明显增高,参与炎症反应[19]。骨免疫的概念表明骨细胞和免疫细胞处于骨髓腔的共同微环境中,骨骼系统和免疫系统经由共同的细胞因子及受体、信号分子和转录因子等调节,免疫系统和骨重建之间存在相互调节作用。免疫系统异常激活通过改变成骨细胞和破骨细胞之间的脱偶联影响骨重建,导致 OP。OP 中起主要作用的是骨代谢的信号传导途径骨保护蛋白(OPG)、核因子-κβ 受体活化因子(RANK)、核因子-κβ 受体活化因子配体(RANKL)分子及相关的信号传导通路组成的 OPG/RANKL/RANK 系统,该信号转导通路系统是破骨细胞分化过程中的调节机制,是成骨细胞与破骨细胞相互作用的重要途径[20]。慢性全身性炎症通过增加破骨细胞的骨吸收,减少成骨细胞的骨形成改变骨代谢,SLE 血清中 IL-1 和 IL-6 等细胞因子能诱导并且增加 RANKL 的表达,RANK 与受体 RANKL 结合后,在 M-CSF 存在的情况下促进破骨细胞前体细胞分化为成熟的破骨细胞,刺激破骨细胞活性,促进骨吸收,导致 OP[21]。同时 TNF-α 能够促进骨吸收及骨基质胶原合成,减弱成骨细胞对维生素 D 的转录反应性,抑制细胞外基质沉积并刺激基质金属蛋白酶的合成,从而降解有机骨质[22]。而且 SLE 患者体内氧化型低密度脂蛋白(oxidized low-density lipoprotein, Ox-LDL)水平升高,Ox-LDL 能够活化 T 细胞,诱导 RANKL 和 TNF -α 的升高,促进 OP 形成[23, 24].

2.2 免疫因素

SLE 是一种系统性自身免疫性疾病,既有细胞免疫的异常又存在体液免疫的失衡,血清中多种自身抗体的存在是疾病的特点。抗 Sm 抗体的存在和抗 SSA(Ro)抗体的缺乏与腰椎 BMD 的增加相关,可能因为这些患者皮疹较常见,治疗者建议避免日照有关[11]。SLE 患者血清可溶性 RANKL /OPG 比例比健康对照组升高,并且与抗 Sm 抗体的水平具有相关性,表明 SLE 疾病本身参与了骨质疏松的发病过程[25]。Mak A 报道高水平的抗双链 DNA 是预测 10 年后髋关节骨折的独立危险因素,进一步强化了 SLE 的疾病活动是导致骨丢失和骨折的重要驱动因素[26]。SLE 患者抗心磷脂抗体阳性与 OP 存在一定的关系,抗心磷脂抗体阳性患者出现骨坏死和 OP,可能与骨微循环中微血栓形成有关[27,28]。SLE 患者免疫调节功能紊乱,T、B 细胞功能异常是其突

出特征之一,机体内 T、B 细胞的功能紊乱会引起机体 OPG/RANKL 信号传导系统异常[29]。初发 SLE 患者外周血淋巴细胞 OPG、RANKL 的基因表达存在异常,与正常人比较,初发 SLE 患者外周血 OPG、RANKL 的 mRNA 表达显著降低(中国骨质疏松杂志 2009 年第 1 期)。另外 SLE 患者低补体 C4 水平降低也容易出现 OP,尤其在脊柱[30]。不可否认 SLE 病情活动、脏器损害与 BMD 降低关系密切,容易导致腰椎和股骨的 BMD 降低,出现 OP,导致骨折[31,32]。

2.3 代谢因素

维生素 D 的缺乏, 高同型半胱氨酸血症和低甲状腺素水平都是在 SLE 中诱导 OP 的代谢性因素。维生素 D 可以调节钙、磷代谢维持骨矿物质平衡,同时也可影响神经、肌肉、免疫、造血等多种组织器官的功能,活性维生素 D 主要是通过与维生素 D 受体结合发挥其调节代谢影响免疫的生物学作用[33]。SLE 患者维生素 D 缺乏或不足已经被许多研究证实[34-38],其中 16 – 96% 的 SLE 患者表现维生素 D 的不足,4 – 54% 的患者表现维生素 D 的缺乏[39]。维生素 D 缺乏或不足的原因涉及多方面的因素首先 SLE 患者存在多系统损害,光敏感、疲劳、关节肿痛减少室外运动避免日晒,疾病活动、肾炎、自身免疫肝病可引起肝肾合成减少,肠道受累引起吸收减少,部分患者体内存在维生素 D 抗体可直接减少其血清浓度,其次免疫抑制剂影响维生素 D 的代谢,服用硫酸羟氯喹或泼尼松均影响 25 羟维生素 D 的水平[40]。

同型半胱氨酸(Homocysteine, Hcy)是人体非必需氨基酸硫氨酸代谢的中间产物,是一个动脉粥样硬化、血栓性疾病及认知功能障碍的危险因素,近来的研究发现 Hcy 的升高与老年性骨质疏松相关,且被认为是骨质疏松相关骨折的独立危险因子,机制主要是通过增加骨吸收,抑制骨形成及胶原蛋白的交联而减少骨密度,降低骨质量,增加骨质疏松骨折的危险性[41]。已经证实 SLE 患者血浆中 Hcy 水平增加[42,43], 但没有研究表明在高同型半胱氨酸和 SLE 继发性 OP 之间存在联系[44]。

骨矿物质代谢受甲状腺激素(thyroid hormone, TH)、甲状旁腺激素、1,25 羟 D_3 的共同调控。这些激素相互协调共同维持骨细胞的活性、骨骼的重建和钙的代谢平衡,适当水平的 TH 对骨骼的生长发育和重建至关重要,TH 水平异常时,因正常骨代谢受到干扰,导致骨质疏松和骨折风险增加。SLE 患者甲状腺功能的异常较多见,常伴有甲状腺功能减退或者存在针对甲状腺的自身抗体而导致低甲状腺素水平[45,46],并且认为这种亚临床甲减与狼疮肾炎密切相关[47]。因此可能 SLE 患者骨质疏松与低甲状腺素水平之间存在一定的关系。

2.4 影响骨质量的固有因素

OP 的危险因素包括高龄、低体重和绝经,这些因素也是导致 SLE 继发性 OP 产生的独立危险因素。性别和种族对于 SLE 的影响尚不清楚,一些研究发现白种人和非非洲裔的加勒比种族是 SLE 患者 OP 的独立危险因素[48, 49],但一些文献报道认为非洲裔的美国妇女比白种人髋部和腰椎的骨密度低[50],在激素治疗的 SLE 患者中,中国人 OP 的发病率为 4% ~6%,比白种人的 12% ~18% 发病率相对较低[8]。SLE 绝经前女性中日常钙的摄入与骨密度并无相关性[51],报道并未证明吸烟和饮酒 SLE 患者 OP 松的危险因素[10, 52], 但饮酒与香港男性狼疮患者的骨量丢失有相关性[15]。

2.5 药物因素

SLE 药物治疗与 OP 也存在密切的关系。首先糖皮质激素在 SLE 的治疗中广泛应用,对于 OP 来说激素是一把双刃剑,激素既诱发骨丢失导致 OP 和骨折,另一方面激素又可以控制疾病活动和全身的炎症而减缓骨量丢失[4]。SLE 患者脊柱骨量丢失和激素的使用之间存在剂量依赖关系,在醋酸泼尼松剂量每天大于 7.5 mg 的患者腰椎有明显的骨量减少[9]。硫酸羟氯喹则通过抑制 25 羟基维生素 D 向 1,25 双羟维生素 D 转化而干扰骨代谢[35],而另外的研究则认为硫酸羟氯喹是 OP 的保护因素[53],硫酸羟氯喹的使用与高水平的 25 羟基维生素 D 相关,可能是 1,25 双羟维生素 D 活性代谢形式减少的一种假象[54]。环孢素 A 和他克莫司等钙调酶抑制剂在 SLE 中的使用越来越多,钙调酶抑制剂的使用可能导致维生素 D 抵抗状态的产生而影响维生素 D 的正常生理代谢[55, 56]。其他药物如口服抗凝剂和肝素、抗癫痫药以及甲氨蝶呤、环磷酰胺等对于 SLE 继发的骨质疏松都有一定的作用[57]。

2.6 激素水平

除了甲状腺激素之外,性激素对于骨密度的代谢也有一定的作用,雌激素在骨形成和骨吸收过程中起着重要作用,雌激素水平及其受体的表达可能对骨形成与骨丢失关系密切。高雌激素水平,低雄激素水平与 SLE 的骨量丢失密切相关,例如硫酸脱氢表雄酮和低骨密度之间呈正相关[14],给予糖皮质

激素治疗的 SLE 患者普拉睾酮可以改善骨丢失[14, 58]。SLE 患者血清中雌激素及其活性代谢产物明显升高,但与雌激素受体的表达无关[60]。

3 治疗

SLE 继发 OP 的治疗一方面是原发病的治疗,一方面是糖皮质激素诱导的 OP,糖皮质激素治疗的开始 6 个月内,骨质丢失尤为明显而迅速,要在糖皮质激素刚开始使用时即采用加强锻炼、监测骨密度等预防措施。美国风湿病学会给出了糖皮质激素诱导的骨质疏松的治疗原则[59, 60],同时与中国和英国等国家的 OP 诊治指南类似[61]:①首先强调了钙剂和维生素 D 的基础治疗作用,指出对于接受任何时间的糖皮质激素患者来说,无论使用激素量大小,在正常饮食摄入之外均应添加 1.2 ~ 1.5 g/d 的元素钙,同时需补充维生素 D。②双膦酸盐:在药物治疗方面进一步肯定了双膦酸盐的治疗作用,强调对于绝经期后女性和 50 岁以上男性,根据 FRAX 评分将糖皮质激素诱导的骨质疏松患者分为低、中、高 3 种危险度。针对不同危险度患者的防治建议不尽相同;绝经期后女性和 50 岁以上男性若预期使用激素超过 3 个月,在低危和中危患者中,除骨折低危人群中预期激素 <7.5 mg/d 的患者外,无论骨密度高低均需给予双膦酸盐药物干预。而所有骨折高危人群,无论糖皮质激素使用剂量多少和疗程长短,均需给予双膦酸盐药物干预。对绝经期前女性和 50 岁以下男性应根据有无脆性骨折史进行分类干预。对于有脆性骨折史的患者,若患者为男性或无怀孕可能的女性,当预期使用糖皮质激素 1-3 个月且剂量不小于泼尼松 5 mg/d 时,应给予双膦酸盐药物干预;若糖皮质激素用量 >3 个月,无论剂量大小均应给予双膦酸盐药物干预。对该部分患者有可能怀孕的女性,若糖皮质激素应用超过 3 个月,且剂量不小于 7.5 mg/d,应给予半衰期短的双膦酸盐如阿仑膦酸钠。

【参 考 文 献】

[1] Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus, 2006, 15(5):308-318.

[2] Johnson AE, Gordon C, Palmer RG, et al. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis and rheumatism, 1995, 38(4):551-558.

[3] Jakes RW, Bae SC, Louthrenoo W, et al. Systematic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: prevalence, incidence, clinical features, and mortality. Arthritis care & research, 2012, 64(2):159-168.

[4] Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. Arthritis care & research 2012, 64(1):2-8.

[5] Pons F, Peris P, Guanabens N, et al. The effect of systemic lupus erythematosus and long-term steroid therapy on bone mass in pre-menopausal women. British Journal of Rheumatology, 1995, 34(8):742-746.

[6] Kipen Y, Buchbinder R, Forbes A, et al. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. The Journal of rheumatology, 1997, 24(10):1922-1929.

[7] Formiga F, Moga I, Nolla JM, et al. Loss of bone mineral density in premenopausal women with systemic lupus erythematosus. Annals of the rheumatic diseases, 1995, 54(4):274-276.

[8] Li EK, Tam LS, Young RP, et al. Loss of bone mineral density in Chinese pre-menopausal women with systemic lupus erythematosus treated with corticosteroids. British journal of rheumatology, 1998, 37(4):405-410.

[9] Jardinet D, Lefebvre C, Depresseux G, et al. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. Rheumatology, 2000, 39(4):389-392.

[10] Mendoza-Pinto C, Garcia-Carrasco M, Sandoval-Cruz H, et al. Deleze-Hinojosa M et al: Risks factors for low bone mineral density in pre-menopausal Mexican women with systemic lupus erythematosus. Clinical rheumatology, 2009, 28(1):65-70.

[11] Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. Lupus, 2005, 14(2):106-112.

[12] Bhattoa HP, Bettembuk P, Balogh A, et al. Bone mineral density in women with systemic lupus erythematosus. Clinical rheumatology, 2002, 21(2):135-141.

[13] Formiga F, Nolla JM, Mitjavila F, et al. Bone mineral density and hormonal status in men with systemic lupus erythematosus. Lupus, 1996, 5(6):623-626.

[14] Bhattoa HP, Kiss E, Bettembuk P, et al. Bone mineral density, biochemical markers of bone turnover, and hormonal status in men with systemic lupus erythematosus. Rheumatology international, 2001, 21(3):97-102.

[15] Mok CC, Ying SK, To CH, et al. Bone mineral density and body composition in men with systemic lupus erythematosus: a case control study. Bone, 2008, 43(2):327-331.

[16] Lilleby V, Lien G, Frey Froslie K, et al. Frequency of osteopenia in children and young adults with childhood-onset systemic lupus erythematosus. Arthritis and rheumatism, 2005, 52(7):2051-2059.

[17] Trapani S, Civinini R, Ermini M, et al. Osteoporosis in juvenile systemic lupus erythematosus: a longitudinal study on the effect

of steroids on bone mineral density. Rheumatology international, 1998, 18(2):45-49.

[18] Stagi S, Cavalli L, Bertini F, et al. Cross-sectional and longitudinal evaluation of bone mass and quality in children and young adults with juvenile onset systemic lupus erythematosus (JSLE): role of bone mass determinants analyzed by DXA, PQCT and QUS. Lupus, 2014, 23(1):57-68.

[19] Robak E, Sysa-Jedrzejewska A, Dziankowska B, et al. Association of interferon gamma, tumor necrosis factor alpha and interleukin 6 serum levels with systemic lupus erythematosus activity. Archivum immunologiae et therapiae experimentalis, 1998, 46(6):375-380.

[20] Danks L, Takayanagi H. Immunology and bone. Journal of biochemistry, 2013, 154(1):29-39.

[21] Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. The New England journal of medicine, 1995, 332(5):305-311.

[22] Vitale RF, Ribeiro Fde A. The role of tumor necrosis factor-alpha (TNF-alpha) in bone resorption present in middle ear cholesteatoma. Brazilian journal of otorhinolaryngology, 2007, 73(1):117-121.

[23] Frostegard J, Svenungsson E, Wu R, Gunnarsson I, Lundberg IE, Klareskog L, Horkko S, Witztum JL: Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. Arthritis and rheumatism, 2005, 52(1):192-200.

[24] Svenungsson E, Fei GZ, Jensen-Urstad K, et al. TNF-alpha: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. Lupus, 2003, 12(6):454-461.

[25] Carmona-Fernandes D, Santos MJ, Perpetuo IP, et al. Soluble receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio is increased in systemic lupus erythematosus patients. Arthritis research & therapy, 2011, 13(5):R175.

[26] Mak A, Lim JQ, Liu Y, et al. Significantly higher estimated 10-year probability of fracture in lupus patients with bone mineral density comparable to that of healthy individuals. Rheumatology international, 2013, 33(2):299-307.

[27] Sangle S, D'Cruz DP, Khamashta MA, et al. Antiphospholipid antibodies, systemic lupus erythematosus, and non-traumatic metatarsal fractures. Annals of the rheumatic diseases, 2004, 63(10):1241-1243.

[28] Jones LC, Mont MA, Le TB, et al. Procoagulants and osteonecrosis. The Journal of rheumatology, 2003, 30(4):783-791.

[29] Li Y, Toraldo G, Li A, et al. B cells and T cells are critical for the preservation of bone homeostasis and attainment of peak bone mass in vivo. Blood, 2007, 109(9):3839-3848.

[30] Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. Arthritis care and research: the official journal of the Arthritis Health Professions Association, 1995, 8(3):137-145.

[31] Lee C, Almagor O, Dunlop DD, et al. Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. Rheumatology, 2006, 45(1):53-60.

[32] Mendoza-Pinto C, Garcia-Carrasco M, Sandoval-Cruz H, et al. Risk factors of vertebral fractures in women with systemic lupus erythematosus. Clinical rheumatology, 2009, 28(5):579-585.

[33] Heikkinen S, Vaisanen S, Pehkonen P, et al. Nuclear hormone 1alpha,25-dihydroxyvitamin D3 elicits a genome-wide shift in the locations of VDR chromatin occupancy. Nucleic acids research, 2011, 39(21):9181-9193.

[34] Borba VZ, Vieira JG, Kasamatsu T, et al. Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 2009, 20(3):427-433.

[35] Huisman AM, White KP, Algra A, et al. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. The Journal of rheumatology, 2001, 28(11):2535-2539.

[36] Toloza SM, Cole DE, Gladman DD, et al. Vitamin D insufficiency in a large female SLE cohort. Lupus, 2010, 19(1):13-19.

[37] Yeap SS, Othman AZ, Zain AA, et al. Vitamin D levels: its relationship to bone mineral density response and disease activity in premenopausal Malaysian systemic lupus erythematosus patients on corticosteroids. International journal of rheumatic diseases, 2012, 15(1):17-24.

[38] Sumethkul K, Boonyaratavej S, Kitumnuaypong T, et al. The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. Rheumatology international, 2013, 33(6):1461-1467.

[39] Mok CC. Vitamin D and systemic lupus erythematosus: an update. Expert review of clinical immunology, 2013, 9(5):453-463.

[40] Carvalho JF, Blank M, Kiss E, et al. Anti-vitamin D, vitamin D in SLE: preliminary results. Annals of the New York Academy of Sciences, 2007, 1109:550-557.

[41] Vacek TP, Kalani A, Voor MJ, et al. The role of homocysteine in bone remodeling. Clinical chemistry and laboratory medicine, CCLM / FESCC, 2013, 51(3):579-590.

[42] Sabio JM, Vargas-Hitos JA, Martinez-Bordonado J, et al. Relationship between homocysteine levels and hypertension in systemic lupus erythematosus. Arthritis care & research, 2014, 66(10):1528-35.

[43] Lazzerini PE, Capecchi PL, Selvi E, et al. Hyperhomocysteinemia: a cardiovascular risk factor in autoimmune diseases? Lupus, 2007, 16(11):852-862.

[44] Rhew EY, Lee C, Eksarko P, et al. Homocysteine, bone mineral density, and fracture risk over 2 years of followup in women with and without systemic lupus erythematosus. The

Journal of rheumatology, 2008, 35(2):230-236.

[45] Appenzeller S, Pallone AT, Natalin RA, et al. Prevalence of thyroid dysfunction in systemic lupus erythematosus. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases, 2009, 15(3):117-119.

[46] Kumar K, Kole AK, Karmakar PS, et al. The spectrum of thyroid disorders in systemic lupus erythematosus. Rheumatology international, 2012, 32(1):73-78.

[47] Gao H, Li C, Mu R, et al. Subclinical hypothyroidism and its association with lupus nephritis: a case control study in a large cohort of Chinese systemic lupus erythematosus patients. Lupus, 2011, 20(10):1035-1041.

[48] Lakshminarayanan S, Walsh S, Mohanraj M, et al. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. The Journal of rheumatology, 2001, 28(1):102-108.

[49] Yee CS, Crabtree N, Skan J, et al. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. Annals of the rheumatic diseases, 2005, 64(1):111-113.

[50] Lee C, Almagor O, Dunlop DD, et al. Association between African American race/ethnicity and low bone mineral density in women with systemic lupus erythematosus. Arthritis and rheumatism, 2007, 57(4):585-592.

[51] Chong HC, Chee SS, Goh EM, et al. Dietary calcium and bone mineral density in premenopausal women with systemic lupus erythematosus. Clinical rheumatology, 2007, 26(2):182-185.

[52] Almehed K, Forsblad d'Elia H, Kvist G, et al. Prevalence and risk factors of osteoporosis in female SLE patients-extended report. Rheumatology, 2007, 46(7):1185-1190.

[53] Boyanov M, Robeva R, Popivanov P. Bone mineral density changes in women with systemic lupus erythematosus. Clinical rheumatology, 2003, 22(4-5):318-323.

[54] Ruiz-Irastorza G, Egurbide MV, Olivares N, et al. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology, 2008, 47(6):920-923.

[55] Lee CT, Ng HY, Lien YH, et al. Effects of cyclosporine, tacrolimus and rapamycin on renal calcium transport and vitamin D metabolism. American journal of nephrology, 2011, 34(1):87-94.

[56] Grenet O, Bobadilla M, Chibout SD, et al. Evidence for the impairment of the vitamin D activation pathway by cyclosporine A. Biochemical pharmacology, 2000, 59(3):267-272.

[57] Di Munno O, Mazzantini M, Delle Sedie A, et al. Risk factors for osteoporosis in female patients with systemic lupus erythematosus. Lupus, 2004, 13(9):724-730.

[58] Sanchez-Guerrero J, Fragoso-Loyo HE, Neuwelt CM, et al. Effects of prasterone on bone mineral density in women with active systemic lupus erythematosus receiving chronic glucocorticoid therapy. The Journal of rheumatology, 2008, 35(8):1567-1575.

[59] Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis and rheumatism, 2001, 44(7):1496-1503.

[60] Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis care & research, 2010, 62(11):1515-1526.

[61] Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas, 2013, 75(4):392-396.

(收稿日期: 2014-10-23)