·综述·

绝经后骨质疏松症的临床中药治疗进展

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摘要:绝经后骨质疏松症(postmenopausal osteoporosis, PMOP)是绝经后妇女的常见病及多发病,主要因绝经后妇女的卵巢功能减退、雌激素水平下降,导致骨生成和骨吸收的代谢失衡。其特征是全身骨量减少和骨组织的微细结构破坏,临床主要表现为骨痛和骨折风险增加。大量研究表明,中医药可以提高绝经后骨质疏松症患者的骨密度,改善其疼痛症状,在防治绝经后骨质疏松症方面有其独特的优势。目前对绝经后骨质疏松症的研究主要分为单味中药的实验研究和复方中药的临床研究。通过对近 5 年国内外对绝经后骨质疏松症的中药治疗进行相关回顾,在单味中药方面,根据绝经后骨质疏松症的病机特点和用药频次,主要从骨测量指标、细胞因子变化、基因水平等方面综述了淫羊藿、杜仲、骨碎补 3 种常用中药的实验研究进展;在复方中药方面,普遍认为肾虚是绝经后骨质疏松的主要病机,此外与肝脾不足、血瘀痰浊等密切相关,主要论述了补肾法在临床上治疗绝经后骨质疏松中的应用,并探讨未来治疗绝经后骨质疏松症可能的研究方向。

关键词:绝经后骨质疏松症;中药;治疗

The clinical progress in the treatment of postmenopausal osteoporosis using traditional Chinese medicine

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Abstract: Postmenopausal osteoporosis is a common and popular disease in postmenopausal women. Its basic pathogenesis is metabolic imbalance of bone formation and bone absorption caused by a decline of ovarian function and a drop in estrogen level. The characteristics of the disease are bone mass loss of the whole body, the breakdown of bone microstructure, bone pain, and the increase of fracture risk. A great quantity of research indicates that traditional Chinese medicine treatment for postmenopausal osteoporosis can improve the bone mineral density of postmenopausal women and reduce the symptom of bone pain. It has distinct advantage. Currently, the research in postmenopausal osteoporosis mainly includes the experimental research of single Chinese herb and the clinical research of Chinese compound formula. This paper summarizes recent experiment development of three commonly used Chinese herbs from bone measurement index, the change of cytokines, and gene level aspects according to the pathogenesis and medication frequency of postmenopausal osteoporosis. In Chinese compound use aspects, it is believed that kidney deficiency is the main pathogenesis of postmenopausal osteoporosis. Liver and spleen deficiency and blood stigma are also involved. The paper elucidates the application of kidney-nourishing therapy in postmenopausal osteoporosis, and explores the possible future research direction for postmenopausal osteoporosis therapy.

Key words: Postmenopausal osteoporosis; Traditional Chinese medicine; Treatment

绝经后骨质疏松症(PMOP)指妇女绝经后因卵巢功能衰退、雌激素水平下降而导致体内的骨吸收大于骨形成,出现以全身骨量减少和骨显微结构破坏为特征的一种代谢性疾病,临床主要表现为骨痛和骨折率增加。中医学中无“绝经后骨质疏松症”这一病名,依据其临床症状及病因病机,多将其归属为“骨痿”的范畴。据有关资料显示,全国骨质疏松患者已近 7000 万人,PMOP 约占 80%,而且随着人口不断老龄化,其患病率还将进一步增加[1]。因此

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PMOP 的防治日益受到国内外学者的重视。

1 单味中药

笔者对 2000 – 2013 年间用于治疗 PMOP 的 91 首疗效较为确切的验方进行统计分析显示,在出现的 110 味中药中,用药频次前 10 位的中药依次为淫羊藿、熟地、黄芪、当归、杜仲、补骨脂、丹参、山茱萸、山药、骨碎补。主要为补虚药和活血化瘀药。这些单味药代表着中医治疗 PMOP 的核心用药,为临床用药提供了理论参考。一直以来,大量国内外学者都试图从现代药理学角度阐述这些经验用药的机理,其中实验研究较为成熟的有淫羊藿、杜仲、骨碎补等。

1.1 淫羊藿

淫羊藿又名仙灵脾,性味辛、甘、温,归肝、肾经,具有补肾壮阳、祛风除湿的作用。其抗 PMOP 的有效成分主要为黄酮类物质,如淫羊藿苷、淫羊藿素等[2]。

目前有关淫羊藿抗 PMOP 的作用机制尚不清楚,一般认为其分子机制可能是多种基因的差异表达[3]。骨保护素(osteoprotegerin, OPG)是近年来防治骨质疏松症领域的重大发现,属于肿瘤坏死因子(tumor necrosis factor, TNF)受体家族的新成员。它与细胞核因子 kB 受体活化因子配体(receptor activator of nuclear factor κB ligand, RANKL)、细胞核因子 kB 受体活化因子(receptor activator of nuclear factor κB, RANK)组成 OPG/RANKL/RANK 系统,其中 OPG 是 RANKL 的假性受体,可与 RANK 竞争性结合 RANKL,阻止 RANKL 与 RANK 之间的相互作用,从而抑制破骨细胞的分化与活性,抑制骨重吸收过程[4]。最新实验研究表明,淫羊藿苷可通过增加 OPG mRNA 的表达来抑制破骨细胞(osteoclast, OC)的分化和成熟,从而有效抑制骨吸收[5][6]。

对成骨细胞(osteoblast, OB)来说,淫羊藿苷虽然不能促进其增殖,但可能通过上调骨形态形成蛋白-2(the bone morphogenetic protein-2, BMP-2)、骨形态形成蛋白-4(BMP-4),进而促进其分化过程中的关键转录因子 Cbfα1 (Core-binding factor α1)的表达,并启动 Cbfα1 下游的一系列成骨相关基因的表达,从而促进成骨细胞的分化[7]。

此外,近年来随着干细胞(stem cells, SCs)研究的深入,骨髓腔内的脂肪细胞尤其是脂肪形成在 PMOP 发病中的作用逐渐引起人们的关注。宋纯理等[8]就骨质疏松发病机制提出了“脂肪细胞过剩”途径的假说,进而提出通过抑制骨髓干细胞(bone marrow stem cells, BMSCs)的脂肪分化,使得在促进其分化为 OB 的同时抑制 OC 的分化与增殖,为本病的防治提供了新的理念。过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPAR)的亚型 PPARγ 是脂肪分化的主要调控因子,可通过阻止 Cbfα1 的表达来抑制 OB 的活性,对 BMSCs 的成脂分化起关键性调控作用。淫羊藿含药血清可抑制 PMOP 大鼠 BMSCs 成脂分化过程中 PPARγ mRNA 的表达,从而抑制 BMSCs 成脂分化,达到防治 PMOP 的目的[9]。因此调控 BMSCs 成骨和成脂分化平衡是淫羊藿防治 PMOP 的重要机制之一。许应星等[9]进一步研究发现,淫羊藿的这一机制可能是通过对 wnt/β-catenin 信号通路的调节实现的。

另外,刘波等[11]认为淫羊藿还可通过提高性激素水平,清除活性氧,发挥对 PMOP 的防治作用。武密山等[12]则认为这与其能选择性上调下丘脑和海马雌激素受体 α(estrogen receptorα, ERα)及 ERβ mRNA 的表达有关。

1.2 杜仲

杜仲性温,味甘,归肝、肾经,具有补肝肾、强筋骨、止痛、安胎的功效。其有效化学成分主要为木脂素类和黄酮类等。

大量实验研究表明,杜仲能提高去势大鼠的 BMD 值,缓解骨小梁微结构破坏,改善其骨生物力学性能,具有明显的抗 PMOP 作用[13-15]。与淫羊藿略有不同的是,杜仲主要对 RANKL 及其 mRNA 表达有明显的抑制作用,对 OPG 及其 mRNA 的表达与模型组相比无显著差异[16]。另外,杜仲对 BMSCs 的成脂成骨分化也具有调节作用。张贤等[17]通过镜下观察发现,模型组大鼠股骨和腰椎骨中均含有大量的脂肪,骨小梁密度也显著下降,而杜仲组偶见脂肪颗粒,骨小梁较为致密。说明杜仲对去势大鼠所致的骨质疏松具有良好的干预作用,也为宋氏等提出的“脂肪细胞过剩”假说提供了佐证。其对 BMSCs 的调控多与刺激 BMP-2[18]、转化生长因子 β(transforming growth factor β, TGFβ)和成纤维生长因子 2[19](fibroblast growth factor 2, FGF2)的表达相关。

1.3 骨碎补

骨碎补性温,味苦,归肝、肾经,具有补肾, 活血化瘀的功效。骨碎补总黄酮是其主要的有效成分。

随着人们对 PMOP 认识的逐渐深入,骨量已不再作为评价抗骨松疗效的唯一指标,与骨量丢失同时存在的骨结构退变越来越受到重视,骨碎补总黄酮不仅能增加去势大鼠的骨量,还能改善松质骨的超微结构及脯氨酸羟化程度,增强骨强度,对防治 PMOP 具有积极意义[20,21]。

最新研究表明,骨碎补总黄酮的抗 PMOP 作用可能存在以下几种机制:①促进成骨细胞 OPG 的表达,抑制破骨细胞的活性并诱导其凋亡[22];②降低外周血清中白细胞介素 1(interleukin-1, IL-1)、白细胞介素 6(interleukin-6, IL-6)含量以及提高降钙素(calcitonin, CT)水平,从而抑制骨吸收的进程[23];③通过神经递质瘦素(leptin, LEP)介导的交感神经活动,降低去卵巢 OP 大鼠血清中 LEP、IL-6 水平和骨组织 β_2-肾上腺素受体(β_2-adrenergic receptor, β_2ADR)表达,以达到抑制骨吸收的目的[24];④降低去卵巢 OP 大鼠血清蛋白本酶 K(Cathepsin K)的浓度,抑制其在骨再吸收过程中对骨组织的降解作用[25];⑤上调 Cbfa1 表达的水平,促进 BMSCs 的成骨分化[26]。

2 复方制剂

目前临床上对 PMOP 的中医辩证分型还存在争议,但普遍认同肾虚是其主要病机,此外与肝脾不足、血瘀痰浊等密切相关。《内经》中已记载有"肾主骨、生髓"、"骨痿者,补肾法治之"的论述。因此,补肾法是中医治疗 PMOP 的基本大法。

六味地黄丸(胶囊)是治疗肝肾阴虚证的代表方,李东胜等[27]研究发现:其可发挥类雌激素样作用,改善患者骨结构力学及机械力学性能,提升血清中雌二醇(E_2)、降钙素(CT)和骨钙素(bone gla protein, BGP)的水平,调节人体内环境微量元素平衡,证实了其用于防治 PMOP 的可行性。

陈健等[28]用自拟方巴戟密骨饮治疗 PMOP 属肝肾不足患者发现,其不仅可有效改善患者临床症状,且能提高患者 BMD 值及血清 OPG 水平,有效降低患者血清 RANKL 水平,是防治 PMOP 的有效药物。

陈树清等[29]从脾肾论治,方用固肾健脾汤(龟板、龙骨、淫羊藿、补骨脂等),其观察结果表明,该方不但能明显缓解 OP 引起的疼痛,减少骨折的发病率,还能降低 PMOP 患者的内脂素水平,发挥对体内脂代谢的抑制作用。

向楠[30]则认为 PMOP 所导致的脂代谢异常是中医痰邪为患的表现,其所创的补肾化痰方,在降低 TNF-α 和 IL-6 的水平,抑制破骨细胞活性的同时,还能通过降低 PPARγ 的表达,抑制 BMSCs 成脂分化,继发性地促进骨形成。表明该方降脂化痰作用在防治 PMOP 过程中具有积极意义。

3 问题与展望

综上所述,中药在防治 PMOP 方面有其独特的优势。其着重于整体,可以多环节、多靶点、全方位地调节机体内环境的平衡,同时还避免了西药存在的副作用大、疗效不稳定、联合应用意见不一等问题,具有良好的应用前景,但尚存在以下几点问题:①缺乏统一的诊断和疗效评定标准;②单味药研究中用药质量参差不齐,动物模型不统一且缺乏对分子或基因水平的深入研究,实验可重复性差;③所研究的大多为经验方、自拟方,用药繁杂,各研究成果之间缺少可比性。

可以预见,单一的中西药治疗都无法满足临床防治 PMOP 的需求。因此努力发挥中医药优势,并结合西医有效治疗,实行优势互补,进一步探索有效而安全的个体化治疗方案,将是未来防治 PMOP 领域的发展方向。

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