Osteoporosis therapies might lead to intervertebral disc degeneration via affecting cartilage endplate

Zhen Sun, Zhuo-Jing Luo*

Department of Orthopedics, Xijing Hospital, Fourth Military Medical University, West Changle Road, Xi'an, 710032, China

A B S T R A C T

Osteoporosis and intervertebral disc degeneration (IDD) are both age-related diseases of the musculoskeletal system. With the average life expectancy longer than ever, the morbidity caused by these two diseases is increasing. Nowadays, treatment strategies for osteoporosis are mainly aimed at increasing the mineral density of the bone. Some of these therapies, including vitamin D, calcium, bisphosphonates, Wnt signal activators and parathyroid hormone regulators, have been suggested to be capable of causing calcification of the cartilage endplate in the intervertebral disc. This alteration could block nutrient and oxygen transportation to the center part of the disc, thus lead to intervertebral disc degeneration. Consequently, we hypothesize that osteoporosis therapies might be a potential risk for IDD. This assumption indicates that we should take the alterations of the cartilage endplate into consideration in further osteoporosis treatment to avoid IDD in the patient.

Introduction

Osteoporosis is a disease characterized by the systemic impairment and structural deterioration of bone tissue. It could lead to reduced bone mineral density and complicated bone fractures such as vertebral compression fractures, forearm fractures and hip fractures, and related pains [1]. IDD is an important factor that leads to low back pain, which results in worldwide socioeconomic implications. These two diseases may coexist in aged population and the treatment strategies for osteoporosis may impact on the intervertebral disc of the spine. It is notable that studies have reported osteoporotic patients tend to present increased disc heights in comparison to the normal population, indicating osteoporosis could delay IDD [2]. Therefore, treatment for osteoporosis might reduce or terminate the unknown protection for the intervertebral disc. Currently, treatment options for osteoporosis include therapies mitigate or reverse the loss of bone [3]. With the application of antiresorptive agents and osteoanabolic agents, these options are aimed for inhibiting bone resorption and stimulating bone formation. In addition, nonpharmacologic approaches are also important for osteoporosis to limit fracture risk. Because these strategies influence the balance of calcium deposition in the musculoskeletal system, they might also have a pathological impact on the cartilage endplate of the intervertebral disc.

Cartilage endplate in intervertebral disc

The intervertebral disc consists of three sub-parts, the central gelatinous nucleus pulposus (NP), the surrounding annulus fibrosus (AF) and the cartilage endplate connecting adjacent vertebras [4]. The cartilage endplate is a horizontal layer of hyaline cartilage and forms as an important morphologically and functionally distinct junction between the disc and the vertebral body. In normal adult human disc, the blood supply is limited to the outer few millimeters of the AF. This unique structural character makes the disc depend solely upon bulk fluid flow for the transport of nutrient and oxygen through the cartilage endplate. In addition, there are vascular terminations in the vertebra-endplate zone acting as canals for diffusion of nutrient and oxygen toward the intervertebral disc [5].

Osteoporosis therapies could lead to cartilage endplate calcification

The goal of osteoporosis therapy is to rebalance bone resorption and apposition, increase bone mineral density and reduce the fracture risk. Nowadays, drugs available for osteoporosis treatment include antiresorptive agents and osteoanabolic agents. These therapies are aimed for inhibiting bone resorption or stimulating bone formation [6]. While these agents can up-regulate the bone mineral density, they could also enhance the phosphate deposition of cartilage, thus result in cartilage calcification in some degree. Because the cartilage endplate of the disc belongs to hyaline cartilage, it could be affected by therapies for osteoporosis.

It is well known that vitamin D and calcium intake are essential and regular treatment for osteoporosis. However, the application of vitamin D and calcium can cause cartilage calcification [7,8]. Among the antiresorptive therapies, bisphosphonates represent the most frequently

* Corresponding author.
E-mail address: zhuojingluo@126.com (Z.-J. Luo).

used agents for the management of osteoporosis. It has been shown bisphosphonates could affect cartilage metabolism with specific changes in mineralization [9,10]. Studies have shown that the Wnt signals play an essential role in promoting osteoblast differentiation and mineralization [11,12]. Therefore, one of the most commonly used options for osteoporosis is to activate the Wnt signaling pathway as a therapeutic target. These therapies include antibodies against sclerostin or Dickkopf-1, etc [13]. However, the activation of Wnt signal could mediate calcification in cartilage [14]. Multiple reports indicate that Wnt signals promote osteogenic differentiation of multipotent progenitors during endochondral ossification [15,16]. These findings suggest that the therapies aiming for Wnt activation could cause the calcification of cartilage endplate in the disc. Moreover, novel osteoporosis drugs such as calcilytics, which is used to stimulate the secretion of parathyroid hormone, could also cause calcium deposition in the cartilage [17]. Taken together, it is reasonable to assume that treatment for osteoporosis therapies could lead to cartilage endplate calcification in the intervertebral disc.

Cartilage endplate calcification plays an important role in IDD

IDD is characterized by a series of changes including cell phenotype alternation, cell death, altered matrix synthesis and breakdown of extracellular matrix. Anatomically, the NP showed extracellular matrix degradation and water content reduction. The AF showed disruption of the collagen lamellae as fissures extend. Among these, the calcification of the cartilage endplate is thought to play an important role in IDD progress. Major age-related changes in the cartilage endplate of the disc in humans are reported to occur at the end of the first decade of life [19]. Along with aging, pathological changes occur in the cartilage endplate with abnormal stress load damage. During this process, calcification of the cartilage endplate is one of the most common pathological characters [20]. Studies have shown that the calcification of the cartilage endplate is an important contributor to IDD by obstructing nutrient and oxygen supply to the center NP of the disc [21,22]. This abnormal condition leads to cell death and inflammatory factors accumulation in the NP and thus results in the decrease of the extracellular matrix [4]. This pathological state alteration the mechanical balance of the disc, and cause increased lamellar disorganization and fissures in the AF. Therefore, cartilage endplate calcification plays an important role in IDD.

While calcification of the cartilage endplate plays an important role in IDD, it is noteworthy that that there are many other pathological changes in IDD, such as neovascularization, inflammatory cytokines accumulation, cartilage endplate and vertebrae structural damage and extracellular matrix change. In the study of Li et al. deletion of Opg was found to increase neovascularization and inflammatory cytokines expression in the intervertebral disc and lead to IDD [23]. Also, Xiao et al found that osteoporosis of the vertebra and osteochondral remodeling of the endplate could to cause angiogenesis and affect matrix metabolism and lead to IDD in ovariectomized mice [24]. In the study of Luo et al. salmon calcitonin treatment was found to effectively delay the process of IDD by vertebrae structure preservation [25]. Moreover, studies have found that abnormal WNT signaling could result in endplate damage such as Schmorl nodes and lead to age-related spinal pathology [26,27]. Notably, cartilage endplate and vertebrae change can be found both in osteoporosis and IDD. This phenomenon could explain the positive correlation of these two diseases and support the assumption that osteoporosis could accelerate IDD in some cases [18,27]. For this reason, proper alendronate application aiming to manage vertebrae and endplates structures while not cause excessive cartilage endplate calcification, could retard the progression of lDD [28,29]. Nevertheless, we could not ignore the possibilities of osteoporosis therapies in inducing IDD by cartilage endplate calcification.
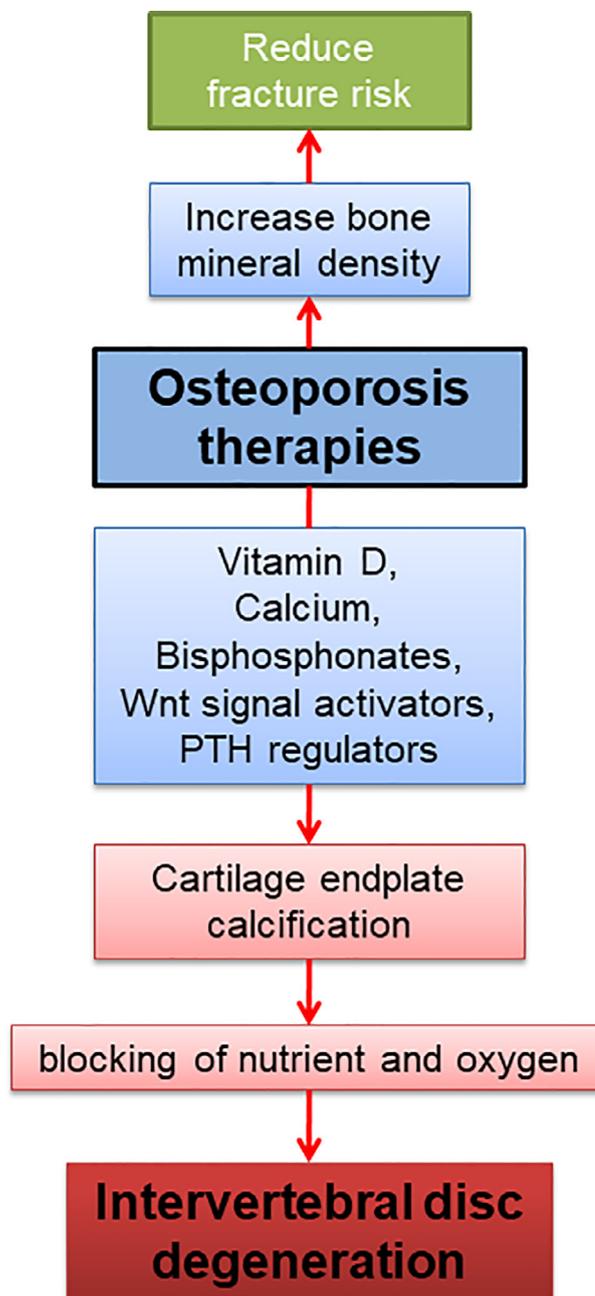

Fig. 1. Schematic representation for explaining the potential mechanism of osteoporosis therapies in inducing intervertebral disc degeneration. Like the tip of the iceberg, it is well known that osteoporosis therapies can increase bone mineral density and reduce the fracture risk. However, potential risk might exist in the impact of these therapies on cartilage endplate, such as calcification. These pathological changes could block nutrient and oxygen to the disc and eventual lead to intervertebral disc degeneration.

Hypothesis

We hypothesize that osteoporosis therapies might result in cartilage endplate calcification, thus lead to IDD (Fig. 1). This hypothesized condition could be more common in aged population which have shown early IDD pathological feature.

Consequences of the hypothesis

With the extending of the expected average life span, osteoporosis and IDD are attracting more and more attention as age-related health

conditions. The coexistence of these two diseases could be more common in aged population. Nowadays, treatment strategies for osteoporosis are mainly aimed at increasing the mineral density of the bone. However, these therapies might cause the cartilage endplate calcification. This undesired effect could eventually lead to IDD by blocking nutrient and oxygen transportation to the center part of the disc. Clinically, this assumption indicates us that we should take these pathological alterations of the cartilage endplate into consideration in further osteoporosis treatment to avoid IDD in the patient.

Conflicts of interest statement

None declared.

Acknowledgement

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.02.003.

References

[1] Kageyama G. The Diagnosis and treatment of osteoporosis. Rinsho Byori 2015;63:570–9.

[2] Ravault PP, Meunier P, Sambin P, Cret R, Bianchi GS. An early sign of spinal osteoprosis: enlargement of lumbar disc spaces. Rev Lyon Med 1969;18:603–13.

[3] Aguilar EA, Barry SD, Cefalu CA, Abdo A, Hudson WP, Campbell JS, et al. Osteoporosis diagnosis and management in long-term care facility. Am J Med Sci 2015;350:357–63.

[4] Mirza SK, White 3rd. AA. Anatomy of intervertebral disc and pathophysiology of herniated disc disease. J Clin Laser Med Surg 1995;13:131–42.

[5] Tomaszewski KA, Saganiak K, Gladysz T, Walocha JA. The biology behind the human intervertebral disc and its endplates. Folia Morphol (Warsz) 2015;74:157–68.

[6] McClung MR. Emerging therapies for osteoporosis. Endocrinol Metab (Seoul) 2015.

[7] Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC, Ross FP. Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity. Ann Intern Med 1995;122:511–3.

[8] Lockefeer JH. Vitamin D poisoning; real and spurious. Ned Tijdschr Geneeskd 1990;134:1931–4.

[9] Reginster JY, Neuprez A, Dardenne N, Beaudart C, Emonts P, Bruyere O. Efficacy and safety of currently marketed anti-osteoporosis medications. Best Pract Res Clin Endocrinol Metab 2014;28:809–34.

[10] Renders GA, Vermeer JA, Leung PM, Reynaert F, Prins C, Langenbach GE, et al. Implications of high-dosage bisphosphonate treatment on bone tissue in the jaw and knee joint. Calcif Tissue Int 2014;95:436–45.

[11] Saidak Z, Le Henaff C, Azzi S, Marty C, Da Nascimento S, Sonnet P, et al. Wnt/beta-catenin signaling mediates osteoblast differentiation triggered by peptide-induced alpha5beta1 integrin priming in mesenchymal skeletal cells. J Biol Chem 2015;290:6903–12.

[12] Liou SF, Hsu JH, Chu HC, Lin HH, Chen IJ, Yeh JL. KMUP-1 promotes osteoblast differentiation through cAMP and cGMP pathways and signaling of BMP-2/Smad1/5/8 and Wnt/beta-catenin. J Cell Physiol 2015;230:2038–48.

[13] Cairoli E, Zhukouskaya VV, Eller-Vainicher C, Chiodini I. Perspectives on osteoporosis therapies. J Endocrinol Invest 2015;38:303–11.

[14] Narcisi R, Cleary MA, Brama PA, Hoogduijn MJ, Tuysuz N, ten Berge D, et al. Long-term expansion, enhanced chondrogenic potential, and suppression of endochondral ossification of adult human MSCs via WNT signaling modulation. Stem Cell Rep 2015;4:459–72.

[15] Churchman SM, Ponchel F, Boxall SA, Cuthbert R, Kouroupis D, Roshdy T, et al. Transcriptional profile of native CD271+ multipotential stromal cells: evidence for multiple fates, with prominent osteogenic and Wnt pathway signaling activity. Arthritis Rheum 2012;64:2632–43.

[16] Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. Dev Cell 2005;8:739–50.

[17] Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Papapoulos S, Bone 3rd HG, et al. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2011;96:2441–9.

[18] Turgut M, Uslu S, Uysal A, Yurtseven ME, Ustun H. Changes in vascularity of cartilage endplate of degenerated intervertebral discs in response to melatonin administration in rats. Neurosurg Rev 2003;26:133–8.

[19] Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. Spine (Phila Pa 1976) 2002;27:2631–44.

[20] Roberts S, Evans H, Trivedi J, Menage J. Histology and pathology of the human intervertebral disc. J Bone Joint Surg Am. 2006;88(Suppl 2):10–4.

[21] Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. Spine (Phila Pa 1976) 2004(29):2700–9.

[22] Chanchairujira K, Chung CB, Kim JY, Papakonstantinou O, Lee MH, Clopton P, et al. Intervertebral disk calcification of the spine in an elderly population: radiographic prevalence, location, and distribution and correlation with spinal degeneration. Radiology 2004;230:499–503.

[23] Li XF, Xue CC, Zhao YJ, Cheng SD, Zhao DF, Liang QQ, et al. Deletion of Opg leads to increased neovascularization and expression of inflammatory cytokines in the lumbar intervertebral disc of mice. Spine 2017;42:E8–14.

[24] Xiao ZF, He JB, Su GY, Chen MH, Hou Y, Chen SD, et al. Osteoporosis of the vertebra and osteochondral remodeling of the endplate causes intervertebral disc degeneration in ovariectomized mice. Arthritis Res Ther 2018;20:207.

[25] Luo Y, Zhang L, Wang WY, Hu QF, Song HP, Zhang YZ. The inhibitory effect of salmon calcitonin on intervertebral disc degeneration in an ovariectomized rat model. Eur Spine J 2015;24:1691–701.

[26] Makitie RE, Niinimaki T, Nieminen MT, Schalin-Jantti C, Niinimaki J, Makitie O. Impaired WNT signaling and the spine-heterozygous WNT1 mutation causes severe age-related spinal pathology. Bone 2017;101:3–9.

[27] Wang L, Cui W, Kalala JP, Hoof TV, Liu BG. To investigate the effect of osteoporosis and intervertebral disc degeneration on the endplate cartilage injury in rats. Asian Pac J Trop Med 2014;7:796–800.

[28] Zhou Z, Tian FM, Wang P, Gou Y, Zhang H, Song HP, et al. Alendronate prevents intervertebral disc degeneration adjacent to a lumbar fusion in ovariectomized rats. Spine 2015;40:E1073–83.

[29] Luo Y, Zhang L, Wang WY, Hu QF, Song HP, Su YL, et al. Alendronate retards the progression of lumbar intervertebral disc degeneration in ovariectomized rats. Bone 2013;55:439–48.