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Editorial

Metformin and Bone Metabolism

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Editorial

Metformin is a member of biguanide antidiabetic drugs which has been widely used for treatment of Type 2 Diabetes Mellitus (T2DM) over 40 years. Bone is a highly dynamic tissue and its homeostasis mainly depends on the balance between bone resorption and bone formation through regulation of osteoblasts and osteoclasts. Recent studies showed that metformin has beneficial effects in maintaining bone metabolism [1,2]. Intriguingly, it has been reported that metformin has no effect on glucose levels in nondiabetic individuals [3,4]. These evidences suggested that metformin might be a considerable medication option for treatment of bone loss or prevention of fracture in patients with T2DM. However, its mechanism of action is becoming complicated and not fully understood according to recent emerged data. The aim of this review was to elaborate the potential signalling pathways of metformin on regulation of bone metabolism.

Regulation of Metformin in Osteoblasts

Osteogenic mechanism of metformin is always associated with the activation of AMP-Activated Protein Kinase (AMPK). Metformin is carried through cell membrane by the help of Organic Cation Transporters (OCT) and further stimulate intracellular uptake and action on the respiratory chain complex I which would increase cellular AMP/ATP ratio [5]. These changes could activate the cellular energy sensor AMPK to promote osteoblast proliferation and differentiation [6]. Recent *in-vitro* and *in-vivo* studies indicated that metformin could prevent bone loss by activating the expression of osteoblast genes Runt-related transcription factor 2

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(Runx2) and Lrp5, reducing receptor activator of of nuclear factor k B ligand (RANKL) level and stimulating Oteoprotegerin (OPG) expression in osteoblasts [7,8]. An *in-vitro* study showed that metformin had a direct osteogenic effect on osteoblasts by mediate the activation of phosphorylated Extracellular Signal-Regulated Kinase (ERK 1/2) signalling and stimulated the expression of endothelial and inducible nitric oxide synthases (e/iNOS) [9]. In addition, a study also found that metformin could significantly decrease intracellular Reactive Oxygen Species (ROS) production and apoptosis, and subsequent enhancement of Runx2 and Insulin-Like Growth Factor 1 (IGF-1) gene expression to directly mediate osteogenic effect on osteoblasts in glucose culture [10]. Small Heterodimer Partner (SHP) could be activated by metformin which mediates the AMPK/USF-1/SHP pathway to increase the osteoblastogenesis directly [11]. A recent study demonstrated that metformin could directly promote the osteoblast differentiation of Mesenchymal Stem Cells (MSCs) by inhibiting GSK3β/Wnt/β-Catenin pathway and indirectly inhibited GSK3β by activation of AMPK signalling pathway [12].

Regulation of Metformin in Osteoclasts

Metformin also showed its regulatory effects on AMPK to decrease osteoclastogenesis through inhibiting the signalling activation of three kinase/phosphatase enzymes, including LKB1, Calmodulin-Dependent Protein Kinase Kinase β (CaMKKβ) and TGF-β-Activated Kinase 1 (TAK1) [13-15]. Studies have indicated that the activation of AMPK by metformin could be suppress RANKL-induced osteoclast formation and further reduce bone resorption [16-18]. Previous studies have demonstrated that accumulation of AGEs in the collagen played a crucial role in connection between bone alterations and diabetics, and AGEs could cause to increase bone turn by inhibiting osteoblastic phenotypic expression and increase osteoclastic resorption [19-21]. Furthermore, activation of AMPK by metformin mediation could suppress inflammation and osteoclastogenesis by ruling mammalian Target of Rapamycin (mTOR) and Nuclear Factor-kB (NF-kB) activity [22]. On the other hand, metformin effects mTOR signalling through AMPK dependent and independent pathways [23].

The potential regulatory mechanisms of metformin on osteoblast and osteoclast are summarized and showed in Fig. 1. Most of literatures proved that metformin has the positive effect on the maintenance of bone homeostasis via stimulating bone-formation osteoblast and inhibiting bone-resorption osteoclast. The growing evidences indicated that metformin could be a promising medication option in the prevention of osteoporosis, in particular to prevent the loss of bone mass and fracture in patients with T2DM. Multiple clinical and pre-clinical studies have demonstrated that metformin owns the beneficial effects in osteogenesis, however, an *in-vivo* study showed that no osteogenic effects of metformin in ovariectomized C57BL/6 mice [24-26]. Moreover, a clinical study also showed no significant change in bone formation in metformin diabetic users [27]. These controversial results might be arisen from different conditions such as experimental methods, concentrations and duration of treatment with

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metformin, and test species or population, for example a study indicated that high concentration of metformin inhibited osteoblasts differentiation [28]. Therefore, further studies should investigate if metformin has beneficial effects on bone turnover and bone healing under a safe and effective dosage which can be applied clinically. Additional studies also might focus on whether metformin could be used either alone or in combination with other anti-osteoporosis medications.

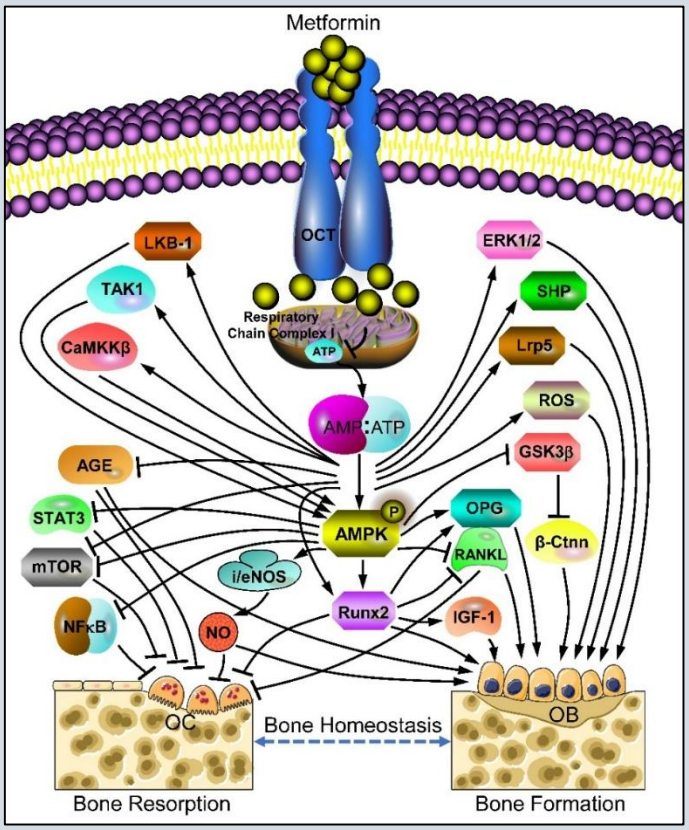

Figure 1: The multiple signalling pathways in which metformin affects bone metabolism.

References

1. Mu W, Wang Z, Ma C, Jiang Y, Zhang N, Hu K, et al. Metformin promotes the proliferation and differentiation of murine preosteoblast by regulating the expression of sirt6 and oct4. Pharmacol Res. 2018;129:462-74.
2. Gu Q, Gu Y, Yang H, Shi Q. Metformin enhances osteogenesis and suppresses adipogenesis of human chorionic villous mesenchymal stem cells. Tohoku J Exp Med. 2017;241(1):13-9.
3. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998;338(26):1876-80.
4. Widen E, Eriksson JG, Groop LC. Metformin normalizes nonoxidative glucose metabolism in insulin-resistant normoglycemic first-degree relatives of patients with NIDDM. Diabetes. 1992;41(3):354-8.
5. Takane H, Shikata E, Otsubo K, Higuchi S, Ieiri I. Polymorphism in human organic cation transporters and metformin action. Pharmacogenomics. 2008;9(4):415-22.

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6. Ma L, Wu X, Ling LE, Wang DS, Liu HC. The transmembrane transport of metformin by osteoblasts from rat mandible. Arch Oral Biol. 2009;54(10):951-62.
7. Gao Y, Li Y, Xue J, Jia Y, Hu J. Effect of the anti-diabetic drug metformin on bone mass in ovariectomized rats. Euro J Pharmacol. 2010 Jun 10;635(1-3):231-6.
8. Mai QG, Zhang ZM, Xu S, Lu M, Zhou RP, Zhao L, et al. Metformin stimulates osteoprotegerin and reduces RANKL expression in osteoblasts and ovariectomized rats. J Cell Biochem. 2011;112(10):2902-9.
9. Cortizo AM, Sedlinsky C, McCarthy AD, Blanco A, Schurman L. Osteogenic actions of the anti-diabetic drug metformin on osteoblasts in culture. Eur J Pharmacol. 2006;536(1-2):38-46.
10. Zhen DH, Chen YR, Tang XL. Metformin reverses the deleterious effects of high glucose on osteoblast function. J Diabetes Complicat. 2014;24(5):334-44.
11. Marycz K, Tomaszewski KA, Kornicka K, Henry BM, Wroński S, Tarasiuk J, et al. Metformin decreases reactive oxygen species, enhances osteogenic properties of adipose-derived multipotent mesenchymal stem cells. *In-vitro* and increases bone density *in-vivo*. Oxid Med Cell Longev. 2016:9785890.
12. Ma J, Zhang ZL, Hu XT, Wang XT, Chen AM. Metformin promotes differentiation of human bone marrow derived mesenchymal stem cells into osteoblast via GSK3β inhibition. Eur Rev Med Pharmacol Sci. 2018;22(22):7962-8.
13. Carling D, Sanders MJ, Woods A. The regulation of AMP-activated protein kinase by upstream kinases. Int J Obesity. 2008;32(4):S55-9.
14. Woods A, Johnstone SR, Dickerson K, Leiper FC, Fryer LG, Neumann D, et al. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade, Curr. Biol. 2013;13(22):2004-8.
15. Oakhill J, Scott J, Kemp B. Structure and function of AMP-activated protein kinase. Acta Physiol. 2009;196 (1):3-14.
16. Lee YS, Kim YS, Lee SY, Kim GH, Kim BJ, Lee SH, et al. AMP kinase acts as a negative regulator of RANKL in the differentiation of osteoclasts. Bone. 2010;47(5):926-37.
17. Martin T, Mundy G. Can osteoclasts be excluded? Nature. 2007;445:E19.
18. Roato I, D'Amelio P, Gorassini E, Grimaldi A, Bonello L, Fiori C, et al. Osteoclasts are active in bone forming metastases of prostate cancer patients. PLoS One. 2008;3(11):e3627.
19. Katayama Y, Akatsu T, Yamamoto M, Kugai N, Nagata N. Role of nonenzymatic glycosylation of type I collagen in diabetic osteopenia. J Bone Miner Res. 1996;11:931-7.
20. Miyata T, Notoya K, Yoshida K, Horie K, Maeda K, Kurokawa K, et al. Advanced glycation end products enhance osteoclast-induced bone resorption in cultured mouse unfractionated bone cells and in rats implanted subcutaneously with devitalized bone particles. J Am Soc Nephrol. 2017;8:260-70.
21. Li Y, Wang L, Zhang M, Huang K, Yao ZH, Rao PC, et al. Advanced glycation end products inhibit the osteogenic differentiation potential of adipose-derived stem cells by modulating Wnt/β-catenin signalling pathway via DNA methylation. Cell Prolif. 2020;53:12834.
22. Shao X, Cao X, Song G, Zhao Y, Shi B. Metformin rescues the MG63 osteoblasts against the effect of high glucose on proliferation. J Diabetes Res. 2014:453940.
23. Yan H, Zhou HF, Hu Y, Pham CT. Suppression of experimental arthritis through AMP-activated protein kinase activation and autophagy modulation. J Rheum Dis Treat. 2015;1(1):5.
24. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48(7):1292-9.
25. Melton III LJ, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. J Bone Miner Res. 2008;23(8):1334-42.
26. Jeyabalan J, Viollet B, Smitham P, Ellis S, Zaman G, Bardin C, et al. The anti-diabetic drug metformin does not affect bone mass *in-vivo* or fracture healing. Osteoporos Int. 2013;24(10):2659-70.
27. Hegazy SK. Evaluation of the anti-osteoporotic effects of metformin and sitagliptin in postmenopausal diabetic women. J Bone Miner Metab. 2015;33(2):207-12.
28. Gaber T, Strehl C, Buttgereit F. Metabolic regulation of inflammation. Nat Rev Rheumatol. 2007;13:267-79.

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