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Short Commentary

Metformin and Its Different Faces in the Skeleton Biology

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Commentary

Besides being a leading drug in therapy of type 2 diabetes, metformin is gaining a broader interest as a significant factor influencing metabolism of the bones. Although diverse roles of metformin in functioning of the skeleton have recently been revealed, the molecular mechanisms of this relationship still remain largely unknown.

Metformin affects bone tissue at different levels. Recent animal-based studies point that metformin can reverse a negative influence of diabetes-related hyperglycemia on the Bone Marrow Stromal Cells (BMSCs). Being the precursors of osteoblasts and osteocytes, BMSCs play an important role in bone development, remodeling and regeneration [1]. The experiments by Li and co-workers [2] performed on the bone marrow isolates of either control (PBS-injected) or metformin-injected, healthy or diabetic mice have demonstrated the presence of 346 unique metabolites, associated with a general and diabetes- specific response to metformin. The authors of this work also found glutamate and succinate, the components of the tri carboxylic acid cycle, to be reduced to a proper level in diabetic mouse stromal cells upon metformin treatment. The results of the work by Li et al. thus indicate some new metabolic pathways which may become a target of bone therapy, for instance in diabetic patients.

Metformin, although very efficient at decreasing the blood glucose, may not always exhibit beneficial effects on diabetes-related fracture healing. Recent paper by La Fontaine and co-workers [3] assessed the role of metformin in a femur fracture healing in rats. The authors performed the 6-week experiment on lean (healthy control) rats, diabetic (Zucker) rats and diabetic (Zucker) rats treated with 300 mg/kg of metformin.

They found that metformin successfully reduced the blood glucose and decreased the body weight but exhibited an opposite effect on fracture repair in diabetic rats. These results show that the actual performance of metformin on the skeletal system regeneration needs to be further investigated and the role of diabetes-accompanying neuropathy or angiopathies should not be neglected in this context.

On the other hand, the results of Inouye et al. [4], assesing the healing of bone around titanium-based dental implants, indicated the beneficial effects of metformin on this process. The authors analysed three experimental groups: the nondiabetic Wistar-Kyoto control rats, Goto-Kakizaki (GK) spontaneously diabetic rats (GK group), and GK rats fed metformin (100 mg/kg body weight per day) for 4 weeks (GK + Met group). Inouye et al. concluded that bone healing around the oral implants in type 2 diabetic animals may be improved when a negative influence of hyperglycemia on this process is counterbalanced by metformin.

The influence of metformin as well as other oral, anti-diabetic drugs on bone metabolism was discussed by Paul and Thomas. In this review, the authors cite the studies by Molinuevo and Vestegaard who analysed the effects of metformin on bones. In the experiments on Sprague-Dawley control (non-diabetic) and diabetic rats, Molinuevo have shown that metformin has a pro-osteogenic effect on differentiation of rat Bone Marrow Progenitor Cells (BMPCs). They also demonstrated the metformin action to be mediated by Runx-2 and AMPK activation in BMPCs, leading to further progression of their osteogenesis both *in vitro* and *in vivo*. On the other hand, Vestegaard have demonstrated that the use of metformin can reduce the risk of fractures in diabetes

type 1 and 2 patients, contrary to insulin which did not have any significant influence on decreasing the risk of fractures.

The anabolic influence of metformin on bones in a common, diabetes-associated osteopathy (osteopenia, osteoporosis and fracture incidence) has recently been reviewed by McCarthy. Similarly to Molinuevo these authors emphasised the role of AMPK kinase activation in anabolic actions of metformin treatment, especially in the course of bone marrow stromal cells osteogenesis.

Metformin can serve as a drug stimulating different cellular processes not only in diabetic but also in non-diabetic animals. As shown by Marycz and coworkers [5], metformin can stimulate the proliferation of mouse adipose-derived stem cells (MuASCs) isolated from mice treated for 8 weeks with metformin,as well as increase bone density *in vivo*. The authors of this work have demonstrated a higher proliferative potential of MuASCs, a generation of a robust network of cytoskeletal projections, reduced expression of markers associated with cellular senescence and decreased amount of reactive oxygen species upon metformin stimulation as compared to control (metformin untreated) MuASCs. Metformin-treated MuASCs also exhibited a greater osteogenic differentiation potential, along with a decreased adipogenic differentiation ability. Metformin supplementation also increased bone density *in vivo*. Thus the results of this work show that metformin, besides playing a leading role in a therapy of diabetes, may also find an application in different bone regenerative strategies, in diabetes-free animals.

Metformin also seems to find a broad application in a worldwide battle with different types of cancers, which is especially vital in a context of cancers affecting the skeletal system, e.g., osteosarcoma. Chen et al. [6] investigated the role of metformin on *in vitro* migration and invasion of the MG-63 osteosarcoma cell line as well as the sphere formation potential by osteosarcoma stem cell cultures, established by those authors. They noticed metformin efficiently inhibits MG-63 cell lineage proliferation and downregulates the expression of matrix metalloproteinases (MMPs) type 2 and 9, associated with the metastatic potential of those cells. Chen et al. also demontrated that metformin disables the sphere formation in osteosarcoma stem cell cultures and induces the loss of stemness in these cells. Maintenance of stemness is critical for cancer stem cells survival and cancer tissue renewal [7]. Upon metformin stimulation, the authors observed a decreased activation of stem cell specific transcription factors: OCT-4 and NANOG, as well as a reduced expression of stem cell-specific surface markers: CD90, CD133, and SSEA-4. Based on the molecular analyses, Chen et al. concluded that the beneficial effects of metformin rely on the activation of AMPK/mTOR/S6 pathway in both types of osteosarcoma cells (MG-63 and CSCs).

Summary

Considering the most recent literature reports, it is seems plausible that metformin may soon become a multi-functional drug, decreasing the effects of diabetes, but also targeting the functions and regeneration of the skeletal system both in normal and under diabetic conditions.

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