DOCTORAL THESIS

Investigation on the Correlation Between Methylglyoxal and Diabetic Complications - Osteoporosis

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disease which could be characterized by uncontrollable high blood glucose (hyperglycemia) and diverse complications in various organs. These complications include activation of stress responses in bone such as oxidative stress and inflammation which have been implicated in various bone diseases, including osteoporosis. Under stress situations such as hyperglycemia, decrease of bone formation and increase of bone resorption could be detected in bone. From previous reports, diabetes is a major risk factor of osteoporosis in which several osteoporotic symptoms, such as low bone mineral density and bone fracture were exacerbated in osteoporotic patients with diabetes. Hyperglycemia is known to result in formation and accumulation of non-enzymatic glycation of proteins, and methylglyoxal (MG), a reactive advanced glycation end-product precursor, was found to be abnormally accumulated in diabetic patients. MG induces various stress responses and may be a key metabolite causing diabetes-associated osteoporosis. By investigating the linkage of pathogenic mechanisms between MG and bone turnover, it could help us to develop new therapeutic strategies on combating osteoporosis in diabetic patients.

Using *in vivo* model in which rats were treated with STZ and MG, we have found that both STZ and MG could lead to decreased bone mineral density and osteoporosis, as measured using micro-CT. In addition, we have shown that apoptosis and osteoclastic activation occurred in proximal end of tibia. Therefore we have demonstrated *in vivo* that MG leads to osteoporosis, and that MG could exacerbate bone degeneration by inhibiting bone formation and triggering resorption. MG may therefore be the critical linkage between diabetic mellitus and osteoporosis.

Although it has been shown MG could be involved in the progress of osteoporosis by disturbing osteoclastic function and cell death, bone turnover involves both osteoblasts and osteoclasts. Therefore in this proposal the effect of MG on osteoporosis will be investigated using both the *in vivo* model with MG-treated rats as well as *in vitro* model with osteoblast and osteoclast cultured with MG.

It is envisaged that the findings obtained in this project will provide invaluable information on the impact of MG on bone mineral density and architecture through its effect on osteoclast and osteoblast activity, and that MG and its downstream effect may help us to develop possible therapeutic strategies in treating osteoporosis in diabetic patients.