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Literature Review

The Effect of MST 1 Inhibition Through Hippo Pathway on Diabetes Mellitus (DM) Induced Osteoporosis

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Abstract

Osteoporosis is a chronic metabolic disorder of the musculoskeletal system associated with reduced bone strength. One of the causes of secondary osteoporosis is diabetes mellitus (DM). The prevalence of both disorders keeps increasing with time. Therefore, this review is conducted to find a possible solution to prevent DM-induced osteoporosis. Diabetes mellitus mainly affects the bone through glucose uptake during the bone remodeling process. Glucose uptake through GLUT 1 is regulated by MST 1, which is an upstream kinase of the Hippo signaling pathway. MST 1 is responsible for regulating cell growth, proliferation, and apoptosis. In the bone remodeling process, MST 1 plays a role by regulating actin ring structures and the integrin signaling pathway. Moreover, DM is also associated with increased oxidative stress. Increased oxidative stress will activate Hippo signaling pathway. This will trigger cellular apoptosis as the Hippo signaling pathway plays a role mainly as a tumor suppressor. Increased cellular apoptosis will cause an imbalance in the bone remodeling process, disrupting bone quality. Inhibition of MST 1 through the Hippo signaling pathway will increase cell growth and reduce cellular apoptosis. Increased cell growth might increase osteogenesis during the bone remodeling process, thus resulting in better bone quality in DM-induced osteoporosis

1. Introduction

Osteoporosis is a chronic metabolic musculoskeletal disorder associated with reduced bonestrength.¹ According to WHO, approximately 200 million people had osteoporosis worldwide in 2015. The risk factors for osteoporosis, include old age, female, low physical activities, vitamin D and/or calcium deficiency, low sun exposure, smokers, decreased estrogen level, family history of osteoporosis, and bigger body size.² Other conditions that might aggravate osteoporosis are metabolic and endocrine disorders, such as diabetes mellitus.³

Diabetes increases the risk of osteoporosis up to 6.4 - 6.9 fold.⁴ According to WHO, in 2018, there were 422 million people worldwide with diabetes mellitus.⁵ Diabetes mellitus is a disorder marked by high blood glucose levels, with diagnostic criteria of random blood glucose levels >200 mg/dL.⁶ High blood glucose levels will increase cell destruction due to oxidative stress.⁷

Glucose uptake through glucose transporter (GLUT) 1 is regulated by a kinase protein, MST 1, which also regulates osteoblast mineralization and osteoprotegerin gene in bone resorption.⁸ MST 1 or Mammalian Ste-20-like Kinase-1 is a protein kinase homologous to Hpo in the Hippo pathway, which regulates proliferation and apoptosis.⁹ MST 1 is a growth-suppressive protein kinase that can be activated by oxidative stress, protein kinase C inhibitor, cell-to-cell contact, and strausporine.¹⁰ Inhibition of MST 1 using anticancer agents will also inhibit osteoclastogenesis in bones.⁷

Studies about MST 1 inhibitor using anticancer agents have been conducted before MST 1 inhibition using XMU-MP1 in mice model with cardiac hypertrophy resulted in increased heart function and decreased apoptosis.¹¹ Another study conducted on diabetic mice model showed that the inhibition of MST 1 using XMU-MP1 has a protective effect on pancreatic β -cells as well as resulted in increased hepatocytes.¹² However, there were still very few studies regarding MST 1 inhibition on the bone remodeling process. Therefore, this study is conducted, considering the high prevalence of osteoporosis and diabetes mellitus worldwide.

2. Review

Bone Structure

Anatomically, bones are classified into long, short, flat, and irregular bones. Based on its structure, a bone consists of a cortex located around the bone marrow and trabecula located inside the bone marrow. Bones can also be classified into

woven bones with a weaker structure formed during primary osteogenesis and lamellar bones formed by collagen fibers.¹³ Unless a pathological condition occurs, woven bones can be found in the embryonic skeleton and will otherwise be turned into lamellar bones with age. Bones comprise osteoblasts, osteocytes, osteoclasts, and bone lining cells and are sheathed by endosteum and periosteum.¹⁴

Osteoblasts are cells responsible for producing extracellular matrix, mineralization, and osteocalcin production. Osteoblasts are regulated by parathyroid hormones (PTH), bone morphogenic protein (BMP), transforming growth factor-beta 1 (TGF- β 1), activins, inhibins, myostatin, and Wnt/ β -catenin pathway.¹⁵ Osteoblasts' interaction with bone matrix with the help from integrin will lead to osteoblasts' organization during osteoid synthesis.¹⁶ Osteoblasts are located in one continuous layer all over bone surfaces surrounding the bone, and will be opened up once resorption by osteoclasts starts.¹⁵ Mature osteoblast will form single-layered cuboidal cells and can either turn into osteocytes or bone lining cells, or die.¹⁶

Osteocytes are located in dendritic form and are surrounded by a mineralized matrix. In trabecular bones, the osteocytes are more rounded, whereas in cortical bones, the osteocytes are more elongated.¹⁶ Osteocytes play a role in fibroblast growth factor 23 (FGF-23) release, affecting renal secretions of phosphate.¹⁵ Osteocytes also have mechanoreceptors, enabling the cells to detect mechanical loads.¹⁷ Mechanical loads will regulate the production of the second messenger on osteoblast and osteoclasts which will in turn regulate both cells.¹⁶ Those mechanical loads can also be forwarded to the bone marrow using osteocytes dendrites, inducing bone resorption process.¹⁷

Osteoclasts are cells which are responsible for bone resorption, as well as for producing clastokine, which is essential for osteoblasts and hematopoietic stem cells regulation.¹⁶ Osteoclast's activity is induced by PTH, tumor necrotic factor-alpha (TNF- α), cardiotropin, prostaglandin E₂, bradykinin, oncostatin M, and some interleukins. Whereas estrogen, calcitonin, retinoid, and interferon-alpha and beta (IFN- α and IFN- β) will inhibit osteoclasts' activity.¹⁵

Bone Remodeling Process

The bone remodeling process is a turnover process to replace old bones with new ones, which will change the size, shape, and orientation of the

bone. This process leads to bone repair to adjust to bio-mechanic and homeostatic changes without changing the overall shape and size of the bones. The bone remodeling process consists of bone resorption and bone formation, which are activated by basic multicellular unit.¹⁴

The bone remodeling process is initiated by bone resorption by osteoclasts which occurs in 7-14 days and will then be followed by bone formation which occurs within months. In an adult skeleton, the bone remodeling process will supply calcium to the extracellular space and will provide skeletal elasticity and strength.¹⁹ The remodeling process occurs more frequently in trabecular bones and is stimulated by micro-cracks and subsequent osteocytes apoptosis.¹⁵ In normal conditions without changes in mechanical loads, remodeling will occur faster in the bone cortex.¹⁴ Increased mechanical load and fatigue will inhibit osteoblasts and stimulate local osteocytes activities.¹⁶ Balanced formation and resorption during the bone remodeling process will not cause skeletal increase or decrease.¹⁸ Inhibited osteoclasts activities will prevent bone resorption, leading to a condition known as osteopetrosis. Meanwhile, increased resorption due to increased osteoclasts activities will cause a condition known as osteoporosis.²⁰

Osteoporosis

Osteoporosis is a skeletal disorder marked by a bone mineral density (BMD) T-score of 2.5 standard deviations or lower than the average of young healthy women.¹ Osteoporosis is associated with decreased bone mass and quality, as well as increased fracture risk due to systemic homeostatic changes. These conditions lead to signs and symptoms of back pain, vertebral fractures, and osteopenia. Osteoporosis can be divided into primary and secondary osteoporosis. Primary osteoporosis is caused by post-menopausal estrogen decrease and microarchitecture damage related to the aging process due to changes in BRU. Secondary osteoporosis is caused by long-term glucocorticoid use, enteropathy, DM, rheumatoid arthritis, liver diseases, multiple myeloma, and many more. Osteoporosis risk factors include being older than 65 years of age, smokers, abnormal body mass index (BMI), history of fracture, weight loss in people older than 50 years old, excessive alcohol consumption, and physical inactivity.¹⁹

In normal conditions, cancellous bones have horizontal and vertical trabeculae, enabling them to withstand pressure well. However, in osteoporotic bones, decreased bone mass is associated with the tendency to lose horizontal trabeculae. This loss decreases the interconnectivity of cancellous

bones, making the vertical trabeculae more susceptible to pressure thus causing osteoporotic compression fractures.²¹ Decreased bone interconnectivity will also induce lipid degeneration in the bone marrow.²² The histopathological image of osteoporotic bones in hematoxylin-eosin (HE) staining depicted widened bone marrow without cellular structures, which are surrounded by thin or radial structure and lipid vacuole.²³ The trabeculae will be shown as a homogenous and acellular structure with thinned horizontal trabeculae which will be compensated by thickened vertical trabeculae. This condition will give an anisotropic image of the trabeculae, which, if persisted, will lead to the thickening of areolar space.²² The bone cortex might seem normal with some osteocytes decreased in density and number.²³ These conditions can be found in all parts of the skeleton in different degrees between one and another.²² Osteoporosis can also be determined using Fracture Risk Assessment Tool (FRAX), Dual-Energy X-Ray Absorptiometry (DEXA), peripheral quantitative computed tomography (pQCT), as well as other radiologic imaging to determine the history of fractures.¹⁹

Diabetes Mellitus (DM)

Diabetes mellitus (DM) diagnosis is established if random blood glucose level ≥ 200 mg/dL, fasting plasma glucose ≥ 126 mg/dL, 2-hours plasma glucose ≥ 200 mg/dL during oral glucose tolerance test (OGTT), or A1C level $\geq 6.5\%$.²⁴ DM can be classified into DM type 1 (T1D), which is due to the autoimmune condition of pancreatic β -cells resulting in inadequate insulin production; DM type 2 (T2D), which is due to insulin resistance; gestational diabetes mellitus, which is a condition of hyperglycemia below the diagnostic threshold which happens on the second or third trimester of pregnancy, and specific types of DM due to other causes.²⁵

The autoimmune process in T1D is associated with specific human leukocyte antigens (HLA), which provide antigen presentation which will generate an immune response against insulin producing cells on pancreatic islets and trigger autoantibody formation, further damaging the islets.²⁸ Autoimmune destruction of pancreatic β -cells in T1D resulted in people with T1D being totally reliant on exogenous insulin treatment and are usually diagnosed at an early age without presenting any diabetic complications.²⁹ Meanwhile, risk factors of T2D such as obesity, old age, low socioeconomic status, and genetic factors contribute less than in T1D. Insulin resistance in T2D is usually due to ectopic fat deposition,

Langerhans islets inflammation, and apoptosis. Insulin resistance in T2D affects insulin secretion. Thus, insulin secretion in T2D patients with obesity is relatively higher than in non-obese patients, although it is still below the normal value.³⁰

Relation Between Diabetes Mellitus (DM) and Osteoporosis

The effect of DM on the skeleton is attributed to its deleterious effects on osteoblasts and bone formation. However, its effect on osteoclasts and bone resorption might not be direct as hyperglycemia has been shown to inhibit osteoclasts' differentiation and functions.³¹ One of the diagnostic criteria is high HbA1C level, which has a positive association with pentosidine content in the trabeculae. Pentosidine is the most common advanced glycation end products (AGEs) and is a good predictor for microvascular and macrovascular complication, and serves as a surrogate marker for its content in the bone and bone strength.³²

T1D has been particularly associated with a variety of bone complications. This association is because T1D is also associated with decreased insulin-like growth factor 1 (IGF-1), which directly stimulates osteoblast differentiation, matrix production, and mineralization via the IGF-1 receptor signaling pathway.³¹ Whereas people with T2D usually have lower bone scores but higher BMD compared to T1D.³² Poor glycemic control on both types of DM also causes excessive calcium excretion and chronically stimulates PTH secretion, disrupting the calcium-PTH-vitamin D axis.³³

Glycemic control also plays a role in determining bone turnover rate.³² Patients with DM have a slower bone turnover rate, marked by elevated sclerostin (SOST) level and lowered carboxy-terminal collagen crosslinks (CTX), procollagen type 1, N-terminal polypeptide (P1NP), and serum osteocalcin level. An elevated SOST level will stimulate the secretion of the Receptor Activator of Nuclear Factor κ B-Ligand (RANKL) which will, in turn, stimulate osteoclasts activation. Elevated SOST level will also inhibit Wnt canonical pathway, which will inhibit osteoblasts' activity.²⁹ Insulin resistance in DM will also lower osteoprotegerin (OPG) level, which reduces bone formation and turnover. The hyperglycemic state of DM will also decrease the differentiation potential of mesenchymal stem cells into osteoblasts, increase osteocytes differentiation, and decrease bone remodeling rate by decreasing RANKL/OPG ratio. In a condition in which the bone remodeling process is disrupted,

the bones will not be renewed, therefore disrupting the quality of the bones.³²

Glucose Metabolism in Bone

Glucose is an important nutrient for osteoblasts as the cells express some GLUT types, namely GLUT 4, which is important for insulin-controlled glucose uptake and GLUT 1, which plays a role in osteogenesis and osteoblast differentiation. Aside from expressing GLUTs, osteoblasts also express insulin receptors, although its role in glucose uptake has yet to be established. However, in DM, deletion of insulin receptors will decrease the number of osteoblasts and decrease osteogenesis and bone mass. Bone glucose metabolism is mainly done through aerobic glycolysis with lactate as the end product, although in mature osteoblasts it can also be done through active oxidative phosphorylation. Glycolysis in osteoblasts is directly regulated by PTH through regulation of glucose consumption and indirectly by IGF-1 through the mTORC2 signaling pathway. Glycolysis is also regulated by Wnt3a, which binds to Lrp5 and increases the expression of GLUT 1, HK2, LDHa, and PDK downstream. Wnt regulated glycolysis will decrease histone acetylation by affecting citrate and acetyl CoA, thus suppressing adipogenic and chondrogenic transcription factors. This process is important in producing intermediate metabolites and balancing reactive oxygen species (ROS), favoring adipogenesis.³¹

The hyperglycemia will induce non-canonical Wnt/PKC pathway and PPAR- γ upregulation, resulting in increased adipogenesis and damaged bone structure.³³ A glucose level of 5 mM will cause glucose-pyruvate synergy, which will induce osteoclasts differentiation. Osteoclastogenesis can also be induced by RANKL which will increase glycolysis, oxidative phosphorylation, and lactate production which is consistent with the increased number, size, and abundance of mitochondrial crypts. Oxidative phosphorylation is an important process for osteoclastogenesis, whereas aerobic glycolysis is important for mature osteoclasts. However, in *in vitro* osteoclastogenesis, glycolysis limitation did not have a significant impact as the medium contains pyruvate and fatty acid, which can be used for oxidative phosphorylation. Bones also play a role in glucose homeostasis by producing osteokines, such as osteocalcin, BMP, SOST, and RANKL. Bone-produced hormones, such as PTHrP, adiponectin, and lipocalin also regulate glucose homeostasis.³¹

The Roles of Mammalian Ste-20-like Kinase 1 (MST 1)

MST 1 is an upstream protein kinase in Hippo signaling pathway¹⁰, which was originally found in *Drosophila melanogaster*.³⁴ The Hippo signaling pathway has tumor suppressive characteristics and regulates cell growth, proliferation, and apoptosis.¹⁰ This signaling pathway also plays a role in tissue regeneration and organ size regulation during the post-trauma healing process.³⁴ The Hippo signaling pathway in mammals comprises of signaling pathways of MST 1 and 2, Salvador scaffold protein (Sav), large tumor suppressor kinase (LATS) 1 and 2, and transcription factors of yes-associated protein (YAP) and WW domain-containing transcription regulator 1 (TAZ).³⁵

The Hippo pathway is stimulated by stress factors such as cellular density, mechanical stimuli, and the G-protein signaling pathway (GPCR), which will phosphorylate YAP/TAZ.³⁶ Phosphorylated YAP/TAZ will be located in the cytoplasm before being degraded by β -TrCP mediated proteasome.³⁵ Unphosphorylated MST 1 is activated by oxidative stress, cell-to-cell contact, PKC inhibitor, and staurosporine.¹⁰ Oxidants, such as hydrogen peroxide, will oxidize thioredoxin, which will induce its dissociation from MST 1 thus inhibiting MST 1 activities.³⁷

In diabetic conditions, MST 1 was found to be highly upregulated in beta-cells, whereas no MST 1 signal was observed in non-diabetic subjects. MST 1 upregulation in diabetic conditions occurred through caspase-mediated cleavage and autophosphorylation.¹² Caspase-mediated cleavage can also be identified in non-apoptotic cells undergoing terminal differentiation to maintain certain cellular states. MST 1 can also be phosphorylated in response to IGF-1 as it contains a classical AKT phosphorylation site.³⁷ MST 1 inverted relationship with AKT and the ability to phosphorylate PDX1 might cause T2D. Although MST 1 activities will not be found during the early stage of T2D, it will induce cell apoptosis once AKT activities stopped.³⁶ MST 1 also plays a role in stabilizing GLUT 1 and modulating AMPK, which are important in regulating glucose uptake, including during osteogenesis.⁸

The Hippo pathway regulates actin ring structure and integrin signaling pathway, which will later regulate osteoclasts differentiation. The integrin signaling pathway is modulated by integrin-linked protein (ILK), which can also be inhibited by MST 1. ILK-MST 1 bond will modulate the rearrangement of the osteoblast actin cytoskeleton. This bond can only be found in conditions in which differentiation does not occur.

The Hippo pathway can be affected by extracellular matrix rigidity.³⁸ Moreover, the Hippo pathway can also be affected by F-actin structures and shear stress.³⁴

MST 1 Inhibition

The disruption of the Hippo signaling pathway will result in decreased or removed MST 1 activities, thus resulting in YAP being dephosphorylated. MST 1 inhibition through YAP resulted in its translocation to the nucleus regardless of cellular density.³⁹ YAP/TAZ dephosphorylation and translocation might cause an interaction with domain transcription enhancing factor 1-24 (TEAD 1-4), which will induce gene expression and facilitate cellular proliferation.³⁸ A prior study about MST 1 inhibition using XMU-MP1 showed increased YAP expression, which, in turn, increased the number of cardiomyocytes.¹¹ MST 1 inhibition can also activate STAT3, Wnt β -catenin, and Notch, increasing cellular proliferation.³⁵

Another study showed that MST 1 inhibition improved the osteogenic and adipogenic differentiation capability of the mouse bone marrow mesenchymal stem cells (mBMSCs). This result occurs because MST 1 inhibition might overcome anchorage-dependent apoptosis, improve mBMSCs adhesion to the extracellular matrix, and improve cell proliferation. MST 1 is also known to interact with integrin thus its inhibition will result in deregulation of integrin, which changes their expression profile. Changes in integrin expression might contribute to cell survival, adhesion, and proliferation.⁴⁰

Prior studies on the digestive system show that MST 1 deficient mice showed induced proliferation or tumorigenesis of the liver and colon. MST 1 depletion also led to a significant increase in non-small cells lung cancer (NSCLC) foci number, while its overexpression led to an increased proliferation rate of NSCLC.⁴¹ Another study suggests that MST 1 inhibition significantly reduces the number of cardiomyocytes undergoing apoptosis. However, MST 1 is not a critical determinant of the size of the myocardial infarction caused by permanent ischemia. The study also suggests that apoptosis regulation by MST 1 during cardiac remodeling is parallel to the changes in cardiac function. Thus, inhibiting endogenous MST 1 improves cardiac function after myocardial infarction in the mice heart.⁴² In research done on human hair keratinocytes, XMU-MPI was found effective in inducing cell cycle arrest, although it did not significantly increase YAP1 activity.⁴³ In

another study done on human-derived iPSC cardiomyocytes (hiCMs), a combination of XMU-MP1 and SIP successfully increased YAP1, further increasing proliferation in low-density hiCMs.⁴⁴

3. Summary

Diabetes mellitus (DM) has been established as one of the causes of secondary osteoporosis, resulting in defects in bone density and, further, a higher chance of fractures. MST 1, as an upstream kinase in the Hippo signaling pathway responsible for regulating cell growth, proliferation, and apoptosis, plays an important role in both DM and osteoporosis. Therefore, MST 1 inhibition may result in increased cell growth and proliferation, thus preventing osteoporosis as one of the complications of DM. Prevention of osteoporosis as a DM complication would be a great milestone as the prevalence of both conditions increase over time. Although prior studies on the effect of MST 1 inhibition in osteoporosis have not been done much, its effect on other tissues gave positive outcomes. However, further studies on the effect of MST 1 inhibition on osteoporosis have to be done to establish its role.

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Authors' Contributions

All authors have contributed to the final manuscript. The contribution of each author as follow: collected the data, drafted the manuscript and designed the figures, devised the main conceptual ideas and critical revision of the article. All authors discussed the results and contributed to the final manuscript.

Conflict Of Interest

The authors state there is no conflict of interest.

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