Review Article

Hip Fracture Risk and Effects of Exercise Therapy in Preventing Bone Deterioration in Diabetes Mellitus

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Abstract

Diabetes mellitus is a metabolic disease assuming hyperglycemia as its main symptom, and the number of patients has continued increasing all over the world. Its major complications such as neuropathy, nephropathy and retinopathy by microangiopathy and cerebral vascular disease and heart disease by macroangiopathy, are well known. Recently it has been recognized that hip fracture risk is increased in diabetics as compared with non-diabetics. Although increasing risk of falls due to neuropathy, deterioration of muscle strength and retinopathy seems to be associated with fracture risk, it has been shown that deterioration of bone *per se* decreases bone strength and causes fractures in diabetes mellitus. Diabetes mellitus and osteoporosis had previously been considered as quite different diseases in pathogenesis or pathology, but it has been clarified that these two diseases have some common factors such as insulin, oxidative stress and advanced glycation end products. So recently the relationship between diabetes mellitus and hip fracture has attracted attention, and it has been suggested that various factors related to diabetes such as glycemic control, insulin sensitivity and so on are associated with bone fragility. It has been shown that bone strength is determined by bone mineral density and bone quality, and it has been suggested in particular that deterioration of bone quality is related to increased fracture risk in diabetics. Exercise therapy is well known as one of the basic treatments for glycemic control as well as diet therapy or pharmacotherapy, and many studies about its effects have been published. However, few studies concerning the effects of exercise therapy in preventing bone deterioration have been conducted. In this review, we describe bone deterioration and its mechanism in diabetes mellitus and the effects of exercise therapy on bone properties, including our own findings.

Keywords: Diabetes mellitus; Osteoporosis; Fracture risk; Bone mineral density; Bone quality; Exercise therapy

Introduction

The number of adult diabetics has continued increasing explosively and by 2015 it had reached 415 million all over the world [1]. Among them are 94.2 million people aged from 65 to 79 and it is expected that this number will increase further to 200.5 million by 2040. On the other hand, it is known that hip fracture is one of the representative fragility fractures caused by osteoporosis. It is shown that the number of new patients with hip fracture has increased in the nationwide surveys every five years since 1987 in Japan [2]. Cooper et al. [3] have also reported that the number occurring in the world each year is estimated to increase from 1.66 million in 1990 to 6.26 million by 2050.

Diabetes mellitus is a metabolic disease assuming chronic hyperglycemia as its main symptom, and its major chronic complications such as neuropathy, nephropathy and retinopathy by microangiopathy and cerebral vascular disease and heart disease by macroangiopathy are well known. Recently other complications such as depression, periodontal disease and degradation of muscular strength [4,5] have also been recognized. In addition, it has been shown in meta-analysis that hip fracture risk is increased in diabetics as compared with non-diabetics [6,7]. It is thought that the occurrence of hip fracture in diabetics will rise with increase of the number of the elderly diabetics in the future. Hip fracture causes degradation of quality of life (QOL) and vital prognosis [8], so it is very important to prevent it from early stage in diabetes mellitus.

In general there are two major causes for hip fracture. One of them is falling and the other is osteoporosis, which means the decline of bone strength. It has been reported that the risk of falls increases in diabetics [9-11], and that hyperglycemia is a risk factor of falls in elderly type 2 diabetics [10]. Tilling et al. [12] have reported that the fall risk in diabetics with neuropathy increases 5 times compared with that in non-diabetics. Many other factors such as deterioration of muscle strength or lower-extremity function, decreased visual acuity due to retinopathy, and so on seem to be associated with an increasing risk of falls in diabetics. On the other hand, it has recently been recognized that strength of the bone *per se* deteriorates in diabetes mellitus. It has been shown that bone strength is determined by bone mineral density (BMD) and bone quality, with the former taking 70% of the role, and the latter taking 30% [13]. It has been shown that decreased BMD of the femoral neck is correlated with risk of hip fracture in non-diabetics [14,15]. It is generally known that the BMD in type 1 diabetes decreases more than that of non-diabetics, and it increases the risk of fractures. In type 2 diabetes mellitus, many studies have shown similar or higher BMD relative to non-diabetics, with

some other studies even showing reduced BMD, so the relationship between BMD and fracture risk has not been elucidated enough. Recently it has been shown that the deterioration of bone quality such as microarchitecture, bone metabolic turnover, and collagen cross-link causes bone fragility in type 2 diabetes mellitus [6,16-19]. Therefore it is necessary to recognize that the deterioration of bone itself also increases the risk of fractures in diabetes mellitus.

Although diabetes mellitus and osteoporosis had previously been considered as quite different diseases in pathogenesis or their pathology, it has been clarified that those two diseases have some common factors such as insulin, oxidative stress and advanced glycation end products (AGEs). So recently the relationship between diabetes mellitus and hip fracture has attracted attention. Many studies showing effects of exercise therapy on postmenopausal or senile osteoporosis have been published up to now. However studies with respect to the effects of exercise therapy in preventing bone fragility in diabetes mellitus have seldom been reported. In this review article, we describe the changes of the bone in diabetes mellitus and the effects of exercise therapy on bone properties including BMD, bone quality and bone strength with our own findings.

Hip fracture risk in diabetes mellitus

Albright et al. [20] first reported about the relationship between diabetes and bone metabolism as a loss of bone mass in diabetic patients with poor glycemic control in 1948. In the 1990's, many studies with respect to BMD in diabetes were reported with the spread of dual-energy X-ray absorptiometry (DXA). Various findings about the bone metabolism in diabetes have since been published.

It has been shown in meta-analysis that hip fracture risk is increased 6.94 times in type 1 diabetics and 1.38 times in type 2 diabetics as compared with non-diabetics [6]. It has also been shown in systematic review to be 6.3 times in type 1 diabetes and 1.7 times in type 2 diabetics as compared with non-diabetics [7]. BMD of type 1 diabetics is lower than that of non-diabetics. It is thought that it is due to a lack of absolute insulin action [21-24] and that the risk of fractures increases as a result. On the other hand, in type 2 diabetes, several studies have shown similar [23,25,26] or higher [27-29] BMD compared with that in non-diabetics, while it has been reported that BMD decreased in type 2 diabetics [30-33]. Some studies using animal models of type 2 diabetes have also shown that BMD decreased relative to the controls without diabetes [34-42]. So it seems to be difficult to suppose the risk of hip fracture only depending on BMD in type 2 diabetes mellitus. However, Schwartz et al. [43] have shown that the lower T-score of BMD in the femoral neck was associated with hip fracture risk in older type 2 diabetics and that type 2 diabetics had a higher risk of hip fracture than non-diabetics when they had equal BMD. In addition, BMD takes 70% of the role in bone strength related to the fracture risk directly as mentioned above. Therefore decreased BMD is considered to be a risk factor of the hip fracture, and measurement of BMD seems to be useful partially for clinical evaluation of a fracture risk, and we should not disregard BMD.

On the other hand, recently it has been shown in many studies that the deterioration of bone quality causes bone fragility and increases the risk of fracture in diabetes mellitus. Bone strength is determined by BMD and bone quality, so it is very important to clarify the change of bone quality and its causes in diabetes mellitus to explain an increase of the fracture risk. Previous studies provide various knowledge and suggestions to elucidate the causes of increasing hip fracture risk in diabetes, although all of them do not necessarily show the results in

femur. Bone quality is determined by both structural properties and tissue material quality, with the former depending on microarchitecture, and the latter on metabolic turnover and intermolecular cross-link of collagen. It is possible to evaluate the bone microarchitecture by using DXA, microcomputed tomography (μ-CT) and high resolution peripheral quantitative computed tomography (HR-pQCT). It has been reported that cortical porosity at distal region of radius which is a bone in forearm and tibia which is a bone in lower leg was significantly higher in patients with type 2 diabetes compared with non-diabetic controls and furthermore that type 2 diabetics with past history of a fracture had higher levels of cortical porosity than non-fractured diabetics using HR-pQCT [17,18]. In addition, it has been shown that the trabecular bone score (TBS), which is a texture parameter related to bone microarchitecture, in lumber vertebrae measured by DXA was lower in type 2 diabetics relative to that in non-diabetic controls, and suggested that it may help to predict osteoporotic fractures in type 2 diabetes mellitus [44,45]. Those studies are useful to understand the changes of bone quality in the femur because the composition in distal radius or tibia is similar to that in proximal region of the femur. Bonaccorsi et al. [46] have also shown that the TBS at femoral neck and total hip was lower in type 2 diabetics compared with non-diabetic controls although there was no significant difference in BMD at the same region of interest, and that TBS is an excellent tool in identifying fragility fractures. In the studies using animal models, Fu et al. [19] have reported that the trabeculae of the distal femur were thinner and less connected and that the cortical bone was thicker in type 2 diabetic KK-Ay mice as compared with normal mice and it has been shown that trabecular bone volume fraction in the femur was decreased in type 2 diabetes mellitus compared to the controls [38,40,41]. Thus it has been clarified that the microarchitecture in both cortical bone and trabecular bone deteriorates in diabetes mellitus and that their porosity deteriorates the bone strength, and increases the risk of fractures as a result.

Furthermore it has been shown that intermolecular cross-link of collagen, a material property, is related to bone strength as well as structural properties [47]. Saito et al. [16] showed that bone strength of the femur declined without regard to BMD in WBN/Kob diabetic rats and that this was due to decreased enzymatic cross-link formation and increased pentosidine content in bone collagen, an AGE, causing degradation of bone quality. In addition, more recently Nilsson et al. [48] showed that trabecular and cortical microarchitecture in radius and tibia was better in the group with type 2 diabetes compared to that in non-diabetic control group and concluded that increased fracture risk in type 2 diabetes depends on physical impairment and on reduced bone material strength, although it is not a study with respect to the femur. Therefore it is thought that material quality such as metabolic turnover or intermolecular cross-link of collagen is also very important in consideration of bone strength in diabetes mellitus as well as microarchitecture.

Factors related to deterioration of BMD and bone quality

It has been reported that the loss of bone mineral content (BMC) is aggravated by the negative calcium balance in poorly controlled diabetes [33]. Terada et al. [49] have shown that the proliferation and differentiation potency of osteoblast was inhibited by high glucose culture media in *in vitro* study. Botolin et al. [50] have also shown that chronic hyperglycemia suppressed osteoblast gene expression. In study using type 2 diabetic animal models, it has been reported that the BMD in the proximal region of the femur showed a negative correlation with blood glucose level [42]. Li et al. [51] have reported

that higher HbA1c levels increase the risk of hip fracture in type 2 diabetes mellitus. Therefore hyperglycemia seems to cause osteoblastic dysfunction and decrease bone mass.

Insulin is well known as the hypoglycemic hormone, and has been shown to be related to bone remodeling. It has been reported that fasting insulin level was positively associated with BMD in femoral neck, radius and spine in non-diabetics [52,53]. Kawaguchi et al. [54] have also suggested that insulin signals are associated with the facilitation of bone formation. It is thought that a main target of insulin is osteoblast with insulin receptors. Fulzele et al. [55] have shown that mice lacking insulin receptors in osteoblasts have significantly reduced bone formation and bone mass. So insulin is thought to have an important role in bone formation. On the other hand, Ferron et al. [56] have shown that insulin signals in osteoblasts activate osteocalcin and also facilitate the differentiation of osteoclasts by repressing the expression of osteoprotegerin, a factor repressing osteoclast differentiation. It has been shown that high insulin levels impaired the trabecular micro-structure [19] and that hyperinsulinemia was not beneficial to the BMD of the femur in KK-Ay type 2 diabetic mice [57]. In addition, improvement of insulin resistance was beneficial to the BMD of the tibia or femur in type 2 diabetic animal models [57,58], although it has been reported that insulin sensitivity was inversely associated with BMD in non-diabetics [59]. Thus insulin has an important role in bone turnover, but it has not been clarified whether insulin has similar effects on bone metabolism in diabetes mellitus as in non-diabetics.

It is also well known that some proteins are associated with bone formation or resorption, and used as markers of bone turnover. It has been reported that osteoblastogenesis is suppressed by hyperglycemia and the level of blood osteocalcin, one of the biochemical osteoplastic markers, is lower in diabetes mellitus in both clinical [60,61] and animal studies [16,19,36,38-40,42,62]. It has been shown that the blood osteocalcin level was improved by glycemic control [60,63,64] and that it contributes to the prevention of a decrease in BMD as a result [32,33]. That is to say, there is a close relationship among blood glucose, insulin level and bone turnover and it suggests the importance of glycemic control for prevention of fractures in adults with type 2 diabetes, although it has not been clarified whether glycemic control is directly effective in decreasing the fracture risk.

Recently the mechanism related to deterioration of material property in diabetes mellitus has been gradually clarified. It is well known that hyper-production of active oxygen increases oxidative stress in lifestyle related disease including diabetes mellitus. It has also been shown that oxidative stress is elevated in diabetic Torii rats [36]. Intermolecular collagen cross-links are divided into lysyl oxidase regulated enzymatic cross-link and oxidation or glycation induced non-enzymatic cross-link, which means AGEs cross-link by the formation mechanism [65]. It has been thought that decline of osteoblast function due to increased oxidative stress or long-term hyperglycemia reduces the activity of lysyl oxidase, and causes AGEs collagen cross-link formation, and as a result, decreases bone strength in diabetes mellitus [66-68]. Pentosidine is just one of many AGEs in bone, and it is shown that the quantity of pentosidine formed has a positive correlation with total AGEs. Odetti et al. [69] have shown that plasma pentosidine has a significant exponential correlation with age and a liner correlation with the cortical bone pentosidine. So it has recently come to be used as a surrogate marker of bone quality [47]. It has been shown that the quantity of serum pentosidine increases in diabetes mellitus [16,69], and that there is a significant positive correlation between pentosidine level and fracture risk in type 2 diabetics [70,71].

Effects of exercise therapy in preventing deterioration of BMD and bone quality

Diabetes mellitus is a metabolic disease with chronic hyperglycemia as its main symptom, so glycemic control is the most important aim to prevent its complications. Exercise therapy is well known as one of the basic treatments for glycemic control, as well as diet therapy or pharmacotherapy. Although effects of exercise therapy on glycemic control through the improvement of insulin sensitivity have been shown in many studies so far, we can find few studies with respect to its effects on bone properties such as BMD or bone quality in diabetes mellitus.

In general, mechanical loading on the bone is thought to be effective in maintaining or increasing BMD. In studies using C57BL/6J normal mice, Kodama et al. [72] have reported that jumping training increased periosteal bone formation and bone strength. Umemura et al. [73] have also reported that jumping training increased BMD, cortical and total BMC in the femur. In clinical research intended for non-diabetics, it has been reported that resistance training and walking exercise was beneficial for preservation of BMD [74], and that walking exercise increased the BMD of femoral neck [75,76]. Many previous studies using normal animal models have also shown that a treadmill running exercise was beneficial for increasing BMD [77-81]. Wu et al. [78] reported that the treadmill running exercise at a rate of 12 m/min for 30 min per day 6 days a week for 4 weeks increased the BMD of the femur compared to non-exercise control mice. Hamrick et al. [80] also reported that the treadmill running exercise (12 m/min, 30 min/day), 5 days a week for 4 weeks increased the BMD of the distal metaphysis of the femur. Hagihara et al. [79] showed that increases in BMD of the femur were obtained by moderate running load at frequency of 4 and 5 days per week. In addition, Huang et al. [82] have shown that endurance treadmill running exercise for 60 min 5 days a week for 8 weeks was beneficial to biomaterial properties of the femur, as measured by a three-point bending test without increased BMD. With respect to the effects of exercise on bone turnover marker levels, some studies of them have shown an increase in bone formation markers [78,83] and others have shown no change [79,82], while it has been shown that bone resorption marker levels were decreased by the exercise [79,81,83]. So it is thought that exercise such as jumping and walking gives mechanical stimulation to the bones and is effective for both facilitating bone formation and suppressing bone resorption in non-diabetics. However, it was recently published that bone's response to mechanical loading is suppressed in C57BL/6-Ins2[Akita]/J (Akita) diabetic mice, and that osteocytes, which are the primary bone mechanosensing cells, have impaired responses to loading in hyperglycemic conditions [84]. Therefore mechanical loading on the bone may not be always beneficial to bone metabolism in diabetics.

Exercise therapy for type 2 diabetes has been carried out for glycemic control, not for bone metabolism, as its main purpose up to now as mentioned above. So only a few studies about the effects of exercise on bone metabolism in type 2 diabetes mellitus have been published. In clinical research, Bello et al. [85] reported that the multicomponent training program including walking, resistance and aquatic exercise three days per week for 32 weeks increased the ward's triangle BMD with fat-free mass in postmenopausal women with pre-diabetes and type 2 diabetics. Mathey et al. [86] have reported that treadmill running exercise for 89 days increased BMD of metaphysis

and diaphysis in the femur and also increased bone strength and suppressed the increase of fat mass in obese diabetic Zucker rats compared with being sedentary, whereas it had no effect on blood glucose or insulin concentrations. More recently, effects of exercise on bone mass, bone strength and so on have been shown in studies using diabetic animal models. Hinton et al. [58] have shown in a study using Otsuka Long-Evans Tokushima Fatty (OLETF) rats, obese type 2 diabetic animal models, that voluntary wheel running for 36 weeks was beneficial to both BMD of the femur and to increased structural and material properties of the femur compared to sedentary controls. Ortinau et al. [87] have also shown that voluntary wheel running was beneficial not only to glycemic control and preventing body fat accumulation, but also to tissue-level stiffness and strength of the femur in OLETF rats. In addition, Minematsu et al. [88] have shown that long-term voluntary wheel running for 17 months was effective on BMD and BMC of the tibia in OLETF rats together with glycemic control and that trabecular bone connectivity at metaphysis of the proximal tibia appears to be relatively well maintained in the running group, whereas trabecular bone of the sedentary group is disconnected. Those studies are very valuable for showing the effects of exercise on BMD and bone quality in type 2 diabetes, but it has not been determined what intensity, duration and term are the most beneficial. We have shown that the treadmill running exercise with slow speed, long duration (5 m/min, 120 min) 5 days a week for ten weeks was more effective in preventing BMD of the femur from decreasing than fast, short duration loading (12 m/min, 30 min) which was effective on BMD in normal mice [80], together with preventing hyperglycemia, hyperinsulinemia and visceral fat contents, in KK-Ay type 2 diabetic mice [57], although it had no effect on bone quality such as microarchitecture and blood pentosidine level. Those studies suggest that low grade loading; long time and long term exercise are beneficial to bone properties in type 2 diabetes mellitus.

It has been suggested that various factors are associated with bone fragility in type 2 diabetes, but the mechanism of the effects of exercise therapy in preventing the deterioration of bone property has not been clarified. It has been shown that running exercise prevented increases in blood glucose, HbA1c levels and insulin levels [57,58,87,88] and improved glucose tolerance [57,58]. So exercise-induced glycemic control seems to contribute directly or indirectly through some other factors to BMD and bone strength. Body weight has also been thought to be beneficial to BMD as a mechanical loading on bone similar to exercise. It was reported that heavyweight and obesity have a protective role for BMD of the femur neck in healthy elderly [89] and that a positive correlation is found between BMD and body mass index (BMI) in diabetics [90,91]. However it has been shown that fat mass is inversely, and lean mass is positively associated with bone mass [92] and that abdominal visceral fat has an association not only with decreasing BMD but also with decreasing bone strength and cortical porosity [93]. Some studies using diabetic animal models have shown that exercise prevented the increases in body fat contents [57,86,87] or increased fat-free mass [88,89] and contributed to bone properties as a result. Therefore it is necessary to consider the relationship between bone metabolism and changes in fat mass by exercise together with glycemic control.

It has been shown that blood osteocalcin concentration is significantly lower in type 2 diabetics than in non-diabetics. Recently animal studies have shown that osteocalcin is related not only to bone formation but also to glucose metabolism and fat mass [94,95]. However, exercise did not increase the bone formation marker levels compared with non-exercise group, whereas bone resorption marker levels in exercise group were lower in comparison with that in non-exercise group [57,58,86-88]. Therefore effects of exercise in preventing bone loss in diabetes seem to depend on suppressing the bone resorption through improvement in carbohydrate and fat metabolism, not depending on stimulating the osteoblast function. Therefore, in diabetes mellitus, many factors such as glycemic control, improvement of insulin sensitivity, decreasing in fat mass and so on by exercise are thought to be beneficial to bone properties more than mechanical loading on the bone.

It is thought that inflammation and oxidative stress are also associated with bone deterioration. It has been suggested that C-reactive protein (CRP), which is one of the markers of inflammation, is inversely associated with BMD, and could be considered an adjunctive tool for the screening of osteoporosis [96]. Kasapis et al. [97] have shown in systematic review that physical activity has an inverse relationship with serum CRP levels. de Lemos et al. [98] have reported that swimming exercise for 12 weeks decreased serum CRP levels compared with being sedentary in Zucker diabetic fatty rats, a type 2 diabetic animal model. We too have found out that a treadmill running exercise for 10 weeks suppressed serum CRP levels and was also beneficial to BMD of the femur in comparison with non-exercise controls in KK-Ay diabetic mice [57]. Therefore CRP may have the potential to be a marker indicating the change in BMD or bone quality through exercise in type 2 diabetes. It will be necessary to investigate the relationship between oxidative stress marker level and bone properties by exercise in the future, too.

Conclusion

Many factors such as blood glucose, insulin sensitivity, inflammation and oxidative stress are associated with bone fragility in diabetes mellitus. Although studies with respect to effects of exercise therapy on bone properties in diabetes mellitus are only the few, those studies suggest that exercise therapy is effective in preventing the deterioration of BMD and bone quality through improvement in glycemic control, insulin sensitivity, inflammation and so on more than mechanical loading on the bone. In addition, it is suggested that exercise with low, long duration loading and long term is effective for bone metabolism. Further investigations will be necessary to establish the most effective exercise program including modality, loading level, duration, frequency and term to prevent the risk of fractures in diabetes mellitus. Furthermore, it may be necessary to make studies of combined effects with diet therapy same as treatment for primary osteoporosis in the future.

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