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EFFECT OF BONE TURNOVER MARKERS IN DIABETIC RETINOPATHY

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ABSTRACT

Diabetic retinopathy is the most frequent microvascular complication of diabetes mellitus and one of the leading causes of blindness worldwide. Diabetic retinopathy has a complex process and various bone turnover markers play a key role in pathogenesis and progression of diabetic retinopathy. Previous studies have shown that bone turnover markers such as serum calcium, vitamin D, phosphate, parathyroid hormone, alkaline phosphatase have significant effect on microvascular changes in diabetic patients. Further studies should be done to evaluate the level of various bone turnover markers in diabetic retinopathy and critically appraise the level and quality of existing studies.

KEYWORDS: Diabetic retinopathy, calcium, phosphate, vitamin D, parathyroid hormone, alkaline phosphatase, microvascular complications.

INTRODUCTION

Diabetic retinopathy (DR) is among the most common diabetic complications, and is the leading cause of blindness among working-aged individuals worldwide.[1] Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have signs of DR and of these, a further one third of DR is vision-threatening DR, including diabetic macular oedema (DME). The prevalence of DR varies from 20% to 80% as reported in different studies. Recent estimates suggest that the number of people with diabetic retinopathy will increase to 191 million by 2030.[2] DR has a complex process and many risk factors have been established, such as poor glycaemic control, long duration of diabetes, smoking, inflammation, obesity, and hypertension. In DR, vision loss generally develops as a sequela of neovascularization of the retina, leading to vitreous haemorrhage and retinal detachment.

EFFECT OF BONE TURNOVER MARKERS ON DIABETIC RETINOPATHY

The bone is constantly being remodelled to maintain a healthy skeleton structure as per an individual's needs. Various bone turnover markers are used to determine the risk of fracture independently of bone mineral density (BMD). These markers are divided into three categories, indicating the number of osteoblasts, bone formation or resorption.[3] Several diabetic complications including nephropathy, retinopathy and peripheral neuropathy are associated with a higher fracture risks in diabetic patients. Even previous studies have revealed an important association between bone metabolism and energy metabolism[4], which influences the risk of DR.

Among the various bone turnover markers, calcium homeostasis plays an important role in development of type 2 diabetes mellitus (T2DM). The secretion of insulin in response to an elevated concentration of plasma glucose is a Ca^{2+}dependent process. Alterations in insulin secretion have also been involved with disorders in blood glucose homeostasis[5], and increasing cytosolic calcium has been associated with an increase in the expression of GLUT4 transporters in the myocyte, which, in turn, increases the insulin-stimulated glucose transport activity in these cells.[6] There are various mechanisms by which calcium play a role in retinal microvascular changes such as reducing retinal albumin leakage and capillary permeability, which protects the blood-retinal barrier[7], inhibiting platelet aggregation and blood viscosity[8], up-regulating endothelium-dependent relaxation because of an increase in nitric oxide synthesis[9], inhibiting apoptosis of vascular endothelial cells in blood vessels[10], antioxidant and antiradical activity[11], protecting against reactive oxygen species or inhibiting the expression of the inflammatory and upstream VEGF regulator, ICAM-1.[12]

Apart from calcium, elevated serum phosphate levels, even within the normal range, are also implicated in the pathogenesis of vascular disease by inducing vascular calcification in large and medium sized vessels and development of endothelial dysfunction.[13]

Similarly, Vitamin D deficiency has been shown to alter insulin synthesis and secretion in both humans and animal models. Improvement in action of insulin may be mediated by vitamin D directly through the presence of Vitamin D receptors in skeletal muscles, stimulation of expression of insulin receptors in bone marrow cells and through vitamin D activation of peroxisome proliferator activator receptorδ, a transcription factor involved in the control of metabolism of fatty acids in adipose tissue and skeletal muscle.[14] The indirect role of vitamin D is via the regulation of pools of intracellular and extracellular calcium and control of normal influx of calcium through the membranes of cells. Vitamin D receptors are expressed extensively in the retina[15], and an animal study showed that calcitriol was a potent inhibitor of retinal neovascularization in an oxygen-induced ischemic retinopathy mouse model.[16] This evidence indicated that vitamin D may play a role in the pathogenesis of diabetic retinopathy.

Parathyroid hormone has also been implicated in the pathogenesis and progression of diabetes mellitus. Approximately 40% of patients with primary hyperparathyroidism have impaired glucose tolerance. Insulin resistance present in patients with hyperparathyroidism probably arises from a raised intracellular free calcium concentration, which reduces insulin-stimulated glucose transport. With the progression of insulin resistance there is impaired glucose tolerance, and finally diabetes mellitus may result.

Alkaline phosphatase (ALP) is an enzyme found in several tissues throughout the body with the highest concentration found in bone and liver. Elevated level of ALP in the blood are most commonly caused by liver disease or bone disorders. However, mild elevation of serum ALP has also been observed in diabetic patients.[17] But the effect of ALP on risks of microvascular complications of diabetes mellitus is still not clear.

A longer disease duration, the presence of diabetic complication, and inadequate diabetic control all have been reported to have low BMD and increased fracture risk in diabetic patients.[18] A significant association between presence of DR and low BMD has been observed, hence DR may be considered as a marker of low BMD.

Though studies have been done on effect of these bone turnover markers in DR but to the best of our knowledge, none of the studies have shown the effect of all these markers collectively.

RELATION BETWEEN BONE TURNOVER MARKERS AND DIABETIC RETINOPATHY

Many studies have been performed across the world to determine the effect of bone turnover markers in diabetic retinopathy. **Stratton et al (2001)**[19], have given evidence that poor glycaemic control and long duration of diabetes are independent risk factors of Diabetic retinopathy**. J Levy et al (1986)**[20], conducted a study which showed that there is no correlation between plasma calcium and duration of diabetes. However, the alteration in calcium homeostasis accompanies the diabetic state**. Sorva A, Tilvis R.S. (1990)**[21] conducted a study on geriatric inpatients, and showed that the ratio of ionized calcium concentration and serum total calcium concentration were inversely related to body weight, diastolic blood pressure and plasma glucose. **Pittas AG et al (2006)**[22], conducted a prospective study which suggested a potential beneficial role for both vitamin D and calcium intake in reducing risk of type 2 diabetes. **Cecilia M. Giachelli (2009)[7],** conducted a study which concluded that hyperphosphatemia promotes vascular calcification in part by promoting smooth muscle cells to undergo an osteochondrogenic phenotype change through a mechanism requiring sodium -dependent phosphate cotransporters. Upregulation of sodium phosphate cotransporters in smooth muscle cells by disease state and cytokines may facilitate vascular calcification even when serum phosphate levels are in normal range**. Van Dam RM et al (2006)**[23] conducted a study which indicated that there is inverse associations between calcium and magnesium intake and risk of type 2 diabetes in predominantly white population. **Dhingra R et al (2007)**[24], concluded in a prospective study that higher serum phosphorous levels are associated with an increased cardiovascular risk in individuals free of chronic kidney disease and cardiovascular disease in the community. These observations emphasized the need of additional research to elucidate the potential link between phosphorous homeostasis and vascular risk. **Cecilia M. Giachelli (2009)**[7] conducted a study which concluded that hyperphosphatemia promotes vascular calcification in part by promoting smooth muscle cells to undergo an osteochondrogenic phenotype change through a mechanism requiring sodium -dependent phosphate cotransporters. Upregulation of sodium phosphate cotransporters in smooth muscle cells by disease state and cytokines may facilitate vascular calcification even when serum phosphate levels are in normal range. **Rukshana C. Shroff (2010)**[25] conducted a study which concluded that vascular calcification occurs in response to deranged calcium and phosphate metabolism in chronic kidney disease and is characterized by vascular smooth muscle cell damage and attrition. **B. Maestro et al (2002)**[26] conducted a study which suggested stimulation of phosphatidylinositol 3 kinase activity by 1,25 dihydroxy vitamin D3, which could mediate, at least in part, the potentiation of insulin response. **Begona Maestro et al (2000)**[27], conducted a study which showed an important role of 1,25(OH)2D3 as a genomic stimulator of insulin receptor mRNA levels, insulin receptor number and insulin responsiveness for glucose transport in U-937 human promonocytic cells. These effects appeared to be mediated by increase in both vitamin D receptor gene and protein expression. **Ute Zietz et al (2003)**[28],

conducted an experimental study in mice which concluded that disruption of vitamin D receptor signalling pathway is associated with a pronounced impairment in oral glucose tolerance and insulin secretory capacity, together with a reduction in pancreatic insulin mRNA levels in normally fed mice. **Taverna MJ et al (2005)[9],** conducted a study in which he observed that in a cohort of Caucasians with C-peptide negative type 1 diabetes, a novel association between the functional folk vitamin D receptor polymorphism and severe diabetic retinopathy, especially among subjects with fewer than 25 year of diabetes duration. **H. Taylor, A. A. Taylor (2001)**[29], conducted a study which concluded that approximately 40% of patients with primary hyperparathyroidism have impaired glucose tolerance. Insulin resistance is present in hyperparathyroidism and probably arises from a raised intracellular free calcium concentration which, by decreasing normal insulin stimulated glucose transport, increases the requirement for insulin. **Belfiore F et al (1973)**[11], conducted a study which concluded that some serum enzymes including alkaline phosphatase show changed activities in diabetes mellitus. The level of serum alkaline phosphatase found to be increased in diabetes mellitus but not correlated with blood sugar concentration**. J. Stephan and V. Pakovsky (1980)**[30] conducted a study which showed that positive correlations between the activity of bone isoenzyme and urinary hydroxyproline excretion in diabetes are similar to those found in osteoporosis. **Rao GM, Morghom LO (1986)**[31] conducted a study which showed positive correlation between serum alkaline phosphatase and blood glucose level of diabetic patients. **Bonds DE et al (2006)**[32], conducted a study which concluded that women with type 2 diabetes mellitus are at increased risk for fractures. This risk is also seen among black and non-Hispanic white women after adjustment for multiple risk factors including frequent falls and increased bone mineral density**. Gilbert MP et al (2015)**[33] conducted a study which concluded that patients with type 2 diabetes mellitus have an increased risk of fragility fractures. **Lim Y et al (2016)**[34], conducted a study which concluded that the presence of diabetic retinopathy is significantly associated with a reduced bone mineral density and increased prevalence of osteoporosis in diabetic women.

CONCLUSION

Although the results in previous studies appeared to be largely similar, there are inadequate evidence that will support a particular result. Moreover, most of researches have been conducted worldwide but there are limited studies done in Indian population. So, further studies in this field are required to determine the effect of bone turnover markers in DR in Indian population and examine the potential association between bone turnover markers and diabetic retinopathy which may provide beneficial role in therapy for diabetic retinopathy.

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