

## Study of Bone Turnover Markers in Diabetic Retinopathy

Sabah S<sup>1</sup>, Khan S<sup>1</sup>, Maheshwari R<sup>3</sup>, Siddiqui SS<sup>4</sup>

<sup>1</sup>Junior resident, MS Ophthalmology, Institute of Ophthalmology, JNMCH, AMU, Aligarh

<sup>2</sup>Assistant professor, Institute of Ophthalmology, JNMCH, AMU, Aligarh

<sup>3</sup>Professor, Institute of Ophthalmology, JNMCH, AMU, Aligarh

<sup>4</sup>Associate professor and Director, Rajiv Gandhi Center for Diabetes and Endocrinology, JNMCH, AMU, Aligarh

Corresponding Author: Akhtar N<sup>2</sup>

**Abstract:** Diabetic retinopathy is the most frequent microvascular complications of Diabetes mellitus and one of the leading causes of blindness worldwide. DR 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. Our study aims to summarize and evaluate the level of various bone turnover markers in DR and critically appraise the level and quality of existing studies.

**Keywords:** Diabetic retinopathy, calcium, phosphate, vitamin D, Parathyroid Hormone, alkaline phosphatase, Microvascular complications

Date of Submission: 20-01-2019

Date of acceptance: 04-02-2019

### I. Introduction

Diabetic retinopathy (DR) is among the most common diabetic complications, and is the leading cause of blindness among working-aged individuals worldwide<sup>1</sup>. 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 edema (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<sup>2</sup>. DR has a complex process and many risk factors have been established, such as poor glycaemia control, long duration of diabetes, smoking, inflammation, obesity, and hypertension. In DR, vision loss generally develops as a sequelae 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<sup>3</sup>. 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<sup>4</sup>, 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<sup>2+</sup> dependent process. Alterations in insulin secretion have also been involved with disorders in blood glucose homeostasis<sup>5</sup>, and increasing cytosolic calcium has been associated with an increase in the expression of GLUT4 (Glucose Transporter 4) transporters in the myocyte, which, in turn, increases the insulin-stimulated glucose transport activity in these cells<sup>6</sup>.

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<sup>7</sup>.

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 receptor- $\delta$ , a transcription factor involved in the control of metabolism of fatty acids in adipose tissue and skeletal muscle<sup>8</sup>. 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<sup>9</sup>, and an animal study showed that calcitriol was a potent inhibitor of retinal neovascularization in an oxygen-induced ischemic retinopathy mouse model<sup>10</sup>. 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<sup>11</sup>. 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<sup>12</sup>. 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. So, this study aims to summarize and evaluate the level of various bone turnover markers in DR and critically appraise the level and quality of existing studies.

## **II. Materials And Methods**

We are conducting a cross-sectional study (taking sample size 60 with 30 study group and 30 control group), after taking ethical clearance from Ethical Committee, Jawaharlal Nehru Medical College and Hospital, A. M. U., Aligarh. In this study we are trying to compare the effects of various bone turnover markers in diabetic patients with diabetic retinopathy with those without diabetic retinopathy. An informed written consent will be taken from each patient before participation in the study. The study population will be drawn from the diabetic patients with duration of diabetes more than 5 years who will attend the Rajiv Gandhi Center for Diabetes and Endocrinology, and subsequently be referred to the Retina Clinic, Institute of Ophthalmology, of the same hospital, for their ocular evaluation.

A clinical history will be taken with the help of a structured questionnaire including demographic data, duration of diabetes, treatment taken, presence of any other complications of diabetes, addictions, dietary habits, family history of diabetes, and blood pressure.

The laboratory profile of each patient would comprise of:

Blood sugar (both fasting  $\geq 126$ mg/dl and 2 hours blood glucose on 75 gm oral glucose tolerance test (OGTT)  $\geq 200$ mg/dl in diabetes), HbA1c (greater than or equal to 6.5 % in diabetes)<sup>13</sup>.

Serum calcium (normal physiological range- 8.9-10.1 mg/dl), serum phosphate (normal physiological range - 2.5-4.5 mg/dl), vitamin D (normal physiological range 20-76 pg/ml), serum alkaline phosphatase (normal physiological range 41-133), parathyroid hormone (normal physiological range 11-54 pg/ml)<sup>14</sup>.

According to WHO criteria, T score  $\leq -2.5$  is osteoporosis, T score -2.5 to -1.0 is osteopenia, T score  $\geq -1.0$  is normal BMD.

The ocular examination will comprise of refraction (undilated), slit lamp biomicroscopy as well as dilated fundoscopy with the use of 78D/90D Volk lens. A fundus photograph using Visucam 500 will be taken and secured as an objective evidence of the subjective findings seen on 78D/90D slit lamp biomicroscopy.

A diagnosis of diabetic retinopathy will be made as per ETDRS classification.

## **III. Discussion**

Many studies have been performed across the world to determine the effect of bone turnover markers in diabetic retinopathy. Results of some of the studies have been mentioned below.

**Stratton et al (2001)**<sup>15</sup>, have given evidence that poor glycaemic control and long duration of diabetes are independent risk factors of Diabetic retinopathy. **J Levy et al(1986)**<sup>16</sup>, 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. **Pittas AG et al (2006)**<sup>17</sup>, 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)**<sup>7</sup>, 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)**<sup>18</sup> 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. **Ute Zietz et al (2003)**<sup>19</sup>, 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)**<sup>9</sup>, 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. **W. H. Taylor, A. A. Taylor(2001)**<sup>20</sup>, 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)**<sup>11</sup>, 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. **Rao GM, Morghom LO(1986)**<sup>21</sup> conducted a study which showed positive correlation between serum alkaline phosphatase and blood glucose level of diabetic patients. **Bonds DE et al(2006)**<sup>22</sup>, 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. **Lim Y et al(2016)**<sup>23</sup>, 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.

#### IV. Conclusion

Although the results in previous studies appeared to be largely similar, there are inadequate evidence that will support a particular result. So, further studies in this field are required and the results obtained will be added to that already established fact in our literature. Moreover, Most of researches have been conducted worldwide but there are limited studies done in Indian population. Hence, our study aims 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 so possible interventions can be given accordingly.

#### References

- [1]. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. *Ophthalmic Epidemiol.* 2007; 14:179–83.
- [2]. Pescosolido N, Buomprisco G. Psychological exams as early indicator of diabetic retinopathy. 2014; 10: 61-5.
- [3]. Sorensen MG, Henriksen K Biochemical markers in preclinical models of osteoporosis *Biomarkers*, May-June 2007;12:266.
- [4]. Lerchbaum E, Schwetz V, Nauck M, et al. Lower bone turnover markers in metabolic syndrome and diabetes: the population-based Study of Health in Pomerania. *NutrMetab Cardiovasc Dis* 2015;25(5):458-63.
- [5]. Mears D. Regulation of insulin secretion in islets of Langerhans by Ca<sup>2+</sup> channels. *J Membr Biol* 2004; 200:57–66.
- [6]. Ojuka EO, Jones TE, Nolte LA. Regulation of GLUT4 biogenesis in muscle: evidence for involvement of AMPK and Ca<sup>2+</sup>. *Am J Physiol Endocrinol Metab* 2002;282: E1008–E1013.
- [7]. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int.* 2009; 75:890–897.
- [8]. Luquet S, Gaudel C, Holst D, Lopez-Soriano J, Jehl-Pietri C, Fredenrich A, Grimaldi PA. Roles of PPAR delta in lipid absorption and metabolism: a new target for the treatment of type 2 diabetes. *BiochimBiophys Acta* 2005; 1740: 313-317.
- [9]. Taverna MJ, Selam JL, Slama G. Association between a protein polymorphism in the start codon of the vitamin D receptor gene and severe diabetic retinopathy in C-peptide-negative type 1 diabetes. *J. Clin. Endocrinol. Metab.* 2005; 90: 4803–4808.
- [10]. Albert DM, Scheef EA, Wang S, Mehraein F, Darjatmoko SR, Sorenson CM, Sheibani. Calcitriol is a potent inhibitor of retinal neovascularization. *Investig. Ophthalmol. Vis. Sci.* 2007; 48:2327–2334.
- [11]. Belfiore F, Vecchio LL, Napoli E. Serum enzymes in diabetes mellitus. *Clin Chem.* 1973; 19:447-452.
- [12]. Dede AD, Tourmis S, Dontas I, Trovas G. Type 2 diabetes mellitus and fracture risk. *Metabolis.*2014; 63:1480-1490.
- [13]. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS50: Risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia.* 2001; 44:156–163.
- [14]. Levy J, Stern Z, Gutman A, Naparstek Y, Gavin JR 3rd, Avioli LV. Plasma calcium and phosphate levels in an adult noninsulin-dependent diabetic population. *Calcif Tissue Int* 1986; 39:316–18.
- [15]. Reference adopted from Current medical diagnosis and treatment, Edition 2015, author, Maxine A. Papadakis, Stephen J. McPhee.
- [16]. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM. Official positions of the international society for clinical densitometry and executive summary of the 2005 position development conference. *J Clin Densitom.* 2006; 9:4-14.
- [17]. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; 29: 650-56.
- [18]. Shroff RC, Mc Nair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, Rees L, Shanahan CM. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. *J Am Soc Nephrol.* 2010; 21:103-12.
- [19]. Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J.* 2003; 17: 509-11.
- [20]. Taylor, WH, Khaleeli, AA. Coincident diabetes mellitus and primary hyperparathyroidism. *Diabetes Metab. Res. Rev.* 2001; 17: 175–80.
- [21]. Rao GM, Morghom LO. Correlation between serum alkaline phosphatase activity and blood glucose levels. *Enzyme.* 1986; 35:57-9.

- [22]. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. *J Clin Endocr Metab.*2006; 91:3404-10.
- [23]. Lim Y, Chun S, Lee JH, Baik KH, Lee WK, Yim HW, Kang MI. Association of bone mineral density and diabetic retinopathy in diabetic subjects: the 2008-2011 Korea National Health and Nutrition Examination Survey. *Osteoporosis Int.*2016;27:2249-57.

Akhtar N. "Study of Bone Turnover Markers in Diabetic Retinopathy." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, vol. 18, no. 2, 2019, pp 22-25.