Glycemic Control and the Microvascular Outcome "Retinopathy" in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Diabetic retinopathy is the most common complication of Diabetes and one of the leading cause of preventable blindness. Vascular endothelial growth factor is now known to be a key modulator of angiogenesis and vascular permeability and plays a major role in the pathogenesis of Diabetic Retinopathy. Uncontrolled hyperglycemia is one of the most important risk factors for Diabetic retinopathy and Diabetic macular edema. Serum Glycated Hemoglobin(HbA1c) is the most widely used clinical parameter for the evaluation of glycemic control in patients with diabetes. The purpose of this study was to determine whether glycemic control of patients with Diabetic retinopathy due to type 2 diabetes was related to VEGF plasma levels.

Material and methods: This is a prospective study which included 40 retinopathy patients(19 males and 21 females) due to type 2 diabetes mellitus. The diagnosis of Diabetic Retinopathy was performed by fundus examination after pupil dilation using slit lamp bio-microscopy. Under strict aseptic precautions fasting venous blood samples were collected for HbA1c and VEGF estimation. Serum VEGF levels were estimated using RayBio Human VEGF-A ELISA kit.

Results: In this study the HbA1c levels of 40 diabetic retinopathy patients were correlated with their serum VEGF levels and the results were interpreted using Pearson's correlation with the software SPSS version 21 for statistical significance. The results showed that HbA1c levels have a significant positive correlation with plasma VEGF concentrations (r: 0.8775, $P<0.001$).

Conclusion: The present study shows that poor glycemic control is significantly positively correlated with increased levels of plasma VEGF in patients with type 2 diabetes. So strict glycemic control and normalization of HbA1c is one of the most effective ways to prevent progression of Diabetic retinopathy. As VEGF has been shown to be clearly implicated in the development of Diabetic retinopathy, it affirms the importance of glycemic control in patients with Diabetic retinopathy.

Keywords: Diabetic retinopathy, Vascular Endothelial Growth Factor, Diabetic Macular Edema, Glycated Hemoglobin (HbA1c).

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease, easily the most important health challenge of the present century, some even calling it the biggest global health crisis we face when one looks at the economic burden it carries, especially in third world countries.According to the International Diabetes Federation, in 2015, about 415 million people were suffering from diabetes worldwide, and this number is expected to exceed 640 million by the year 2040.India has an estimated 77 million people with diabetes, which makes it the second most affected in the world, after China. Diabetes is also beginning to appear much earlier in life in India, meaning that chronic long-term complications are becoming more common. All these mean that the implications for the Indian healthcare system are enormous.[1] Retinopathy is a specific microvascular complication of DM and was first described by Henry Noyes in 1869, in a person with advanced diabetes.[2] Diabetic Retinopathy (DR) has been implicated as the leading cause of vision loss in adults aged 20–74 years.[3] In 2010, of the 285 million people affected worldwide with diabetes, over one-third had signs of DR, and a third of these were afflicted with vision-threatening diabetic retinopathy (VTDR), defined as severe non-proliferative DR (NPDR) or proliferative DR (PDR) or the presence of diabetic macular edema (DME).[4] These estimates are expected to rise further due to the increasing prevalence of DM, ageing population and the increasing life expectancy of diabetics. It is interesting to note that patients with type 2 diabetes in Western countries have a higher prevalence of DR than their Asian counterparts.[5]

Serum hemoglobin A1c (HbA1c) is the most widely used clinical parameterfor the evaluation of glycemic control in patients with diabetes. Hyperglycemia is one of the most important risk factors for DR and DME. A meta-analysis of three large population-based studies found a graded relationship between the level of glycemia and frequency of retinopathy signs.[6] The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) provided strong evidence that tight control of glycemia (HbA1c <7%) reduces the risk of development and progression of DR in both type 1 and type 2 diabetes.[7]

Vascular endothelial growth factor (VEGF) is a key modulator of angiogenesis and vascular permeability and is upregulated by inflammatory cytokines.[8] Anti-VEGF agents have been

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used successfully for the treatment of both PDR and DME.[9] The vitreous levels of VEGF are positively correlated with the development of neovascularization in different ocular disease entities including DR. Furthermore significantly raised VEGF plasma levels have been observed in patients with DR comparedto non-diabetic controls.[10] These findings suggest that plasma VEGF levels may be used as a potential indicator for neovascularisation in diabetic patients and that the underlying pathomechanism implies systemic as well as local ocular angioneogeneticpathways.[11] The purposeof this study was to determine whether glycemic control of patients with DR due to type 2 diabetes was related to VEGF plasma levels.

MATERIAL AND METHODS

This is a prospective study conducted at the Research Laboratory of the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai after obtaining approval from the Institutional Ethical Committee. Study group included 40 retinopathy patients(19 males and 21 females) due to type 2 diabetes mellitus. The mean age group of the patients was 64.2 ± 7.42. Patients with both non proliferative and proliferative retinopathy were included in the study. All the patients were referred by the Department of Diabetology, Madras Medical College Hospital after a thorough clinical and ophthalmic evaluation. Patients on treatment with anti-inflammatory drugs like steroids were excluded. Subjects with chorioretinal abnormalities, uncontrolled hypertension and other vasoproliferative disorders were excluded. The diagnosis of DR was performed by fundus examination after pupil dilation using slit lamp bio-microscopy. Under strict aseptic precautions fasting blood samples were collected by venepuncture. HbA1c was done for all the subjects. For VEGF estimation serum was separated and stored at -20 ºC. Serum VEGF levels were estimated using RayBio Human VEGF-A ELISA kit.

RESULTS

This study was conducted to study the correlation between glycemic control and the serum VEGF levels in retinopathy patients due to type 2 diabetes mellitus. 40 type 2 diabetics were subjected to the study and all the data were expressed as mean ± S.D. The results were interpreted using Pearson's correlation with the software SPSS version 21 for statistical significance.

Table 1 shows that HbA1c levels have a significant positive correlation with plasma VEGF concentrations (r: 0.8775,*P*< 0.001).

Fig 1, scatter diagram has HbA1c values on its X axis and VEGF values on its Y axis and it shows a significant positive correlation between the two parameters.

Mean HbA1c (%)	Mean VEGF (pg/ml)	R value	*P* value
6.97 ± 0.80	140.97 ± 42	0.8775	< 0.001**
P value < 0.05 – significant			

Table-1: Correlation of HbA1c and VEGF values

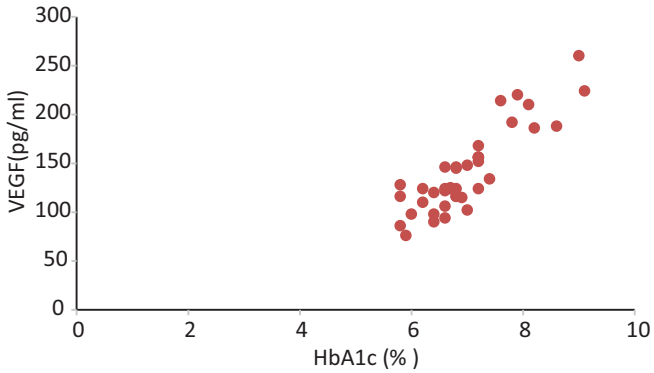

Figure-1: Correlation of HbA1c and VEGF levels

DISCUSSION

With the present number of diabetics in the world reaching epidemic proportions added with increased life expectancy and improved healthcare for them, the incidence of DR, a common microvascular complication of diabetes, is expected to rise to alarming levels. As DR can affect visual acuity and proliferative type of DR even leading to blindness, it is one of the important complications of diabetes which needs timely management. Chronic hyperglycemia and its sequelae are responsible for its pathogenesis. A number of interconnecting biochemical pathways have been proposed as potential links between hyperglycaemia and diabetic retinopathy, notably the polyol pathway, and activation of diacylglycerol- (DAG-) PKC pathways. These promote accelerated formation of advanced glycation endproducts (AGEs), oxidative stress and subclinical inflammation and leukostasis – all leading to accumulation of sorbitol and fructose within the nerve. This in turn leads to increased water content within the nerves, reduced membrane Na^+K^+ATPase activity and intra-axonal sodium accumulation which reduces nerve conduction velocity and brings about structural breakdown of the nerve. Local retinal ischemia causes secretion of substances like VEGF. The most important VEGF-mediated mechanism in the pathogenesis of diabetic retinopathy are the breakdown of the BB and angiogenesis, both considered as important events in the progression of proliferative DR and diabetic macular edema, which can lead to blindness. Study done by Wang et al[12] shows that there is a significant increase in plasma and vitreous VEGF levels in diabetic retinopathy patients when compared to normal healthy subjects.

Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Therefore, the HbA1c level reflects the mean glucose concentration over the previous period (approximately 8-12 weeks, depending on the individual) and provides a much better indication of long-term glycemic control than blood and urinary glucose determinations.

This study shows a significant positive correlation between HbA1C and serum VEGF values which is consistent with the

findings of Claus Zehetner et al.[13] Alsoa study by Kakizawa H et al[14] showed that plasma VEGF was elevated in poorly controlled diabetic patients compared with healthy subjects and plasma VEGF concentrations declined after hospitalized treatment with either insulin or oral hypoglycemic agents in combination with diet. There was a significant correlation between plasma VEGF concentration and both fasting plasma glucose (FPG) and HbA1c. So a good glycemic control can improve levels of VEGF and may provide beneficial effects on diabetic vascular complications.

CONCLUSION

The present study shows that poor glycemic control is significantly positively correlated with increased levels of plasma VEGF in patients with type 2 diabetes. So strict glycemic control and normalization of HbA1c is oneof the most effective ways to prevent progression of DR. As VEGF has been shown to be clearly implicatedin the development of DR, it affirmsthe importance of glycemic control inpatients with Diabetic Retinopathy.

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