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Original Article

Correlation of various serum biomarkers with the severity of diabetic retinopathy

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ABSTRACT

Hyperglycemia induced inflammation and angiogenic factors are implicated as a contributor to the onset and progression of diabetic retinopathy (DR) in type 2 diabetes mellitus patients (T2DM). Tumor necrosis factor (TNF-alpha) and C-reactive protein (CRP) are inflammatory cytokines which induce retinal VEGF and are involved in the progression of proliferative diabetic retinopathy (PDR). Therefore the aim of the present study is to investigate the relationship between diabetic retinopathy and systemic inflammation in patients with type 2 diabetes mellitus.

Materials and methods: Patients with T2DM, with or without diabetic retinopathy were included in the study. Serum inflammatory cytokines, vascular growth factor were studied in different stages of DR.

Results: Patients with T2DM with and without diabetic retinopathy were compared. Patients with diabetic retinopathy had increased serum levels of inflammatory cytokines CRP, TNF-alpha, as well as VEGF compared to serum levels of diabetic patients without retinopathy.

Conclusion: T2DM patients with retinopathy have higher levels of circulating inflammatory cytokines and VEGF compared to patients without retinopathy. These proinflammatory cytokines and angiogenic factors are involved in the progression of DR and proliferative diabetic retinopathy. The results showed the importance of inflammation and vascular endothelial growth factor in the progression of NPDR and PDR.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder charcterised by microvascualr and macrovascualr complication [1]. Common risk factors for diabetic complications are poor glycemic control, hypertension, obesity, hyperlidemia, duration of diabetes [2].

Diabetic retinopathy (DR) is a microvascular complication of diabetes and the leading cause of vision loss in T2DM patients in India and Asia [3]. Diabetic retinopathy is chracterised by microaneurysm which leads to hemorrhage and neovascualrisation in advanced stage of diabetic retinopathy i.e. proliferative diabetic retinopathy [4]. Inflammation and endothelial dysfunction are the important components responsible for the progression of diabetic retinopathy [5]. Hypertension, poor glycemic control and hyperlipidemia are considered as the important risk factors in the development of diabetic retinopathy [6]. Increased levels of circulating inflammatory cytokines have been shown to predict the onset and progression retinopathy.

Dysfunction of the vascular endothelium is an important factor in the pathogenesis of diabetic complications. Inflammation supported by endothelial cells through the synthesis of inflammatory molecules such as cytokines, chemokines and adhesion molecules in diabetic patients plays an important role in the progression of diabetic retinopathy [7]. Several studies on animals and human tissue have reported elevated inflammatory cytokines and adhesion molecules in vitreous of diabetic patients [8].

The aim of the present study was to investigate whether there are differences between patients with T2DM with and without diabetic retinopathy with respect to inflammatory cytokines. Serum levels of TNF-alpha, CRP and VEGF were measured in

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diabetic retinopathy patients. The association of serum cytokines with the increasing and diabetic patients without retinopathy.

2. Subjects, materials and methods

2.1. Subjects

In the present study 200 randomly selected patients from retinal department of LV Prasad Eye Institute, GMR Varalakshmi campus, Vishakhapatnam was included in the study. Of the 200 subjects n = 50 healthy subjects (Group 1), n = 150 are T2DM patients among which n = 50 are diabetic patients without retinopathy (Group 2), n = 50 are diabetic patients with NPDR (non-proliferative diabetic retinopathy), n = 50 are diabetic patients with PDR (proliferative diabetic retinopathy). Diabetic retinopathy stage was estimated by retinal examination using Ophthalmoscope by an Ophthalmologist.

Subjects who are healthy normal and type 2 diabetic patients aged 40–80 years who gave the consent for the study were included in the study. Subjects who did not give the consent and below 40 years, pregnant women, type 2 diabetic patients with other diabetic complications other than DR were excluded from the study.

2.2. Materials and methods

Age, sex, body mass index, regular medication, duration of diabetes were recorded and history of retinopathy were recorded. Blood samples were collected from subjects for the biochemical estimations such as HbA1c (glycosylated haemoglobin) estimated by HPLC method, lipid profile and creatinine were estimated by colorimetric method using Excel kits in autoanalyser (CAREX), CRP were estimated by turbedometric analysis using Excel kits in auto analyser (CAREX), tumor necrosis factor (TNF-alpha) and vascular endothelial growth factor (VEGF) were estimated by Elisa method using Elisa micro plate reader (Lisaquant 3000, TULIP Diagnostics Pvt Ltd).

2.3. Ethics statement

The present study was approved by the ethics committee of LV Prasad Eye Institute, GMR Varalakshmi campus, Vishakhapatnam and followed the guidelines of the Helsinki declaration.

2.4. Inflammatory cytokines assays

Serum was collected from patient blood by centrifugation (3000 rpm, 15 min) and frozen at −20 °C. Serum was analysed in a 100 count microplate ELISA reader for the estimation of TNF-alpha (pg/ml), VEGF (pg/ml), insulin (μIU/ml) were estimated by standard clinical laboratory methods using Biospes Elisa kits procured from InfoBio, Mumbai. ELISA analysis were performed according to the manufacture's instruction and all standards were within limits of detection.

2.5. Statistics

Statistical analysis was performed using SPSS 7.0 (SPSS, IBM). The comparative analysis between the different groups was performed using Krushkal Walis test, ANOVA was used for analyse values with normal distribution. The accepted level of significance for all analysis was $P < 0.05$ and $P < 0.1$.

2.6. Results

Depending on the presence and severity of DR of the more severely affected eye, the patients with DR were divided into NPDR, PDR. Patients with diabetic retinopathy (11.2 ± 0.4) had significantly higher HbA1c-levels compared to the patients without diabetic retinopathy (8.4 ± 1.6, $P = 0.011$). Metabolic control, insulin and creatinine levels showed a significant difference among different groups was shown in (Table 1).

Statistically significant differences were only found in CRP, TNF-alpha and VGEF levels among different groups, with the highest levels found in PDR and NPDR groups of diabetic patients with retinopathy ($P \leq 0.023$) compared to diabetics without retinopathy ($P \leq 0.014$) and normal healthy subjects ($P \leq 0.034$) (Table 2).

The multifunctional growth factor (VEGF), is involved in the development of diabetic retinopathy (ref), ($P = 0.05$) which was shown in the present study. Inflammation is a mediator in endothelial dysfunction, and is involved in the development of diabetic retinopathy (Kocabora M Selim, 2010). In the present study, above Table 2 showed that diabetic retinopathy patients have statistically significant elevated serum levels of CRP ($P = 0.005$) and TNF-alpha ($P = 0.0001$) compared to diabetics without retinopathy.

Elevated levels of CRP, TNF-alpha and VEFG were seen in comparison of different subgroups based on the severity of diabetic retinopathy. Where significant difference of these markers was observed among NPDR and PDR groups. The presence and severity of DR correlated with the serum levels of CRP, TNF-alpha, and VEGF (Fig. 1).

3. Discussion

In the present study inflammatory parameters and VEGF were compared in patients with and without diabetic retinopathy in type 2 diabetic patients. Increased levels of inflammatory parameters (TNF-alpha, CRP) were observed in diabetic retinopathy patients compared to patients without retinopathy. In addition similar result was also observed with vascular endothelial marker VEGF levels in diabetic retinopathy patients [9]. Moreover, the levels of these parameters were also high in PDR group compared to NPDR groups.

Increased CRP levels in the progression of Diabetic retinopathy was due to retinal tissue damage and triggering the complement activation like TNF-alpha and angiogenesis of the retinal vascular system leading to more severe disease. It is one marker which shows significant rise when diabetics develop vascular

Table 1
Laboratory variables of the patients studied. Glycosylated haemoglobin, insulin levels and lipids profile.

Variables measured	Normal	Diabetic without retinopathy	Diabetic retinopathy		P value
			NPDR	PDR	
HbA1c (%)	5.43 ± 2.4	8.42 ± 1.6	10.6 ± 0.2	12.4 ± 0.6	0.0015
Insulin (μUI/ml)	29.11 ± 1.3	47.42 ± 3.3	24.12 ± 2.2	22.87 ± 3.3	0.0023
Creatinine (mg/dl)	0.63 ± 1.3	0.95 ± 0.3	1.01 ± 0.4	1.21 ± 0.2	0.032

HbA1c: Glycosylayted haemoglobin; all the values are expressed as Mean ± SEM. Comparison among groups was done using Krushkal-Wallis test, where $P \leq 0.001$ and $P \leq 0.05$ is considered as significance.

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