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Serum Haptoglobin, Ceruloplasmin and CRP Levels: Markers of Diabetic Retinopathy

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Abstract - Background : Inflammation has been recognised as a critical contributor to retinal capillary closure, one of the main pathogenic event in diabetic retinopathy. The relationship between acute phase markers of inflammation and diabetic retinopathy was studied. Materials and Methods : 60 Type 2 Diabetes patients attending OPD/IPD of Tertiary care hospital were included. They were divided into three groups of 20 each. Group I: without retinopathy. GroupII: with non proliferative diabetic retinopathy (NPDR). GroupIII: with proliferative diabetic retinopathy (PDR). Results were compared with 20 normal controls. FBS, HbA1c, haptoglobin, ceruloplasmin and CRP were analysed on auto analyzer Hitachi 911(Roche)..

Keywords : Non proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), acute phase proteins, ceruloplasmin, haptoglobin and CRP.

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Serum Haptoglobin, Ceruloplasmin and CRP Levels: Markers of Diabetic Retinopathy

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Results : Diabetic patients with retinopathy had significantly higher levels of ceruloplasmin compared to normal controls ($p<0.05$ & <0.01 respectively). Diabetic patients with or without retinopathy had significantly raised levels of serum haptoglobin compared to control ($p<0.05$). NPDR patients had significantly raised levels of haptoglobin when compared to group I patients. CRP levels in patients of retinopathy were elevated compared to normal controls and diabetics without retinopathy ($p<0.05$).

Conclusion : Levels of ceruloplasmin, haptoglobin and CRP were significantly increased in diabetic retinopathy as compared to controls and patients without retinopathy. This may point to increase in serum viscosity leading to micro vascular sequelae. These proteins may serve as marker for progression of diabetic retinopathy.

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I. Introduction

Micro vascular complications cause serious morbidity in diabetics. Diabetic retinopathy is the most frequent vision threatening complication in these patients[1]. Understanding the cause and course of diabetic vascular pathology is important. Diabetic retinopathy is multifactorial complication. Persistent hyperglycemia causes metabolic stress (via sorbitol pathway) responsible for early retinal capillary dysfunction and lesions as micro aneurysm, basement membrane thickening, increased permeability and alteration of retinal blood flow[2]. The importance of thrombotic tendency in the aetiology of diabetic retinopathy is widely accepted which in turn may be related to protein composition changes in the plasma.

Haptoglobin, haemoglobin binding protein, plays role in providing protection against heam driven oxidative stress but raised levels as seen in acute phase reaction can increase serum viscosity having important implication in microcirculation pathology[3]. Ceruloplasmin, a copper containing metalloenzyme, possesses antioxidant property (e.g. ferroxidase activity), but elevated levels can promote vasculopathic effect[4]. Systemic inflammation marker CRP is synthesized in hepatocyte in response to cytokines released from site of inflammation. Raised levels of CRP are suggestive of low grade inflammation and are independent marker of vascular disease in diabetes[5]. Chronic inflammation can be potential mediator of diabetic retinopathy and measurement of inflammation markers like CRP, haptoglobin and ceruloplasmin may identify patients at higher risk of progression of disease. Relationship between stages of diabetic retinopathy and inflammation activity was also studied.

II. Material And Methods

60 male and female patients of Type 2 Diabetes (age 40-70 years) visiting Ophthalmology OPD of Tertiary care hospital were included in the study. Patients with previous history of any ocular inflammatory disease or acute inflammatory disease process were excluded from the study. Patients were divided into three groups of 20 each. Group I: without retinopathy, Group II: with NPDR and Group III: with PDR. Results were compared with 20 normal age and sex matched controls (non diabetic)

Overnight fasting blood sample was collected for biochemical investigations. FBS, HbA1c, haptoglobin, ceruloplasmin and CRP were analysed on auto analyzer Hitachi 911(Roche).

The fundus was examined by direct ophthalmoscopy, indirect ophthalmoscopy and/ or slit lamp bio microscopy using +90 D, +78 D lenses. Fundus fluorescein angiography was performed where

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clinically needed. Study protocol was approved by ethical committee of the institution.

III. Statistical Analysis

Mean and standard deviation were computed. The difference between two groups was seen by applying t-test. The level of significance considered was 0.05.

IV. Results

The mean age of patients of PDR (group III) was higher than patients in other two groups. Retinopathy patients had longer duration of diabetes as compared to patients who had no fundus changes (table 1). FBS of all the patients was >140mg/dl and HbA1c was > 7.0 g% showing poor glycemic control.

Diabetic patients with retinopathy (group II&III) had significantly higher levels of ceruloplasmin as compared to normal controls ($p<0.05$ & <0.01 respectively). Diabetic patients with or without retinopathy had significantly raised levels of serum haptoglobin compared to controls ($p<0.05$). NPDR patients had significantly raised levels of haptoglobin when compared to group I patients. CRP levels in patients of retinopathy were elevated as compared to normal controls and diabetics without retinopathy ($p<0.05$) Table II.

V. Discussion

In an attempt to identify the etiological factors and possible risk in the pathogenesis of retinal micro vascular changes, acute phase proteins were studied in various stages of diabetic retinopathy. Its precise cause is uncertain but there is evidence that an imbalance in haemostatic mechanism may be entailed in its initiation and progression. Pathophysiological changes include retinal capillary closure, thrombosis, non-perfusion, capillary leakage and increased serum viscosity[6]. Severity of retinopathy is known to increase with duration of disease as observed in the present study[7]. This may be due to damage caused to retinal vasculature by long standing metabolic abnormality. Excess glucose is metabolised via sorbitol pathway creating metabolic stress in vascular cells, which can impaired cells ability to handle free radicals. Excess glucose can also be channelled to form diacyl glycerol activating protein kinase C pathway and hyperglycemia can cause non enzymatic glycosylation of various proteins making them non functional[8].

There is metabolic and oxidative stress in uncontrolled diabetes, ceruloplasmin is thought to be a scavenger so its levels increase. But high levels of ceruloplasmin can cause vascular injury by generating free radicals and oxidizing LDL making it more atherogenic. ROS disrupt copper binding to ceruloplasmin, thereby impairing its normal protective function as liberated copper may promote oxidative pathology[9]. Ceruloplasmin levels were significantly higher in retinopathy patients as compared to controls. Some studies have shown that it takes part in pathological development of diabetic retinopathy and had a close relation with severity of pathological changes[10-11].

Haptoglobin is a positive acute phase reactant giving protection against Hb induced oxidative stress. Its levels increased in diabetic patients and further elevated in patients with NPDR showing oxidative damage playing role in vascular complication. Surprisingly haptoglobin levels were lower in PDR patients compared to NPDR patients, probable reason may be haptoglobin is getting lost in proteinuria because PDR patients are more likely to have proteinuria as well. This needs further investigation. Other workers have also observed increase in haptoglobin levels in diabetic retinopathy patients. Serum haptoglobin correlates with serum viscosity and it has positive effect on erythrocyte aggregation kinetics[3,12-13]. Hence increased levels may be responsible for development of micro vascular disease.

Increased inflammatory activity in diabetic retinopathy, as reflected by significantly increased levels of CRP, is associated with endothelial dysfunction. CRP is not only an inflammation marker but does contribute in vascular pathogenesis. By triggering complement activation it may exacerbate tissue damage leading to more severe disease. It is one marker which shows significant rise when diabetics start developing vascular complications. Our results are in agreement with other studies[14-15].

VI. Conclusions

Inflammatory pathway plays pivotal role in development and progression of diabetic complications. Elevated concentration of CRP and haptoglobin may be good predictor of onset of micro vascular complications in diabetes. Further studies on CRP as a marker for different stages of retinal vascular disease are needed. So that early diagnosis and treatment can slow progression and prevent blindness.

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Table 1 : Mean age and duration of diabetes in & controls.

Groups	Age in years	Duration in years
Control	45.25±7.33	-
Group I	52.95±11.5	8.5±4.8
Group II	51.1±7.93	10.65±6.75
Group III	58±7.26*	13.9±7.19#

group III VS controls ----- */# p<0.05*
group III VS group I----------#

Table 2 : Mean ceruloplasmin, haptoglobin & CRP levels in diabetic patients with/without retinopathy & controls.

Investigations	Controls	Group I	Group II	Group III
Ceruloplasmin(mg/dl)	65.17±8.4	74.18±19.2	79.48±7.8*	81.01±14.16**
Haptoglobin (mg/dl)	179.4±132.7	274.2±126.4*	401.36±187.7**#	295.24±153.3*
CRP (mg/dl)	2.43±2.9	2.98±4.2	7.49±8.37*#	6.67±4.3*#

group I/group II/group III VS controls ----- */# p<0.05 ** p<0.01*
group II / group III VS group I----------#