

**Original article:**

## **Study of C - reactive protein and intraocular pressure in Type 2 Diabetics**

**Dr. Tasneem J Ansari, Dr. Prathamesh H Kamble, Dr. Vrushali Parate**

Assistant Professor, Physiology, NKP Salve Institute of Medical Sciences, Nagpur.

Assistant Professor, Physiology, B.J. Government Medical College, Pune.

Assistant Professor, Physiology, Punjabrao Deshmukh Memorial Medical College and Research Center, Amravati

---

### **Abstract**

Diabetes and its complications are spreading like an epidemic. Studies have proven diabetes as a subclinical inflammatory state. The present research was undertaken to study whether this inflammatory status in diabetics affects the eye. 50 Type 2 diabetic male subjects in the age group of 45 to 60 years, having duration of Diabetes more than 6 years were compared against 50 healthy age matched controls. Anthropometric measurements and Intraocular pressure of the subjects and controls were taken after which there blood investigations were done which included Fasting, Post meal blood sugar, Glycosylated hemoglobin, C-Reactive protein. The values obtained for weight, BMI, Fasting, Post meal blood sugar, Glycosylated hemoglobin, C-Reactive protein were significantly higher in Type 2 Diabetics as compared to controls. A positive linear correlation was found between glycated hemoglobin and C – Reactive protein levels suggesting that the long term glycemic status influence the C – Reactive protein levels. The significantly higher values of intraocular pressure in Type 2 Diabetics and positive linear correlation between glycated hemoglobin and intraocular pressure suggests that the long term glycemic status influences the intraocular pressure and that it may be one of the factors that might have led to increase in intraocular pressure. Thus improving blood sugar control may help improve intraocular pressure control. No correlation was found between intraocular pressure and C – Reactive protein levels suggesting that though diabetics are at increased risk of raised intraocular pressure, the subclinical inflammatory status associated with diabetes might not have contributed to it.

**Key words:** Type 2 Diabetics, C – Reactive protein, glycated hemoglobin

---

### **Introduction**

Diabetes is a syndrome complex and the only non infectious condition to be classified as a silent epidemic. Diabetes mellitus apart from hyperglycemia and insulin resistance is also characterized by oxidative stress and inflammation. Studies have confirmed reports in literature that a low grade inflammation exists in Type 2 diabetes mellitus patients<sup>(47)</sup> and any inflammatory response is associated with recruitment of inflammatory cells along with release of inflammatory mediators from these cells. The macrophage derived cytokines IL1 & IL6 are primarily responsible for acute phase response which is a protective change in plasma protein function by hepatocytes. C Reactive protein (CRP) is an acute phase protein & blood CRP level

rises from trace levels to high microgram/ml levels during inflammatory conditions/diseases. Also IL6 & CRP levels predict the development of Type 2 diabetes & support a possible role for inflammation in diabetogenesis.<sup>(1)</sup>

Diabetic eye complications extend from simple change in eye glass prescription to irreversible total blindness. It has been studied that incidence of chronic open angle glaucoma is more in diabetics than in non diabetics. It is also the most common cause of neovascular glaucoma.<sup>(2)</sup>The most common risk factor for glaucoma is a raised intraocular pressure and it is the most modifiable risk factor for glaucoma. So to study whether diabetes affects the IOP of the eye and whether it is

a risk factor for Glaucoma the present study was undertaken.

### **Material & Methods**

*Study set up:* The study was carried out in the Department of physiology at Indira Gandhi Government Medical College, Nagpur.

*Study group:* 50 Type 2 diabetic male subjects in the age group of 45 to 60 years, having duration of Diabetes more than 6 years were screened thoroughly and after fulfillment of the inclusion and exclusion criteria were included in the study. Females, smokers and subjects who were diagnosed cases of hypertension, CVD, congenital/ischemic heart disease, Rheumatoid arthritis, T.B, connective tissue diseases, inflammatory bowel diseases, COPD/respiratory diseases, glaucoma, iritis, myopia and those taking hypolipidemic drugs, NSAIDs, corticosteroids and thiazolidinediones were excluded from the study.

*Control group:* For comparison separate group of male subjects belonging to the same age group of 45 to 60 years and having nearly same height and built were selected. They belonged to the same ethnic group, socioeconomic status as that of the study group except that they did not have abnormal blood sugar levels (no history of diabetes or disorder of defective sugar metabolism). The selection of Control Group was based on detail history, physical examination and investigations as used for the Study Group. All the subjects from control group also met the exclusion criteria.

*Study protocol:* Clearance by Institutional Ethics Committee was obtained. After selection of the subjects, they were explained the detailed plan of work and aim of the present research project. A written informed consent was obtained from them. After selection, the subjects from both the Study and Control Group were given appointment and were asked to report in the department of physiology for measurement of anthropometric

parameters and blood investigations. The blood investigations included Fasting blood sugar (FBS) and Post meal blood sugar (PMBS) estimated by Glucose Oxidase Biosensor method, Glycosylated hemoglobin (HbA1c) estimated by cation – exchange resin method, C-Reactive protein (CRP) measured by a quantitative turbidimetric test, CRP Turbilatex method and Intraocular pressure (IOP) measured by Indentation Tonometry using Schiottz tonometer.

*Statistical analysis:* The statistical analysis of the observations was carried out. Mean and standard deviation was calculated and significance of difference was tested statistically by the unpaired student's "t test" at  $p \leq 0.05$ . Correlation was studied and was tested for statistical significance.

### **Results**

The study group and the control group were statistically comparable with respect to age. The weight and BMI of diabetics was significantly higher than the controls as shown in Table I.

The mean values obtained for FBS, PMBS, HbA1c, CRP, IOP were significantly higher in Type 2 Diabetic subjects as compared to controls as shown in Table no. II

Table no. III shows a significant positive co relation between glyated hemoglobin and C – Reactive protein and between glyated hemoglobin and intraocular pressure. No correlation was found between C – Reactive protein and intraocular pressure.

### **Discussion:**

The diabetics and the controls were age and height matched. The significantly higher values for weight and BMI for diabetics suggests that the diabetics were obese. Also the FBS, PMBS and HbA1c levels were higher in diabetics suggesting that they had poorly controlled diabetes. This hyperglycemic state leads to non-enzymatic glycation of intracellular and extra cellular proteins with the

formation of advanced glycation end products (AGEs), a heterogeneous group of compounds that have been implicated in the pathogenesis of many of the complications of diabetes<sup>(3),(4)</sup>.

Kathryn (2004) et al also suggested that low grade inflammation associated with diabetes and its complications might be mediated in part by AGEs.<sup>(5)</sup> Engagement of RAGE by AGEs activates key transduction pathways such as p21 ras, extra cellular signal-related kinases 1 and 2, and nuclear factor- $\kappa$ B, and this cascade of events leads to enhanced expression of proinflammatory mediators.<sup>(6)</sup> Macrophages release IL-6, Tumor necrosis factor-  $\alpha$ , & IL-1 $\beta$  upon stimulation with AGEs. The stimulation of monocyte\macrophage by AGEs might therefore be an initial signal of an inflammatory cascade leading to CRP production in the liver. E.Wright JR et al in 2006 also suggested that AGEs trigger the production of reactive oxygen species (ROS). ROS are also produced as a result of glucose overload within the mitochondria. Once formed, ROS activate NF $\kappa$ B which results in the transcriptional activation of genes relevant for inflammation & one of the many sequel to the generation of ROS is cytokine induced stimulation of acute phase reactant synthesis such as CRP by the liver.<sup>(7)</sup> Similarly Caparevic Z et al (2006)<sup>(8)</sup>, Hala EL- Mesallamy et al (2007)<sup>(9)</sup> have also shown increased serum C Reactive protein levels in diabetics.

The IOP was found to be significantly increased in Diabetics as compared to controls. These findings are in congruence with the findings of Klein BE et al (1984)<sup>(10)</sup>, Dielemans I (1996)<sup>(11)</sup>, Wu SY et al (1997)<sup>(12)</sup>. The factors responsible for the increase in IOP as suggested by Clark CV 1986 and Cristiansson in 1961 were autonomic dysfunction or genetic factors.<sup>(13),(14)</sup> Hollows FC in 1966 had suggested that the elevated blood glucose levels in diabetes may induce an osmotic

gradient and attract fluid into the intraocular space, resulting in elevated IOP.<sup>(15)</sup> Davis et al in 1984 have reported that the glucose levels in aqueous humor of patients with diabetes were significantly higher compared to the levels in persons without diabetes<sup>(16)</sup>. Tsuyoshi Sato in 2002 also observed that a high glucose level; up regulates fibronectin expression in trabecular meshwork cells. It is thus possible that the over expression of fibronectin in the trabecular meshwork cells of patients with diabetes may play a role in the resistance\blockage of aqueous outflow and contribute to elevated IOP.<sup>(17)</sup>

Tsuyoshi Sato in 2002 also observed that the trabecular meshwork cells when grown in high glucose medium exhibit reduced cell proliferation and this may be linked to the excess fibronectin synthesis.<sup>(17)</sup> Alvarado J in 1984 had suggested that the loss of trabecular meshwork cells could result in a reduced outflow facility thus leading to elevated IOP.<sup>(18)</sup>

Thus, the trabecular meshwork cells when exposed to high glucose milieu from the aqueous humor leads to fibronectin up regulation, alters the structural component, compromises resiliency, reduces cellularity, blocks aqueous outflow in trabecular meshwork and leads to increase in IOP. This increase in IOP may thus increase the risk of Glaucoma in the Diabetics.<sup>(17)</sup> The statistical correlation coefficient of 0.547 between glycated hemoglobin and serum C - reactive protein levels is in agreement with the findings of Dana E. King et al (2003)<sup>(19)</sup>, Pftzner A (2006)<sup>(20)</sup> who also reported significant correlation between glycated hemoglobin and C – Reactive protein levels.

Studies have shown that levels of C - reactive protein may increase as the percentage of glycated hemoglobin increases i.e. more is the blood sugar level (uncontrolled diabetes) more may

be the inflammation, endothelial dysfunction, and insulin resistance at the physiologic level.<sup>(21)</sup>

The correlation between glycated hemoglobin Farnaz Memarzadeh et al (2008)<sup>(22)</sup>, Dielemans I et al (1996)<sup>(23)</sup> who also showed a positive association between them. In our study those with higher HbA1C values also had higher IOP. This observation gives the meaning that the glycated hemoglobin may be one of the factor leading to increased IOP in diabetics and thus suggesting that improved blood sugar control may indeed help improve IOP control.

The correlation between intraocular pressure and C – Reactive protein was non significant. Simone de Voogd (2006) also did not find any correlation between IOP and CRP<sup>(24)</sup> suggesting that though IOP was elevated in diabetics, the cause for this elevation may not be inflammation. To conclude, Diabetes is associated with a chronic subclinical inflammatory state as evidenced by increase in CRP level but it is not related to and may not be a factor leading to increase in IOP in diabetics. Other factors like vascular dysregulation<sup>(24)</sup>, genetic factors<sup>(24)</sup>, neovascularisation, increase in the amount of aqueous humor (caused due to the increased glucose levels in the aqueous humor causing osmosis)<sup>(16)</sup>, upregulation in the fibronectin expression<sup>(17)</sup> and reduction in the cellularity<sup>(18)</sup> of the trabecular meshwork may be responsible for the raised IOP in diabetics.<sup>(24)</sup>

**Conclusion :**

The increase in the incidence of Type 2 Diabetes is mainly the result of genetic predisposition and a higher standard of living that has changed eating habits and led to a more sedentary lifestyle. Lifestyle interventions such as exercise and weight loss and therapy with statins and ACE inhibitors have been shown to be effective in lowering CRP and other inflammatory markers, improve insulin sensitivity and endothelial function. Thus modification of unhealthy diet and lifestyle factors and use of pharmacological agents with anti-inflammatory properties may help in diabetes prevention and treatment.

It has been long appreciated by physicians that diabetic patients develop cardiovascular disease more commonly than similarly aged patient. That there might be an underlying chronic inflammatory process is a story that has been unfolded in the last few years. These path physiologic insights lead the practitioner to intervene in a number of ways before the patient experiences a first potentially catastrophic event. CRP may thus act as a valuable diagnostic and prognostic marker of further diabetic complications including cardiovascular risk. Also, routine eye screening in diabetics may help in detecting the ocular diseases early and tight control of the long term glycemic status may help in reducing the risk of Glaucoma and associated blindness in the diabetic subjects.

Table I: Comparison of Weight and BMI

Variable	Study group Mean ± Std.Deviation	Control group Mean ± Std.Deviation	p value
Weight	59.36 ± 7.928	56.08 ± 6.586	0.028*
BMI	23.81± 3.113	22.30 ± 3.420	0.024*

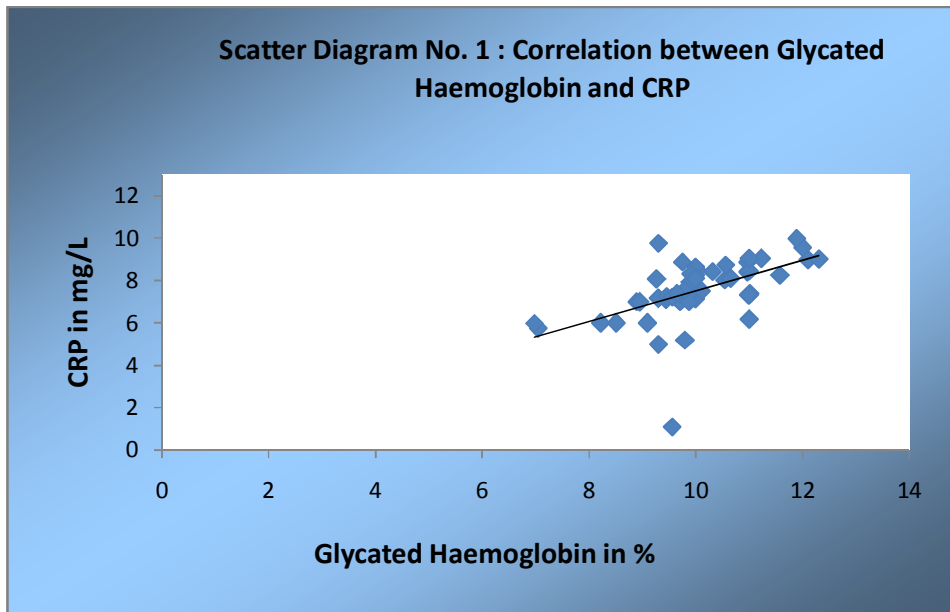
\*-denotes statistically significant

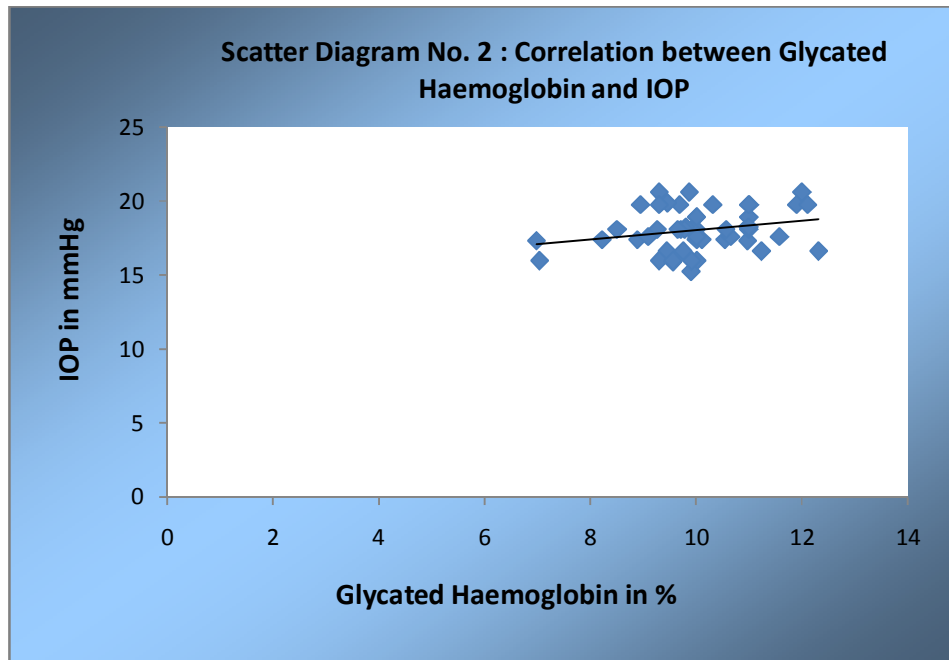
Table II: comparison of FBS, PMBS, HbA1c, CRP, IOP

Variables	Study group Mean $\pm$ Std.Deviation	Controls Mean $\pm$ Std.Deviation	P value
FBS	172.22 $\pm$ 21.56	91.16 $\pm$ 12.34	<0.001*
PMBS	299.80 $\pm$ 21.70	123.64 $\pm$ 8.26	<0.001*
HbA1c	10.04 $\pm$ 1.11	4.99 $\pm$ 1.15	<0.0001*
CRP	7.537 $\pm$ 1.47	3.98 $\pm$ 1.52	<0.0001*
IOP	17.53 $\pm$ 1.45	14.89 $\pm$ 1.43	<0.0001*

Table III: Correlation between HbA1c, CRP and IOP

Correlations	HbA1c*CRP	HbA1c*IOP	CRP*IOP
Pearson Correlation Coefficient (r)	0.547	0.478	0.215
p-value	<0.001*	<0.001*	0.136





#### References:

1. Hong Ding Chris R Triggle. Endothelial cell dysfunction & the vascular complications associated with type 2 diabetes: assessing the health of endothelium. *Vascular health & risk management* 2005;1(1):55-71.
2. Park, K. Text Book of Preventive and Social Medicine Jabalpur;M/S Banarsidas Bhanot Publishers 2005,pp- 311-315.
3. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end products:a review. *Diabetologica* 2001; 44:129-146.
4. Thornalley PJ. Cell activation by glycated proteins: AGE receptors, receptor recognition factors and functional classification of AGEs. *Cell Mol Biol* 1998;44:1013-1023.
5. Kathryn CB Tan, Wing- sun Chow, Sideny Tam, Richard Bucala, John Betteridge. Association between acute phase reactants and advanced glycation end products in type 2 diabetes. *Diabetes Care* January 2004;27:223-228.
6. Vlassara H, Brownlee M, Manogue KR, Dinarello CA, Pasagian A. Cachectin\TNF and IL-1 induced by glucose modified proteins: role in normal tissue remodeling. *Science* 1998;240:1546-1548.
7. E Wright JR, JL Scism-Bacon and LC Glass. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int J Clin Pract.* March 2006;60(3):308–314.
8. Caparevic Z, Kostic N, Ilic S, Stojanovic D, Ivanovic AM. Oxidized LDL and C-reactive protein as markers for detection of accelerated atherosclerosis in type 2 diabetes. *Med Pregl* 2006 Mar-Apr,59(3-4):160-4.
9. Hala El-Mesallamy, Salwa Suwailem, and Nadia Hamdy: Evaluation of C - reactive protein, Endothelin-1, Adhesion molecule(s), and Lipids as Inflammatory markers in type 2 diabetes mellitus patients. *Mediators inflamm* 2007; 2007: 73635
10. Klein BE, Klein R, Moss SE. Intraocular pressure in diabetic persons. *Ophthalmology* 1984 Nov;91(11):1356-60
11. Dielemans I, DeJong PTVM, Stolk R, et al. Primary open angle glaucoma, intraocular pressure and Diabetes mellitus in the general elderly population:The Rotterdam Study. *Ophthalmology* 1996; 103:1271-1275.
12. Wu SY, Leske MC. Association with intraocular pressure in the Barbados eye study. *Arch Ophthalmol.* 1997;115:1572-1576.
13. Clark CV, Mapstone R. The prevalence of diabetes mellitus in the family history of patients with primary glaucoma. *Doc Ophthalmol.* 1986;62:161–163.[Pubmed]

14. Christiansson, J. Intraocular pressure in diabetes mellitus. *Acta. Oph.*, 39, 155, 1961.
15. Hollows FC, Graham PA. Intraocular pressure, glaucoma and glaucoma suspects in a defined population. *Br J Ophthalmol* 1966; 50:570-586.
16. Davies PD, Duncan G, Pynsent PB, Arber DL, Lucas VA. Aqueous humor concentration in cataract patients and its effect on the lens. *Exp Eye Res* 1984;39:605-09.
17. Tsuyoshi Sato and Sayon Roy. Effect of high glucose on fibronectin expression and cell proliferation in trabecular meshwork cells. *Investigative Ophthalmology and visual Science* January 2002,vol. 43, No.1:170-175
18. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. *Ophthalmology* 1984;91:564-79.
19. Dana EK, Arch GM, Thomas AB and William SP. C-Reactive Protein and Glycemic Control in Adults With Diabetes. *Diabetes Care* 2003; 26:1535-1539
20. Pftzner A, Forst T. High sensitivity C-reactive protein as cardiovascular risk marker in patients with Diabetes mellitus. *Diabetes Technol Ther* 2006 Feb;8(1):28-36.
21. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 2000;102:1000-1006.
22. Farnaz Memarzadeh, Mei Ying-Lai, Stanley PA, Rohit Varma, and Los Angeles Latino Eye Study Group. Associations with Intraocular Pressure in Latinos: The Los Angeles Latino Eye Study, *Am J Ophthalmol* 2008;146(1):69-76.
23. Dielemans I, DeJong PTVM, Stolk R, et al. Primary open angle glaucoma, intraocular pressure and Diabetes mellitus in the general elderly population: The Rotterdam Study. *Ophthalmology* 1996; 103:1271-1275.
24. Simone de Voogd, Roger CW Wolfs, Nomdo MJ, Jacqueline CM Witteman, Albert Hofman and Paulus TVM de Jong. Atherosclerosis, C - reactive protein, and Risk for Open-Angle Glaucoma: The Rotterdam Study. *Investigative Ophthalmology and Visual Science* sept. 2006, Vol. 47, No.9.

Date of submission: 02 March 2014

Date of Publication: 09 June 2014

Source of support: Nil; Conflict of Interest: Nil