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Systemic C-Reactive Protein Levels in Normal-Tension Glaucoma and Primary Open-Angle Glaucoma

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1. Introduction

Glaucoma is the second leading cause of visual loss worldwide [1-2]. It is becoming an increasing cause of blindness as the world's population ages, and perhaps presents an even greater public health challenge than the first-placed cataract, since the disease is irreversible. A recent estimate suggests that roughly 80 million people will be diagnosed with glaucoma by 2010, with 4.5 million of those suffering bilateral blindness [3]. Glaucoma is a general term for a group of ocular diseases characterized by progressive thinning of the neuroretinal rim of the optic nerve head and loss of the retinal nerve fiber layer, together with a particular pattern of visual field loss. Primary open-angle glaucoma (POAG) is the most common type of glaucoma, with a prevalence rate ranged from 0.5 to 8.8% in different population based prevalence studies [4-12]. The exact cause of glaucoma is still elusive yet after years of extensive research. Traditionally, elevated intraocular pressure (IOP) has been identified as a primary risk factor in this illness and IOP lowering remains the principle and the only available treatment. However, factors quite independent of IOP may be responsible for glaucoma [13]. Approximately one third to one half of patients with POAG consistently have IOPs within the normal range of less than 22 mmHg [14-17], identified as having normal tension glaucoma (NTG) [18]. Besides, some glaucoma patients continue to present disease progression despite effective lowering of IOP. The Early Manifest Glaucoma Trial (EMGT) showed that glaucoma progression rate in the treatment group was 45% as compared with 62% in the nontreated control group [19]. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), substantial visual field loss occurred in 10.7% of medically treated and 13.5% of surgical treated participants during 5 years of follow up [20]. It is clear that glaucoma is a multifactorial disease and cannot be prevented or cured by IOP reducing therapy alone.

Risk factors other than IOP elevation may be responsible for glaucoma progression. Several large scale trails have found aging, systemic blood pressure, nocturnal hypotension, ocular perfusion pressure, migraine, disk hemorrhage, and diabetes to be related to open-angle glaucoma (OAG). Vascular dysregulation and blood flow disturbances have been reported

as glaucoma is often accompanied by widespread cerebrovascular and systemic cardiovascular diseases [21]. Leske and colleagues had presented predictors of OAG disease progression in the EMGT trial including lower systolic perfusion pressure, lower systolic blood pressure, and cardiovascular disease history [22]. In the Rotterdam eye study, patients with an ocular perfusion pressure lower than 50 mmHg had a four times greater risk of developing OAG than those with a perfusion pressure of 80 mmHg [23]. The Egna-Neumarkt study found positive correlations between systemic blood pressure and both the diagnosis of OAG and elevated IOP [24]. Recently, perfusion instability, rather than a progressive decline in ocular blood flow, has been suggested to contribute to OAG. The capacity of an organ to maintain a constant blood flow or nutrient supply in response to local vascular parameter changes rely on its autoregulation [25]. Failure of stable blood flow regulation may lead to ischemic damage of the optic nerve or retinal ganglion cells. Challenges to normal ocular blood flow include increased IOP, fluctuating blood pressure, a resultant decrease in ocular perfusion pressure, or a rise in local tissue metabolic demands. The proposed underlying medical conditions which may contribute to ocular vascular regulatory dysfunction include atherosclerosis, vasospasm, and endothelial dysfunction.

Atherosclerosis is a chronic progressive vascular disease results from the deposition of lipids, inflammatory cells and connective tissue within arterial walls, leading to plaque formation and intimal thickening. Over time this results in obstruction to flow, compromised perfusion and tissue ischemia [26-27]. Decades ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate atherosclerosis and cardiovascular diseases. However, this prediction needed revision. Recent research has shown that inflammation and endothelial dysfunction play a key role in atherosclerosis. Aging, cigarette smoking, hypertension, diabetes, elevated low-density lipoprotein (LDL) levels, genetic alterations, elevated plasma homocysteine concentrations, and infectious microorganisms were shown to perturb the normal barrier and the secretory function of endothelial cells and alter the homeostatic properties of the endothelium [28-29]. The injury may initiate an inflammatory response in the artery wall, increase the adhesiveness of the endothelium to leukocytes or platelets, induce the endothelium to have procoagulant properties, and to form vasoactive molecules, cytokines, and growth factors. With the migration of smooth muscle cells which intermixed with macrophages and lymphocytes, a fibrous tissue developed overlying a core of lipid and necrotic tissue, the atheroma formed. The lesion may intrude the lumen and alter the blood flow [29-30]. Atherosclerosis is now clearly an inflammatory disease. Several different inflammatory markers with different biologic activities were reported to be involved in increased cardiovascular risk or disease progression [31-34]. Among which, C-reactive protein (CRP) was reported an independent risk factor for coronary artery disease in healthy population [31-32].

CRP is a primitive acute phase inflammatory protein released in response to acute injury, infection, or other inflammatory stimuli [35]. Discovered in 1930 by Tillet and Frances, CRP owes its name to the ability of this protein to precipitate pneumococcal C-polysaccharide in the presence of calcium. CRP is known to be produced primarily in the liver, synthesized by hepatocytes in response to intermediary inflammatory cytokines particularly IL-6. It reaches peak levels quickly in approximately 50 hours, falls once the inflammatory stimulus is removed and has a half-life of 18 hours, and is not subject to diurnal variation [36]. Other

possible sites of CRP expression include atherosclerotic plaque, normal human artery, heart, kidney and adipocytes [37-38]. The CRP levels vary in different age groups and races. Woloshin et al. reported the CRP levels in American adults increase from 1.4mg/L at age 20-30 to 2.7 mg/L at age > 80 [39]. Anand et al. reported that sampling from 4 communities in Canada, the CRP level is highest among the aboriginal Americans, followed by south Asians, Europeans, and lowest in Chinese [40]. Traditionally, serum CRP levels were measured by rate nephelometry, which had a poor sensitivity in detecting concentrations below 6 to 10 mg/L. With the introducing of a commercially available latex particle-enhanced immunoturbidimetric assay, the detecting limit can be lowered to 0.15mg/L, that is the so-called high-sensitivity CRP. CRP has recently been proposed as a marker of inflammation involved in endothelial dysfunction and atherogenesis [41-42]. Clinical studies have shown that elevated CRP levels in healthy populations predict vascular events such as myocardial infarction (MI) and stroke, as well as the development of diabetes. The guidelines for cardiovascular diseases have recommended using CRP for population screening or to monitor treatment [43].

In glaucoma, several reports have identified compromised peripheral endothelial cell function in patients with NTG and OAG [44-47]. However, a corollary correlation between atherosclerosis and OAG has yet to be identified, and very few reports had addressed the relationship between CRP and glaucoma. Leibovitch et al. reported that the CRP levels was significantly elevated in the patients with NTG [48]. On the other hand, the Rotterdam eye study found neither atherosclerosis nor serum CRP to be important risk factors for the development of OAG [27]. Su et al. reported that after carefully excluding patients with systemic diseases such as diabetes mellitus, hypertension, hypercholesterolemia, ischemic heart disease and cerebrovascular accidents, there was no statistically significant difference in the CRP levels between NTG, POAG and control subjects. Their finding suggested that the previously reported CRP elevation in the NTG patients could possibly be a confounded result [49]. Data from the Korean population reported by Choi et al. also supported this finding [50]. Certain diseases such as coronary artery disease (CAD), CAD's associated risk factors, and medications such as calcium channel blockers, angiotensin converting enzyme inhibitors (ACEIs), lipid lowering drugs, aspirin, nitrate, or hormone replacement therapy can affect the CRP level. Therefore, it would be more appropriate to determine the association between CRP and glaucoma after excluding those patients with systemic diseases [51-56].

Being a marker of systemic inflammation, how CRP plays a pathogenic role in the vascular endothelium is a subject of debate. Previously CRP was believed to be produced exclusively in the liver, but recent data suggests that CRP is also produced in human atheroma [38, 57-58]. CRP was reported to have numerous effects on endothelial cells that could support a pro-inflammatory, pro-thrombotic role [59], but some investigators have shown that through protecting the eNOS protein expression, CRP may play a compensatory role in the arterial endothelium locally during inflammation [60]. Whether CRP is harmful or beneficial in the vascular micro-environment and whether it is a cause or a result of endothelial dysfunction in glaucoma requires further investigation. The negative results between CRP and glaucoma implied that either the systemic CRP level does not reflect its local influence, or that the CPR abnormality does not exist in patients with glaucoma.

A marker intended for screening, diagnosing, or guiding therapy requires good sensitivity, specificity and predictive values. Sometimes markers can be highly associated with an outcome, especially with large sample sizes, but still have very poor diagnostic accuracy. The prevalence of CAD is low compared to the high prevalence of a mildly elevated CRP, thus the positive predictive values are low in the general population.[61] Given the even lower prevalence of glaucoma, the value of CRP for a risk assessment seems limited. CRP will be more useful if it is mechanistically related to glaucoma, especially when its modulation affects the disease outcome. The range in the variation of CRP level is wide and can be influenced by many systemic diseases or drugs. Thus the application of using the systemic CRP level to evaluate patients with POAG or NTG requires more verification.

Authors	Study design	Subjects / Ethnicity	Findings
Leibovitch et al. (2005) [48]	Case control study	20 NTG, 30 controls / Israel	NTG patients had higher high-sensitivity CRP level
De Voogd et al. (2006) [27]	Prospective population-based cohort study	3842 patients, mean followed-up 6.5 years / Netherlands	Serum high-sensitivity CRP level was not an important risk factor for OAG
Su et al. (2006) [46]	Case control study	40 NTG, 40 controls / Taiwan	High-sensitivity CRP level did not differ between NTG and controls
Su et al. (2007) [49]	Case control study	40 NTG, 40 POAG, 40 controls / Taiwan	No difference in the high-sensitivity CRP level between NTG, POAG and controls
Su et al. (2008) [47]	Case control study	30 NTG, 30 POAG, 30 controls / Taiwan	High-sensitivity CRP level did not differ between NTG, POAG and controls
Choi (2009) [50]	Case control study	38 NTG, 38 controls / Korea	No difference in the high-sensitivity CRP level between NTG and controls

CRP: C-reactive protein, NTG: normal-tension glaucoma, OAG: open-angle glaucoma, POAG: primary open-angle glaucoma

Table 1. Summary of the findings of the studies evaluating serum CRP levels in glaucoma patients

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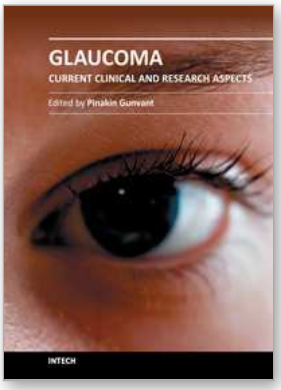

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