

Metabolic abnormalities in patients with primary open-angle glaucoma

Moses Elisaf¹, George Kitsos², Eleni Bairaktari³,
Rigas Kalaitzidis¹, Christos Kalogeropoulos² and Kostas Psilas²

Department of Internal Medicine¹, Department of Ophthalmology², Laboratory of Biochemistry³, University Hospital, University of Ioannina, Ioannina, Greece

ABSTRACT.

Purpose: Although there are few data on the underlying mechanisms of primary open-angle glaucoma (POAG), it has been suggested that metabolic diseases may play a role in the evolution of the disease. We carried out the present study to investigate the involvement of metabolic disturbances in POAG pathogenesis.

Material/methods: Serum metabolic parameters were evaluated in 49 POAG patients without a known history of diabetes mellitus and 72 age and sex matched individuals without glaucoma (control group).

Results: Among the metabolic parameters examined, only fasting serum glucose and uric acid levels were found significantly higher in patients with glaucoma compared to the control population (117 ± 17 mg/dl vs 105 ± 11 mg/dl, $p=0.05$ and 6.2 ± 1.9 mg/dl vs 5 ± 1.2 mg/dl, $p=0.006$, respectively). Additionally, a considerably greater proportion of patients had disturbances of the carbohydrate metabolism and hyperuricemia.

Conclusion: We conclude that disturbances of carbohydrate and uric acid metabolism could play a role in glaucoma damage and pathogenesis.

Key words: diabetes mellitus – glucose intolerance – hyperuricemia – metabolic abnormalities – primary open-angle glaucoma – uric acid.

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Primary open-angle glaucoma (POAG) is a major cause of blindness. However, there are limited data concerning the underlying mechanisms of the disease. It has been suggested, although disputed, that diabetes mellitus and blood pressure changes may play a role in POAG pathogenesis (Wilson et al. 1987; Dielemans et al. 1996; Mitchell et al. 1997; Tielsch et al. 1997). There is a paucity of data with regard to the contribution of other metabolic factors in the etiology of the disease. We undertook the present study to evaluate risk factors for POAG among patients who were followed up in our Ophthalmology Clinic and were investigated for the presence of metabolic disorders.

Material and Methods

We studied 49 patients with POAG for more than 3 years and 72 age and sex matched individuals with normal intraocular pressure (control group). Glaucoma patients used topical antiglaucomatic treatment [beta-blockers, such as timolol (14 patients) and betaxolol (19 patients), or pilocarpine (8 patients), dipivefrine (6 patients), and dorzolamide (6 patients); 4 patients used combination therapy with a beta-blocker and one of the other drugs] and the intraocular pressure did not exceed the 22 mmHg (17.8 ± 1.1 mmHg). No patient had undergone previous ocular surgery. Patients and controls with a known history of diabetes mellitus or pri-

mary dyslipidemia necessitating the use of hypolipidemic drugs were excluded. Additionally, subjects on drugs that potentially affect serum metabolic parameters (allopurinol, uricosuric drugs, corticosteroids, thiazides, beta-blockers, losartan, etc) were not included in the study. At the Clinic a detailed medical history was obtained including a history of hypertension, systemic vascular disease, and the use of antihypertensive or other drugs. Furthermore, in all individuals a complete ophthalmologic history was taken and a full ophthalmologic examination was carried out including: visual acuity, slit lamp examination, applanation tonometry (three times daily: 8 a.m., 2 p.m., 9 p.m.), gonioscopy, fundus examination (cup/disc ratio) and examination of the visual field (Humphrey automated perimetry, full-threshold 30–2). The criteria for definite POAG were based on the presence of both visual field defects and optic disk damage on the open-angle of anterior chamber and the deep anterior chamber, without the presence of characteristics of congenital or secondary, rubeotic or angle-closure glaucoma (Mitchell et al. 1997; Asman & Heijl 1992; Leske et al. 1994; Leske et al. 1995).

After a 14 h overnight fast, blood samples were obtained for the determination of serum glucose, insulin, uric acid, urea, creatinine and lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoproteins A1 and B and lipoprotein (a) [Lp(a)]. Body weight and height were recorded and body mass index (BMI) was calculated. A 24 h urine specimen was tested for protein and creatinine. Microalbuminuria was also assessed

in a 24 h urine sample. An oral glucose tolerance test was performed using 75 g of glucose and serum glucose and insulin levels were measured two hours later.

Individuals with seated blood pressure >140/90 mmHg or on antihypertensive drugs were regarded as hypertensives. We classified lipid disorders as follows (Elisaf et al. 1997): hypercholesterolemia was defined as a serum level of LDL cholesterol >160 mg/dl, hypertriglyceridemia as a serum triglyceride level >200 mg/dl, and hypoalphalipoproteinemia as a serum level of HDL cholesterol <35 mg/dl for men and <45 mg/dl for women. Subjects with high serum ApoB levels (>130 mg/dl) were considered to have hyperapobetalipoproteinemia and individuals with increased (≥ 25 mg/dl) serum Lp(a) levels were considered as having Lp(a) excess. Hyperuricemia was defined as serum uric acid levels >6 mg/dl for women and >7 mg/dl for men. According to the new proposed criteria, the diagnosis of diabetes mellitus relied on a fasting serum glucose level of ≥ 126 mg/dl, or a two hour serum glucose of 200 mg/dl during an oral glucose tolerance test using a glucose load that contains the equivalent of 75 g of an anhydrous glucose dissolved in water. Impaired fasting glucose was defined as a fasting serum glucose level greater than 110 mg/dl but less than 126 mg/dl (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). We also diagnosed impaired glucose tolerance in individuals with fasting glucose <126 mg/dl and a two hour post load serum glucose >140 mg/dl but lower than 200 mg/dl according to the previous WHO criteria.

Laboratory determinations

Serum cholesterol and triglyceride were determined by enzymatic colorimetric assay using the Olympus AU560 Clinical Chemistry analyser (Olympus Diagnostica, Hamburg, Germany), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulphate-magnesium. LDL cholesterol was calculated using the Friedewald formula (Friedewald et al. 1972). Serum ApoA1 and ApoB were measured by immunonephelometry on a Behring BN100 Nephelometer (Dade Behring, Liederbach, Germany). Lp(a) levels were determined by the enzyme immunoassay Macra Lp(a) (Trinity Biotech, Jamestown, NY, USA). The lower limit of detectability was 0.8 mg/dl. In cases of Lp(a) levels lower than

Table 1. Clinical parameters of the study population.

Parameters	Patients with POAG (n=49)	Control population (n=72)	p
Age (years)	65 \pm 9	63 \pm 8	NS
Sex (M/F)	34/15	52/20	NS
History of hypertension (n, %)	19 (38.8)	27 (37.5)	NS
Blood pressure (systolic, diastolic), mmHg	132 \pm 12/82 \pm 14	130 \pm 11/80 \pm 15	NS
Smoking (n, %)	16 (32.6)	21 (29.2)	NS
Body weight (kg)	65.4 \pm 13.2	65.7 \pm 12.0	NS
Body mass index (kg/m ²)	25 \pm 13	24 \pm 2	NS
Drugs (n, %)			
Aspirin	11 (22.5)	15 (20.9)	NS
Calcium channel blockers	11 (22.5)	14 (19.5)	NS
Angiotensin converting enzyme inhibitors	6 (12.2)	7 (9.7)	NS

Table 2. Metabolic parameters of the study population.

Parameters	Patients with POAG (n=49)	Control population (n=72)	p
Fasting glucose (mg/dl)	117 \pm 17	105 \pm 11	0.05
2H glucose (mg/dl)	164 \pm 69	142 \pm 58	NS
Fasting insulin (mU/L)	8.6 \pm 4.5	8.9 \pm 4.0	NS
2H insulin (mU/L)	75.8 \pm 70.6	64.8 \pm 64.6	NS
Uric acid (mg/dl)	6.2 \pm 1.9	5.0 \pm 1.2	0.006
Total cholesterol (mg/dl)	233.7 \pm 45.9	237.5 \pm 49.0	NS
HDL cholesterol (mg/dl)	50.6 \pm 14.9	51.8 \pm 14.4	NS
LDL cholesterol (mg/dl)	160 \pm 36	156 \pm 42	NS
Triglycerides (mg/dl)	145.3 \pm 49.4	152.7 \pm 64.8	NS
Apolipoprotein A1 (mg/dl)	156.9 \pm 25.9	162.5 \pm 29.0	NS
Apolipoprotein B (mg/dl)	134.4 \pm 35.2	131.4 \pm 33.6	NS
Lipoprotein (a) (mg/dl)	11.9 \pm 12.5	12.15 \pm 11.8	NS
Proteinuria (mg/24 h)	32.9 \pm 36.4	39.0 \pm 36.3	NS
Microalbuminuria (mg/24 h)	13.4 \pm 23.1	11.0 \pm 11.5	NS

0.8 mg/dl, the value of 0.8 mg/dl was used for statistical reasons. Serum and urine uric acid levels were determined by a uricase/PAP method, while plasma glucose levels were measured by the hexokinase method. Insulin levels were determined by a Microparticle Enzyme Immunoassay (MEIA) on a AXSYM analyser (ABBOTT GmbH Diagnostika, Wiesbaden-Delkenheim, Germany). Urine total protein was measured by a turbidimetric method using sulfosalicylic acid for the precipitation of proteins as fine particles and quantification of the turbidity produced at 620 nm. Urinary albumin concentration (microalbuminuria) was measured by immunonephelometry on a Behring BN100 nephelometer (Dade Behring, Liederbach, Germany).

Statistical analysis

The results were expressed as means \pm SD. Unpaired students' t-test or Mann Whitney U-test were used for statistical analysis where appropriate. The chi-square test

was used to test the differences in frequencies. Statistical significance was accepted at $p < 0.05$.

Results

Clinical parameters of the study population are shown in Table 1. The two groups were well controlled in terms of age, sex, body weight, BMI, smoking habit, history of hypertension, blood pressure values or prescribed drugs. As shown in Tables 2 and 3 there were no differences in serum lipid levels or in the incidence of dyslipidemia between the two groups. However, patients with glaucoma had significantly increased fasting serum glucose and uric acid levels compared to the control group. Furthermore, even though we excluded subjects with a known history of diabetes mellitus, a considerably greater proportion of patients had disturbances of the carbohydrate metabolism (Table 3). Thus, a

Table 3. Incidence of metabolic abnormalities of the study population.

Disturbance	Patients with POAG		Control population		P
	n	%	n	%	
Diabetes mellitus*	8/49	(16.3%)	2/72	(2.8%)	0.05
Impaired fasting glucose*	27/49	(55.1%)	19/72	(26.4%)	0.05
Impaired glucose tolerance**	27/49	(55.1%)	22/72	(30.5%)	0.05
Hyperuricemia	17/49	(34.7%)	9/72	(12.5%)	0.05
Hypercholesterolemia	17/49	(34.7%)	24/72	(33.3%)	NS
Hypertriglyceridemia	9/49	(18.4%)	8/72	(11.1%)	NS
Hypoalbuminemia	5/49	(10.2%)	7/72	(9.7%)	NS
Hyperapobetalipoproteinemia	20/49	(40.8%)	27/72	(37.5%)	NS
Lp(a) excess	5/49	(10.2%)	7/72	(9.7%)	NS

* According to the new proposed criteria (9). ** According to the previous WHO criteria.

considerable proportion of glaucoma patients comply with the recently proposed criteria for the diagnosis of diabetes mellitus or impaired fasting glucose (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). Furthermore, a greater proportion of patients had hyperuricemia compared to the control group. The raised serum uric acid levels and the increased incidence of hyperuricemia in POAG patients compared to the control group persisted even when individuals with abnormalities of the carbohydrate metabolism were excluded [5.9 ± 1.8 mg/dl vs 4.8 ± 1.1 mg/dl and 27% vs 10.5%, $p=0.05$ for both comparisons]. There were not significant differences in the proteinuria or microalbuminuria between patients and controls.

Finally, it is worth mentioning that there were not significant differences in the values of metabolic parameters and in the incidence of metabolic abnormalities between glaucoma patients on topical beta-blockers and glaucoma patients not taking beta-blockers (data not shown).

Discussion

Even though previously published data have supported the relation between diabetes and POAG, the association between these two entities has been controversial (Dielemans et al. 1996; Mitchell et al. 1997; Tielsch et al. 1995). However, our study clearly showed that disturbances of carbohydrate metabolism are fairly common in patients with POAG compared to a carefully selected age and sex matched control population, despite the exclusion of patients with a known history of diabetes mellitus. Thus, both serum glucose levels and the incidence of diabetes mel-

litus or the impaired fasting glucose or glucose tolerance were increased in POAG patients compared to the controls. These results point out the potential significance of carbohydrate intolerance in the pathogenesis of POAG. A number of explanations have been proposed for the association between disturbances of the carbohydrate metabolism and glaucoma, including optic nerve damage as a result of the vascular or other effects of diabetes (Becker 1971), autonomic dysfunction leading to increased IOP (Armstrong et al. 1960; Mapstone & Clark 1985) and genetic factors (Clark & Mapstone 1986).

For the first time in the literature we have shown that abnormalities of urate metabolism are also more common in glaucoma patients compared to the control population. Similarly to the carbohydrate metabolism abnormalities, these disturbances cannot be ascribed to drug-induced effects, since individuals on drugs possibly affecting carbohydrate or urate metabolism were excluded. Controversy exists regarding the association of abnormalities of uric acid and glucose metabolism. Increased serum uric acid levels have been reported in patients with insulin resistant states, including patients with non insulin dependent diabetes mellitus (NIDDM) and may in part be related to hyperinsulinemia, known to increase urate tubular reabsorption in concert with sodium (Cappuccio et al. 1993). However, normal or even low levels of uric acid have been reported in patients with poorly controlled NIDDM and appear to result from a defect in the tubule transport of urate rather than from hyperfiltration (Magoula et al. 1991). The transport defect may in part be attributed to the hyperglycemia and the underlying diabetic condition, as it can be induced

by glucose infusion in healthy subjects (Bonones & Dana 1946; Christensen & Steenstrup 1958). In our study urate metabolism abnormalities observed in POAG patients cannot be ascribed to the co-existent carbohydrate metabolism disturbances, since they were also observed in the subset of patients without diabetes mellitus or impaired glucose tolerance.

Interestingly, increased concentrations of uric acid have been shown in the aqueous humor from some glaucomatous human eyes (Jampel et al. 1998). Furthermore, in vitro studies have indicated that interactions between uric acid and ascorbate can change the viscosity of some glycosaminoglycans (Liu et al. 1984; Lam et al. 1984). Thus, since ascorbate is a known constituent of aqueous humor, and the trabecular meshwork contains glycosaminoglycans as a portion of the extracellular matrix, it is tempting to suggest that increase in uric acid levels may have important implications in trabecular meshwork physiology in glaucomatous eyes (Jampel et al. 1998). However, there are no studies correlating aqueous humor and plasma uric acid levels, while experiments in rabbits and rats, in which hyperuricemia was induced, failed to significantly raise the levels of uric acid in the aqueous humor (Bonney et al. 1986, 1988).

In our study there was no difference in serum lipid parameters or the incidence of dyslipidemia in glaucoma patients in accordance with some previously published data in patients with suspected glaucoma, which showed that lipid analysis was unhelpful in determining whether glaucoma was present (Chisholm & Stead 1988). In contrast to previously published data showing that a high BMI was strongly associated with a low risk of POAG (Leske et al. 1995), there were no differences in the BMI between patients and controls. This finding can be explained taking into account the higher incidence of carbohydrate intolerance in our cohort, as well as the well known relation between body weight and disturbances of carbohydrate metabolism.

A considerable number of our patients were taking topical beta-blockers that might affect serum lipid and carbohydrate metabolism parameters (Stewart et al. 1999; Bartlett et al. 1999; Mirza et al. 2000; Velde & Kaiser 1983). However, there were no significant differences in the values of these parameters between patients on and off topical beta-blockers.

We conclude that disturbances of

carbohydrate and uric acid metabolism could play a role in glaucoma damage and pathogenesis.

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Corresponding author:

Moses Elisaf, MD, FRSH
Associate Professor of Medicine
Department of Internal Medicine
Medical School, University of Ioannina
GR 451 10 Ioannina
Greece
Tel: +30 651 97500
Fax: +30 651 45944