Evaluation of Homocysteine and Plasminogen Activator Inhibitor-1 Changes in Age Related Macular Degeneration

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ABSTRACT

Age-related maculopathy (ARM) and its late stage, age-related macular degeneration (ARMD), are degenerative disorders of the central part of the macula. They are the leading cause of visual impairment and legal blindness among older persons. The cause of ARMD remains unknown, previous studies suggest an association of markers of angiogenesis, hemostasis, and endothelial dysfunction with ARMD. The role of homocysteine and PAI-1have been more controversial, so the purpose of this study was to evaluate the association between levels of plasma homocysteine and PAI-1 and age-related macular degeneration (ARMD). Forty eight age –related macular degeneration cases (23 atrophic and 25 exudative neovascular forms) and 30 controls with matched age and sex distribution were included in this study. Body mass index (BMI), lipid profile, plasma leptin, homocysteine and plasminogen activator inhibitor-1(PAI-1) levels were estimated. The present study points to an association of ARMD and dyslipidemia, and obesity. Also, there were a significant increase in the levels of plasma homocysteine and PAI-1 in exudative neovascular age-related macular degeneration ("wet" type). There was a highly positive correlation between level of leptin and PAI-1 and BMI in exudative neovascular form. ***In conclusion,*** *the present study provides solid evidence that impaired fibrinolysis probably related to obesity, acting in concert with hyperhomocysteinemia may be involved in the pathogenesis of age-related macular degeneration. The strategies aimed at reducing the level of homocysteine and controlling the overproduction of plasminogen activators inhibitor-1 might offer protection against retinal damage in blinding retinal diseases especially exudative neovascular age-related macular degeneration.*

INTRODUCTION

Age-related maculopathy (ARM) and its late stage, age-related macular degeneration (ARMD), are degenerative disorders of the central part of the macula and are the leading causes of visual impairment and legal blindness among older persons[(1)]. ARMD has two main presentations, atrophic and exudative. Although the atrophic form, which is slowly progressive, accounts for 90% of all cases, the exudative neovascular form accounts for 88% of all cases of blindness attributable AÖRMD[(2)]. However, the cause of ARMD remains unknown, recognized risk factors are age[(3)] and heredity[(4)]. Hypertension, high levels of serum cholesterol and high body mass index are accepted systemic risk factors and

tobacco smoking is important environmental exposure factor[5,6].

Exudative neovascular ARMD involves a degenerative process that leads to proliferation of neovascularization into the subretinal pigment epithelium or between the outer retinal layer and the retinal pigment epithelium layer. Previous study has reported increased levels of plasma vascular endothelial growth factor, von Willebrand factor, and fibrinogen, as well as increased plasma viscosity in patients with ARMD. These findings suggest an association of markers of angiogenesis, hemostasis, and endothelial dysfunction with ARMD[7].

Homocysteine is a sulfhydryl-containing amino acid that is derived from demethylation of methionine, and can be influenced by genetic defects, renal impairment, and various drugs and diseases[8]. High levels of plasma homocysteine are toxic to the vascular endothelium by releasing free radicals, creating an environment of hyper coagulability, and modifying the vessel wall[9]. Previous studies suggested a possible involvement of increased plasma homocysteine levels in ARMD[10,11] but others did not find this association[12].

Choroidal neovascularization (CNV) growing under the retina in the exudative forms of age-related macular degeneration causes irreversible photoreceptors damage and is the primary cause of low vision and blindness. Insight into the molecular mechanisms associated with subretinal neovascularization is important since current therapeutic modalities are limited and concern only a small percentage of affected individuals. One of the central features of neovascularization is the elaboration of specific extracellular proteases by the involved endothelium. Urokinase plaminogen activator (uPA), the uPA receptor (uPAR), plasminogen, plasminogen activator inhibitor-1 (PAI-1), and matrix metalloproteases such as MMP-2 have been shown to be the major mediators in this angiogenic proteolytic cascade[13].

Although the roles for uPA, uPAR, and plasminogen in ocular angiogenesis are well documented[14], the role of PAI-1 has been more controversial. Previous reports suggest that PAI-1 can be both proangiogenic and antiangiogenic, depending upon its levels, supporting the concept of proteolytic balance in angiogenesis[15,16]. Elevated PAI-1 levels have been correlated clinically not only with a poor prognosis in patients suffering from a variety of cancers [17], but also with various chorioretinal pathologies[18].

So the purpose of this study was to evaluate the association between levels of plasma homocysteine and PAI-1 and age-related macular degeneration (ARMD).

SUBJECTS & METHODS

The study was conducted in the outpatient ophthalmic clinic, Research Institute of Ophthalmology. Forty eight patients (29 males and 19 females) were selected.

The patients underwent complete ocular examination with slit-lamp biomicroscopy, fundus photography, and fundus fluorescein angiography and were classified into:

1- Twenty three cases of "geographic atrophy" ("dry") ARMD with a mean age ±SD of 70.75±5.3 years, was defined as discrete area of retinal de-pigmentation, at least 175 μm in diameter, characterized by a sharp border and visible choroidal vessels (Fig. 1).
2- Twenty five cases of "neo-vascular" ("wet") ARMD with a mean age ±SD of 71.2±2.3 years, includes serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina (Fig. 2).

A complete history was obtained, to exclude associated diabetes, smoking, and use of systemic and ocular medications. Ocular exclusion criteria were history or presence of diabetic retinopathy, retinal vascular occlusion, and anterior ischemic optic neuropathy, all conditions found to be associated with elevated plasma homocysteine and PAI-1[13,19].

The normal control group with matched age and sex without ARMD included 30 subjects (18 males and 12 females), with a mean age of 69.2±4.2 years.

Body mass index (BMI) was calculated as weight in kilograms over height in meters squared for all groups.

Biochemical analysis:

After overnight fasting (more than12 hour) 3 ml of venous blood samples were collected and immediately processed in EDTA tubes. After 10 min of centrifugation (2500 x g) at 4°C the plasma was rapidly pipetted off and subjected to the following parameters:

1- The homocysteine level was determined by high-performance liquid chromatography (HPLC) according to Ubbink et al.[20]. HPLC analyses were performed on a Shimadzu LC-10A system consisting of a LC-10AT pump with a FCV-10AL low-pressure gradient flow control valve, a SIL-10AXL sample injector, a RF-10AXL fluorescence detector. As the main outcome measure, hyperhomocysteinemia was defined as a plasma homocysteine level of 15μmol/l or more[21].
2- The activity of plasminogen activator inhibitor type-1 assays were measured with a commercial Enzyme-linked-immunosorbent assay (ELISA) kit (Hyphen BioMed –France)[22].
3- Plasma leptin levels were determined by Radioimmunoassay technique according to the method of Considine et al.[23].

The other portions of blood samples (3ml) were allowed to clot and the separated sera were used to estimate the following parameters:-

4- Total cholesterol was determined by the method of Allain et al.[24].
5- Triglyceride, and HDL-cholesterol according to Fossati and Prencipe[25], and Grove[26] respectively.

Statistical analysis

Statistical analysis was done using statistical package for social studies (SPSS) program (ver. 15). Student's *t*-test and Chi square (χ^2) test were used to assess differences. Correlation coefficient was used to measure the relationship between two numerical characteristics. The results were considered significant when $P < 0.05$.

RESULTS

Results obtained from Table (1) showed that, there was a significant increase in the levels of the BMI, and leptin, in ARMD (dry and wet types). And there was a significant increase in the levels of total cholesterol, and triglyceride, and a significant decrease in the level of HDL-cholesterol in exudative neovascular age-related macular degeneration ("wet"type).

There was a significant increase in the level of plasma homocysteine in exudative neovascular age-related macular degeneration ("wet"type) and a significant increase of PAI-1 levels in dry ARMD and exudative neovascular age-related macular degeneration (Table 2).

There was a highly positive significant correlation between BMI and the levels of leptin (r=0.8066, p<0.001) and also a highly positive significant correlation between the levels of leptin and PAI-1(r=0.881, p<0.0001) in exudative neovascular age-related macular degeneration (Table 3).

Table (1):- Demographic characteristics and some biochemical parameters (Mean±SD) in patients with age-related macular degeneration and control subjects.

	Control N=30	*ARMD N=48*	
		Dry ARMD N=23	Neovascular ARMD N=25
Gender M/F	18/12	14/9**	15/10***
Age,(years)	69.2±4.2	70.75±5.3¶	71.2±2.3¶
BMI (kg/m^2)	25.3±1.2	31.1±2.35*	34.9±1.6*
Leptin (ng/ml)	8.34±3.15	15.21±2.77*	17.28±1.37*
Total cholesterol (mg/dl)	181.6±13.2	187.0±14.5¶	238.0±13.24*
Triglycerides (mg/dl)	98.5±10.8	102.0±6.5¶	158.0±23.0*
HDL- cholesterol (mg/dl)	57.5±5.5	58.8±4.9¶	43.6±14.3*

*M= males; F= females; BMI= body mass index. ARMD= Age–related Macular Degeneration. *p<0.001, ¶ P > 0.05 (Student's t-test) relative to control ** P = 0.949, *** P = 1.0 (Chi square test).*

Table (2): Blood levels (mean±SD) of homocysteine (μmol/l) and PAI-1(ng/ml) in patients with age-related macular degeneration and control subjects

	Control N=30	***ARMD N=48***	
		Dry ARMD N=23	**Neovascular ARMD N=25**
Homocysteine(μmol/l)	8.79±2.5	9.2±1.5	16.1±3.9*§
PAI-1(ng/ml)	4.6±1.28	6.46±1.73*	8.91±4.1*§

*ARMD= Age –related Macular Degeneration. *p<0.05 is significant relative to controls. § P<0.05 is significant relative to Dry AMD.*

Table (3): Correlation between plasma leptin, BMI and PAI-1 in cases with Neovascular age related macular degeneration.

Parameters	*r*	*P value*
Leptin-BMI	0.8066	0.001
Leptin-PAI-1	0.881	0.0001

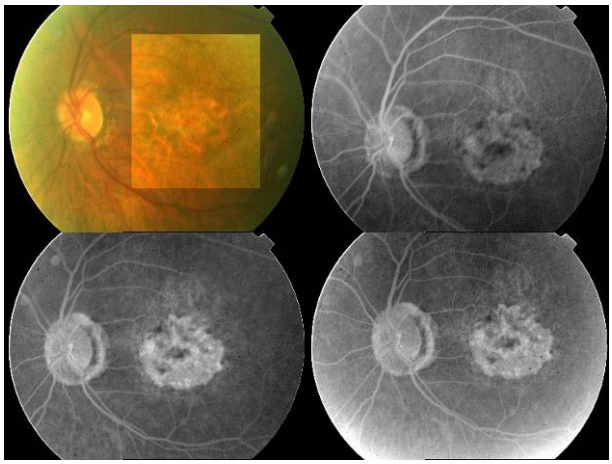

Figure 1: ARMD atrophic type, the box enhancement shows a yellowish area in the colored photograph. Fluorescein angiography shows early hyper-fluorescence corresponding to the yellowish area in the colored photograph and the lesion is not leaking in the late phases.

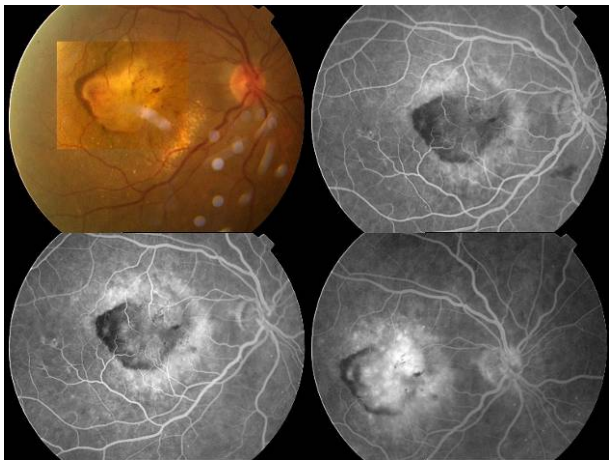

Figure 2: Wet ARMD; occult type choriodal neovascular membrane, the box enhancement shows a yellowish area in the colored photograph with a rim of blood around it. Fluorescein angiography shows early blocked fluorescence corresponding to the yellowish area in the colored photograph and the lesion late leaking in the late phases of undermined origin.

DISCUSSION

Age-related macular degeneration is a complex multifactorial disease whose pathogenesis is poorly understood. Numerous epidemiological studies have tried to elucidate modifiable environmental risk factors for macular degeneration. Many of these risk factors represent a cardiovascular risk profile[27,6,28].

The results in the current study showed that there was a significant increase of BMI and a disturbance of systemic biomarker of lipid profile in ARMD patients, which reflect the association between the obesity and the incidence of this disease[6]. This association confirms the results of previous studies and strongly supports the hypothesis that atherosclerosis mechanisms are involved in the pathogenesis of ARMD by affecting the flow and permeability of choroidal vessels through thickening of the Bruch membrane and decreased perfusion of choroidal capillaries[29].

In the choroid, the changes that occur with aging include increased thickness of the Bruch membrane, flattening of the capillaries and narrowing of their lumina, thickening and sclerosis of the precapillary arterioles, and focal choriocapillary dropout. Moreover, in patients with advanced stages of ARMD, the decrease in choriocapillary density and diameter is significantly greater than in normal maculae[30]. Using fluorescein angiography, Costa and associates[31] demonstrated delayed choriocapillary filling patients with ARMD and decreased visual acuity. They suggested that chronic compromise of the choroidal circulation is an important cause of visual impairment in ARMD. Arteriosclerosis related to aging is suspected to be the underlying cause of this ischemia.

The present study points to an association of ARMD and hyperhomocysteinemia.

Homocysteine is a highly reactive amino acid, its blood levels is sex related (10%–12% higher in men) and age-related, with gradual elevation with age, especially in the older population. Levels higher than 15μmol/l are considered to be included in the hyperhomocysteinemic range[32].

Several experimental systems have yielded numerous possible mechanisms to account for the vascular effects homocysteine. Homocysteine has mitogenic activity in vascular smooth muscle cells which could cause arterial wall thickening. It can also induce intracellular release of calcium in these cells, thereby increasing their proliferation and the mass of extracellular matrix[33]. Another theory postulated that, homocysteine causes oxidative injury of endothelial cells and enhances the peroxidation of low density lipoprotein, thereby promoting the atheromatous process. Increased homocysteine could also augment thrombotic events, as it inhibits the expression of thrombomodulin secreted by the endothelial cells to prevent activation of protein C[34]. In addition, homocysteine enhances the activity of factors V and VII and the adhesion of platelets to the endothelium. The toxicity of

homocysteine to the vascular endothelium may also account for association with choroidal neovascularization: homocysteine-induced damage of the choriocapillary endothelium can lead to vascular occlusion and neovascularization[9].

Alternatively, homocysteine may cause thickening of the choriocapillary vessel wall or induce increased mass of extracellular matrix in the choroid, thus promoting ischemia with consequent neovascularization[35]. The increased resistance of choroidal vessels and decreased choroidal perfusion may also causes retinal pigment epithelial atrophy and stimulates the release of vascular endothelial growth factor (VEGF) for neovascularization[10].

The role of VEGF as a critical factor in the control of the growth of abnormal blood vessels from the choroid directly attacks a central problem in this disease. The profound vascular permeability induced by VEGF is potentially of even greater importance in the treatment of established neovascular ARMD lesions, in which leakage of fluid from new vessels causes visual loss through retinal edema and exudation damaging to photoreceptor cell function, subretinal fluid and hemorrhage[36].

In the current study, the presence of association between ARMD, and increased levels of PAI-1 may suggest a role of impaired fibrinolysis and hemostasis in ARMD. PAI-1 is a principal inhibitor of fibrinolysis and is reported to increase with increasing age, as well as in a variety of age related processes, including atherosclerosis, dyslipidemia, and obesity [37]. The results in this study obtained that, there was a positive correlation between increased BMI and increased levels of leptin and also, there was a positive correlation between increased levels of PAI-1 and increased levels of leptin in neovascular ARMD.

In obesity, leptin produced almost exclusively from adipocytes, and it has been found to influence different processes, such as platelet aggregation, angiogenesis and oxidative stress[38] and could trigger PAI-1 production from various cell types, such as adipocytes, endothelial cells, smooth muscles cells, hepatocytes, and/ or platelets[39].

PAI-1 is the primary inhibitor of urokinase-type plasminogen activator (uPA) and tissue type plasminogen activator (tPA), which both activate plasminogen (Plg) into its active form, plasmin. uPA is secreted as an inactive precursor that binds with high affinity to a specific cell surface-anchored receptor (uPAR). It is generally believed that uPA at the cell surface initiates a protease cascade, which in turn leads to the breakdown of the extracellular matrix and thereby promotes cellular migration[40].

Lambert and colleagues[16] suggested that, PAI-1 is associated with ocular angiogenesis in a dose-dependent fashion. The present data suggest an association between higher mean PAI-1 levels and either atrophic or exudative neovascular form of ARMD compared with control subjects, this is in accordance with the results obtained by previous study[41].

Although the exact mechanism of action of PAI-1 in the development of pathological angiogenesis remains to be elucidated, at least three different

hypotheses can be formulated. PAI-1 could prevent excessive matrix degradation against uPA-mediated degradation, thereby providing a cell adhesion substrate for endothelial cell migration. It has been shown *in vitro* that excessive proteolysis prevents the coordinated assembly of endothelial cells into capillary shoots[42]. PAI-1 could also be considered as the molecular switch that governs uPAR- and/or integrin-mediated cell adhesion and release. Finally, through the inhibition of plasmine, uPA, and tPA, PAI-1 could promote angiogenesis by reducing the angiostatin generation from plasminogen[18,43].

In conclusion, the present study provides solid evidence that impaired fibrinolysis probably related to obesity, acting in concert with hyperhomocysteinemia may be involved in the pathogenesis of age-related macular degeneration. The strategies aimed at reducing the level of homocysteine and controlling the overproduction of plasminogen activators inhibitor-1 might offer protection against retinal damage in blinding retinal diseases especially exudative neovascular age-related macular degeneration.

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تقييم التغير فى مستوى الهموسستين و مثبط منشط البلازمينوجين-١ في حالات ضمور المقوله الشيخوخى

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معهد بحوث أمراض العيون

يعتبر مرض ضمور المقولة الشيخوخي و مرحلته المتأخرة من الامراض التي تؤدي الي الاضطراب في الرؤية و الاصابة بالعمي بين كبار السن و لكن السبب الرئيسي في الاصابة بهذا المرض غير معروف علي وجه التحديد. بعض الدراسات السابقة أوضحت أن هناك علاقة بين مرض ضمور المقولة الشيخوخي و قياس بعض دلالات تكون الأوعية الدموية و دلالات وقف النزف الدموي و دلالات خلل وظائف الخلايا المبطنة للأوعية الدموية و قد وجد أن دور الهموسستيين و مثبط منشط البلازمينوجين-١ في هذا المرض مثار خلاف و جدل و لهذا فان هدف هذا البحث هو تقييم العلاقة بين مستوي الهموسستيين و مثبط منشط البلازمينوجين-١ في الدم و حدوث مرض ضمور المقولة الشيخوخي في مرحلته المتأخرة.

تضمنت هذه الدراسة مجموعتين : المجموعة الأولي و تشمل ٤٨ حالة مصابين بمرض ضمور المقولة الشيخوخي و تم تقسيمهم الي ٢٥ حالة (exudative neovascular) و ٢٣ حالة (atrophic) . المجموعة الضابطة و تشمل عدد ٣٠ شخصا من الأصحاء من نفس نوع و سن المجموعة الأولي. خضعت المجموعتين للاختبار القياسي لمؤشر كتلة الجسم و تم تقدير مستويات كل من دهون الدم و هرمون اللبتين و مستوي الهوموسستيين و مثبط منشط البلازمينوجين-١ .

و قد أشارت النتائج الي وجود ارتباط ملحوظ بين مرض ضمور المقولة الشيخوخي و الاختلال في دهون الدم و السمنة كما وجد ت زيادة ذو دلالة احصائية في مستوي الهموسستيين و مثبط منشط البلازمينوجين١و حالات exudative neovascular age-related macular degeneration

كما وجدت علاقة ايجابية ذو دلالة احصائية بين مستوى هرمون اللبتن ومؤشر كتلة الجسم و مثبط منشط البلازمينوجين-١ فى نفس المجموعة.

تخلص هذه الدراسةالى اعتبار ارتفاع مستوى الهموسستيين و مثبط منشط البلازمينوجين- ١من العوامل الايضية الخطرة التنتصاحب مرض السمنة، قد تؤدي الى حدوث مرض ضمور المقولة الشيخوخي في مرحلته المتأخرة. و من هنا نوصى بوضع استراتيجية علاجية للتحكم في زيادة تكوين مثبط منشط البلازمينوجين-١ والتقليل من مستوى الهموسستيين وهذا قد يؤدى الى حمايه شبكية العين ويحد من تطور مرض ضمور المقولة الشيخوخي.