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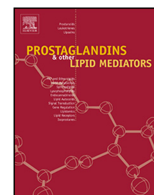

Original research article

"Association between platelet activating factor acetylhydrolase and diabetic retinopathy: Does inflammation affect the retinal status?"

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ABSTRACT

Aim: To assess the role of plasma platelet activating factor acetylhydrolase (PAF-AH) in pathogenesis and progression of diabetic retinopathy (DR).

Materials and methods: Sixty eight diabetics and 23 age-frequency-matched non-diabetic patients underwent blood sampling and the plasma PAF-AH activity was calculated. The diabetic patients were further classified into two groups, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification, based on indirect fundoscopy and fluorescein angiography. Thirty seven patients with non-proliferative DR (NPDR) and 31 patients with proliferative DR (PDR) were finally included in the study.

Results: The plasma PAF-AH activity was increased in diabetic patients with PDR (0.206 μmol/min/ml) compared to control group (0.114 μmol/min/ml, post-hoc Bonferroni comparison test: $p < 0.0001$) and to NPDR group (0.147 μmol/min/ml, post-hoc Bonferroni comparison test: $p = 0.012$).

Conclusions: The activity of PAF-AH in the plasma increases in parallel with DR severity.

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1. Introduction

Diabetic retinopathy (DR) is the leading cause of blindness worldwide and the most severe ocular complication in diabetic patients, who are estimated to be 439 million (7.7% among adults aged 20–79 years old) by the year 2030 [1]. The prevalence of DR worldwide is 34.6% and equals to 93 million patients, directly related to 97.5% of patients with type 1 diabetes mellitus (DM) and 77.8% of patients with type 2 DM, suffering from DR after 15 years of DM [2–4]. The pathogenesis of DR seems to be associated with the sorbitol pathway, the action of free radicals and nitric oxide, the accumulation of advanced glycation end products (AGEs) in the tissues, the changes induced in growth factors, and dehydroascorbate (uncharged form of Vitamin C) [5]. Moreover, the duration of DM, the levels of HbA_{1c} and the blood pressure have proven to be major risk factors, implicating in the progression of DR [2].

Platelet activating factor (PAF, 1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocho-line) is a low molecular weight phospholipid which is involved in inflammation [6]. The affinity of PAF with its receptor (PAF-R, flt-1), a *trans*-membrane G-protein, along with the action of the PAF acetylhydrolases (PAF-AHs), seem to regulate the action of PAF [6,7]. The PAF-AHs represent a heterogeneous group of phospholipases (plasma/secreted and intracellular PAF-AHs), which exhibit high selectivity for phospholipids with short acyl chains at the sn-2 position, without affecting normal membrane phospholipids [7]. These phospholipases inactivate PAF through a hydrolytic cleavage of the sn-2 ester bond and the release of free acetate and biologically inactive lyso-PAF [7]. Beside its systemic action, PAF is released by the ocular tissues, including the iris, ciliary body, retina and vascular endothelium, implicating in ocular inflammation [8]. The retinal tissue responds to physiological and pathological stimuli, releasing metabolites from membrane phospholipids, eicosanoids (prostaglandins PGE2, PGF2, PGD2 and thromboxane A2) and PAF [9]. The activation of PAF results in the degeneration of small vessels and the death of endothelial cells, being related to the pathogenesis of ischemic retinopathies, such as diabetic retinopathy, retinal vein occlusion and retinopathy of prematurity [9].

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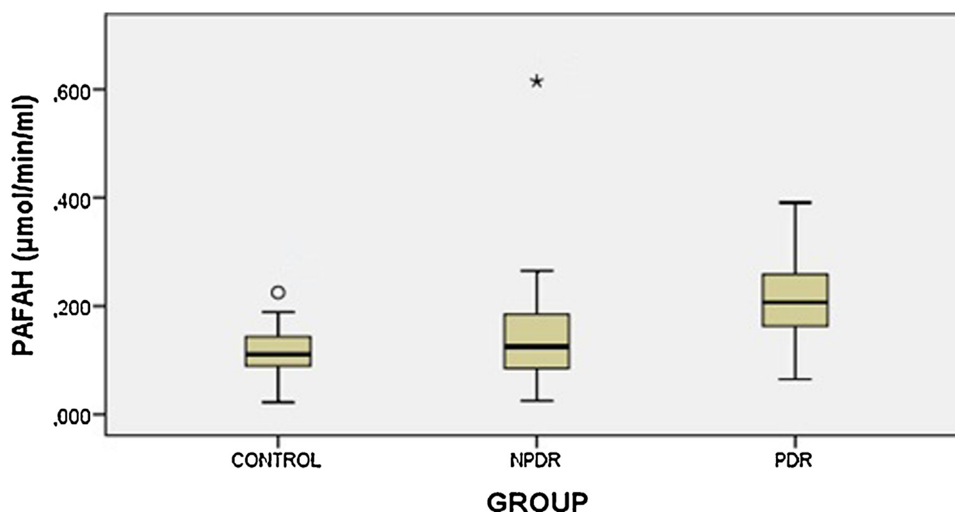

Fig. 1. Box plot. The mean values of participants' PAF-AH activity (in mmol/min/ml) for each group separately. The mean, the minimum, the maximum and the extreme values of PAF-AH activity are presented for each group (NPDR = Non-proliferative diabetic retinopathy, PAF-AH: platelet activating factor acetylhydrolase, PDR = proliferative diabetic retinopathy). A statistically significant increase in plasma PAF-AH activity was noted in PDR group compared to control and to NPDR groups (post-hoc Bonferroni comparison test: $p < 0.0001$ and $p = 0.012$, respectively).

The involvement of PAF in a variety of ocular diseases, including retinal ones and diabetic retinopathy, was the motivation to study the activity of plasma PAF-AH in diabetic patients. Investigating the role of the enzyme in pathogenesis and progression of diabetic retinopathy could contribute to therapeutic strategies.

2. Materials and methods

2.1. Patients

This is a cross-sectional randomized study, conducted at the 1st University Eye Clinic of General Hospital of Athens G. Gennimatas (1st Department of Ophthalmology, Medical School, National & Kapodistrian University of Athens), from June 2012 to March 2013. Sixty eight Type 2 diabetic patients were classified into two groups, according to their retinal status and the Early Treatment Diabetic Retinopathy Study (ETDRS) classification scheme, as following: 37 patients with non-proliferative DR (NPDR), and 31 patients with proliferative DR (PDR). Twenty three sex- and age-frequency-matched non-diabetic patients, with no retinal alterations, were also included in the study and served as the control group. The study was performed in accordance to the tenets of the Declaration of Helsinki and the protocol used was approved by the ethics committee of the University Hospital. Written informed consent was obtained from all participants.

The classification of the participants into three groups was performed according to their systemic and ocular history, as well as the ocular examination. The patients of NPDR group had at least one eye with lesions of this grade, provided that the other did not suffer from PDR. PDR alterations of at least one eye were the necessary criterion for the PDR group. The exclusion criteria of the study included retinal lesions in non-diabetic patients and vascular or other type of retinopathy in diabetic group.

2.2. Measurement of best corrected visual acuity

The best corrected visual acuity was measured for all the participants and it was based on Snellen chart.

2.3. Evaluation of the retinal status

It was performed as follow:

2.3.1. Indirect fundoscopy

The diagnosis of retinal lesions in non-diabetics and DR in diabetic groups was performed using slit lamp fundoscopy. Moreover, slit lamp was used to detect iris neovascularization and vitreous hemorrhage.

2.3.2. Optical coherence tomography (OCT)

All diabetic patients underwent OCT (Stratus, Carl Zeiss Meditec, USA) examination.

2.3.3. Fluorescein angiography (FA)

FA was performed in all diabetics who were classified into two groups according to ETDRS system.

2.4. Blood sampling

All participants were subjected to blood sampling, which was used in quantitative calculation of plasma PAF-AH activity. Blood samples (volume 2,5 ml) were stored in a sampling bottle, which contained EDTA (Ethylenediaminetetraacetic acid). EDTA is used extensively to bind metal ions and as an anticoagulant in blood samples used for a complete blood count (CBC). Centrifugation of the samples was followed immediately or within one hour, during which the samples were stored at temperature of 2–8° C (fridge). Centrifugation was performed at 1000 rpm for 10 min at 4° C. After centrifugation the collected plasma was stored in special vials at a temperature of −80° C until the quantitative analysis was performed. The method of collecting and storing samples secured the quality of the analysis, given that hemolysis affects the levels of PAF.

2.5. Quantitative calculation of PAF-AH activity

The quantitative calculation of plasma PAF-AH activity was based on ELISA (Enzyme-linked Immunosorbent Assay) immunoassay technique for human PAF-AH (PAF Acetylhydrolase Assay Kit, Item no.760901, Cayman Chemical) and was performed at Department of Basic Medical Science, Laboratory of Biology of Medical School, according to the manufacturer instructions [10,11]. The change in absorbance (ΔA_{414}/min) per minute was defined by plotting the average values as a function of time to obtain the slope (rate) of the linear portion of the curve. Afterwards, the rate of

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