

# Correlation between metabolic status and diabetic retinopathy evolution in type 1 diabetes

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**Abstract.** Out of the multiple vascular complications of diabetes, retinopathy is the easiest to diagnose and monitor as the examination of the eye fundus is an easy investigation to perform, does not require expensive medical equipment and can be repeated without any risk to the patient. The appearance of the retinal vessels, the optic nerve and the retina can provide useful information on the coronary and cerebral circulation, plasma lipid levels, renal function, and the quality of the arteries of the lower limbs. It is known that visual acuity changes variably depending on the macular alteration and may decrease when edema is installed in the macular region or is altered by the appearance of hemorrhages or the presence of foveolar neovascular tissues resulting from traction retinal detachment. In the absence of proper treatment, diabetes leads to blindness. The lesions that appear are not specific to diabetes, but by combining them they create a clinical picture characteristic of this disease.

## Introduction

Diabetic microangiopathy is the earliest complication of the disease (1). The risk of heart and kidney damage is directly related to the severity of retinopathy (2).

The factors that lead to changes in diabetic retinopathy, generated mainly by insulin deficiency and consequent hyperglycemia are: Increased hemoglobin compared to normal by 10-20%, which blocks the release of oxygen; the increase of intracellular sorbitol which leads to the increase of the osmotic pressure and to the appearance of the cellular edema, which by destroying the pericytes increases the capillary permeability; thickening of the capillary basement membranes, which favors occlusive phenomena; and changes in the figurative elements of the blood, which causes an increase in platelet aggregation (3).

Bilateral lesions of approximately the same severity occur in both eyes, involving similar retinal regions, and predominating in the posterior pole (4).

Overexpression of the vascular endothelial growth factor (VEGF), a signal protein that stimulates the formation of blood vessels, caused by hypoxic conditions, 'leads to the development of microaneurysms, cellular shunts and neovessels.

The present observational study was performed between November, 2007 and November, 2009 on 142 patients diagnosed with type 1 and 2 diabetes, recorded in the wards of diabetology from the Emergency Clinical Hospital 'Sfântul Andrei' Galati and from the Clinical Hospital of Pediatrics 'Saint John' Galati. The study group consisted of 142 subjects with an established diagnosis of diabetes of specialized doctors, respectively, 75 subjects with type 1 diabetes mellitus (DZ1) and 67 subjects with type 2 diabetes mellitus (DZ2).

## Materials and methods

**Subjects.** The present study included 75 patients with type 1 diabetes. All of them were clinically examined, paraclinically investigated and monitored in the 'Sf. Apostol Andrei' Hospital Galatzi and Ophthalmology Department of Constanta Hospital (Romania).

All investigated subjects signed a detailed informed consent and the protocol was conceived in respect with the

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Table I. Correlation indices for retinopathy cases in type 1 diabetes variables.

Variable	Correlations (type 1 diabetes retinopathy)					
	Means	Std. Dev.	Age	Age of onset	CA TOTmg/dl	PROT g/dl
Age	45.8000	5.35724	1.000000			
Age of onset	11.4000	10.45466	0.595449	1.000000		
CA TOT mg/dl	10.9600	1.35019	-0.982959	-0.620230	1.000000	
CA ION mg/dl	4.9600	0.76763	-0.856565	-0.777855	0.925526	-0.669117
MG mg/dl	1.9800	0.10954	-0.477119	0.336171	0.365098	0.749941
Phosphor mg/dl	3.9800	0.39623	0.433408	0.780934	-0.366364	0.244029
Glycaemia	157.4000	45.28576	-0.290182	-0.107087	0.248920	0.284794
Cholesterol	248.2000	69.21127	-0.913477	-0.325948	0.935386	-0.158928
TGO	38.8000	40.60419	-0.892076	-0.232389	0.894968	0.027394
TGP	26.6000	14.87616	-0.647468	-0.090339	0.691044	0.029811

ICH-GCP (International Conference of Harmonization - Good Clinical Practice) recommendations and with The Declaration of Helsinki. Approval of the study was obtained from the ethics committee of the University Emergency Constanta County Hospital.

Given that the evolution of retinopathy is influenced not only by blood sugar levels, but also by numerous risk factors whose correction is as important as obtaining a glycemic profile as close as possible to normal, we aimed to identify risk factors involved in the development of diabetic retinopathy.

Our screening protocol was applied to each subject and included a short anamnesis to detect the presence of risk factors. The criteria evaluated were: i) the relationship between age, sex and ocular complications of diabetes; ii) the values of the usual biological samples and relevant for the hepatic metabolic status, represented by TGO, TGP, cholesterolemia and bilirubinemia of patients with diabetic retinopathy, in order to highlight the degree of correlation between them and the development of diabetic retinopathy (5).

The exclusion criteria for the study were: Patients diagnosed with diabetes of another etiology, onset of menopause in patients included in the study, institution of treatment for osteoporosis, presence of pregnancy in patients included in the study, the presence of other chronic diseases that disrupt bone homeostasis, or the presence of ocular pathology of another known cause.

**Methods.** In order to identify diabetic retinopathy, a complete ophthalmological exam was performed, including visual acuity evaluation, peripheral vision evaluation by Goldmann perimetry, color vision examination, tonometry, slit lamp fundus examination, mydriatic ophthalmoscopy, mydriatic retinal photography following the Early Treatment Diabetic Retinopathy Study (EDTRS) standard seven-field image grading criteria, echography and electroretinography.

**Statistical analysis.** To verify the existence of a linear relationship between the parameters harvested for each batch

the Pearson Correlation Index was calculated using Statsoft Statistics. Programs of evidence and numerical calculation (Microsoft Excell) as well as specialized software for statistical analysis (StatSoft Statistics 9) were used.

## Results

**Analysis of correlations for cases of retinopathy in type 1 diabetes.** Correlation indices including age, cholesterol, glucose, were obtained with the help of the computer program are presented in Table I.

Concerning correlation indicators related to retinopathy, we observed relevant factors which were grouped according to the basic analysis of the determination of the correlation indicator (Table II).

**Age.** In the analysis of the Age indicator we obtained significant correlations, as indicated in Table III. Highly significant values were observed for the correlation between age and cholesterol and TGO tests, with values >0.9 indicating even dependence between values.

**Glycemia.** In the analysis of the Glycemia indicator, significant correlations were identified as indicated in Table IV.

**Cholesterol.** Concerning cholesterol, significant correlations were obtained as indicated in Table V. Significant values were observed for the correlation between cholesterol and serum calcium and TGO.

**TGO.** Table VI shows significant correlations for TGO. Significant values were identified for the correlation between TGO and serum calcium analyses, alkaline phosphatase, glycemia and cholesterol.

**Magnesium.** Table VII shows significant correlations obtained concerning magnesium. Significant values were found for the correlation between magnesium and glycemia and TGO analysis.

Table II. Correlation indices for retinopathy cases in type 1 diabetes variables.

Variable	Correlations (type 1 diabetes retinopathy)						
	Marked correlations are significant at $P < 0.05000$ N=5 (case wise deletion of missing data)						
	CA ION mg/dl	MG mg/dl	Phosphor mg/dl	ALKP U/l	Glycaemia	Cholesterol	TGO
CA ION mg/dl	1.000000						
MG mg/dl	-0.011892	1.000000					
Phosphor mg/dl	-0.369051	0.046078	1.000000				
ALKP U/l	0.544479	0.600251	-0.010527	1.000000			
Glycaemia	0.080043	0.410216	-0.520518	0.595097	1.000000		
Cholesterol	0.808137	0.518352	-0.035371	0.790599	0.118895	1.000000	
TGO	0.701502	0.662100	-0.115298	0.924989	0.413641	0.947259	1.000000
TGP	0.544472	0.515464	-0.052592	0.991391	0.648975	0.732422	0.881821
Height	0.543199	0.332740	-0.137987	0.933160	0.709688	0.609457	0.773559
Weight	0.901667	-0.336419	-0.551591	0.155345	-0.070472	0.504515	0.349557

Table III. Correlation indices for retinopathy cases in type 1 diabetes for certain factors.

Age	Cholesterol	TGO
	-0.99031	-0.90267

Table IV. Correlation indices for retinopathy cases in type 1 diabetes regarding glycemia and TGO.

Glycemia	TGO
	0.413641

*Alkaline phosphatase.* Alkaline phosphatase indicator had significant correlations (Table VIII). Significant values were found for the correlation between alkaline phosphatase and serum calcium, blood glucose and TGO.

## Discussion

It is known that visual acuity is altered variably depending on the macular alteration: It decreases when edema occurs in the macular region or is altered by the appearance of hemorrhages or the presence of foveolar neovascular tissues resulting from traction retinal detachment. In the absence of proper treatment, diabetes leads to blindness. Contrast sensitivity provides more accurate results regarding visual function, with pathological values even in the stage when visual acuity is good and there are no ophthalmoscopic changes. Adaptation to darkness deteriorates in parallel with the condition of the retina, same as in phototoxic retinopathy (6,7). It occurs in the non-proliferative phase of retinopathy and becomes increasingly evident as the retinopathy progresses.

Computerized static perimeter highlights relative scotomas corresponding to nonperfusion areas. The morphological substrate of the perimeter changes is represented by the lesions of the retinal microangiopathy: Hemorrhages, exudates, exudative maculopathy (8). Chromatic vision is disturbed early, even before the onset of retinopathy in 40-50% of cases, and during retinopathy in 80% of cases. Chromatic disorders are evolutionary, consistent with retinal lesions. Dyschromatopsia

Table V. Correlation indices for retinopathy cases in type 1 diabetes regarding cholesterol/CA TOT, and TGO.

Cholesterol	CA TOT mg/dl	TGO
	0.935386	-0.947259

in the blue-yellow axis is due to a selective depression of the spectral sensitivity to blue light. In diabetes, the sensitivity of cones that perceive the color blue is affected, without affecting those who perceive red or green (8).

Symptoms appear early in this disease, but are only observed when massive damage has occurred and complications have developed. Periodic examination identifies early developing diabetic retinopathy and may prevent retinal detachment.

Symptoms of diabetic retinopathy also include: i) blurred or distorted vision, reading difficulties; ii) light or dark points in the visual field; iii) partial or total loss of vision or the sensation of 'seeing through a wave'.

Complications of retinopathy include: Retinal detachment, secondary neovascular glaucoma, hemorrhage, central retinal vein thrombosis, macular edema. As the disease progresses, destructive changes in the retina can cause massive visual disturbances or blindness (7,8).

*Paraclinical investigations.* The diagnosis of diabetic retinopathy is established on the following investigations: The

Table VI. Correlation indices for retinopathy cases in type 1 diabetes regarding TGO/CA TOT, ALKP U/l, glycemia, and cholesterol.

TGO	CA TOT mg/dl	ALKP U/l	Glycemia	Cholesterol
	0.894968	0.924989	0.413641	0.947259

Table VII. Correlation indices for retinopathy cases in type 1 diabetes regarding MG/glycemia, TGO.

MG mg/dl	Glycemia	TGO
	0.410216	0.6621

Table VIII. Table of correlation indices for retinopathy cases in type 1 diabetes regarding ALKP U/l/CA TOT, glycemia, TGO.

	CA TOT mg/dl	Glycemia	TGO
ALKP U/l	0.721598	0.595097	0.924989

examination of the fundus of the eye, after prior dilation with a mydriatic compound, is widely accessible, easily highlighting important lesions and can be repeated without any difficulty and without any risk. However, it cannot highlight incipient lesions, those that are most important for secondary prevention.

Fluorescein angiography (AFG), especially when associated with photography of various retinal fields, provides early information on the presence of microaneurysms or microhemorrhages, as well as other discrete morphological changes that cannot be observed on direct ophthalmoscopic examination. In addition, using different grid-type systems, lesions can be quantified, which is extremely important for monitoring the evolution of changes over time, especially when assessing the effectiveness of a treatment. Finally, the precise location of microaneurysms allows the photocoagulation of incipient lesions, preventing their evolution to more advanced stages (9). It is the most important method of paraclinical investigation in diabetic retinopathy. AFG demonstrates damage to the blood-brain barrier by highlighting areas of extracapillary diffusion of fluorescence or may show ischemic areas produced by capillary occlusion. In the stage of proliferative diabetic retinopathy, intraretinal microvascular abnormalities and neovascular networks are highlighted.

Mode B ultrasound is especially useful in advanced stages, when the retina cannot be examined due to disorders of the transparent media (cataracts, vitreous hemorrhage). Ultrasound can specify the size of a vitreous hemorrhage or the location of a retinal detachment.

The electroretinogram shows early retinal lesions. In the initial stages of the disease the waves a and b are normal. The analysis of the three components of the retinogram expresses the pathological changes that may occur at the level of different structures: Photoreceptor cells (P III wave); internal nuclear layer with Müller cells (P II wave), corneal pigment epithelium (P I wave).

In summary, for type 1 diabetes, there are significant values of the relationship between serum calcium, blood sugar level and cholesterolemia. In addition, significant values of the relationship between proteinemia and glycemia were observed, as well as highly significant values for the correlation with

TGP - values close to the value of 0.9, which may even show dependence between values.

Significant values in patients with type 1 diabetes have been correlated with the age of the disease and with increases in ionic calcium, cholesterolemia and TGP as well, and with highly significant changes in glycemia (value above 0.9) which even shows dependence between these parameters.

Corroborating the existing studies and results obtained in this group analysis, the working hypothesis of our study was confirmed, namely that between the evolution of diabetes and the values of other laboratory tests, except glycemia, there are interesting correlations that may reveal aspects of interest in the future for a better understanding of the development of complications in type 1 diabetes.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

AR, VP, RC, BM, MCMH, and SJ conceived the study, performed the examinations, collected the results, and were involved in the writing, editing and reviewing of the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board Ethics Committee of University Emergency Constanta County Hospital. Written informed consent was obtained from each patient.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no conflict of interests.

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