ORIGINAL ARTICLE

CONTENTS

# Possible role of the *TGFB1* polymorphism rs1800470, trophoblastic growth factor β1 (TGF-β1) and connective tissue growth factor (CTGF) in the progression of diabetic retinopathy in type 2 diabetes mellitus

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## ABSTRACT

**Aim**: To determine the significance of growth factors (TGF-β1 and CTGF) in the development and progression of diabetic retinopathy (DR) in carriers of different genotypes of the *TGFB1* rs1800470 polymorphism in type 2 diabetes mellitus (T2DM).

**Materials and Methods**: 102 individuals with T2DM and DR were examined, who were divided into 3 groups: 1st – with non-proliferative DR (NPDR, 35 individuals), 2nd – with preproliferative (PPDR, 34 individuals) and 3rd – with proliferative (PDR, 33 individuals); 61 individuals were included in the control group. The patients underwent standard ophthalmological examinations. Determination of TGF-β1 in blood serum and intraocular fluid (IOF) and CTGF in IOP was performed by enzyme-linked immunosorbent assay (Invitrogen Thermo Fisher Sci., USA). Alleles rs1800470 (*T869C*) were determined by polymerase chain reaction (TaqMan Mutation Detection Assays Life-Technology test system, USA). For statistical studies, the MedStat and MedCalc v.15.1 software packages (MedCalc Software bvba) were used.

**Results**: Rs1800470 *A/A* carriers had worse visual acuity ($p=0.016$) and higher central retinal thickness and volume ($p<0.001$) compared to *G/G* carriers. In DR the content of TGF-β1 in the blood and IOF and CTGF in IOF significantly exceeded that in controls (by 1.5-5.2 times; $p<0.05$). The highest content of both factors in DR compared to controls was determined in *G/A* and *A/A* rs1800470 carriers. By stages of DR, a significant increase in the content of TGF-β1 in the blood and IOF and CTGF in IOF was established with maximum values in PDR. A higher content of both factors was established in *G/A* and *A/A* carriers compared to *G/G* carriers. In PDR, the blood content of TGF-β1 in *A/A* carriers was 1.2 times higher ($p<0.05$) than in *G/G* carriers. The increase in CTGF content in the IOF when comparing NPDR and PPDR was characteristic only for *A/A* carriers compared to *G/A* and *G/G* carriers (1.2-1.5 times; $p<0.05$). In PDR, the content of this factor was equally high in *G/A* and *A/A* carriers compared to *G/G* rs1800470 carriers (1.3 times; $p<0.05$).

**Conclusions**: Thus, the content of both TGF-β1 and CTGF was higher in carriers of the *G/A* and *A/A* genotypes compared with the ancestral *G/G* genotype. Therefore, the clinically worse course of DR in carriers of the SNP rs1800470 of the *TGFB1* gene could be associated with a higher concentration of TGF-β1 and CTGF in the IOF of such patients.

**KEY WORDS:** diabetic retinopathy, intraocular fluid, rs1800470, *TGFB1*, TGF-β1, CTGF

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## INTRODUCTION

Diabetes mellitus (DM) is an extraordinary medical and social problem of the modern world, which is among the ten leading causes of death among the adult population [1, 2]. The global prevalence of DM was 9.3% (463 million) in 2019 and will increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [2].

Among the microvascular complications of DM, one of the most common is diabetic retinopathy (DR), which accompanies the course of the disease in 26-35% of patients [3]. Almost all patients with type 1 DM develop DR within 20 years after diagnosis; for type 2 DM, the probability of DR during this period is 80% [4]. About half of patients with untreated proliferative DR (PDR) are likely to become blind within 5 years of diagnosis [4].

By the mechanisms of development, DR is a progressive multifactorial neurovascular lesion of the retina, which specifically develops in diabetes and involves damage to neurons, glia and microvascular vessels [5]. The pathogenesis of DR includes disorders of glucose metabolism, insulin reception and some molecular factors that play a role in inflammation, primarily vascular endothelial growth factor (VEGF), as well as other growth factors and molecules, including transforming growth factor-β (TGF-β) [6].

An obligatory component of retinal neovascularization is fibrovascular proliferation, which occurs as a result of hypoxia [7]. The initiator of this process, first of all, is TGF-β. Notch and TGF-β signaling pathways have been shown to be two intracellular mechanisms that control fibrosis in general and play an important role in retinal fibrosis in DR [8]. Members of the TGF-β family play an important role in the pathogenesis of DR by inducing endothelial proliferation, local inflammation, and apoptosis of neurons and Müller cells [9]. Impaired TGF-β reception and signaling is accompanied by pathological angiogenesis, impaired blood-ophthalmic barrier permeability, inflammatory reactions, and tissue fibrosis [10]. Analysis of the content of TGF-β1, TGF-β2, and TGF-β3 in the serum and aqueous humor of patients with different stages of DR showed a 5.5-fold increase in TGF-β1 compared to the control group [11].

Single nucleotide polymorphisms (SNPs) in the TGF-β1 gene (*TGFB1*) have shown a role for this gene in tissue fibrosis and are associated with DR [12]. *TGFB1* SNPs are involved in the development of other complications of diabetes and diabetes-associated diseases [13]. Their direct relationship with the development of PDR has been shown [14].

Connective tissue growth factor (CTGF) initiates fibrotic reactions in DR at all stages [15]. It modulates the actions of many growth factors and extracellular matrix proteins, including VEGF and TGF-β1, leading to tissue reorganization, thickening of the basal lamina, pericyte apoptosis, angiogenesis, and fibrosis [15].

Thus, it can be assumed that growth factors, including TGF-β1 and CTGF, play an important role in the development of DR, which has its own perspective for their possible use as biomarkers of DR and its progression. It is likely that the effect of TGF-β1 and CTGF in DR may vary depending on the polymorphic state of the *TGFB1*, which justifies this study.

## AIM

To determine the significance of growth factors (TGF-β1 and CTGF) in the development and progression of diabetic retinopathy in carriers of different genotypes of the *TGFB1* rs1800470 polymorphism in type 2 diabetes.

## MATERIALS AND METHODS

### DESIGN AND STUDY GROUPS

The study was conducted at the Department of Ophthalmology of the Danylo Halytsky Lviv National Medical University. All studies were conducted in compliance with the basic provisions of the Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki of the World Medical Association on the ethical principles of conducting scientific medical research involving human subjects (1964, with subsequent amendments, including the 2000 version), Order of the Ministry of Health of Ukraine No. 690 of September 23, 2009 and in accordance conclusion of the extract from protocol No. 12 of the meeting of the Ethics Commission on Scientific Research, Experimental Developments, and Scientific Works of the Danylo Halytsky Lviv National Medical University, November 20, 2023.

The study was prospective, cohort, case-control. Patients who were involved in the study provided informed consent.

In total, the study included the results of the examination of 102 people with type 2 diabetes, aged 65.9±0.84 years, 33 men (32.4%), 69 women (67.6%). The diagnosis of DR was made according to the E. Kohner & M. Porta classification, approved by the WHO in 1991, which distinguishes three DR stages – non-proliferative DR (NPDR), pre-proliferative (PPDR) and PDR. According to the diagnosis, the patients were divided into three groups: the 1st group consisted of 35 patients with NPDR, the 2nd – 34 patients diagnosed with PDDR and the 3rd – 33 patients with PDR. The control group consisted of 61 people who did not have diabetes and DR and underwent surgical treatment for age-related cataract.

### OPHTHALMOLOGICAL STUDIES

Ophthalmological studies included visometry, Goldmann tonometry, slit lamp biomicroscopy Haag-Streit BQ 900, (Switzerland), gonioscopy, ophthalmoscopy using contact and non-contact lenses (Volk Optical, USA), spectral optical coherence tomography (OCT) on Optovue RTVue, Optovue, (USA). Maximum corrected visual acuity (MCVA, units), intraocular pressure (IOP, mm Hg) were determined; central retinal thickness (CRT, μm) and retinal volume (CRV, mm3) were determined using OCT.

### LABORATORY STUDIES

Blood sampling was performed in the morning on an empty stomach in an amount of 3 ml from the cubital vein, immediately after sampling the blood was centrifuged to obtain serum. Intraocular fluid (IOF) was collected through anterior chamber paracentesis before surgery or cataract phacoemulsification by aspirating 0.05-0.1 ml through a 1.0 ml disposable syringe (Hemoplast, Etalon +, Ukraine).

**Table 1.** Content of TGF-β1 in blood and intraocular fluid and CTGF in intraocular fluid in carriers of different rs1800470 genotypes

| Indicator | rs1800470 genotypes | | | p |
|---|---|---|---|---|
| | *G/G* | *G/A* | *A/A* | |
| Control group | | | | |
| Blood TGF-β1, pg/ml | 396±85.8 | 404.8±92.4 | 394.3±95.4 | 0.918 |
| IOF TGF-β1, pg/ml | 129 (119-143) | 131 (120-142) | 130 (122-150) | 0.939 |
| IOF CTGF, ng/ml | 1.55±0.46 | 1.74±0.36 | 1.65±0.46 | 0.356 |
| 1-st group (NPDR) | | | | |
| Blood TGF-β1, pg/ml | 470±90.1 | 590±120.1[4] | 586.7±124[4] | 0.094 |
| IOF TGF-β1, pg/ml | 143.5 (125-159) | 215 (146.75-261.5)[4] | 187.5 (155-239.5)[4] | 0.090 |
| IOF CTGF, ng/ml | 2.09±0.49[3] | 2.47±0.55[3] | 3.15±0.37[1.2.4] | <0.001 |
| 2-nd group (PPDR) | | | | |
| Blood TGF-β1, pg/ml | 485 (400-580)[2.3] | 680 (542.5-742.5)[1.4] | 580 (542.5-755)[1.4] | 0.132 |
| IOF TGF-β1, pg/ml | 215(180-230)[2.3.4] | 316 (247.75-347)[1.4] | 266 (255-382.5)[1.4] | 0.012 |
| IOF CTGF, ng/ml | 3.53±0.71[3.4] | 3.39±0.85[3.4] | 4.22±0.35[1.2.4] | 0.016 |
| 3-rd group (PDR) | | | | |
| Blood TGF-β1, pg/ml | 560±66.7[2.3] | 668.2±76.1[1.4] | 669.1±86[1.4] | 0.027 |
| IOF TGF-β1, pg/ml | 537.8±61.48[2.3.4] | 658±69.13[1.4] | 681.91±35.64[1.4] | <0.001 |
| IOF CTGF, ng/ml | 4.22±0.62[2.3.4] | 5.42±0.46[1.4] | 5.49±0.50[1.4] | <0.001 |

Notes: In the case of a normal distribution, the data are presented as M±SD, in the case of a difference in the distribution from normal – as Me (QI-QIII); ANOVA (in the case of a normal distribution) and the Kruskal-Wallis test (in the case of a distribution different from normal) were used to compare data between groups; posterior comparisons were performed using the Scheffe or Dunn test, respectively:
1 – difference from patients in group 1 is statistically significant, $p<0.05$;
2 – difference from patients in group 2 is statistically significant, $p<0.05$;
3 – difference from patients in group 3 is statistically significant, $p<0.05$;
4 – difference from the control group is statistically significant, $p<0.05$
*Source: compiled by the authors of this study*

Carbohydrate metabolism disorders were determined by fasting venous plasma glucose levels and glycated hemoglobin (HbA1c) levels in the blood. TGF-β1 in serum and IOF and CTGF in IOF were determined by solid-phase enzyme-linked immunosorbent assay using commercial test systems from Invitrogen Thermo Fisher Sci. (USA).

SNP *TGFB1* rs1800470 (*T869C*; L10P) genotypes were determined by real-time polymerase chain reaction using the Gene Amp® PCR System 7500 amplifier ("Applied Biosystems", USA). Genomic DNA was isolated from venous blood (PureLink® Genomic DNA Kit For Purification of Genomic DNA; "INVITROGEN"; USA). For genetic analysis, TaqMan Mutation Detection Assays Life-Technology (USA) test systems were used.

## STATISTICAL PROCEDURES

For statistical studies, the software packages MedStat and MedCalc v.15.1 (MedCalc Software bvba) were used. In the case of a normal distribution law, the data are presented as M±SD, in the case of a difference in the distribution law from normal – as Me (QI-QIII). To compare data between groups, ANOVA (in the case of a normal distribution law) and the Kruskal-Wallis test (in the case of a distribution law different from normal) were used.

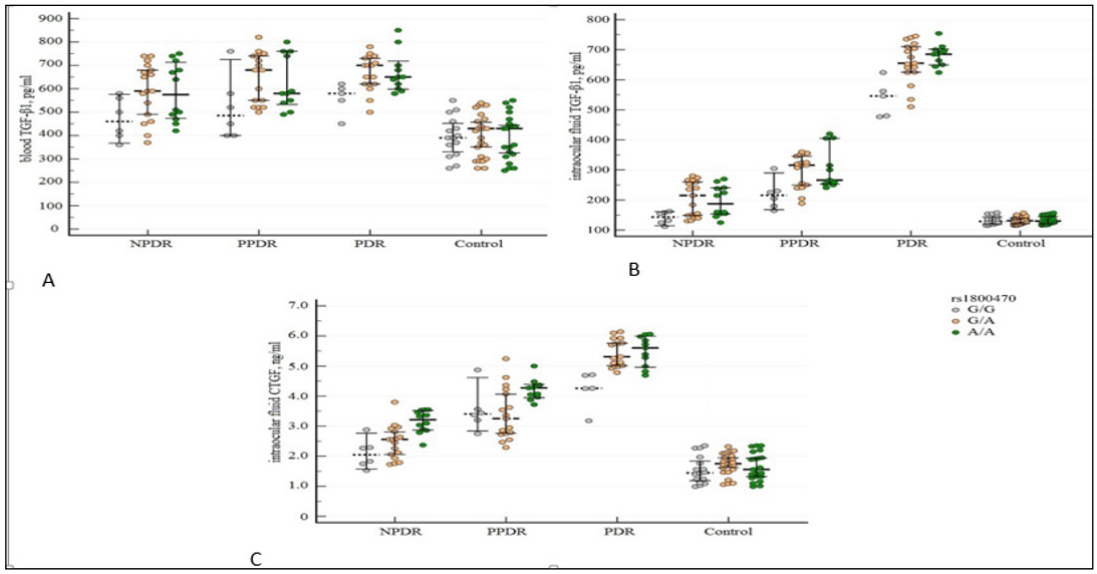


**Fig. 1.** TGF-β1 content in blood and intraocular fluid and CTGF in intraocular fluid in carriers of different rs1800470 genotypes: A) Blood TGF-βI, pg\ml; B) Intraocular fluid TGF-βI, pg\ml; C) Intraocular fluid CTGF, ng\ml
*Picture taken by the authors*

Posterior pairwise comparisons were performed using the Scheffe or Dunn test, respectively. The significance of differences between groups was determined using the χ-square test with Bonferroni correction.

## RESULTS

A comparison of clinical and ophthalmological indicators in the groups of DR patients showed no difference in the level of hyperglycemia and glycated hemoglobin. Instead, visual acuity deteriorated according to the stage of DR (the median was from 0.9 in NPDR to 0.3 in PDR; p<0.001). The CRT and CRV indicators tended to increase according to the stages of DR (compared to the control, they were 1.2 times higher in PPDR, and 1.4 times higher in PDR; p<0.001).

The content of TGF-β1 in the blood in DR was higher than in the control group (1.4-1.55 times; p<0.001), but no significant difference was found between the groups of DR patients. The content of TGF-β1 in the IOF increased significantly more than in the blood (in NPDR it exceeded the control by 1.2 times, in PPDR – by 2.2 times and in PDR – by 5.0 times; p<0.001 for all cases). The content of CTGF in the IOF also increased significantly: it exceeded the control by 1.6 times in NPDR, by 2.2 times in PPDR and by 3.2 times in PDR (p<0.001 for all cases). The intergroup differences in the IOF content of TGF-β1 and CTGF were also statistically significant (p<0.05).

In this study, the main task was to compare the content of the studied growth factors in patients with DR depending on rs1800470 genotype. Analysis of the distribution of rs1800470 genotypes showed no differences between the control group and patients with DR ($\chi^2$=2.788; p=0.835). However, a certain difference in the phenotype of DR patients was found – mutant genotype rs1800470 *A/A* carriers had worse visual acuity (p=0.016) and higher CRT and CRV rates compared to carriers of the ancestral genotype *G/G* (p<0.001). Therefore, it could be assumed that DR had a worse course in *TGFB1* rs1800470 carriers.

Based on the data obtained, an assumption was made about the possible connection of *TGFB1* rs1800470 with the DR phenotype, which could be realized through the effect on the content of growth factors in the blood and IOF. Table 1 shows the content of the studied factors in carriers of different rs1800470 genotypes.

In the control group, no correlation was found between the content of growth factors in the blood and IOF and the carrier of different rs1800470 genotypes (p>0.05). In DR, the content of both TGF-β1 and CTGF significantly exceeded that in the control (by 1.5-5.2 times; p<0.05). It is characteristic that the highest content of both factors compared to the control was determined in *G/A* and *A/A* genotypes carriers (see Fig. 1).

Also, in patients with DR, a clear tendency was established for a higher content of the studied factors in carriers of the heterozygous and mutant genotype (*G/A* and *A/A* rs1800470) compared to carriers of the ancestral *G/G* genotype. For the content of TGF-β1 in the blood, this tendency became significant for PPDR and PDR (see Fig. 1). Thus, in PDR, the content of TGF-β1 in the blood of *A/A* carriers was 1.2 times higher (p<0.05) than in *G/G* carriers.

The intergroup differences in the content of TGF-β1 in the IOF were more pronounced than in the blood (see Fig. 1). The content of this factor in *A/A* rs1800470 carriers exceeded its level in ancestral homozygote *G/G* carriers by 1.2-1.5 times ($p<0.05$). The highest IOF TGF-β1 content was in patients with PDR – it exceeded that in NPDR and PPDR by 3.0-3.8 times ($p<0.05$).

In contrast, the increase in the IOF CTGF content when comparing NPDR and PPDR (see Fig. 1) was characteristic only for *A/A* rs1800470 carriers in comparison with *G/A* and *G/G* carriers (by 1.2-1.5 times; $p<0.05$). In PDR, the content of this factor was equally high in *G/A* and *A/A* carriers compared to *G/G* carriers (1.3 times; $p<0.05$).

Summarizing the results obtained, it could be said that the content of both TGF-β1 and CTGF was higher in *G/A* and *A/A* carriers compared to the ancestral *G/G* genotype, i.e., under the conditions of carriership of the rs1800470 allele *A*. Comparing these data with the results of determining the phenotype, it could be assumed that the worse visual acuity and higher OCT indicators (CRT and CRV) observed in *A/A* carriers could be due to the higher content of the studied growth factors (TGF-β1 and CTGF) in the IOF.

## DISCUSSION

The main function of TGF-β in the immune system is to regulate the proliferation, differentiation and survival of lymphocytes by regulating chemotaxis, activation of lymphocytes, natural killer cells, dendritic cells, macrophages, mast cells and granulocytes [16]. Collectively, it suppresses the development of immunopathology to self or innocuous antigens without compromising the immune response to pathogens.

TGF-β inhibits the differentiation of cytotoxic T lymphocytes (CTL), Th1 and Th2 cells, promotes the generation of peripheral Treg, Th17, Th9 and Tfh cells and the residence of T cells in tissue in response to immune challenges [17]. Similarly, TGF-β controls the proliferation, survival, activation and differentiation of B cells, as well as the development and function of innate cells, including natural killer (NK) cells, macrophages, dendritic cells and granulocytes [17].

Serum TGF-β1 levels may be an additional parameter in predicting the DR development in children with type 1 diabetes [18]. On the other hand, it has been shown that in the retina, TGF-β1 levels can fluctuate independently of changes in its concentration in the blood, which is accompanied by activation of matrix metalloproteinases and remodeling of the cellular matrix [11]. Also, in patients with NPDR, a significant increase in TGF-β1 in the aqueous humor compared with the control group has been shown, confirming its involvement in the development of early vascular changes in DR [19].

In our study, TGF-β1 levels increased in both blood and IOF, but in the latter case the increase was more significant. At the same time, the highest concentrations of TGF-β1 in the IOF were found in patients with PDR, which directly confirmed the importance of this cytokine for its development. The latter may justify the identification of TGF-β1 as a target for targeted therapy [20].

There is evidence that the progression of NPDR to PDR occurs due to the so-called "angiofibrotic switch", which is carried out with the help of CTGF and VEGF [21]. The ratio of CTGF/VEGF in the aqueous humor of the eye was positively correlated with the PDR severity [22]. According to our data, the IOF CTGF content also increased significantly, which was maximally manifested in PDR. This supported the idea of the key importance of the balance of growth factors (VEGF, TGF-β1, CTGF) in the initiation of the angiofibrotic transition and the PDR development. Accordingly, CTGF can also be identified as a possible therapeutic target in the treatment of PDR.

Our study also confirmed numerous results on the significance of SNP *TGFB1* rs1800470 for the development and progression of DR [12-14, 23]. In diabetes, mutations of the *TGFB1* gene are considered an important pathogenetic factor of angiogenesis, endothelial cell proliferation, adhesion and deposition of the extracellular matrix of the retina [12].

However, studies of the association of *TGFB1* SNPs with DR have also had contradictory results. Thus, the absence of associations between rs1800470 genotypes and clinical characteristics or risk factors for DR has been shown [24].

Our study established a worse clinical course of DR in carriers of the mutant genotype *A/A* rs1800470 (worse visual acuity and greater retinal thickness), which was accompanied by higher IOF concentrations of TGF-β1 and CTGF in such patients. The latter was especially true for patients with PDR. This result directly confirmed the pathological role of an increase in the IOF content of growth factors for the DR progression.

This observation also justified the need to study *TGFB1* SNPs to identify a high-risk group, to which, according to our data, mutant allele *A* rs1800470 carriers (genotypes *G/A* and *A/A*) could be attributed. Accordingly, it became obvious that planning of targeted therapy, which should be aimed at inhibiting the TGF-β1/CTGF pathway, should be carried out taking into account the genotypes of *TGFB1* SNPs. In DR, the highest level of TGF-β1 was observed in *A/A* carriers, and the maximum level of CTGF was observed in *G/A* and *A/A* rs1800470 carriers.

## CONCLUSIONS

1. In DR, the content of TGF-β1 in blood and IOF and CTGF in IOF significantly exceeded that in controls (by 1.5-5.2 times; $p<0.05$). The highest content of both factors compared to controls was determined in *G/A* and *A/A* rs1800470 carriers.
2. When stratifying patients, a significant increase in the content of TGF-β1 in blood and IOF and CTGF in IOF was found by stages of DR with maximum values in PDR. A clear trend towards a higher content of factors in *G/A* and *A/A* carriers compared to *G/G* was found. Thus, in PDR, the blood content of TGF-β1 in *A/A* rs1800470 carriers was 1.2 times higher ($p<0.05$) than in *G/G* carriers.
3. The increase in IOF CTGF content when comparing NPDR and PPDR was characteristic only for *A/A* rs1800470 carriers compared to *G/A* and *G/G* carriers (1.2-1.5 times; $p<0.05$). In PDR, the content of this factor was equally high in *G/A* and *A/A* carriers compared to *G/G* carriers of (1.3 times; $p<0.05$).
4. Worse visual acuity and greater CRT and CRV observed in *A/A* s1800470 carriers could be due to the higher IOF content of TGF-β1 and CTGF.

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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