INDONESIAN PHYSICIAN FORUM & INDONESIA COLLEGE OF SURGEONS, INDONESIA
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Commentary

Dear Sir/Madam,

Here are some commentaries to the manuscript entitled **"Comparison of serum and vitreous TGF-β1 levels in proliferative diabetic retinopathy with and without panretinal photocoagulation laser therapy"**

No.	Section	Commentary
A	Title and Affiliation	1. Please write the Title in "sentence case" format → has edited by BMJ editor 2. Please add the authors name and its respective affiliation after the Title → need author confirmation 3. Please add information regarding corresponding author of this study → need author confirmation
B	Abstract	1. Please merged the "Background" and "Purpose" section on the Abstract into one section called "Introduction" → has edited by BMJ editor 2. Please add the analytical statistic used in this study at the "Method" section of the Abstract → has edited by BMJ editor
C	Introduction	1. Please describe the reason why this article evaluates specifically TGF-B1 instead of another marker → has confirmed by Author
D	Method	1. Please describe the selection of 14 patients in this study. Is there any randomization? → has confirmed by Author
E	Result	1. Please merged the information in the description column of the Table 1 → has edited by BMJ editor
F	Discussion	1. The Discussion was too short, please add more discussion regarding this study result → has confirmed by Author
G	Conclusions	1. -

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H	Table, figure and Reference	1. Our journal adopts the "Vancouver Superscript" as the choice of citation format. Please format your *inline citation* and *bibliographic* as an example given below in: → has edited by BMJ editor --Inline citation-- Ponten et al., showed that fasciocutaneus flap could be utilized to cover lower leg soft tissue defects.[1] --Bibliographic-- 1. Pontén B. The fasciocutaneous flap: its use in soft tissue defects of the lower leg. *Br J Plast Surg*. 1981;34(2):215–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7236984
I	Others	1. There were numerous grammatical errors → has edited by BMJ editor 2. Please remove the line number in this artile → has edited by BMJ editor 3. Please complete the checklist attached on the *next page/ sent as a different file.*

----------*Study design specific checklist goes here*----------

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **CLEAR**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **CLEAR**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **CLEAR**
Objectives	3	State specific objectives, including any prespecified hypotheses **CLEAR**
Methods		
Study design	4	Present key elements of study design early in the paper **CLEAR**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **CLEAR**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **CLEAR**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **CLEAR**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **CLEAR**
Bias	9	Describe any efforts to address potential sources of bias **UNCLEAR**
Study size	10	Explain how the study size was arrived at **CLEAR**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **CLEAR**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **CLEAR**
		(*b*) Describe any methods used to examine subgroups and interactions **CLEAR**
		(*c*) Explain how missing data were addressed **CLEAR**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **CLEAR**
		(*e*) Describe any sensitivity analyses **CLEAR**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **CLEAR**
		(b) Give reasons for non-participation at each stage **CLEAR**
		(c) Consider use of a flow diagram -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **CLEAR**
		(b) Indicate number of participants with missing data for each variable of interest **CLEAR**
Outcome data	15*	Report numbers of outcome events or summary measures **CLEAR**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **CLEAR**

		(*b*) Report category boundaries when continuous variables were categorized **CLEAR**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **CLEAR**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **CLEAR**
Discussion		
Key results	18	Summarise key results with reference to study objectives **CLEAR**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **CLEAR**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **CLEAR**
Generalisability	21	Discuss the generalisability (external validity) of the study results **CLEAR**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **CLEAR**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Comparison of serum and vitreous TGF-β1 levels in proliferative diabetic retinopathy with and without panretinal photocoagulation laser therapy

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ABSTRACT

Introduction: A long-term diabetic retinopathy will cause an increase in several growth factors expression like Transforming Growth Factor β (TGF-β). This multipotent cytokine is involved in the process of endothelial cell proliferation. Therefore, this study aims to observe the relationship between TGF-β1 levels in serum and vitreous fluid of Proliferative Diabetic Retinopathy (PDR) patients given Pan Retinal Photocoagulation (PRP) laser therapy.

Method: This was a cross-sectional study involving 14 patients with PDR. TGF-β1 levels of vitreous and peripheral blood were measured using Enzyme-linked Immunosorbent Assay (ELISA) method. The data were statistically analyzed using SPSS software for Windows ver. 23.0 for Mann-Whitney and the Spearman correlation test.

Results: Our subjects consisted of 57.1% males with a mean age of 51.8 years, where dyslipidemia was the most common comorbid disease. Mean serum TGF-β1 level was 12,821.43 ± 5,253.16 pg/ml, while the mean value in vitreous was 3,692.86 ± 333.89 pg/ml. Meanwhile, there was no significant difference in serum and vitreous TGF-β1 levels between subjects with and without PRP laser therapy ($p>0.05$).

Conclusion: There was no significant correlation between TGF-β1 levels in proliferative diabetic retinopathy patients with and without panretinal photocoagulation laser therapy. However, there was a decreasing trend in TGF-β1 levels in the vitreous fluid, indicating that PRP laser therapy has a positive effect on preventing the formation of neovascularization in the eye.

Keywords: TGF-β1 levels, proliferative diabetic retinopathy, panretinal photocoagulation laser

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to the failure of the pancreas to produce sufficient insulin or the occurrence of cell resistance in peripheral tissues.[1] This condition can cause damage to various organs, including the heart, kidneys, and eyes, and even become a risk factor for death from complications.[2,3] Epidemiological estimates in several studies predict that patients with DM will reach 380 million in 2025, with 4 million being at risk for visual loss due to Diabetic Retinopathy (DR).[4]

Diabetic retinopathy is classified into an early stage, namely Non-Proliferative Diabetic Retinopathy (NPDR), and an advanced stage, called Proliferative Diabetic Retinopathy (PDR).[5] The case of a decrease in visual ability occurs due to two mechanisms, namely increased intraretinal

vascular permeability, which leads to macular edema and narrowing of the capillary blood vessels' lumen, to cause macular ischemia.[6]

The state of DR in the long term causes an increase in the expression of several growth factors such as Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), basic Fibroblast Growth Factor (bFGF), and Transforming Growth Factor beta (TGF-β).[7] These biochemical molecules are known to trigger the occurrence of PDR, which leads to the threat of permanent blindness in patients.[8] TGF-β is a multipotent cytokine that works through activin receptor-like kinase-1 (ALK1) and 5 (ALK-5).[9] It is involved in endothelial cell proliferation, formation and degradation of extracellular matrix, and chemotactic and apoptotic processes that lead to the thickening of the capillary basement membrane and impaired systemic blood vessels' regulation.[8–10]

The best treatment for RD patients is to control their blood sugar levels,[11] also, the therapeutic outcome is not aimed at curing or restoring visual function but at slowing the progression of vision loss.[12] Panretinal photocoagulation (PRP) laser therapy reportedly effectively fulfills these goals.[13] It is performed when high-risk PDR is found to numb the ischemic area, thereby inhibiting further neovascularization.[14]

This study investigates the relationship between TGF-β1 levels in serum and vitreous fluid of PDR patients given PRP laser therapy. The results are expected to form the basis for preventing further complications in DM patients, specifically those already having visual complaints.

Material and methods

Study Design

This study was a cross-sectional study involving 14 patients with PDR who had vitrectomy surgery. The history and laboratory tests were conducted to confirm the diabetic status of patients by checking fasting blood sugar and HbA1c levels. Furthermore, routine ophthalmological examinations were carried out, including visual acuity test, intraocular pressure (IOP), examination of the anterior segment of the eye with slit-lamp biomicroscopy, and the posterior segment using funduscopy. The fundoscopic examination results were normal for NPDR and PDR, but only patients with PDR were analyzed. Furthermore, an analysis was conducted to assess the relationship between the duration and number of laser burns given to patients and the changes in TGF-β1 levels examined in the serum and vitreous fluids.

Sample Collection

Vitreous samples were taken using a vitrectomy machine with a volume of 700-1000 µl, while the serum using 3-5 ml blood samples was taken through the median cubital vein. Afterward, they were placed into a vacutainer tube for mobilization and storage.

TGF-β1 Assay

TGF-β1 levels were checked using the human TGF-β1 ELISA reagent kit (Cat. No. MN 55412, R & D Systems, Inc, Minneapolis, USA), where the standard range on the device was 31.2 – 2,000 pg/ml with a detection limit of 4.61 pg/ml.

Processing and Data Analysis

The data were grouped according to the purpose and type of data. Then, they were statistically analyzed using SPSS software for Windows ver. 23.0. The normality test showed that the data

distribution was abnormal. Hence, the Mann-Whitney and the Spearman correlation test were used (Sig. $p \leq 0.05$).

Results

Observations were made to determine serum and vitreous TGF-β1 levels in patients with PDR with or without laser PRP. It was performed on 14 respondents with PDR who had experienced vitrectomy surgery. The univariate data presented in Table 1 shows that the study subjects consisted of 57.1% males and 42.9% females with a mean age of 51.8 years. The most common comorbid disease was dyslipidemia, with 50.0%. The mean serum TGF-β1 level was 12,821.43 ± 5,25 pg/ml, while the mean TGF-β1 level in vitreous was 3,692.86 ± 333.89 pg/ml.

Table 1 Descriptive data of samples

Characteristics	N	(%)
Gender		
Male	8	57.1
Female	6	42.9
Age		
<50 years	3	21.4
≥50 years	11	78.6
Comorbidity		
Dyslipidemia	7	50.0
Hypertension	6	42.9
No comorbid	1	7.1
Serum TGF-β1 levels (mean ± SD)	12,821.43 ± 5,25	
Serum TGF-β1 levels With PRP Laser Therapy		
≤12000 pg/ml	3	21.4
>12000 pg/ml	5	35.7
Serum TGF-β1 levels Without PRP Laser Therapy		
≤12000 pg/ml	4	28.6
>12000 pg/ml	2	14.3
Vitreous TGF-β1 levels (mean ± SD)	3,692.86 ± 333.89	
Vitreous TGF-β1 levels With PRP Laser Therapy		
≤3,600 pg/ml	6	42,9
>3,600 pg/ml	2	14,3
Vitreous TGF-β1 levels Without PRP Laser Therapy		
≤3,600 pg/ml	1	7,1

Table 2 shows the comparison of TGF-β1 levels between patients treated with and without PRP laser therapy. The statistical calculations showed no significant association ($p>0.05$) between serum and vitreous TGF-β1 levels in patients with PDR with or without a history of PRP laser therapy. However, there was a decreasing trend in TGF-β1 levels in the vitreous fluid, indicating that PRP laser therapy has a positive effect on preventing the formation of neovascularization in the eye.

Table 2. Comparative Analysis of Serum and Vitreous TGF-β1 Levels

Variable	Laser History	n	Mean (pg/ml)	SD	p-value
Serum TGF-β1	Yes	8	14,187.5	5,338.9	0.245
	No	6	11,000.0	4,987.6	
Vitreous TGF-β1	Yes	8	3,587.5	352.3	0.104
	No	6	3,833.3	273.3	

The test is done with the Mann-Whitney test.

Discussion

The number of male patients in this study was more than females, while the mean age was 51.8 years and the most common comorbid disease was dyslipidemia. According to Jeffrey G et al. (2011), the development of DR in women can be inhibited by sex hormone receptors. The PDR development can be inhibited by inhibiting hormone receptors, although this mechanism is still unclear.[15] Meanwhile, age above 50 years and a history of metabolic syndrome have been reported as one risk factors in the development of DM and PDR.[16]

The mean value of TGF-β1 levels in patients with or without PRP laser therapy using a vitreous sample was 3,692.86 ± 333.89 pg/ml, while the mean serum level was 12,821.43 ± 5,25pg/ml (Table 1). However, after treatment (Table 2), the vitreous TGF-β1 level in the group treated with laser therapy showed lower values than patients who did not receive PRP laser therapy. In contrast, the serum samples showed higher values in patients that received PRP laser therapy. Consequently, it was concluded that the administration of laser therapy has a good effect in reducing the level of TGF-β1 locally in the eye but has no significant effect systemically.[17] Administration of PRP laser therapy improves the hypoxic state of the retina and the levels of cytokines in the vitreous fluid, thereby preventing proliferation and further neovascularization.[18] Shimura et al. (2009) stated that PRP laser therapy before vitrectomy surgery could reduce levels of angiogenic factors such as VEGF, IL-6, and TGFβ.[19]

TGF-1 is a polypeptide cytokine of the transforming growth factor-beta family. It is a secreted protein that regulates cell growth (cell cycle regulation and death), cell proliferation, cell differentiation, and tumor suppression.[20–22] TGF-β is released into the extracellular matrix as a latent protein complex integrated into a latency-associated protein and one of four TGF-β binding protein isoforms. TGF-β activation, which is necessary for biological activity, happens via poorly known mechanisms that most likely include proteolytic degradation of the related proteins and release of the TGF-β ligand. TGF-β1 is the most common and widely expressed isoform; most researchers have explored or used exogenous TGF-β1 as a biomarker variable.[23]

It has been proposed that pericyte control of endothelial cell proliferation occurs by activating pericyte-secreted latent TGF-β, which entails the proteolytic release of TGF- β from its binding protein. Furthermore, among the six known TGF-β subtypes, only TGF-β1 is inhibitory for endothelial cells and only for particular kinds of endothelial cells.[24]

The retina's oxygenation status controls different growth factors that induce angiogenesis to fulfill the tissue's oxygen demands. Sustained hyperglycemia caused by long-term diabetes causes

many metabolic changes that contribute to retinal hypoxia. It would, however, promote some biomarkers such as insulin-like growth factor-I (IGF-I), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), endothelin (ET), pigment epithelium-derived factor (PEDF), and transforming growth factor-β (TGF-β).[25,26]

TGF-β signaling is necessary for retinal pericyte differentiation during retinal vascular development. The absence of TGF-β signaling produces many microaneurysms, leaky capillaries, and retinal hemorrhages. Furthermore, the lack of differentiated pericytes begins a scenario of structural and functional alterations in the retina similar to those seen in diabetic retinopathy, indicating a related mechanism.[27]

TGF-β is also a neuroprotective protein that contributes to the recovery from diverse neural damage. The activation of stress response proteins and the metabolic activity, such as aldehyde dehydrogenase 3A1 (ALDH3A1), heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor (Nrf2), and hypoxia-inducible factor (HIF), was linked to TGF-β1 mediated antioxidant signaling. It was also shown that TGF-β protects retinal ganglion cells (RGCs) from hyperglycemia-induced damage by activating the antioxidant system, implying a possible anti-diabetic therapy to treat diabetic retinopathy.[28]

According to Zorena et al. (2013), the threshold serum TGF-β1 values that showed a discriminative potential to predict the existence of DR were 443 pg/ml. It was determined by analyzing the receiver operating characteristic (ROC) curves. The computed sensitivity and specificity were 72% and 88%, respectively. TGF-β1 serum concentrations may be an additional criterion in predicting the incidence of DR, according to these findings.[29]

Serum TGF-β1 levels can be influenced by other factors such as hypertension and dyslipidemia.[30,31] In conditions of hyperglycemia, TGF-β1 levels also increase. These findings are in line with several other studies which stated that elevated levels of TGF-β1 are also found in other systemic diseases such as diabetic nephropathy, lung and autoimmune diseases, cancer, cardiovascular disease, hyperglycemia, and hypercholesterolemia.[20,32–34]

Moreover, there is also a correlation between laser burning and the duration of TGF-β1 levels. Measurement of laser timing in a study by Xu et al. (2018) showed that after PRP laser therapy, TGF-β1 levels in the vitreous return to normal in 3 weeks.[35] Previous studies also showed that laser burn ranging from 1,200-to 1,500 and a spot size of 500 μm reduces oxygen demand outside the retina up to 20% and the levels of growth factors in the vitreous.[36] The number of burns in this range can be beneficial as it balances oxygen demand and availability to reduce hypoxic areas. Consequently, this lowers the levels of angiogenic factors, including TGF-β1.[37,38] Meanwhile, the number of burn calculations is expected to provide information about the effect of PRP laser therapy which is believed to prevent severe visual loss for up to 2 years after therapy.[39,40]

Conclusion

Based on the results, there was no significant difference in serum and vitreous TGF-β1 levels between subjects with and without PRP laser therapy. However, the trend of TGF-β1 levels in subjects with PRP laser therapy was lower than in those without panretinal photocoagulation laser therapy.

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Disclosure

Statement of Ethics

The Ethics Committee of Medical Research, Faculty of Medicine, Hasanuddin University, reviewed and approved this study protocol with approval number: 515/UN.4.6.4.5.31/PP36/2021.

Conflict of Interest Statement

The authors state there is no conflict of interest in writing this article.

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Data availability statement

Not applicable

Author Contributions

HSM, RZA, AMI: conception or design of the work, performing the medical examination, analyzing and interpreting the data, laboratory examination and drafting the work. BD, JS: Supervise and quality check of the medical examination, care for patients and perform follow-up after surgery. AS, ICI: project administration, data statistic evaluation, drafting the work and final check for publication.

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TTS Tgl: 15 MAR 2022

PT BANK NEGARA INDONESIA (PERSERO) Tbk KANTOR CABANG UNIVERSITAS NEGERI MAKASSAR

Pejabat Bank | Teller | Pemohon

Ayu Fahnisa

Sah jika ada cetakan komputer atau tanda tangan yang berwenang

Lembar 1 : Debet Nota
Lembar 2 : Debet Nota

PBK 10/SD/0210

NO. TRX. : 61187 308900 001045 4
NO. REK. : 0253621258 IBU ENDANG SRI WAHYUNINGSIH
JUMLAH : IDR 18.215.625,00- TRANSFER KE
7 - MAKASSAR 15/03/2022 10:24:08