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Literature Review: Factors Associated with the Incidence of Diabetic Retinopathy in Patients with Type II Diabetes Mellitus

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Abstract

Diabetes Mellitus (DM) type II is a metabolic disorder caused by insulin resistance in muscle and liver cells, as well as pancreatic beta cell failure. Diabetic retinopathy is one of the diseases that is a microvascular complication of the retina due to chronic hyperglycemia in patients with Type II DM. Chronic hyperglycemia in patients with type 2 DM can change the physiology and biochemistry of cells, resulting in endothelial damage. In this condition, various biochemical pathways are activated, and this affects the occurrence of 4 pathophysiologies of diabetic retinopathy. Several risk factors suspected of triggering diabetic retinopathy are age, duration of disease, poor blood sugar control or hyperglycemia and blood pressure, dyslipidemia, hyperviscosity, kidney failure, anemia, and smoking. Blood sugar control is the most dominant risk factor for diabetic retinopathy among other factors in patients with type II DM. Based on the background, the author is interested in conducting research on risk factors that influence the incidence of diabetic retinopathy. The purpose of this study was to determine the risk factors that influence the incidence of diabetic retinopathy. The research conducted was a Literature Review with a Narrative Review design. Based on the search results, 7 relevant articles were obtained for use in this Narrative Review. The conclusion is that the risk factors suspected of causing diabetic retinopathy include the duration of diabetes mellitus, uncontrolled blood sugar levels, and Type II DM patients with hypertension or dyslipidemia.

Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases with hyperglycemia that occurs due to abnormalities in insulin secretion, insulin function, or both. The prevalence of Diabetes Mellitus based on Basic Health Research in 2018 according to a doctor's diagnosis at the age of 45-54 years increased to 3.9% compared to 2013 which was 3.3%. (Soelistijo, 2021) The duration of suffering from DM affects the possibility of suffering complications. The most common complication found in DM sufferers is diabetic retinopathy, which is 75% in patients who have suffered from DM for 20 years (PERDAMI, 2018). Diabetic retinopathy is an eye disorder that occurs in Type II DM patients due to prolonged hyperglycemia which causes damage to retinal capillaries at various levels. Classification of diabetic retinopathy is divided into two based on severity, namely Proliferative Diabetic Retinopathy (PDR) and Non-Proliferative Diabetic Retinopathy (NPDR) which have mild, moderate, severe severity

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(Hertapanndika et al., 2020; Sardarinia et al., 2022; Salamah et al., 2022; Suman et al., 2023; Ansari et al., 2022; Bilal et al., 2021). Risk factors for diabetic retinopathy in DM patients consist of several modifiable factors such as hyperglycemia, hyperlipidemia, hypertension, obesity, and unmodifiable factors such as duration of DM, age, gender (Mulyani & Ridwan, 2020; El-Metwally et al., 2023; Vijaykumar et al., 2023; Chauke, 2023; Siddiqui et al., 2022).

Based on the official website of The International Agency for the Prevention of Blindness (IAPB), there were 1.1 billion people with visual impairment in the world in 2020, Diabetic retinopathy contributed 0.01% of causes of blindness and 0.04% of causes of moderate-severe visual impairment (Shaniaputri et al., 2022; Sasongko et al., 2025; Pongsachareonnont et al., 2024). Diabetic retinopathy is the second most common complication in Indonesia after nephropathy diabetic, which is 43.1% (Purnama, 2023). Research conducted by Dr. M. Djamil Padang General Hospital between January and December 2016 found 1500 DM patients and 187 people (12.5%) of them suffered from diabetic retinopathy. (Dewi, Fadrian, & Vitresia, 2019) Therapy for diabetic retinopathy includes pharmacological and non-pharmacological therapy. Non-pharmacological therapy can be in the form of healthy lifestyle modifications and glycemic control, while pharmacological therapy is anti-Vascular Endothelial Growth Factor (VEGF) therapy, intravitreal steroid injection treatment used in certain cases such as Diabetic Macular Edema (DME), laser therapy, and vitrectomy (Ulfayani & Haitsam, 2023; Grzybowski et al., 2021; Patil et al., 2023; Wallsh & Gallemore, 2021).

Methods

This study is a study with a literature review method. The literature was obtained through scientific journals or articles downloaded from the PubMed, Gale, MEDLINE and Google Scholar databases. This study is useful for determining the risk factors that influence the incidence of diabetic retinopathy in patients with Type II DM. The next researcher screened the article by referring to the specified criteria, namely the year of publication between 2020-2025 and having relevance to the factors that influence the incidence of diabetic retinopathy in patients with Type II DM. The researcher used several keywords to search for articles, namely "Type II Diabetes Mellitus, Diabetic Retinopathy". The data that was successfully collected will be analyzed negatively in the results and data analysis sections in order to find out the relationship between the clinical characteristics of diabetic retinopathy patients.

Result and Discussion

Table 1. Summary of Studies on Risk Factors and Prevalence of Diabetic Retinopathy in Diabetes Mellitus Patients

No	Journal Name (Year)	Title	Method	Authors	Results
1	Fakumi Medical Journal: Jurnal Mahasiswa Kedokteran (2020)	The Relationship Between Types of Diabetic Retinopathy and Duration of Diabetes Mellitus and HbA1C Levels	Analytical observational with cross-sectional design	Primaputri A, et al.	Diabetic retinopathy occurred in males (61%) and aged 50–54 years (26.5%). High HbA1C levels (> 9.0%) were found in 36 individuals (43%), with a DM duration of < 5 years (51%). The most common type of retinopathy was PDR (68%). The study showed a relationship between HbA1C, duration of DM, and

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					type of diabetic retinopathy.
2	PLoS ONE Journal (2024)	Prevalence and Associated Factors of Proliferative Diabetic Retinopathy Among Adult Diabetic Patients in Northwest Ethiopia, 2023: A Cross-sectional Multicenter Study	Analytical observational with cross-sectional design	Shumye Fi A, et al.	Diabetic retinopathy occurred in males (54.59%) and those aged 48–57 years (33.95%). The most common DM type was Type II (76.72%) with uncontrolled fasting blood glucose (73.72%), irregular DM treatment (47.86%), DM duration < 10 years (81.86%), and coexisting hypertension (30.95%). Hypertension, DM duration > 10 years, and treatment adherence were significant risk factors for proliferative diabetic retinopathy (PDR).
3	Media Hospitalia Journal of Clinical Medicine (2021)	Various Risk Factors of Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients	Analytical observational with cross-sectional design	Nafial Kh N, et al.	Diabetic retinopathy occurred in females (83.7%) and in those under 60 years of age (62.8%), with uncontrolled blood glucose (81.4%) and DM duration < 10 years (79.1%), and a history of hypertension (55.8%).
4	JurnaMU: Jurnal Medis Umum (2025)	The Relationship Between Duration of Type 2 Diabetes Mellitus and HbA1C Levels With Types of Diabetic Retinopathy	Analytical observational using cross-sectional study	Sahela An A, et al.	Most subjects were aged 55–59 and 60–64 years (35.3%), with HbA1C levels analyzed in the same age group and a DM duration > 5 years (52.9%). The dominant type of diabetic retinopathy was NPDR (54.9%).
5	American Academy of Ophthalmology (2023)	Five-Year Incidence of Proliferative Diabetic Retinopathy and Associated Risk Factors in a	Cohort study	Dinesen S MD, et al.	Males were more affected by diabetic retinopathy (56.5%), with an average age of 65. Type II DM was more likely to cause diabetic retinopathy

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		Nationwide Cohort of 201,945 Danish Patients with Diabetes			(74.6%) compared to Type I and others. DM duration > 5 years increased the risk. The study emphasized the importance of controlling systemic factors like HbA1C and blood pressure.
6	Jurnal Multidisiplin Indonesia (2023)	The Effect of Blood Glucose Control, Hypertension, and Dyslipidemia on Diabetic Retinopathy Complications in Type II Diabetes Mellitus Patients	Descriptive observational with retrospective approach	Sinaga BR R, et al.	Females were more affected (56.1%), with an average age > 45 years (93.3%) and DM duration > 10 years (53.7%). Most had uncontrolled blood glucose (62%), hypertension (66.7%), and dyslipidemia (59.2%). PDR was the most common type (63.4%). Poor glycemic control increased the risk of retinopathy 1.8 times, hypertension 2.0 times, and high LDL dyslipidemia 1.3 times in Type II DM patients.
7	SINERGI: Jurnal Riset Ilmiah (2025)	Risk of Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients at RSUP DR. M. Djamil	Descriptive observational with retros		

Diabetic retinopathy is a cause of blindness that occurs mainly in developing countries. The global prevalence of diabetic retinopathy among people with diabetes mellitus is reported to be around 34.4% and approaching 40.3% in developed countries. (Thapa, Khanal, Tan, Thapa, & van Rens, 2020) Around 415 million adults in the world (8.5%) suffer from diabetes. The prevalence of diabetic retinopathy in Indonesian adults with Type 2 DM is 43.1% mild and moderate NPDR, and severe 9.41%, 7.46%, 11.1%, and 12.1% respectively) (Sri Irmandha K, 2021).

Diabetic retinopathy is characterized by hyperglycemia of blood vessels in the retina with damage to the endothelial layer, death of the pericyte layer, namely microvascular contractile cells and thickening of the basement membrane of the blood vessels, triggering capillary occlusion and blood vessel ischemia, causing histopathological changes in the capillaries in the retina so that the retinal capillaries are closed (Sinaga et al., 2023) In a study reported age, gender, hypertension, duration of diabetes, blood glucose control, total serum cholesterol, and triglycerides as risk factors for diabetic retinopathy (Zhang et al., 2022).

From the findings of the journal above, the eligibility criteria were met by 7 research journals published from the year 2020-2024. Analytical observational research methods (4 of 7 journals) and descriptive observational (3 of 7 journals). From these journals, it is stated that the risk

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factors for diabetic retinopathy in Type II DM patients are age > 45 years, long-term suffering from Type II DM accompanied by irregular Type II DM therapy and uncontrolled glycemic control (HbA1C). In addition, a history of Type II DM with hypertension and dyslipidemia makes patients have a higher risk of developing diabetic retinopathy. This is because in patients with high blood glucose levels (hyperglycemia) and uncontrolled can cause many free radicals such as Advanced Glycation End-products (AGE), Sorbitol, and Reactive Oxygen Species (ROS) to form. Prolonged hyperglycemia will trigger increased free radicals, resulting in impaired blood flow, hypoxia, and retinal inflammation (Kakiay & Wigiyanti, 2022).

In the development of diabetic retinopathy, hyperglycemia plays a major role. Hyperglycemia triggers various biochemical pathways that damage blood vessels, such as the glucose metabolism pathway (increased glucose flow), Advanced Glycation End-products (AGEs), Inflammation, and activation of protein kinase C (via the hexosamine pathway). Hyperglycemia also increases superoxide production in mitochondria, causing oxidative stress, which plays a major role in the early symptoms of diabetic retinopathy such as basement membrane thickening, pericyte cell death (blood vessel support cells), and mitochondrial dysfunction. Where this causes hypoperfusion, which then stimulates neovascularization of blood retinal barrier (BRB) damage leading to severe complications that threaten vision (Ansari et al., 2022). Pericyte cell loss not only damages endothelial cells, but is also associated with the appearance of white spots (cotton wool spots), microaneurysms, and spots and bleeding points (dot and blot hemorrhages) these are signs of microvascular damage that causes decreased retinal perfusion (Ansari et al., 2022). As diabetic retinopathy progresses, neovascularization produces new, fragile and permeable blood vessels, which are susceptible to leakage and bleeding into the vitreous. Recurrent vitreous hemorrhage causes the formation of fibrovascular scar tissue. This tissue contraction can lead to severe complications that threaten vision, such as proliferative diabetic retinopathy and diabetic macular edema (Adrian, 2017).

In addition, various inflammatory cytokines IL-1β, IL-6, IL-8, TNF-α, and MCP-1 have been reported to be increased in eye tissues from patients with non-proliferative diabetic retinopathy. The increase in these cytokines produced by activated microglia, endothelial cells, macroglia, and even neurons later, highlights the increased activity of these inflammatory cytokines in the early stages of diabetic retinopathy and the development of inflammatory responses across retinal cell types. The accumulation of these inflammatory mediators contributes to early neuronal cell death in the retina in DM patients. Several identified cytokines, such as MIP-1, IL-1 and IL-3, are also thought to play a role in angiogenesis, suggesting that inflammation also contributes to the development of neovascularization in proliferative diabetic retinopathy (Rübsam et al., 2018)

In patients with proliferative diabetic retinopathy, vitreous concentrations of cytokines and neurotrophins along with other growth factors such as VEGF, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), basic fibroblast growth factor (bFGF) and hepatocyte growth factor (HGF) are increased. This increase is a counter-regulatory mechanism of angiogenesis and inflammation in the eye. In patients with diabetic macular edema, levels of angiopoietin-2 (Ang-2), angiogenesis, increased significantly along with inflammatory cytokines and VEGF (Rübsam et al., 2018).

One of the treatments for diabetic retinopathy is vitrectomy which is commonly performed in patients with diabetic retinopathy, especially in the proliferative stage, to treat complications such as vitreous hemorrhage and retinal traction can also cause damage to the blood retinal barrier (BRB) where, protein levels in the eye fluid (aqueous humor) increase and the retina swells due to inflammation that occurs after surgery. This reaction is mainly caused by natural substances in the body that are released such as prostaglandins, leukotrienes, and various

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cytokines such as interleukins, tumor necrosis factor alpha (TNF-α), and VEGF (Occhiutto et al., 2012).

High HbA1c levels are a major indicator that someone is experiencing chronic hyperglycemia, a condition in which blood sugar levels remain high for a long period of time. In the context of diabetes, HbA1c is used to assess the extent of a patient's blood sugar control in the past two to three months. The higher the HbA1c value, the worse a person's blood glucose control (Adrian, 2017).

Research has shown a strong association between elevated HbA1c levels and the incidence of diabetic retinopathy. One large study, the Diabetes Control and Complications Trial (DCCT), found that every 1% decrease in HbA1c can reduce the risk of developing diabetic retinopathy by 35%. Recent studies in various countries, including Indonesia, also support this finding by showing that patients with higher HbA1c have greater severity of retinopathy. Thus, HbA1c is not only a marker of blood sugar control, but also an important indicator in predicting the risk and progression of diabetic retinopathy. Therefore, maintaining HbA1c levels within normal limits is a crucial step to prevent or slow down eye damage due to diabetes. Routine checks, both HbA1c levels and eye conditions, are highly recommended for people with diabetes to detect and treat retinopathy early (Geany et al., 2022; Keenum et al., 2016; Jawa et al., 2004).

DM patients with hypertension can cause damage to the endothelium in the blood vessels in the retina so that it will increase the expression of Vascular Endothelial Growth Factor (VEGF), then this VEGF will stimulate the expression of Intracellular adhesion Molecule-I (ICAM-I) which will bind the endothelium of blood vessels and leukocytes so that from this bond there is damage to the blood-retinal barrier and retinal capillary occlusion. from this theory, blood pressure is a risk factor that plays a major role in the occurrence of diabetic retinopathy (Mulyani & Ridwan, 2020).

High-density lipoprotein (HDL) has an anti-atherosclerotic effect because it receives cholesterol from peripheral tissues to be sent to the liver through a classic method called Reverse Cholesterol Transport (RCT). The antioxidant function of HDL can also prevent the development of Low-Density Lipoprotein (LDL) particles into ox-LDL particles, and also inhibit the formation of early atheroma in the subendothelium of blood vessels. Low HDL cholesterol levels are often found in patients with metabolic syndrome, diabetes mellitus and diabetic retinopathy. Dyslipidemia is one of the supporting factors in the occurrence of diabetic retinopathy. Dyslipidemia that occurs in DM patients, including low or abnormal HDL cholesterol levels, will trigger biochemical changes and activate glial cells. This will cause changes in growth factor signals, trigger the activation of chemokines and inflammatory cytokines and activate ROS. This will trigger neuroglial degeneration and vascular dysfunction which can then cause diabetic retinopathy. (Harini, Setyanto, Gumilas, & Ernawati, 2022).

Conclusion

Based on the results of research on risk factors that influence the incidence of diabetic retinopathy. it is concluded that the risk factors suspected of causing diabetic retinopathy include age, duration of type II diabetes mellitus, uncontrolled blood sugar levels, hypertension, and dyslipidemia.

Suggestion

Suggestions for further research are to conduct research on other factors related to the incidence of diabetic retinopathy using a better design and not only using variables that have been obtained from the journal above and taking a larger sample size, thus things that can cause bias in research can be reduced.

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