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Evaluating the Risk Factors of Development and Progression of Diabetic Retinopathy: A Review Study

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Abstract

Diabetes is a chronic, underlying, and common disease worldwide that imposes an enormous burden on the health system. Diabetic retinopathy (DR) is a serious complication in the eye caused by diabetes and may lead to visual impairment and blindness. The knowledge about the risk factors of DR is critical for the prevention of disease and developing treatment options. Moreover, DR is a multifactorial disease, and many studies have demonstrated various risk factors associated with it, such as hyperglycemia, hypertension, hyperlipidemia, etc. In this review study, we survey the main risk factors of the development and progression of DR.

Keywords: Diabetic Retinopathy, Risk Factor, Ocular Diseases

1. Context

Diabetes is a chronic, underlying, and common disease worldwide with a lot of effects on the body; it imposes an enormous social and economic burden on the government and health care system. Diabetes is characterized by the increase and dysregulation of blood glucose levels due to insulin resistance or decreased insulin production. It can cause cardiovascular, microvascular, neuropathic, nephropathic, retinopathic, and thrombotic diseases. The microvascular system is damaged in diabetes in the affected patients, especially in the retina, which is called diabetic retinopathy (DR) (1, 2). Diabetic retinopathy is the most critical ocular complication caused by diabetes. The severe stages of DR, including diabetic macular edema (DME) and proliferative DR (PDR), may lead to visual impairment and blindness. Hence, the knowledge about the risk factors of DR is critical for the prevention of disease and developing treatment options. Moreover, DR is a multifactorial disease, and many studies have demonstrated various risk factors associated with it, including hyperglycemia, hypertension, dyslipidemia, prothrombotic state, chronic inflammation, oxidative stress, proinflammatory cytokines, angiogenesis stimulatory molecules, and other factors (3, 4). The current review study surveys the main risk factors of the development and progression of DR.

2. Methodology

In this systematic review, we collected the related articles published in the valid web-based servers and databanks, including the National Center for Biotechnology Information (NCBI)-related servers (e.g., PubMed and PubMed Central), Google Scholar, Web of Sciences, and Scopus in November 2020. Then, we screened the related studies and used them in regular scientific writing.

3. Risk factors of Diabetic Retinopathy

3.1. Duration of Diabetes

According to some studies, prolonged duration of diabetes has been associated with an increase in the risk of DR. Studies have shown that the prevalence of DR is two times higher in patients with longer periods of diabetes compared to new cases. For instance, Zhang et al. observed a longer duration of diabetes in patients with DR ($P < 0.001$), and demonstrated that for each year that diabetes persists, the risk of retinopathy increases by approximately 8% due to increased retinovascular injuries and neovascularization (5-7). In addition, Yin et al. reported a significant correlation between a longer duration of diabetes and DR ($P < 0.001$) (8).

3.2. Hyperglycemia and HbA1c

Many studies have emphasized the relationship between blood glucose control and the clinical outcome of diabetes. According to evidence, in patients with well-controlled blood sugar, the risk of retinopathy and microvascular diseases is significantly lower than in patients with uncontrolled blood glucose levels (9). Glycated hemoglobin, known as HbA1c, is a biomarker for monitoring glycemic control. Some studies have demonstrated that HbA1c levels can be considered an independent risk factor for DR. The higher HbA1c levels are associated with proliferative diabetes and increase the risk of DR incidence (10). Lachin et al. found that for every 1% increase in HbA1c, the risk of DR increases by 22%, although the elevated HbA1c reflects weakly controlled diabetes correlated with DR development (11). One diabetes control and complications trial study on patients with type 1 diabetes who underwent the intensive and tight glycemic control programs confirmed that the risk of new retinopathy arising is reduced by 76% in diabetes cases, and the progression of existing DR is decreased by 54% (9, 12). However, a similar study reported that intensive diabetes control therapy increases the chance of weight gain by about 33%. Also, it increased the risk of severe hypoglycemia by about three times (9). So, in diabetes control therapy, the precise balance must be struck between the advantages of reducing the risk of DR and the risk of intensive glycemic control. Currently, studies suggest that the ideal HbA1c levels are below 7.6% (60 mmol/mol), and keeping this level can be considered a treatment target to prevent the proliferative DR for up to 20 years in type 1 diabetic cases (13). Of course, the American Diabetes Association recommitted a goal of treatment target at 7.0% (14). In addition, the action to control cardiovascular risk in diabetes trial demonstrated that the risk of DR progression in diabetic patients with intensive blood sugar control programs, which had a target HbA1c level of 6.0%, was significantly lower than patients with an HbA1c level of 7.0 - 7.9% (15). Nevertheless, this result emphasized that optimal glycemic control in diabetic patients had an essential role in preventing DR.

In the following, we survey some studies about the relationship between glycemic control and DR progression. Mohamed et al. suggested that an HbA1c level of 7% in existing retinopathy in diabetic patients is ideal for preventing the progression of DR (16). Kilpatrick et al. reported that the long duration of fluctuation of HbA1c causes the risk of DR in type 1 diabetes patients (17, 18). Another study showed that the variability in HbA1c levels was correlated with increased risk of DR in diabetes patients, particularly in the acute hyperglycemia and acute fluctuations in glucose or HbA1c levels. Despite these correlations, some studies have not observed a positive relation between HbA1c and the development of DR in diabetes mellitus (19). Some studies found that fasting plasma glucose (FPG) can also act as a biomarker of predicting DR progression. The level of FPG was significantly higher in cases with DR (20). For instance, Xie et al. observed that in patients with DR, the mean ($\pm$ standard deviation) level of FPG was 8.88 $\pm$ 4.56 mmol/L, but cases without DR had 7.70 $\pm$ 2.80 mmol/L of FPG levels (21). In summary, there is much evidence that better glycemic control leads to a decrease in the risk of DR development.

3.2.1. Glycemic Control

Patients with DR are more likely to take insulin or oral hypoglycemic drugs to control their diabetes. Recently, some studies found a relation between the effect of diabetes treatment programs and reduction of risk factors for DR. In other words, diagnosed and treated diabetes have a better prognosis for DR and can be considered a predictor of DR (22). A study on patients with type 2 diabetes mellitus (DM2) treated with insulin or sulfonylurea derivatives showed that in-time control of diabetes with antidiabetic medications is associated with prevention of DR as an independent statistically significant factor (23). In other words, late insulin or antidiabetic therapy in DM2 patients can be considered as a risk factor for accelerating the development of DR. Thus, well-controlled blood glucose can reduce the risk of DR progression. Other new therapeutic methods are directly related to a reduced risk of DR. For instance, pancreas transplantation is a new therapy for diabetes with dramatic effects on reducing the blood sugar and achieving the euglycemic state. Some case reports observed the progression or even regression of DR after pancreas transplantation. In contrast, some drugs (e.g., thiazolidinediones) have the opposite effect as a blood sugar controller. Some research reported that the use of thiazolidinediones is associated with refractory macular edema. These results yielded that optimal glycemic control by antidiabetic treatments can reduce the prevalence of microangiopathic disorders like DR (23, 24).

3.3. Hypertension

The relation between hypertension and vascular diseases is well-established. Diabetic patients with hypertension have a high risk of developing DR (8, 25), and many

mechanisms are involved in it, including interactions between hormonal control of blood sugar levels and the renin-angiotensin-aldosterone system (26), activating the coagulation, shearing stress of blood flow, retinal capillary endothelial cell damages, etc. Studies have found that the relative risk of DR in patients with hypertension is 1.7 times higher than non-hypertensive individuals. A study demonstrated that for each 10 mmHg increase in systolic blood pressure, the risk of DR is increased by 1.23 times, and the risk of severe retinopathy is increased by 1.19 times; however, this rate was lower in elevation of diastolic blood pressure (27). Another study showed that after 10 years, the risk of developing DR in patients with hypertension was more than two times higher than controls (28). This result confirms the clinical finding that hypertension and diabetes are mostly co-existed.

3.3.1. Blood Pressure Control

Effective control of hypertension (blood pressure less than 150/85 mm Hg) by specific drugs has been shown to decrease the rate of DR progression into severe stages by 34% over 7.5 years (29). In addition, reducing blood pressure in hypertensive diabetic patients could decrease the risk of visual impairment by 47% (30). Controlling the blood pressure to a level of 140/90 is recommended by the Eighth Joint National Committee (JNC 8) (31). The UK Prospective Diabetes Study showed the importance of blood pressure control in patients with DR (32). They found that during 7.5 years, the intensive control of blood pressure on 150/85 mm Hg significantly decreased the development of retinal complications such as microaneurysms ($P < 0.001$), hard exudates ($P < 0.001$), and cotton-wool spots ($P < 0.001$) compared to intensive control of blood pressure on 180/105 mm Hg (11).

A meta-analysis study demonstrated that renin-angiotensin system (RAS) blockades reduce the risk of DR by 7% and decrease the risk of DR progression by 5%, which could also increase the probability of regression of retinopathy (33). A similar study also found that using angiotensin-converting enzyme (ACE) inhibitors could significantly decrease the risk of development and progression of DR and increase the probability of regression. Interestingly, angiotensin receptor blockers (ARBs) have a role in decreasing the incidence of retinopathy (34).

3.4. High Cholesterol and Hyperlipidemia

Elevated serum cholesterol and lipid levels are well-established factors for metabolic disorders, such as cardiovascular diseases and diabetes. Studies have found the relationship between hyperlipidemia and elevated cholesterol levels with DR. Cheng et al. demonstrated that in overweight DM2 patients, high triacylglycerol levels were significantly associated with DR ($P < 0.05$) (35). A Chinese study on DM2 patients confirmed that elevated very low-density lipoprotein (VLDL) and triglyceride (TG) concentrations were independent risk factors for DR (36). Also, Yau et al. found that increased total serum cholesterol level was correlated with an increasing prevalence of macular edema and severe retinopathy in diabetic patients (37). Another study demonstrated that DM1 patients with DR had a significantly higher total serum cholesterol level than a diabetic patient without DR (199 ± 35 mg/dL, 188 ± 36 mg/dL respectively; $P = 0.001$). They suggested that total cholesterol level is an independent risk factor for DR (38).

In contrast, Wong et al. found that a higher total serum cholesterol level is a protective factor for DR. Some studies stated that elevated serum cholesterol and lipid levels are associated with an increased risk of long-term vision loss in DR (20, 39). For instance, a large meta-analysis study reported that diabetic patients with macular edema had higher total cholesterol levels, low-density lipoproteins (LDL), and serum triglycerides. Moreover, high levels of cholesterol and lipids have also been linked with higher hard retinal exudates. Additionally, some new lipid markers such as Apolipoproteins might be a candidate for predicting the prognosis of DR (40).

3.4.1. Hyperlipidemia Control

Studies have shown that treatment of hyperlipidemia improves DR and limits its progression into advanced stages. Statins, HMG-CoA reductase inhibitors, are commonly used for the treatment of high cholesterol. Interestingly, their use has been related to a significantly decreased rate of DR development. Also, their use in diabetic patients with existing retinopathy has been linked to improving visual acuity (41). Fibrates are other medications used to treat hyperlipidemia. A study showed that using the fenofibrate was associated with a lower rate of progression of DR. Furthermore, control of serum cholesterol and lipids is correlated with a lower incidence of complications from diabetic eye disease. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommended a reasonable goal of LDL-cholesterol below 100 mg/dL (42). The diabetes control and complications trial study revealed that in DM1 patients, the rate of improvement of DR was associated with elevated TGs lev-

els and reduced HDL-cholesterol ratio. The action to control cardiovascular risk in diabetes (ACCORD) trial study surveyed the effects of the dyslipidemia treatment on the progression of DR. They investigated two groups: patients who underwent intensive treatment and used daily fenofibrate and simvastatin, and patients with standard treatment taking placebo with simvastatin (15). The intensive treatment group showed improvement in HDL-cholesterol ratio ($P = 0.002$) and a decrease in TG level ($P < 0.001$), which was significantly associated with decreased risk of DR progression compared to other groups ($P = 0.006$) (24, 40). In summary, controlling the high lipid profile levels can decrease the risk of development and progression of DR in diabetic patients.

3.5. Chronic Kidney Disease

In diabetic patients, chronic hyperglycemia leads to microvascular alterations in both the renal glomerulus and retina of the eye, including constriction or occlusion of the vascular Lumina and scant perfusion (43). Thus, both retinopathy and nephropathy are associated with diabetes-related microvascular disorders. Multiple studies have indicated the correlation between chronic kidney disease (CKD) and DR. Kidney function is monitored by patients' glomerular filtration rate (GFR). CKD is defined as estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2. Park et al. reported that CKD and proteinuria had a significant relation with DR (44). Furthermore, Zhang et al. demonstrated that lower eGFR was significantly correlated with increased risk of developing severe DR in existing retinopathy (mean eGFR, 93 mL/min/1.73 m^2, $P < 0.0001$) compared to cases without DR (mean eGFR, 116 mL/min/1.73 m^2) (43). In addition, a Chinese study reported that a GFR rate below $\leq$ 99.4 mL/min/1.73 m^2 in DM2 patients might reflect the presence of early-stage DR (45).

Also, some studies reported that microalbuminuria, proteinuria, and the higher albumin-creatinine ratio were associated with DR. Penno et al. stated that urine albumin-to-creatinine ratio ($\geq$ 300 mg/g) was correlated with DR (46). In another study, Rodriguez-Poncelas et al. stated that any increase in urine albumin-to-creatinine ratio (even greater than $\geq$ 10 mg/g) was significantly associated with DR arising (47). Also, Kodali found that DR and diabetic nephropathy occur more significantly in patients with an albumin-to-creatinine ratio of more than 2 mg/mmol (48). Another study on DM2 patients confirmed that albuminuria was associated with higher prevalence of DR and other microvascular disorders. They suggested that urinary albumin excretion may show a status of generalized vascular damage due to the concentrations of lipoproteins and fibrinogen and subsequent increase in thrombotic diseases followed by microalbuminuria or proteinuria (49, 50). Besides, the Wisconsin epidemiologic study of diabetic retinopathy (WESDR) proved that in patients with long-term diabetes lasting for 10 years, proliferative DR occurred three times more in patients with proteinuria. Also, the combination of GFR with albuminuria can be considered as a prognostic factor for DR arising. Chen et al. found that the risk of DR in patients with microalbuminuria and GFR > 60 mL/min/1.73 m^2 was three times higher than patients with normal albuminuria and lowered GFR (30 - 59.9 mL/min/1.73 m^2) (51). In summary, CKD has been associated with DR and GFR, albuminuria, proteinuria, and their combinations have been important independent predictors of the development and progression of DR (52, 53).

3.6. Lifestyle

The role of lifestyle in the incidence and progression of DR in diabetic patients has been well established. In the following, we survey some risk factors related to the association between lifestyle and DR.

3.6.1. Obesity

Obesity is another risk factor associated with vascular diseases. According to the World Health Organization (WHO), obesity is defined as a body mass index (BMI) of more than 25 kg/m^2. Also, it can be shown by waist-hip ratio and waist circumference, in which greater ratios are positively correlated with DR (20, 28, 54). A study indicated that patients with the highest waist-to-hip ratio are 40 times more at risk of developing DR. In addition, even increased neck and waist circumference have been related to increased risk of DR and progression to severe stages (54). The relation between BMI and DR varies among studies. Increased BMI is linked to the elevated risk of DR, and higher BMI is positively associated with severe stages of DR (29). On the other hand, some studies have reported no correlation between increased BMI and retinopathy (55). A study on DM1 patients showed that obesity with a BMI of > 30 kg/m^2 was the predominant risk factor for DR, even in controlling the other risk factors, i.e., HbA1c and using the cardioprotective agents (56). Also, a study confirmed the association between BMI and DR, though it could not find a statistical significance (28). Cusick et al. surveyed the effect

of BMI on the progression of DR. Contrary to previous results, some studies have reported a significant association between DR and BMI, so that a higher BMI had a protective effect on DR (57). The Wisconsin epidemiologic study of DR reported that the diabetic-underweight patients with BMI < 20 kg/m^2 had a higher incidence of DR than obese patients; in fact, all of the underweight patients during 10 years developed DR. In addition, they observed that underweight patients suffered from a longer duration of diabetes and were more likely to require insulin compared to obese participants. Therefore, they suggested that underweight patients may have weak glycemic control and anticipate severe diabetes more than obese patients (58). Additionally, Wong et al. found that a lower value of BMI was related to DR with no statistically significant difference (59). Finally, obesity is a risk factor for DR, and weight management should be considered as a preventive factor in DR.

3.6.2. Sleep-Disordered Breathing

Sleep-disordered breathing or obstructive sleep apnea (OSA) is denoted by repeated upper airway occlusion, causing blood oxygen unsaturation and sleep disruption (60). This hypoxia has been related to oxidative stress at the endothelial layer, leading to vascular damage and neovascularization associated with DR. Also, severe OSA is associated with higher rates of neovascularization and developing to severe stages of DR. On the other hand, the OSA is highly related to obesity. A study found that 86% of obese diabetic patients are susceptible to OSA (61), and obesity is a risk factor for DR. Additionally, diabetic patients with OSA have a poor response to anti-vascular endothelial growth factor (anti-VEGF) agents like bevacizumab to treating the vascular diseases (62).

3.6.3. Exercise

There is a lot of evidence proving the metabolic advantages of exercising. Exercise can reduce the risk of vascular diseases. A study in women indicated that an increase of 10 min a day in moderate to vigorous activity could reduce the risk of developing DR by 75%, and an increase of 20 min can reduce it by 94% (63). A study surveyed leisure time and physical activity and reported that low-intensity leisure-time physical activity increases the risk of DR by 1.49 times, and low-frequency leisure-time physical activity increases the rate of DR by 2.58 times (64). Health care systems recommend that every adult needs at least 150 minutes of physical activity per week.

3.6.4. Smoking

Recent studies showed that cigarette smoking is significantly related to the development of DR. For instance, Muhlhauser et al. and Uruska et al. confirmed this result in DM1 patients (2, 65). Other studies suggested that smoking is related to early forms of DR (66). However, some other studies reported no correlation between smoking and DR (67). For instance, a study found no significant correlation between cigarette smoking and DR incidence (28). Interestingly, in some studies, DR progression was correlated with non-smoking status in patients (32). The United Kingdom prospective diabetes study 50 (UKPDS 50) found that smoking had a protective effect on DR. Current smokers had a significant decrease in incidence and progression of DR (P = 0.0043 and P = 0.0045, respectively) compared to those who had never smoked (32).

3.6.5. Alcohol Intake

Alcohol intake has a potential impact on DR risk, but it is related to the type of DM and adjusted status. A prospective cohort study by Chen et al. demonstrated a significant association between alcohol intake and DR risk (P = 0.225) (68).

3.7. Age and Sex

Some studies found that DR occurs significantly more in older patients (P = 0.003) and males (P < 0.001) (8). A large-scale study demonstrated that the incidence of DR in males was higher than females (38 $\pm$ 5.5 and 27.1 $\pm$ 4.7%, respectively) in people aged more than 40 years. Additionally, the multivariate model of the Los Angeles Latino Eye Study (LALES) study showed that the male sex significantly had a 50% higher risk of DR than females (P = 0.006) (1, 22, 69). Similarly, a multivariate model of the UKPDS 50 study demonstrated that females had a lower risk of DR progression (32). This evidence suggested that male sex and older ages can be considered as independent risk factors for DR. Nonetheless, some studies did not find any significant relationship between sex and DR (28, 38).

3.8. Inflammatory Factors

The increase in the level of inflammatory factors is associated with an elevated risk of vascular disease such as DR. The higher levels of C-reactive protein (CRP) were observed in patients with mild or severe DR. Increased CRP significantly has been associated with increased risk of macular edema and retinal hard exudates. The increased circulating cytokines in DM2 patients are associated with

increased vascular leakage, DR progression, and macular edema development. Moreover, retinal pigment epithelium (RPE) and glial cells produce the pro-inflammatory cytokines and can be considered as a main target for anti-inflammatory agents for DR treatment (70). Thus, the monitoring of systemic inflammatory markers can be helpful in determining the prognosis of DR.

3.9. Myopia

Myopia is a common problem in all societies. Although, in most cases, it leads to ocular complications such as myopic tractional maculopathy, myopic macular degeneration, and choroidal neovascularization, some studies reported that the prevalence of DR among myopic diabetic patients was significantly lower than non-myopic ones ($P < 0.001$). This result suggested that myopia has a protective role against DR development (71). In contrast, this study found that myopia was associated with DR due to axial length. They reported that for each millimeter increase in axial length, the risk of DR significantly decreased ($P < 0.001$).

3.10. Genetic Polymorphisms

Some gene polymorphisms may lead to a predisposition to the progression of DR, although they are not a modifiable risk factor. Some studies found that the *TCF7L2* gene was associated with DM (72), and overexpression of this gene is related to poor serum glucose control. Some polymorphisms of the *TCF7L2* gene were known to have a role in the development of DR. Ciccacci et al. observed that patients with rs12255372 or rs7903146 polymorphisms in *TCF7L2* had a more chance for developing DR (73). In a meta-analysis by Ding et al., they found that the rs7903146 (T allele in *TCF7L2*) was significantly correlated with the elevated risk of DR ($P \leq 0.001$) (74). Ma et al. reported that *Pro12Ala* polymorphism of the *peroxisome proliferator-activated receptor* $\gamma 2$ (*PPAR*$\gamma 2$) gene is another effective polymorphism on the development of DR (75). The *PPAR*$\gamma 2$ gene has a vital role in metabolic pathways such as glucose metabolism, angiogenesis, and inflammation. Interestingly, Ma et al. showed that the Ala allele has a protective role in DR ($P = 0.03$) (75). Moreover, various studies confirmed that some polymorphisms of the CRP gene could be effective on development and progression of DR. For instance, Peng et al. found that the rs2808629 variants of CRP were significantly correlated with an elevated risk of DR ($P = 0.006$) in DM2 patients. So, this polymorphism of CRP can be considered as an independent genetic risk factor for the development of DR (76). The serum levels of CRP were high in patients with this variant (77). Other nucleotide polymorphisms were found in DR patients, which is related to the progression of DR into severe stages; however, this field is still new and needs further research. Other risk factors for DR include puberty, pregnancy, and cataract surgery (25), which should be considered in future studies.

4. Conclusions

Diabetes is a chronic underlying disease that imposes an enormous burden on the healthcare system. It is the most severe complication in the eye caused by diabetes and may lead to visual impairment and blindness. Therefore, knowledge about different risk factors for DR is essential to prevent and prepare treatment targets or programs and limit the progression of DR. Moreover, DR is a multifactorial disease, and many studies have demonstrated that various risk factors (such as hyperglycemia, hypertension, hyperlipidemia, etc.) can be associated with it.

4.1. Future Perspectives

Future studies can elucidate new risk factors associated with the development and progression of DR and introduce prognostic factors for early detection, prevention, and limiting the progression of DR. Also, these risk factors may help to better understand the pathophysiological state of DR and find novel therapies. Further studies are needed to investigate new factors related to DR in the fields of "omics" of DR, including genomics, proteomics, epigenomics, metabolomics, and glycomics.

Footnotes

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