BIOMEDICINSKA ISTRAŽIVANJA
2023;14(2):230–239

UDK: 617.735:616.379-008.64
DOI: 10.59137/BII202302337A

Review

Dyslipidemia as a risk factor for diabetic retinopathy

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Primljen – Received: 17/10/2023
Prihvaćen – Accepted: 12/12/2023

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Summary

Diabetic retinopathy (DR) is a chronic microvascular complication of diabetes. Due to the dramatic increase in the number of diabetes cases, the prevalence of DR has also risen, making it the leading cause of blindness among the working-age population worldwide, despite the availability of screenings and modern therapeutic options.

Risk factors for the development and progression of DR (duration of diabetes, hypertension, hyperglycemia, dyslipidemia, and genetic factors) have been investigated in numerous epidemiological studies and clinical researches, but the research results were not consistent. In recent years, there has been considerable interest in the study of dyslipidemia in diabetes as one of the factors that could influence the onset and progression of DR, as well as apolipoproteins as potentially better biomarkers for DR. The results of our research also point in that direction.

Identifying the risk factors for DR is crucial for enabling adequate prevention and raising awareness among individuals with diabetes about the importance of taking appropriate measures to prevent this microvascular complication.

Keywords: diabetic retinopathy, diabetes, dyslipidemia, microvascular complications, risk factors

Introduction

Diabetes mellitus (DM) is considered a global epidemic of the 21st century, with a dramatic increase in the number of affected individuals worldwide. In the year 2000, there were 171 million documented cases of diabetes globally, with estimates suggesting that by 2030, approximately 366 million individuals would have DM [1]. However, this number is almost doubled. According to the International Diabetes Federation (IDF) report in 2021, 537 million adults were registered

as having diabetes, with new projections foreseeing 643 million cases by 2030 and 783 million by 2045. It is noteworthy that, according to the same report, three out of four adults with diabetes reside in low- and middle-income countries. Considering the significant number of undiagnosed patients, the issue of diabetes becomes even more complex [2].

Diabetic retinopathy (DR) stands as one of the most common complications of DM. It is one of the four leading causes of visual impairment and is responsible for 12% of new cases of blindness worldwide each year. Among the working-age population (aged 20 to 74 years), it represents the primary cause of legal blindness. DR is a chronic, microvascular, neuroinflammatory, and neurodegenerative complication of DM. It results in damage of the retinal blood vessels, reducing perfusion, leading to ischemia and impairing retinal function.

Chronic hyperglycemia damages various cell types in the retina, including endothelial cells and pericytes of retinal blood vessels, as well as neurons (photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells), glial cells (Müller cells and astrocytes), microglial cells, and cells of the retinal pigment epithelium (RPE). Along with the growing number of individuals affected by DM, the prevalence of patients with retinopathy is also increasing. In 2012, approximately 93 million people worldwide had DR, in 2015, 145 million had some form of DR, and 45 million had vision-threatening retinopathy [3].

In the clinical presentation of DR, the process in the macula, referred to as diabetic macular edema (DME), differs from the process on the retina outside the macula, known as diabetic retinopathy (DR). Both of these clinical entities encompass several severity levels and can manifest separately or in combination. The proposed International classification for DME includes the following categories: DME absent, DME present (mild DME, moderate DME, severe DME). The clinical classification for DR comprises the following categories: no apparent DR, non-proliferative DR (mild NPDR, moderate NPDR, severe NPDR), and proliferative DR (PDR) [4].

Risk factors

There are numerous and complex risk factors for DR. The risk of developing and progressing DR is associated with the duration of the disease, poor glycemic control (hyperglycemia), elevated blood pressure (hypertension), dyslipidemia, genetic factors, impaired renal function (renal disease), pregnancy, obesity, and physical inactivity.

Identifying the risk factors for the development of DR is crucial to enable adequate prevention and raise awareness among individuals with DM about the importance of adopting appropriate measures to prevent the onset of this microvascular complication [5].

The duration of DM is the most significant factor in the development of DR. As the duration of DM increases, the incidence of DR progressively rises. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is one study that has demonstrated that in type 1 diabetes (T1D), after five years of the disease, DR occurs in 25% of cases, after 10 years in 50%, and after 15 years, approximately 80% of cases have some form of retinopathy. In type 2 diabetes (T2D), after five years of the disease, DR develops in 40% of patients, after 15 years in 84%, and after 25 years, 25% of patients have proliferative DR (PDR). In T2D, some form of retinopathy is already observed in 7–39% of cases at the time of disease diagnosis, and within that range, 4–8% of individuals have significantly impaired vision. The reason for this is the prolonged failure to recognize the underlying disease [6].

Glycemic control is one of the most crucial factors influencing the development and progression of DME and DR. While good metabolic control does not prevent the onset of DR, it significantly delays its development

and slows its progression in both T1D and T2D.

The Diabetes Control and Complications Trial (DCCT) from 1993 and the United Kingdom Prospective Diabetes Study (UKPDS) from 1998 are two randomized studies that demonstrated the effectiveness of good metabolic control in preventing DR. Large randomized studies have confirmed that with each 1% reduction in glycated hemoglobin A1c (HbA1c), the frequency of DR decreases by 37%, and for every 10 mmHg reduction in systolic blood pressure, the prevalence of retinopathy decreases by 13%. HbA1c exhibits higher affinity for oxygen, leading to impaired oxygen release in tissues and the development of reactive hypoxia. Accumulation of glycation end-products in the basement membrane results in thickening of the basement membrane and increased capillary permeability [7, 8]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study determined that the target HbA1c should be individually tailored. Stricter targets of 6 to 6.5% are recommended for younger individuals with diabetes, while less stringent targets of around 7–8% are suggested for older patients due to the higher risk of hypoglycemia in older individuals. The occurrence of severe hypoglycemia can be the risk factor for the progression of DR and DME [9]. With the sudden establishment of good metabolic control, patients who have severe DR may experience a temporary additional worsening of DR, a phenomenon known as the "early worsening phenomenon." It is essential to alert patients to this possibility. Considering that T2D often has a subtle onset at the time of diagnosis, around 8% of patients already have cardiovascular disease (CVD), up to 39% have some form of retinopathy in one eye, 18% have retinopathy in both eyes, and 18% have microalbuminuria. One study has determined that 1% reduction in HbA1c (e.g., from 8% to 7.2%) leads to 43% lower risk of progression and 45% lower risk of developing retinopathy in patients with T2D. Additionally, Mohamed et al. have shown that the same reduction in this parameter leads to 40% reduction in the incidence of retinopathy, 25% decrease in the need for laser treatment, and prevents blindness in 25% of cases [10]. Good glycemic control leads to the reduced risk of developing chronic complications over a time period that extends beyond the duration of optimal glycemic control. This phenomenon is known as "metabolic memory" [11].

Hypertension is the significant risk factor and is associated with very high risk of DR and DME progression because it further exacerbates retinal ischemia and damages the endothelial cells of retinal capillaries.

The WESDR study has found that 10 mmHg reduction in blood pressure leads to 35% reduction in the prevalence of retinopathy, 35% decrease in the need for laser therapy, and 50% reduction in the risk of blindness. Additionally, the same study has demonstrated that 10% increase in diastolic blood pressure leads to an earlier onset of DR and increases the risk of proliferative DR or DME [6]. The Hoorn study from 2003, conducted on a sample of 2484 patients, established statistically significant association between elevated blood pressure and the severity of DR, as well as the occurrence of hard retinal exudates. Strict blood pressure control and the reduction of systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg reduce the risk of DR progression by 24% after six years and 34% after nine years, while also lowering the risk of visual acuity decline by up to 7% [10].

According to the recommendations of the National Institute for Health and Clinical Excellence (NICE), in patients with T2D, the target blood pressure should be less than 140/80 mmHg. Achieving this therapeutic goal sometimes requires the use of multiple antihypertensive medications. Among antihypertensives, ACE inhibitors, particularly lisinopril, have been proven to be a good therapeutic option for patients with DR and DME [12].

Genetic factors also play a role, and today there is significant interest in identifying genetic factors involved in the development and progression of DR. Understanding these genes opens up new avenues for prevention and therapeutic strategies. In the absence of a specific gene strongly associated with diabetic vascular complications, several clinical and epidemiological studies have shown that both external and genetic factors play the crucial role in the development of diabetic vascular complications [5].

Positive family history of T2D has been observed to be associated with genetic factors and subsequently with the development of diabetic vascular complications. Supporting the assumption that there is a genetic predisposition for the development of DR, reports of aldose reductase gene polymorphism have been linked to the increased risk of DR and other microvascular complications [13].

According to studies by Maghboli et al. involving 1228 patients, this association has been proven. A strong association between the positive family history of T2D and the occurrence of diabetic retinopathy has been established (p=0.004). The authors conclude that diabetic complications are the result of gene-environment interactions. The family history of diabetes points to the potential genetic and epigenetic basis for DR. Researchers also emphasize the role of epigenetic modifications and metabolic memory in patients with DR who have the positive family history.

Various twin studies point to the important role of genetic factors in diabetes and diabetes complications. Twin and family studies have demonstrated that risk of DR emergence is three times higher in patients with the family hystory of DR than in patients without it for both T1DM and T2DM. Coincidence is dramatically higher among monozygotic twins when compared to dizyigotic twins [14].

These genes are part of different physiological and pathophysiological processes in the body, often associated with inflammation, such as renin – angiotensin aldosterone system, glucose induced pathways, remodeling of the extracellular matrix, vascullar endothelial dysfunction and angiogenesis. The results of some studies are very conflicting and may be caused by factors of ethnic differences.

VEGF activation causes significant damage to the blood- retinal barrier and can also induce neovascularization in proliferative diabetic retinopathy. Several studies suggest that the presence of a single nucleotid (SNP) polimorpolymorphism VEGF-2578C/A can affect the development of DR.

Aldose reductase (ALR) has been significantly implicated in the pathogenesis of DR via poliol pathway, by which excess intracelular glucose in retinal cells is converted to fructose. The AKR1B1 gene is located on cromosome 7q33 and expressed in retinal capillary perictes to produce ALR. Increased ALR and poliol pathway activity has also been shown to be significantly associated with pericyte degeneration, which leads to the breakdown of the blood -retinal barier and the development of exudates and macular edema in DR.

If these findings were confirmed in larger studies, this could pave the way for personalized treatment options for those who are at higher risk of developing different forms of DR [15, 16].

Microalbuminuria, proteinuria (renal disease) is known predictor of PDR development in T1D, and most proteinuria is associated with 95% increased risk of diabetic macular edema (DME). Chronic kidney disease is associated with DR and refractory DME in the T2D population. Cases of improved findings after kidney transplantation have been reported. Elevated albumin and creatinine ratio values have more significant association with the prevalence of DR than reduced glomerular filtration rates, but both correlate with DR in T2D patients [17].

Smoking has been reported as the risk factor for DR progression in the UKPDS

study [8]. Smoking is the independent factor for the development of cardiovascular diseases, especially in individuals with T2D. In the WESDR study, which investigated the impact of other risk factors, smokers with T1D and T2D had 2.4 times higher mortality rate compared to non-smokers [6]. Several studies have aimed to determine smoking (tobacco smoke consumption) as the possible factor for the development and progression of DR.

The association of cigarette smoking with microvascular complications in T2D is complex. A smaller number of studies have shown that smoking is the risk factor for the development of PDR. However, most studies have found that smoking is not the risk factor for the development of PDR [18]. Our study also did not show the statistically significant difference in smoking prevalence between patient groups. Out of the total number of patients in our study, 16% have been smokers, 62% have reported being former smokers, while 22% of patients have never used tobacco [19].

Pregnancy also represents the risk factor for the onset and progression of diabetic retinopathy (DR). During pregnancy, more frequent eye check-ups with an ophthalmologist are recommended due to the potential worsening of retinopathy, resulting in diabetic macular edema (DME) and reduced vision [20, 21].

Physical activity is associated with reduced activity of insulin-sensitive kinases, which can lead to the increase in free fatty acid levels in skeletal muscles. Individuals with low levels of physical activity have higher degree of insulin resistance, meaning reduced insulin sensitivity compared to physically active individuals with the same degree of obesity.

Physical activity is linked to lower risk of cardiovascular disease mortality in people without diabetes and in those with diabetes. There is limited data in the literature regarding the relationship between physical activity and diabetes microvascular complications. One study examining the impact of physical activity on the development of diabetic retinopathy found that individuals who had engaged in physical activity earlier in life had significantly lower incidence of diabetic retinopathy. Physical activity reduces the risk of these complications in two ways: directly, by lowering blood glucose levels and increasing insulin sensitivity, and indirectly, by improving cardiovascular function, increasing high-density lipoprotein (HDL) cholesterol levels, and reducing the risk of developing hypertension [22].

Obesity also holds the important place among the risk factors for the development of diabetic complications and diabetic retinopathy. Obesity is the significant risk factor for the development of diabetic retinopathy and microvascular complications of diabetes and is positively correlated with worsening metabolic control.

Obesity is defined as excess body weight expressed through the body mass index. In overweight or obese individuals, particularly with visceral obesity, adipocytes secrete inflammatory cytokines leading to a condition known as cytokine toxicity. In individuals with type 2 diabetes (T2D) who are obese, there is an elevated level of circulating free fatty acids, leading to the development of lipotoxicity [23].

Dyslipidemia

Dyslipidemia is the significant systemic disorder that also contributes to the development and progression of DR. It has been observed that hard retinal exudates in the macular region are significantly associated with increased serum cholesterol and triglyceride concentrations. Diabetic or atherogenic dyslipidemia includes disruptions in low-density lipoprotein (LDL) levels, elevated triglyceride levels, decreased high-density lipoprotein (HDL) levels, and changes in the size and structure of LDL particles that become

pro-atherogenic, i.e., small and dense. Altered LDL particles more easily penetrate the arterial wall, where they oxidize accelerating atherosclerosis despite the use of statins [19].

Numerous studies have shown that patients with diabetes are at the increased risk of atherosclerotic cardiovascular disease (CVD). This is confirmed by the fact that mortality in patients with diabetes and CVD is 2-3 times higher compared to the non-diabetic population [5]. Data from the DCCT study indicate that traditionally measured lipids (cholesterol and triglycerides) are associated with the risk of DR in individuals with T2D. Elevated HDL concentrations in circulation have an anti-atherogenic effect, whereas low HDL levels increase the risk of DR and diabetic nephropathy [7]. The study from 2011 by Sasongko et al. demonstrated the strong and statistically significant association between HDL and the severity of DR, while no significant associations with traditional lipids were observed [24].

In the Early Treatment Diabetic Retinopathy Study (ETDRS), which included 2709 patients with DR, high LDL values were associated with the higher frequency of hard retinal exudates. The UCgun study and others did not find the association between DR and traditional lipids. According to a meta-analysis from 2015 that included 21 published scientific papers, serum triglycerides were statistically significantly higher in patients with DME compared to those without DME [25].

The UKPDS study has shown that elevated levels of LDL cholesterol are the strong predictor of future cardiovascular events in patients with diabetes. This led to the introduction of LDL as the main therapeutic target in the treatment of these patients using statins [8]. Research has shown that serum LDL particles do not directly participate in the atherosclerosis process. Instead, there is a prior structural modulation of these particles, which are recognized by macrophages in the blood vessel wall through apolipoprotein B (Apo B), initiating the atherosclerosis process [26].

In recent years, it has been recommended to measure non-HDL cholesterol in patients with diabetes as better marker of atherogenicity, representing the difference between total cholesterol and HDL cholesterol. The Chennai Urban Rural Epidemiology Study (CURES) and our study have shown that non-HDL is statistically significantly associated with DR and DME [25]. According to the European recommendations from 2016 for dyslipidemia therapy, besides LDL cholesterol, non-HDL cholesterol and Apo B are included as therapeutic targets for patients with diabetes.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study has demonstrated the effectiveness of fenofibrate in DR treatment. It has evaluated the need for laser treatment after five years of follow-up. The results of this study have showed that the group of patients receiving fenofibrate 200 mg daily reduced the frequency of laser treatment by 30% for PDR and 31% for DME. In the same study conducted on patients whose retinal status was graded as FF, fenofibrate reduced the progression of existing DR. The FIELD and ACCORD studies have provided evidence of the effects of fenofibrate on DR. Australia was the first country to register fenofibrate as the drug for DR treatment in 2013 [27].

Apolipoproteins

Apolipoproteins are proteins representing an important structural and functional component of lipoproteins. They participate in the transport of lipoproteins, their binding to lipoprotein receptors and activation of lipolytic enzymes.

Apolipoprotein E (Apo E) plays a crucial role in plasma lipid metabolism and the lipid homeostasis of the central nervous system. The Apo E gene is polymorphic, with three common alleles, Ɛ2, Ɛ3, and Ɛ4, encoding three main isoforms, leading to the formation

of six different phenotypes (Ɛ2/2, Ɛ2/3, Ɛ2/4, Ɛ3/3, Ɛ4/3, and Ɛ4/4). Apo E is synthesized in the retina by Müller cells, secreted into the vitreous, and rapidly transported to the optic nerve through retinal ganglion cells. There is a significant possibility that it plays the role in intraretinal lipid transport [28, 29].

In recent years, there has been significant interest in studying the association of apolipoproteins Apo A1 and Apo B in DR. Apo A1 is a component of HDL, while Apo B is the component of very low-density lipoproteins (VLDL) and LDL. Studies have shown that Apo A1 has a protective effect and participates in removing excess cholesterol from tissues. Apo B is present in DR and is responsible for transporting cholesterol into tissues, serving as an atherogenic factor. These studies indicate that these two apolipoproteins may be more directly involved in the biophysical changes associated with the development of DR than traditional lipids (total cholesterol, triglycerides, HDL, and LDL). However, the extent of their function and the mechanisms by which they may influence the development of DR remain insufficiently understood.

Several studies have demonstrated the association between serum apolipoproteins Apo A1, Apo B, and the Apo B/Apo A1 ratio with the presence and severity of DR in individuals with T2D [19, 24, 30]. Some studies have shown that among traditional lipids, only HDL was significantly associated with DR, suggesting that apolipoproteins may be better biomarkers for diabetic retinopathy than conventional lipids [31, 32].

Our results confirm the findings mentioned and demonstrate that Apo B was highest in severe non-proliferative DR, lower in moderate, even lower in mild, and the lowest in the group without DR. Additionally, a highly statistically significant difference (p=0.001) was observed between the groups based on the severity of DME, in patients with severe DME having significantly higher Apo B values compared to those with moderate and mild DME. Our study indicates that the average Apo B value can be a good indicator of the presence of DME [19]. In contrast, in the one-year observational study in Kolkata, India, researchers found that Apo A1 was lowest (0.88 ± 0.28) in the group of diabetic individuals without retinopathy and highest in the severe NPDR group (1.67 ± 0.17) [33]. This is in contrast to our research, where patients without DR had statistically significantly higher average values of Apo A1 (1.67 ± 0.24) than patients with PDR (0.96 ± 0.44) (p=0.001) [19]. Sasongko also showed that Apo A1 was negatively correlated with the severity of DR and that Apo A1 was stronger biomarker for DR than the traditional lipid profile in the Australian population [24]. Apo A1 inhibits the oxidation of LDL cholesterol to form oxidized LDL that reduces the anti-inflammatory and antithrombolytic functions of the endothelium, while Apo B has atherogenic properties. Key in the pathogenesis of microangiopathy leading to DR is the effect of the interaction of Apo A1 and Apo B. Precisely because of this, the Apo B/Apo A1 ratio would be the useful parameter that can reflect both lipoprotein pathways, both harmful and protective. A low Apo A1/Apo B ratio is considered the risk for atherosclerosis. In our study, patients without DR had significantly higher average values of Apo A1/Apo B ratio (1.76 ± 0.64) compared to patients with PDR (0.61 ± 0.58). High Apo B/Apo A1 ratio is considered the risk for atherosclerosis. In our research, patients without DR had statistically significantly lower average values (0.63 ± 0.25) than patients with PDR (2.80 ± 2.50) (p=0.001) [19]. Krishnamoorthy et al. also showed in their study of 100 patients with T2D from 2016 that there was the statistically significant correlation of serum apolipoproteins namely Apo A1 (p<0.001), Apo B (p<0.001) and Apo B/Apo A1 ratio (p<0.001) and that apolipoproteins were better biomarkers for DR [32].

Conclusion

While the leading risk factors for the development of diabetic retinopathy (DR), such as the duration of type 2 diabetes (T2D), hypertension, hyperglycemia, dyslipidemia, and genetic factors, have been thoroughly examined in numerous epidemiological studies and clinical research, there are significant variations in the results of different studies.

It has been observed that some patients with long-standing T2D and poor sugar control do not develop DR, while other patients with the shorter duration of T2D and better sugar control develop DR.

Therefore, there is a great interest in researching other possible risk factors that could play the role in the development and progression of DR.

Recognizing the risk factors for the occurrence of DR is essential in order to take appropriate preventive steps and raise awareness among individuals with diabetes.

Funding source. This paper represents a part of the research within the Project 2019 "Association of lipid status and APOE gene polymorphism with diabetic retinopathy in patients with type 2 diabetes", which was funded by the Ministry of Science and Technology of Republic of Srpska.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

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Dislipidemija kao faktor rizika za dijabetičku retinopatiju

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Dijabetička retinopatija (DR) je hronična, mikrovaskularna komplikacija dijabetesa. Zbog dramatičnog porasta broja oboljelih od dijabetesa, bilježi se porast broja pacijenata sa DR tako da i pored dostupnih pregleda i savremenih terapijskih opcija liječenja, DR i dalje ostaje vodeći uzrok sljepila u radno sposobnoj populaciji širom svijeta.

Faktori rizika za nastanak i progresiju DR (dužina trajanja dijabetesa, hipertenzija, hiperglikemija, dislipidemija i genetski faktori) ispitani su u velikom broju epidemioloških studija i kliničkih istraživanja, ali rezultati istraživanja nisu bili dosljedni.

Posljednjih godina postoji veliko interesovanje za proučavanje dislipidemije u dijabetesu kao jednog od faktora koji bi mogao uticati na pojavu i napredovanje DR, kao i apolipoproteina kao potencijalno boljih biomarkera za DR. Rezultati našeg istraživanja takođe idu u tom smjeru. Prepoznavanje rizika za nastanak DR je veoma važno kako bi se sprečavanje DR moglo blagovremeno izvršiti i podići svijest oboljelima od dijabetesa za primjenu odgovarajućih mjera u sprečavanju nastanka ove mikrovaskularne komplikacije.

Ključne riječi: dijabetička retinopatija, dijabetes, dislipidemija, mikrovaskularne komplikacije, faktori rizika