ISSN: 1004-5619
Volume 41, Issue 01, March, 2025

Diabetic retinopathy detection between the past and the present

Sahar Hossam ElHini[1], Mohammed Abdelhakeem[2], Asmaa Anwar Mohamed[3], Mohamed Abdel Hamid[3], Christina Rafat Kamal[4]

Professor of endocrinology and diabetes, Diabetes and endocrinology unit, Internal medicine department, Faculty of medicine, Minia University[1]
Professor of clinical pathology, Clinical pathology department, Faculty of medicine, Minia University[2]
Assistant professor of ophthalmology, Ophthalmology department, Faculty of Medicine, Minia University[3]
Assistant lecturer of internal medicine, Internal medicine department, Faculty of Medicine, Minia University[4]

Keywords:
Diabetes, Retinopathy, OCT, OCTA, TSPO

DOI:
01.1232/Fyxzz.29.01.2025.01

ABSTRACT

Diabetes Mellitus is a collective term for heterogeneous metabolic disorders whose main finding is chronic hyperglycemia. It has several complications that are mainly categorized into microvascular and macrovascular complications. In this article, we focus mainly on diabetic retinopathy, which is a major preventable cause of blindness worldwide. Screening and early detection modalities are the principal interests of researchers in order to stop diabetes complications in the eye. However, most of the known conventional methods are expensive, time-consuming and require high professional expertise. Convenient, rapid and accurate modalities in recent studies are clearly discussed.

1. INTRODUCTION

Diabetes is a chronic, complicated illness that necessitates ongoing medical attention and comprehensive reduction of risk factors that go beyond controlling blood sugar levels. People must get ongoing diabetes self-management education and support in order to feel empowered, avoid acute problems, and lower their chances of developing serious complications [1]. Globally, the prevalence of diabetes has risen at a startling rate. An estimated 500 million individuals worldwide have diabetes [2]. According to the 2017 International Diabetes Federation estimate, 451 million adults worldwide had diabetes in 2017, and 693 million people are predicted to have the disease by 2045. By 2030, the World Health Organization (WHO) predicts that over 19% of all adults worldwide will have diabetes mellitus [3].

Types of Diabetes and Pathophysiology

Diabetes is traditionally categorized into several clinical types, which are classified according to pathophysiology, genetic, metabolic, and other factors. Which are: Type 1 diabetes (including latent autoimmune diabetes in adults), Type 2 diabetes, Gestational diabetes mellitus, Specific types such as

monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes [4].

An autoimmune response in which the body's immune system targets the pancreatic beta cells that produce insulin is the etiology of type 1 diabetes. The body consequently generates either very little or no insulin. The autoimmune reaction is brought on by a confluence of genetic predisposition and an additional environmental trigger, like a viral infection. Additionally, toxins and some nutritional components have been linked. Although T1DM can strike at any age, it most commonly affects children and adolescents [2].

The pathophysiology of type 2 diabetes is complicated and multifaceted. Although insulin resistance and decreased insulin production are thought to be the primary pathogenetic pathways, other factors can result in persistent hyperglycemia: decreased glucagon-like peptide-1 (GLP1) and other incretin effects; decreased glucagon secretion; and increased renal reabsorption of glucose [5].

Risk factors and complications of diabetes:

Type 2 diabetes risk factors include being over 45, obesity, having a family history of diabetes, physical inactivity, having a history of impaired glucose tolerance or impaired fasting glucose, presence of cardiovascular diseases (CVD), polycystic ovarian syndrome, hypertension, dyslipidemia, and gestational diabetes [5].

Numerous microvascular and macrovascular complications that are caused by type 2 diabetes (T2D) result in a significant burden of hospitalizations, quality of life reductions, increased mortality, and costs. To stop the development of these problems, there should be intensive glycemic control combined with risk factor-controlling drugs (such as statins, aspirin, ACEI, and more recently, SGLT2i, GLP-1RA) that help lessen cardiovascular and renal consequences is necessary [6].

Retinopathy, peripheral and autonomic neuropathy, erectile dysfunction, and nephropathy (albuminuria, chronic kidney disease) are among the microvascular complications of diabetes. Heart failure, peripheral artery disease (PAD, diabetic foot, amputation), cerebrovascular disease (CVD, stroke, transient ischemic attack), and coronary artery disease (CAD, myocardial infarction, coronary revascularization, angina) are examples of macrovascular complications [7].

Diabetic retinopathy

About 30 to 40% of people with diabetes develop diabetic retinopathy (DR), the main visual consequence of diabetes. Over 100 million people worldwide suffer from DR, which is a major cause of blindness and visual impairment, particularly in working-age adults [8], [9]. The incidence of retinopathy is 90% in patients with Type 1 DM after 20 years, whereas it is >60% in those with Type 2 DM. Rarely does T1DM cause retinopathy prior to puberty [10]. Fortunately, a large portion of DR-related vision loss may be avoided, and over the past few decades, the incidence of both DR and diabetes-related vision loss has gradually decreased [8].

In addition to the duration of diabetes, chronic hyperglycemia, nephropathy, hypertension, and dyslipidemia are other risk factors linked to retinopathy [11], [12]. In addition to high BMI, pregnancy, puberty, and cataract surgery [13].

Visual loss increases the risk of falls, hip fractures, and mortality by four times. Moreover, Leg amputation and sight loss caused by diabetic retinopathy are independent predictors of early death among people with

ISSN: 1004-5619
Volume 41, Issue 01, March, 2025

type 1 diabetes [14]. Therefore, early detection and screening of diabetic eye disease is mandatory to prevent diabetes complications in the eye.

Diabetic retinopathy screening and follow up

ADA 2025 recommends that patients should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist and recommends the time of eye examination for different types of diabetes as follows:

- Within 5 years after the diagnosis of diabetes, people with type 1 diabetes should have an initial eye examination.
- At the time of diagnosis in people with type 2 diabetes
- individuals of childbearing period with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be screened before pregnancy or in their first trimester, and then monitored every trimester and for 1 year postpartum, according to the degree of retinopathy
- Individuals who develop gestational diabetes Mellitus do not require an eye examination during pregnancy [11], [13].

If retinopathy is present (14):

- Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
- Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy
- Review glycemic, BP and lipid control, and adjust therapy to reach targets
- Screen for other diabetes complications

If retinopathy is not present (14):

- Type 1 diabetes: rescreen annually
- Type 2 diabetes: rescreen every 1 to 2 years
- Review glycemic, BP and lipid control, and adjust therapy to reach targets
- Screen for other diabetes complications

Classification of diabetic retinopathy:

American Academy of Ophthalmology (AAO) 2019 classifies DR as follows:

(TABLE 1) Diabetic Retinopathy Disease Severity Scale and International Clinical Diabetic Retinopathy Disease Severity Scale (ICDRDSS) as follows:

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
0=No apparent retinopathy	No abnormalities
1=Mild NPDR	Microaneurysms only
2=Moderate NPDR	More than just microaneurysms but less than severe NPDR
3=Severe NPDR • U.S. definition	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of 4 quadrants • Definite venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants
• International definition	Any of the following and no signs of proliferative retinopathy: • More than 20 intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in 2 or more quadrants • Prominent IRMA in 1 or more quadrants

4=PDR	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = non-proliferative DR; PDR = proliferative DR.
NOTES: Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR. (15-16)

Conventional techniques for detection of DR:
The crucial step in stopping the advancement of diabetic macular edema, DR and other complications that could lead to loss of vision is the early diagnosis of retinal abnormalities [17]. Current diabetic retinopathy screening techniques include retinal fundus imaging and manual evaluation.

Nonetheless, these methods are greatly exhausting and costly, requiring the expertise of highly qualified professionals for evaluation.

The gold standard imaging technique for detecting diabetic retinopathy is presently stereoscopic *color fundus photography* with seven standardized fields of vision. This method can also assist in identifying DME and mild retinal neovascularization [18]. However, this procedure is laborious and protracted for patients, since it necessitates the collection of pictures from seven distinct fields [19].

Fluorescein angiography (FA), in addition to fundus imaging, is another often-used technique for screening for DR and other retinal diseases. FA is an invasive technique that involves giving sodium fluorescein orally or intravenously and then using rapid sequence photography to assess how well it circulates across the retina [20]. It helps to identify early alterations in capillary closure, the blood-retinal barrier, and the development of microaneurysms [20]. Moreover, FA can identify macular ischemia, unlike fundus photography.

The invasive nature of FA, the time constraints during observation, the requirement for costly equipment, and side effects like sodium fluorescein allergies are some of its disadvantages [21].

Optical coherence tomography angiography (OCTA)
A new non-invasive, non-contact method called OCTA can produce high-resolution pictures of the choroidal and retinal arteries. An important part of DR assessment is identifying areas with or without flow, which is accomplished by OCTA by producing three-dimensional depth-resolved pictures of the retinal and choroidal vascular system. OCTA offers significant benefits over fluorescein angiogram (FA), though its inability to detect arterial leakage. Above all, OCTA is noninvasive and can give comprehensive details regarding the retinal microvasculature in DR without requiring an intravenous contrast material [22].

In the meantime, OCTA image and data acquisition is quicker and easier than FA. Additionally, in contrast to conventional dye-based angiography, OCTA offers depth-resolved images and can enable distinct visualization of the superficial, middle, and deep retinal capillary plexuses, potentially providing more pathological information [23].

Optical coherence tomography (OCT):
OCT is a new optical imaging method that has become an established standard for retinal tomographic imaging and high-resolution measurements. OCT produces noninvasive, noncontact, high-resolution cross-

sectional images of the retina. Because it does not rely on pupillary dilation or dye injection, as other methods do, it lowers the possibility of allergic reactions that could be fatal. OCT images are in the form of 2D or 3D data sets, representing optical reflection or scattering in a cross-sectional plane [24].

OCT makes it possible to quantify retinal thickness more precisely and to image the retina more effectively. Numerous studies have demonstrated that the incidence of diabetes has varying effects on the inner retinal layers, making accurate measurement of retinal thickness one of the most significant biomarkers retrieved from OCT pictures. Therefore, it is preferable to precisely measure and quantify each retinal layer's properties independently, especially each layer's thickness [21].

OCT enables the effective segmentation of all intraretinal layers and quantitative and qualitative measures of retinal properties, as well as the detection of minor changes in retinal thickness as diabetes progresses. Therefore, it may be able to identify early retinal abnormalities in patients with diabetes, which could then postpone any more complications, identify the likelihood of developing DR, and be used for preventive treatment before the illness worsens [25].

Serum biomarkers:

DR pathophysiology is multifactorial and has different mechanisms such as proinflammatory mediators, increased levels of oxidative stress and VEGF secretion. It also causes impairment of neurotransmitters and neuroprotective factors throughout the retina. In addition to the rupture of endothelial junctions, the formation of pericyte ghosts, thickening of the basement membrane, and further neovascularization occur [26].

The inflammatory reactions that occur locally in the retina are mediated by activated microglia which are present in the plexiform layers of the retina, that become overly reactive and secretes pro-inflammatory mediators such as cytokines and chemokines. Hence, microglia present a critical target for therapeutic intervention in the prevention and treatment of neurodegenerative diseases in the retina [27].

Translocator protein (TSPO)

Translocator protein (TSPO; 18 kDa) is a highly structurally conserved hydrophobic protein located on the outer mitochondrial membrane (OMM). It is responsible for normal physiological cell function, mitochondrial transport, and mitochondrial homeostasis maintenance [28].

It is distributed in steroidogenic tissues, and one important function is translocating cholesterol from the cytoplasm into mitochondria, which is the rate-limiting step in the synthesis of neurosteroids and other steroids. TSPO expression has been detected in the human retina and the Retinal pigment epithelium (RPE) [29], [30].

It was reported that TSPO was decreased in the early stage of DR in the retina of DR rat models [31].

DR includes mitochondrial dysfunction and oxidative stress damage, both of which accelerate retinal neuronal apoptosis. Correspondingly, TSPO has been suggested to play a role in the regulation of glucose metabolism and relieves diabetic neuropathy by reportedly raising neuroactive steroid levels. Thus, TSPO has been identified as a potential target for diabetes management [32].

[33] reported significantly higher expression levels of TSPO in the peripheral blood of patients with diabetes than in the controls, and a higher TSPO level n the active proliferative DR subgroup than in the

inactive proliferative DR subgroup.

Notably, several studies have demonstrated that modulation of microglia can improve disease outcomes in murine DR models. Thus, targeting TSPO to modulate microglia-mediated inflammation could represent a potential therapeutic approach during the early disease phase [34].

Conclusion

Serum biomarkers consider new trends in the early detection and monitoring of DR in addition to the detection of the effectiveness of different treatment modalities. They have the privilege of not being invasive and don't require expensive equipment. Moreover, human experience doesn't interfere with their results.

References

[1] American Diabetes Association Professional Practice Committee; Introduction and Methodology: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S1–S5.

[2] Soomro MH, Jabbar A. Diabetes etiopathology, classification, diagnosis, and epidemiology. In BIDE's Diabetes Desk Book 2024 Jan 1 (pp. 19-42). Elsevier.

[3] Ohiagu FO, Chikezie PC, Chikezie CM. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomedical Research and Therapy. 2021 Mar 31;8(3):4243-57.

[4] American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S27–S49.

[5] Tokhirovna EG. Risk factors for developing type 2 diabetes mellitus. Education Science and Innovative Ideas in The World. 2024 Jan 10;36(5):64-9.

[6] Arnold SV, Khunti K, Tang F, Chen H, Cid-Ruzafa J, Cooper A, Fenici P, Gomes MB, Hammar N, Ji L, Saraiva GL. Incidence rates and predictors of microvascular and macrovascular complications in patients with type 2 diabetes: results from the longitudinal global discover study. American heart journal. 2022 Jan 1;243:232-9.

[7] Arnold SV, Khunti K, Tang F, Chen H, Cid-Ruzafa J, Cooper A, Fenici P, Gomes MB, Hammar N, Ji L, Saraiva GL. Incidence rates and predictors of microvascular and macrovascular complications in patients with type 2 diabetes: results from the longitudinal global discover study. American Heart Journal. 2022 Jan 1;243:232-9.

[8] Tan TE, Wong TY. Diabetic retinopathy: Looking forward to 2030. Frontiers in Endocrinology. 2023 Jan 9;13:1077669.

[9] Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clinical & experimental ophthalmology. 2016 May;44(4):260-77.

[10] Sultan S, Memon RA. Microvascular complications: Diabetic eye disease. In BIDE's Diabetes Desk

Book 2024 Jan 1 (pp. 181-199). Elsevier.

[11] American Diabetes Association Professional Practice Committee; 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S252–S265.

[12] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 2012 Mar 1;35(3):556-64.

[13] Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, Simó R. Screening for diabetic retinopathy: new perspectives and challenges. The Lancet Diabetes & Endocrinology. 2020 Apr 1;8(4):337-47.

[14] Filiberto A, Amin K, Julie L. Retinopathy diabetes Canada clinical practice guidelines expert committee. Canadian Journal of Diabetes. 2018;42:210-6.

[15] Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, Ying GS. Diabetic retinopathy preferred practice pattern®. Ophthalmology. 2020 Jan 1;127(1):P66-145.

[16] Wilkinson CP, Ferris III FL, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampik A, Pararajasegaram R, Verdaguer JT, Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003 Sep 1;110(9):1677-82.

[17] Amin J, Sharif M, Yasmin M. A review on recent developments for detection of diabetic retinopathy. Scientifica. 2016;2016(1):6838976.

[18] Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology. 1991 May 1;98(5):786-806.

[19] Goh JK, Cheung CY, Sim SS, Tan PC, Tan GS, Wong TY. Retinal imaging techniques for diabetic retinopathy screening. Journal of diabetes science and technology. 2016 Mar;10(2):282-94.

[20] Cunha-Vaz JG. Diabetic retinopathy: surrogate outcomes for drug development for diabetic retinopathy. Ophthalmologica. 2000 Dec 1;214(6):377-80.

[21] Ghazal M, Al Khalil Y, Alhalabi M, Fraiwan L, El-Baz A. Early detection of diabetics using retinal OCT images. InDiabetes and Retinopathy 2020 Jan 1 (pp. 173-204). Elsevier.

[22] Yang Z, Tan TE, Shao Y, Wong TY, Li X. Classification of diabetic retinopathy: Past, present and future. Frontiers in endocrinology. 2022 Dec 16;13:1079217.

[23] Sun Z, Yang D, Tang Z, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: an updated review. Eye. 2021 Jan;35(1):149-61.

[24] Vermeer KA, Mo J, Weda JJ, Lemij HG, de Boer JF. Depth-resolved model-based reconstruction of attenuation coefficients in optical coherence tomography. Biomedical optics express. 2013 Dec 23;5(1):322-37.

[25] Ferreira JT, Alves M, Dias-Santos A, Costa L, Santos BO, Cunha JP, Papoila AL, Pinto LA. Retinal neurodegeneration in diabetic patients without diabetic retinopathy. Investigative ophthalmology & visual science. 2016 Nov 1;57(14):6455-60.

[26] S. Stem M, W. Gardner T. Neurodegeneration in the pathogenesis of diabetic retinopathy: molecular mechanisms and therapeutic implications. Current medicinal chemistry. 2013 Sep 1;20(26):3241-50.

[27] Kinuthia UM, Wolf A, Langmann T. Microglia and inflammatory responses in diabetic retinopathy. Frontiers in immunology. 2020 Nov 6;11:564077.

[28] Shoshan-Barmatz V, Pittala S, Mizrachi D. VDAC1 and the TSPO: expression, interactions, and associated functions in health and disease states. International journal of molecular sciences. 2019 Jul 8;20(13):3348.

[29] Klee K, Storti F, Barben M, Samardzija M, Langmann T, Dunaief J, Grimm C. Systemic knockout of Tspo in mice does not affect retinal morphology, function and susceptibility to degeneration. Experimental eye research. 2019 Nov 1;188:107816.

[30] Storti F, Klee K, Todorova V, Steiner R, Othman A, van der Velde-Visser S, Samardzija M, Meneau I, Barben M, Karademir D, Pauzuolyte V. Impaired ABCA1/ABCG1-mediated lipid efflux in the mouse retinal pigment epithelium (RPE) leads to retinal degeneration. Elife. 2019 Mar 13;8:e45100.

[31] Zhou Y, Ou Y, Ju Z, Zhang X, Zheng L, Li J, Sun Y, Liu X. Visualization of translocator protein (18 kDa)(TSPO) in the retina of diabetic retinopathy rats using fluorine-18-DPA-714. Annals of Nuclear Medicine. 2020 Sep;34:675-81.

[32] Tien T, Zhang J, Muto T, Kim D, Sarthy VP, Roy S. High glucose induces mitochondrial dysfunction in retinal Müller cells: implications for diabetic retinopathy. Investigative ophthalmology & visual science. 2017 Jun 1;58(7):2915-21.

[33] Guo Y, Sun Z, Wang L, Jiang R, Shu Q, Xu G. Increased expression of TSPO-VDAC complex is correlated with NLRP3 inflammasome activation in diabetic retinopathy. Molecular Medicine Reports. 2022 Oct 5;26(6):353.

[34] Jiang M, Xie H, Zhang C, Wang T, Tian H, Lu L, Xu JY, Xu GT, Liu L, Zhang J. Enhancing fractalkine/CX3CR1 signalling pathway can reduce neuroinflammation by attenuating microglia activation in experimental diabetic retinopathy. Journal of Cellular and Molecular Medicine. 2022 Feb;26(4):1229-44.