DIABETES MELLITUS AND ITS INFLUENCE ON THE INCIDENCE AND PROCESS OF DIABETIC RETINOPATHY

Janka Poráčová[1], Melinda Nagy[2], Marta Mydlárová Blaščáková[1], Mária Konečná[1], Vincent Sedlák[1], Mária Zahatňanská[3], Tatiana Kimáková[4], Hedviga Vašková[1], Viktória Rybárová[1], Mária Majherová[5], Ivan Uher[6]

[1]Department of Biology, Faculty of Humanities and Natural Sciences, University of Prešov, Prešov, Slovak Republic
[2]Department of Biology, Faculty of Education, J. Selye University, Komárno, Slovak Republic
[3]Institute of Pedagogy, Andragogy and Psychology, Faculty of Humanities and Natural Sciences, University of Prešov, Prešov, Slovak Republic
[4]Department of Public Health and Hygiene, Faculty of Medicine, Pavol Jozef Šafárik University, Košice, Slovak Republic
[5]Department of Physics, Mathematics and Technologies, Faculty of Humanities and Natural Sciences, University of Prešov, Prešov, Slovak Republic
[6]Institute of Physical Education and Sports, Pavol Jozef Šafárik University, Košice, Slovak Republic

SUMMARY

Objectives: The main aim of the study was to show the effect of diabetes in relation to the gender of the patients, duration of the disease, and on the incidence of diabetic retinopathy. In this study, we investigated the prevalence of these two diseases, pathological ocular changes and progression of disease occurrence in relation to the duration of the disease with respect to their impact on the quality of vision of the patient.

Methods: The prospective observational cross-sectional study included 3,951 patients (1,838 males, 2,113 females) with diabetes mellitus from 7 districts of eastern Slovakia. Patients with diabetes mellitus and diabetic retinopathy were identified by special screening in the number of 2,093 (1,094 females and 999 males). Subjects were divided by sex and by duration of diabetes into 5 groups: patients with diabetes under 5, 10, 15, 20, and over 20 years. We differentiated between proliferative and non-proliferative forms of diabetic retinopathy and monitored changes in visual quality. Manifestations of pathological changes were recorded using special examination methods in the eye clinic. We observed a decrease in vision by two lines, pathological changes on the retina and the occurrence of practical blindness.

Results: Of the total number of diabetic patients examined, diabetic retinopathy was also present in more than half of the patients. The major form represented in the patients was the non-proliferative form of retinopathy. The obtained results confirmed that the representation of patients with diabetic retinopathy increases with increasing duration of diabetes. Similarly, pathological changes characteristic of this type of late complication of diabetes were also more frequent, such as deterioration of visual acuity, the appearance of aneurysms, hard exudates macular edema, and gradual loss of vision, which can result in practical blindness.

Conclusion: The percentage of people with diabetic retinopathy increases with the duration of diabetes, as well as the increased frequency of pathological late complication of diabetes, including deterioration of visual acuity, the development of aneurysms, hard exudates, macular oedema, and gradual loss of vision, which can result in practical blindness. Early diagnosis of the disease and introduction of appropriate treatment would alleviate the symptoms of the disease in more than half of the patients, so more frequent preventive check-ups with an ophthalmologist should be performed in diabetic patients to avoid detection of the disease in its late stages.

Key words: diabetes mellitus, diabetic retinopathy, pathological changes of retina, visual acuity, practical blindness

Address for correspondence: I. Uher, Institute of Physical Education and Sports, Pavol Jozef Šafárik University in Košice, Ondavská 21, 040 11 Košice, Slovak Republic. E-mail: ivan.uher57@gmail.com

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INTRODUCTION

Diabetes is one of the diseases of civilisation, the prevalence of which has been steadily increasing in recent decades. It is a chronic, metabolic disease characterised by elevated blood glucose levels which, over a period of time, causes serious damage to the heart, blood vessels, eyes, kidneys, and nervous system. The most common is type 2 diabetes, usually in adults, which is related to cells becoming resistant to insulin or not making enough insulin. In the last three decades, the prevalence of type 2 diabetes has increased dramatically in all countries. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin. Approximately 422 million people worldwide have diabetes, most of them living in low- and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year (1).

The most common late, chronic complications of diabetes include diabetic retinopathy (DR), nephropathy, neuropathy, cardiovascular complications, metabolic syndrome, and others.

The main risk factors for diabetic retinopathy are persistent hyperglycaemia, hypertension, dyslipidaemia, and in women, pregnancy. It is among the most common microvascular complications in diabetic patients. Consistent with the increasing prevalence of diabetes in developed and developing countries, diabetic retinopathy is one of the most common causes of vision loss in middle-aged working adults worldwide. Based on the presence or absence of retinal neovascularization, diabetic retinopathy is clinically classified as non-proliferative (NPDR) and proliferative (PDR) form.

Depending on the severity of retinal vascular lesions, NPDR is categorized into mild, moderate and severe forms. Mild NPDR shows microaneurysms, while the moderate form of NPDR presents with additional signs of compromised vessel integrity, haemorrhage, etc. (2). The severe form of NPDR is accompanied by more pronounced signs of retinal ischaemia, such as venous globules and intraretinal microvascular abnormalities (IRMAs). For patients with mild to moderate NPDR, systemic control of hyperglycaemia, hypertension, and dyslipidaemia is critical in preventing progression and reducing the severity of retinopathy. However, if blood glucose levels fall rapidly, diabetic retinopathy will worsen in 10 to 20% of patients within 3 to 6 months (3). In patients with PDR, newly formed blood vessels that protrude from the ischaemic retinal surface cause bleeding into the vitreous. Persistent retinal hypoxia further leads to iris neovascularization and refractory glaucoma. Proangiogenic factor has also been found in retinas with hypoxia in patients with diabetic retinopathy (4).

Metabolic abnormalities in diabetes induce overproduction of mitochondrial superoxide in vascular endothelial cells (ECs), which in turn leads to increased production of advanced glycation end products (AGEs), upregulation of the receptor for AGEs and its activating ligands, activation of the protein kinase C pathway, and overactivation of the hexosamine pathway. These pathways increase levels of intracellular reactive oxygen species and can cause irreversible cell damage through epigenetic changes such as histone modifications, DNA methylation, and noncoding RNA (5).

In persistent hyperglycaemia, oxidative stress, various signalling pathways, and epigenetic modifications induce inflammation. Levels of proinflammatory cytokines and chemokines such as monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and IL-6 are elevated in patients with diabetic retinopathy (6).

The important functions of inflammation in the initiation and progression of diabetic retinopathy have been empirically confirmed by the therapeutic efficacy of corticosteroids for diabetes mellitus and diabetic retinopathy (7). In patients with diabetes, leukocyte adhesion and infiltration can damage retinal vascular endothelial cells and neuroglial cells.

Comprehensive therapeutic and preventive procedures including intervention of systemic risk factors, active screening for diabetic retinopathy and specialised ophthalmological treatment reduce vision loss by 90%. A prerequisite for effective screening for diabetic retinopathy is to ensure early detection and treatment and early and regular ophthalmological examination of diabetic patients (8).

The vision loss in diabetic retinopathy is primarily attributed to retinal vascular abnormalities, including retinal hyperpermeability, hypoperfusion and neoangiogenesis, which lead to anatomical and functional changes in retinal neurons and glial cells. Recent advances in retinal imaging using optical coherence tomography technology and pharmacological treatments, particularly the use of vascular endothelial growth factor receptor drugs and corticosteroids, have revolutionized the clinical management of diabetic retinopathy (9). Early diagnosis of diabetic retinopathy is crucial for the prevention of vision loss, therefore, routine ophthalmological examinations are recommended for all diabetic patients at intervals dependent on the severity of the disease.

To investigate the effect of diabetes mellitus on visual quality, we focused on the occurrence of diabetic retinopathy as one of the outcomes of the pathophysiology of the primary disease. We investigated the influence of gender and duration of diabetes on the manifestation of pathological changes in vision. The results highlighted the necessity of regular screening in the prevention of diabetic retinopathy in order to halt or reverse vision loss in the diabetic patients.

MATERIALS AND METHODS

The research sample consisted of diabetic patients from 7 districts of eastern Slovakia. The research was carried out in cooperation with specialized eye clinics. The data were collected consecutively over a period of three years from patients with diabetes mellitus. In our research we did not use a control group. A total of 3,951 patients with diabetes mellitus participated in the study, 1,838 were males and 2,113 females. Out of the given set of diabetic patients, 2,093 respondents had a diagnosis of diabetic retinopathy, of which 999 were males and 1,094 females. We divided the study sample according to gender and duration of diabetes into 5 groups: patients with diabetes up to 5, 10, 15, 20, and over 20 years.

We distinguished between proliferative and non-proliferative forms of diabetic retinopathy. In a sample of patients with diabetic retinopathy, we observed pathological signs of the disease related to a decrease in visual acuity (vision), the pathological changes observed on the retina and the incidence of practical blindness. In the patients, we determined the quality of visual acuity at near and distance.

Subsequently, intraocular pressure was measured with a Pulsair desktop tonometer (Keeler, USA) and the ocular background was checked with a Shin-Nippon slit lamp (Shin Nippon Machinery Co., Ltd., Japan), which provides a wider field of view, higher resolution, and the use of multiple filters is possible, which improves the overall quality of light intensity.

The state of the ocular background was recorded using high quality photo-documentation, this process was mediated by the use of a Fundus camera Topcon TRC 50 EX. The retina was photographically documented and subsequently analysed into deeper layers using optical coherence tomography (OCT) on an OCT:OPKO/OTI Spectral OCT machine (Optos, UK). This examination is used to detect details of the macula, optic nerve and blind spot. The information obtained by OCT scanning produces high quality, high resolution images of the layers of the retina, providing a complete cross-sectional view of the retinal structure and tissue.

Statistical evaluation was performed using MS Office v. 13 (MS Excel) and Statistica v. 12, where we calculated differences between phenomena (phenomena analysis of relative frequencies).

RESULTS

The results of our study show the prevalence of diabetic retinopathy in patients in the studied years, the occurrence of its proliferative or non-proliferative form, the influence of the duration of diabetes on the individual pathological changes in vision related to the disease.

A total of 3,951 respondents (1,838 males and 2,113 females) participated in the population-based cross-sectional study during the three years of follow-up. Out of the total diabetic patients screened, 2,093 patients were diagnosed with diabetic retinopathy, 999 males and 1,094 females. The proliferative form of diabetic retinopathy developed in 316 respondents, 146 males and 170 females. The non-proliferative form of diabetic retinopathy was found in 1,777 patients, 853 males and 924 females (Table 1).

Table 1 shows the frequency in representation of respondents with diabetes, diagnosed diabetic retinopathy and its detected forms of occurrence. The values in the table are given as absolute and relative frequencies.

Table 2 shows the frequencies of respondents with diabetic retinopathy and the observed visual changes – visual acuity, pathological changes on the retina, and practical blindness. Of the total number of diabetic retinopathy patients examined, a decrease in vision of 2 lines was found in 1,440 patients, 675 males and 765 females. Pathological retinal changes were diagnosed in 786 patients, including 365 males and 421 females.

Practical blindness was observed in 179 respondents, 89 males and 90 females (Table 2). The values in the table are given as absolute and relative frequencies.

The statistical differences obtained were not significant for the individual comparisons regarding the prevalence of diabetic retinopathy, the prevalence of its forms and the prevalence of visual impairment by gender. Thus, we can conclude that the prevalence of diabetic retinopathy, the incidence of its forms and visual impairment affect both males and females.

Figure 1 shows the increasing tendency of all three symptoms studied and the comparison between genders and duration of diabetes.

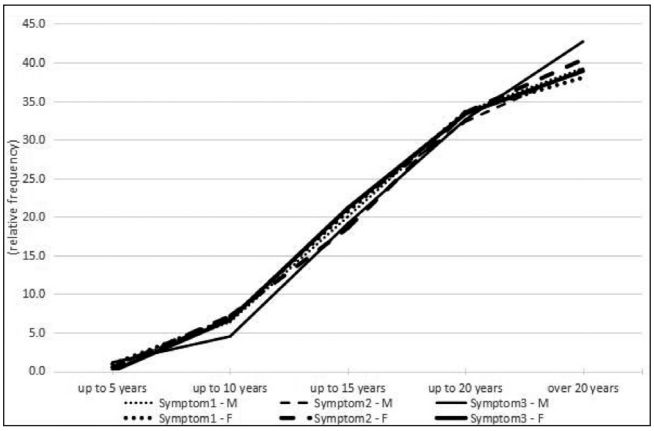

Fig. 1. *Dynamics of changes in symptom expression in relation to duration of diabetes.*

Symptom 1 – visual acuity decrease by 2 lines; Symptom 2 – pathological changes of retina; Symptom 3 – practical blindness; M – males; F – females

There was only a slight increase in the incidence of the proliferative form of diabetic retinopathy (Table 3). The figures represent the values of the comparison test and significance at the respective significance level.

DISCUSSION

Diabetic retinopathy is retinal damage that occurs as a result of diabetes. It causes damage to the small blood vessels on the retina. It often arises and progresses unnoticed and can lead to blindness. Diabetic retinopathy can occur even in uncomplicated diabetes, without symptoms and without pain, so prevention in the form of regular eye examinations is essential. In advanced findings, retinal haemorrhages, small infarcts and fluid in the retina appear.

The most dangerous form is proliferative diabetic retinopathy, which is characterized by the formation of neoplastic blood vessels in the retina that are unstable and can easily bleed into the retina or vitreous. Sometimes these blood vessels can become

Table 1. *Frequency in representation of respondents with diabetes, diagnosed diabetic retinopathy and detected forms of occurrence*

Investigated diseases	Males n (%)	Females n (%)	Total n (%)
Diabetes mellitus	1,838 (46.5)	2,113 (53.5)	3,951 (100.0)
Diabetes mellitus + DR	999 (47.7)	1,094 (52.3)	2,093 (100.0)
Proliferative form DR	146 (46.2)	170 (53.8)	316 (100.0)
Non-proliferative form DR	853 (48.0)	924 (52.0)	1,777 (100.0)

DR – diabetic retinopathy

Table 2. *Frequencies of respondents with diabetic retinopathy and observed visual changes*

Variables	Males n (%)	Females n (%)	Total n (%)
Visual acuity decreased by 2 lines	675 (46.9)	765 (53.1)	1,440 (100.0)
Pathological changes of retina	365 (46.4)	421 (53.6)	786 (100.0)
Practical blindness	89 (49.7)	90 (50.3)	179 (100.0)

Table 3. *Incidence of proliferative and non-proliferative form of diabetic retinopathy comparing males and females*

	Proliferative form DR		Non-proliferative form DR	
	Males	**Females**	**Males**	**Females**
< 5 years	0 (0.0)	1 (0.6)	7 (0.8)	7 (0.8)
5–10 year	9 (6.2)	10 (5.9)	55 (6.4)	56 (6.1)
10–15 year	30 (20.5)	35 (20.6)	165 (19.3)	195 (21.1)
15–20 year	50 (34.2)	58 (34.1)	279 (32.7)	294 (31.8)
> 20 year	57 (39.0)	66 (38.8)	347 (40.7)	372 (40.3)

DR – diabetic retinopathy

scarred, often leading to retinal detachment. As well as affecting the blood vessels, diabetes also damages the macula – the yellow spot that is the site of the sharpest vision in the eye. In this case, swelling of the macula occurs. As a result of the fluid in the macula, photoreceptors are rapidly damaged and visual acuity rapidly declines (10).

The number of people with an increase in the prevalence of diabetes mellitus in the years 2017–2020 in the Slovak Republic was the highest in 2019 with the number of 24,347 patients, of which diabetes mellitus type 1 occurred in 1,381, and type 2 in 20,748; and the lowest in 2018 with the number of 21,372 patients, of which diabetes mellitus type 1occurred in 1,342, and type 2 in 18,177.

When comparing the prevalence of diabetes mellitus between 2017 and 2020, the total number of people with diabetes mellitus by type of diabetes in the Slovak Republic was the highest in 2019 at 370,665, of which 27,124 were type 1 and 336,968 type 2; and the lowest in 2020, with a total amount of 352,130 patients, of which 26,171 were type 1 and 320,688 type 2 (11).

Diabetic retinopathy is a common complication of diabetes mellitus, usually leading to complete blindness. The cause of vision loss is diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR) such as vitreous haemorrhage, tractional retinal detachment and neovascular glaucoma. By 2030, the prevalence of diabetes is projected to increase by 69% in developing countries and 20% in industrialized countries.

By 2030, the number of patients with diabetes in Africa is projected to increase to more than 18 million, with some estimates as high as 24 million (12). Diabetic retinopathy is the most common microvascular complication of diabetes and affects 3–4% of people in Europe. The relative risk of diabetic retinopathy is higher in patients with type 1 compared to type 2 diabetes. Diabetes is responsible for approximately 15% of all cases of blindness (best corrected visual acuity less than 0.02) in Germany. It is the leading cause of blindness in the working-age population in industrialized countries (13).

Retinal changes are diagnosed in patients with type 1 diabetes before adolescence; about one-third of patients have signs of diabetic retinopathy at the time of initial diagnosis of diabetes mellitus. The risk of proliferative diabetic retinopathy is higher in type 1 than in type 2 diabetes. Diabetic macular oedema is more common in type 2 diabetes (prevalence after 15 years of disease: type 1 vs. type 2, 15% vs. 25%) (14).

Diabetic retinopathy is one of the leading causes of vision loss in individuals aged 20–64 years. Cherchi et al. (15) investigated the difference between the prevalence of diabetic retinopathy in patients according to gender and the duration of type 2 diabetes in a retrospective cross-sectional study. Diabetic retinopathy of all grades had a significantly higher prevalence in males (22.0%) compared with females (19.3%). Among patients with diabetic retinopathy, there was a significantly higher prevalence of NPDR and PDR forms in males compared to females.

Females had similar age and BMI, but longer duration of diabetes, worse metabolic glycaemic outcomes, and greater prevalence of hypertension and chronic renal failure (CRF) of any degree compared with males. No significant differences were found between sexes in terms of drug therapy for diabetes and associated pathologies. In the sample of patients with type 2 diabetes mellitus studied, males showed a higher prevalence of diabetic retinopathy compared to females, despite a lower prevalence of risk factors, suggesting that male gender per se may be a risk factor for the development of diabetic retinopathy.

Diabetic retinopathy can be classified as non-proliferative and proliferative. The mild course of NPDR is related to the walls of blood vessels in the retina becoming weakened by small bulges (microaneurysms), sometimes leaking fluid and blood into the retina away from the macula. NPDR can progress to a more severe type, sometimes called preproliferative, is characterized by leakage of fluid and/or blood close to the macula, which precedes the more advanced form of proliferative diabetic retinopathy. In proliferative diabetic retinopathy, the damaged blood vessels become occluded, causing new, abnormal blood vessels to grow in the retina and may leak into the vitreous, resulting in vision loss (16).

Regular glycaemic and blood pressure control can reduce the risk of diabetic retinopathy and delay its progression. Higher HBA1c levels, longer duration of diabetes, hypertension and chronic renal failure are among the globally recognised risk factors for the development of diabetic retinopathy. Differences between males and females, both in the prevalence of type 1 and type 2 diabetes and in the incidence of chronic complications, have been reported in several epidemiological studies (17).

Diabetic retinopathy often develops during pregnancy, suggesting a possible role of sex hormones in retinal damage in diabetes in females (18). The inconclusive results on gender differences in diabetic retinopathy may be related to ethnic differences, selection of a population with mixed subjects with a prevalence of type 1 and type 2 diabetes mellitus, or it may be an otherwise unspecified set of individuals, low numbers of observations, and differences in medical treatment of diabetes or related pathologies between the sexes.

As new therapies for diabetic retinopathy become available (from laser therapies to vitrectomy and intravitreal corticosteroids, anti-vascular endothelial growth factors and more ad-

vanced stem cell, and ribonucleic acid interference technologies), it is challenging to assess all of its risk factors. Gender differences between men and women, also differences in health status, often result from biological, social, cultural, and political differences in the organization of society (19).

In our study, we found no statistically significant differences in the prevalence of diabetes and diabetic retinopathy between males and females. We observed an increase in the prevalence of diabetic retinopathy compared to the duration of primary disease in all respondents.

There was also an increase of 2 orders of magnitude in the number of patients according to the duration of diabetes mellitus at diagnosis of visual impairment, from 3 (within 5 years of DM duration) to 143 (over 20 years of DM duration) in the 1st year of follow-up, from 4 (within 5 years of DM duration) to 191 (over 20 years of DM duration) in the 2nd year of follow-up, and from 5 (within 5 years of DM duration) to 222 (over 20 years of DM duration) in the 3rd year of follow-up, respectively.

Slightly lower values were recorded for the diagnosis of eye disease with pathological changes on the retina, from 1 (in the period up to 5 years of DM) to 89 (in the period over 20 years of DM) in the 1st year of follow-up, respectively, from 1 (in the period up to 5 years of DM) to 105 (in the period over 20 years of DM) in the 2nd year of follow-up, and from 2 (in the period up to 5 years of DM) to 119 (in the period over 20 years of DM) in the 3rd year of follow-up. Diabetic retinopathy is associated with an increased risk of cardiovascular mortality. In this regard, there are studies that point to the fact that postmenopausal females with diabetes are at higher risk than males (20).

Differences in macrovascular complications in males and females are known. Microvascular complications in type 2 diabetes mellitus between the sexes have not been studied in detail. A large study conducted in the United States revealed that in diabetic patients over 40 years of age, males have a 50% higher prevalence of diabetic retinopathy than females (21). On the other hand, the LALES study (22) showed no statistically significant difference in the prevalence of diabetic retinopathy between the sexes. Similar results were observed in our study where there were no significant differences in the incidence of diabetic retinopathy between genders.

Some studies suggest that male gender is a risk factor for diabetes in both adults and adolescents in Western countries. In non-European countries, the prevalence of diabetes appears to be higher in females (23).

The skewed distribution of risk factors between the genders may be due to differences in lifestyle (24), and sex hormones may also play an important role. Diabetic retinopathy often progresses during pregnancy, which is associated with higher levels of estrogen and progesterone (25). However, it has been shown that women adhering to a strict metabolic control regimen during pregnancy do not show an increased risk of progression to diabetic retinopathy, although the risk often increases again in the postpartum period because the strict metabolic regimen is often no longer adhered to (26). Fong et al. point out that diabetic retinopathy caused blindness in 86% of patients with onset of diabetes at a younger age (27). The occurrence of blindness as a consequence of diabetic retinopathy in one-third of the respondents was noted to be related to their older age. In our case, practical blindness was detected in 76% of males and 72% of females with a longer duration of diabetes (over 15 years) in the mean follow-up of 3 years.

Gelcho and Gari (28) in their study investigated the prevalence and factors associated with diabetic retinopathy. Of the 373 patients examined, 154 (41.3%) had a diagnosis of diabetic retinopathy. They found that the risk of developing diabetic retinopathy was more than 3.17 times higher in patients older than 40 years than in those younger than 27 years. Males compared to females had a higher risk of diabetic retinopathy 2.34 times higher than females. Increased incidence of diabetic retinopathy (2.86 times) was found in patients with duration of 5 years or more as compared to duration of diabetes mellitus of less than 5 years.

Almost a half of diabetic retinopathy is developed in the first five years of diabetes (29). This is consistent with a study conducted by Chisha et al. (30) showing a 47% incidence of diabetic retinopathy in the first five years of diabetic disease. This is because patients with type 2 diabetes come for treatment if they already have a visual impairment. Studies conducted in Pakistan show an increased incidence of diabetic retinopathy by 22% in patients with diabetes of up to 5 years duration (31, 32).

In our respondents, diabetic retinopathy developed especially with a duration of diabetes of more than 10 years in up to 93% of males and females.

CONCLUSION

The key role in the prevention of vision loss caused by diabetic retinopathy is played by special examinations, early diagnosis, ensuring the best possible compensation of diabetes with medications and reducing the effect of all systemic risk factors that slow down the onset and progression of diabetic retinopathy. In our study population, out of the total number of diabetic patients examined, diabetic retinopathy was present in more than half of the patients. The main form represented in the patients was the non-proliferative form of retinopathy. The obtained results confirmed that the representation of patients with diabetic retinopathy increases with the duration of diabetes mellitus. Pathological changes characteristic of this type of late complication of diabetes, such as deterioration of visual acuity, the occurrence of aneurysms, hard exudates of macular edema, and gradual loss of vision, which may result in practical blindness, were also more frequent. We found no statistically significant difference in the incidence of diabetic retinopathy between males and females. Vision loss caused by diabetic retinopathy can be reduced by more than 90% with comprehensive treatment and preventive procedures. The diabetologist recommends the patient for the examination, but the patient takes responsibility for completing the ophthalmological examination, hence the need for education and self-monitoring of diabetic patients.

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Conflicts of Interest

None declared

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