REVIEW

Treatment of early complications on eye fundus in patients with diabetes mellitus

Iva Akmadža[1], **Milan Vrkljan**[2]

1 University of Zagreb School of Medicine, Šalata 3b, 10 000 Zagreb, Croatia
2 Department of Endocrinology, Diabetes and Metabolic Diseases „Mladen Sekso", University Hospital Center „Sestre Milosrdnice", University of Zagreb Medical School, Vinogradska cesta 29, 10000 Zagreb, Croatia

Corresponding author:
Iva Akmadža, University of Zagreb School of Medicine, Šalata 3b, 10 000 Zagreb, Croatia,
e-mail: iva.akmadža@gmail.com;
Telephone: 00385919343330

DOI: 10.21040/eom/2016.2.3.5

Received: August 5th 2016
Accepted: September 2rd 2016
Published: September 15th 2016

Copyright: © Copyright by Association for Endocrine Oncology and Metabolism. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is prorly cited.

Funding: None.
Conflict of interest statement: The authors declare that they have no conflict of interest.
Data Availability Statement: All relevant data are within the paper.

Abstract

Early ocular complications in patients with diabetes mellitus (DM) mostly refer to non-proliferative diabetic retinopathy (NPDR). Generally speaking, diabetic retinopathy (DR) is one of the most common causes of blindness and the most common cause of blindness between the age of 20 and 65. DM is a disease characterized by metabolic disorders of carbohydrates, lipids and proteins. The main characteristic is hyperglycemia, which affects all organs by different pathogenetic pathways. The presence of DR is associated with the duration of DM, glycemic control and blood pressure. DR is a microangiopathy and is diagnosed by simple indirect ophthalmoscopy. It is very important to perform regular eye examinations in patients with DM, whereas DR is usually asymptomatic in the early stage of the disease. Optical coherence tomography (OCT) has the great importance in diagnostics of DR. Besides indirect ophthalmoscopy and OCT, fluorescein angiography and ultrasound are also widely used to diagnose DR. The prevention of the disease is most important, which is in domain of internal medicine specialist, diabetologist and general practitioner. Intravitreal anti-vascular endothelial growth factor therapy is the gold standard in treatment of NPDR associated with diabetic macular edema (DME) and impaired vision. Intravitreal injections of corticosteroids and laser photocoagulation are also used. The current and future treatment modalities are presented in the text that follows.

Keywords: diabetes mellitus, diabetic retinopathy, treatment, glucocosteroids, laser photocoagulation, anti-vascular endothelial growth factor

1. Introduction

Early ocular complications in patients with diabetes mellitus (DM) refer to the disease known as diabetic retinopathy (DR), actually its early form called non – proliferative diabetic retinopathy (NPDR). There are approximately 50 million cases of blindness worldwide and 2.5 million of those are caused by DR [1]. This fact confirms that DR is a serious disease, which deserves our attention and has an important role in medical discussions with the aim of achieving the best care for our patients. DR is a chronic, microvascular complication of DM. DR represents a major public health problem with worldwide prevalence ranging from 2% to 11.7% [1,2].

Diabetic macular edema (DME) can appear within NPDR as a consequence of increased capillary permeability. The fluid leaking from the blood vessels damages nerve cells of the retina leading to its degeneration. DME is the main cause of vision loss in people suffering from DR [3]. If DME affects fovea, the state is called cystoid macular edema (CME) [4].

The treatment of these entities is an interesting part of medical research. Some of the new treatment options are replacing previous ones with excellent results. In the same time, there are many other treatment modalities whose effectiveness is still in the process of scientific research but which offer promising results for the future treatment of NPDR and DME.

2. Epidemiology of diabetic retinopathy and risk factors

DR is the most common cause of blindness between the age of 20 and 65 [3]. There are approximately 50 million cases of blindness worldwide and 2.5 million of those cases are caused by DR [1].

The most influential predictor of DR is the duration of DM. DR will appear in each patient with DM after certain period of time. Almost all patients with DM type 1 and more than 60% of those with DM type 2 have some type of retinopathy 20 years after the diagnosis [5, 6]. DM can be discovered incidentally during the ocular fundus examination in patients without previous history of DM. The second important predictor of DR is glycemic control. DM showing significant fluctuations of glucose levels in the blood is associated with increased risk for development of DR. Once developed, DR progression is less dependent on duration of DM and more dependent on glycemic control [7]. Blood pressure is also an important risk factor. Increased blood pressure and uncontrolled hypertension is also associated with increased risk of developing DR. Thus, the duration of diabetes, uncontrolled hyperglycemia and high blood pressure are major and the most important risk factors for the development of DR [7].

There are many others, less significant, but not irrelevant risk factors for the DR. These are the type of diabetes, age, puberty, obesity, decreased physical activity, disorders of coagulation factors, renal disease, smoking, pregnancy, hyperlipidemia and ethnicity [1]. DR is more prevalent in DM type 1. It occurs in more than 95% of DM type 1 with the duration of diabetes for 15 years or longer. In DM type 2, the prevalence of DR is approximately 58% [7]. In patients with DM type 1, DR rarely appears before the age of 13. The risk of developing DR increases after puberty [8]. In patients with DM type 2, DR occurs more often in patients younger than 50 years of age. DR may worsen during pregnancy and is far more challenging to control DR in cigarette smokers. When it comes to ethnicity, DR is verified more often in African Americans than Caucasians [1].

3. Pathogenesis and types of diabetic retinopathy

Long-term hyperglycemia has the main role in the pathogenesis of DR. It leads to the thickening of vascular basement membrane, loss of pericytes and vascular endothelial cells. The loss of pericytes decreases vascular stability and disrupts the control of endothelial proliferation [9]. Direct cause of pericyte loss is unknown, but some evidence exists hyperglycemia-induced accumulation of sorbitol and non – enzymatic glycation of the proteins play important role [9]. Thinning of the blood vessels causes increased vascular permeability, promotes formation of microaneurysms and clots formation within microaneurysms. Consequently, this leads to bleeding, exudation and edema within the ocular fundus. All these changes represent microangiopathy that leads to decreased blood supply of the retina, which

is sensitive to hypoxia. Hypoxia stimulates secretion of vascular endothelial growth factor (VEGF) which promotes angiogenesis and the development of proliferative diabetic retinopathy (PDR). Newly formed blood vessels have an aberrant structure and are prone to bleeding. The process of neovascularization spreads to vitreous which results with hemophtalmus (vitreous hemorrhage) and the appearance of vitreoretinal adhesions, which may lead to the tractional retinal detachment. In the later stages, iridal neovascularization (rubeosis iridis) appears and neovascular glaucoma can also develop because the new blood vessels grow in the area of trabecular meshwork [10].

There are two types of DR: NPDR and PDR. NPDR is the initial stage of DR characterized with microaneurysms, bleeding, exudates and edema. PDR is the latter stage that appears as a result of disease progression. It is characterized by neovascularizations, vitreous hemorrhage, vitreoretinal adhesions that can lead to tractional retinal detachment and the possible development of neovascular glaucoma [10].

It is necessary to underline the importance of appearance of DME, which is not exclusively associated with the stage of DR. The occurrence of DME represents increased capillary permeability, which is most often presented as a diffuse maculopathy. It is also the leading cause of vision loss in patients with DR [3].

4. Fundoscopic findings and clinical presentation of non – proliferative diabetic retinopathy and diabetic macular edema

Fundoscopic findings in NPDR are characteristic. The main features are microaneurysms and hemorrhages that can be presented as dot, blot and flame-shaped hemorrhages, exudates (cotton wool and hard exudates), edema and intraretinal microvascular abnormalities (IRMA). DME can appear in any type of DR. If DME affects fovea, it can cause vision loss. Therefore, vision loss can occur in patients with NPDR. DME is a consequence of both intracellular and extracellular fluid accumulation. Intracellular edema develops as a result of axoplasmic flow in hypoxia. Extracellular fluid accumulation develops as a result of increased permeability of blood vessels which leads to dysfunction of the blood – retinal barrier [11]. The fluid is eventually reabsorbed, but the "sediment" in form of lipid exudate lags behind and present as yellow blot on the fundus and it is called hard exudate [8]. Clinically significant macular edema (CSME) is defined as: retinal thickening within 500 μm of the center of the fovea; hard, yellow exudates within 500 μm of the center of the fovea with adjacent retinal thickening; at least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea [10].

Clinical presentation of NPDR is different in terms of duration of the disease and involvement of macula. It is very important to practice regular eye examinations, as there are usually no symptoms at the beginning of the disease. The disease is bilateral. The most important cause of the symptoms in NPDR is DME. The main symptom of macular edema is blurred central vision. Furthermore, central vision in macular edema can be wavy, distorted. It can also be presented as a color vision deficiency, where patient complains on colors being "washed out".

The scotomas can also appear [12,13]. DME, which can appear in any type of DR, is the main cause of visual deterioration in patients with DR and by progression it can lead to the next symptom: total vision loss [3]. Independently from DME, symptoms in NPDR can be blots and dark stripes floating in the visual field, if retinal bleeding exists. Whereas bleeding can spontaneously disappear, blots in visual fields can also disappear and appear if bleeding shows up again [14]. Metamorphopsia, a distortion of observed image, includes macropsia (image in visual field is larger than normal) and micropsia (image in visual field is smaller than normal) [15].

5. The diagnosis of non–proliferative diabetic retinopathy and diabetic macular edema

Whereas clinical presentation of NPDR is unrecognized in the beginning of the disease because symptoms don't have to be present although changes on retina have already appeared, it is very important to start with

regular eye examinations timely in order to recognize all retinal changes regardless of symptom absence and to prevent its progress [8,16-18]. Regular eye examinations should be performed once a year. In DM type 1 regular eye examinations should start 3 to 5 years after the disease has been diagnosed. In patients with DM type 2, eye examination should be done immediately after the diagnosis, because some patients already have signs of DR [8,16]. Screening is crucial to verify the disease before clinical symptoms are present.

Each clinical examination, including eye examination, starts with taking the basic information about their vision problems and his medical history. Questions should be conceived in a way that they are clear and comprehensive with DM and its complications. Ophthalmological examination should include questions regarding visual disorders (blurred vision, worsened visual acuity, distorted image in central visual field or "washed out" images) and/or scotomas. It is also important to ask patient about systemic diseases or pregnancy. Pregnant women with DM diagnosed before pregnancy have increased risk of DR progression during the pregnancy. They should perform regular eye examinations before conception, early in the first and the last trimester. However, patients with gestational DM are not at risk of DR; thus, eye examinations are not mandatory in these women [16, 8]. Systemic diseases that can worsen clinical presentation of DR are arterial hypertension, proteinuria and renal function. It is very important to monitor glycated hemoglobin (HbA1c), which is the best surrogate for measuring glycemic control [16, 8].

Ophthalmological examination should include measurements of visual acuity, intraocular pressure and slit-lamp biomicroscopy [8]. Optical coherence tomography (OCT) should also be performed in order to thoroughly examine the ocular fundus and macula. OCT is a non-invasive and non-contact method that uses light reflection close to infrared area to take cross-section pictures of ocular structures, especially of the macula, which is important to prove the presence of DME [19]. The most important examination for DR diagnosis is indirect ophthalmoscopy that visualizes fundus through previously dilated pupil. All previously mentioned characteristic changes in NPDR can be seen on the fundus. Ultrasound is also used in diagnosing DR. Ultrasound is useful if blurriness or any other obstruction of visual pathway exists in parts of the eye in front of the retina (e.g. cataract (clouding of the lens) and clouding of the cornea in keratitis) [19]. A great importance in diagnosis of DR is given to fluorescein angiography which uses fundus - cameras to produce digital fundus photography. Fundal images are immediately available and don't require photographic processing which enables doctor to see fundus image in real time. Obtained fundal image has been proven as effective screening method for DR [1].

Therefore, timely detection of retinal changes implies timely treatment, which prevents patients with DM from vision loss.

6. Treatment of non – proliferative diabetic retinopathy and diabetic macular edema

6.1. Systemic treatment and prevention

Both systemic and local treatment regimens are presented in table 1. Prevention is the cornerstone of NPDR treatment. Regular diabetologist's and ophthalmologist's visits should recognize possible pathological retinal changes in a timely manner, in order to reveal the risk of developing NPDR and progression of NPDR in severe types. Therapeutic interventions applied to the retina are not the only way to treat this disease. Strict control of glycemia, blood pressure and other modifiable risk factors are the first-line treament. Therefore, first-line treatment is in domain of diabetologist and general practitioner. Optimal glycemic control is defined as: fasting glucose < 6 mmol/L, postprandial glucose < 8 mmol/L and HbA1c < 7% [20-22]. Good glycemic control decreases the risk of developing and progression of DR [1,8,23]. It has also been shown that the decreased risk of developing complications extends even after the period of optimal glycemic control. That phenomenon is called metabolic memory [6,24]. Apart from glycemic control, it is also important to control other factors that cause systemic imbalance such as blood pressure control and control of lipid level in the blood. It is also important to stop smoking cigarettes because smoking cigarettes is also the risk factor for developing DR.

Blood pressure is the risk factor for developing DR, so it is necessary to control the blood pressure in order to slow down the progression of DR and visual impairment [6,25,26]. Renin – angiotensin system has a role in pathophysiology of DR. Thus, it is clear that microalbuminuria in diabetics is treated with ACE – inhibitors and/or angiotensin II receptor blockers in the first line [6,27]. Reference range of blood pressure in diabetics is a bit different than reference range in healthy people. It is important to control blood pressure and keep it in values within that range to achieve the best possible disease control. For adult diabetics these values should be under 130/80 mmHg and in patients with proteinuria, decreased glomerular filtration and cardiovascular diseases these values should be under 125/75 mmHg [27, 6]. It is thought that dialysis and renal transplantation can influence the prevention of DR progression and can give better results in laser treatment [6,28]. The control of lipid levels is also important, because hyperlipidemia is the risk factor for developing DR. The treatment of hyperlipidemia by statins and fibrates leads to decreased number of hard exudates that are precipitated lipids [6,29,30]. LDL cholesterol should be < 2.8 mmol/L and triglycerides < 1.7 mmol/L. Anemia should also be treated since it is also associated with DR [6,31].

Spontaneous vision recovery appears in 35% of the patients with good glycemia and blood pressure control after 6-month period [32-36]. Patients should be aware of the importance in strict control of the systemic factors in order to make other therapy effective and rational. Timely treatment interventions decreased DR progression significantly and thereby decreased the risk of vision loss by more than 90% [37].

6.2. Local treatment

New golden standard for treatment of NPDR with DME and impaired vision is anti – VEGF therapy (intravitreal injections of anti-VEGF drugs - ranibizumab, bevacizumab, aflibercept) [11]. They act by decreasing intraocular VEGF levels, which results in decreased permeability of blood vessels [38,39]. Anti – VEGF therapy is not equally effective in each patient, which can be explained by variations in nucleotide polymorphisms (SNPs) on VEGF – A gene [40, 41]. Three anti - VEGF drugs are currently available: bevacizumab (Avastin), aflibercept (Eylea) and ranibizumab (Lucentis) [42]. Aflibercept blocks all isoforms of VEGF (VEGF – A, VEGF – B) and also the placental growth factor. Due to its long half-life, aflibercept injection are usually administered every two months. Aflibercept is recommended as an initial therapy in those patients whose basic visual acuity is 20/50 or worse at the beginning of the treatment. The negative side of this drug is its relatively high price, which makes it less available drug to an average patient. Bevacizumab and ranibizumab blocks all isoforms of VEGF – A. Injections are given more often than aflibercept injections (usually every month) [43,44,45]. FDA approved aflibercept and ranibizumab for DME treatment and Avastin for colorectal cancer treatment. However, studies showed that intravitreal injections of Avastin lead to improvement of visual acuity, alleviate optic disc and macular edema and can be used for treatment of different eye diseases, especially NPDR associated with DME [46]. Local and systemic adverse effects of anti - VEGF drug use can appear. Serious local adverse effects that can appear are endophthalmitis, retinal detachment, hemophthalmus and iatrogenic traumatic cataract. Mild and moderate adverse effects include intraocular pressure, vitreous detachment, floaters and conjunctival hemorrhage. Systemic adverse effects include: non-ocular hemorrhage, arterial thromboembolism, myocardial infarction, cerebrovascular incidents and even death. It is important to be extremely cautious when treatin patients with the history cerebrovascular incident or transient ischemic attack (TIA) [37], since severe cerebrovascular complications are well recognized complications of anti – VEGF treatment [47, 48].

Intravitreal injections of glucocorticoids (triamcinolone, dexamethasone intravitreal implants) are also used in treatment of DR. Glucocorticoids are potent immunosuppressants which also inhibit VEGF secretion, prevent the loss of endothelial intracellular connections and the secretion of inflammation mediators. Therefore, glucocorticoids are the first line treatment of DME [11]. The most common indications for glucocorticoid use are seen in pseudophakic patients (patients with artificial intraocular lenses), in patients that have chronic DME (lasts more than 3 years) and in patients that have already been treated with glucocorticoids and showed no signs of increased intraocular pressure. Adverse effects of intravitreal glucocorticoid use can also appear.

Table 1. The comparation of treatment modalities used for NPDR and DME

	Anti – VEGF therapy	Corticosteroids	Laser photocoagulation
Mechanism of action	Decrease of intraocular VEGF	Decrease of intraocular proinflammatory cytokines	The coagulation of microaneurysms or retinal pigment epithelium
Types	Aflibercept, bevacizumab¸ ranibizumab	Fluocinolon acetate, dexametason intravitreal implants	Focal and grid laser
Side effects	Possible systemic and local side effects (endophthalmitis, haemophthalmus, myocardial infarction, death)	The increase of intraocular pressure and cataract	The rupture of Bruch membrane, hemorrhage, vision loss
Therapeutic approach	To individualize therapy according to patient's condition		

The most common are cataract and increased intraocular pressure [47].

The golden standard for NPDR and DME treatment was laser photocoagulation. Recently, indications for laser photocoagulation are reduced because of the new drugs (anti – VEGF therapy) that took an important role in DME treatment [4]. The main type of photocoagulation in patients with CSME is a focal photocoagulation that uses two basic techniques – direct photocoagulation and "grid" technique. The first one is used for focal edema and directly coagulates microaneurysms. The latter one directly coagulates pigment epithelium in the area of edema. Laser photocoagulation uses laser beam passing through transparent optical parts and stops on the retina. Photocoagulation uses light to create a thermal burn in retinal tissue. When energy from a strong light source is absorbed by the retinal pigment epithelium (RPE) and is converted into thermal energy, coagulation necrosis occurs and predominantly affects microaneurisms. In diffuse macular edema only pigment epithelium, choriocapillaris and photoreceptors are coagulated by laser beam, while capillaries, as the cause of the leakage remain intact [10]. There are possible adverse effects of laser photocoagulation such as rupture of Bruch membrane followed with hemorrhage, which may occur if great energy is applied on small area, and also vision loss as a result of macular damage if patient looks straight to the laser beam [49].

There are many different protocols and guidelines in treatment of NPDR and DME. It is important that each patient gets an individual therapeutic approach because the variations in disease expression and treatment efficacy are also different among patients. The future of NPDR and DME treatment lies in gene therapy, which has to be studied more thoroughly. It has already been mentioned that different patients react differently to given therapy. There could be more information in this area by researching genetic profiles of each patient in

order to make better treatment plans. Nanotechnology in the form of drug delivery systems, sustained – released medications and stem cell therapy are also on the horizon [37]. Anti – vascular growth factor agents (high dose of anti – vascular endothelial growth factor drugs, encapsulated cells, DARP proteins), inhibitor of multiple growth factors (Squalamine), steroids (betamethasone microspheres, danazol), cytokine inhibitors (angiopoetin, tumor necrosis factor (TNF), interleukins, chemokine inhibitors, kallikrein – kinin inhibitors, integrin inhibitors) are also considered [47]. Each of the previously mentioned treatment option for NPDR and DME represents a cornerstone for new research and treatment improvements.

7. Conclusion

NPDR and associated DME present serious complications of DM. Long-term hyperglycemia has the main role in the pathogenesis of DR. Diabetic diet, increased physical activity and pharmacotherapy are important for prevention and treatment of DR. It is important to educate patients about the nature of the disease, self-control and importance of regular examinations. Multidisciplinary approach including family doctor, diabetologist, ophthalmologist and psychologist is important in order to achieve expected treatment results. It is important to emphasize that the absence of symptoms does not imply the absence of the disease. Therefore, screening for DR is the cornerstone of prevention and treatment. Therapeutic interventions like intravitreal injections of anti – VEGF, glucocosteroids and laser photocoagulation are an important local treatment modalities. Treatment should be individualized based on patient's functional status, comorbidities and the stage of DR.

Author contributions

IA performed literature review, wrote the article and gave the final approval. MV gave the idea for the article, critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

References

1. McGavin DM. Diabetic retinopathy: Clinical Findings and Management. Community Eye Health 2003; 16 (46): 21.

2. Dwivedi RN, Krishna G. Epidemiology of Diabetes in India. Indian J Community Med 1999; 24: 40–4.

3. Mavija M, Jakšić V, Mavija Z, Markić B, Rašeta N, Ljubojević V. Udruženost dijabetičke retinopatije i dijabetičkog makularnog edema. Acta Ophthalmol 2014; 40 (2).

4. Bowling B. Retinal vascular disease. In: Bowling B, ed. Kanski's Clinical Ophthalmology: A systermatic approach. 8 th ed. Sydney, Australia: Sounders Ltd. 2016:520-37.

5. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy: XVII: The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998; 105(10): 1801-15.
http://dx.doi.org/10.1016/S0161-6420(98)91020-X

6. Kaštelan S, Tomić M, Mrazovac V, Pavan J, Salopek – Rabatić J, Lukenda A. Diabetic retinopathy - risk factors and treatment. Medicina Fluminensis 2010; 46(1): 48-54.

7. Zrinšćak O. Dijabetička retinopatija. Bolesničke novine 2012; 12 (18): 3-5.

8. Vislisel J, Oetting T. From One Medical Student to Another, 2010. Available: http://www.EyeRounds.org/tutorials/diabetic-retinopathy-med-students/. Accesssed: 4/ 2016.

9. Hammes HP, Lin J, Renner O, Shani M, Lundqvist A, Betsholtz C, Brownlee M, Deutsch U. Pericytes and the pathogenesis of diabetic retinopathy. Diabetes 2002; 51(10): 3107-12.
http://dx.doi.org/10.2337/diabetes.51.10.3107

10. Vukojević N. Minimal argon laser photocoagulation of retinal pigment epithelium in diabetic macular edema. University of Zagreb, 2007. Available: http://medlib.mef.hr/358/1/Microsoft_Word_- Disertacija Nenad_Vukojevic.pdf. Accessed: 3/2016.

11. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines, 2012; Available: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf. Accessed: 3/2016.

12. American Academy of Ophthalmology. What is macular edema? 2010. Available: http://www.aao.org/eye-health/diseases/what-is-macular-edema. Accessed: 3/2016.

13. Mayo Clinic. Diabetic Retinopathy, 2015. Available: http://www.mayoclinic.org/diseases-conditions/diabetic retinopathy/basics/symptoms/con-20023311. Accessed: 3/2016.

14. National Eye Institute. Facts About Diabetic Eye Disease, 2015. Available: https://nei.nih.gov/health/diabetic/retinopathy/. Accessed: 3/2016.

15. Achiron A, Lagstein O, Glick M, Gur Z, Bartov E, Burgansky-Eliash Z. Quantifying metamorphopsia in patients with diabetic macular oedema and other macular abnormalities. Acta Ophthalmol 2015; 93(8): 649-53.
http://dx.doi.org/10.1111/aos.12735

16. American Academy of Ophthalmology. Diabetic Retinopathy, Preferred Practice Pattern. San Francisco: American Academy of Ophthalmology, 2008. Available: http://www.aao.org/ppp. Accessed: 3/2016.

17. Olafsdottir E, Andersson DK, Dedorsson I, Stefansson E. The prevalence of retinopathy in subjects with and without type 2 diabetes mellitus. Acta Ophthalmol 2013; 92(2): 133-7.
http://dx.doi.org/10.1111/aos.12095

18. Jiménez-Báez MV, Márquez-González H, Bárcenas-Contreras R, Morales-Montoya C, Espinwosa-García LF. Early diagnosis of diabetic retinopathy in primary care. Colomb Med 2015; 46(1): 14-8.

19. Cerovski B, Vukojević N, Petriček I. Anamneza i pregled oka. In: Cerovski B, Kutija MB, Jukić T, Juratovac Z, Mandić JJ, Kalauz M, eds. Oftalmologija i optometrija. 1st ed. Zagreb, Croatia: Stega tisak d.o.o., 2015:17-40.

20. Verona E. Samokontrola šećerne bolesti. Bolesničke novine 2012; 12 (18):1-3.

21. Vrkljan M, Vizner B, Sekso M, Čabrijan T. Kako brinuti o svojoj šećernoj bolesti. Zagreb, Croatia: BIROTISAK d.o.o.

22. Josipović J. Dijabetes i vaši bubrezi. Bolesničke novine 2012; 12(18): 11.

23. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977.
http://dx.doi.org/10.1056/NEJM199309303291401

24. Marshal SM, Flyvbjerg A. Prevention and early detection of vascular complications of diabetes. BMJ 2006; 333: 475-80.
http://dx.doi.org/10.1136/bmj.38922.650521.80

25. Klein R, Klein BE, Moss SE, Cruickshanks KJ. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-13.
http://dx.doi.org/10.1136/bmj.317.7160.703

26. Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol 2007; 3: 428-38.
http://dx.doi.org/10.1038/ncpneph0559

27. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. Diabetes Care 2002; 25: 134-47.
http://dx.doi.org/10.2337/diacare.25.1.134

28. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report Number 9. Ophthalmology 1997; 98: 766-85.

29. Chew EY, Klein ML, Ferris FL. Association of elevated serum lipid levels with retinal hard exudates in diabetic retinopathy: Early Treatment Diabetic Retinopaty Study (ETDRS) Report 22. Arch Ophthalmol 1996; 114: 1079-84.
http://dx.doi.org/10.1001/archopht.1996.01100140281004

30. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular oedema. Am J Ophthalmol 2004; 137: 675-82.

31. Singh R, Gupta A, Bhansali A. Spontaneous closure of microaneurysms in diabetic retinopathy with treatment of coexisting anaemia. Br J Ophthalmol 2005; 89: 248-9.
http://dx.doi.org/10.1136/bjo.2004.050252

32. Andrade GC, Dias JR, Maia A, Farah ME, Meyer CH, Rodrigues EB. Intravitreal injections of ziv-aflibercept for diabetic macular edema: A Pilot Study. Retina 2016; 36(9): 1640-5.
http://dx.doi.org/10.1097/IAE.0000000000001000

33. Diabetes Control and Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Eng J Med 1993; 329: 977-86.
http://dx.doi.org/10.1056/NEJM199309303291401

34. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.
http://dx.doi.org/10.1016/S0140-6736(98)07019-6

35. Gray A, Clarke P, Farmer A, Holman R; United Kingdom prospective diabetes study (UKPDS) group. Implementing intensive control of blood glucose concentration and blood pressure in type 2 diabetes in England: cost analysis (UKPDS 63). BMJ 2002; 325:860.
http://dx.doi.org/10.1136/bmj.325.7369.860

36. Stratton IM, Cull CA, Adler AI, Matthews DR, Neil HA, Holman RR. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). Diabetologia 2006; 49: 1761-9.
http://dx.doi.org/10.1007/s00125-006-0297-1

37. Calvo P, Abadia B, Ferreras A, Ruiz-Moreno O, Verdes G, Pablo LE. Diabetic Macular Edema: Options for Adjunct Therapy. Drugs 2015; 75(13): 1461-9.
http://dx.doi.org/10.1007/s40265-015-0447-1

38. Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. Ther Adv Endocrinol Metab. 2013; 4(6): 151–69.
http://dx.doi.org/10.1177/2042018813512360

39. Stewart M. Anti-vascular endothelial growth factor drug treatment of diabetic macular edema: the evolution continues. Curr Diabetes Rev 2012; 8: 237–46.
http://dx.doi.org/10.2174/157339912800840488

40. Stitt AW, Lois N, Medina RJ, Adamson P, Curtis TM. Advances in our understanding of diabetic retinopathy. Clin Sci 2013; 125(1): 1-17.
http://dx.doi.org/10.1042/CS20120588

41. Abedi F, Wickremasinghe S, Richardson AJ, Makalic E, Schmidt DF, Sandhu SS, et al. Variants in the VEGFA gene and treatment outcome after anti-VEGF treatment for neovascular age-related macular degeneration. Ophthalmology 2013; 120: 115–21.
http://dx.doi.org/10.1016/j.ophtha.2012.10.006

42. Klinika Svjetlost. Anti-VEGF terapija. Available: http://svjetlost.hr/split/usluge/dijabetes-i-retina/anti-vegf-terapija/18. Accessed: 8/2016.

43. Das A, McGuire PG, Monickaraj F. Novel pharmacotherapies in diabetic retinopathy: Current status and what's in the horizon? Indian J Ophthalmol 2016; 64(1): 4-13.
http://dx.doi.org/10.4103/0301-4738.178154

44. Labriola LT, Kesen M, Csaky KG. Pharmacokinetics of anti-vascular endothelium growth factor pharmacological agents. In: Das A, Friberg TR, eds. Therapy for Ocular Angiogenesis. 1st ed. Philadelphia: Wolters Kluwer Lippincott Williams Wilkins; 2011; 140-53.

45. Stewart MW. Aflibercept (VEGF-TRAP): The next anti-VEGF drug. Inflamm Allergy Drug Targets 2011; 10(6): 497-508.
http://dx.doi.org/10.2174/187152811798104872

46. Banaee T, Shoeibi N, Saeedi HG. Effects of intravitreal bevacizumab injection on the clinical manifestations of nonproliferative diabetic retinopathyin patients with macular edema: a systematic review. Rev Clin Med 2016; 3(2): 63-8.

47. Das A, McGuire PG, Monickaraj F. Novel pharmacotherapies in diabetic retinopathy: Current status and what's in the horizon? Indian J Ophthalmol 2016; 64(1): 4-13.
http://dx.doi.org/10.4103/0301-4738.178154

48. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: A systematic review and meta-analysis. JAMA Ophthalmol 2016; 134: 21-9.
http://dx.doi.org/10.1001/jamaophthalmol.2015.4070

49. GF Dowler J. Laser management of diabetic retinopathy. J R Soc Med 2003; 96(6): 277-9.
http://dx.doi.org/10.1258/jrsm.96.6.277