Diabetic Retinopathy Clinical Practice Guidelines: Customized for Iranian Population

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Abstract

Purpose: To customize clinical practice guidelines (CPGs) for management of diabetic retinopathy (DR) in the Iranian population.

Methods: Three DR CPGs (The Royal College of Ophthalmologists 2013, American Academy of Ophthalmology [Preferred Practice Pattern 2012], and Australian Diabetes Society 2008) were selected from the literature using the AGREE tool. Clinical questions were designed and summarized into four tables by the customization team. The components of the clinical questions along with pertinent recommendations extracted from the above-mentioned CPGs; details of the supporting articles and their levels of evidence; clinical recommendations considering clinical benefits, cost and side effects; and revised recommendations based on customization capability (applicability, acceptability, external validity) were recorded in 4 tables, respectively. Customized recommendations were sent to the faculty members of all universities across the country to score the recommendations from 1 to 9.

Results: Agreed recommendations were accepted as the final recommendations while the non-agreed ones were approved after revision. Eventually, 29 customized recommendations under three major categories consisting of screening, diagnosis and treatment of DR were developed along with their sources and levels of evidence.

Conclusion: This customized CPGs for management of DR can be used to standardize the referral pathway, diagnosis and treatment of patients with diabetic retinopathy.

Keywords: Clinical Practice Guidelines; Diabetic Retinopathy; Iran

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INTRODUCTION

Diabetes mellitus (DM) is a critical public health issue globally and its prevalence is increasing mostly in developing countries.[1-4] The number of diabetics between 20 and 79 years of age is estimated to be 415 million people in the world and is expected to rise to 642 million in 2040.[5] Iran is one of the most populous countries of the Middle East and the prevalence of diabetes in Iran ranges from 7.7% to 14% in the population aged over 20 years.[2,6,7] In addition, it is estimated that Iran would take the second place in diabetes annual growth after Pakistan.[2]

Diabetic retinopathy (DR) is one of the major complications of diabetes and leading cause of visual impairment or blindness.[8-16] Evidence reveals that nearly all type I and 60% of type II diabetic patients develop some degrees of retinopathy 20 years after diagnosis.[17] Given the increasing number of diabetics worldwide, it is expected that the prevalence of DR increases especially in developing countries.[14] Similarly, DR is a major cause of visual impairment and loss in Iran.[10,11,18,19] Based on the current data, 37% and 29.6% of diabetic cases have some degrees of DR in Tehran and Yazd provinces, respectively.[11,19] On the other hand, therapeutic interventions can prevent the development of severe visual impairment caused by DR in up to 90% of cases.[20]

National clinical practice guidelines (CPGs) comprise thorough clinical recommendations based on valid evidence and are adapted considering their safety, efficacy, cost of diagnostic or therapeutic interventions, and the nation's needs. These guidelines increase the efficacy of interventions and provide equity in access to treatment for all members of the society. Since CPGs focus on a particular problem, for instance one disease, they can help both the physicians and the patients in making an appropriate decision. These instructions can also be effective in guiding health care policy makers at a national scale. Therefore, clinical guidelines increase both accessibility and quality of health care services.[21,22]

Paragraph D, article 32 of the Fifth 5-Year Development Plan of Iran and the Strategic Objective No. 75 of the Iranian Ministry of Health and Medical Education emphasize on the development, adaptation and implementation of clinical practice guidelines, and extension of health care services and development of evidence based health care at a national level.[23,24]

Considering the growing prevalence of diabetes and DR in Iran, its impact on public health, costs imposed on the health care system, and in order to establish the objectives of the Fifth 5-Year Development Plan of Iran and the Strategic Objective No. 75 of the Iranian Ministry of Health and Medical Education, DR CPGs were customized for Iranian population under supervision of the Office for Healthcare Standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education.

METHODS

The DR CPGs were adapted for Iranian population in the Knowledge Management Unit (KMU), Ophthalmic Research Center, Shahid Beheshti University of Medical

Sciences, Tehran, Iran. The adapting team included the director and the research deputy of the Ophthalmic KMU, five vitreoretinal specialists, a PhD by research candidate (a Master's of Science degree holder in Optometry), a Master's of Science degree holder in biostatistics, and the head of the office for healthcare standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education.

Searching and Identifying the Current Clinical Guidelines

The National Guidelines Clearinghouse (NGC), Guidelines International Network (G-I-N), National Institute for Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group, National Health and Medical Research Council (NHMRC), Cochrane, Bandolier, CADTH, Trip Database, PubMed (Clinical queries), Google Scholar, SID, Medlib, Magiran were the databases and websites that were explored in order to extract the relevant clinical guidelines.

Screening the Guidelines

The extracted guidelines were screened using the AGREE (appraisal of guidelines for research and evaluation) tool.[25] Ultimately, 3 DR guidelines by the Royal College of Ophthalmologists (2013),[26] American Academy of Ophthalmology (Preferred Practice Pattern 2012),[20] and Australian Diabetes Society (2008)[27] were selected as the reference CPGs.

Methods Used for Customizing Recommendations

Evaluating and appraising the reference CPGs' recommendations

Initially, 20 questions on DR were designed and the questions' components (PICO; Patient, Intervention, Comparison, Outcome) were entered in Table 1. Subsequently, the answers to the questions were extracted from the reference CPGs and the responses were recorded in the same table.

In the process of extraction and analysis of the responses, the questions were evaluated once again and broken down into smaller questions if necessary, and all the above-mentioned steps were repeated for each.

Analyzing the supporting evidence

The details of each evidence were recorded in Table 2. Tables 3 shows the levels of evidence.

Evaluating the recommendations in terms of clinical benefits and adaptability

After completing Tables 1 and 2, the customization team composed the clinical recommendations respecting the clinical benefits including cost, benefits, and side effects and then recorded those in Table 4. Consequently, the recommendations were revised in Table 5 according to three customization criteria: 1- applicability (access to proper equipments, skills at using them, and their affordability for patient), 2- acceptability (patient's preferences, cultural considerations and patient's acceptability of the therapeutic protocol), 3-compatibility (similarity between patient's characteristics/disease type and their interference with studied evidence).

Consensus

All recommendations together with complementary instructions and Tables 1, 2, 4 and 5 were sent to the chairs of the retina and vitreous departments at Ahvaz Jundishapur, Gilan, Iran, Isfahan, Mashad, Tabriz, Tehran, Shahid Beheshti, Shahid Sadoughi, Shiraz and Zahedan Universities of Medical Sciences. As the experts in the field of DR, they were asked to score each recommendation in terms of clinical benefits and customizability, and to provide a total score for each recommendation at the end. In addition, they were asked to provide any further evidence that could potentially change the recommendation.

Analyzing the consensus scores and developing the final recommendations

Experts scored the recommendations based on the RAM model.[28] The scores were analyzed and the agreement level for each recommendation was identified. The agreed recommendations were considered as the final

Table 1. Analysis of recommendations

Question	P	I (E)	C	O	Type of question	Referenced guidelines	Phrase of recommendation	Level of evidence	Inconsistency of recommendations	Technical breakthrough	New systematic review	New Studies
						G1						
						G2						
						G3						

P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; G1, American Academy of Ophthalmology (2012); G2, Royal College of England (2013); G3, Australian Diabetes Association (2008)

Table 2. Analysis of the supporting evidence

Evidence code	P	I (E)	C	O	Effect size	Statistical values	Level of recommendation

P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes

Table 3. Level of evidence

Level of evidence	Type of evidence
I	Meta-analysis
	Systematic reviews
	Randomized clinical trial
II	Clinical trial
	Well-designed cohort
	Well-designed case control
	Cross-sectional
III	Surveys
	Descriptive
	Case series studies
IV	Experts opinion, consensus

recommendations. The experts discussed the non-agreed ones in a session and after applying the required changes, the final recommendations were developed.

All customized recommendations are presented in the results section of this article along with their reference numbers and their evidence levels (EL).

RESULTS

Recommendations for Screening, Risk Factors and Follow-up

Screening and examination

As reported by the screening programs in the US, England, and Australia, the modality of choice to screen for DR is retinal digital imaging with mydriasis which has a sensitivity of 73-96% and specificity of 78-99%. Considering its feasibility, this test is recommended for screening of DR in Iran as well.[29-36]
(EL: I)

Considering the few reported side effects of tropicamide eye drop 1% (1 to 6 in 20,000 cases in different studies) and to improve the sensitivity of funduscopy, it can be used to provide mydriasis for DR screening in diabetic patients except in those with history of glaucoma.[37-44]
(EL: I)

Risk factors

Duration of diabetes

Regardless of the type, those with longer disease duration are at greater risk for development and progression of DR. Therefore:

- Funduscopy is strongly recommended for type II diabetics at their first eye examination.
- It is recommended that type I diabetics undergo funduscopy 3 to 5 years after diagnosis of diabetes.[17,45-54]
  (EL: II)

If patients are found to have signs of retinopathy, a follow-up plan should be set up based on the severity of the retinopathy.
(EL: Consensus - IV)

Blood sugar

Although tight glycemic control does not necessarily prevent the development of DR, it is recommended that diabetic patients control blood glucose and HbA1C levels in order to reduce the risk of DR progression and consequently the need for treatment.[45,55-60]
(EL: I)

Blood pressure

Target systolic blood pressure of less than 130 mmHg is recommended for diabetic patients to slow down the progression of DR.[61-65]
(EL: I)

Serum lipids

- Elevated serum lipid levels increase the risk of development and progression of DR. Therefore, control of serum lipids with statins and fibrates is recommended in diabetic patients.[66-81]
  (EL: I)
- Hyperlipidemia has been identified as a risk factor for exudative diabetic macular edema. Therefore, control of serum lipids is recommended as a preliminary therapeutic measure in diabetic patients.[66-81]
  (EL: II)

Kidney disorders

- It is recommended that the patients with diabetes and coexisting kidney disease undergo careful retinal examination due to the risk of developing DR (up to 58%)[82]
- It is recommended that the patients with advanced DR undergo thorough renal function evaluation due to the risk of developing kidney disorders (about 15%).[82]

(EL: II)

Vitamin D

As vitamin D deficiency can be associated with progression of DR, consultation with a specialist (endocrinologist, gastroenterologist, or nephrologist) is warranted for diabetic patients with vitamin D deficiency and coexisting renal and gastrointestinal problems.[83-85]
(EL: II)

Smoking

Cigarette smoking has been associated with lower incidence of DR, however, considering the higher rate of morbidity and mortality among smokers, smoking cessation is recommended.[64,77,86-94]
(EL: II)

Pregnancy

A two-fold increase in the risk of DR development during pregnancy warrants educating diabetic women planning a pregnancy. In addition, they should be monitored by regular blood glucose checks and retinal examination during and after the course of pregnancy.[95-102]

A thorough assessment of DR is recommended before planning a pregnancy.[95-102]
(EL: I)

Genetics

It appears that certain genes are involved in the development and progression of DR that could vary by ethnicity and geographical origin.[103-122]
(EL: II)

Therefore, it is recommended that patients with positive family history of DR undergo more frequent eye examinations.
(EL: Consensus - IV)

Coexisting eye diseases with diabetes

- Other diabetic eye diseases such as cataract, optic neuropathy, extraocular muscle paralysis, rubeosis iridis, and the delay in corneal epithelium healing should be taken into consideration in patients with DR.[123-126]
- It is recommended to examine the iris and angle for the presence of neovascularization prior to initialization of mydriatic eye drops.[123-126]
- Diabetic candidates for keratorefractive surgery should be well informed about the delayed corneal epithelium wound healing prior to surgery.[123-126]
  (EL: II, Consensus - IV)

Referral and follow-up approach in patients with diabetes

It is recommended to examine the patients with R2 level DR (preproliferative) according to the National Screening Committee Severity Classification System or level 43 (moderate NPDR) according to the Early Treatment Diabetic Retinopathy Study (ETDRS) Severity Classification System at 4-month intervals.[37,63,127-131]

Diabetic patients should be referred to and followed by ophthalmologists according to the following protocol:[37,63,127-131]

- All type 2 diabetic patients should undergo fundus examination (with pupil dilatation) and visual acuity measurements at the time of diagnosis and at least every 2 years thereafter.
  (EL: I)
- Patients with signs of nonproliferative DR (NPDR) should be examined annually or every 3-6 months depending on the severity of DR.
  (EL: III)
- Patients with mild to moderate NPDR should be examined closely for sight threatening retinopathy.
  (EL: I)

Table 4. Clinical benefits of the recommendations

Question	Phrase of recommendation	Level of evidence	Costs	Clinical effectiveness of the recommendation				Clinical effectiveness score	
				Side effects	Side benefits	Effect size	Low	Moderate	High

P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

Table 5. Adaptability of the recommendations (external validity)

Question	P	I	C	O	Type of the question	Phrase of recommendation	Adaptability of the recommendation			Adaptation score	Total score
							Applicability	Acceptability	Compatibility/ External validity		
										Low	Low
										Moderate	Moderate
										High	High

P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

- High-risk diabetic patients (long diabetes duration, poor blood glucose control, high blood pressure or high serum lipids) should be examined annually even in the absence of DR.
  (EL: I)
- Children with prepubertal onset of diabetes should be assessed for DR when they reach puberty.
  (EL: III)
- Diabetic women who become pregnant should undergo a comprehensive eye examination in the first trimester and be monitored closely throughout pregnancy.
  (EL: I)

Recommendations for Diagnosis

Retinal imaging

Indications for fluorescein angiography

It is recommended that patients with DR undergo fluorescein angiography in the following conditions:[132-135]

- In cases where funduscopic findings cannot justify the visual impairment (to rule out macular ischemia).
  (EL: III)
- To identify leaking lesions and capillary non-perfusion areas that cannot be detected clinically.
  (EL: II)
- To evaluate the macular capillary network
  (EL: I)

Precautions for fluorescein angiography

- It is recommended that patients with known history of cardiovascular diseases, allergy, and lung or kidney disorders have appropriate consultation before undergoing fluorescein angiography.
- Fluorescein angiography should be carried out where equipments for resuscitation, atropine and adrenaline are available.[97,136-143]
- In patients with prior hand, axillary or breast lymph node dissection, dye injection in the ipsilateral side is contraindicated.[97,136-143]
  (EL: Consensus - IV)

Different types of fluorescein angiography

Wide-field fluorescein angiography is superior in cases with peripheral retinal lesions as it could alter the classification of the DR and therapeutic and follow-up approaches.
(EL: II)

Availability of wide-field fluorescein angiography can be limited to the major ophthalmology centers.[144,145]
(EL: Consensus - IV)

Other imaging modalities

New imaging modalities for evaluation of DR include optical coherence tomography (OCT), retinal thickness analysis (RTA) techniques, and fundus autofluorescence (FAF).[146-173]

- Due to the particular properties of OCT such as demonstrating different layers of retina, the use of OCT is recommended in the following conditions:
  - To determine the macular thickness in diabetic macular edema (before and after treatment)
  - To detect vitreoretinal traction or any membrane on the macula
- Due to the particular properties of new fluorescein angiography techniques (SLO [Scanning Laser Ophthalmoscopy] Angiography) such as high-speed imaging, high resolution, possibility of digitally storing the images, and integrating the patients' data from different medical centers, it is suggested these imaging modalities be available in the majority of public and private settings.
- FAF can investigate functional changes in retinal pigment epithelium (RPE) without the injection.
  (EL: III)

Classification of DR and diabetic macular edema

The most appropriate classification system (severity grading) of DR and diabetic macular edema (DME) could be selected based on the level of health care service offered. Due to the lower complexity, the lower-level health care provider can utilize the International Clinical

Disease Severity Scale and the subspecialty eye care centers can use the ETDRS severity scale to classify the severity of DR and macular edema.[29-32,127,174-186]
(EL: IV)

Recommendations for Treatment

Laser therapy

Indications for panretinal photocoagulation (PRP)

According to Diabetic Retinopathy Study (DRS), PRP should be performed at the high-risk proliferative DR (PDR) stage. However, early PRP may be considered for severe NPDR and early PDR in the following conditions:[98,135,187-214]

1. Elderly diabetes type II patients.
2. Prior to cataract surgery.
3. In one-eyed patients where the vision of the other eye was lost due to PDR.
4. Patients who cannot be regularly examined and followed.
5. Pregnancy.

(EL: I)

- If possible, PRP should be delivered on the same day of the diagnosis of high-risk PDR and if not, within 2 weeks from the time of diagnosis.
  (EL: II)
- PRP should be postponed until clinically significant macular edema (CSME) is treated.
  (EL: II)
- Coexisting high-risk PDR and CSME should be treated with combined PRP plus intravitreal antivascular endothelial growth factor (VEGF) injection or macular laser photocoagulation (MPC).
  (EL: Consensus - IV)
- In cases with fresh vitreous hemorrhage, PRP is usually applied after intravitreal injection of anti-VEGF when the ocular media is clear.
  (EL: Consensus - IV)
- In patients with florid type DR, PRP may be applied with shorter intervals (3-5 days between PRP sessions instead of 1-4 weeks).
  (EL: Consensus - IV)
- Patients should be followed every 1-4 weeks during the course of PRP and every 2-4 months thereafter until regression of the neovessels and a stable condition is obtained. (ETDRS).
  (EL: I)
- In patients with shallow anterior chamber who are predisposed to acute glaucoma attack, YAG laser peripheral iridotomy should be performed before PRP.
  (EL: Consensus - IV)
- In patients who are unable to maintain eye fixation during PRP such as those with nystagmus, retrobulbar anesthesia may be considered in order to avoid unwanted macular burns.
  (EL: Consensus, IV)
- Patients should be informed about the possible complications of PRP such as visual field restriction and reduced amplitude of accommodation before treatment.
  (EL: Consensus - IV)

Indications of macular laser treatment

Macular laser photocoagulation should be considered in the following conditions:[135,191,215-218]

- Presence of clinically significant macular edema (CSME) according to ETDRS.

(Most recent studies recommend intravitreal injection of anti-VEGF in cases with center involving macular edema and visual acuity of less than 20/30 to 20/40; however, if the macular center is spared and visual acuity is higher than 20/30 to 20/40, macular laser photocoagulation can be applied.)
(EL: I)

- Any of the following conditions even in the absence of CSME features:
  - Progression of macular edema towards the central parts of the macula
  - Patients who cannot be followed every 3 months
  - Cataract surgery candidates with leaking macular lesions may receive macular laser treatment preoperatively.
  - Permanent vision loss in the fellow eye due to CSME.
  - In order to prevent aggravation of macular edema, PRP candidates with coexisting DME should receive intravitreal anti-VEGF injection prior to laser treatment.

(EL: I, II)

Follow-up after macular laser photocoagulation

- According to DRS and ETDRS, patients should be followed at 2-4 month intervals after macular laser treatment; decision for retreatment will be based upon visual acuity (20/30 or 20/40) and involvement of the central macula thereafter.[135,215,216]
  (EL: I)

New laser therapy techniques

New laser treatment techniques can minimize the damage to the internal retinal layers and include the followings:[219-231]

- Minimally invasive subthreshold laser
- Pattern automated scanner laser (PASCAL)

(EL: I)

Recommendation: Considering the lower risk of retinal damage with minimally invasive subthreshold technique, a limited number of laser machines equipped with these technologies are recommended to be available in ophthalmology centers.[219-231]
(EL: IV – Consensus)

Intravitreal injection

Indications

Intravitreal injection of anti-VEGF drugs is recommended in the following conditions:[169,232-326]

- Diabetic patients with diffuse macular edema and poor prognosis for focal laser treatment
- Patients with PDR or florid PDR and no response to laser therapy
- Patients with neovascularization of iris (NVI) and neovascular glaucoma (NVG)
- For patients with concomitant DR and cataract, consultation with a retinal specialist may be considered prior to cataract surgery whether intravitreal injection should be carried out at the time of cataract surgery

(EL: I)

Intravitreal injection before vitrectomy

- Patients with PDR and active neovascularization who have been planned for vitrectomy may receive intravitreal anti-VEGF injection within one week before surgery to minimize intraoperative and early postoperative bleeding.[327]
  (EL: I)
- Patients with advanced DR and active fibrovascular tissue who are vitrectomy candidates may receive intravitreal anti-VEGF injection within one week before the surgery to minimize the risk of bleeding during and after the surgical procedure.[328-332]
  (EL: I)
- Extensive fibrovascular tissue increases the risk of traction retinal detachment following intravitreal injection of anti-VEGF drugs; the time interval between the injection and vitrectomy should be not more than 2-3 days in such cases.[328-334]
  (EL: II)

Intravitreal agents

None of the intravitreal anti-VEGF agents is preferred over the others and the treatment choice depends on the availability and cost.[215,240,244,247,284,302,303,315,316,318,321,332-333]
(EL: Consensus - IV)

Complications

Complications of intravitreal injection treatment:

- Specific potential complications:
  - o Anti-VEGF drugs: Thromboembolic events, blood pressure elevation, myocardial infarction (MI) and stroke.

Recommendation: Patients with the past history of MI, stroke, thromboembolism, or uncontrolled hypertension, should receive intravitreal anti-VEGF injection after consultation with a cardiologist.[238,239,307,333,335,336]
(EL: I)

Recommendation: Intravitreal triamcinolone injection is not recommended for phakic eyes with the past history of glaucoma.[238,239,307,333,335-337]
(EL: I)

- General complications:

Endophthalmitis, retinal detachment, lens damage and cataract, vitreous hemorrhage, subconjunctival hemorrhage and pain.

Recommendation: Intravitreal injection should be carried out under aseptic conditions to prevent endophthalmitis. In addition, the anatomy of the eye should be kept in mind to minimize the risk of damage to ocular tissues.[238,239,307,333,335-337]
(EL: IV)

Recommendation: Intravitreal anti-VEGF injection is not recommended in eyes with advanced PDR and significant fibrous proliferation due to the risk of traction retinal detachment except in vitrectomy candidates.[238,239,307,333,335-337]
(EL: II)

Vitrectomy

Indications

Vitrectomy is recommended for diabetic eyes in the following conditions:[157,338-350]

- Vitreous opacity
  - o Severe non-clearing, recurrent vitreous hemorrhage
- Retinal detachment (RD)
  - o Tractional RD involving or threatening the macula
  - o Combined rhegmatogenous and tractional RD
- Diffuse CSME with taut hyaloid face and no response to previous intravitreal injections and laser photocoagulation
- Active and extensive fibrovascular proliferation

(EL: IV)

Considerations

- Early vitrectomy is recommended in the following conditions:

o Severe vitreous hemorrhage in patients with diabetes type I (EL: I)
o Patients with very poor vision (5/200) and severe vitreous hemorrhage (EL: I)
o Active fibrovascular proliferation (EL: II)
o Severe PDR refractory to PRP (EL: I)

Further recommendation

Studies have shown that while stopping anti-coagulant medications decreases the risk of vitreous hemorrhage during vitrectomy, at the same time it increases mortality. Therefore, decision regarding maintenance or perioperative discontinuation of anticoagulation therapy should be made before vitrectomy by having appropriate consultations about patients' systemic conditions.[351-353]
(EL: II)

Cataract surgery in diabetic patients

Patients should undergo thorough retinal examination prior to the surgery.[261-263,354-370]
(EL: II)

Coexisting PDR should be treated with PRP preoperatively if media is clear. However, in eyes with poor visualization due to cataract, fundus examination should be performed as soon possible following cataract surgery.[261-263,354-370]
(EL: I)

Patients with DME should receive intravitreal injection of steroid or anti-VEGF preoperatively to lower the risk of DME aggravation.[261-263,354-370]
(EL: I)

Patients should undergo more frequent retinal examinations postoperatively due to their increased risk for progression of DR.[261-263,354-370]
(EL: II)

OCT should be done postoperatively to monitor diabetic macular edema.[261-263,354-370]
(EL: II)

Diabetic patients who are cataract surgery candidates should be well informed about the risk of DR progression and probable consequent decreased vision and the necessity of frequent eye examination postoperatively.[261-263,354-370]

DISCUSSION

Considering the high prevalence of DM and the role of DR as a leading cause of visual impairment and blindness, clinical practice guidelines for DR was adapted for Iranian population at the Knowledge Management Unit, Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran at the request of the Ministry of Health and Medical Education to promote the diagnostic and therapeutic services and enhance community access to evidence-based eye care.[10,11,18,371] Different management aspects of DR including screening, risk factors, follow-up, diagnosis and treatment were taken into account in this guideline.

The retinal experts reached consensus for the majority of the CPGs' recommendations and approved them as the final recommendations. However, those with no agreement upon were discussed, reviewed and revised, and the final recommendations were composed as follows:

Recommendations for Screening, Risk Factors and Follow-up

Recommendation for vitamin D

This recommendation was primarily described as "Vitamin D level is recommended to be checked in diabetics and treatment is advised for vitamin D deficient patients to decrease the risk of developing DR". However, vitamin D administration is not completely in the field of ophthalmology and could result in adverse effects in some patients. Therefore, this recommendation was ultimately revised to "As vitamin D deficiency can be associated with progression of DR, consultation with a specialist (endocrinologist or gastroenterologist, or nephrologist) is warranted for diabetic patients with vitamin D deficiency and coexisting renal and gastrointestinal problems." in order to share the responsibility of correcting Vitamin D with other specialists; hence minimizing the adverse outcomes.

Recommendations for Diagnosis

Recommendation for precautions for fluorescein angiography

Considering the large number of patients in whom fluorescein angiography is recommended, this recommendation was reviewed and after taking patients safety and consultation costs into account was revised from "Relevant consultations are recommended prior to performing fluorescein angiography in patients with history of heart and vascular problems, drug allergy, and lung and kidney diseases" to "It is recommended that patients with known history of cardiovascular diseases, allergy, and lung or kidney disorders have appropriate consultation before undergoing fluorescein angiography".

Recommendation for different types of fluorescein angiography

This recommendation was primarily described as "Wide-field fluorescein angiography is superior for peripheral retinal lesions and could alter patient's classification and impact treatment and follow-up plans". However, with respect to the experts' opinion, clinical preferences, and costs, this recommendation was reviewed and the indications became clearer and the ultimate recommendation was changed to "Wide-field fluorescein angiography is superior in cases with peripheral retinal lesions as it could alter the classification of the DR and therapeutic and follow-up approaches. Availability of wide-field fluorescein angiography can be limited to the major ophthalmology centers".

Recommendation for other imaging modalities

With respect to the consensus reached and the viewpoints of the technical committee of the Ministry of Health and Medical Education, the recommendation for retinal imaging underwent major revision and the final version was composed.

The primary recommendation was as follows:

"New imaging techniques for retinopathy include Heidelberg retina angiograph (HRA), optical coherence

tomography (OCT), retinal thickness analyzer (RTA) and fundus autofluorescence (FAF).

a. OCT in DR is recommended for the following scenarios:
   1. Macular thickness measurements, follow-up or treatment of macular edema
   2. To diagnose tractional macular thickening.
b. HRA, as an angiographic tool has the following characteristics:
   1. Providing digital images
   2. High speed angiography
   3. High resolution.
c. FAF is employed for evaluating the functional RPE changes without need to inject any dye."

It is recommended to use these imaging tools, for the above-mentioned purposes with exception of RTA that has no clinical application.

However, following experts' consensus and considering the professional suggestions of the mentioned committee to specify the clinical application of the recommendation, the recommended conditions for using OCT were revised. In addition, specific characteristics of the new fluorescein angiography techniques including high speed, high resolution, and saving images in digital format were described. The application of FAF was also defined more precisely and the final version was composed as follows:

"New imaging modalities for evaluation of DR include new angiographic, retinal thickness analysis (RTA) techniques, optical coherence tomography (OCT) and fundus autofluorescence (FAF).

- Due to the particular properties of OCT such as demonstrating different layers of retina, the use of OCT it is recommended to be used in the following conditions:
  - To determine the macular thickness in diabetic macular edema (before and after treatment)
  - To detect vitreoretinal traction or any membrane on the macula.
- Due to the particular properties of new fluorescein angiography techniques (SLO [Scanning Laser Ophthalmoscopy] Angiography) such as high-speed imaging, high resolution, possibility of digitally storing the images, and integrating the patients' data from different medical centers, it is suggested that these imaging modalities be available in the majority of public and private settings.
- FAF can investigate functional changes in retinal pigment epithelium (RPE) without the injection."

Recommendations for Treatment

Recommendations for treatment are the most important part in this clinical guideline, therefore the customization team revised them multiple times based on the experts' opinions.

Recommendation for indications of macular laser treatment

This recommendation was primarily written as follows:

"Macular Laser treatment is recommended in the following scenarios:

1. Presence of CSME according to ETDRS study
2. One of the following conditions even in the absence of diagnostic criteria for CSME:
   - Macular edema progressing to central macula (leaking upper macular lesions, hard exudate approaching the central macula)
   - In patients incapable of regular follow-up every 3 months
   - Cataract surgery candidates (in patients with cataract who have leaking macular lesions in their fundus, laser treatment of macular edema is recommended before the cataract surgery)
   - Permanent vision loss in the fellow eye as a result of CSME
   - In PRP candidates, laser treatment of macula is recommended prior to or concurrent with PRP to prevent worsening of macular edema."

This recommendation was revised to emphasize on intravitreal anti-VEGF injections as one of the principal treatments for macular edema as below:

"Macular laser photocoagulation should be considered in the following conditions:

- Presence of clinically significant macular edema (CSME) according to ETDRS.

(More recent studies recommend intravitreal injection of anti-VEGF in cases with center involving macular edema and visual acuity of less than 20/30 to 20/40; however, if the macular center is spared and visual acuity is higher than 20/30 to 20/40, macular laser photocoagulation can be applied.)

- Any of the following conditions even in the absence of CSME features:
  - Progression of macular edema towards the central parts of the macula
  - Patients who cannot be followed every 3 months
  - Cataract surgery candidates with leaking macular lesions may receive macular laser treatment preoperatively.
  - Permanent vision loss in the fellow eye due to CSME.
  - In order to prevent aggravation of macular edema, PRP candidates with coexisting diabetic macular edema (DME) should receive intravitreal anti-VEGF injection prior to undergoing laser treatment."

Recommendation for follow-up after macular laser photocoagulation

The primary recommendation of the customization team for follow-up after laser treatment of the macula was:

"After laser treatment for macular edema, follow-up is recommended every 2-4 months until stabilization of the condition. Subsequent laser retreatment will be planned based on visual acuity (better than 20/30) and no involvement of central fovea." According to the Ministry of Health and Medical Education Technical Committee, the reason of disagreement in the consensus process was re-evaluated. For this purpose and in order to make this recommendation more practical, a determinant VA for retreatment was extracted from two valid references;[215,135] VA of "20/30" was replaced by "20/30 or 20/40" and the final recommendation was composed as:

"According to DRS and ETDRS, patients should be followed at 2-4 months intervals after macular laser treatment; decision for retreatment will be based on visual acuity (better than 20/30 or 20/40) and involvement of the central fovea thereafter."

Recommendation for new laser therapy techniques

Considering the high cost of the instrument equipped with minimal invasive subthreshold technique, the initial recommendation "Considering the availability, lower rate of retinal damage and the higher speed of laser procedure with the retinal laser platform by the minimal invasive subthreshold technique, it is recommended for ophthalmologists to use the above-mentioned retinal laser platform" was replaced by "Considering the lower risk of retinal damage with minimally invasive subthreshold technique, a limited number of laser machines equipped with these technologies are recommended to be available in ophthalmology centers".

In conclusion, customized diabetic retinopathy clinical practice guidelines for Iranian population was composed by applying the higher grade existing evidence in the literature, the opinions of Iranian medical universities' faculty members under technical supervision of the Office for Healthcare Standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education. Hence, in addition to fulfilling strategic objective No. 75 of this ministry, the provided recommendations can standardize the screening, referral, diagnosis, treatment and follow-up of patients with diabetic retinopathy.

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Conflicts of Interest

There are no conflicts of interest.

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