

Telemedicine for Diabetic Retinopathy Screening in Croatia: A Dream That Could Become a Reality

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ABSTRACT

Diabetic retinopathy (DR) is the leading cause of preventable blindness in working-age adults associated with devastating personal and socioeconomic consequences. The increasing use of anti-vascular endothelial growth factor (anti-VEGF) agents over the past decade and telemedicine implementation in systematic DR screening resulted in a declining trend of new blindness due to diabetes in several countries. Telemedicine is the remote delivery of healthcare services over the telecommunications infrastructure. It allows healthcare providers to evaluate, diagnose, and treat patients without the need for an in-person visit. Teleophthalmology is a telemedicine branch, mostly focused on diabetic retinopathy and retinopathy of prematurity. Screening for DR in Croatia is commonly performed annually, only by ophthalmologists using dilated slit-lamp biomicroscopic fundus examination. Due to the insufficient number of ophthalmologists and the lack of a formal call system, many diabetic patients do not perform annual screening. In an ideal DR screening model in Croatia, each diabetes center in university or general hospitals throughout Croatia (17 centers) would have one small digital fundus camera and an educated nurse who would perform dilated fundus photography. Electronic images from diabetes centers would be transferred for remote grading to the same hospitals' ophthalmology departments or a central grading center for DR screening in Croatia. Grading for DR would be performed by an ophthalmologist, medical retina specialist. Patients would be annually invited by mail from the National Diabetes Registry to come to the nearest diabetes center for a fundus photographing and DR screening. Each patient with a positive result would be promptly referred to the medical retina specialist at the closest ophthalmology department for further examination and treatment.

Key words: diabetes mellitus, diabetic retinopathy, telemedicine, screening, Croatia

Introduction

Diabetes is the most frequent endocrine disease in developed countries and one of the most common non-communicable diseases (NCDs) globally, estimated to have affected 463 million people in 2019 and projected to affect 578 million by 2030 and 700 million by 2045¹. It is among the top ten causes of death in adults and was estimated to have caused 4.2 million deaths globally in 2019¹. Besides the high rate of premature mortality and lower quality of life, diabetes and its long-term complications also impose a significant economic impact on countries, health systems, and individuals with diabetes and their families. In 2019, global health expenditure on diabetes had been USD 760 billion, and International Diabetes Federation (IDF) projects that total diabetes-related health expenditure

will reach 825 billion by 2030 and USD 845 billion by 2045¹.

Diabetic retinopathy (DR) is a long-term microvascular complication of diabetes and the leading cause of blindness in working-age adults associated with devastating personal and socioeconomic consequences². According to the META-EYE Study, more than one-third of people with diabetes worldwide have DR, and 10.2% have vision-threatening DR (VTDR), including proliferative DR (PDR) and diabetic macular edema (DME)³. Vision loss due to diabetes can be prevented if retinopathy is early diagnosed in its painless and asymptomatic stages and appropriately and timely treated. The WHO Universal Eye Health: A Global Action Plan 2014–2019 outlined the need to reduce the prevalence of preventable blindness, including that related to diabetes⁴. The increasing use of anti-

vascular endothelial growth factor (anti-VEGF) agents over the past decade and telemedicine implementation in systematic DR screening resulted in a declining trend of new visual impairment and blindness due to diabetes in several countries^{5,6}. Thus, establishing successful DR screening programs worldwide is an essential task that would benefit from both sociopolitical acceptance and health care professional commitment on a long-term basis.

What Is Telemedicine?

There are many definitions of telemedicine, but in most cases, all definitions say that telemedicine is managing patients from a distance. That is true, but as telemedicine is not a medical specialization per se, we cannot say that telemedicine is just managing patients in a remote area or from a distance, which is, in fact, its essential purpose. However, as we know, the basic techniques of patient examination in medicine are observation, auscultation, and percussion and to perform that from a distance is merely impossible and to make telemedicine possible, the improvement in telecommunication, computers, and also in medicine was necessary to allow us today to speak about telemedicine. Thus, telemedicine is the integration and implementation of modern technology in telecommunication, computers, and medicine, and without any part of this chain, telemedicine would be impossible⁷.

Telemedicine began with the invention of the telephone in the 19th century when doctors started to manage and advise their patients by the phone. Further improvement in telemedicine development happened on 14th February 1946 with the first electronic computer named ENIAC. Some advances in medicine were also needed to implement telemedicine principles significantly. As the picture speaks more than a thousand words, visualization of inner body structures was a big step forward done by W. Röntgen in 1895. In that same year, W. Einthoven made another big step forward with ECG diagnostics. Also, from that time till these days, significant improvements were made in biochemistry and laboratory diagnostics. All these small but significant parts of the telemedicine chain were necessary to make it possible.

Here one could probably say that we forgot something, and yes, we did not speak about the Internet yet. We may consider the Internet as a breakthrough in telecommunications. In short, we may say that the Internet, the computer network of all networks, as we know it today, has its roots in the ARPANET project from 1969 when it was constructed, computer networks were able to survive a nuclear attack.

Over the years, every part of the telemedicine chain improved more and more. Telecommunications became much faster, and computer graphics became much more precise and realistic. Computer graphics improvements were so high that the human eye could not register several colors that can be seen even on a standard home computer, and improved diagnostic technology makes the circle of telemedicine finally completed.

As said before, telemedicine is not a separate specialization in medicine. However, telemedicine principles are applied in different branches of modern medicine, so today we speak about teleophthalmology, teleradiology, telecardiology, telepathology, etc.

We also can divide telemedicine into synchronous and asynchronous parts⁸. Synchronous or “online” is the kind of telemedicine when the giver and receiver of the telemedicine care are on the different side of the telemedicine bridge simultaneously, and the medical care is given in real-time. We are talking about asynchronous telemedicine when some amount of time shift is present. We cannot forget that practicing medicine means permanent education, so telemedicine principles are beneficial in permanent education.

Moreover, finally, we cannot forget the General Data Protection Regulation (GDPR). Like Apollo, the physician, swears us all, and Asclepius, Hygieia, Panacea, and all the gods and goddesses as our witnesses, we must keep our patient’s data confidential. The Internet is nowadays everything, but it is not a safe place, and we must have that on our minds. So, we must obtain the security of a patient’s data during telemedicine implementation in patients management. Let us say that we have Alice and Bob, and they are on each side of the telemedicine bridge, and Eve is an “intruder” and wants to see what Alice and Bob are doing. The security of network communication between Alice and Bob is based on the three most important characteristics: confidentiality, integrity, and availability (Figure 1)⁹. The abbreviation “CIA” describes these security conditions of data transfer over the network. Confidentiality is obtained by encryption, which can be symmetric or asymmetric. Symmetric encryption means that Alice and Bob have the same private keys, while in asymmetric encryption, both sides, Alice and Bob, must have their own personal and public key. Encryption disables the third person, in this case, Eve, to access our patient’s original data. The data integrity secures Alice and Bob that the data would not be changed during network transfer, and that data is the same as the original. Hashing is the name of the algorithm or a method that enables data integrity. Data that must be transferred over the network pass through the Hash function, and then we get a unique data code on which another side, in this case, Bob, may check by entering of decrypted data in the Hash function. One of the most common Hash functions today is SHA256. This function generates a 256-bit code no matter how big the original data are. Availability is obtained by the possibility of communication at every moment. That is made possible by redundant communication canal or by the redundant communication system. In short, that would be about the security of network communication and the security of data in transit. Similar principles of confidentiality, integrity, and availability obtain the protection of data on a data basis.

Telemedicine for Ophthalmology

Telemedicine for ophthalmology or teleophthalmology is a telemedicine branch that delivers eye care through

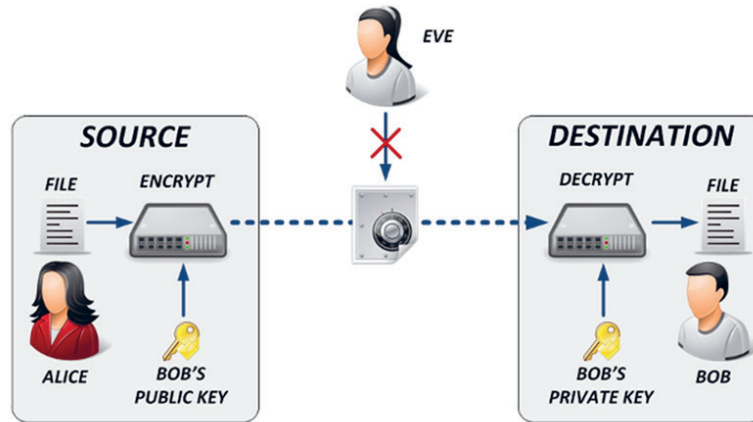


Fig. 1. The principles of telemedicine today.

digital medical equipment and telecommunications technology. Today, teleophthalmology applications include access to the ophthalmologist for patients in remote areas, ophthalmic disease screening, diagnosis and monitoring, and distant learning¹⁰. Teleophthalmology enables health professionals to take ocular images and allow the ophthalmologist, health care professionals, and researchers on the other side to carry out the abovementioned requests. The required equipment includes a camera that can take ocular images and a computer terminal with network capabilities that transfers the images. Current teleophthalmology is mostly focused on the two areas, DR and retinopathy of prematurity (ROP). Successful use of telemedicine in these areas has provided benefits to patients, health care systems, and society. Although effective treatments for high-risk DR have existed for more than four decades, DR remains the leading cause of new blindness among working-age adults. A significant contributor to that is the patients' inability to access regular fundus examinations.

Telemedicine programs can improve patient access to the annual DR screening through patient imaging in a primary care setting or diabetes care center¹¹. Given the high proportion of currently unable patients possibility to obtain a fundus examination at the proper frequency, expansion of telemedicine for ophthalmology programs would likely result in the earlier provision of care for eyes with DR. Telemedicine for ROP has a proven ability to improve access to eye care for premature infants at high risk for ROP¹². Timely diagnosis and treatment of ROP are essential for successful outcomes, especially in remote areas.

These two clinical areas demonstrate that telemedicine can successfully improve and extend ophthalmic care using imaging technology. Other telemedicine areas within ophthalmology, such as intraocular pressure monitoring, optic nerve analysis, macular disease monitoring, visual field analysis, and anterior segment diagnosis, are also being established. Also, the capacity to perform remotely, face-to-face exams, and consults in routine and emergent clinical situations is advancing with improved two-way communication technologies.

Screening for Diabetic Retinopathy

Screening for DR is an essential cost-effective part of diabetes management^{13,14}. However, even if enough ophthalmologists are available, using ophthalmologists to screen every person with diabetes usually is not feasible and is likely to be an inefficient use of resources. Theoretically, a screening examination could include a complete ophthalmic examination with best-corrected visual acuity after refraction, pupil dilation, slit-lamp biomicroscopic fundus examination, and the latest retinal imaging, such as with wide-field retinal photography and optical coherence tomography (OCT). However, such screening examinations are not performed routinely, even in high-income countries.

The current guidelines suggest the minimum screening examination components should include a screening vision examination (before pupil dilation) and a retinal examination adequate for DR classification¹⁵. Nowadays, low-cost fundus cameras are widely available, and fundus photography telemedicine has become a good option for obtaining the retinal examination¹⁶. This method involves an educated nurse or trained photographer taking retinal images and sending them to a remote trained reader (typically an ophthalmologist) for interpretation. Fundus photography telemedicine has been shown to have acceptable sensitivity and specificity for DR screening compared to in-person screens¹⁷. It is also cost-effective and generally well-liked by patients¹⁸. Although fundus photography telemedicine increases screening rates and its implementation in systematic DR screening resulted in a declining trend of new visual impairment and blindness due to diabetes in several countries^{5,6}, still there are logistical barriers, lack of educated professionals, cost issues, and time delays. Such limitations created interest in assessing images using fully automated artificial intelligence (AI)-based grading systems¹⁹. In real-time, the system decides whether a patient requires a referral, and it is much cheaper than having ophthalmologists conduct screening. In April 2018, the US Food and Drug Administration (FDA) approved an AI algorithm, developed by IDx, used

with Topcon Fundus camera (Topcon Medical) for DR identification²⁰. The device, called IDx-DR, is a software program that uses an AI algorithm to analyze images of the eye taken with a retinal camera Topcon NW400. The digital images of a patient's retinas are uploaded to a cloud server on which IDx-DR software is installed. If the images are of sufficient quality, the software provides one of two results: (1) "more than mild diabetic retinopathy detected: refer to an eye care professional" or (2) "negative for more than mild diabetic retinopathy: rescreen in 12 months". If a positive result is detected, patients should see an eye care provider for further diagnostic evaluation and necessary treatment as soon as possible.

Regardless of the screening method, the most important is that the DR screening service must be well connected with the proper ophthalmology department in which all further diagnostic procedures and treatments (laser, intravitreal injections, vitrectomy) if needed, will be performed^{21,22}. The guidelines suggest that patients with positive results will not benefit from the DR screening program without adequate and timely access to ophthalmic care¹⁵. Therefore, DR screening should only be initiated after sufficient access for facilities with access to minimal treatment, including a laser machine's availability within three months of screening.

Current Status of Screening for Diabetic Retinopathy in Croatia

The Republic of Croatia is a country located in Central and Southeast Europe on the Adriatic Sea coast. It has an area of 56,594 square kilometers and a population of 4,067,500. According to the Croatian National Diabetes Registry, 315,298 of Croatian adults (7.8% of the population) had diabetes in 2019²³. Besides the high prevalence of diabetes, an additional burden is that almost 40% of patients have not been diagnosed with diabetes, so the total number of diabetic patients in Croatia is estimated to be 500,000²³. The official prevalence of DR and blindness due to diabetes in Croatia is unfortunately unknown because the registry of diabetic eye disease and blindness due to diabetes is insufficient and not regularly updated.

In Croatia, there are no national recommendations or clinical guidelines on diabetic retinopathy screening and treatment. Screening for DR is commonly performed annually²⁴, using dilated slit-lamp biomicroscopic fundus examination only by ophthalmologists, mostly medical retina specialists. Sometimes longer intervals between screening (e.g., 1.5 or 2 years) are recommended, particularly for older patients with type 2 diabetes, previously no signs of diabetic retinopathy, and good metabolic control. Neither nurses, technicians, nor optometrists are included in the fundus photographing or screening. There are about 400 active ophthalmologists in Croatia, among them 45 medical retina specialists trained to screen and treat DR and DME. No new technologies such as automated grading, electronic data transfer systems (including telemedicine), artificial intelligence are introduced into the DR screening in Croatia. OCT is used only for diagnosing and monitoring of

DME. There is neither a formal call-recall system nor people with diabetes are invited for screening from the diabetes register, GP register, or dispensing records. They attend for fundus examination by verbal recommendation of a diabetologist or GP or by their own request. There is also no national survey or system to monitor the screening frequency or if people attend for fundus examination.

In Croatia, PDR and DME are treated according to the Diabetic Retinopathy Guidelines by the Royal College of Ophthalmologists, London, UK²⁵, and Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA)²⁶. Laser photocoagulation, intravitreal injection (anti-VEGF, steroids), and vitrectomy are available for patients with PDR and DME in ophthalmology departments in all university hospitals, several general hospitals, and private practices. However, unfortunately, due to many diabetic patients and the insufficient number and time of medical retina specialists and VR surgeons, the situation is serious with a too long period, about six to eight months, from PDR and DME diagnosis to the start of their treatment.

Ideal Model for Screening for Diabetic Retinopathy in Croatia

In an ideal DR screening model in Croatia, each diabetes center in university or general hospitals throughout Croatia (17 centers) would have one small digital fundus camera and an educated nurse or technician who would perform dilated fundus photography. Electronic images from screening diabetes centers would be transferred (electronic data transfer) for remote grading (telemedicine) to the same hospitals' ophthalmology departments where the diabetes centers are located. Grading would be performed by an ophthalmologist, medical retina specialist working there. In parts of Croatia, where there are no ophthalmologists, the images would be transferred for grading to a central grading center for DR screening in Croatia that is less expensive than relocating ophthalmologists. Patients would be annually invited by mail from the National Diabetes Registry to come to the nearest diabetes center for a fundus photographing and DR screening. Each patient with a positive result would be promptly referred to the ophthalmologist, medical retina specialist at the nearest ophthalmology department for further examination and treatment. During the screening, the educated nurse would conduct continuous education of patients on the importance of regular DR screening and good control of well-known risk factors: glycemia, arterial hypertension, and dyslipidemia to prevent vision loss due to diabetes. Significant, but not unbearable, barriers to implementing this ideal screening model in Croatia are lack of equipment (digital fundus cameras) and deficiency of educated nurses and technicians for fundus photographing. Also, there are no electronic data transfer systems (including telemedicine) in ophthalmology in Croatia. Still, such systems are used routinely in radiology, so it should not be a problem to implement them in ophthalmology.

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TELEMEDICINA U PROBIRU DIJABETIČKE RETINOPATIJE U HRVATSKOJ: SAN KOJI BI MOGAO POSTATI STVARNOST

SAŽETAK

Dijabetička retinopatija (DR) vodeći je uzrok preventabilne sljepoće radno-aktivnih osoba povezan s razornim osobnim i socioekonomskim posljedicama. Sve veća primjena anti-VEGF lijekova u zadnjem desetljeću i uvođenje telemedicine u sustavni probir DR-a rezultirali su smanjenjem novonastale sljepoće zbog dijabetesa u nekim državama. Telemedicina je pružanje zdravstvenih usluga na daljinu putem telekomunikacijske infrastrukture. Pružateljima zdravstvenih usluga time je omogućeno postavljenje dijagnoze i liječenje bolesnika bez potrebe za osobnom posjetom. Teleoftalmologija je grana telemedicine uglavnom usmjerena na dijabetičku retinopatiju i retinopatiju nedonoščadi. Probir DR-a u Hrvatskoj provode samo oftalmolozi, obično jednom godišnje, pregledom očne pozadine nekontaktnim lećama na biomikroskopu. Zbog nedovoljnog broja oftalmologa i nepostojanja formalnog sustava poziva, mnogi bolesnici sa šećernom bolešću ne provode godišnje očne preglede. U idealnom modelu probira DR-a u Hrvatskoj, svaki centar za dijabetes u sveučilišnim ili općim bolnicama diljem Hrvatske (17 centara) imao bi jednu malu digitalnu fundus kameru i educiranu medicinsku sestru koja bi izvodila slikanje očne pozadine u midrijazi. Slike iz centara za dijabetes elektronski bi se prenosile na očitavanje u oftalmološke odjele istih bolnica ili u središnji centar očitavanja i probira DR u Hrvatskoj. Očitavanje slika i stupnjevanje DR-a izvodio bi oftalmolog, subspecijalist za stražnji segment oka. Bolesnici bi jednom godišnje poštom bili pozivali iz Nacionalnog registra za dijabetes da dođu u najbliži centar za dijabetes radi probira DR-a slikanjem očne pozadine. Svaki bolesnik s pozitivnim nalazom bio bi odmah upućen subspecijalistu za stražnji segment oka najbližeg oftalmološkog odjela na daljnju dijagnostičku obradu i liječenje.