Doctoral School of Interdisciplinary Medicine

Diabetic retinopathy screening using telemedicine tools

PhD Thesis

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3. Eszes, DJ, Szabó, JD, Russell, G, Paulik, E, Nagymajtényi, L, Facskó, A, Petrovski, G, Petrovski, BÉ. Socio-economic inequalities and health-related behaviour – experiences from the screening of diabetic retinopathy in Hungary. NKE XI. Konferenciája "Krónikus betegségek megelőzése". Szeged, 2017.08.30 - 09.01. Népegészségügy 95:160-161. (2017)

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Abbreviations

ATA	American Telemedicine Association
AMD	age-related macular degeneration
Anti-VEGF	anti-vascular endothelial growth factor
BMI	body mass index
DCCT	Diabetic Control and Complication Study
DM	diabetes mellitus
DME	diabetic macular edema
DR	diabetic retinopathy
DRM	DR module
ETDRS	Early Treatment Diabetic Retinopathy Study
GP	general practitioners
IAPB	International Agency for the Prevention of Blindness
ICO	International Council of Ophthalmology
IDF	International Diabetes Federation
IQR	interquartile range
IRMA	intraretinal microvascular abnormalities
M	mydriatic
M0	no maculopathy
M1	presence of maculopathy
NHS	National Health Services
NVD	neovascularization of the optic disc
NVE	neovascularization elsewhere
Non-DR	nondiabetic retinopathy
NM	non-mydriatic
OCT	optical coherence tomography
PRP	panretinal laser photocoagulation
RAAB	standardized rapid assessment of avoidable blindness
R0	preretinopathy
R1	background retinopathy

R2	preproliferative retinopathy
R3A	active proliferative retinopathy (R3A)
R3S	stable proliferative retinopathy
ROG	referral outcome grader
QoL	quality of life
SD	standard deviation
SES	socio-economic status
SPHS	self-perceived health status
STR	sight-threatening retinopathy
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
VA	visual acuity
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization

1. Introduction

The global prevalence of diabetes mellitus (DM) among adults (age 20 years and older) was 10.5% worldwide in 2021 [1], more than double the 4.7% level in 1980 [2], while its prevalence still shows an increasing tendency due to obvious obesity epidemic and aging of the population [3-5]. In 2016, 1.6 million deaths were directly attributed to DM, with more than half of them occurring in the lower- and middle-income countries. In Hungary, a total of 1 346 443 patients (14% of the population) suffered from DM in the same age group in 2019 [6], and some degree of diabetic retinopathy (DR) could be observed among 19% of the patients with type 1 DM (T1DM) and 24% in those suffering from type 2 DM (T2DM) for 3 or 4 years [7].

According to the World Health Organization (WHO) forecast, DM will be the seventh leading cause of death in 2030, while DR will be the leading cause of vision loss among active adults in industrialized countries [8]. DR is the fourth most common cause of blindness in the overall population, but it is second among active adults in industrialized countries [9], accounting for a significant drop in quality of life (QoL) and working ability of the patients [10, 11]. DR is the most common late complication of DM in people aged 20 to 64 years—the working-age population, and except for where effective screening programs have been implemented, it is the leading cause of blindness and reduced vision in this group in the developed countries [10, 12]. In a study, comparing data from 35 populations (Caucasian, Asian, Hispanic and African American) in the United States (U.S.), Europe and Asia, the global prevalence of sight-threatening retinopathy (STR) was estimated at 10.2% for all DM patients [12]. Ophthalmological symptoms in most people with DR develop only in the late stages of the disease, when treatments are no longer effective. The most important risk factor for DR is the duration of diabetes: according to WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) the prevalence of some degree of retinopathy in T1DM patients is 8% after 3 years, 25% after 5 years, 60% after 10 years and 80% after 15 years. In the same group, the prevalence of proliferative DR after 20 years is 50% [13].

Other known risk factors for developing DR are type of DM, elevated HbA_1c, age, gender, high blood pressure, and retinopathy stage, while other correlating risk factors are being investigated. Unfortunately, 50% of the people with diabetes are unaware of the attributes of their disease and the compliance with screening tests are poor. The disease is determined by the outcome of the complications. Since high blood sugar levels and fat damage the wall of the arteries, it is not surprising that people with diabetes have 2 to 4 times higher cardiovascular mortality rate and 2 to 4 times higher risk of stroke than patients without diabetes. Renal failure is also a common complication, estimated to affect 30–40% of the patients with diabetes, while 60–70% of the patients develop neuropathy. Loss of sensation is particularly important because it can lead to injuries going undetected, which can cause serious infections and possible amputations. People with diabetes can be more than 25 times more at risk of amputation than people without diabetes. This is not only an individual problem, but a societal problem as well. According to a 2009 survey, the average annual health expenditure for diabetic patients was $1205 per capita and for those with complications this number was $2276 per capita. Half of this cost is made up of medicines, but only a quarter of the expenditure on drugs is for antidiabetics [14]. Similarly, the treating expenses doubled in Germany and in the U.S., where $174 billion was spent on the treatment of diabetes in 2007 [14]. The Hungarian data only cover the costs of the National Health Insurance Fund, while other economic aspects like time off from work or restricted work due to complications of the disease are not included. DR is caused by damage to the retinal microvasculature. Proper screening for DR is an important milestone towards achieving early and efficient laser photocoagulation and/or anti-vascular endothelial growth factor (anti-VEGF) treatment for preventing visual loss [15]. Fundus screening is considered as secondary prevention, since early detection and treatment can prevent blindness caused by DR. Proper glycemic control can help to prevent the development of DR, slow the progression of the disease and reduce the risk of blindness. The Diabetic Control and Complication Study (DCCT) investigated the effect of hyperglycemia in patients with T1DM. Intensive therapy reduced the risk of DR progression by 54%. A United Kingdom Prospective Diabetes Study (UKPDS) investigated the protective effect of glycemic control in T2DM patients. Results show that strict glycemic control reduces microvascular complications by 25%, and decreasing HbA1c by one point reduces the need for fundus laser treatment by 35% [16].

In the last decade, three new technological developments can be highlighted in the prevention of DR-related visual impairment: the advent of non-invasive optical coherence tomography (OCT) has made possible a faster detection of diabetic macular edema (DME), new tools for advanced ophthalmic therapy like intravitreal anti-VEGF injections have made not only prevention but also visual acuity (VA) improvement an achievable goal, and the development of non-mydriatic (NM) fundus cameras and teleophthalmology have created a new basis for fundus screening in DR [17, 18].

Depending on the severity of DR, four stages can be distinguished in general: preretinopathy (R0), when normal conditions can be seen, but damage to the blood vessels can be detected and small aneurysms may occur. Background retinopathy (R1), when microaneurysms spot-like, striated or puddle-like retinal haemorrhages can be seen. Preproliferative retinopathy (R2), when the symptoms mentioned above increase because of the ischemic condition of the retina. The venous circulation slows down, venules become dilated and strong oxygen deficit develops. At the stage of proliferative retinopathy (R3A), neovascularisation and scar tissue have formed due to the lack of oxygen of the retina, which in addition to the risk of retinal detachment the iridocorneal may also be affected causing secondary glaucoma [19]. A further subclassification exists for stable proliferative retinopathy (R3S) in patients who have received panretinal laser photocoagulation (PRP) under R3A and then became “stable”; these cases are considered to be safe to keep in a surveillance clinic [20]. Once fundus lesions appear as a complication of DM, the patient has either low, intermediate, or high risk for developing some grade of DR. Therefore, the focus should rather be on raising prevention programs and early detection, as well as successful treatment of the basic disease.

DR is usually asymptomatic before the appearance of any vision loss, but it is detectable by retinal imaging techniques objectively. Several recommendations highlight the need for continuous eye screening and monitoring of people with DM. This is due to the rapid progression of the disease, therefore, its treatment can only be successful in slowing down the progression and preventing the development of severe stages if timely therapy can occur [21].

In October 1989, in the Saint Vincent Declaration [22], the WHO and the International Diabetes Federation (IDF) set the goal of reducing the incidence of diabetes-related blindness by at least one third, significantly extending the life expectancy of people with diabetes and improving their quality of life (QoL) in Europe. As a follow-up, in 1990, a protocol for the ophthalmic screening of people with DM in Europe was established in London. Recommendations were made for the organization of DR screening, based upon standard images of the different stages of DR to be referred when planning laser treatment. Annual eye examinations for people with diabetes are a problem worldwide, and despite recommendations, for example, in the USA, about 50% of patients with a previous diagnosis of diabetes do not receive an annual eye examination [23].

According to the current national recommendations, people with DM should have an eye examination every year from the time diabetes is diagnosed, and every 2-4 months if eye complications progress [24, 25]. In case of severe preproliferative or proliferative DR and clinically significant macular edema, immediate fundus laser treatment or anti-VEGF injection is required. In order to manage people with DM within the optimal time range, regular ophthalmological follow-up is needed, with a focus on the fundus examination. In the absence of continuous monitoring of the fundus, the patients are treated only after the appearance of more severe symptoms or complications, in which case therapy is usually more difficult and less effective [26].

Table 1 shows the International Clinical Diabetic Retinopathy Disease Severity Scale DR stage grading and the International Council of Ophthalmology (ICO) 2017 recommendation for the frequency of ophthalmic follow-up in patients with DM [27]. People with T1DM should have annual eye examinations from the 5th year of DM onwards, and every six months from the 10th year onwards according to the recommendations of The American Academy of Ophthalmology [28]. According to the latest UK National Screening Committee recommendation (2016), annual screening is necessary for those at higher risk of visual impairment, and for low-risk DM patients who have had no abnormalities in two consecutive years of fundus examination, biennial fundus screening is sufficient. This modification is due to the fact that recent studies analyzing the financial aspects of DR screening have shown that annual screening is not always cost-effective [29].

Table 1 Screening and Referral Recommendations Based upon the International Classification of Diabetic Retinopathy* and Diabetic Macular Edema for High-Resource Settings [27]

Classification	**Re-examination or Next Screening Schedule**	**Referral to Ophthalmologist**
DR		
No apparent DR, mild nonproliferative DR, and no DME	Re-examination in 1–2 yrs	Referral not required
Mild nonproliferative DR	6–12 mos	Referral not required
Moderate nonproliferative DR	3–6 mos	Referral required
Severe nonproliferative DR	<3 mos	Referral required
Proliferative DR	<1 mo	Referral required
DME		
Non–center-involving DME	3 mos	Referral required
Center-involving DME	1 mo	Referral required

DME = diabetic macular edema; DR = diabetic retinopathy.

∗ In cases where diabetes is controlled.

1.1. Diabetic retinopathy screening

In the past, over a long period of time, direct ophthalmoscopy was the basic method used for the early diagnosis of DR. It has, however, proven not to be an optimal technique for DR screening, as it is subjective, requires pupil dilation, it is labourous, time consuming, and has low sensitivity [26]. In the last decades, digital imaging and telemedicine have become the focus of clinical studies on DR screening. Fundus cameras are diagnostic devices specifically designed to examine the fundus of the eye, they can also take digital images so that the photos can be stored and compared with previous images. At the beginning, fundus cameras could only see the fundus after dilating the pupil (mydriatic (M)), but the new cameras can take high-quality photos even with a narrow pupil. The development of these NM fundus cameras has eliminated the inconvenience and risk of pupil dilation with good technical results [26]. While the ophthalmoscopic examination and the 7-field, stereoscopic, pupil-dilated 30-degree fundus photography require a qualified professional and are time-consuming, the NM digital photography can be performed by a trained person without the presence of an ophthalmologist [30, 31].

Early Treatment Diabetic Retinopathy Study (ETDRS) 7-field 30' images taken after pupil dilation are considered the gold standard for DR detection and classification. Despite its high sensitivity and specificity, this test method has not been widely used because it is expensive and time-consuming. The appearance of NM fundus cameras in the early 2000s made fundus photography without pupil dilation possible with acceptable technical results [32]. Several studies have reported the benefits of non-mydriatic cameras for early detection of DR. Since the appearance of the new digital fundus cameras, several studies have also focused on the amount of images needed for screening of the eyes of patients with DR, as well as, which retinal areas should be imaged, and whether pupil dilation is necessary for regular monitoring [30, 31]. The sensitivity and specificity of digital fundus photos have been analyzed, and in 1995, the British Diabetes Association meeting set a minimum expected specificity of 80% and target specificity of 95% for adequate DR screening [29]. Although mydriasis reduces the number of inappreciable images, it does not significantly increase the specificity and sensitivity of detecting any degree of retinopathy [33]. A 2004 study found higher specificity and sensitivity of 3x45-degree images compared to 1-field images [34]. This was later confirmed by several studies. Vujosevic et al. compared the 1- and 3-field NM digital images with the "gold standard" ETDRS 7-field stereo, dilated 30-degree retinal images [31]. No studies have been performed with a direct ophthalmoscope, as previous studies have already confirmed its low sensitivity [33]. The 1-field photos did not reach the sensitivity target (<80%), which would be expected for an effective screening program [31]. This contradicts the 2004 recommendation of the American Academy of Ophthalmology saying that a central, 1-field image would be appropriate for screening DR [32]. There are, otherwise, not many studies comparing 3-field NM and M digital photography with standard ophthalmic examination, but they all found high consistency in the results obtained [30, 35]. In 1989, Moss et al. compared the 7-field stereoscopic images with 2-field and 4-field 30-degree stereo images, finding 80% and 91% match between the results of the evaluation [36]. Scanlon et al. in 2003 reported a sensitivity of 80.2% and a specificity of 96.2% for 2-field photographs taken under pupil dilation [29]. Unfortunately, there is still no consensus on the number of NM 45-degree retinal images. In England, the national screening run by the National Health Services (NHS) with a large coverage, uses 2-field images under pupil dilation, while the DR screening in Scotland, which is similarly effective, uses 1-field photos; meanwhile, the Joslin Vision Network in the U.S. relies on 3-field NM photos [37, 38].

1.2. Telemedicine

The rapid development of telecommunications and digital imaging methods have created the basis for telemedicine. The safe and efficient electronic transfer of medical data has made it possible to provide healthcare services without the need for a doctor-patient encounter. Since diagnosis is based largely on image information, ophthalmology is a particularly appropriate field for the development of telemedicine networks that can greatly improve the availability, quality and efficiency of healthcare. Telemedicine gives the opportunity for close cooperation between the internal medicine and ophthalmology specialists, which will certainly improve the effectiveness of DM treatment. A NM camera is a powerful tool for telemedicine, to schedule the next eye examination and to establish an immediate, more detailed examination by an ophthalmologist. However, this method is not a substitute for a comprehensive eye examination. With telemedicine, it seems possible to provide early ophthalmological treatment for patients, cooperation between diabetologists and ophthalmologists, closer monitoring of patients with DM. It can provide the human and technical resources that are the main problem and task for preventing blindness caused by DR in Hungary and in many other developed European countries.

Screening programs for fundus photography should be close to, or integrated into, the environment where the patient's diabetic check-up takes place. During a screening examination, the following basic data should be recorded: patient's social security number, age, gender, type of diabetes, duration of diabetes, presence of systemic diabetes-related diseases, body mass index (BMI), previous eye diseases, eye injuries, eye treatments, HbA1c, blood pressure, VA, date of last fundus examination, diabetes treatment and other medication. Telemedical transfer of the images taken by the fundus camera allows for easy evaluation and quick decisions concerning further investigations and treatments. Due to digital storage, any progression can be monitored, and the input into the database provides the physician with continuous information regarding the diabetic patient's ophthalmological status [21, 39].

In 2004, the American Telemedicine Association (ATA) and the Ocular Telehealth Special Interest Group established guidelines for telemedicine screening of DR and classified screening programs into 4 categories. These categories define the level of clinical validation for a program and define the program goals (Table 2). The ATA guidelines use ETDRS 30°, stereo 7-standard field, color images as the gold standard for DR diagnosis and grading and comparing all tele-ophthalmology programs to this gold standard [38].

Photos taken without pupil dilation can be sent to the evaluation site via the internet, making the use of digital images increasingly flexible. Records are evaluated at a reading center in a central location, but in recent years, portable tablets have made it possible to do this anywhere in the world after connecting to the internet. It is important to evaluate on a proper screen, the latest recommendation is that the minimum resolution is 1080 vertical resolution (1920x1080), the recommended standard is 1200 (1920x1200) and at least 60% of the photo should be visible on the screen [29].

Table 2 Description of each category within the American Telemedicine Associations levels of clinical validations including the levels of DR that can be distinguished.

	Category 1	**Category 2**	**Category 3**	**Category 4**
Level of categorization	• No or minimal DR • More than minimal DR	• No or minimal DR • Mild or moderate DR • Sight threatening DR or DME	• No DR • Mild DR • Moderate DR • Severe non – proliferative DR • Early proliferative DR • High risk DR • DME	• No DR • Mild DR • Moderate DR • Severe non – proliferative DR • Early proliferative DR • High risk DR • DME
Capabilities	Screening	Screening and Risk stratification	Screening, Risk stratification, treatment recommendations	Exceeds ETDRS seven field photos in determining level of DR/DME. Can replace ETDRS photos in clinical/research programs
Example Programs	Ophdiat (Paris, France) [40]	EyeCheck (Netherlands) [41]	Joslin Vision Network (Massachusetts, USA) [42-45]	None
	EyePacs (California, U.S.) [46]	NHS Diabetic Eye Screening program (United Kingdom) [47-51]	University of Alberta (Alberta, Canada) [52-54]	
	Digiscope (Maryland, U.S.) [55]			

Systematic screening programs for people with diabetes were launched in the early 2000s. In Iceland, Scotland, Wales, Northern Ireland and England, successful national DR screening networks have been established. Furthermore, there are several regional and local programs in numerous European countries [56-58]. The largest telemedicine screening network in the US is run by the Department of Veterans Affairs, which estimates that around 90% of veterans with diabetes receive annual DR screening [59]. The real success of the DR screening can be seen in the significant reduction of visual impairment caused by DR in these patients.

Much research around the world has been focused on the use of telemedicine tools for fundus imaging and screening, the UK system being at the top in terms of reliability, precision, and standardized input and output. The results so far have been very promising, with each study being reported to date emphasizing the high sensitivity for detecting several fundus lesions in the initial stages of DR by a standard fundus camera and a grading software [60].

The Spectra DR software is designed to comply the requirements of the UK NHS national screening program for DR; the screening program is highly complex and requires a high level of sophistication in the software to meet its requirements. Spectra DR enables to create patient appointments, data entry, image capture, and grading. Patient results are generated together with a report regarding the patients' screening prediction via a “plug-in” algorithm. Using nonmydriatic or investigational hand-held portable cameras, a quick and simple DR evaluation process will likely improve the patients' willingness to participate in future screening tests.

Iceland began regular DR screening for T1DM patients in 1980, resulting in the reduction of disease-related blindness from 2.4% to 0.5% [21]. The Icelandic population used for the cohort study and development of a commonly used risk calculator (Risk Medical Solutions, Iceland) is much more homogenous when it comes to ethnic and socioeconomic differences compared to the population in Hungary. In Sweden and England, the free screening for DR has reduced the incidence of diabetes-caused blindness by more than one-third in Stockholm and by more than two-third in Newcastle over 10 years [65, 66]. Studies have reported a decreasing incidence of severe DR in developed countries due to screening programs [61-63]. Europe's goal was set in Liverpool in 2005 to have ophthalmic screening for at least 80% of the diabetic population by 2010, and to have adequate laser capacity to treat patients. Vision 2020, launched by the WHO and the International Agency for the Prevention of Blindness (IAPB), has identified the reduction of blindness caused by DR as one of its key priorities [64]. Nevertheless, with these new screening and telemedicine tools, it is realistic to expect similar results to be achieved in other European countries, including Hungary, within 5 to 10 years [65]. From a socio-economic aspect, the DR screening programs have been found to be useful and cost-effective [66, 67].

Previous projects have led to the need for our own study. The present research explores the subjective experience of DM patients of the telemedicine tools and examination while participating in a free fundus camera screening program conducted in a South-Eastern county (Csongrád) in Hungary and obtains feedback on whether they would participate in such an examination in the future. Furthermore, demographic factors such as age, gender, economic activity, and socioeconomic status (SES) (level of education, support from family, and subjectively perceived financial status) on the health and behavior of DM patients are examined for their effect upon participation in future screening programs.

The development of optimized and effective DR screening programs is becoming eminent. This study further investigates the prevalence of DR and its different grades in patients with DM in Csongrád County, using a handheld fundus camera (Smartscope Pro Optomed, Finland) in Hungary for the first time. Moreover, we investigated the risk factors for developing DR and the diabetology/ophthalmology screening patterns and frequencies.

2. Aims of the study

- To use a handheld fundus camera (Smartscope Pro Optomed, Finland) to obtain fundus images for grading the DR.
- To investigate the patients' satisfaction when using fundus camera examination as a telemedicine tool.
- To determine the effect of demographic and socio-economic status (SES) factors upon participation in a DR screening program
- To determine the subjectively perceived satisfaction with the classical pupil dilation versus fundus camera examination based on the following variables: gender, age, occupation, education, marital status, HbA1c, presence of hypertension, and attendance of blood sugar screening.
- To observe the prevalence of DM types and DR grade in the studied population in Hungary compared to the UK-based classification system.
- To determine the reliability, satisfaction, and willingness to attend again in a classical or fundus camera examination for DR screening.

3. Methods

3.1. Diabetic Retinopathy Screening Using Telemedicine Tools

A free screening test was performed on a random population of 89 patients with both eyes (178) with confirmed DM diagnosis. Handling of the fundus camera and the image acquisitions were performed by a qualified professional in a darkened room, which were then forwarded through a secure internet connection to a specialist doctor/ophthalmologist (A. F./M. C. M.) or referral outcome grader (ROG) (G. R./P. K.) for evaluation. In case of too narrow pupils, another image was taken after ensuring normal intraocular pressure level and applying cyclopentolate (5 mg/mL) eye drops to achieve mydriasis. The assessment of the fundus images was performed within 10 working days using Spectra DR software. The recordings were safely deposited and kept inaccessible to third parties for 10 years at a central server, so they will be available in further comparative studies on DR.

The images were taken with an 18-megapixel Canon EOS digital camera which was attached to a Canon CR2 color, NM, 45° retinal camera. Two pictures were taken of the participants' eyes: one with the macula and the other with the optic nerve in the center — this is in accordance with the UK screening standards [68]. In the case of amblyopia or nontransparent media (e.g., cataract, corneal or visual axis obstructing conditions), the patients were excluded from the study. During image evaluation, the graders (A. F./M. C. M./G. R./P. K.) classified the signs and the stages of DR and maculopathy according the standardized UK-based software Spectra DR and graded the images in alignment with the UK standard grading protocols [69]. Each image was evaluated in two stages: first, the ROG (G. R./P. R.) evaluated them, and then a supervisor/ophthalmic consultant confirmed the diagnosis (A. F./M. C. M.). At the end, an expert opinion regarding the grade of retinopathy was sent back to the screening site, i.e., stage of retinopathy (R0/1/2/3A/S) and absence or presence of maculopathy (M0/1). Other discovered abnormalities were not diagnosed in this study, although they were recorded, as they can provide further information about other symptoms which may have occurred in the past, and therefore may require medical attention over a specified period of time.

The classification of the DR was as follows:

- M0: no maculopathy was detected; repeated screening was recommended in a year.
- M1: there was a sight-threatening maculopathy; within one month a medical examination is required.
- R0: there was no clinical anomaly; repeated screening was recommended in a year.
- R1: mild nonproliferative stage, microaneurisms, spot- or blot-like hemorrhages, or exudates could be seen; control examination was recommended in a year.
- R2: moderate or severe nonproliferative stage, major bleeding(s), cotton-wool spots, venous looping, and intraretinal microvascular abnormalities (IRMAs) were visible; control examination was required within one month.
- R3A: active proliferative stage, neovascularization of the optic disc (NVD) or elsewhere (NVE) or preretinal bleeding, vitreous bleeding, preretinal fibrosis, and tractional retinal detachment could be observed; immediate medical examination was required within two weeks.
- R3S: stable proliferative retinopathy; a retinal image showing stable post-PRP laser with no signs or reactivation or active referable retinopathy; only to be determined in the presence of “benchmark images” taken at the time of discharge for comparison; screening intervals may be at the discretion of the trained ROG.

Other recorded, but not reported, changes/fundus pathology included age-related macular degeneration (AMD), changes in the optic nerve due to glaucoma, and any other signs of eye disease.

3.1.1. Self-Completed Questionnaire

The self-completed questionnaire collected information about the individual's demographic status such as age, gender, economic activity (full-time, part-time, and retired), SES such as education (primary, secondary, and higher), and marital status (married or lives with a partner, single, separated or divorced, and widowed). The general part of the questionnaire was based on the European Health Interview Survey 2009 [70], and it collected data about DR associated exposure parameters and some other health connected characteristics, type of DM, or presence of hypertension, as well as the type of eye diseases. Furthermore, data were collected about the frequency of measuring blood sugar levels and about participation in screening tests, which are important for preventing retinopathy, including the frequency of attending Diabetology or Ophthalmology specialist clinics. Questions regarding the perceived reliability of results (yes/no/maybe), willingness to participate again (yes/no/maybe), comfortability (dissatisfied/satisfied/acceptable) of the tests performed, and the overall perception of the screening examinations as well as whether they would participate in a similar examination next time were being asked/collected as well. Some categories underwent merging due to missing data, for example, the frequency of blood sugar measurement (monthly/less than a month, weekly/every few days, and daily/more than once a day). If the participants could not understand or read the questionnaire for whatever reason, they received professional help accordingly.

3.2. Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Fundus Camera

3.2.1. Physical Examination

A cross-sectional study was conducted in the Departments of Ophthalmology and Internal Medicine Diabetology Unit, University of Szeged, Szeged, Hungary, between November 2015 and December 2016. All examinations were voluntary and free of charge to the participants; patients were recruited consecutively from the Diabetology Outpatient Clinic. Written informed consent was obtained from all participants. The detection of DR was based upon examination with a handheld fundus camera (Smartscope Pro Optomed, Finland) in a dark room by qualified professionals. The results were evaluated by a qualified specialist after data/file were transferred securely. In the case of constricted pupil, another image was taken after ensuring normal intraocular pressure level and applying cyclopentolate (5 mg/mL) eye drops to achieve mydriasis. The assessment of the fundus images was performed using the Spectra DR software (Health Intelligence, UK). The recordings were safely deposited and kept inaccessible to third parties for 10 years at a designated server, so that later they will be accessible for further comparative studies on DR.

The images acquired with the Optomed Smartscope Pro digital handheld camera included two pictures from the participants' eyes—one with the macula—and another with the optic nerve—in the center—which is in line with the English screening requirements [71]. In case of presence of amblyopia or nontransparent media (e.g., cataract and corneal or visual axis obstructing conditions), the patients were excluded from the study. During image evaluation, the graders (A.F./G.P./G.R.) classified the signs and stages of DR and maculopathy in the standardized English-based software Spectra DR and graded the images in alignment with the English standard grading protocols [72]. Each image was evaluated in two stages: first, the referral outcome graders/ROGs (D.E./G.R.) evaluated them, and then a supervisor/ophthalmic consultant confirmed the diagnosis (A.F./G.P.). At the end, an expert opinion regarding the grade of retinopathy was provided, which included the stage of retinopathy (R0/1/2/3A) and the absence or presence of maculopathy (M0/1). Other discovered abnormalities were not diagnosed in this study, although they were recorded, as they can provide further information about other symptoms, which may have occurred in the past, and therefore may require medical attention over a specified period of time.

The classification of the DR was performed in the same way as in the first telemedicine study described earlier [73]. All the stages could be combined with sight-threatening maculopathy which was determined by the presence of exudates regardless of VA or red lesions with a VA of 6/12 or worse after pinhole correction. In these cases, medical examination was required within a month (M1).

3.2.2. Self-Completed Questionnaire

Participants were asked to fill out a questionnaire which was based on the European Health Interview Survey 2009—and included demographic characteristics such as gender, age, and place of residency. Using the place of residency, the distance to the healthcare facility was categorized as <10 km or ≥10 km.

The marital status was categorized as married or lives with a partner, single, separated or divorced and widowed; due to the low sample size, categories were merged together as living alone or living in partnership. SES of the study participants was examined: education and economic status. The economic status was characterized as working—full time and working—

part-time, unemployed, retired, temporarily laid off, and student; due to the lack of data between each category, the categories were allocated and merged as inactive or active. The level of education was measured as primary, secondary, or higher education (college, university, or higher).

Data were collected about self-perceived health status (SPHS) and characterized as bad, satisfactory, and good. Information was also collected about "Perception of what the subject can do for his/her health status," and the information was categorized as almost nothing (nothing/little) or much more (much/very much).

Health behavior was assessed by alcohol consumption, smoking, physical activity, and diet (no/yes). Smoking was classified as yes/quit/never smoking, while alcohol consumption was classified as no/yes. Physical activity was defined according to the amount or occasions spent in the previous month in cycling, walking: daily/weekly more time, weekly, once/no activity at all (inactive).

Information was also collected about the DM-related and other health conditions, for example, if the study participant has/had hypertension: no/yes. If yes, data were collected about the duration of the hypertension (years). If the participant attended blood pressure controls, a recording was made about the last measurement of the systolic and diastolic blood pressures in millimeters of mercury (mmHg).

Information was further collected about other health conditions, for example, VA (<0.3 or ≥ 0.3), HbA1c level (normal $<7\%$ or elevated $\geq 7\%$), type of diabetes mellitus (T1DM or T2DM), use of medications, DM in the family or occurrence of diabetic maculopathy. In addition, data about the attendance at healthcare services like diabetology (monthly, every 3rd month, every 6th month, yearly, more than a year, or no attendance) were also collected.

3.3. Statistical Analysis

The analysis of the data in the first telemedicine study was performed by descriptive statistical analysis on *N* number of participants, and percent distribution, median, and interquartile range (IQR) are being shown. The Chi-square (χ^2) and Fisher's exact tests were used to test differences of the distributions of categorical variables. The relationship between two variables was considered statistically significant when $p < 0.05$. The graphs were made in GraphPad Prism 5.01 (GraphPad Software Inc., La Jolla, CA, USA). The statistical analysis of the data was performed by using Stata (Intercooled Stata 8.0, Stata Corporation, College Station, TX, USA) and Excel software (Microsoft Corporation, USA).

The analysis of the data in the second handheld camera-supported screening study was performed by descriptive statistics; percentage distribution, mean and standard deviation (SD), and in case of nonnormality of continuous variables, median and IQR and range (minimum, maximum) are shown. Normality of the continuous variables was tested on a histogram, Q-Q-plot, and by Shapiro-Wilk and Kolmogorov-Smirnov test. The Independent Sample *T*-test was used to compare the means of the continuous, numerical variables, when the normality assumption was satisfied; otherwise, Mann–Whitney *U* test was used. Homogeneity of variance was analyzed with the Levene test.

Chi-square (χ^2) and Fisher's exact tests were used to test the differences of the distribution of categorical variables; for multiple comparisons, the 2-sample *z*-test with Bonferroni correction was applied to detect the differences in the proportions between the studied groups. If the sample within each column was 1 or less, then the *z*-test could not be used. The significance limit was set at $p < 0.05$. The statistical analysis of the data was performed by IBM SPSS Statistics Version 24 software.

3.4. Ethical Issues

The Regional and Institutional Human Medical Biological Research Ethics Committee of the Albert Szent-Györgyi Health Centre, University of Szeged, approved the study protocol (number 197/2015). The research provided anonymity to the participants. Before the beginning of a test, the participants signed a written consent form in which they agreed to permit the use of data for research purposes.

4. Results

4.1. Diabetic Retinopathy Screening Using Telemedicine Tools

89 people's 178 eyes were examined in the study out of which 30 were male (33.7%) and 59 were female (66.3%). **Table 3** shows the demographic characteristics of the patients, the median age of whom ranged between 56 and 68 years of age and had median HbA1c of 7.2% (ranging between 6.4 and 7.9%). **Table 4** shows the distribution of the types of DM and DR stages in the study population, based upon and compared to the classification system and software used in the UK (Spectra DR). Twenty percent of the participants had T1DM out of which 70.8% had T1DM diagnosed by a Diabetology Department, the rest being yet undiagnosed or latent disease patients. Mild nonproliferative DR (grade R1) was detected in 23.0% of the participants, while higher (moderate/R2 and proliferative/R3) grade DR was present in 1.4% and 1.4% of the subjects, respectively; maculopathy/M1 was present in 5.4% of the studied group (representative images of each grade were captured and processed in the Spectra software as shown in **Figure 1**). Other retinal pathology was detected in 28.4% of the participants. There was an overall left-shift in the distribution of earlier stages of DR in the UK population compared to the one represented by the Hungarian graded images and based upon the Spectra DR software, probably due to the existence of a well-established screening system in the UK and early detection of the disease.

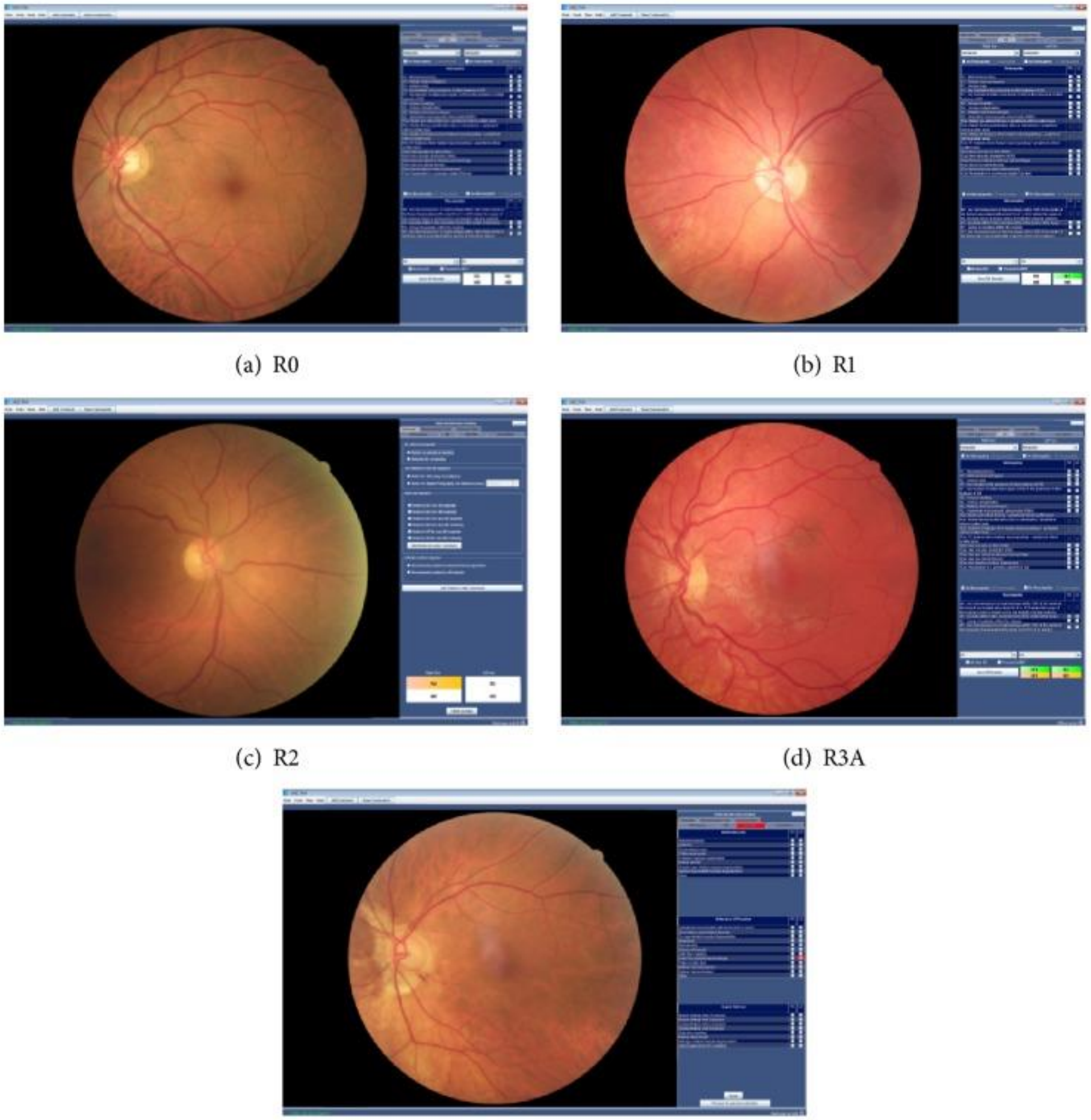

Figure 1 Spectra DR based grading of the DR. Representative images from the study of the different grading stages.

Table 3 Patients' demographics (N=89)

Variables	**n (%)**
Gender	
Male	30 (33.7)
Female	59 (66.3)
Age (median, IQR)	63.0 (56-68)
HbA1c (median, IQR)	7.2 (6.4-7.9)
Hypertension*	
No	17 (19.1)
Yes	68 (76.4)
Occupation	
Full-time	20 (22.2)
Part-time	8 (9.3)
Retired	61 (68.5)
Education*	
Primary	21 (23.6)
Secondary	47 (52.3)
Higher	20 (21.8)
Marital status	
Married or lives with a partner	49 (55.6)
Single, separated or divorced	21 (24.1)
Widowed	18 (20.4)
Attendance of blood sugar screening	
Monthly/less than a month	19 (20.8)
Weekly/every few days	35 (39.6)
Daily/more than once a day	35 (39.6)

IQR: interquartile range.

* The remaining percent of participants either were not aware of their disease (hypertension) or provided no response (education)

Table 4 Distribution of the DM types and DR grade in the studied population in relation to the UK-based grading system implemented by the Spectra™ analysis.

	T1DM	T2DM	R0	R1	R2	R3	M1
Csongrád County, Hungary	20.2%	79.8%	73.0%	23.0%	1.4%	1.4%	5.4%
East Anglia, UK	15.0%	85.0%	68.7%	27.5%	0.6%	0.3%	3.2%

According to the self-perceived satisfaction with the classical pupil dilation versus fundus camera examination, 20.4% versus 83.6% of the participants expressed satisfaction, respectively, while 37.0% versus 9.1% were unsatisfied, and 42.6% versus 7.3% could not decide. The classical pupil dilation versus fundus camera test was rated as reliable by 75.5% versus 72.0%, as probably reliable by 18.4% versus 16.0%, and as unreliable by 6.1% versus 12.0%, respectively. The willingness to participate in a classical pupil dilation versus fundus camera examination in the future was found to be positive by 78.2% versus 67.3%, while 9.1% versus 10.9% responded that they would not attend, and 12.7% versus 21.8% responded as they might participate. There was no significant difference between the satisfaction with the examination (p=0.9) and reliability (p=0.3), although the willingness to participate differed significantly between the classical versus fundus camera examination (p=0.01) (Table **5**).

Table 5 Reliability, satisfaction, and willingness to participate again in a classical or fundus camera examination for DR screening. (N=89)

Variables	**Classical examination** n (%)	**Fundus camera examination** n (%)	***p***
Reliability of the examination			
Yes	67 (75.5)	64 (72.0)	
No	6 (6.1)	11 (12.0)	0.3
Maybe	16 (18.4)	14 (16.0)	
Willingness to participate again			
Yes	70 (78.2)	60 (67.3)	
No	**8 (9.1)**	**10 (10.9)**	**0.01***
Maybe	11 (12.7)	19 (21.8)	
Satisfaction with the comfort of the screening			
Satisfied	18 (20.4)	74 (83.6)	
Dissatisfied	33 (37.0)	8 (9.1)	0.9
Acceptable	38 (42.6)	7 (7.3)	

***p<0.05**

The economic activity significantly affected the participation in a blood sugar screening (p=0.001). Sixty percent of those employed in a part-time job had done blood sugar screening more than once a day or daily, 20% weekly/every few days or monthly/less than a month. The daily/more than once a day screening was 33.3% among retired, while the weekly/every few days screening was 55.6%, and the monthly/more than once a month was 11.1% in this age/patient group. Among the full-time workers, the daily/more than once a day and monthly/less than once a month screening was 45.5% versus 54.5% (**Figure 2**(a)). Similarly, marital status (being married or living with a partner) significantly impacted the likeliness to attend blood sugar screening (p=0.04); this population had a higher daily/more than once a day blood sugar screening attendance, with a frequency of 50% compared to those living alone (single, separated, or divorced: 30.8%; widowed: 18.2%); the latter two populations had otherwise the highest weekly/every few days attendance (single, separated, or divorced: 53.9%; widowed: 72.7%). The least frequent or monthly/less than once a month screening attendance was the highest among married or living with a partner population (28.6%), while it was the smallest among widowed participants (9.1%) (**Figure 2**(b)).

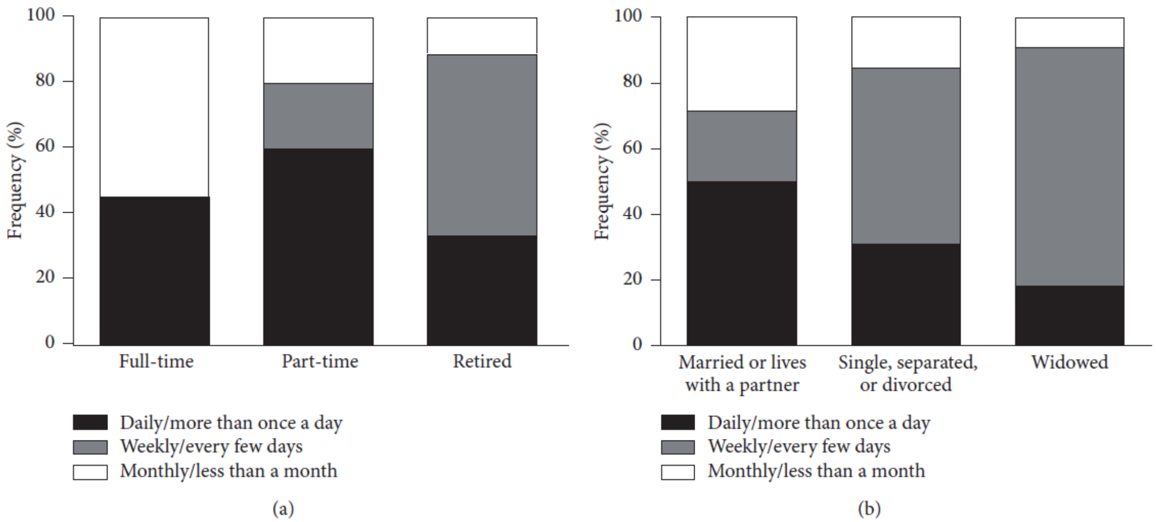

Figure 2 Effect of economic activity (a) and marital status (b) on the blood sugar screening frequency.

The willingness to participate in the annual fundus camera screening was the highest among the full-time workers (91.7%) and the lowest among part-time workers (20.0%) Those who reported maybe versus no attendance were higher among part-time workers (40.0% versus 40.0%, respectively), while the willingness to participate differed significantly between the analyzed economical groups (p=0.003) (**Figure 3**(a)). The satisfaction with the fundus camera screening also increased significantly with the level of education [primary (69.2%); secondary (82.8%); higher [(100%), p=0.003] (**Figure 3**(b)).

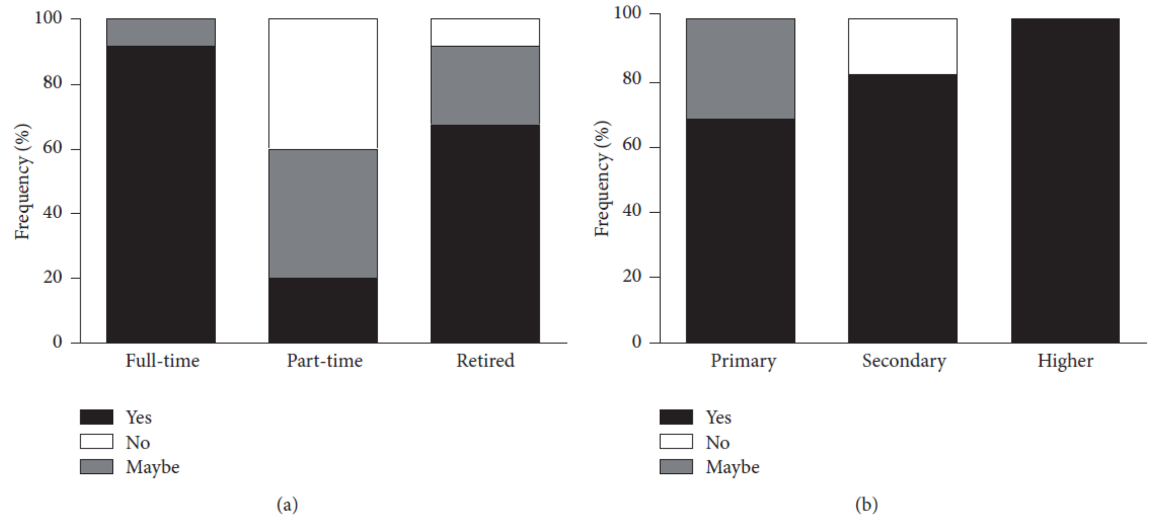

Figure 3 Economic activity in relation to willingness (a) and educational level in relation to satisfaction (b) in participating in fundus screening examination.

Among participants with secondary or higher education, the most common argument used against the classical fundus exam was "I cannot see clearly after." The participants with primary school level education had significantly higher rate of stating dissatisfaction of the pupil dilation examination. This reason was not stated among higher educated patients, although the "I cannot drive after" reason seemed to appear more often in this group of patients.

4.2. Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Fundus Camera

The data were collected from a total of 848 participants with known DM in Csongrád County, South-Eastern region in Hungary (**Figure 4**). Out of the initial participants, 787 (92.8%) had available fundus camera images and answered the self-administered questionnaire. T1DM was present in 13.5% (*N*=52) of participants, while T2DM was present in 86.5% (*N*=334) of the participants. Among T1DM and T2DM patients, 25.0% (*N*=13) and 33.5% (*N*=112) had DR, respectively. A large part of the participants had inappreciable fundus camera images/results 46.2% (*N*=363) when using the handheld camera, and therefore were excluded from the further analysis (**Figure 4**).

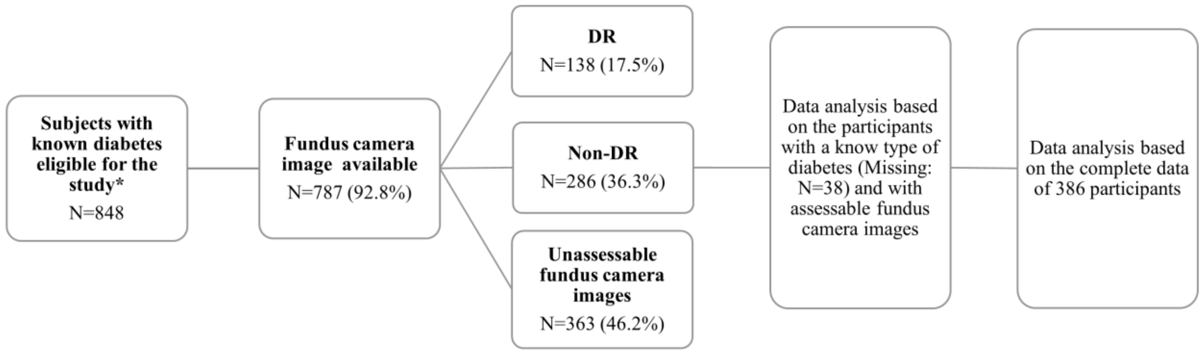

Figure 4 Flowchart of the study sample. DR: diabetic retinopathy; Non-DR: Nondiabetic retinopathy; N: number. *Fulfilled the self-completed questionnaire and had a fundus camera image taken

The data analysis was based on the remaining 386 individuals, who had assessable fundus camera images and possessed complete data about the type of diabetes and the risk parameters studied.

Table 6 shows the characteristics of the studied participants. Gender, age, and marital status showed no significant proportion differences between the study groups, while SES showed significant ratio differences in the T1DM group. The proportion of the DR differed significantly in the education and perceived financial status groups, and it was significantly higher among those with higher education (secondary/higher being 61.5%/30.8%) and perceived bad financial status (63.6%). The distance travelled to the healthcare service showed a nearly significant association with the DR—participants living more than 10 km away from the healthcare services had a higher proportion of DR (61.5%).

Table 6 Characteristics of the study sample.

	T1DM N=52		T2DM N=334	
	DR n (%)	**Non-DR** n (%)	**DR** n (%)	**Non-DR** n (%)
Gender				
Male	7 (53.8)	23 (59.0)	47 (42.0)	94 (42.3)
Female	6 (46.2)	16 (41.0)	65 (58.0)	128 (57.7)
Age (mean±SD)	70.8±6.0	66.4±12.2	66.4±12.8	65.7±13.0
Distance to the healthcare services				
<10km	**5 (38.5)**	**27 (69.2)**	75 (67.0)	140 (63.4)
≥10km	**8 (61.5)**	**12 (30.8)**	37 (33.0)	81 (36.6)[a]
Education				
Primary	**1 (7.7)**	**15 (40.5)**	54 (48.2)	94 (43.5)
Secondary	**8 (61.5)**	**10 (11.2)**	30 (26.8)	79 (36.6)
Higher	**4 (30.8)**	**12 (32.4)**	28 (25.0)	43 (19.9) [b]
Perceived financial status				
Bad	**7 (63.6)**	**8 (22.2)**	24 (23.1)	58 (27.6)
Satisfactory	**2 (18.2)**	**23 (63.9)**	70 (67.3)	131 (62.4)
Good	**2 (18.2)**	**5 (13.9)**	10 (9.6)	21 (10.0) [c]
Marital status				
Living alone	1 (7.7)	5 (13.9)	37 (33.0)	60 (27.8)
Living in partnership	12 (92.3)	31 (86.1)	75 (67.0)	156 (72.2) [d]
Economic status				
Active	9 (69.2)	21 (55.3)	**21 (18.7)**	**63 (28.9)**

***p*<0.05** T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: non-diabetic retinopathy; N: number; SD: standard deviation
Missing data: a) 1; b) 8; c) 25; d) 7

Table 7 and **8** show the results of the SPHS and the health behavior of the individuals, neither of which showed a significant relationship with the disease for both, T1DM and T2DM groups (p<0,05).

Table 7 Self-perceived health status of the study sample.

	T1DM N=52		**T2DM** N=334	
	DR n (%)	**Non-DR** n (%)	**DR** n (%)	**Non-DR** n (%)
Self -perceived health				
Bad	2 (15.4)	7 (18.4)	28(25.2)	65 (29.3)
Satisfactory	7 (53.8)	24 (63.2)	64 (57.7)	135 (60.8)
Good	4 (30.8)	7 (18.4)	19 (17.1)	22 (9.9)[a]
What the person can do for his/her health				
Very much/Much	10 (83.3)	30 (78.9)	91 (82.0)	167 (76.6)
Little/Nothing	2 (16.7)	8 (21.1)	20 (18.0)	51 (23.4)[b]

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: non-diabetic retinopathy; N: number
Missing data: a) 2; b) 7

Table 8 Health behavior of the study participants.

	T1DM N=52		T2DM N=334	
	DR n (%)	**Non-DR** n (%)	**DR** n (%)	**Non-DR** n (%)
Physical activity in the last month				
Every day/more times a week	6 (46.1)	26 (66.7)	61 (57.0)	118 (55.9)
Weekly	5(38.5)	6 (15.4)	17 (15.9)	40 (19.0)
Only once in the last month/Inactive	2 (15.4)	7 (17.9)	29 (27.1)	53 (25.1)[a]
Diet				
Yes	13 (100.0)	35 (92.1)	85 (77.3)	175 (81.8)
No	0 (0.0)	3 (7.9)	25 (22.7)	39 (18.2)[b]
Smoking				
Yes	5 (41.7)	6 (16.2)	8 (7.3)	21 (9.8)
Quit	2 (16.6)	8 (21.6)	38 (34.9)	74 (34.4)
Never	5 (41.7)	23 (62.2)	63 (57.8)	120 (55.8)[c]
Alcohol consumption				
Yes	7 (53.8)	11 (28.9)	35 (32.4)	79 (36.6)
No	6 (46.2)	27 (71.1)	73 (67.6)	137 (63.4)[d]

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: non-diabetic retinopathy; N: number
Missing data: a) 16; b) 11; c) 13; d) 11

Table 9 shows the characteristics of the health status of the study participants. A significant difference was only present in case of diabetes medication use and presence of diabetic maculopathy in T2DM patients having DR and non-DR, with the rest of the parameters included (hypertension, VA, HbA1c, duration of DM, and familiar presence of DM) showing no significant proportion differences between the studied groups.

Table 9. Characteristics of the health status of the study participants.

	T1DM N=52		T2DM N=334	
	DR n (%)	**Non-DR** n (%)	**DR** n (%)	**Non-DR** n (%)
Hypertension	4 (30.8)	21 (55.3)	97 (87.4)	190 (88.4)
Systolic blood pressure (median, IQR, Range)	153 (133-162) 120-191	135 (129-150) 120-158	130 (122-140) 105-189	130 (123-140) 100-169
Diastolic blood pressure (mmHg) (median, IQR, Range)	84 (80-85) 78-95	80 (70-85) 58-90	80 (75-85) 60-104	80 (70-85) 60-101
Duration of hypertension (year) (median, IQR, Range)	18 (3-42) 3-52	11 (7-20) 2-53	20 (10-40) 2-56	20 (10-37) 3-56
VA				
<0.3	0 (0.0)	0 (0.0)	6 (16.7)	2 (5.5)
≥0.3	3 (100.0)	2 (100.0)	30 (83.3)	38 (95.0)[a]
HbA1c				
Elevated (≥7%)	13 (100.0)	37 (93.4)	88 (82.2)	170 (79.4)
Duration of diabetes (median, IQR, Range)	20 (14-24) 10-38	20 (13-27) 1-60	13 (8-20) 0-38	15 (8-20) 0-40
Diabetes medication	5 (41.7)	13 (34.2)	***86 (77.5)***	***187 (86.6)***
Diabetes in the family	6 (46.1)	21 (53.8)	52 (46.8)	124 (56.6)
Diabetic maculopathy	***7 (53.8)***	***2 (5.1)***	***81 (73.6)***	***15 (6.8)***

Chi-square-test: p<0.05 T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: non-diabetic retinopathy; N: number; IQR: interquartile range
Missing data: a) 305

Mild nonproliferative retinopathy without maculopathy (R1M0) was detected in 6% of the T1DM patients having DR, and 23% of the T2DM patients having DR. Among the patients having DR, R1 with maculopathy (R1M1) was present in 82% of the T1DM group, and 66% of the T2DM group. Both moderate nonproliferative retinopathy with maculopathy (R2M1) and active proliferative retinopathy with maculopathy (R3M1) were detected in 6% of the T1DM patients having DR. Among the T2DM patients having DR, the prevalence of R2M1 was 4%, while the prevalence of R3M1 was 7% (**Figure 5**)

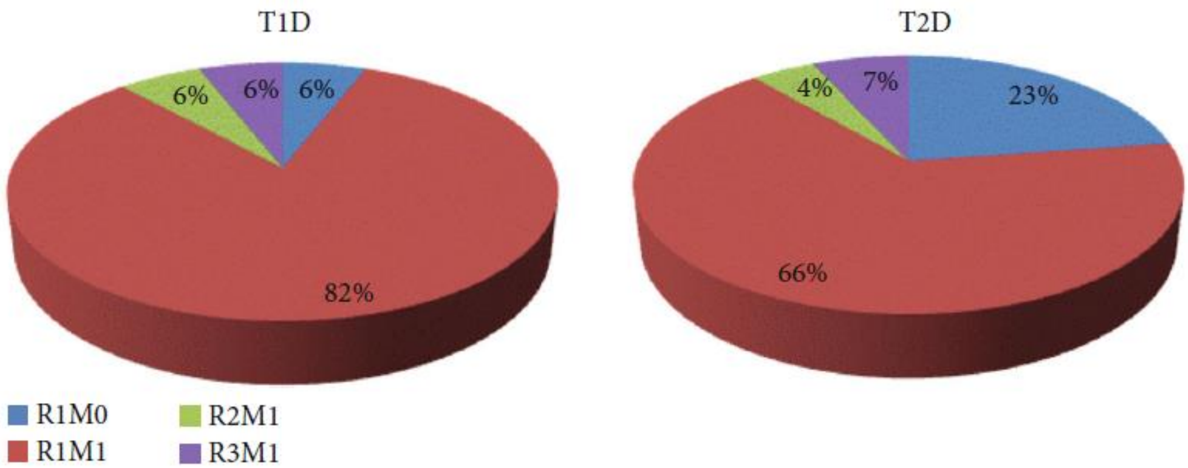

Figure 5 Distribution of the diabetic retinopathy according to the type of diabetes mellitus. T1D type 1 diabetes mellitus; T2D: type 2 diabetes mellitus.

The level of HbA1c affected the participation in the diabetology screening, with those having HbA1c > 7% representing more than 50% of all quarter yearly attendance for both types of DM (**Figure 6**). About 10% of the population had no diabetology screening attendance for those having HbA1c > 7% for both types of DM and HbA1c < 7% T2DM. For both types of DM, the yearly attendance was below 5%, while more than yearly attendance was absent for all studied groups, and low for T2DM patients having HbA1c > 7% (**Figure 6**).

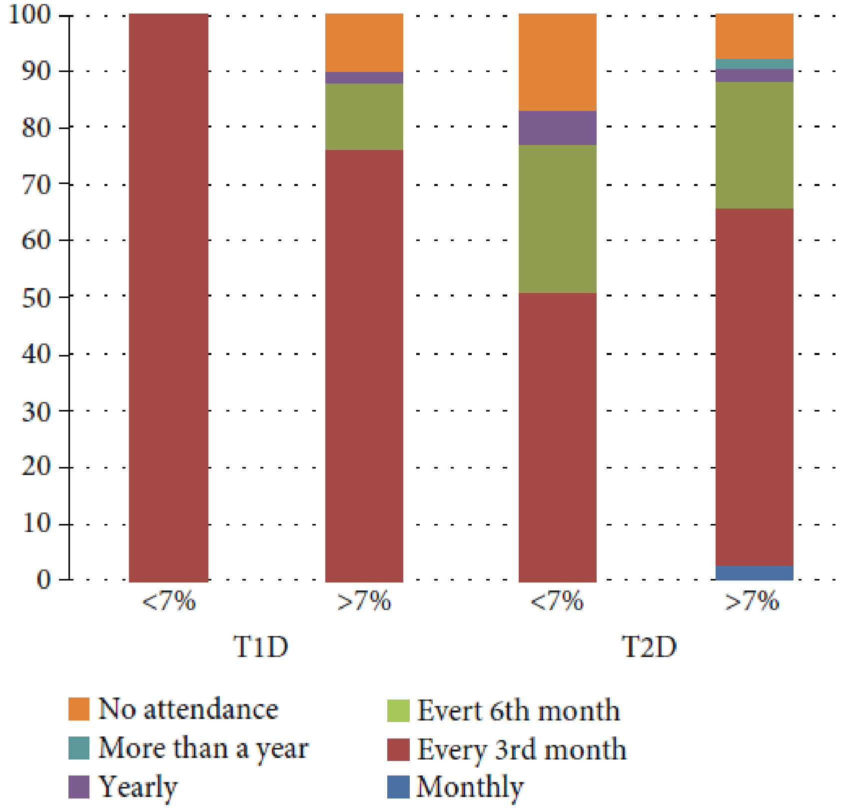

Figure 6 Attendance rate in the diabetology screening among those with normal or elevated HbA1c. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus. ∗Data presented are based on the one individual in case of the T1D group having HbA1c<7%

5. Discussion

5.1. Diabetic Retinopathy Screening Using Telemedicine Tools

The first study aimed to investigate the patients' experience with the use of telemedicinal tools for screening of DR and the ability to collect the parameters needed to calculate DR risk (age, gender, type and duration of DM, HbA1c, hypertension, and fundus image grading) in a southeastern county (Csongrád) in Hungary. The justification for using health care tools aimed at screening DR is well founded, due to the high availability of tools for DR prevention and avoidance of late complications such as STR. The population of Csongrád County is very plausible for initiating such a study, since it has higher prevalence of DM compared to other counties in Hungary [6]. In addition, the study followed the progressive trend of DM worldwide and examined the willingness to participate in screening tests, the attitude towards screening examination, and the influence of demographics and socioeconomic factors like education, financial, and marital status. Regarding the risk factors, the SES has been already shown to have a very significant impact on the attendance in screening examinations, while occupation has been related to a greater impact on nonattendance in screenings [74]. The screening frequency for blood sugar levels in full-time workers was indeed significantly lower in our study, but the willingness to participate in fundus screening examination was higher in that subpopulation.

From the standpoint of DR formation and progression, it is 76.4% of the patients who had high blood pressure which, by itself or as a co-morbidity, gives poorer prognosis for the DM patients due to a predisposition for premature vascular sclerosis. The occurrence of DR in the studied sample population was 25.5%, which is higher than any previous results reported in Hungary [26], although somewhat expected in Csongrád County.

Although the Diabetology guidelines recommend blood glucose levels to be checked several times a day, only a little over a quarter of the participants performed it accordingly. Strikingly, 60% of the study participants checked their blood glucose level every few days, if not more rarely. Upon diagnosis with DM, the Diabetologist or the General Practitioner informed the patient of the possible complications from the disease and recommended an annual eye screening test. Our results are in line with the International Diabetes Federation's (IDF) observation that 50% of the people with DM are unaware of the characteristics of their disease [75]. In Hungary, the number of known patients with diabetes is nearly 14% of the total population. It would take 100 ophthalmologists (from the total of 968 practicing) working full-time if only annual screenings were to be carried out by using traditional tools on a population like this. This may change by using the telemedicine system [65]. Introducing a new screening program is always challenging, but previous studies from other countries show promising results. DR could be detected at an early stage using digital imaging even in rural areas [55]. Diabetes causing vision loss is successfully confined in countries like Iceland, where regular screening was implemented.

Only one third of the participants in our study had not visited an ophthalmologist, while 12.4% of them have been diagnosed with DM within a year; only 56.2% of the participants complied with the one-year recommendation. In the UK, compliance in the first year was 45% for patients attended classical screening and 50% for those attended in fundus camera screening [76]. After using a mobile fundus camera screening unit to reach more patients, the compliance climbed to 80% in the fifth year [77]. Compliance is a highly influential factor of cost effectiveness because of the fixed costs (digital imaging camera, computer system, etc.) [76]. Patient satisfaction affects the attendance rate of the screening. Responses to the subjective experiences perceived during fundus examination showed satisfactory results: more than three-quarters of the participants were satisfied with the fundus imaging method and one out of five with the conventional test. In both cases, three-quarters of the participants considered the results of the study to be reliable, a significant difference being found between the two screening techniques. There were fewer problems than expected (e.g., subjects being not able to drive after pupil dilation), but it can be a factor which is most likely related to older age of the sampled population. It is interesting to note, however, that during the procedure of pupil dilation, one quarter of the subjects found administering eye drops being irritating or uncomfortable, in particular, those who had lower education.

There is a level of contradiction in the assessment of reliability and satisfaction in the study, since significantly more people were willing to participate in the classical retinal screening method than in the fundus imaging examination (78.2% versus 67.3%). A possible weakness of the study is the size of the sample. 83.6% of the participants were dissatisfied with the examination, which raises the suspicion they could have chosen “Other” as their answer and as having no other comments, this might have been done out of necessity. Among the inconvenience experienced during the test with pupil dilation, the “Other” category was chosen by only 4.1% in which no mention of any reasons for the selection made was stated whatsoever.

During the analysis, the economic activity and education appeared to pose an effect on the individual's willingness to participate in the screening test. The preference was strongest among full-time employees, for whom it was presumably important to see well after the test in order to be able to continue their work during the same day. Based on the level of education, the few subjects that evaluated the fundus camera test as satisfactory were those who found eye drops to be the most uncomfortable in the traditional test. These data are somewhat contradictory, as mydriatic drops are always needed in conventional tests. People with higher education found only the driving restriction and the bad sight after the examination as a negative aspect of the screening; in this context, they were 100% satisfied with the fundus camera test.

The telemedicine part of the study also concerns data safety and patient anonymity preservation which are now guided by an EU law contained in the Charter of Fundamental Rights of the European Union, Article 8 (2000/C 364/01) [78], as well as the need to safely store and make backup files for high resolution fundus images acquired from the patients, and their retention; these rules were followed in the present study entirely. The issue of having decentralized DR screening and fundus imaging services close to the patients and centralized image reading remains to be evidenced in future telemedicinal studies for screening DR in Hungary, the UK grading system being the golden standard for achieving the task properly.

In conclusion, the analyzed demographic and socioeconomic factors showed a significant relationship with the future participation in the fundus camera screening for DR. The participants' age or gender appears not to affect the experience (satisfaction) of the examination (e.g., fundus examination under pupil dilation). However, the level of education appears to have an important role: higher educated patients were more likely to participate in pupil dilation examination using an ophthalmoscope. This is in contradiction with the fact that only slightly more than half of the participants in this group took part in such screening examination within a period of one year. It was also not confirmed that the distribution of DR grades in this study is similar to the results of previous national studies [26, 65], as Csongrád County is not a representative population comparable to other parts of Hungary where the prevalence of DM and DR is lower. Further research is therefore needed on a larger or more representative sample from different counties in Hungary where the percent of distribution of patients diagnosed with DM varies.

In general, the treatment of DM patients is an interdisciplinary task of primary care physicians, diabetologists/dietologists, ophthalmologists/optometrists, and public health specialists. These professionals are responsible for giving lifestyle advice and for directing patients towards more appropriate screening tests. Ophthalmic monitoring is required every year after the diagnosis of diabetes and every other year for patients with excellent glycemic control without retinopathy at the previous examination but annually if there are risk factors [79]. Furthermore, if retinopathy is manifest to some degree, the screening time should be reduced to half a year (in the case of nonproliferative retinopathy) and three months (for preproliferative retinopathy). In case of proliferative retinopathy patients should go immediately to an ophthalmologist, in order to initiate laser treatment in time and thus save the eye from STR. The present state, unfortunately, seems to involve lack of realistic assessment or judgment of the risk from complications by the patients, and therefore a neglect to participate in the recommended screening tests. Constant maintenance of normal blood sugar levels is indispensable. Fast, easy, and accurate fundus camera examination is an alternative to the traditional, time-consuming, and “unsatisfactory” fundus test under pupil dilation. The patients, who tried this method, agreed that this new way was more satisfactory than the one they got used to, while they appreciated its reliability in the same way. Indeed, in the UK, due to the systematic screening implemented, DR is no longer the leading cause of blindness in the working age population [80].

5.2. Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Fundus Camera

DR is the most common late complication of DM in the working-age population and the leading cause of blindness in the elderly, accounting for a significant drop in the quality of life (QoL) and working ability for the patients [10, 11]. In a study comparing data from 35 populations, the global prevalence of STR was estimated to 10.2% for all DM patients [12]. Our study found high rates of R2M1 and R3M1, moderate and active proliferative retinopathy (6% and 7% for T1D and T2DM, respectively), which is similar to the world average found so far.

A previous study in Hungary found the prevalence rate of DM in participants aged 20-69 years to be 7.47% [81]. More recently, a study from Hungary showed 24.5% of all incident DM cases to be T2DM [82]. The same study also showed T1DM to be the most common form of DM in children and adolescents, with its frequency having a tendency of continuous rising, while the occurrence of medically treated cases of T2DM not to be increasing. The prevalence of T2DM, however, is increasing due to an obesity epidemic and aging of the population, hence, one may expect a dramatic increase in DM during the next decades [3-5]. In the Csongrád County, South-Eastern region of Hungary, the studied cohort showed an approximate 1 : 7 ratio of T1DM : T2DM cases.

The population in Csongrád County in Hungary is characterized by significant SES differences, and these appear to reflect upon significant proportion differences, in particular, in the T1DM population. It has been previously reported that poorer populations having Medicaid insurance in the U.S. are associated with worse DR follow-up in predominantly rural patients [83]; this population appears to be similar to the rural population in Csongrád County, Hungary. A statistically significant relationship between diabetes complications, age group, educational level, job status, relationship with family members, number of family visits, and the reassurance provided by the family, type of leisure activities, health status, years with diabetes, smoking, type of treatment, fried food consumption and income, sense of security and communication in living environment, and daily intake of vegetables, has also been reported in a study cohort of T2DM patients [84]. Furthermore, no statistical interaction could be found between SPHS and gender, while reporting the self-perceived health as poor has been associated with higher reporting of chronic diseases, including diabetes [85].

Although hypertension, VA, HbA1c, duration of DM, and familiar presence of DM showed no significant difference in our study, another study on a population having T2DM found a statistically significant difference between SPHS and the levels of HbA1c; the latter study also showed age, level of education, mode of treatment, adherence to treatment, and level of exercise to be factors having statistically significant differences from, and therefore an influence on, self-reported health in a single province in Turkey [86]. Patients with T1DM have been shown to have a faster decrease in the perceived health and functioning over time compared to aged persons from the general population [87].

The distribution of the DR showed similar retinopathy with maculopathy (R1M1) presence (82% in the T1DM group and 66% in the T2DM group) compared to an English study on both DR types (89% had a diagnosis of R1M1 in one eye in those screened positive for maculopathy (M1) in at least one eye) [88]. Our handheld camera produced unassessable fundus image results in nearly half of the participants when used by newly trained image acquisition staff (DJE and DJS); however, in an older population having T2DM, this can also be due to the presence of optic axis opacities such as cataract and vitreous hemorrhage. In our study, 6% and 7% of the T1DM and T2DM population, respectively, had R3M1 (proliferative diabetic retinopathy with maculopathy), while 6% and 4% of the T1DM and T2DM population, respectively, had R2M1 (preproliferative diabetic retinopathy with maculopathy); therefore, a total of 23% of the population had higher chance for DM-associated cataracts and or vitreous hemorrhages, as well as poor fixation due to macular edema. A limitation of our study is the fact that such changes were not recorded at the time the screening was conducted. Other studies have, however, shown that such handheld cameras can provide comparable results to standard fundus cameras [89]. Later versions of this camera (The Optomed Aurora) appear to have a built-in instant quality feedback software that aids the photographer to gain information when the image is assessable. In the latter study, the two cameras used reached high agreement on the diagnosis of retinopathy and maculopathy at all the levels of retinopathy. Sufficient training of paraprofessional health care staff can lead to obtaining higher quality images with a portable nonmydriatic fundus camera [90]. Known risk factors for developing DR are age, gender, duration and type of DM, elevated HbA_1c, high blood pressure, and retinopathy stage, while other risk factors are being investigated. DR is caused by damage to the retinal microvasculature. Proper screening for DR is an important milestone towards achieving early and efficient treatment for preventing visual loss [15]. For optimal effect, laser treatment must be applied as early as possible after the formation of new pathological retinal vessels, at which time most patients are asymptomatic. In addition, anti-VEGF drugs or steroids injected into the vitreous of the eye may reduce diabetic macular edema [91, 92]. Other European countries like Iceland, Denmark, Sweden, and England have successfully implemented nationwide DR screening programs. In Iceland, diabetic blindness prevalence has decreased 4-5 fold after the introduction of systematic DR screening, and a similar success rate has been observed in Denmark [21].

Hungary, at present, has no coordinated national screening program for DR, despite the clear need and high number of patients with DM. Furthermore, in many parts of the country, there are no clear communication channels between general practitioners (GPs), diabetologists, and ophthalmologists regarding screening and sharing results from a DR assessment. Today, a newly diagnosed DM patient must be actively referred for an eye examination by his/her GP or endocrinologist, and often the patient her-/himself must book the appointment. In addition, the interval between eye examinations is at the ophthalmologist's discretion. A standardized rapid assessment of avoidable blindness (RAAB) with the DR module (DRM) has recently been used in Hungary in people aged 50 years and older: 20.0% of the 3523 participants had a known or newly diagnosed DM; 20% of the participants with known DM had a blood glucose level of ≥200 mg/dL; and 27.4% had never had an ophthalmological examination for DR. The prevalence of DR and/or maculopathy was found to be 20.7%, while the prevalence of STDR was 4.3% in one or both eyes among the participants with DM in Hungary [93]. This finding is lower than the one determined in Csongrád County in Hungary, which can certainly underline disparities in the DR grading standards used or the distributional difference of DR throughout the different counties in the country.

A systematic DR screening in Csongrád County, could have significantly reduced the total load of ophthalmologist examinations, and thus increased the overall capacity in ophthalmology—a field with vast capacity challenges [85]. More importantly, the lack of systematic DR screening also puts patients with a high risk of eye disease progression at an even higher risk, as they are not receiving the regular follow-up examinations needed. The WHO guidelines for DR screening [10, 11] recommend annual eye examinations for patients with diabetes and biennially for persons with excellent glycemic control and no retinopathy at the previous examination. The ICO recommends biennial screening for DM patients without retinopathy. In general, there is a low annual incidence of STR, and 97% of the screening visits do not lead to any active treatment [94]. However, with the increasing prevalence of DM, especially T2DM, and limited eye care capacity, advocating for a personalized health care approach towards patient-tailored screening and recommendation for each individual patient has been proposed.

In Iceland for example, a path of improving cost-efficacy of screening systems has been chosen by reducing the number of unnecessary screening visits. Based on a biennial screening model, the following risk variables have been included to improve risk predictions for each individual patient: age, gender, diabetes duration, type of diabetes, HbA_1c level, blood pressure, and retinopathy stage. A European collaborative network has used this model to calculate the most appropriate interval between examinations for each patient, the outcome of which was a reduction of 17-23% in the screening visits needed, compared to the biennial screening model [94, 95]. A personalized screening approach would have the advantage of recommending more frequent screening intervals to high-risk patients and less frequent to low-risk patients. The risk variable profile also shows significant alterations between different countries and also between different ethnic- and socioeconomic populations within the same country and region, thus, the one-size-fits-all approach may not be the best for diverse populations globally.

In conclusion, this study in the Csongrád County, South-Eastern region, Hungary, determined the prevalence of DM and DR, which appeared to follow the country trend, except for the slightly higher STR. SES appears to affect the DR rate, in particular, for T1DM. The DR screening using the Smartscope Pro Optomed handheld camera, although simple and dynamic, requires much training and experience to achieve proper levels of image assessability if future use in telemedicine or artificial intelligence screening programs or personalized medicine is planned.

6. Summary

The prevalence of diabetes mellitus and diabetes-related vision loss are increasing worldwide because of the obesity epidemic and aging of the population. As a secondary prevention, screening programs and telemedicine tools can provide the opportunity to reduce the incidence of diabetes-caused blindness.

In our first study, a free screening test was performed on a random population, and we explored the patients' experience with the use of telemedicine tools for screening of DR. Previously, only slightly more than half of the participants complied with the one-year screening recommendation. The occurrence of DR in the studied sample population was higher than any previous results in Hungary. This new screening method was found to be reliable and satisfactory which takes an important role on the patients' compliance. The fundus camera test was preferred mostly by the full-time employees thanks to the non-mydriatic method which could accommodate them from missing work.

In the second study, the prevalence of DM and DR in the studied population in Hungary was determined, which followed the country trend with a slightly higher sight-threatening DR than the previously reported national average. The SES appeared to affect the DR rate, in particular, for T1DM. Although DR screening using handheld cameras seems to be simple and dynamic, much training and experience, as well as overcoming the issue of decreased optic media clarity in the eye is needed to achieve proper level of image assessability, in particular, when keeping in mind application of handheld cameras in future telemedicine or artificial intelligence screening programs.

From the perspective of improving the quality of life of people with DM, the most important goal to achieve is prevention of complications. Fundus imaging techniques are fast and cost-effective without the presence of a specialist and can be used to reach large numbers of patients. Our results call upon attention for the importance of having general and diabetes-specific health education to improve the screening efficiency and avoid complications of DM.

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9. Appendix

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Research Article

Diabetic Retinopathy Screening Using Telemedicine Tools: Pilot Study in Hungary

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Introduction. Diabetic retinopathy (DR) is a sight-threatening complication of diabetes. Telemedicine tools can prevent blindness. We aimed to investigate the patients' satisfaction when using such tools (fundus camera examination) and the effect of demographic and socioeconomic factors on participation in screening. *Methods.* Pilot study involving fundus camera screening and self-administered questionnaire on participants' experience during fundus examination (comfort, reliability, and future interest in participation), as well as demographic and socioeconomic factors was performed on 89 patients with known diabetes in Csongrád County, a southeastern region of Hungary. *Results.* Thirty percent of the patients had never participated in any ophthalmological screening, while 25.7% had DR of some grade based upon a standard fundus camera examination and UK-based DR grading protocol (Spectra™ software). Large majority of the patients were satisfied with the screening and found it reliable and acceptable to undertake examination under pupil dilation; 67.3% were willing to undergo nonmydriatic fundus camera examination again. There was a statistically significant relationship between economic activity, education and marital status, and future interest in participation. *Discussion.* Participants found digital retinal screening to be reliable and satisfactory. Telemedicine can be a strong tool, supporting eye care professionals and allowing for faster and more comfortable DR screening.

1. Introduction

The global incidence of diabetes mellitus (DM) among adults (age 18 years and older) was 9% worldwide in 2014 [1], while its prevalence still shows an increasing tendency due to obvious obesity epidemic and aging of the population [2–4]. In Hungary, a total of 865 069 patients (9.5% of the population) suffered from DM in the same age group in 2011 [5], and some degree of diabetic retinopathy (DR) could be observed among 19% of the patients with type 1 DM (T1DM) and 24% in those suffering from type 2 DM (T2DM) for 3 or 4 years [6]. DR is the fourth most common cause of blindness in the overall population, but it is in second place among active adults in industrialized countries [7], accounting for a significant drop in quality of life (QoF) and working ability of the patients [8, 9]. In a study comparing data from 35 populations, the global prevalence of sight-threatening retinopathy (STR) was estimated at 10.2% for all DM patients [10]. Known risk factors for developing DR are age, gender, duration, and type of DM, elevated HbA_1c, high blood pressure, and retinopathy stage, while other correlating risk factors are being investigated. Unfortunately, 50% of the people with diabetes are unaware of the characteristics of their disease and the compliance in attending screening programs is poor. The disease is determined by the outcome of the complications. Since high blood sugar and fat destroy the wall of the arteries, it is not surprising that people with diabetes have 2 to 4 times higher cardiovascular mortality rate and 2 to 4 times higher risk of strokes than patients without diabetes. Renal failure is also a common complication with the estimated number of 30–40% of the patients with diabetes, while 60–70% of the patients develop neuropathy. This is not only an individual problem, but a societal problem as well. According to a 2009 survey, the average annual health expenditure for diabetic patients was $1205 per capita and for patients with complications this number was $2276 per capita. Half of this cost is made up of drugs, but only a quarter of the cost spent on drugs is for antidiabetics [11]. Similarly, the treating expenses doubled in Germany and America, where $174 billion was spent on the treatment of diabetes in 2007 [11]. The Hungarian data cover only the cost of the National Health Insurance Fund, while there are other economic aspects like time off from work or restricted work due to complications of the disease. DR is caused by damage to the retinal microvasculature. Proper screening for DR is an important milestone towards achieving early and efficient laser photocoagulation and/or anti-vascular endothelial growth factor (anti-VEGF) treatment for preventing visual loss [12]. Depending on the severity of DR, four stages can be distinguished in general: preretinopathy (R0), background retinopathy (R1), preproliferative retinopathy (R2), and active proliferative retinopathy (R3A) [13]. A further subclassification exists for stable proliferative retinopathy (R3S) in patients who have received panretinal laser photocoagulation (PRP) under R3A and then became "stable"; these cases are considered safe to keep in a surveillance clinic [14]. Once fundus lesions appear as a complication of DM, the patient has an apparent DR with either low, intermediate, or high risk for developing some grade of DR. Therefore, the focus should rather be on raising prevention programs and early detection, as well as successful treatment of the basic disease.

DR is usually asymptomatic before the appearance of any vision loss, but it is detectable by retinal imaging techniques objectively and by accurately taken best corrected VA measurements. Much research around the world has been focused on the use of telemedicine tools for fundus imaging and screening, the UK system standing up at the top in terms of reliability, precision, and standardized input and output. The results so far have been very promising, with each study being reported to date pointing out the high sensitivity for detecting several fundus lesions in the initial stages of DR by a standard fundus camera and a grading software [15].

The Spectra DR software is designed around the requirements of the UK National Health Service (NHS) national screening program for DR; it is highly complex and requires a high level of sophistication in the software to meet its requirements. Spectra DR enables patient appointments to be created, data entry, image capture, and grading. A generation of patient results is provided together with a report regarding the patients' screening prediction via a "plug-in" algorithm. With the use of nonmydriatic or investigational hand-held portable cameras, a quick and simple DR evaluation process will likely improve the patients' willingness to participate in future screening tests.

In 1980, Iceland began regular DR screening for T1DM patients, which resulted in the reduction of disease-related blindness from 2.4% to 0.5% [16]. The Icelandic population being used for the cohort study and development of a commonly used risk calculator (Risk Medical Solutions, Iceland) is much more homogenous when it comes to ethnic and socioeconomic differences compared to the population in Hungary. Nevertheless, with these new screening and telemedicine tools, it is realistic to expect similar results to be achieved in other European countries, including Hungary, within 5 to 10 years time [17].

The present research explores how DM patients subjectively experience the telemedicine tools and examination through participation in a free fundus camera screening program conducted in a southeastern county (Csongrád) in Hungary and obtains feedback on whether they would participate in such an examination in the future. Furthermore, demographic factors such as age, gender, economic activity, and socioeconomic status (SES) (level of education, support from family, and subjectively perceived financial status) are examined for their effect upon participation in future screening programs.

2. Methods

A free screening test was performed on a random population including 178 eyes from 89 patients with confirmed DM diagnosis. Handling of the fundus camera and the image acquisitions were performed by a qualified professional in a darkened room, which were then forwarded through a secure internet connection to a specialist doctor/ophthalmologist (A. F./M. C. M.) or ROG (G. R./P. K.) for evaluation. In case of constricted pupil, another image was taken after ensuring normal intraocular pressure level and applying cyclopentolate (5 mg/mL) eye drops to achieve mydriasis. The assessment of the fundus images was performed within 10 working days using Spectra DR software. The recordings were safely deposited and kept inaccessible to third parties for 10 years at a central server, so that later they can be used in further comparative studies on DR.

The images were acquired by an 18-megapixel Canon EOS digital camera which was connected to a Canon CR2 color, nonmydriatic, 45° retinal camera. Two pictures were taken of the participants' each eye: one with the macula and another with the optic nerve in the center—this is in line with the UK screening requirements [18]. In case of presence of amblyopia or nontransparent media (e.g. cataract and corneal or visual axis obstructing conditions), the patients were excluded from the study. During image evaluation, the graders (A. F./M. C. M./G. R./P. K.) classified the signs and the stages of DR and maculopathy in the standardized UK-based software Spectra DR and graded the images in alignment with the UK standard grading protocols [19]. Each image was evaluated in two stages: first, the ROG (G. R./P. R.) evaluated them, and then a supervisor/ophthalmic consultant confirmed the diagnosis (A. F./M. C. M.). At the end, an expert opinion regarding the grade of retinopathy was sent back to the screening site, that is, stage of retinopathy (R0/1/2/3A/S) and absence or existence of maculopathy (M0/1). Other discovered abnormalities were not diagnosed in this study, although they were recorded, as they can provide further information about other symptoms which may have occurred in the past, and therefore may require medical attention over a specified period of time.

The classification of the DR was as follows:

M0: no maculopathy was detected; repeated screening was recommended one year later.

M1: there was a sight-threatening maculopathy; within one month a medical examination is required.

R0: there was no clinical anomaly; repeated screening was recommended one year later.

R1: mild nonproliferative phase, microaneurisms, dot- or blot-like hemorrhages, or exudates could be seen; control examination was recommended one year later.

R2: moderate or severe nonproliferative phase, major bleeding(s), cotton-wool spots, venous looping, and intraretinal microvascular abnormalities (IRMAs) were visible; control examination was required within one month.

R3A: active proliferative phase, neovascularization of the optic disc (NVD) or elsewhere (NVE) or preretinal bleeding(s), vitreous bleeding, preretinal fibrosis, and tractional retinal detachment could be observed; immediate medical examination was required within two weeks.

R3S: stable proliferative retinopathy; a retinal image showing stable post-PRP laser with no signs or reactivation or active referable retinopathy; only to be determined in the presence of "benchmark images" taken at the time of discharge for comparison; screening intervals may be at the discretion of the trained ROG.

Other recorded, but not reported, changes/fundus pathology included age-related macular degeneration (AMD), glaucoma changes in the optic nerve, and any other signs of eye disease.

2.1. Self-Completed Questionnaire. The self-completed questionnaire collected information about the individual's demographic status such as age, gender, economic activity (full-time, part-time, and retired), SES such as education (primary, secondary, and higher), and marital status (married or lives with a partner, single, separated or divorced, and widowed). The general part of the questionnaire was based on the European Health Interview Survey 2009 [20], and it collected data about DR associated exposure parameters and some other health connected parameters, type of DM, or presence of hypertension, as well as the type of eye diseases. Furthermore, data were collected about the frequency of measuring blood sugar levels and also about participation in screening programs, which are important for preventing retinopathy, including the frequency of attending Diabetology or Ophthalmology specialist clinics. Questions regarding the perceived reliability of results (yes/no/maybe), willingness to participate again (yes/no/maybe), comfortability (dissatisfied/satisfied/acceptable) of the tests performed, and the overall perception of the screening examinations as well as whether they would participate in a similar examination next time were being asked/collected as well. Some categories underwent merging due to missing data, for example, the intensity of blood sugar measurement (monthly/less than a month, weekly/every few days, and daily/more than once a day). If the participants could not understand or read the questionnaire for whatever reason, they received professional help accordingly.

2.2. Statistical Analysis. The analysis of the data was performed by descriptive statistical analysis on N number of participants, and percent distribution, median, and interquartile range (IQR) are being shown. The Chi-square (χ^2) and Fisher exact tests were used to test differences of the distributions of categorical variables. The relationship between two variables was considered statistically significant when $P < 0.05$. The graphs were made in GraphPad Prism 5.01 (GraphPad Software Inc., La Jolla, CA, USA). The statistical analysis of the data was performed by using Stata (Intercooled Stata 8.0, Stata Corporation, College Station, TX, USA) and Excel software (Microsoft Corporation, USA).

2.3. Ethical Issues. The Regional and Institutional Human Medical Biological Research Ethics Committee of the Albert Szent-Györgyi Health Centre, University of Szeged, approved the study protocol (number 197/2015). The research provided anonymity to the participants. Before the beginning of a test, the participants signed a written consent form in which they agreed to permit the use of data for research purposes.

3. Results

178 eyes of 89 people were examined in the study out of which 30 were men (33.7%) and 59 were women (66.3%). Table 1 shows the demographic characteristics of the patients, the median age of whom ranged between 56 and 68 years of age and had median HbA1c of 7.2% (ranging between 6.4 and 7.9%). Table 2 shows the distribution of the types of DM and the stages of DR in the screened population, based upon and compared to the UK grading system and software (Spectra DR). Twenty percent of the participants had T1DM out of which 70.8% had T1DM diagnosed by a Diabetology department, the rest being yet undiagnosed or hidden disease patients. Mild nonproliferative DR (grade R1) was detected in 23.0% of the participants, while higher (moderate/R2 and proliferative/R3) grade DR was detected in 1.4% and 1.4% of the subjects, respectively; maculopathy/M1 was present in 5.4% of the studied group (representative images from these were captured from each grade and processed in the Spectra software as shown in Figure 1). Another retinal pathology was detected in 28.4% of the participants. There was an overall left-shift in the distribution of earlier stages of DR in the UK population compared to the one represented by the Hungarian graded images and based upon the Spectra DR software, probably due to the existence of a well established screening system in the UK and early detection of the disease.

According to the self-perceived satisfaction with the classical pupil dilation versus fundus camera examination,

Table 1: Patients' demographics.

Variables	Percent (%)
Gender	
Male	33.7%
Female	66.3%
Age (median, IQR)	63 (56–68)
HbA1c (median, IQR)	7.2 (6.4–7.9)
Hypertension*	
No	19.1%
Yes	76.4%
Occupation	
Full-time	22.2%
Part-time	9.3%
Retired	68.5%
Education*	
Primary	23.6%
Secondary	52.3%
Higher	21.8%
Marital status	
Married or lives with a partner	55.6%
Single, separated, or divorced	24.1%
Widowed	20.4%
Attendance of blood sugar screening	
Monthly/less than a month	20.8%
Weekly/every few days	39.6%
Daily/more, than once a day	39.6%

IQR: interquartile range.
*The remaining percent of participants either were not aware of their disease (hypertension) or provided no response (education).

20.4% versus 83.6% of the participants expressed satisfaction, respectively, while 37.0% versus 9.1% were unsatisfied, and 42.6% versus 7.3% could not decide. The classical pupil dilation versus fundus camera examination was found to be definitely reliable by 75.5% versus 72.0%, possibly reliable by 18.4% versus 16.0%, and unreliable by 6.1% versus 12.0%, respectively. The willingness to participate in a classical pupil dilation versus fundus camera examination was found to be positive by 78.2% versus 67.3%, while 9.1% versus 10.9% responded that they would not participate, and 12.7% versus 21.8% responded as maybe doing it. There was no significant difference between the satisfaction from the examination ($P = 0.9$) and reliability ($P = 0.3$), although the willingness to participate significantly differed between the classical versus fundus camera examination ($P = 0.01$) (Table 3).

The economic activity significantly affected the participation in a blood sugar screening ($P = 0.001$). Sixty percent of those employed in a part-time job had attended blood sugar screening more than once a day or daily, 20% weekly/every few days or monthly/less than a month. The daily/more than once a day attendance was 33.3% among retired, while the weekly/every few days screening was 55.6%, and the monthly/more than a month was 11.1% in this age/patient group. Among the full-time workers, the daily/more than once a day and monthly/less than a month screening was 45.5% versus 54.5% (Figure 2(a)). Similarly, marital status (being married or living with a partner) significantly impacted the likeliness to attend blood sugar screening ($P = 0.04$); this population had a higher daily/more than once a day blood sugar screening attendance, with a frequency of 50% compared to those living alone (single, separated, or divorced: 30.8%; widowed: 18.2%); the latter two populations had otherwise the highest weekly/every few days attendance (single, separated, or divorced: 53.9%; widowed: 72.7%). The least frequent or monthly/less than a month screening attendance was the highest among married or living with a partner population (28.6%), while it was the smallest among widowed participants (9.1%) (Figure 2(b)).

The willingness to participate in the annual fundus camera screening was the highest among the full-time workers (91.7%) and the lowest among part-time workers (20.0%) Those who reported maybe versus no attendance were higher among part-time workers (40.0% versus 40.0%, resp.), while the willingness to participate differed significantly between the analyzed economical groups ($P = 0.003$) (Figure 3(a)). The satisfaction with the fundus camera screening also increased significantly with the level of education (primary (69.2%) and secondary (82.8%); higher (100%), $P = 0.003$) (Figure 3(b)).

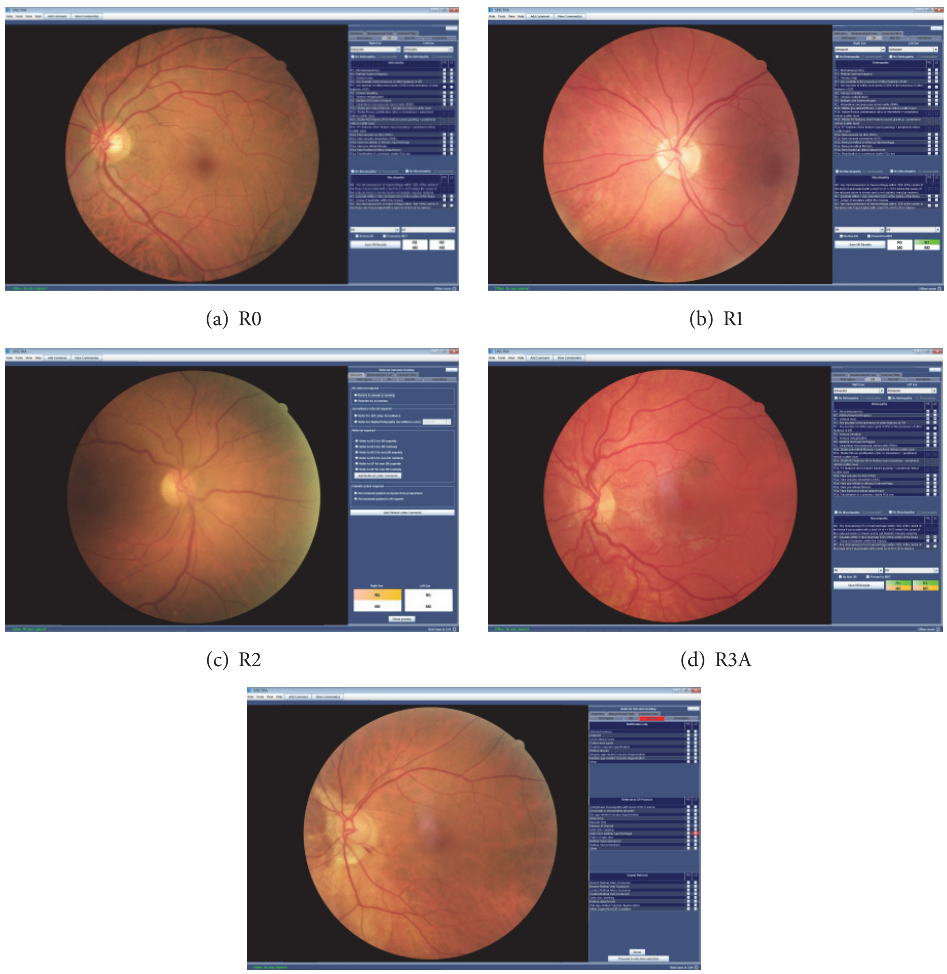
Among participants with secondary or higher education, the most common argument used against the classical fundus exam was "I cannot see clearly after." The participants with primary school level education had significantly higher rate of stating dissatisfaction of the pupil dilation examination. This reason was not stated among higher educated patients, although the "I cannot drive after" reason seemed to appear more often in this group of patients.

4. Discussion

The present study aimed to investigate the patients' experience with the use of telemedicinal tools for screening of DR and the ability to collect the parameters needed to calculate DR risk (age, gender, type and duration of DM, HbA1c, hypertension, and fundus image grading) in a southeastern county (Csongrád) in Hungary. The justification for using health care tools aimed at screening DR is high, due to the great availability of tools for DR prevention and avoidance of late complications such as STR. The population of Csongrád County is very plausible for initiating such a study, since it has a known higher prevalence of DM compared to other counties in Hungary [5]. In addition, the study followed the progressive trend of DM worldwide and examined the willingness to participate in screening tests, the attitude towards screening examination, and the influence of demographics and socioeconomic factors like education, financial, and marital status. Regarding the risk factors, the SES has been already shown to have a very significant impact on the attendance in screening examinations, while occupation has been related to a greater impact on nonattendance in screenings [21]. The screening frequency for blood sugar levels in full-time workers was indeed significantly lower in our study, but the willingness to participate in fundus screening examination was higher in that subpopulation.

Table 2: Distribution of the DM types and DR grade in the studied population in relation to the UK-based grading system implemented by the Spectra™ analysis.

	T1DM	T2DM	R0	R1	R2	R3	M1
Csongrád County, Hungary	20.2%	79.8%	73.0%	23.0%	1.4%	1.4%	5.4%
East Anglia, UK	15.0%	85.0%	68.7%	27.5%	0.6%	0.3%	3.2%



(a) R0
(b) R1
(c) R2
(d) R3A
(e) M1

Figure 1: Spectra DR based grading of the DR retinopathy. Representative images of the different grading stages are shown in the studied population.

From the standpoint of DR formation and progression, it is 76.4% of the patients who had high blood pressure which, by itself or as a codisease, gives poorer prognosis for the DM patients due to a predisposition for premature vascular sclerosis. The occurrence of DR in the studied sample population was 25.5%, which is higher than any previous results in Hungary [22], although somewhat expected in Csongrád County.

Although the Diabetology guidelines recommend blood glucose levels to be checked several times a day, only a little over a quarter of the participants performed it accordingly. Strikingly, 60% of the study participants performed blood glucose testing every few days, if not more rarely. Upon diagnosis with DM, the Diabetologist or the General Practitioner informed the patient of the possible complications from the disease and recommended an annual eye screening test. Our results coincide with the International Diabetes Federation's (IDF's) observation that 50% of the people with DM are not aware of the characteristics of their disease [23]. In Hungary, the number of known patients with diabetes makes nearly 10% of the total population. It would take 100 ophthalmologists (from the total of 968 practicing) working full-time if they want to carry out only the annual screenings by using traditional tools on such a sized population. This may change by using the telemedicine system [17]. Introducing a new screening program always faces challenges, but previous studies from other countries show promising results. DR could be detected at early stages by digital imaging even in

Table 3: Reliability, satisfaction, and willingness to participate again in a classical or fundus camera examination for DR screening.

Variables	Pupil dilation $N = 89$ (%)	Fundus camera $N = 89$ (%)	P^*
Reliability of the examination			
Yes	75.5%	72.0%	
No	6.1%	12.0%	0.3
Maybe	18.4%	16.0%	
Willingness to participate again			
Yes	78.2%	67.3%	
No	9.1%	10.9%	0.01*
Maybe	12.7%	21.8%	
Satisfaction with the comfort of the screening			
Dissatisfied	37.0%	9.1%	
Satisfied	20.4%	83.6%	0.9
Acceptable	42.6%	7.3%	

$^*P < 0.05$.

rural areas [24]. Diabetes causing vision loss is successfully confined in countries like Iceland, where regular screening was implemented.

In our study, only a third of the participants had not visited an ophthalmologist, while 12.4% of them have been diagnosed with DM within a year; only 56.2% of the participants complied with the one-year recommendation. In the UK, patients compliance in attending traditional screening was 45% and 50% in fundus camera screening in the first year [25]. After using a mobile fundus camera screening unit to reach more patients, the compliance elevated to 80% in the fifth year [26]. Compliance is a highly influential factor of cost effectiveness because of the fixed costs (digital imaging camera, computer system, etc.) [25]. Patient satisfaction affects the attendance rate of the screening. The response to the subjective experiences perceived during fundus examination did produce satisfactory results: more than three-quarters of the participants were satisfied with the fundus camera examination and one out of five with the traditional method. In both cases, three-quarters of the participants considered the results of the study to be reliable, a significant difference being found between the two screening procedures. There were fewer problems than expected (e.g., subjects being not able to drive after pupil dilation), but it can be a factor which is most likely related to older age of the sampled population. It is interesting to note, however, that during the procedure of pupil dilation, one quarter of the subjects found administering eye drops being irritating or uncomfortable, in particular, those who had lower education.

There is a level of contradiction in the assessment of reliability and satisfaction in the study, since significantly more people were willing to participate in the traditional retinal screening method than in the fundus camera test (78.2% versus 67.3%). A possible weakness of the study is the size of the sample. 83.6% of the participants were dissatisfied with the examination, which raises the suspicion they could have chosen "Other" for their response to having no other comments, and this could have been done out of necessity. Among the inconvenience experienced during the test with pupil dilation, the "Other" category was chosen by only 4.1% in which no mention of any reasons for the selection made was stated whatsoever.

During the analysis, the economic activity and education appeared to pose an effect on the individual's willingness to participate in the screening test. The fundus camera test was preferred mostly by the full-time employees, with whom it was presumably important to see well after the test in order to be able to continue their work during the same day. Based on the level of education, the few subjects that evaluated the fundus camera test as satisfactory were those who found eye drops to be the most uncomfortable in the traditional test. These data are somewhat contradictory, as mydriatic drops are always required in traditional testing. People with higher education found only the driving restriction and the bad sight after the examination as a negative aspect of the screening; in this context, they were 100% satisfied with the fundus camera test.

The telemedicine part of the study also concerns data safety and patient anonymity preservation which are now guided by an EU law contained in the Charter of Fundamental Rights of the European Union, Article 8 (2000/C 364/01) [27], as well as the need to safely store and make backup files for high resolution fundus images acquired from the patients and their retention; these rules were followed in the present study entirely. The issue of having decentralized and near the patient DR screening and fundus imaging services and centralized image reading remains to be evidenced in future telemedicinal studies for screening DR in Hungary, the UK grading system being the golden standard for achieving the task properly.

In conclusion, the analyzed demographic and socioeconomic factors showed a significant relationship with the future participation in the fundus camera screening for DR. The participants' age or gender appears not to affect the experience (satisfaction) of the examination (e.g., fundus examination under pupil dilation). However, the level of

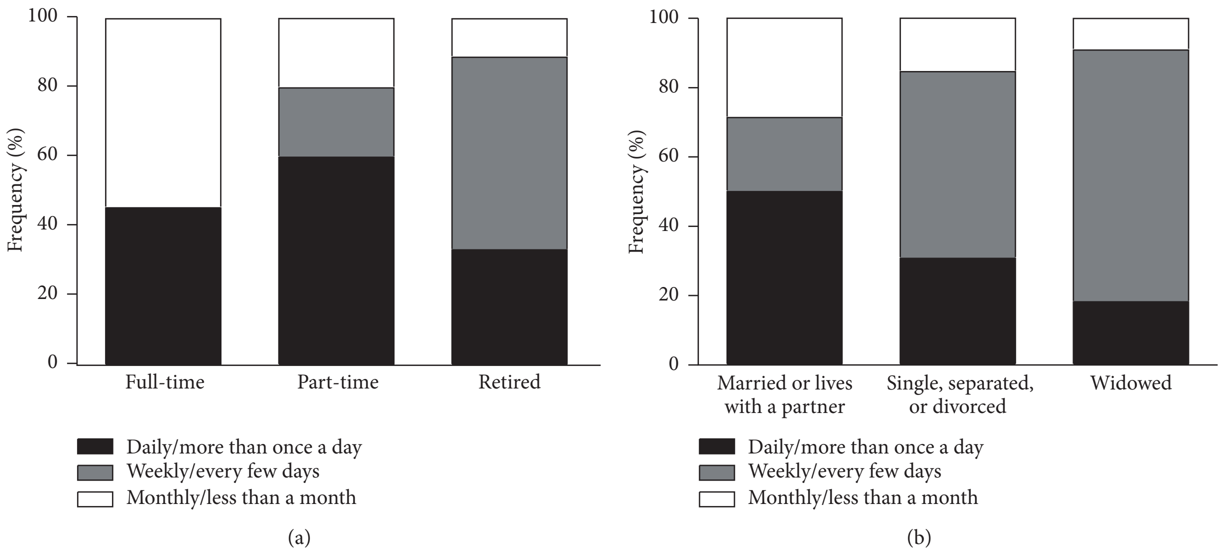


Figure 2: Effect of economic activity (a) and marital status (b) upon the blood sugar screening frequency.

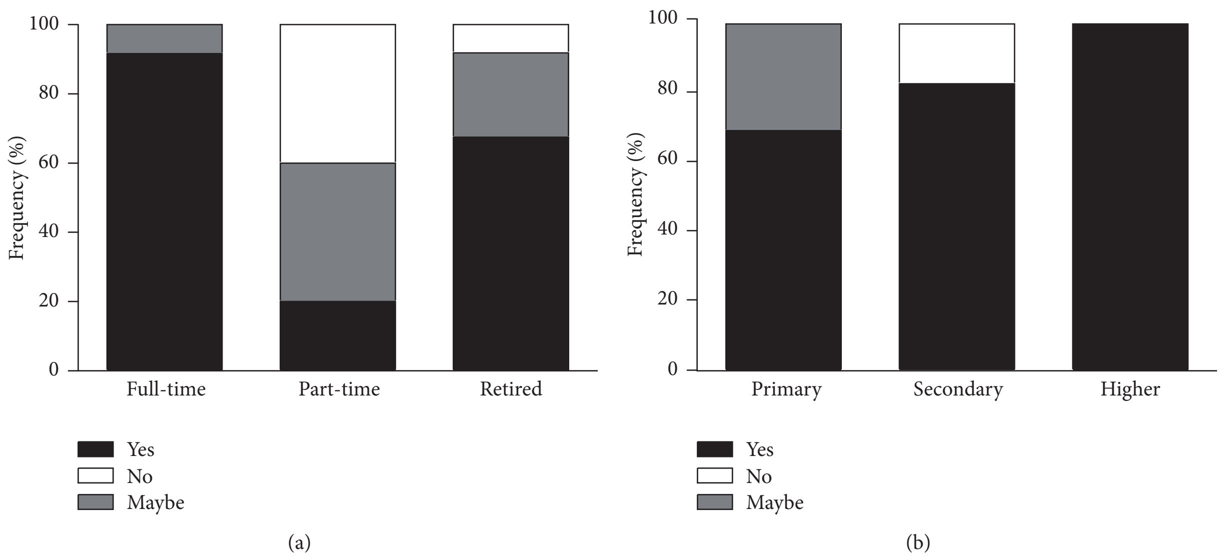


Figure 3: Economic activity in relation to willingness (a) and educational level in relation to satisfaction (b) in participating in fundus screening examination.

education appears to have an important role: higher educated patients were more likely to participate in pupil dilation examination using an ophthalmoscope. This is in contradiction to the fact that only slightly more than half of the participants in this group took part in such screening examination within a period of one year. It was also not confirmed that the distribution of DR grades in this study is similar to the results of previous national studies [17, 22], as Csongrád County is not a representative population comparable to other parts of Hungary where the prevalence of DM and DR is lower. Further research is therefore needed on a larger or more representative sample from different counties in Hungary where the percent of distribution of patients diagnosed with DM varies.

In general, the treatment of DM patients is an interdisciplinary task of primary care physicians, diabetologists/dietologists, ophthalmologists/optometrists, and public health specialists. These professionals are responsible for giving lifestyle advice and for directing patients towards more appropriate screening tests. Ophthalmic monitoring is required every year after the diagnosis of diabetes and every other year for patients with excellent glycemic control without retinopathy at the previous examination but annually if there are risk factors [28]. Furthermore, if retinopathy is manifested to some degree, the screening time should be reduced to half a year (in the case of nonproliferative retinopathy) and three months (for preproliferative retinopathy). In case of proliferative retinopathy patients should go immediately to an ophthalmologist, in order to initiate laser treatment in time and thus save the eye from STR. The present state, unfortunately, seems to involve lack of realistic assessment or judgment of the risk from complications by the patients, and therefore a neglect to participate in the recommended screening tests. Constant maintenance of normal blood sugar levels is indispensable. Fast, easy, and accurate fundus camera examination is an alternative to the traditional, time-consuming, and "unsatisfactory" fundus test under pupil dilation. The patients, who tried this method, agreed that this new way is more satisfaction than the one they got used to, while they appreciated its reliability in the same way. Indeed, in the UK, due to the systematic screening implemented, DR is no longer the leading course of blindness in the working age population [29].

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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Research Article

Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Fundus Camera: The Experience from the South-Eastern Region in Hungary

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Purpose. Diabetic retinopathy (DR) is the leading cause of vision loss among active adults in industrialized countries. We aimed to investigate the prevalence of diabetes mellitus (DM), DR and its different grades, in patients with DM in the Csongrád County, South-Eastern region, Hungary. Furthermore, we aimed to detect the risk factors for developing DR and the diabetology/ophthalmology screening patterns and frequencies, as well as the effect of socioeconomic status- (SES-) related factors on the health and behavior of DM patients. *Methods*. A cross-sectional study was conducted on adults (>18 years) involving handheld fundus camera screening (Smartscope Pro Optomed, Finland) and image assessment using the Spectra DR software (Health Intelligence, England). Self-completed questionnaires on self-perceived health status (SPHS) and health behavior, as well as visual acuity, HbA1c level, type of DM, and attendance at healthcare services were also recorded. *Results*. 787 participants with fundus camera images and full self-administered questionnaires were included in the study; 46.2% of the images were unassessable. T1D and T2D were present in 13.5% and 86.5% of the participants, respectively. Among the T1D and T2D patients, 25.0% and 33.5% had DR, respectively. The SES showed significant proportion differences in the T1D group. Lower education was associated with a lower DR rate compared to non-DR (7.7% vs. 40.5%), while bad/very bad perceived financial status was associated with significantly higher DR proportion compared to non-DR (63.6% vs. 22.2%). Neither the SPHS nor the health behavior showed a significant relationship with the disease for both DM groups. Mild nonproliferative retinopathy without maculopathy (R1M0) was detected in 6% and 23% of the T1D and T2D patients having DR, respectively; R1 with maculopathy (R1M1) was present in 82% and 66% of the T1D and T2D groups, respectively. Both moderate nonproliferative retinopathy with maculopathy (R2M1) and active proliferative retinopathy with maculopathy (R3M1) were detected in 6% and 7% of the T1D and T2D patients having DR, respectively. The level of HbA1c affected the attendance at the diabetology screening (HbA1c > 7% associated with >50% of all quarter-yearly attendance in DM patients, and with 10% of the diabetology screening nonattendance). *Conclusion*. The prevalence of DM and DR in the studied population in Hungary followed the country trend, with a slightly higher sight-threatening DR than the previously reported national average. SES appears to affect the DR rate, in particular, for T1D. Although DR screening using handheld cameras seems to be simple and dynamic, much training and experience, as well as overcoming the issue of decreased optic clarity is needed to achieve a proper level of image assessability, and in particular, for use in future telemedicine or artificial intelligence screening programs.

1. Introduction

Diabetes mellitus (DM) is a major medical and societal challenge due to its rapid increase in global prevalence and devastating late complications [1, 2]. The global occurrence of DM among adults (>18 years of age) was 8.5% in 2014, and this has nearly doubled from its 4.7% level in 1980 [3]. In 2016, 1.6 million deaths were directly attributed to DM, with more than half of them occurring in the lower- and middle-income countries. According to the WHO forecast, DM will be the seventh leading cause of death in 2030, while diabetic retinopathy (DR) will be the leading cause of vision loss among active adults in industrialized countries [4]. DR is the most common late complication of DM in people aged 20 to 64 years—the working-age population, and except for where effective screening programs have been implemented, it is the leading cause of blindness and reduced vision in this group in the developed world [5, 6]. In a study comparing data from 35 populations, the global prevalence of sight-threatening retinopathy (STR) was estimated at 10.2% for all DM patients [6].

In Hungary, a total of 865 069 patients (9.5% of the population) suffered from DM among adults (>18 years of age) in 2011 [7], and some degree of DR could be observed among 19% of the patients with type 1 DM (T1D) and 24% in those suffering from type 2 DM (T2D) for 3 or 4 years [8]. Systematic DR screening and monitoring has been proven to be cost-effective in reducing blindness and visual impairment in patients having DM. Screening enables optimized timing of laser and medical therapy that may halt disease progression [9]. The WHO guidelines [10] for DR screening state that "annual eye examinations are recommended for patients with diabetes (and every other year for persons with excellent glycemic control and no retinopathy at the previous examination...)." "Such programs need systematic evaluation for their impact on health outcomes, cost effectiveness and health equity." The WHO recommendation further states "Member States should choose the most appropriate interval between examinations" [10].

The development of optimized and effective DR screening programs is becoming eminent. The aim of this study was to investigate the prevalence of DR and its different grades in patients with DM in the Csongrád County—a South-Eastern region in Hungary, using for the first time in this country a handheld fundus camera (Smartscope Pro Optomed, Finland). Moreover, we aimed to detect the risk factors for developing DR and the diabetology/ophthalmology screening patterns and frequencies, as well as the effect of socioeconomic status- (SES-) related factors on the health and behavior of DM patients.

2. Patients and Methods

2.1. Physical Examination. A cross-sectional study was conducted between the Departments of Ophthalmology and Internal Medicine Diabetology Unit, University of Szeged, Szeged, Hungary, between November 2015 and December 2016. All examinations were voluntary and free of charge to the participants, and the patients were recruited consecutively from the Diabetology Outpatient Clinic. Written informed consent was obtained from all participants. The study was approved by the local ethical committee of the University of Szeged (No.197/2015). The detection of DR was based upon examination with a handheld fundus camera (Smartscope Pro Optomed, Finland) in a dark room by qualified professionals. The results were directly evaluated by a qualified specialist without the need to do data/file transfer. In the case of constricted pupil, another image was taken after ensuring normal intraocular pressure level and applying cyclopentolate (5 mg/mL) eye drops to achieve mydriasis. The assessment of the fundus images was performed using the Spectra DR software (Health Intelligence, UK). The recordings were safely deposited and kept inaccessible to third parties for 10 years at a designated server, so that later they can be used in further comparative studies on DR.

The images acquired with the Optomed Smartscope Pro digital handheld camera included two pictures from the participants' eyes—one with the macula—and another with the optic nerve—in the center—which is in line with the English screening requirements [11]. In case of presence of amblyopia or nontransparent media (e.g., cataract and corneal or visual axis obstructing conditions), the patients were excluded from the study. During image evaluation, the graders (A.F./G.P./G.R.) classified the signs and stages of DR and maculopathy in the standardized English-based software Spectra DR and graded the images in alignment with the English standard grading protocols [12]. Each image was evaluated in two stages: first, the referral outcome graders/ROGs (D.E./G.R.) evaluated them, and then a supervisor/ophthalmic consultant confirmed the diagnosis (A.F./G.P.). At the end, an expert opinion regarding the grade of retinopathy was provided, which included the stage of retinopathy (R0/1/2/3A) and the absence or existence of maculopathy (M0/1). Other discovered abnormalities were not diagnosed in this study, although they were recorded, as they can provide further information about other symptoms, which may have occurred in the past, and therefore may require medical attention over a specified period of time.

The classification of the DR has been described before [13]—in brief: (R0) no clinical anomaly—repeated screening was recommended one year later; (R1) mild nonproliferative—presence of microaneurysms, dot- or blot- like hemorrhages, or exudates—control examination was recommended one year later; (R2) moderate or severe nonproliferative—presence of major bleeding(s) and intraretinal microvascular abnormalities (IRMAs)—control examination was required within one month; (R3A) active proliferative—presence of neovascularization of the optic disc (NVD) or elsewhere (NVE) or preretinal bleeding(s), vitreous bleeding, preretinal fibrosis, and tractional retinal detachment—immediate medical examination was required within two weeks. All the stages were combined with sight-threatening maculopathy which was determined by the presence of exudates regardless of visual acuity (VA), or red lesions with a VA of 6/12 or worse after pinhole correction, that is within 1 disc diameter of the center of the fovea, and/or a group of exudates where the area of exudates that is greater than or equal to half the disc area, and this area is all within the macular area (as defined by the ETDRS macular grid) when medical examination was required within a month (M1).

2.2. Self-Completed Questionnaire. Participants were asked to fill out a self-administered questionnaire which was based upon the European Health Interview Survey 2009—it included demographic characteristics such as gender, age, and place of residency. From the place of residency, the distance to the healthcare facility was calculated as <10 km or ≥10 km.

The marital status was categorized as married or lives with a partner, single, separated or divorced and widowed; due to the low sample size, categories were merged together as living alone or living in partnership. SES of the study participants was examined: education and economic status. The economic status was characterized as working—full time and working—part-time, unemployed, retired, temporarily laid off, and student; due to the lack of data between each category, the categories were allocated and merged as inactive or active. The level of education was measured as primary, secondary, or higher education (college, university, or higher).

Data were collected about self-perceived health status (SPHS) and characterized as bad satisfactory, and good. Information was also collected about "Perception of what the subject can do for his/her health status," and the information was categorized as almost nothing (nothing/little) or much more (much/very much).

Health behavior was assessed by alcohol consumption, smoking, physical activity, and diet (no/yes). Smoking was classified as yes/quit/never smoking, while alcohol consumption was classified as no/yes. Physical activity was defined according to the amount or occasions spent in the previous month in cycling, walking: daily/weekly more time, weekly, once/no activity at all (inactive).

Information was also collected about the DM-related and other health conditions, for example, if the study participant has/had hypertension: no/yes. If yes, data were collected about the duration of the hypertension (years). If the participant attended blood pressure controls, a recording was made about the last measurement of the systolic and diastolic blood pressures in millimeters of mercury (mmHg).

Information was further collected about other health conditions, for example, VA (<0.3 or ≥0.3), HbA1c level (normal <7% or elevated ≥7%), type of diabetes mellitus (T1DM or T2DM), use of medications, DM in the family or occurrence of diabetic maculopathy. In addition, data about the attendance at healthcare services like diabetology (monthly, every 3rd month, every 6th month, yearly, more than a year, or no attendance) were also collected.

2.3. Statistical Analysis. The analysis of the data was performed by descriptive statistics; percentage distribution, mean and standard deviation (SD), and in case of nonnormality of continuous variables, median and interquartile range (IQR) and range (minimum, maximum) are shown. Normality of the continuous variables was tested on a histogram, Q-Q- plot, and by Shapiro-Wilk and Kolmogorov-Smirnov test. The Independent Sample T-test was used to compare the means of the continuous, numerical variables, when the normality assumption was satisfied; otherwise, Mann–Whitney U test was used. Homogeneity of variance was analyzed with the Levene test.

Chi-square (χ^2) and Fisher test were used to test the differences of the distribution of categorical variables; for multiple comparisons, the 2-sample z-test with Bonferroni correction was applied to detect the differences in the proportions between the studied groups. If the sample within each column was 1 or less, then the z-test could not be used. The significance limit was set at $P < 0.05$. The statistical analysis of the data was performed by IBM SPSS Statistics Version 24 software.

2.4. Ethical Issues. The Regional and Institutional Human Medical Biological Research Ethics Committee of the Szent-Györgyi Albert Clinical Center, University of Szeged approved the study protocol (No. 197/2015). The research provided anonymity to the participants. Before the beginning of a test, the participants signed a voluntary written consent form in which they agreed to permit the use of data for research purposes.

3. Results

The data were collected from a total of 848 participants with known DM in the Csongrád County, South-Eastern region in Hungary (Figure 1). Out of the initial participants, 787 (92.8%) had available fundus camera images and answered the self-administered questionnaire. T1D was present in 13.5% ($N = 52$) of participants, while T2D was present in 86.5% ($N = 334$) of the participants. Among the T1D and T2D patients, 25.0% ($N = 13$) and 33.5% ($N = 112$) had DR, respectively. A large portion of the participants had unassessable fundus camera images/results 46.2% ($N = 363$) when using the handheld camera, and therefore excluded from the further analysis (Figure 1).

The data analysis was based upon the remaining 386 individuals, who had assessable fundus camera images and possessed complete data about the type of diabetes and the risk parameters studied.

Table 1 shows the characteristics of the studied participants. Gender, age, and marital status showed no significant proportion differences between the study groups, while SES showed significant proportion differences in the T1D group. The proportion of the DR differed significantly in the Education and Perceived Financial Status groups, and it was significantly higher among those with higher education (secondary/higher being 61.5%/30.8%) and perceived bad financial status (63.6%). The distance travelled to the healthcare service showed a nearly significant association with the DR—participants living more than 10 km away from the healthcare services had a higher proportion of DR (61.5%).

Tables 2 and 3 show the results of the SPHS and the health behavior of the individuals, neither of which showed a significant relationship with the disease for both, T1D and T2D groups.

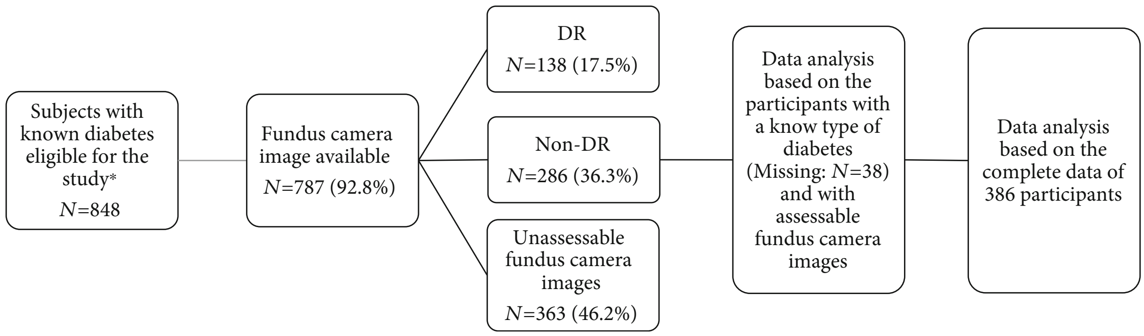

Figure 1: Flowchart of the study sample. DR: diabetic retinopathy; Non-DR: nondiabetic retinopathy; N: number. *Fulfilled the self-completed questionnaire and had a fundus camera image taken.

Table 1: Characteristics of the study sample.

	T1D $N = 52$ (%)		T2D $N = 334$ (%)	
	DR $N = 13$ (%)	Non-DR $N = 39$ (%)	DR $N = 112$ (%)	Non-DR $N = 222$ (%)
Gender				
Male	7 (53.8)	23 (59.0)	47 (42.0)	94 (42.3)
Female	6 (46.2)	16 (41.0)	65 (58.0)	128 (57.7)
Age (mean ± SD)	70.8 ± 6.0	66.4 ± 12.2	66.4 ± 12.8	65.7 ± 13.0
Distance to the healthcare services				
<10 km	*5 (38.5)*	*27 (69.2)*	75 (67.0)	140 (63.4)
≥10 km	*8 (61.5)*	*12 (30.8)*	37 (33.0)	81 (36.6)[a]
Education				
Primary	*1 (7.7)*	*15 (40.5)*	54 (48.2)	94 (43.5)
Secondary	*8 (61.5)*	*10 (11.2)*	30 (26.8)	79 (36.6)
Higher	*4 (30.8)*	*12 (32.4)*	28 (25.0)	43 (19.9)[b]
Perceived financial status				
Bad	*7 (63.6)*	*8 (22.2)*	24 (23.1)	58 (27.6)
Satisfactory	*2 (18.2)*	*23 (63.9)*	70 (67.3)	131 (62.4)
Good	*2 (18.2)*	*5 (13.9)*	10 (9.6)	21 (10.0)[c]
Marital status				
Living alone	1 (7.7)	5 (13.9)	37 (33.0)	60 (27.8)
Living in partnership	12 (92.3)	31 (86.1)	75 (67.0)	156 (72.2)[d]
Economic status				
Active	9 (69.2)	21 (55.3)	*21 (18.7)*	*63 (28.9)*

$P < 0.05$. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: nondiabetic retinopathy; N: number; SD: standard deviation. Missing data: (a) 1; (b) 8; (c) 25; (d) 7.

Table 4 shows the characteristics of the health status of the study participants. A significant difference was only present in case of diabetes medication use and presence of diabetic maculopathy in T2D patients having DR and non-DR, with the rest of the parameters included (hypertension, VA, HbA1c, duration of DM, and familiar presence of DM) showing no significant proportion differences between the studied groups.

Mild nonproliferative retinopathy without maculopathy (R1M0) was detected in 6% of the T1D patients having DR, and 23% of the T2D patients having DR. Among the patients having DR, R1 with maculopathy (R1M1) was present in 82% of the T1D group, and 66% of the T2D group. Both moderate nonproliferative retinopathy with maculopathy (R2M1) and active proliferative retinopathy with maculopathy (R3M1) were detected in 6% of the T1D patients having DR. Among the T2D patients having DR, the prevalence of R2M1 was 4%, while the prevalence of R3M1 was 7% (Figure 2).

The level of HbA1c affected the participation in the diabetology screening, with those having HbA1c > 7% representing more than 50% of all quarter yearly attendance for both types of DM (Figure 3). About 10% of the population had no diabetology screening attendance for those having HbA1c > 7% for both types of DM and HbAc < 7% T2D. For both types of DM,

Table 2: Self-perceived health status of the study sample.

	T1D $N = 52$		T2D $N = 334$	
	DR $N = 13$ (%)	Non-DR $N = 39$ (%)	DR $N = 112$ (%)	Non-DR $N = 222$ (%)
Self -perceived health				
Bad	2 (15.4)	7 (18.4)	28 (25.2)	65 (29.3)
Satisfactory	7 (53.8)	24 (63.2)	64 (57.7)	135 (60.8)
Good	4 (30.8)	7 (18.4)	19 (17.1)	22 (9.9)[a]
What the person can do for his/her health				
Very much/much	10 (83.3)	30 (78.9)	91 (82.0)	167 (76.6)
Little/nothing	2 (16.7)	8 (21.1)	20 (18.0)	51 (23.4)[b]

$P < 0.05$. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: nondiabetic retinopathy; N: number. Missing data: (a) 2; (b) 7.

Table 3: Health behavior of the study participants.

	T1D $N = 52$		T2D $N = 334$	
	DR $N = 13$ (%)	Non-DR $N = 39$ (%)	DR $N = 112$ (%)	Non-DR $N = 222$ (%)
Physical activity in the last month				
Every day/more times a week	6 (46.1)	26 (66.7)	61 (57.0)	118 (55.9)
Weekly	5 (38.5)	6 (15.4)	17 (15.9)	40 (19.0)
Only once in the last month/inactive	2 (15.4)	7 (17.9)	29 (27.1)	53 (25.1)[a]
Diet				
Yes	13 (100.0)	35 (92.1)	85 (77.3)	175 (81.8)
No	0 (0.0)	3 (7.9)	25 (22.7)	39 (18.2)[b]
Smoking				
Yes	5 (41.7)	6 (16.2)	8 (7.3)	21 (9.8)
Quit	2 (16.6)	8 (21.6)	38 (34.9)	74 (34.4)
Never	5 (41.7)	23 (62.2)	63 (57.8)	120 (55.8)[c]
Alcohol consumption				
Yes	7 (53.8)	11 (28.9)	35 (32.4)	79 (36.6)
No	6 (46.2)	27 (71.1)	73 (67.6)	137 (63.4)[d]

$P < 0.05$. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: nondiabetic retinopathy; N: number. Missing data: (a) 16; (b) 11; (c) 13; (d) 11.

the yearly attendance was below 5%, while more than yearly attendance was absent for all studied groups, and low for T2D patients having HbA1c > 7% (Figure 3).

4. Discussion

DR is the most common late complication of DM in the working-age population and the leading cause of blindness in the elderly, accounting for a significant drop in the quality of life (QoL) and working ability for the patients [5, 14]. In a study comparing data from 35 populations, the global prevalence of sight-threatening retinopathy (STDR) was estimated to 10.2% for all DM patients [6]. Our study found high rates of R2M1 and R3M1, moderate and active proliferative retinopathy (6% and 7% for T1D and T2D, respectively), which is similar to the world average found so far.

A previous study in Hungary found the prevalence rate of DM in participants aged 20-69 years to be 7.47% [15]. More recently, a study from Hungary showed 24.5% of all incident DM cases to be T2D [16]. The same study also showed T1D to be the most common form of DM in children and adolescents, with its frequency having a tendency of continuous rising, while the occurrence of medically treated cases of T2D not to be increasing. The prevalence of T2D, however, is increasing due to an obesity epidemic and aging of the population, hence, one may expect a dramatic increase in DM during the next decades [1, 2, 10]. In the Csongrád County, South-Eastern region of Hungary, the studied cohort showed an approximate 1 : 7 ratio of T1D : T2D cases.

The population in the Csongrád County in Hungary is characterized by significant SES differences, and these appear to reflect upon significant proportion differences, in particular, in the T1D population. It has been previously reported that poorer populations having Medicaid insurance in the U.S. are associated with worse DR follow-up in predominantly rural patients [17]; this population appears to be similar to the rural population in the Csongrád County, Hungary. A statistically significant relationship between

Table 4: Characteristics of the health status of the study participants.

	T1D $N = 52$		T2D $N = 334$	
	DR $N = 13$ (%)	Non-DR $N = 39$ (%)	DR $N = 112$ (%)	Non-DR $N = 222$ (%)
Hypertension	4 (30.8)	21 (55.3)	97 (87.4)	190 (88.4)
Systolic blood pressure (median, IQR, range)	153 (133-162) 120-191	135 (129-150) 120-158	130 (122-140) 105-189	130 (123-140) 100-169
Diastolic blood pressure (mmHg) (median, IQR, range)	84 (80-85) 78-95	80 (70-85) 58-90	80 (75-85) 60-104	80 (70-85) 60-101
Duration of hypertension (year) (median, IQR, range)	18 (3-42) 3-52	11 (7-20) 2-53	20 (10-40) 2-56	20 (10-37) 3-56
Visual acuity				
<0.3	0 (0.0)	0 (0.0)	6 (16.7)	2 (5.5)
≥0.3	3 (100.0)	2 (100.0)	30 (83.3)	38 (95.0)[a]
HbA1c				
Elevated (≥7%)	13 (100.0)	37 (93.4)	88 (82.2)	170 (79.4)
Duration of diabetes (median, IQR, range)	20 (14-24) 10-38	20 (13-27) 1-60	13 (8-20) 0-38	15 (8-20) 0-40
Diabetes medication	5 (41.7)	13 (34.2)	*86 (77.5)*	*187 (86.6)*
Diabetes in the family	6 (46.1)	21 (53.8)	52 (46.8)	124 (56.6)
Diabetic maculopathy	*7 (53.8)*	*2 (5.1)*	*81 (73.6)*	*15 (6.8)*

$P < 0.05$. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; DR: diabetic retinopathy; Non-DR: nondiabetic retinopathy; N: number; IQR: interquartile range. Missing data: (a) 305.

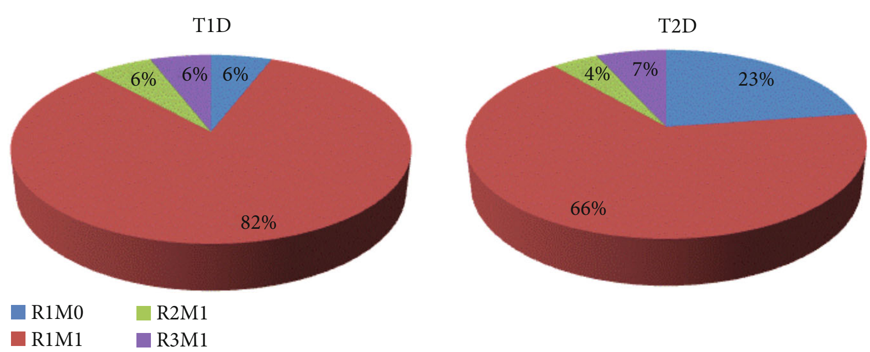

Figure 2: Distribution of the diabetic retinopathy according to the type of diabetes mellitus. DM: diabetes mellitus; T1D and T2D: type 1 and 2 DM.

diabetes complications, age group, educational level, job status, relationship with family members, number of family visits, and the reassurance provided by the family, type of leisure activities, health status, years with diabetes, smoking, type of treatment, fried food consumption and income, sense of security and communication in living environment, and daily intake of vegetables, has also been reported in a study cohort of T2D patients [18]. Furthermore, no statistical interaction could be found between SPHS and gender, while reporting the self-perceived health as poor has been associated with higher reporting of chronic diseases, including diabetes [19].

Although hypertension, VA, HbA1c, duration of DM, and familiar presence of DM showed no significant difference in our study, another study on a population having T2D found a statistically significant difference between SPHS and the levels of HbA1c; the latter study also showed age, level of education, mode of treatment, adherence to treatment, and level of exercise to be factors having statistically significant differences from, and therefore an influence on, self-reported health in a single province in Turkey [20]. Patients with T1D have been shown to have a faster decrease in the perceived health and functioning over time compared to aged persons from the general population [21].

The distribution of the DR showed similar retinopathy with maculopathy (R1M1) presence (82% in the T1D group and 66% in the T2D group) compared to an English study on both DR types (89% had a diagnosis of R1M1 in one eye in those screened positive for maculopathy (M1) in at least one eye) [22]. Our handheld camera produced unassessable fundus image results in nearly half of the participants when used by newly trained image acquisition staff (DJE and DJS); however, in an older population having T2D, this can also be due to the presence of optic axis opacities such as

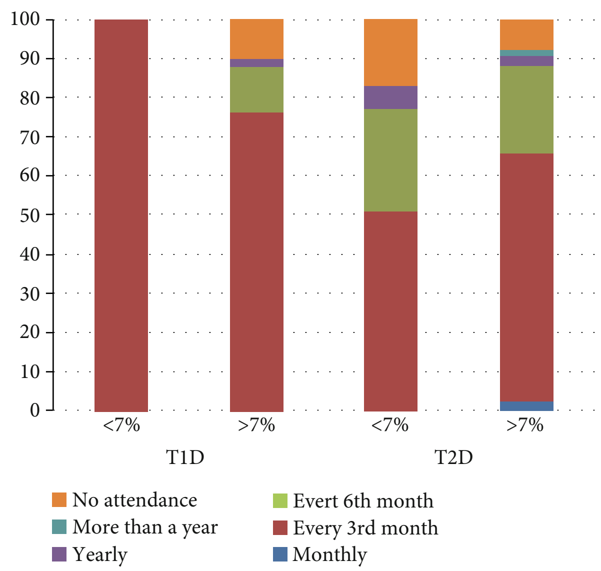

Figure 3: Attendance rate in the diabetology screening among those with normal or elevated HbA1c. T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus. *Data presented are based upon the result of 1 individual in case of the T1D group having HbA1c <7%.

cataract and vitreous hemorrhage. In our study, 6% and 7% of the T1D and T2D population, respectively, had R3M1 (proliferative diabetic retinopathy with maculopathy), while 6% and 4% of the T1D and T2D population, respectively, had R2M1 (preproliferative diabetic retinopathy with maculopathy); therefore, a total of 23% of the population had higher chance for DM-associated cataracts and or vitreous hemorrhages, as well as poor fixation due to macular edema. A limitation of our study is the fact that such changes were not recorded at the time the screening was conducted. Other studies have, however, shown that such handheld cameras can provide comparable results to standard fundus cameras [23]. Later versions of this camera (The Optomed Aurora) appear to have a built-in instant quality feedback software that aids the photographer to gain information when the image is assessable. In the latter study, the two cameras used reached high agreement on the diagnosis of retinopathy and maculopathy at all the levels of retinopathy. Sufficient training of paraprofessional health care staff can lead to obtaining higher quality images with a portable nonmydriatic fundus camera [24]. Known risk factors for developing DR are age, gender, duration and type of DM, elevated HbA_1c, high blood pressure, and retinopathy stage, while other risk factors are being investigated. DR is caused by damage to the retinal microvasculature. Proper screening for DR is an important milestone towards achieving early and efficient treatment for preventing visual loss [9]. For optimal effect, laser treatment must be applied as early as possible after the formation of new pathological retinal vessels, at which time most patients are asymptomatic. In addition, antivascular endothelial growth factor (VEGF) drugs or steroids injected into the vitreous of the eye may reduce diabetic macular edema [25, 26]. Other European countries like Iceland, Denmark, Sweden, and England have successfully implemented nationwide DR screening programs. In Iceland, diabetic blindness prevalence has decreased 4-5 fold after the introduction of systematic DR screening, and a similar success rate has been observed in Denmark [27].

Hungary, at present, has no coordinated national screening program for DR, despite the clear need and high number of patients with DM. Furthermore, in many parts of the country, there are no clear communication channels between GPs, diabetologists, and ophthalmologists regarding screening and sharing results from a DR assessment. Today, a newly diagnosed DM patient must be actively referred for an eye examination by his/her GP or endocrinologist, and often the patient her-/himself must book the appointment. In addition, the interval between eye examinations is at the ophthalmologist's discretion. A standardized rapid assessment of avoidable blindness (RAAB) with the DR module (DRM) has recently been used in Hungary in people aged 50 years and older: 20.0% of the 3523 participants had a known or newly diagnosed DM; 20% of the participants with known DM had a blood glucose level of ≥200 mg/dL; and 27.4% had never had an ophthalmological examination for DR. The prevalence of DR and/or maculopathy was found to be 20.7%, while the prevalence of STDR was 4.3% in one or both eyes among the participants with DM in Hungary [28]. This finding is lower than the one determined in the Csongrád County in Hungary, which can certainly underline disparities in the DR grading standards used or the distributional difference of DR throughout the different counties in the country.

A systematic DR screening in the Csongrád County, South-Eastern region in Hungary, could have significantly reduced the total load of ophthalmologist exams, and thus increase the overall capacity in ophthalmology—a field with vast capacity challenges [19]. More importantly, the lack of systematic DR screening also puts patients with a high risk of eye disease progression at an even higher risk, as they are not receiving the regular follow-up examinations needed. The WHO guidelines for DR screening [5, 14] recommend annual eye examinations for patients with diabetes and biennially for persons with excellent glycemic control and no retinopathy at the previous examination. The International Council for Ophthalmology (ICO) now recommends biennial screening for DM patients without retinopathy. In general, there is a low annual incidence of STR, and 97% of the screening visits do not lead to any active treatment [29]. However, with the increasing prevalence of DM, especially T2D, and limited eye care capacity, advocating for a personalized health care approach towards patient-tailored screening and recommendation for each individual patient has been proposed.

In Iceland for example, a path of improving cost-efficacy of screening systems has been chosen by reducing the number of unnecessary screening visits. Based on a biennial screening model, the following risk variables have been included to improve risk predictions for each individual patient: age, gender, diabetes duration, type of diabetes, HbA_1c level, blood pressure, and retinopathy stage. An European collaborative network has used this model to calculate the most appropriate interval between examinations for each patient, the outcome of which was a reduction of 17-23% in the screening visits needed, compared to the biennial screening model [29, 30]. A personalized screening approach would have the advantage of recommending more frequent screening intervals to high-risk patients and less frequent to low-risk patients. The risk variable profile also shows significant alterations between different countries and also between different ethnic- and socioeconomic populations within the same country and region, thus, the one-size-fits-all approach may not be the best for diverse populations globally.

In conclusion, this study in the Csongrád County, South-Eastern region, Hungary, determined the prevalence of DM and DR, which appeared to follow the country trend, except for the slightly higher STDR. SES appears to affect the DR rate, in particular, for T1D. The DR screening using the Smartscope Pro Optomed handheld camera, although simple and dynamic, requires much training and experience to achieve proper levels of image assessability if future use in telemedicine or artificial intelligence screening programs or personalized medicine is planned.

Data Availability

Data from this study are available on request through the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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