Doctoral School of Interdisciplinary Medicine

Diabetic retinopathy screening using telemedicine tools

Summary of the PhD Thesis

Dóra Júlia Eszes

Supervisors:
Dr. Beáta Éva Petrovski, PhD
Prof. László Nagymajtényi, MD, PhD, DSc

Department of Public Health
Albert Szent-Györgyi Medical School
University of Szeged

Szeged
2022

Introduction

The global prevalence of diabetes mellitus (DM) among adults (age 20 years and older) was 10.5% worldwide in 2021, which has more than doubled from its 4.7% level in 1980, while its prevalence still shows an increasing tendency due to the obvious obesity epidemic and aging of the population. 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, 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.

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. 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, accounting for a significant drop in quality of life and working ability of the patients. 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. In a study comparing data from 35 populations, the global prevalence of sight-threatening retinopathy was estimated at 10.2% for all DM patients. 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 also investigated. Unfortunately, 50% of the people with DM 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 damage the wall of the arteries, it is not surprising that people with DM have 2 to 4 times higher cardiovascular mortality rate and 2 to 4 times higher risk of stroke than patients without DM. Renal failure is also a common complication with an estimated 30–40% of the patients with DM, 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 medicines, but only a quarter of the expenditure spent on drugs is for antidiabetics. Similarly, the treating expenses doubled in Germany and in the U.S., where $174 billion was spent on the treatment of DM in 2007. 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. 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). 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. 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. 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 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.

The Spectra DR software is designed to comply 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 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. 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.

Iceland began regular DR screening for T1DM patients in 1980, resulting in the reduction of disease-related blindness from 2.4% to 0.5%. 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. Studies have reported a

decreasing incidence of severe DR in developed countries due to screening programs. 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.

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-Eeastern 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 the Csongrád County, using for the first time in Hungary a handheld fundus camera (Smartscope Pro Optomed, Finland). Moreover, we investigated the risk factors for developing DR and the diabetology/ophthalmology screening patterns and frequencies.

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 SES factors upon participation in a DR screening program
- To determine the self-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 in comparison to the UK-based grading system.
- To determine the reliability, satisfaction, and willingness to participate again in a classical or fundus camera examination for DR screening.

Methods

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 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 images were taken with an 18-megapixel Canon EOS digital camera which was attached 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.

A self-completed questionnaire collected information about the individual's demographic status. The general part of the questionnaire was based on the European Health Interview Survey 2009, and it collected data about DR associated exposure parameters and some other health connected parameters.

Diabetic retinopathy screening in patients with diabetes using a handheld fundus camera

A cross-sectional study was conducted in the Departments of Ophthalmology and Internal Medicine Diabetology Unit, University of Szeged, Szeged, Hungary, in the period between November 2015 and December 2016. 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. 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 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.

A self-completed questionary collected data about DR associated exposure parameters and some other health connected parameters, and about the individual's demographic status.

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 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's exact 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.

Results

Diabetic retinopathy screening using telemedicine tools

89 people's 178 eyes were examined in the study out of which 30 were men (33.7%) and 59 were women (66.3%). 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%). Twenty percent of the participants had T1DM out of which 70.8% had T1DM diagnosed by the Diabetology department, the rest being yet undiagnosed or hidden morbidity 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. Other retinal pathology was detected in 28.4% of the participants.

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 examination was found to be reliable by 75.5% versus 72.0%, probably 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 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 significantly differed between the classical versus fundus camera examination (p=0.01).

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 once 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%. 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%).

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). The satisfaction with the fundus camera screening increased significantly with the level of education (primary (69.2%) and secondary (82.8%); higher [(100%), p=0.003].

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 the Csongrád County, South-Eastern Region in Hungary. 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 the T1DM and T2DM patients, 25.0% (N=13) and 33.5% (N=112) had DR, respectively. A large part 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. 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.

Gender, age, and marital status showed no significant proportion differences between the study groups (T1DM vs T2DM), while SES showed significant ratio differences. 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%).

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%.

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. 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%.

Discussion

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). 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-disease, 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. 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. 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 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, as Csongrád County is not a representative population comparable to other parts of Hungary where the prevalence of DM and DR is lower.

Diabetic retinopathy screening in patients with diabetes using a handheld fundus camera

The second study found high rates of R2M1 and R3M1, moderate and active proliferative retinopathy (6% and 7% for T1DM and T2DM, respectively), which is similar to the world average found so far. 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 T1DM population. 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 self-perceived health status and the levels of HbA1c. Our handheld camera produced unassessable fundus image results in nearly half of the participants when used by newly trained image acquisition staff; 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. Sufficient training of paraprofessional health care staff can lead to obtaining higher quality images with a portable nonmydriatic fundus camera. 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 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 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.

Acknowledgement

I would like to express my gratitude to Professor Edit Paulik for allowing me to enter the Ph.D program, to Professor Andrea Facskó, Professor György Ábrahám, Professor Csaba Lengyel and Professor Tamás Várkonyi for allowing me to work in their Departments of Ophthalmology and Internal Medicine Diabetology Unit.

I would like to acknowledge my supervisors, Professor László Nagymajtényi and Dr. Beáta Éva Petrovski, for their invaluable advice, continuous support, and patience during my PhD study. Their immense knowledge and plentiful experience have encouraged me in all the time of my academic research and daily life.

Special thanks to Professor Goran Petrovski for his mentorship and support throughout the project.

Many thanks to Dr. Dóra Júlia Szabó, Dr. Tamás Zeffer, who took their time to help me manage the participants.
I would like to thank my colleagues, Dr. Tamara Horváth, Dr. Richárd Nagymihály, Dr. Natasha Josifovska for a cherished time spent together in the PhD room, and in social settings.

Last, but not least, I am grateful to all of my family, especially my husband and my children. Without their tremendous understanding and encouragement in the past few years, it would be impossible for me to complete my studies.

List of publications of the author

Publications related to this Thesis:

I. **Eszes, DJ**, Szabó DJ, Russell G, Kirby P, Paulik E, Nagymajtényi L, Facskó A, Moe MC, Petrovski BE. Diabetic Retinopathy Screening Using Telemedicine Tools: Pilot Study in Hungary. Journal of Diabetes Research, 2016: 4529824. https://doi.org/10.1155/2016/4529824

IF: 2.717

II. **Eszes DJ**, Szabó DJ, Russell G, Lengyel C, Várkonyi T, Paulik E, Nagymajtényi L, Facskó A, Petrovski G, Petrovski BÉ. Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Camera: The Experience from the South-Eastern Region in Hungary. Journal of Diabetes Research, 2021: 6646645. https://doi.org/10.1155/2021/6646645

IF: 4.061

Presentations related to the subject of the Thesis

1. **Eszes DJ**, Petrovski BÉ, Paulik E, Dégi R, Facskó A, Petrovski G. Screening for diabetic retinopathy using telemedicine tools – Patients' experience in a south-eastern county in Hungary. Magyar Szemészeti Társaság Kongresszusa. Pécs, 2015.06.18 - 06.20. *Szemészet* 152:(suppl. I.) p. 101.
2. **Eszes DJ**, Szabo DJ, Russell G, Kirby P, Paulik E, Nagymajtenyi L, Facsko A, Moe C M, Petrovski G, Petrovski BÉ. Screening for diabetic retinopathy using telemedicine tools — patients' experience in a southeastern county in Hungary. 18th Danube-Kris-Mures-Tisa (DKMT) Euroregional Conference on Environment and Health. Újvidék, 2016.06.02-06.04. Book of Abstracts (Škrbić B, ed.; ISBN 978-86-6253-059-2), p. 73.
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)
4. **Eszes, DJ**, Szabó, JD, Russell, G, Lengyel Cs, Várkonyi T, Paulik E, Nagymajtényi L, Facskó A, Petrovski G, Petrovski BÉ. Using telemedicine tool to screen diabetic retinopathy among diabetic patients in County Csongrád, Hungary. Magyar Diabetes Társaság XXIX. Kongresszusa. Pécs, 2021. 09. 02-09.05. *Program*, p. 23.