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EPIDEMIOLOGICAL ASPECTS OF DIABETES MELLITUS AND DIABETES-RELATED EYE COMPLICATIONS IN HUNGARY

PhD thesis

Gábor Tóth, MD, FEBO

Clinical Medicine Doctoral School

Semmelweis University

Supervisor: János Németh, MD, PhD, DSc
Zoltán Zsolt Nagy, MD, PhD, DSc

Official reviewers: Eszter Fodor, MD, PhD
Péter Vámosi, MD, PhD

Head of the Complex Examination Committee:
Judit Fidy, MD, PhD, DSc

Members of the Complex Examination Committee:
Katalin Gombos, MD, PhD
Antal Szabó, MD, PhD

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List of abbreviations

DM – Diabetes Mellitus

DMP – Diabetic Maculopathy

DR – Diabetic Retinopathy

DRM – Diabetic Retinopathy Module

GP – General practitioner

HCSO – Hungarian Central Statistical Office

M0 – No maculopathy

M1 – Observable maculopathy

M2 – Referable maculopathy

OGTT - Oral glucose tolerance test

OPSD – Other Posterior Segment Diseases

PCVA – Pinhole Corrected Visual Acuity

PreDM – Prediabetic

R0 – No diabetic retinopathy

R1 – Mild background diabetic retinopathy

R2 – Observable background diabetic retinopathy

R3 – Referable background diabetic retinopathy

R4 – Proliferative diabetic retinopathy

R5 – Ungradable diabetic retinopathy

RAAB – Rapid Assessment of Avoidable Blindness

STDR – Sight-Threatening Diabetic Retinopathy

VI – Visual Impairment

WHO – World Health Organization

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease with hyperglycemia that can lead to development of microvascular and macrovascular complications [1]. Factors leading to hyperglycemia include decreased insulin secretion, reduced glucose utilization and increased glucose production [2]. It is broadly classified into type 1 and type 2 DM [3].

The prevalence of DM and diabetic retinopathy (DR) is rapidly increasing worldwide [4]. It is estimated that in 2015, 415 million people in the world had DM, and that number will increase to 642 million by 2040. Almost 58 million adult people living in Europe have DM, and its regional prevalence was estimated to be 8.8% in 2017 [5]. Prevalence of DM is growing continuously worldwide due to the aging of the population and increasing rate of obesity [6,7].

DR and diabetic maculopathy (DMP) are important microvascular complications of DM. The prevalence of DR is estimated to be 34.6% in people with DM [8], and DR is responsible for 1.0–4.8% of blindness globally. [9,10] It is one of the leading causes of blindness among middle-aged persons in high-income countries [11]. Epidemiological data about DM and DR are necessary for public health and health economics, because almost 25% of total health care spending in the USA stems from the financing of DM and its complications [12]. Prevalence of blindness due to DR is even more important in the estimation of the financial and social burden of DR and blindness caused by DM [13].

With development of primary care, primary eye care and screening programs, regular control of DM and timely treatment of DR, visual impairment and blindness due to DM and its complications can largely be prevented [8,11].

VISION 2020: the Right to Sight and, the more recent initiatives, the World Health Organization (WHO) Global Action Plan 2014–2019 and the WHO World Report on Vision are global initiatives to reduce avoidable blindness by the year 2020 and further decrease in the next decade, respectively. The first step in achieving this target among persons with DM is to obtain baseline data on the prevalence of DM, DR, and ophthalmological status of patients with DM for planning and monitoring eye care programs [14,15]. For this reason, a population-based surveys are needed to estimate

both the prevalence and pattern of DM and DR. Population-based surveys on DM and DR are rare because it is thought that data collection is difficult and expensive [16].
Only few population-based surveys on DM were conducted in Hungary. Vamos et al reported the results of Hungarostudy 2002 with a sample size 12643 of adult people in 2008 [17]. Thereafter Jermendy et al. reported their prevalence of DM based on data of 1803 participants aged 20-69 years in 2010 [18].

Only few data are available concerning the prevalence of blindness among patients with DM in developed countries [19], especially in Hungary [20, 21]. Reliable epidemiological data are essential to support the planning and implementations of public health programmes [22]. The rapid assessment of avoidable blindness (RAAB) (**Figure 1**) is a quick and efficient population-based survey technique to estimate the prevalence and causes of blindness among people aged 50 years and older in a defined geographic area. [23] Estimation of prevalence of DM and DR is possible with the optional diabetic retinopathy module (DRM). Reliability and validity of the RAAB + DRM method were demonstrated [16,19,24,25].

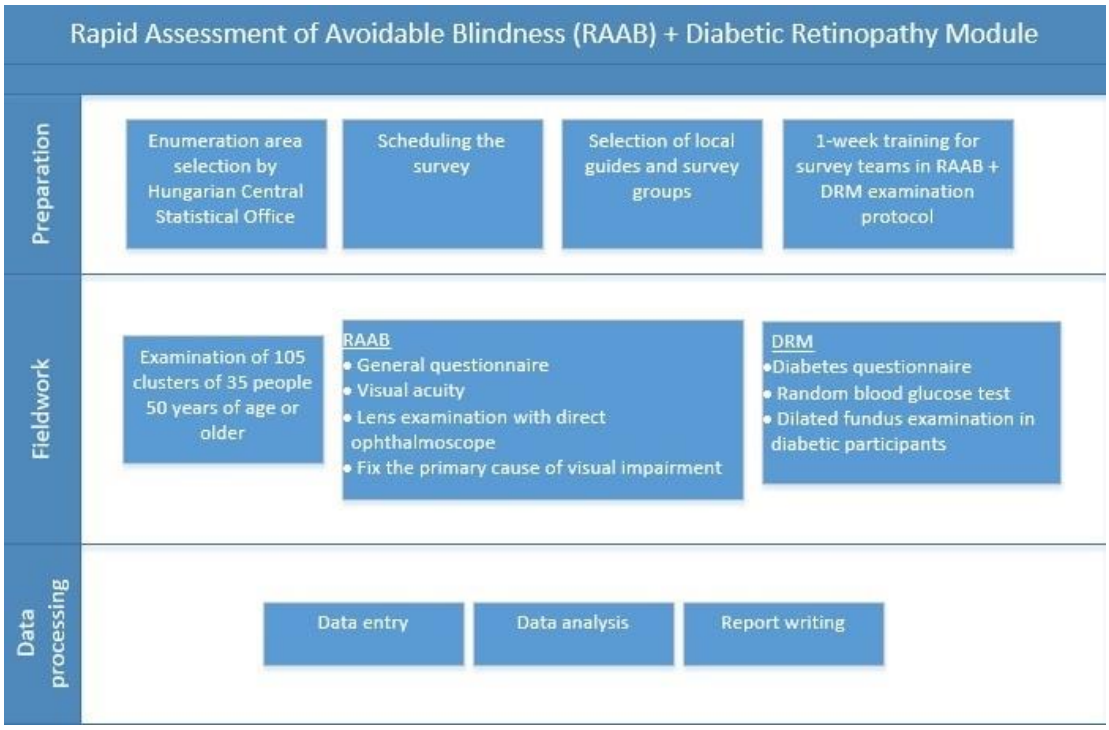

Figure 1. Schematic flowchart of Rapid Assessment of Avoidable Blindness with Diabetic Retinopathy Module survey in Hungary [26].

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2. Objectives

The objective of our research was to survey the epidemiological aspects of DM and diabetes-related eye complications using the standardized RAAB + DRM methodology in Hungary. In order to achieve this objective, the aims of the present study were:

1. To estimate the prevalence of DM, DR and diabetes-related blindness in persons aged 50 years and older in Hungary.

2. To estimate the prevalence of DM in the adult population of Hungary.

3. To analyse a special subgroup of survey participants whose random blood glucose was found to be between 140-200 mg/dl.

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3. Results

3.1. Study population

Table 1. Projected population of Hungary by age and gender in 2015 [27] and the sample population [28].

	Males		**Females**	
Age groups	Hungary	Sample	Hungary	Sample
50-59	591157 (37.2%)	363 (28.5%)	651435 (30.0%)	543 (24.1%)
60-69	561940 (35.4%)	447 (35.1%)	710814 (32.8%)	768 (34.1%)
70-79	301662 (19.0%)	335 (26.3%)	495940 (22.9%)	625 (27.8%)
80+	133288 (8.4%)	128 (10.1%)	310507 (14.3%)	314 (14.0%)

In total, 3675 people aged 50 years or older were included in the 105 clusters (**Figure 2**) in the RAAB + DRM survey, of whom 3523 (95.9%) were examined (1273 males and 2250 females). The 50–59 age group was underrepresented, and the 70–79 age group was slightly overrepresented in the sample, compared to the distribution by age and sex of the projected population of Hungary [28] (**Table 1**).

Figure 2. Geographical distribution of the 105 survey clusters [26].

Regional distribution of the entire survey population is shown in **Table 2** [29].

Table 2. Regional distribution of survey clusters and participants [29].

	Western Hungary		**Central Hungary**		**Eastern Hungary**	
	N	**%**	**N**	**%**	**N**	**%**
Clusters	38	36.2%	29	27.6%	38	36.2%
Total number of participants	1330	36.2%	1015	27.6%	1330	36.2%
Examined participants	1278	36.3%	951	27.0%	1294	36.7%

Rural and urban clusters are shown on **Figure 3**. In the survey population there were 1573 (44.6%) rural and 1950 (55.4%) urban participants (**Table 3**). There were not significant differences between rural and urban groups in the sample regarding to sex and age (p=0.960 and p=0.228) [30].

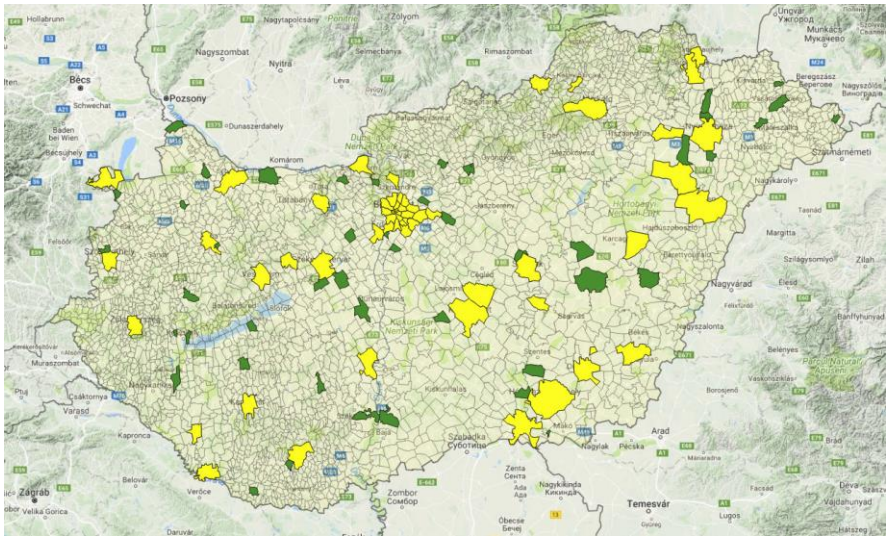

Figure 3. Rural (green) and urban (yellow) settlements among the 105 survey clusters.

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Table 3. Demographic characteristics of the rural and urban survey population in Hungary. Significant P values are ***bold.*** DM = diabetes mellitus, SD = standard deviation [30].

	Rural *n* (%)	**Urban *n* (%)**	**P value**
Clusters	46 (43.8%)	59 (56.2%)	
Participants enumerated	1610 (43.8%)	2065 (56.2%)	
Participants examined	1573 (44.6%)	1950 (55.4%)	
Sex			0.960
Male	569 (36.2%)	704 (36.1%)	
Female	1004 (63.8%)	1246 (63.9%)	
Age groups (years)			
50-59	424 (27.0%)	482 (24.7%)	0.131
60-69	569 (36.2%)	646 (33.1%)	0.058
70-79	385 (24.5%)	575 (29.5%)	**0.0008**
80+	195 (12.4%)	247 (12.6%)	0.809
	Rural (SD)	**Urban (SD)**	
Mean age (years)	66.5 (9.9)	67.4 (10.0)	0.228

3.2. Diabetes mellitus

3.2.1. Diabetes mellitus in people aged 50 years and older

Of the 3523 examined persons, 705 had DM (known or new), thus prevalence of DM in people aged 50 years and older was 20.0% (95% CI: 18.5 to 21.5). There were 661 known cases (93.8%) and 44 new cases (6.2%). There was no significant difference in DM prevalence by gender. Among known diabetic participants, the mean duration of DM was 11.0±10.0 years. Prevalence of DM was the lowest between 50-59 year-old participants and increased with age (**Table 4**). Based on our age and gender composition data from 2015 census, the age- and sex-adjusted prevalence of DM was estimated to be 19.3% in the population aged 50 years or older in Hungary [28].

Table 4. Prevalence of known and newly diagnosed diabetes by age group and gender in the full survey population in Hungary [28].

Age groups (years)	**Males**		**Females**		**Full sample**	
	N	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
50-59	53	14.6% (11.0-18.1)	65	12.0% (8.8-15.1)	118	13.0% (10.5-15.5)
60-69	103	23.0% (18.9-27.2)	145	18.9% (16.4-21.3)	248	20.4% (18.2-22.6)
70-79	81	24.2% (19.6-28.7)	153	24.5% (21.2-27.8)	234	24.4% (21.7-27.0)
80+	26	20.3% (12.4-28.2)	79	25.2% (20.3-30.0)	105	23.8% (19.4-28.1)
All ages	263	20.6% (18.4-22.9)	442	19.6% (17.9-21.3)	705	20.0% (18.5-21.5)

Prevalence of DM (**Table 5**), and age of participants with DM (68.5±9.2 years vs. 68.8±9.5 years vs. 69.4±9.1 years) were not significantly different between Western-, Central- and Eastern Hungary [29].

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Table 5. Prevalence of known and newly diagnosed diabetes in Western-, Central- and Eastern Hungary in the full survey population [29].

	Western Hungary		**Central Hungary**		**Eastern Hungary**	
	N	**%**	**N**	**%**	**N**	**%**
People with diabetes	249	19.5%	185	19.5%	271	20.9%
People without diabetes	1029	80.5%	766	80.5%	1023	79.1%

Of the 1573 examined rural participants, 343 had DM (21.8%). Of the 1950 examined urban participants, 362 had DM (18.6%). The difference was significant between these two groups (p=0.016) (**Table 6**) [30].

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Table 6. Rural and urban prevalences of diabetes by age group and gender in the survey population in Hungary [30].

Age groups (years)	Rural						Urban					
	Males		Females		Full rural sample		Males		Females		Full urban sample	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
50-59	24	15.0% (10.3-21.4)	36	13.6% (10.0-18.3)	60	14.2% (11.2-17.8)	29	14.3% (10.1-19.8)	29	10.4% (7.3-14.5)	58	12.0% (9.4-15.2)
60-69	53	25.0% (19.7-31.2%)	78	21.9% (17.9-26.4)	131	23.0% (19.8-26.7)	50	21.3% (16.5-27.0)	67	16.3% (13.0-20.2)	117	18.1% (15.3-21.3)
70-79	40	28.2% (21.4-36.1)	63	25.9% (20.8-31.8)	103	26.8% (22.6-31.4)	40	20.7% (15.6-27.0)	91	23.8% (19.8-28.3)	131	22.8% (19.5-26.4)
80+	11	20.0% (11.6-32.4)	38	27.1% (20.5-35.0)	49	25.1% (19.6-31.7)	15	20.6% (12.9-31.2)	41	23.6% (17.9-30.4)	56	22.7% (17.9-28.3)
All ages	128	22.5% (19.3-26.1)	215	21.4% (19.0-24.1)	343	21.8% (19.8-23.9)	135	19.2% (16.4-22.3)	227	18.2% (16.2-20.5)	362	18.6% (16.9-20.4)

The number and distribution of known and newly diagnosed DM is shown in **Table 7**. Among participants with known DM, 80.0% had a blood glucose level lower than 200 mg/dl [28].

Table 7. People with known and newly diagnosed diabetes and random blood sugar level in people with known diabetes [28].

		Males		Females		Total	
		N	%	N	%	N	%
All people with diabetes	Known diabetes	249	94.7	412	93.2	661	93.8
	Newly diagnosed diabetes	14	5.3	30	6.8	44	6.2
	Total	263	100.0	442	100.0	705	100.0
People with known diabetes	Blood sugar <200 mg/dl	192	77.1	337	81.8	529	80.0
	Blood sugar ≥200 mg/dl	57	22.9	75	18.2	132	20.0
	Total	249	100.0	412	100.0	661	100.0

We did not find any significant difference ($p \geq 0.05$) regarding regional disparities of blood sugar level ≥200 mg/dl and newly diagnosed DM between Western-, Central- and Eastern Hungary (**Table 8**) [29].

Table 8. People with known and newly diagnosed diabetes and random blood sugar level in people with known diabetes in the survey population in Western-, Central- and Eastern Hungary ($p \geq 0.05$) [29].

	Western Hungary		**Central Hungary**		**Eastern Hungary**		**P value**
	N	**%**	**N**	**%**	**N**	**%**	
Known diabetes	238	95.6%	172	93.0%	251	92.6%	0.331
Blood sugar <200 mg/dl	189	79.4%	144	83.7%	196	78.1%	0.347
Blood sugar ≥200 mg/dl	49	20.6%	28	16.3%	55	21.9%	0.347
Newly diagnosed diabetes	11	4.4%	13	7.0%	20	7.4%	0.331

Proportion of known and newly diagnosed DM was not different between rural and urban areas. Among people with known DM, 78.1% of rural- and 81.9% of urban

participants had a blood glucose level lower than 200 mg/dl (**Table 9**). Among known diabetic participants, the mean duration of DM was 9.9 years [standard deviation (SD) 9.0 years] among rural- and 11.4 years (SD 10.7 years) among urban participants, the difference was not significant between the two groups [30].

Table 9. People with known and newly diagnosed DM and random blood sugar level in rural and urban areas in the survey population in Hungary. Significant P values are ***bold.*** DM = diabetes mellitus [30].

	Rural *n* (%)	**Urban *n* (%)**	**P value**
People with known DM	320 (93.3%)	341 (94.2%)	0.619
Blood sugar ≥ 200 mg/dl	70 (21.9%)	62 (18.2%)	0.235
Blood sugar < 200 mg/dl	250 (78.1%)	279 (81.9%)	0.235
People with new DM	23 (6.7%)	21 (5.8%)	0.619

Of the participants with known DM, 447 (67.7%) were taking tablets, 102 (15.4%) used insulin, 57 (8.6%) were treated with both and 55 (8.4%) were not using any medical treatment (**Table 10**). We did not find any difference between participants with or without medical treatment regarding the blood sugar level. But significantly more participants had a blood glucose level higher than 200 mg/dl among people who were treated with insulin compared to patients treated with tablets (38.3% vs. 13.4%; $p<0.001$) [28].

Table 10. Treatment in people with known diabetes mellitus [28].

Treatment of diabetes	Males		Females		Full sample	
	N	%	N	%	N	%
No treatment	11	4.4%	10	2.4%	21	3.2%
Diet only	11	4.4%	23	5.6%	34	5.1%
Tablets	165	66.3%	282	68.4%	447	67.6%
Insulin	47	18.9%	55	13.3%	102	15.4%
Tablets+Insulin	15	6.0%	42	10.2%	57	8.6%
Other	0	0.0%	0	0.0%	0	0.0%
Total	249	100%	412	100%	661	100%

3.2.2. Participants without diabetes mellitus with random blood glucose between 140-200 mg/dl

Among participants without DM, 322 (9.1%) had a blood glucose level ≥ 140 mg/dl and < 200 mg/dl. The possible number of such prediabetic (preDM) patients in the Hungarian population was 380920 persons, with a 4.3% prevalence. We found an increasing tendency with age in the prevalence of preDM, 7.2% among people 50-59 years old, 9.5% in 60-69, 9.6% in 70-79 and 11.9% in 80+ years age groups [26].

3.2.3. Estimated number of people with diabetes mellitus in people aged 18 years and older

Based on our age- and sex- adjusted prevalence of DM value among persons aged 50 years and older and considering the earlier published Hungarian DM age distribution data [31], the number of people with DM was estimated to be 807885, and the DM prevalence was 9.9% in the adult population of Hungary [26].

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3.3. Diabetic retinopathy screening coverage

Of the participants with known DM, 302 (45.7%) had an ophthalmological examination for DR once during the past 12 months, 66 (10.0%) 13–24 months ago, 112 (16.9%) more than 24 months ago, and 181 (27.4%) had never had an eye examination (**Table 11**) [28].

Table 11. Last eye examination for diabetic retinopathy among people with known diabetes mellitus [28].

Last eye examination	**Males**		**Females**		**Full sample**	
	N	**%**	**N**	**%**	**N**	**%**
Never	83	33.3%	98	23.8%	181	27.4%
0-12 months ago	104	41.8%	198	48.1%	302	45.7%
13-24 months ago	18	7.2%	48	11.7%	66	10.0%
>24 months ago	44	17.7%	68	16.5%	112	16.9%
Total	249	100%	412	100%	661	100%

Proportion of participants who never had a fundus examination for DR was significantly (p=0.01) lower in Middle-Hungary (19.1%) compared to Western- (29.0%) and Eastern Hungary (31.5%) (**Figure 4**) [29].

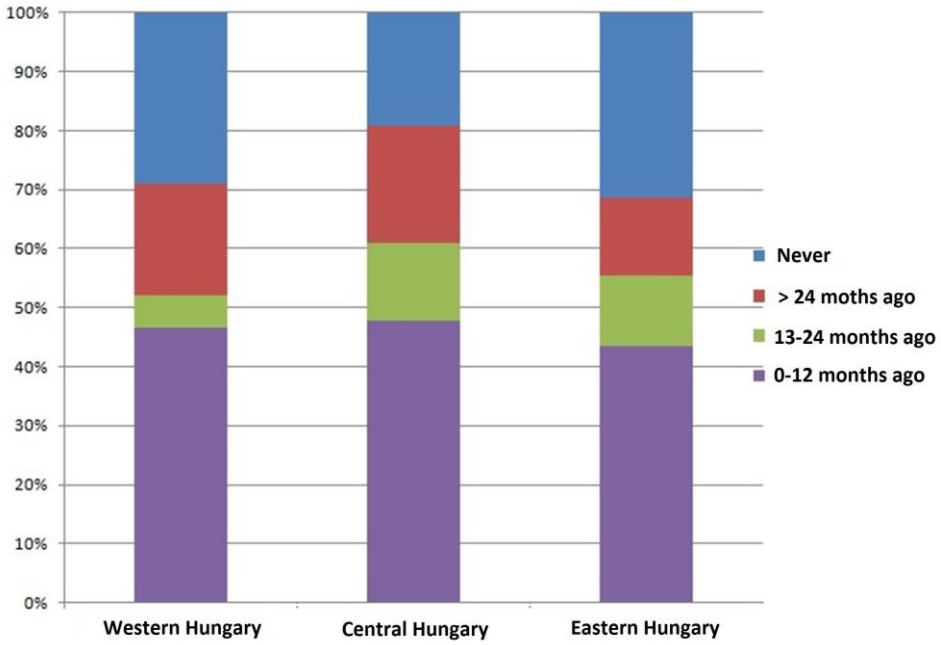

Figure 4. Regional disparities of last fundus examinations among people with known diabetes mellitus [29].

People who were living in urban areas were singificantly more likely (p=0.007) to have a fundus examination in the past 12 months for DR compared to those living in rural areas and significantly more participants (p=0.002) had never had a fundus examination for DR in rural than in urban areas (**Figure 5**) [30].

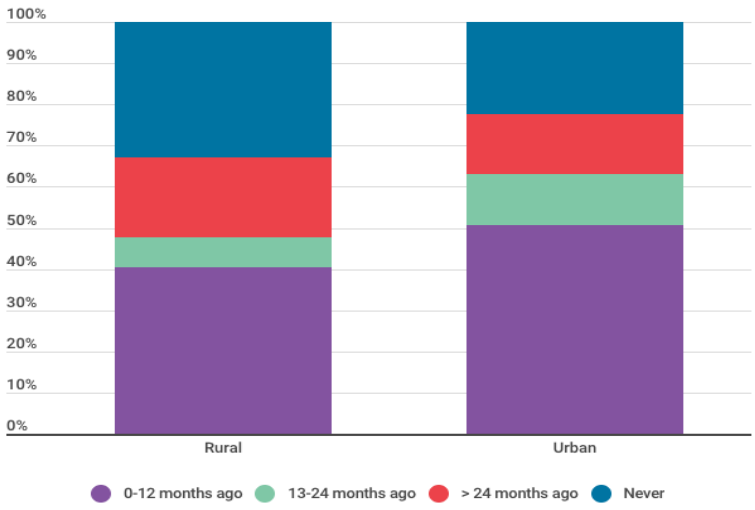

Figure 5. Rural-urban disparities of last fundus examinations among people with known diabetes mellitus.

3.4. Diabetic retinopathy and maculopathy in people aged 50 years and older

Of the 705 participants who had DM (known and new cases), 561 (79.6%) agreed to have a fundus examination. Among them, 142 [20.1% (16.4 to 23.9)] showed any sign of DR, and 56 [7.9% (5.7 to 10.2)] showed any sign of DMP. The remaining 144 participants (20.4%) did not agree to pupil dilatation and fundus examination. Prevalence of any DR and/or DMP was 20.7% (16.9 to 24.5) in people with DM (**Table 12**). Prevalence of DR was 4.0% (3.3–4.8) among all participants [28].

Prevalence of DR and/or DMP was slightly higher among males in every age group, but the difference was never significant. We found an increase of the prevalence of DR by age (**Table 13**), from 16.9% and 16.5% prevalence rates of DR in the age groups of 50-59 years and 60-69 years, respectively, increased to 20.9% in the age group of 70-79 years and to 23.8% in the age group of 80+ years [26].

Altogether, 28 of the participants with known DM [4.0% (2.7–5.2)] had any retinal laser treatment previously [28].

Sight-threatening DR [STDR; R4 (proliferative retinopathy) and/or M2 (referable DMP)] was seen in 30 [(4.3% (2.8 to 5.8)] patients with DM. Prevalence of STDR was 0.9% (0.5–1.2) among all participants [28].

Out of 30 participants with STDR, 18 (60%) had had a fundus examination in the past 12 months, two (6.6%) had had one between 12 and 48 months ago, nine (30%) had had one more than 48 months ago, and one (3.3%) had never had a fundus examination [28].

DR was not significantly different among patients with known DM who were taking medical treatment compared to those who were not (22.2% vs. 9%; p=0.21). DR was even commoner among participants who were taking insulin compared to those who were taking only tablets (37.1% vs. 17%; p<0.001) [28].

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Table 12. Prevalence of diabetic retinopathy in participants with diabetes and in the survey population in Hungary. DR = diabetic retinopathy. *Proliferative retinopathy (R4), referable maculopathy (M2), or both [28].

		Among participants with diabetes	**Full sample**
	N	**% (95% CI)**	**% (95% CI)**
DR grade			
No DR (R0)	419	59.4% (54.9-64.0)	11.9% (10.6-13.2)
Background DR – mild (R1)	105	14.9% (11.7-18.1)	3.0% (2.4-3.6)
Background DR – observable (R2)	10	1.4% (0.6-2.3)	0.3% (0.1-0.5)
Background DR – referable (R3)	10	1.4% (0.5-2.4)	0.3% (0.1-0.5)
Proliferative DR (R4)	10	1.4% (0.6-2.3)	0.3% (0.1-0.5)
Ungradable (R5)	7	1.0% (0.3-1.7)	0.2% (0.1-0.3)
Any retinopathy	**142**	**20.1% (16.4-23.9)**	**4.0% (3.3-4.8)**
Maculopathy grade			
No maculopathy (M0)	505	71.6% (67.4-75.9)	14.3% (13.1-15.6)
Maculopathy – observable (M1)	24	3.4% (1.4-3.7)	0.7% (0.3-0.9)
Maculopathy – referable (M2)	32	4.5% (2.2-4.9)	0.9% (0.4-1.2)
Any maculopathy	56	7.9% (5.7-10.2)	1.6% (1.1-2.0)
Any retinopathy and/or maculopathy	**146**	**20.7% (16.9-24.5)**	**4.1% (3.4-4.9)**
Sight threatening DR* (R4 and/or M2)	**30**	**4.3% (2.8-5.8)**	**0.9% (0.5-1.2)**
Any laser scars	28	4.0% (2.7-5.2)	0.8% (0.5-1.0)

Table 13. Prevalence of any diabetic retinopathy and/or maculopathy by age and gender.

Age groups (years)	Males		Females		Full sample	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
50-59	12	22.6% (11.8-33.5)	8	12.3% (3.6-21.0)	20	16.9% (9.8-24.1)
60-69	18	17.5% (9.0-25.9)	23	15.9% (10.0-21.7)	41	16.5% (11.8-21.3)
70-79	21	25.9% (15.6-36.3)	28	18.3% (10.4-26.2)	49	20.9% (14.8-27.0)
80+	9	34.6% (15.6-53.6)	16	20.3% (10.4-30.1)	25	23.8% (15.0-32.6)
All ages	60	22.8% (17.5-28.1)	75	17.0% (12.7-21.2)	135	20.7% (16.9-24.5)

We did not find any important difference between participants who agreed (561; 79.6%) and who did not agree (144; 20.4%) to pupil dilatation and fundus examination. Average age was 68.9 years (SD 9.1 years) among dilated participants and 69.2 years (SD 10.1 years) in patients who did not undergo pupil dilatation. Altogether 35.4% of the non-dilated participants were male and 64.6% of them were female as well as 37.8% and 62.2% of dilated patients, respectively. Pinhole corrected visual acuity (PCVA) in 87.5% of the participants in both groups was better than 0.3. Only one patient (0.7%) in the non-dilated group and 9 participants (1.6%) in the dilated group had a PCVA worse than 6/60 [severe visual impairment (VI) or blindness]. Primary cause of visual impairment at the only one participant with DM who refused the dilatation was glaucoma [28].

No significant difference was found regarding prevalence of DR between Western-, Central- and Eastern Hungary (**Table 14**) [29].

Table 14. Proportion of participants who refused and underwent fundus examination, as well as prevalence of diabetic retinopathy in diabetic pepole in Western-, Central- and Eastern Hungary. DM = diabetes mellitus; DR = diabetic retinopathy [29].

	Western Hungary		**Central Hungary**		**Eastern Hungary**	
	N	**%**	**N**	**%**	**N**	**%**
Participants with DM who refused fundus examination	39	15.7%	49	26.5%	56	20.7 %
Participants with DM who underwent fundus examination	210	84.3%	136	73.5%	215	79.3%
RD	**60**	**24.1%**	**33**	**17.8%**	**53**	**19.6%**
No DR	150	60.2%	103	55.6%	162	59.8%

Significantly more participants with DM have refused fundus examination in rural- than in urban areas (p=0.002) (**Table 15**). DR was significantly more common among urban than rural subjects (p=0.015). There was not significant difference between the areas for prevalence of STDR and/or M2 in people with DM [30].

Table 15. Refusal rate of fundus examination, as well as prevalence of DR and/or DMP and STDR in rural and urban areas in diabetic persons in Hungary. DR = diabetic retinopathy, DMP = diabetic maculopathy, STDR = sight-threatening diabetic retinopathy [30].

	Rural *n* (%)	**Urban *n* (%)**
Refused fundus examination	86 (25.1%)	58 (16.0%)
DR and/or DMP	58 (16.9%)	88 (24.3%)
STDR	16 (4.7%)	14 (3.9%)

3.5. Blindness, severe, moderate and early visual impairment due to diabetes

The prevalence rates of blindness and severe VI in participants with DM were 1.0% and 0.6%, respectively, compared with 0.9% and 0.5%, respectively, among persons without DM aged ≥50 years **(Table 16**). The mean age was 70.5 years (SD 13.7 years) of blind participants with DM and 77.8 years (SD 11.2 years) among blind participants aged ≥50 years without DM, representing a statistically non-significant difference. Normal vision was significantly more common among people without DM compared to people with DM (p=0.017) [26].

Table 16. Prevalence of early-, severe- and moderate visual impairment, as well as blindness among people with and without diabetes in the full survey population in Hungary. VI = visual impairment [26].

	Persons with diabetes		**Persons without diabetes**		**p**
	N	**% (95% CI)**	**N**	**% (95% CI)**	
Normal vision	583	82.7% (79.8-85.6)	2430	86.2% (84.7-87.7)	**0.017**
Early VI	61	8.7% (6.7-10.6)	202	7.2% (6.1-8.2)	0.179
Moderate VI	50	7.1% (5.2-9.0)	147	5.2% (4.3-6.1)	0.052
Severe VI	4	0.6% (0.0-1.1)	13	0.5% (0.2-0.7)	0.716
Blindness	7	1.0% (0.3-1.7)	26	0.9% (0.6-1.2)	0.862

Most frequent causes of blindness were DR, cataract and other posterior segment diseases (OPSD) in people with DM as well as OPSD (76%) among persons without DM (**Table 17**). The term "OPSD" was used for any other retinal diseases besides DR (most frequent diseases were age-related macular degeneration, glaucoma, myopic degeneration, rhegmatogenous retinal detachment and central retinal vein occlusion). "Other eye diseases" was used for phthisis and cataract complications. Two (0.3%) participants with DM were blind due to DM (PCVA<3/60] and 10 (1.4%) patients with DM had any visual impairment (PCVA <6/18 and ≥3/60) in people aged ≥50 years with DM [26].

Significantly more people (p=0.048) with DM were blind (PCVA) <3/60) in rural [6 (0.9%)] than in urban [1 (0.1%)] areas. Blindness due to DM in people with DM was significantly more common (p=0.021) in rural- [2 (0.3%)] than in urban areas [0 (0%)] too [30].

Table 17. Primary causes and prevalences of visual impairment among people with and without diabetes in the full survey population in Hungary. DM = diabetes mellitus, VI = visual impairment [26].

	Blindness				**Severe VI**				**Moderate VI**				**Early VI**			
	DM		**Non-DM**		**DM**		**Non-DM**		**DM**		**Non-DM**		**DM**		**Non-DM**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Refractive error	0	0	0	0	0	0	0	0	10	20	37	25	19	31	88	43
Cataract	2	28	5	19	0	0	6	46	24	48	74	50	29	47	83	41
Diabetic retinopathy	2	28	0	0	2	50	0	0	3	6	0	0	5	8	0	0
Other posterior segment diseases	2	28	20	76	2	50	4	30	8	16	27	18	5	8	20	9
Other eye disease	1	14	1	3	0	0	3	23	5	10	9	6	3	4	11	5
Total	**7**	**100**	**26**	**100**	**4**	**100**	**13**	**100**	**50**	**100**	**147**	**100**	**61**	**100**	**202**	**100**

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4. Discussion

We observed that the prevalence of DM was 20.0% in people aged 50 years and older and estimated 9.9% with a number of people with DM 807885 in the total adult population in Hungary in 2015 (8160454 inhabitants). Prevalence of DR was 20.7%, and prevalence of STDR was 4.3% among diabetic participants in persons aged 50 years and older [26,28]. Additionally, the prevalence of blindness among persons with DM was 1.0% in persons aged 50 years and older in Hungary in 2015. DR was responsible for 28% of blindness and 50% of severe VI in people with DM aged ≥50 years [26]. Almost one-third of people with known DM have never had a fundus examination for DR [28]. DR screening coverage was the highest in Central Hungary [29]. Prevalence of DM was higher, prevalence of DR was lower, and DR screening coverage was lower in rural than in urban areas in Hungary among people aged 50 years and older [30].

As far as we know, our RAAB + DRM study was the first population-based survey on DM and DR in Hungary and the first RAAB with DRM in the European Union [26,28-30,32-37]. Prevalence of DM and DR in people older than 50 is even more important because prevalence of blindness and severe VI is the highest in this population. Prevalence of undiagnosed DM is debated, because exact diagnostic procedures are expensive and time consuming [26].

In our present study, a 20.0% prevalence of DM was found in the Hungarian population aged 50 years and older [28]. Earlier RAAB with DRM studies with the same method and in the same age groups from America and the Middle East reported slightly higher (ranged from 21.0% to 29.7%) [16,24,25,38,39] DM prevalence values than ours (20.0%). It is known that prevalence of DM is very high in the countries of the Middle East [4]. In Moldova, the geographically closest country, the prevalence of DM among people aged 50 years or older was relatively low (11.4%) [19].

Our DM prevalence values were similar (18.7% vs. 18.1%) in age group 55–64 and lower in age group 65–74 as well as in the 75 and older age group (22.1% vs. 27.4% and 24.2% vs. 27.7%, respectively) compared to the data of the Hungarian Central Statistical Office (HCSO) in 2013 (not reported database of HCSO based on general practitioners (GP) database). Overall, our prevalence value was slightly lower

(20.4%) than in the HCSO data (24.9%) in people 55 years and older. Our DM prevalence values in the corresponding age groups were lower than the recently published Hungarian results by Domján [31] (18.7% vs. 24.1%) in the age group 55-64 years and in the age group 65-74 years (22.1% vs. 26.2%) but was higher in age group 75+ (24.2% vs. 22.5%).

There was an increasing tendency from the 13% prevalence of DM in the age group of 50–59 to 20.4% (60–69), 24.4% (70–79), and 23.8% (80+), respectively. The increasing prevalence of DM in older age groups is well-known, and our results are consistent with findings of Shaw et al [4].

About 80% of all people with DM live in low- and middle-income countries [22]. Primary care should be improved mostly in developing countries, to enhance the ratio of diagnosed DM. Of all participants with DM, 93.8% were aware that they have DM in Hungary, which is higher than in other RAAB + DRM surveys (ranged from 80% to 89.6% [16,19,24,25,38]. The higher awareness in Hungary might be in connection with the fact that high quality primary care is available in the entire country and also shows that health provision works well. Only 20.0% of participants with known DM had a blood glucose level higher than 200 mg/dl, which was definitely low compared to other RAAB + DRM surveys (ranged from 40% to 73% [16,19,24,25,38,39]. Modern, available treatment methods, effective secondary prevention may help to reduce high blood glucose level. Patients who were treated with insulin had more common a blood sugar levels higher than 200 mg/dl compared to those who were taking tablets. Maintaining satisfactory blood glucose level, specially HbA1C level, is important for preventing DR [40].

There are no exact national data about prevalence of DM among people older than 50 in Europe. Due to differences in methodologies, comparisons between results are not easy. Surveys from the geographically nearest countries with similar socioeconomic environments reported lower prevalence of DM than regional European data (20–79 years) (8.8%) [5]. From Central-Europe, a Slovakian study reported 7.0% in 2005 (among people over 18 years of age) [41], and a Croatian survey reported 6.1% in 2008 (between ages 18–65) [42] in its adult population.

Several earlier studies can be found about prevalence of DM in Hungary, but these surveys are not population-based, not current, or only small-sample. Vamos et al.

[17] reported a 6.2% (≥18 years) prevalence of DM in 2002, based on self-reported diagnosis of DM, in a sample of 12643 adults. Jermendy et al. [18] reported 8.6% prevalence of DM in the age group of 20–69 years old in Hungary in 2010, based on data collected from selected GPs from eight selected counties in a sample of 1803 subjects. An estimation based on the database of the National Health Insurance Found on the prescribing patterns of glucose lowering drugs stated that the number of registered people with DM type 2 was 727000 in Hungary in 2014 with a prevalence rate of 7.3% in the entire population [43,44].

However, the prevalence of DM is growing yearly, and only several up-to-date data are available about the prevalence of DM in Hungary, but these studies comprise only small samples [31] or did not cover all age groups [28]. According to our result [28], with a larger sample size and a standardized population-based survey method, the DM prevalence in the adult population of Hungary was estimated to be 9.9% in 2015, a value that was lower than Domján's 11.7% in 2012 [31]. Our data represent a 59% DM prevalence increase since 2002 compared with Domján's estimation (89%) [17, 31].

According to Domján et al., 10.1% of all people with DM are under 50 years of age [31]. When we calculate with Domján's prevalence distribution and or prevalence value, the estimated number of adult people with DM in Hungary was 807885 in 2015. If we calculate Domján's values in the entire adult population, the estimated number should have been 953325 in 2012, a value that is notably higher (18% difference) than our calculated value. Differences may be explained by several factors. Domjan's data were based on telephone interviews [31], while ours was a population-based survey [28]. In Domján's paper, the sample size was low compared with ours (1000 vs 3675, respectively), their data were 3 years earlier than ours (2012 vs. 2015), and geographical coverage was not reported while our survey covered representatively the entire country. In total, the 62.5% landline phone penetration rate, the unreported answer-seizure ratio and 23.2% refusal rate have a much larger bias in the results than our 4.1% rate of non-participation. Domján's unknown rate vs. our 6.2% undiagnosed DM, as well as possible different definitions of DM (pure self report vs. partially self report with random blood glucose level measurement) may also distort the results [28,31]. The last possible cause why we found lower number of patients with DM than Domján might be also connected to our method: only one random glucose measurement and the

possibility that RAAB + DRM methodology might have low sensitivity to discover undiagnosed DM subjects in the population [26].

Based on earlier experiences from Hungarian diabetic and ophthalmic practices, it is supposed and there are some anecdotal mentions that the number of undiagnosed DM might be as high as the number of known DM patients in Hungary or at least half of them. In opposition to these earlier anecdotal mentions, the results of the Hungarian RAAB + DRM population based survey showed that the proportion of newly diagnosed (unknown) DM in Hungary was found to be only 6.2% of all people with DM. The reason of the great difference might be due to the fact that the RAAB + DRM study used only one random glucose measurement. Because of the strict criteria of newly diagnosed DM (random blood glucose level 200 mg/dl or higher) the real proportion of subjects with undiagnosed DM might be underestimated. Thus we intended to analyse also people with random glucose level between 140 and 200 mg/dl to possibly identify some of the other portions of unknown DM in our study population. If we regard our random blood sugar level results similar, as status following oral glucose tolerance test (OGTT), an additional 9.1% of our survey population had preDM. We might consider that those who were tested by random glucose measurement around 2 hours after their eating (breakfast or lunch), they possible did intake similar dose of carbohydrates as during the OGTT official test procedure, because an average breakfast or an average lunch (in Hungary or in Europe) contains around 47-78 g carbohydrates and 70-130 g carbohydrates, respectively, while during the official OGTT test the intake is 75 g glucose [26,45,46]. We think that one portion of those with random blood glucose level between 140 and 200 mg/dl might be persons with impaired glucose tolerance (IGT) or preDM and some other portion might be diabetic patients, especially those who did not eat before the random glucose test sampling. People with preDM have a higher risk of developing DM. Some of these participants have presumably not only preDM, but DM. These cases of DM could be verified with standardized OGTT. For this reason prevalence of undiagnosed DM in the survey population may be higher than 1.2%, as we earlier reported among people aged 50 years and older, and its prevalence is estimated to be between 1.2-10.3% in this age group. This means that estimated number of adult people with DM in Hungary should be between 807885 and 1188805, and

prevalence of DM should be between 9.9% and 14.2% in the adult population of Hungary, which can already exceed Domján's 11.7% [31].

Rural-urban difference in prevalence of DM is important to assess the needs and deficiencies of healthcare system in different types and sizes of settlements. It is known, that prevalence of DM is higher in areas of low socioeconomic status [47]. Prevalence of DM, in rural areas of developing countries is estimated to be higher than in urban areas [48]. On the other hand an earlier Nigerian study reported almost ten times higher urban (7%) than rural (0.6%) DM prevalence value [49]. Other RAAB + DRM surveys reported also higher urban than rural DM prevalence from developing countries too [24,25]. Rural and urban DM prevalence are considered similar in developed countries, because risk factors do not differ markedly [50]. A study from the USA reported higher rural than urban prevalene of DM (9.7% vs 9.0) in 2012 [7]. So, the results are contradictory which may be explained with different survey methods, social structure and pattern of settlements as well as with different rural-urban definitions. Therefore comparisons between results are not easy. Data on rural-urban disparities from developed countries, especially from Central and Eastern Europe are rare.

In Moldova, the geographically closest country, the prevalence of DM was higher in urban (13.5%) than in rural (10.3%) areas in people aged 50 years and older [19]. An earlier Hungarian survey, from 2002 reported similar DM prevalence data among adults in rural and in urban areas (6.2% vs. 6.1%) [17]. We found significantly higher prevalence of DM in rural (21.8%) than in urban (18.6%) areas among people aged 50 years and older in Hungary. The difference may be explained with the special socioeconomic characteristics of Hungary. Since of the fall of the communist economic system in 1989, Hungary has experienced meaningful social and economic progress, as well as changes in settlement structure and migration patterns. Due to the collaps of collective farming and the decline of heavy industry, essential changes took place in the Hungarian society. The impoverished, unskilled urban labour migrated to rural areas because of the lower cost of living, while young, skilled workers tended to migrate to urban areas because of the lack of rural job opportunities. New business investments are mostly implemented in urban setting [51]. As a result, people to rural areas usually have lower income and worse living conditions in Hungary [52]. Rural-urban migration or immigration into Western-Europe of younger people has even increased since 2004,

when Hungary became a member of the European Union [53]. These circumstances are contributing to concentration of unskilled, unemployed people, increasing of unemployment rate and aging of the population in rural areas in Hungary [54]. Such living conditions and lower level of subjective well-being are associated with high-calorie diet, poor nutrition, obesity and tobacco use, as well as may contribute to higher rate of DM prevalence in rural areas [29].

An important finding in terms of diabetic eye care programs in Hungary could be that 27.4% of people with known DM participants never had a fundus examination and 16.9% of them had it more than 2 years ago. Only around half of the participants with known DM had an eye examination in the past year, which is the basic requirement of the Hungarian national guidelines for all patients with DM. That is why better-organized primary eye care or a national screening program (e.g., telemedicine services) would be necessary to increase screening coverage in the entire country, providing equal access countrywide. Furthermore, telemedical eye-screening programs would be cost effective possibilities for supporting primary eye care and they could decrease the financial burden of DM [55]. However, there was no significant difference regarding DM or DR between Western-, Central- and Eastern Hungary, DR screening coverage was higher in Central- compared to Western and Eastern Hungary, thus proportion of participants who never had a fundus examination for DR was the lowest in Middle-Hungary (19.1%). According to the rural-urban disparities, 32.8% of rural and 22.3% of urban people with DM never had a fundus examination. Only 40.3% of rural and 50.7% of urban participants with known DM had an eye examination in the past year. Lower rural than urban diabetic and other regional disparities in screening coverage can be explained with limited availability of eye care services and long appointment waiting lists in rural areas. Possibly, ophthalmological consultations or examinations are more accessible in urban areas and larger cities, than in rural settlements. For these reasons, for equal or at least available primary care services, primary eye care should be improved, especially in rural areas in Hungary.

According to our survey, the prevalence of any sign of DR, DMP, and DR plus DMP was 20.1%, 7.9%, and 20.7%, respectively, in people with DM aged 50 years and older.

As Yau reported, 34.6% of all people with DM in the world have some form of DR [8]. Prevalence of DR among participants with DM was lower in Hungary (20.1%) compared to the results of RAAB + DRM surveys from other countries (Saudi Arabia: 27.8% and 34.5% [16,38]; Mexico: 38.9% [24]; Jordan: 48.0% [39]; Moldova: 55.9% [19]. These data are consistent with expectations because DR prevalence is higher in low-income and middle-income countries [22]. There are several explanations for the rarer complications of DM in developed countries. Evidences suggest, that existing structure of healthcare systems, newest medications, early effective intervention possibilities and healthy lifestyle are involved in better prevention and higher reduction of diabetes-related complications in developed countries [40], Higher awareness of DM might also contribute to the lower level of eye complications in Hungary. Mexico refutes this statement, however Chiapas (as Polack reported [24] is one of the poorest states of Mexico.

Schneider et al. [21] reported a far higher prevalence of DR (60.2%) among patients with DM in Hungary than our current findings. The weakness of their study is that it estimates the prevalence of DR in people with DM visiting clinics; therefore, it overestimates the prevalence.

With further examination, we found an increasing tendency with age. This could be explained by the well-known phenomenon that a longer duration of DM is associated with the higher existence of DR [24].

DR is one of the leading causes of blindness and severe visual impairment among middle-aged people worldwide [8]. However, the risk of vision loss due to DR and DMP can be reduced with continuous control of blood glucose level, regular ophthalmological examinations (at least once a year), and timely and effective treatment.

According to Domján's data, 89.9% of patients with DM type 2 are older than 50 years [31]. For these reasons, the prevalence of blindness due to DR has a higher importance among patients over 50 years of age. Among them, the prevalence rates of blindness, severe, moderate and early VI were tendentially higher in people with DM than in people without DM.

In our study, 4.3% of participants with DM and 0.9% of all survey subjects had sight-threatening DR. Fortunately, the proportion of STDR was clearly lower (4.3%)

than in other RAAB with DRM studies (ranged from 5.7% to 21% [16,19,24,25,38,39]. Sixty percent of STDR patients had a fundus examination in the past 12 months, and 30% of patients with STDR hadn't had an ophthalmological examination in the past 48 months.

Patients who were taking medical treatment had significantly more DR and participants who were using insulin even more significantly.

We found higher DR prevalence in urban (24.3%) than in rural (16.9%) areas. This result may seem illogical regarding to the higher rural DM prevalence. However, emergence of DR is multifactorial and depends on several factors. Inadequate control of blood sugar, blood pressure, triglycerides, cholesterol and microalbuminuria increases the risk of development of DR [56]. Irregular follow-up eye examinations, insulin use, DM duration and HbA1c level are well-known risk factors too [57]. Different DR prevalence values were reported between different ethnicities, it was the highest among Afro-Americans and lowest among Asians [8]. Lower socio-economic status and deprivation are associated with increased prevalence of DR [58]. As Ruta reported, DR prevalence is higher in developing countries and among minority groups in developed countries [22]. However, the reported results and risk factors are contradictory, as well as comparisons between studies due to different survey methods, screening techniques (indirect ophthalmoscope or digital photography) and population characteristics are difficult [8], Some studies reported a continuously increasing DR prevalence due to aging and increasing rate of obesity [59]. On the other hand several surveys reported a decrease in prevalence of DR due to modern diabetic and ophthalmic treatment methods [60].

DR may be influenced by several, less examined factors, including healthcare, behaviour, biology and attitude [61]. The higher urban than rural DR prevalence in Hungary may be attributed to other circumstances. More rural (25.1%) than urban (16.0%) participants with DR had refused pupil dilatation and fundus examination. The blood glucose level was not significantly different between the two groups, but we were not able to examine the HbA1c level which would be more suitable indicator for inconvenient treated DM. Difference in hypertension prevalence, treatment regimens, availability of primary care (e.g. earlier diagnosis of DM in rural areas), patient compliance, lifestyle and environmental effects may contribute to our findings [62].

Only 28% of blind patients with DM and 0.3% of all people with DM were blind due to DM. However, DM enhances not only blindness among people with DM but also cataract and OPSD. Blindness due to OPSD was more common in people without DM than in people with DM. However, it does not mean that prevalence of OPSD is higher in people without DM compared to persons with DM, but the main cause of blindness, which is not related to DM. The blindness prevalence in people with DM in Hungary was lower (1.0%) than that in other RAAB + DRM surveys (Moldova: 1.6% [19]; Suriname: 1.9% [25]; Saudi Arabia: 2.3% [16]; Mexico: 4.5% [24]. DR is one of the main causes of avoidable blindness and severe VI in the working-age population in developed countries [8]. Nevertheless, the risk of visual impairment due to DM could be decreased by regular control of the blood sugar level and at least annually performed ophthalmological examinations [11]. A well-functioning healthcare system and early modern treatment methods are essential in the prevention of DM-related complications. We have to draw the attention to the importance of regular eye examinations because almost every third patient with known DM never had an ophthalmological examination for DR and did not receive appropriate eye care in Hungary [28]. Patients who were not screened for 3 years or more have a 4-fold larger risk for proliferative DR. The rate of uncontrolled people might be similar to other established economy countries in Europe where systemic telemedical screening has not been introduced yet [63].

We did not find a difference regarding to STDR between ural and urban areas. But interestingly, rural participants with DM were blind significantly more common compared to urban subjects and rural people with DM were even more common blind due to DM. This result strengthens the recommendation too, that diabetic eye screening coverage should be increased first of all in rural areas to decrease the prevalence of avoidable blindness in rural settlements.

Limitations of this study include that diagnosis of newly diagnosed DM based only on one random measurement of blood glucose, as well as fundus examination was performed only with a binocular indirect ophthalmoloscope, and these may have underestimated the prevalence of DM and DR, respectively. Hereafter, the survey did not include people aged under 50 years of age. Our survey's most important limitation was that 20.4% of participants with DM did not undergo fundus examination, because they refused the pupillary dilatation. Consequently, they are considered not to have any

DR and therefore this may cause an under-estimation of the prevalence of DR in patients with DM. However, we did not find any significant difference between dilated and non-dilated participants and there was not any considerable visual impairment among non-dilated participants due to DM. Moreover, the 20.4% refusal rate was lower than in RAAB + DRM surveys in Taif, Saudi Arabia (28%) [16], but higher than in Mexico (18%) [24] or in Moldova (1%) [19]. Most common causes of the refusal of the pupillary dilatation were: need to drive a car, fear of blurred vision, activity after the eye examination or the participant had already had a retinal examination within a short period of time [37].

Strengths of this study are that it included a nationally representative sample, members of the survey teams were well-trained and well as quality was always and important basic requirement during the implementation of the study according to the international well-accepted RAAB + DRM method [16,19,24,25].

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5. Conclusions

Our studies aimed to estimate the prevalence of DM and diabetes-related eye complications in Hungary.

The estimated prevalence of DM was in line with findings of other RAAB + DRM surveys and slightly lower than those recently published for the adult population of Hungary. However, if we extend our estimation, prevalence of undiagnosed DM may be higher and thus prevalence of DM may reach a higher value, even up to 14.2%.

Prevalence of DR in people aged older than 50 years was slightly lower than expected. Optimizing the availability of eye care would be essential to decrease the high proportion of uncontrolled ophthalmological effects of DM. Primary prevention, as well as collaboration among primary eye care doctors, diabetologists, and ophthalmologists should be intensified to increase eye-fundus screening activity and follow-up of patients to decrease the prevalence of STDR and DR-induced blindness. Improving the availability of eye care – especially in rural areas – would be essential to prevent and avoid blindness caused by DM. Human resource needs and costs could be decreased and efficiency of telemedical reading centers could be improved by development of automated image analysing softwares. Due to the large number of DM patients, there is an urgent need for the start of a nationwide, well-organized, and financed telemedical eye-screening program.

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6. Summary

Our RAAB with DRM survey was conducted by the Department of Ophthalmology of Semmelweis University between April and July 2015 in Hungary. We estimated the prevalence of DM, DR and diabetes-related blindness in Hungary.

Seven hundred five (20.0%) out of 3,523 had known (661) or newly diagnosed DM (44) in the participants aged 50 years and older. The estimated number of people with DM was 807885 in the adult (≥ 18 years) population in Hungary with 9.9% prevalence.

Prevalence of DM was higher in East-Hungary (20.9%), than in West- (19.5%) and in Middle-Hungary (19.5%). Prevalence of DM was higher in rural (21.8%) than in urban (18.6%) areas (p=0.016).

Prevalence of DR and/or DMP was 20.7% and prevalence of STDR was 4.3% in one or both eyes among participants with DM. Prevalence of DR was higher in West-Hungary (24.1%), than in Middle- (17.8%) and in East-Hungary (19.6%). Prevalence of DR was higher in urban (24.3%) compared to rural (16.9%) areas (p=0.015).

The prevalence rates of blindness and severe VI in people with DM aged ≥50 years were 1.0% and 0.9%, respectively. DR was responsible for 28% of blindness and 50% of severe VI among participants aged ≥50 years with DM.

The estimated prevalence of DM was in line with findings of other RAAB + DRM surveys and slightly lower than those recently published for the adult population of Hungary. However, if we extend our estimation, prevalence of undiagnosed DM may be higher and thus prevalence of DM may reach a higher value, even up to 14.2%.

Prevalence of DR in people aged older than 50 years was slightly lower than expected. Optimizing the availability of eye care would be essential to decrease the high proportion of uncontrolled ophthalmological effects of DM. Primary prevention, as well as collaboration among primary eye care doctors, diabetologists, and ophthalmologists should be intensified to increase eye-fundus screening activity and follow-up of patients to decrease the prevalence of STDR and DR-induced blindness. Due to the large number of DM patients, there is an urgent need for the start of a nationwide, well-organized, and financed telemedical eye-screening program.

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8. Bibliography of the candidate's publications

8.1. Thesis related publications

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