• Investigation •

Relationship between diabetes mellitus and cataract in Hungary

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Abstract

● **AIM:** To examine the coexistence of diabetes mellitus (DM) and cataract in Hungary. The effects of DM on the cataract surgical results were also in the focus of analysis.

● **METHODS:** Statistical data analysis of the results of the Rapid Assessment of Avoidable Blindness with Diabetic Retinopathy (RAAB+DR) module conducted in Hungary in 2015. This cross-sectional, population-based, national survey included 3523 people aged 50 years and over. Participants of the survey were examined on-site. Visual acuity, main cause for visual impairment (using direct and indirect ophthalmoscopes), in case of best corrected visual acuity (BCVA) ≤0.5 and blood glucose level (random test with glucometer) were examined.

● **RESULTS:** The prevalence of cataract was 23.4%, and DM was 20.0%. The occurrence of cataract steadily increased with age. Among the examined participants with DM, the prevalence of cataract was significantly (P=0.012) higher (+35%) than that in non-diabetic subjects (29.5% *vs* 21.8%). Following aging (OR=15.2%, P<0.001), DM proved to be the most independent influencing risk factor (OR=49.9%, P<0.001). The presence of DM was neither an influencing factor for complications of cataract surgery, nor for postoperative visual acuity.

● **CONCLUSION:** DM appears to be one of the main risk factors for developing cataract. Other risk factors, such as age, sex and environment also play an influencing role. Diabetes does not seem to affect the occurrence of cataract surgical complications.

● **KEYWORDS:** cataract; diabetes mellitus; Rapid Assessment of Avoidable Blindness
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INTRODUCTION

Cataract is the leading cause of visual impairment and shows an increasing trend worldwide[1]. It is responsible for one out of three cases of blindness and for every sixth case of moderate to severe visual impairment[2]. According to estimations, approximately 3.2 billion international dollars (on US purchasing power parity) would be needed annually to cover global cataract surgical costs[3] at just 80% of necessary cataract surgery coverage.

Cataract is a multifactorial disease, in which diabetes mellitus (DM) is one of the important determinants. Scientific research has revealed a causal biochemical relationship between DM and cataract development[4-6]. However, statistical results on the topic have been mixed so far, despite the increasing prevalence of DM worldwide[7].

Our research group's aim was to analyse the coexistence of DM and cataract in the elderly population, based on survey data gathered through a national Rapid Assessment of Avoidable Blindness survey with Diabetic Retinopathy module (RAAB+DR). Specific possible influencing factor, such as the current blood sugar level was analysed. The correlations between DM and cataract surgical complications and postoperative visual acuity were also studied.

SUBJECTS AND METHODS

Ethical Approval The Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (Budapest, Hungary) granted approval for this study. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Our study was based on the national RAAB+DR survey performed by Semmelweis University in Hungary between

April and July 2015, a global initiative with standardised protocol consisting of a questionnaire (on ophthalmological history and possible DM) and on-site examinations. The latter included visual acuity assessment with simplified Snellen chart, direct/indirect ophthalmoscopy and finger-prick random blood glucose testing using a digital glucometer (Dcont® Trend, 77Elektronika Kft., Hungary). In case of best corrected visual acuity (BCVA) ≤0.5, the main cause for visual impairment was determined. Five teams of one senior resident or a specialised ophthalmologist, one nurse and one assistant were trained for five days in the use of the eye examination protocol, blood sugar measurement, grading of diabetic retinopathy (DR) according to the Scottish DR grading scheme[8] and use of the RAAB software. Participating doctors were also trained to use binocular indirect ophthalmoscope prior the fieldwork. Inter-observer variation tests were conducted until an agreement was achieved regarding visual acuity, lens assessment and DR grading (Kappa at least 0.75). The methodology[9-12] and Hungarian main results[12-14] have been described in details in earlier publications.

The representative sample consisted of 3675 individuals aged 50 years and over, corresponding to 105 clusters of 35 people, out of which 3523 were actually examined. The datasets generated and analysed during the current study are available in the RAAB repository: http://raabdata.info/repository/. The Hungarian Central Statistical Office used the RAAB algorithm to select the census enumeration areas throughout the country at random, with a probability proportional to size. Each survey team approached the residential homes one by one in the selected enumeration area until 35 eligible examined residents were reached[9-10]. Certain age groups were under- or overrepresented in our sample.

Participants who had undergone cataract surgery or been diagnosed with cataract causing BCVA≤0.5 during the examination were considered as subjects with cataract. The type of cataract was not determined during the survey, only the existence of cataract was registered. In seven cases where the absence of lenses (aphakia) was corrected with glasses, intracapsular extraction (ICCE) was assumed, since there was no reliable information on the type of cataract surgery performed. Two participants with past cataract surgery due to injury were excluded from the cataract sample. Perioperative and postoperative complications were assessed on the basis of available documentation, patients' reports and our examinations. Only the general type of surgical complications (perioperative/postoperative) and cases in which posterior capsule opacification (PCO) was the cause for deteriorating vision were noted by the examining physician. No further details on the complications were captured.

Table 1 Overview of the analysed sample *n* (%)

Parameters	Data
Sample	3675
Examined sample	3523 (96)
Age (range)	67.0 (50-96)
Sex	
Female	2250 (64)
Male	1273 (36)
Cataract prevalence	823 (23.4)
Surgery	438 (12.4)
Diagnosed	385 (10.9)
DM prevalence	705 (20)
Known	661 (18.8)
Diagnosed	44 (1.2)

Participants were considered to have DM if previously diagnosed, took medications for it or their actual random blood glucose test showed elevated glucose levels (≥200 mg/dL or 11.1 mmol/L). The majority (661 people) had prior knowledge of the disease, but an additional 44 (6.2%) were diagnosed during the RAAB survey[11]. The new cases were directed to a general practitioner for further examination. In all DM cases, dilated fundus examination was conducted with binocular indirect ophthalmoscope.

Regarding of place of residence, settlements with more than 10 000 inhabitants were considered as cities, and others were counted as villages.

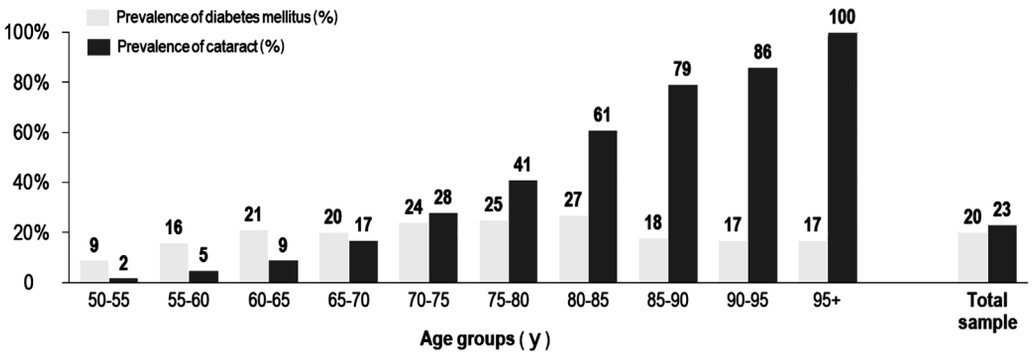
Statistical Analysis RAAB software version 6 (ICEH, LSHTM, London, United Kingdom) was used to capture and analyse the data. It allowed data entry, validation of data, sample size calculations and standardised data analysis. Excel-based analyses were performed on the gathered data using standard statistical methods (Pearson Chi-square, Mann-Whitney, Kruskal-Wallis, Dunnett's, *Z*-test and logistic binary regression tests). The prevalence estimates provide 95% confidence intervals (CIs) for cluster sampling, and $P<0.05$ was considered statistically significant.

RESULTS

In the total sample (Table 1) of 3523 participants, the prevalence of cataract was 23.4%, and that of DM was 20.0%. Adjusted figures based on actual Hungarian age and sex distribution were 20.9% and 19.4%, respectively.

With aging, the prevalence of cataract gradually increased, reaching 100% over the age of 95y. The prevalence of diabetes showed similar growth until the age of 70 to 75y. After this age—after a temporary stagnation—a gradual decrease could be seen (Figure 1).

In general, the prevalence of cataract was 35% higher in diabetic subjects than in their non-diabetic counterparts (29.5% *vs* 21.8%, $P=0.012$; Pearson Chi-square), making DM a



406 (12%)	500 (14%)	623 (18%)	592 (17%)	525 (15%)	435 (12%)	277 (8%)	130 (4%)	29 (1%)	6 (0.2%)	**Total**	3 523 (100%)
36 (9%)	82 (16%)	128 (21%)	120 (20%)	127 (24%)	107 (25%)	76 (27%)	23 (18%)	5 (17%)	1 (17%)	**DM**	705 (20%)
8 (2%)	26 (5%)	54 (9%)	102 (17%)	150 (29%)	179 (41%)	170 (61%)	103 (79%)	25 (86%)	6 (100%)	**Cataract**	823 (23%)

Figure 1 Prevalence of cataract and DM in different age groups.

significant determinant for cataract. A total of 208 persons had both diabetes and cataract (Figure 2).

To examine causality by excluding effects of confounding factors, such as age, sex and environment, logistic binary regression analysis was performed. Examining these features one by one, we found that aging [odds ratio (OR)=1.15, 95% confidence interval (CI), 1.14-1.17], DM (OR=1.51, 95%CI, 1.24-1.8), being an urban resident (OR=1.28, 95%CI, 1.09-1.50) and being female (OR=1.41, 95%CI, 1.19-1.67) all increase the prevalence of cataract independently. Analysing the above factors together by regression, we have found that they enhance each other's effects. DM was revealed to be a significant risk factor for cataract (OR=1.30, 95%CI, 1.05-1.61). Aging, urban living (>10 000 inhabitants) and female sex were also found to be statistically significant influencing factors.

Based on the logistic binary regression the predicted prevalence of cataract could be calculated for all ages (Figure 3).

Regarding the randomly measured blood sugar levels, no significant difference was observed in the prevalence of cataract according to the randomly measured blood sugar levels (29.7% at normal *vs* 29.0% at elevated blood sugar levels, *P*=0.859). Examining the time period living with DM, diabetic subjects experiencing cataract were aware of their disease for an average of 12.3y, while the subjects who did not have cataract were aware of their diabetes for 9.8y. One quarter of the diabetics having less than 10y of known illness and 35% of the patients with over 10y of diabetic history had cataract (*P*=0.02). This implies that the risk for cataract is considerably higher (*P*<0.001) for people with long-lasting diabetes compared to the non-diabetic population.

The average age for cataract surgery in Hungary was 69.8±9.2y in both sexes, and there was no significant difference between the diabetic and non-diabetic sub-groups (69.7 *vs* 69.8y). In our study, we found 13 cases (3%) with perioperative complications and 41 cases (9%) with late

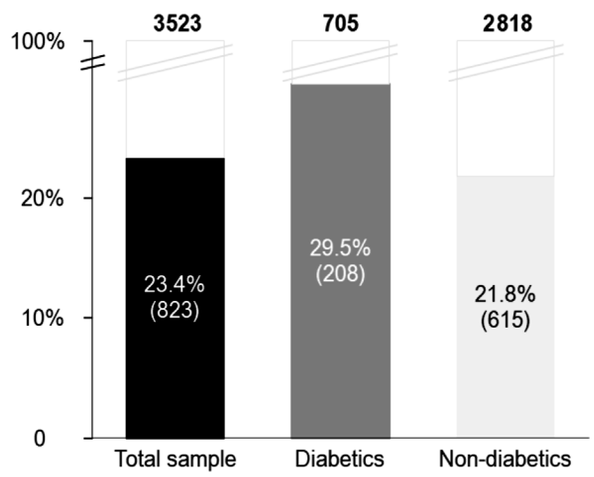


Figure 2 Co-existence of cataract and DM and prevalence of cataract in sub-groups.

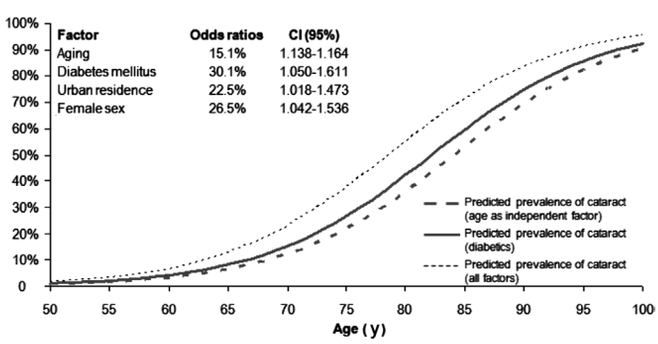


Figure 3 Predicted prevalence of cataract: all observed factors combined, age and DM as an independent factor.

surgical complications in all examined subjects who underwent cataract surgery (*n*=438). The overall complication rate was 12.3%. Neither the frequency of perioperative cataract surgical complications (2.8% *vs* 3.4%, *P*=0.637) nor the number of early and late surgical complications (12.8% *vs* 11.1%, *P*=0.962) showed significant differences between people without and with DM. The visual acuity of non-diabetic and diabetic patients who underwent cataract surgery was not significantly different; 75.7% of the patients had better BCVA than 0.5 (77.3% *vs* 74.4%, *P*=0.626; Table 2).

Table 2 BCVA in patients who underwent cataract surgery %

BCVA	>0.5	>0.3, <0.5	>0.1, <0.3	>0.05, <0.1	>0.017, <0.05	Light sensation	No light sensation
Non-DM	77.3	9.6	5.8	1.5	1.7	3.4	0.8
DM	74.4	8.4	9.9	2.0	2.5	3.0	0

BCVA: Best corrected visual acuity; DM: Diabetes mellitus.

DISCUSSION

A variety of publications supports the hypothesis that the initiating biochemical mechanism (the generation of polyols from glucose by aldose reductase) of diabetic cataract development results in increased osmotic stress in the lens fibres. This leads to swelling and rupture, inducing apoptosis in lens epithelial cells and finally to the development of cataract[4]. Recently a direct inhibition interaction has been revealed between aldose reductase and inducible nitric oxide synthase in human lens epithelial cells in diabetic cataract[6].

According to our population-based analysis, DM was statistically confirmed to be a risk factor for the development of cataract, irrespectively of its type. The type of DM (1 or 2) had not been captured during the survey and could not be accurately determined based on available data. These results coincide with some previous findings: in six low- and middle-income countries diabetes was associated with significant (2.10-2.80 times) higher odd for cataract, regardless of its type[15]. Based on other research, the five-year incidence rate of cortical cataract was two times higher in subjects with impaired fasting glucose (IFG), but there were no significant associations between incident nuclear cataract/cataract surgery and DM/IFG[16]. Moreover, the Visual Impairment Project showed that DM was an independent risk factor for posterior subcapsular cataract when present for more than five years[17].

Since cataract is a multifactorial disease, the effect of other influencing determinants that were considered in the survey also had to be taken into account: age, sex or environmental factors. To determine causality, the effect of these possible confounding factors had to be examined more closely.

Aging was a dominant, significant risk factor in the development of cataract: the prevalence of cataract in the age cluster of 50 to 55y was only 2%, while it reached 100% in the 95+ age group. In contrast, the prevalence of DM considerably increased in the age group of 55 to 65y, then continued to rise slowly until the ages of 70 to 75y. A steep decrease could be observed after a temporary stagnation until the ages of 80 to 85y. This phenomenon may be explained by the early mortality of patients with diabetes, which is also supported by international data[18]. Given the cross-sectional nature of the design, there could be no adequate monitoring of the emergence of cataract because longitudinal data have not been available.

The calculated predicted probability for cataract implies that, in addition to aging, DM is the most powerful influencing factor among the examined factors, followed by sex (female) and place of residence (urban; Figure 3). We supposed that the duration of living with DM and its severity might influence the development of cataract. Therefore, we analysed the prevalence of cataract based on the time span of existing diabetes before the emergence of cataract and the actual blood sugar level of patients.

Patients with DM and cataract were found to be aware of their disease longer (12.3y) than those who did not have cataract (9.8y). Overall, the time living with diagnosed diabetes is a risk factor for cataract. A study also showed an association of increased cataract risk with diabetes duration of 10y or longer[1]. It should be noted that our figures rely on the accuracy of the questionnaire filled out based on the participants' answers. It is possible that the DM may have existed years before the diagnosis.

If sex is considered as an independent influencing factor for cataract, the relative risk is higher among females (OR=1.41, 95%CI=1.19-1.67) compared to males. The type of cataract was not determined during our investigation. While some studies have shown an associated risk for nuclear sclerosis[19] and others for cortical cataract in females, the Pathologies Oculaires Liées à l'Age (POLA) study found increased odds for cortical cataract in females (OR=1.67), as did the Visual Impairment Project (age-adjusted relative risk of 1.8; 95%CI, 1.3-2.6) and the Lens Opacities Case-Control Study (OR=1.51)[20-22]. Other studies found no significant difference based on sex in the presence of any cataract, specific cataract types or cataract surgery in the Chinese population of Singapore[23]. In our study, no significant differences were observed in the prevalence of cataract between subgroups with normal and abnormal current blood sugar levels. In contrast to our findings, the Beaver Dam Eye Study showed that an increased glycated haemoglobin level was associated with increased risk of nuclear and cortical cataract in patients with DM[21]. In our case, the random glucose sampling provided only an instantaneous value that did not represent the carbohydrate metabolism. Glycosylated haemoglobin, type A1C (HbA1c) measures would have provided greater insights; unfortunately, due to the nature of the survey and the budget limit, this information was not available.

In addition to affecting the emergence of cataract, diabetes could impact surgical results. Therefore, the diabetic patients with visually significant cataract pose unique challenges during surgery, and they may be prone to a more difficult postoperative recovery[24]. Biochemically, DM causes several changes in the anterior segment. One of the most important changes in the crystalline lens is cataract formation. The basement membrane of the lens (or lens capsule) is known to be thicker in diabetics. This thickened capsule is more friable and may also affect performing capsulorhexis during phacoemulsification[25]. Inoue *et al*[26] demonstrated that corneal endothelial cell density was decreased in diabetic patients as compared to healthy control groups. In our sample, the first cataract surgery was performed on average at the age of 69.8y. This coincides with the findings of other European surveys[27-28].

However, the success of surgical interventions shows considerable variations. In our study, among the examined the patients who underwent cataract surgery, the postoperative visual acuity was very similar in patients with DM and without DM. Visual acuity after cataract surgery was better than 0.5 in 76.4% of the cases (non-DM 77.3% and DM 74.4%; P=0.626). In patients with DM, different cataract surgery results were published. Henricson *et al*[27] found that, among these patients, 89% of the surgeries reached a visual acuity better than 0.5. In other study this ratio in diabetic patients was even lower: 71%[29]. The Hungarian results lag behind international statistics. Furthermore, the cataract surgery results in the cases of patients with DM are considered to be average. However, these findings should be treated with care, since a large number of surgeries were performed many years before our examination. In those cases, late complications also may have had time to develop (*e.g.*, PCO). Moreover, outdated surgery techniques were included in the sample. Other eye diseases could have also affected the visual acuity. Based on the RAAB survey's protocol, only the main cause of visual impairment was determined.

Regarding the relationship between surgical complications and DM, international findings show a mixed picture. In general, cataract surgeries have 5% to 10% complication rates. Westcott *et al*[30] found that 66 of the 742 eye surgeries (8.9%) had complications. A study found evidence that patients with DM had higher complication rates following cataract surgery[4]. However, according to another study, it was only in non-diabetics who underwent phacoemulsification that a statistically significant difference could be confirmed. Our Hungarian figures are somewhat worse than the international results. Within this small sample, complications were not significantly more common in patients with DM than in non-diabetic patients. The most common late complication was posterior capsule opacification.

The main conclusion is that DM appears to be one of the main risk factors for developing cataract. However, other risk factors, such as age, sex and environment, also play a crucial role. In contemporary cataract surgery the diabetes does not seem to influence the occurrence of cataract surgical complications.

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Authors' contributions: Pék A conducted the survey, analysed the data and wrote the article. Tóth G, Sándor GL, Szabó D conducted the survey and analysed the data. Papp A and Nagy ZZ planned the survey and reviewed the manuscript. Limburg H and Németh J designed the survey, edited and reviewed the manuscript. All authors agree with the final version of the manuscript and agree to be accountable for all aspects of the work.

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