PREVALENCE OF DIABETIC RETINOPATHY AND THE SIGNIFICANCE OF GENETIC FACTORS IN THE DEVELOPMENT OF DIABETIC RETINOPATHY IN PATIENTS WITH DIABETES MELLITUS TYPES 1 AND 2 IN SLOVAKIA (DIARET SK). OVERVIEW OF CURRENT OBSERVATIONS AND STATUS OF EPIDEMIOLOGICAL STUDY DIARET SK.

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SUMMARY

Introduction: Diabetic retinopathy (DR) is the second most common microvascular complication and the most common cause of blindness in patients with diabetes mellitus (DM). Despite the ongoing research, the findings of diabetic retinopathy epidemiological and risk factors are, until now, not consistent. More finding may be revealed by epidemiological studies, consistently mapping DR epidemiology under the current possibilities of investigations and treatment of the DM.
DIARET SK: DIARET SK Study, with 5 000 enrolled patients with diabetes mellitus in the Slovak Republic, is, until now, the largest epidemiological study to set the prevalence of diabetic retinopathy. The primary aim is to establish the prevalence of diabetic retinopathy in patients with diabetes mellitus type I and II, according to the duration of the disease. The secondary aim is to establish prevalence of the different stages of the DR and diabetic macular edema (DME) and analysis of the risk factors influence. Included are patients with DM type I and II regardless to the ocular complications history and the period of DM duration. Each enrolled patient has both complex diabetic and ophthalmic examinations. Projects to establish DR prevalence: Tens of projects concerned with diabetic retinopathy epidemiology with different approaches to establish the prevalence and with different patients population. Results from different studies vary significantly (from 12.3 % to 66.9 %). The results depend on the design of the study and the patients recruitment, used examination methods, specific patients population with regard to the geography, prevalence of risk factors, period of diabetes duration, glycated hemoglobin (HbA1C) level, blood pressure, and is higher in type I diabetic patients. The most accurate results are from population epidemiological studies with well-controlled patient recruitment and uniform complex examination that are similar to the DIARET SK study.
Conclusion: The DIARET SK study represents the largest epidemiological study to establish the prevalence of the diabetic retinopathy in patients with DM type I and II. Thanks to the quality design, similar to the already published studies, but with larger number of patients and newest examinations methods, the DIARET SK study has the aspiration to obtain the most accurate up to date data of diabetic retinopathy prevalence and risk factors influence to its outbreak. The patients' recruitment started in February 2015. The expected date of patients' recruitment termination is in the end of the year 2015, and the data analysis in 2016.

Key words: diabetic retinopathy, prevalence, epidemiological study, macular diabetic edema, diabetes mellitus

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ÚVOD

Diabetes mellitus is a chronic metabolic disease caused by a disorder of the carbohydrate mechanism, which is characterised by hyperglycaemia ensuing from a number of metabolic abnormalities such as impaired insulin secretion, peripheral resistance to insulin, increased production of glucose in the in the liver and hyperglucagonemia.

Chronic DM causes several health complications. It increases the risk of microvascular complications, including damage to sight and blindness, nephropathy and neuropathy. In patients with DM there is also an increased risk of macrovascular complications, which may result in myocardial infarction or stroke. The origin and course of these complications is closely linked to the presence of persistent hyperglycaemia. Advanced aged of the patient or concurrent incidence of other pathologies further increases the seriousness of these complications.

Diabetic retinopathy is the second most common microvascular complication of diabetes, and the most common cause of blindness in individuals with DM [1]. It is caused by damage to the retinal capillaries as a consequence of metabolic changes generated by DM. Diabetic retinopathy may in any stage be complicated by DME, in which fluid percolates through the haemato-ocular barrier into the area of the macula, resulting in the formation of edema.

Diabetic retinopathy is classified with regard to the presence of specific retinal symptoms. It occurs in a number of stages as mild, medium and severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). DME may originate in any stage of diabetic retinopathy [1, 2]. We refer to clinically significant macular edema (CSME) when the centre of the macula is afflicted according to precisely defined criteria [3] and at least one of the following criteria is met: 1) retinal edema up to 500 µm from the centre of the foveal avascular zone (FAZ), 2) hard exudates within a scope up to 500 µm from the centre of the FAZ with contiguous macular edema and 3) edema of the size of one papillary diameter or larger, which partially encroaches into the area 1PD from the centre of the FAZ. Sight threatening retinopathy is defined as severe NPDR, PDR or CSME.

In 2013 DM afflicted 382 million people worldwide. It is expected that by 2035 this number will increase by 64.5% to 592 million people [4, 5]. With regard to the worldwide increase in the number of DM patients, it is expected that in the near future DR and DME will be the most common cause of blindness with deterioration of central visual acuity, together with age-related macular degeneration.

We can observe the same trend also in Slovakia [6]. In 1995 there were 201 315 diabetics registered in Slovakia, in 2000 this had risen to 256 138 and in 2013 up to the amount of 340 445, which represents an increase of more than 59.1% over 18 years. From this number of patients, ocular complications were determined in 67 792 diabetics, of whom 1 200 were blind. This data also covers other ocular pathologies, and it is not possible to determine the prevalence of DR from this.

Knowledge about the prevalence of DR has not been sufficiently examined. The results from the studies published to date differ markedly, depending on the specific population, treatment in the sense of hyperglycaemia and the method of implementing the study to determine prevalence. The majority of the published studies worked with a number of hundreds of observed patients and did not have sufficient statistical strength to provide detailed mapping of the epidemiology of DR. More observations may be brought by epidemiological studies which map the epidemiology of DR consistently on a large number of patients under the conditions of contemporary options of treatment and compensation of DM.

The DIARET SK study "Prevalence of DIAbetic RETinopathy and the significance of genetic factors in the development of diabetic retinopathy in patients with diabetes mellitus types 1 and 2 in Slovakia", with a number of 5000 observed patients ranks amongst large population epidemiological studies for determining the prevalence of DR and DME. Each patient shall undergo a complex diabetological and ophthalmological examination. Thanks to this fact it shall be possible to determine the prevalence of diabetic retinopathy and its individual stages with the highest precision to date. At the same time it shall be possible to identify the influence of risk factors on the origin and progression of DR.

In this article we describe the fundamental characteristics of the project for determining the prevalence of diabetic retinopathy and the status of DIARET SK within the framework of existing projects.

DIARET SK

DIARET SK is a multicentric epidemiological study with diagnostic intervention. The primary objective of DIARET SK is to determine the prevalence of DR in patients with DM types 1 and 2 in Slovakia, depending on the duration of the disease. A secondary objective is to determine the prevalence of the individual stages of DR and DME on the basis of a complex ophthalmological examination. Special attention will be devoted to the influence of risk and anamnestic factors on the origin of DR and DME. A large number of patients and a large volume of data is required in order to meet these objectives.

Tertiary objectives include a description of the cohort of patients in the sense of demographics, treatment and compensation of DM, including the incidence of accompanying microvascular and macrovascular diseases, and determining the influence of ocular complications on the quality of patient life by means of the validated questionnaire NEI VFQ-25. A separate element of the DIARET SK project is a genetic sub-study focusing on the identification of genes which contribute to the occurrence of DR. The hereditary component of sight threatening DR has been estimated at 25-50% [7]. The identification of specific genes contributing to the development of DR is the subject of a number of the latest research studies [8].

Patients

The survey includes patients who report to a district diabetologist for regular examinations. The inclusion criteria are age over eighteen years and diagnosed diabetes mellitus types 1 or 2, regardless of the length of the disease. All patients are included in observation regardless of the presence of DR or other ocular complication in their anamnesis. Before entering the study the patient must sign an informed consent form for inclusion in the epidemiological survey and genetic research.

The expected number of the observed patient population is 5000. A total of 4500 patients shall be included by means of random selection. The remaining 500 places are reserved for patients with DM type 1 or 2 with a length of duration of 20 years or longer, or with length of duration of DM of 5 years or less with anamnesis of DR, which is not very common within the population. Via this method we shall determine that even less common groups of patients are sufficiently represented for the statistical analysis. The gathering of

data shall take place in 54 diabetological and 19 ophthalmological centres.

During the study each patient undertakes two visits to a doctor. The first examination and recruitment of patients takes place with a district diabetologist within the framework of a regular check-up. The diabetologist records the current details determined during the visit, as well as selected retrospective data. For the purpose of isolating DNA, the diabetologist shall take a sample of peripheral blood. At the second examination an ophthalmologist shall record the retrospective anamnesis, including previous ocular pathologies, family anamnesis of immediate relatives, treatment of DR and DME, and shall conduct a complex ophthalmological examination. The examination with the ophthalmologist shall cover: collection of quality of life questionnaires NIE VFQ-25, the above-mentioned anamnesis, determination of bet corrected visual acuity, examination of the iris using a slit lamp (identification of rubeosis), biomicroscopic examination of the eye in mydriasis, examination with a fundus camera and OCT of the macular region with the aim of determining central retinal thickness and the volume of the macula. Best corrected visual acuity is determined with the use of ETDRS optotypes and is recorded in a score of letters. The presence / absence of DR shall be confirmed using 1-3 fundus photographs under an angle of 45°/50°, according to the type of retinopathy.

The influence of damage to sight as a consequence of DR or DME on the quality of the patient's life shall be evaluated with the use of the questionnaire NEI VFQ-25 [9]). This represents a validated questionnaire specialised in measuring the quality of life of patients with damage to sight. The questionnaire together with the instructions for completion shall be handed to the patient by the diabetologist. The patient shall complete the questionnaire between the visits to the diabetologist and the ophthalmologist, and submit the completed questionnaire to the ophthalmologist. The questionnaire was developed in co-operation with the RAND company, in co-operation with the National Eye Institute (NEI), and validated within the conditions of Slovakia [10].

Projects for determining the prevalence of DR and DME

The epidemiology of diabetic retinopathy has been the subject of dozens of projects with various approaches to determining the prevalence, with a different patient population. The results from the individual studies differ considerably (from 12.3% to 66.9%). The most precise results are from population epidemiological studies with well controlled patient recruitment and a uniform complex examination, which are similar to the DIARET SK project.

Of population studies, the best known and most widely read is the Wisconsin Eye Study of Diabetic Retinopathy (WESDR) [11-13], which also included an observation of the largest number of patients (total 2366) from a well defined population within the framework of one region. This study implemented recruitment of patients in the 1980s, with subsequent prospective 30 year observation, and defined the fundamental observations on diabetic retinopathy and the risk factors in connection therewith. It determined a strong dependency of the prevalence of diabetic retinopathy on the length of duration of diabetes. After 25 years of observation, taking into account the mortality rate, the prevalence of DR was 97%, PDR 42% and DME 29% in patients with type 1 DM. The majority of diabetics are at risk of diabetic retinopathy.

Thanks to the prospective observation, the WESDR study was able to study not only the overall incidence of the individual stages of DR, but also the annual incidence in the sense of occurrence of hitherto undiagnosed DR, or change of stage. The overall incidence over a 4-year period was 40%. In patients diagnosed with diabetes before the age of 30 years (insulin-dependent patients) the incidence of any diabetic retinopathy was 59%. In patients diagnosed with diabetes after the age of 30 the incidence was 47% in patients treated with insulin and 24% in patients without insulin treatment. A progression of patients into the more serious, proliferative form observed over 4 years was observed in 11% of patients diagnosed with diabetes before the age of 30 years; 7% of patients diagnosed with diabetes over the age of 30 on insulin therapy and 2% of patients without insulin. During the course of 25 years of observation, the risk of progression of retinopathy into a more serious stage of the disease was 83.1%, whilst the finding improved in 17.8% of patients. Meta-analyses [14, 15] confirmed that the prevalence of diabetic retinopathy progressively decreases and is lower in patients diagnosed since the year 2000 in comparison with the preceding years. Thanks to modern treatment and patient management, patients diagnosed at present have better control of glycaemia and lower incidence of retinopathy. Over the course of time, thanks to healthcare interventions, the incidence and seriousness of DR may progressively decrease, despite the increasing overall number of diabetics. The progressive reduction of the incidence of DR at the same time indicates that the studies realised in the 1980s do not describe the current dynamic and epidemiology of diabetic retinopathy. As a result new studies of the type of DIARET SK are necessary, in order to consistently map the epidemiology of diabetic retinopathy under the conditions of the current options for treatment of DM.

Data has also been processed by a number of meta-analyses. The results vary depending on the demographic data and selection of studies included in the meta-analyses: from 40.3% in the study by Kempen et al. [16], 34.6% in the study by Yau et al. [15] to 27.9% in the study by Ruta et al. [17]. For the purposes of this study, we chose the meta-analysis by Yau et al. [15] as the main source, with 35 studies and 22 896 patients incorporated in the observation. Another advantage of this meta-analysis is the processing of results of diabetic retinopathy in sub-groups of patients according to the presence of risk factors. The overall prevalence of DR was 34.6% (95% CI 34.5%–34.8%) for the results of DR, 6.96% (6.87%–7.04%) for proliferative DR, 6.81% (6.74%–6.89%) for diabetic macular edema and 10.2% (10.1%–10.3%) for sight threatening retinopathy. The overall prevalence increased with the duration of diabetes, the HbA1C value and blood pressure. The prevalence was higher in type 1 diabe-

tics in comparison with type 2 DM.

A separate theme is the prevalence of DR in patients with a short duration of DM up to 5 years. The frequent incidence of retinopathy may be partially explained by the underestimated time of duration of DM. Many patients are not diagnosed and referred to a diabetologist for regular care until several years after the origin of diabetes. Diabetic retinopathy may originate also during this period. However, its development in a proportion of diabetics may be influenced by factors other than diabetes. A study on groups of patients with the same demographic parameters [18] demonstrated a prevalence of any type of retinopathy in 34.6% of patients with DM type 2 and 8.8% of patients without diabetes. The incidence of retinopathy in the non-diabetic population was linked only with increased systolic blood pressure. The conclusion of the study is that a proportion of retinopathies in diabetics are caused by other factors, primarily hypertension. Blood pressure thus represents an independent risk factor, which may contribute to the occurrence of retinopathy by mechanisms independent of diabetes. However, in epidemiological projects of the type of DIARET SK it is not possible to distinguish retinopathy according to the cause of origin, and the overall prevalence is presented as diabetic retinopathy.

Another type of study which attempts to determine the prevalence of DR is analyses of electronic databases of patient insurance and records. This type of survey works with a higher number of patients, but at the price of retrospective secondary gathering of data. Another problem is that all the necessary data is available only for a certain proportion of patients, and examination of the ocular fundus may be lacking. In a recently published analysis from Catalonia conducted on 108 723 patients with type 2 DM [19] and implemented by means of photography of the retina, the prevalence of DR was 12.3% (95% CI 12.1% to 12.5%). This result differs markedly from the meta-analysis of population studies with a prevalence of 34.6%, and points to the methodological complications in connection with determining prevalence from retrospective data.

Another important observation from the studies to date is the large variation in the observed prevalence of diabetic retinopathy. Prevalence evidently depends on the specific patient population in the sense of duration of DM and compensation of glycaemia, hypertension and other risk factors. Another factor influencing the results is the design of the study, the method of examining DR and the period during which the study was conducted. Despite continuing research, observations concerning the epidemiology and risk factors of DR remain inconsistent. The large variation in the results also means that it is not possible to use the findings of individual studies unequivocally on Slovak patients. More observations in this area may be provided by studies of the type of DIARET SK, which consistently map the epidemiology of DR under the conditions of current options of treatment and compensation of DM. The results from Slovakia shall represent a unique evaluation of our patients and may not necessarily correspond with certain international publications.

A large advantage of the DIARET SK project is the large number of patients included in the observation. The typical numbers of observed patients in the studies included in the meta-analyses were in the range of hundreds of patients. The largest number of patients (2366) was in the WESDR study [12,13] and the ARIC study, featuring 1908 diabetics [20]. With regard to the size of the sample, DIARET SK shall be a significant epidemiological study focusing on an observation of DR. Increased statistical strength and precision of determining prevalence and risk factors should correspond to this fact.

The latest themes in research into diabetic retinopathy include determination of the influence of genetic factors. The influence of genetic factors is confirmed by a range of indirect evidence. Differences have been determined in the incidence of DR between African Americans and Americans of European origin. Family aggregation among immediate relations [21] and higher concordance of incidence in monozygotic twins in comparison with dizygotic twins attest to the influence of genetic factors. The hereditary component of sight threatening DR has been estimated at 25-50% [7]. However, the most convincing evidence originates directly from genetic analyses. A linkage analysis has detected a number of loci in the human genome which demonstrated a linkage with DR, even though the genes themselves have not yet been identified. Only a small number of genome -wide association studies (GWAS) have been conducted to date. The results of these studies have not yet been reproducible, and they lack the statistical strength to detect variants also with a medium sized influence [22, 23]. At present a number of projects are under way, the results of which are expected in the coming years [8]. The genetic sub-study of DIARET SK, including a large number of patients, may bring unique results in this area.

Quality of life has been observed in a number of studies [24]. A substantial influence of deterioration of sight on quality of life has been demonstrated from 0.98 for patients with good vision to 0.67 among patients with visual acuity of ≤ 20/200. The total numbers were less than 100 patients, and DIARET SK with its large number of patients shall unequivocally contribute to an improved determination of data relating to the quality of life of patients with DR.

With regard to the unavailability of current data on the prevalence of DR and DEM in Slovakia, this study provides a targeted epidemiological view of the prevalence of this pathology within the conditions of the Slovak Republic. It shall subsequently be possible to evaluate the mutual relationships between the demographic characteristics of a patient with DM and DR, the risk factors in connection with the primary pathology and the development of ocular microvascular complications, and last but not least also genetic factors, which could provide an answer to the possible association of the family element in these patients. As a result, a further objective of this project is to create a material, knowledge and methodological infrastructure, and thus contribute to a solution to this problem, or identifying certain genetic factors which contribute to the pathogenesis of DR, or identifying genetic markers which would enable an

early identification of individuals with an increased susceptibility to the onset of DR when still in the pre-clinical stage of diabetes, since it is unequivocally confirmed that the earlier the stages in which the development of DR is identified, the more effective the preventive measures, which in their final result may then save the sight of patients with DM.

CONCLUSION

Despite continuing research, knowledge about the epidemiology and risk factors of DR is so far inconsistent. Further observations may be provided only by studies of the type of DIARET SK, which consistently map the epidemiology of DR under the conditions of the current options of treatment and compensation of DM.

Epidemiological data in the conditions of the Slovak Republic is so far lacking, and the relationship of DR and genetic factors is considered to represent fundamental research which could provide a closer view of the correlation between the development of DR in patients with primary DM and congenital predisposition.

The DIARET SK study represents a significant epidemiological study for determining the prevalence of DR in patients with DM types 1 and 2. In its quality it ranks among similar studies conducted abroad, not only due to the large number of patients but also thanks to the methodology and use of the latest available inquiries.

The genetic sub-study represents basic innovative research in an area in which at present there are no universally accepted conclusions concerning the influence of individual genetic markers.

Recruitment of patients has been taking place in 54 diabetological and 19 ophthalmological centres since February 2015. The expected date for closure of patient recruitment is autumn 2015.

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