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CORRELATION OF DIABETIC MACULOPATHY AND LEVEL OF DIABETIC RETINOPATHY

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A b s t r a c t: One of the retinal changes during diabetic disease is appearance of diabetic maculopathy, which main characteristic is development of edema in the area of m.lutea. It is the main cause of decrease in vision and is found in about 10% of diabetic patients.

The aim of this paper is to determine the frequency of diabetic maculopathy, prevalence of the found type of maculopathy and correlation with retinopathy level.

Material and methods: the study comprised consecutive type 2 diabetic patients referred to the Unit for Laser Photocoagulation of the Clinic for Eye Diseases by ophthalmologists from other health centers. A total number of 86 patients were recruited in the study. Both ophthalmoscopic and biomicroscopic examinations of eye fundus as well as fluorescein angiography were performed. Grading of severity and level of both maculopathy and retinopathy has been done according to International Classification.

Results: A high presence of maculopathy in the examined patients (89.5%) was found as a result of previous high selection of diabetic patients by their ophthalmologists. The high selection has also an impact on correlation of diabetic maculopathy onset and disease duration, where parallelism with its appearance was registered, but this could also suggest that retinal microvascular changes appear very early, prior to clinical manifestation of diabetes. Diabetic maculopathy was most frequently found in preproliferative and proliferative diabetic retinopathy (93.6% and 95.3%). Severe forms of diabetic maculopathy with huge edema, numerous hard exudates and significant zones of capillary "drop out" of foveal capillary net are also associated with preproliferative and proliferative diabetic retinopathy. The most frequent type of diabetic maculopahty was the mixed one, where in addition to exudative characteristics, elements of ischemia and diffuse leakage were also found in 56% of the cases.

Conclusion: Diabetic maculopathy is only one of the manifestations of diabetic disease and it is the main cause of visual acuity impairment in diabetic patients. It is a reflection of already existing more significant and advanced biochemical and pathophysiological processes on the level of retinal microcirculation. The mixed type of diabetic maculopathy was predominant and its onset and severity was in correlation with concurrent diabetic retinopathy. Prevention of retinal changes and sight presservation in these patients, in addition to timely and adequate ophthalmologic treatment, induces multidisciplinary approach since the principal cause of microvascular complications is hyperglycemia in correlation with many risk factors, such as hypertension and dyslipidemia.

Key words: diabetic maculopathy, macular edema, diabetic retinopathy.

Introduction

Diabetic disease in its developmental course results in polymorphic changes of eye fundus which lead to consecutive progressive and significant deterioration of visual function in majority of patients. Retinal diabetic changes are considered to be the main cause of blindness in industrialized countries (CDC), but similar trend has been observed in the rest of the world as well (Balasubramanyam 2002). In addition to proliferative diabetic retinopathy, the most common cause of visual impairment is diabetic maculopathy and onset of macular edema (Wilkinson 2003). Macular edema is found in about 10% of the diabetics with prevalence in the population of non-insulin dependent diabetic patients. It is the most common cause of decrease of visual function in non-proliferative diabetic retinopathy (Bek 1999, Chew and Ferris III, 2006). Diabetic retinopathy has been classified according to the International Severity Grading Scale for Retinal Diabetic Changes (Table 1).

In line with the same International Classification (Wilkinson 2003), diabetic macular edema is categorized according to the severity of retinal edema and hard exudates as follows:

- Small DME – presence of retinal thickening or hard exudates on posterior pole, but distant from the center of the macula.
- Moderate DME – presence of retinal thickening or hard exudates which approach the center of m. lutea, but not involving the center of macula lutea.
- Severe DME – presence of retinal thickening or hard exudates, involving the center of m. lutea.

The **aim of the paper** is to determine the frequency of diabetic maculopathy, prevalence of the found type of maculopathy and correlation with retinopathy level.

Table 1 ‡ Tabela 1

International Severity Grading Scale for Diabetic Retinopathy (DR)
CLASSIFICATION OF DIABETIC RETINOPATHY
(Modification of the final scale of severity from ETDRS – G. A. Charls)

Internacionalna skala za te`ina na dijabeti~na retinopatija (DR)
KLASIFIKACIJA NA DIJABETI^NATA RETINOPATIJA
(Garcia A. Charles – modifikacija na poslednata ETDRS skala)

NO DIABETIC RETINOPATHY. Diabetes mellitus without ophthalmoscopically evident diabetic retinopathy.
NON PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)
Mild: Microaneurysms, mild retinal hemorrhages, hard exudates, soft exudates.
Moderate: More retinopathy than mild but less severe than the 4, 2, 1 rule.
Severe: Any one of the following **(4, 2, 1 rule):**
Ma/H severe in 4 quadrants
VB in at least 2 quadrants
IRMA in at least 1 quadrant
Very severe: At least two criteria of the 4, 2, 1 rule.
PROLIFERATIVE DIABETIC RETINOPATHY (PDR)
Without high risk characteristics (s HRCs)
NVE in any extent without VH/PRH.
NVD less than one quarter disc area.
With high risk characteristics (c HRCs)
NVD equal or greater than one quarter disc area in size
VH/PRH with any wizened or with NVE equal to or grater than one half the disc area in size
Advanced
Extensive vitreous hemorrhage (which does not permit visualization of the new vessels)
Traction retinal detachment involving the macula
Neovascular glaucoma
Phthisis bulbi

Ma – microaneurysm, H – hemorrhage, VB – venous bleeding, IRMA – intraretinal microvascular anomalities, VH – vitreous hemorrhage, PRH – preretinal hemorrhage, NVE – neovascularization elsewhere, NVD – neovascularisation of the disc, PRH – preretinal hemorrhage.

Material and Methods

The study comprised consecutive type 2 diabetic patients referred to the Clinic for Eye Diseases by ophthalmologists from other health centers. The patients were examined and treated by the author of this study at the Unit for

Laser Photocoagulation in the period between January 2005 and February 2006. A total number of 86 patients, 38 males and 48 females were recruited for the purpose of the study. Besides anamnestic data of the disease, ophthalmologic examinations in all patients were carried out: determination of visual acuity by Snellen's optotypes with corrected refraction, measurement of eye pressure, examination of anterior segment on biomicroscope, examination of posterior segment by contact biomicroscopy using adequate lens (panfunduscope) and indirect biomicroscopy with high-dioptre lens (78 D), fluorescence angiography, native color and red free photography.

Type of diabetic maculopathy (exudative, edematous, ischemic and mixed) is classified according to the angiographic findings and clinical characteristics, dominant ischemic maculopathy being the one where capillary "drop out" on perifoveolar capillary net is present for more than 12 hours.

Diabetic maculopathy and macular edema as well as current diabetic retinopathy were classified according to the previously mentioned International Classification.

Results

The study included 86 patients, 38 men (44.2%) at the age of 49–73 years (average age 63.3 years) and 48 women (55.8%) at the age of 51–74 years (average age 62.1 year) that were suffering from diabetes mellitus type II, with disease duration of 5–26 years. Out of the 86 examined patients (172 eyes), maculopathy was detected in 77 patients (89.5%) in addition to retinopathy. General characteristics of the examined group are given in Table 2. A mild domination of females versus males has been observed, but there was no statistical significant association with its presence. The same refers to the average age and diabetes duration between examined male and female patients.

Table 2 – Tabela 2

Characteristics of the examined group
Karakteristiki na ispituvanata grupa

Sex	No. of patients	Age (mean age)	Duaration of DM	With maculopathy
Male	38	49–73 (61.8)	5–26 (15.4)	34
Female	48	51–74 (62.8)	5–26 (13.4)	43
		P > 0.05	P > 0.05	P > 0.05

* Fisher exact test.

Distribution of diabetic maculopathy and involvement of either one or both eyes is presented in Table 3. In the majority of these patients, diabetic maculopathy was found in both eyes (61 patient, 84.7%). In 11 patients, that is, in 4 men and 7 women, diabetic maculopathy was observed unilaterally. There was a discrepancy between the number of patients presented in the previous table (Table 2), which is due to the fact that a vitreous hemorrhage in the other eye was identified in 5 patients. It was a result of the advanced diabetic retinopathy and thus, it was not possible to inspect the eye fundus. These patients were excluded from the examined group when presenting the lateralization of the process, although it could be assumed that similar changes in the area of m. lutea were also found in that eye.

Table 3 – Tabela 3

Distribution of diabetic maculopathy

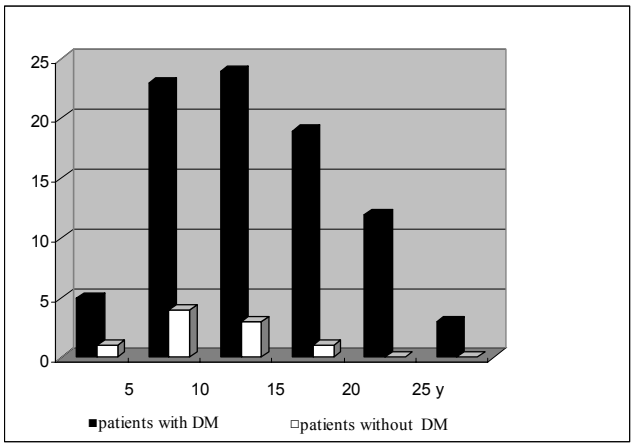
Distribucija na dijabeti~nata makulopatija

Sex	Male	Female
Bilateral	27	34
Unilateral	4	7

P > 0.05

*Fisher exact test.

Graph. 1 shows the correlation between onset of diabetic maculopathy and duration of diabetes mellitus. No significant differences can be observed in the frequency of maculopathy and diabetes duration, but parallelism of maculopathy appearance can be seen.



Graphic 1 – Correlation of diabetes mellitus duration with diabetic maculopathy

Grafikon 1 ‡ Korelacija na dijabeti~nata makulopatija so dol`ina na traewe na DM

Table 4 presents correlation between level of diabetic retinopathy of examined eyes and diabetic maculopathy with severity of macular edema. Eyes whose fundus was not examined due to vitreous hemorrhage, were excluded from this analysis. Bigger presence of diabetic maculopathy in both pre-proliferative and proliferative forms of diabetic maculopathy can be noticed in these eyes as well as severe forms of diabetic maculopathy where edema is more distinct and involves the center of macula lutea. Maculopathy associated with non-proliferative retinopathy (moderate and mild) was found in 45%, whereas with pre-proliferative (severe and very severe) and proliferative retinopathy in 93.6% and 95.3%, respectively.

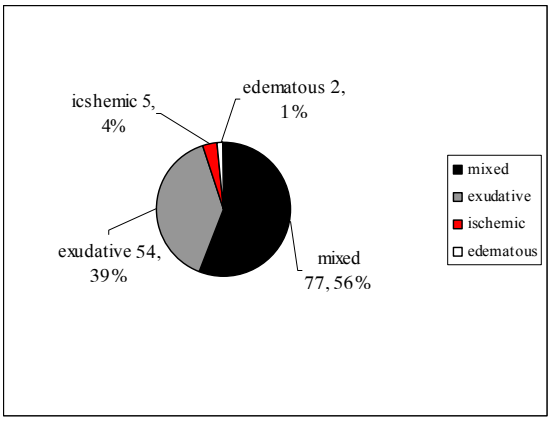
Table 4 ‡ Tabela 4

Correlation between diabetic retinopathy level of the examined eyes and severity of diabetic macular edema (DME)

Korelacija na stepenot na dijabeti~nata retinopatija na egzaminiranite o~i so te`inata na dijabeti~nata makularen edem (DME)

Level of diabetic retinopathy					
DME	Mild	Moderate	Severe	Very severe	Proliferative
No edema	4	18	3	1	3
Mild	–	7	2	1	6
Moderate	–	9	7	12	18
Severe	–	2	13	24	37

Presence of all types of diabetic maculopathy is shown on Graph. 2 where the mixed type of diabetic maculopathy is most frequent and found in 77 eyes, that is 56%.



Graphic 2 – Presence of certain types of diabetic maculopathy

Grafikon 2 ‡ Zastapenost na oddelni tipovi dijabeti~na makulopatija

Discussion

Basic and essential characteristic which defines the entity of diabetic maculopathy is presence of retinal edema at the posterior pole of the retina between vascular arches. It results from the accumulation of fluid and other plasma materials (lipids, lipoproteins), which is ophthalmoscopically manifested as edema of the retina. Macular edema was found in 11% of type 1 diabetic population whereas this percent increased to 8.4 in type 2 diabetics (Klein 1984). Sparrow *et al.* (1993) found a slightly bigger prevalence of maculopathy in patients without insulin treatment and the reduction of vision due to maculopathy was revealed in 10% of this population. According to Fine (1986) macular edema was found in 10% of the diabetics and even in 40% of these patients retinal thickening by edema affected the center of macula lutea. The obtained percent of diabetic maculopathy in our study (89.5%) is significantly the greatest as compared to literature reports, which can be explained by high selection of patients who were referred to our Unit for Laser Therapy by ophthalmologists from other health centers.

According to the Wisconsin Epidemiologic Study (WESDR 1984) the prevalence of maculopathy was 28% in the adult type of diabetics whose diabetes duration was 20 years or longer and maculopathy was found in 3% of the patients already in the first 5 years of the disease. High patient selection in our study also reflected on the correlation between diabetic maculopathy and diabetes duration. Small differences and parallelism in the onset of diabetic maculopathy have been noticed. However, this fact could also be comprehended in context of the suggestion of Hamman given at the 65th Scientific Session of the American Diabetes Association, based on the disordered glucose tolerance test (GTT) that diabetic changes of the retina may appear earlier even when values of blood glucose are smaller, i.e. during non-manifested diabetic disease (cited by Hammes 2005). Furthermore, Hamman considers that urgent screening of diabetic retinopathy is necessary immediately upon diagnosing the disease since diabetes may be manifested even after 3–5 years from disease onset.

There is a positive correlation between the level of concurrent retinopathy and maculopathy where, besides retinal edema, macula exhibits other alterations in a big percentage in proliferative retinopathy as compared to non-proliferative one (Kojima et al. 1990). Prevalence of macular edema increases proportionally with the severity of diabetic retinopathy (Massin-Korobelnik *et al.* 1994). In case of non-proliferative retinopathy, it is found in 6%, in pre-proliferative in 20–60%, whereas in proliferative retinopathy, it is found in even 70–74% (Gaudric *et al.* 1993). Although the findings of our study have shown

higher presence of maculopathy in all groups, there is a ratio in their relation that is consistent with data in the literature demonstrating frequency of maculopathy in severe pre-proliferative and in proliferative forms of above 90%.

According to clinical manifestation and angiographic findings, there are several types of diabetic maculopathy, but in practice these types of maculopathy are combined in majority of the cases (van Meel 1996, Bailey *et al.* 1998). In the extensive analysis of diabetic lesions of macula conducted by Bailey *et al.* (1998), the exudative type of maculopathy prevailed and was found in about 70% of the patients. The results obtained in our study match with literature findings. Mixed type of maculopathy that has been dominant, is a result of greater impairment of macular capillary net. In eyes which belonged to the group of pre-proliferative and proliferative retinopathy, in addition to numerous aneurysms and creation of hard exudates, diffuse leakage of colour with smaller or greater zones of ischemia could be observed.

Dysmetabolic syndrome, that is characteristic for diabetic disease, by damaging blood vessels, mostly the small ones, compromises tissue supply that results in damage of all organs of the human body. Diabetic retinopathy is a bilateral and almost parallel process, although there might exist certain differences between the degree of development of diabetic retinopathy in both eyes. Changes that occur in the retina during the course of the disease are a result of continual chronic repetitive damages where one degree of the disease leads to another one, more advanced, which increases the risk of visual impairment (Balasubramanyam *et al.* 2002, Rosenbaum 2002). The process involves a great number of pathophysiological mechanisms and biochemical processes on intracellular level that in complex cascade events act synergically. The changed path of glucose degradation in the tissues such as retina, with high oxygen requirement, results in big production of free oxygen radicals (ROS-reactive oxygen species) in conditions of reduced anti-oxidative protection and formation of numerous intermediary products of glycoxylation (AGEs – advance glucation end products). Created substances lead to perturbation of the function of cell enzymes such as GAPDH (gliceraldehin 2 phosphate dehydorgenase), activation of cellular izoenzyme group of protein kinase (PKC) and MAP kinases and translocation of transcriptic Nfkapa B, with consecutive expression of proinflammation genes and production of leukines [inerleukines (ICAM1), E-selectin] as well as pro-angiogenic substances, VEGF (Vascular Endothelial Growth Factor), in the first place (Brownlee 2005). Created substances are a cause of disorders in blood retinal barrier and formation of retinal intercellular edema that is manifested with edema onset on the macula, but they are aslo a cause of endothelial proliferation in the created "permissive milieu" due to reduced number and role of pericytes.

In spite of the compex biochemical cellular processes that bring about retinal changes, the common major cause that initiates pathological processes on genetically determined basis is hyperglycemia emphasized by other associated conditions (dyslipidemia, hypertension). This perpetuets the vicious cycle resulting in diabetic microangiopathic changes. The overriding importance of regulation of glycemia, dyslipidemia and hypertension in preventing the development of microvascular complications in diabetes, was stressed by the American Diabetes Association (ADA, 2005) where strict criteria in the treatment of diabetic patients have been postulated.

Conclusion

Diabetic maculopathy is only one of the manifestations of diabetic disease and it is the main cause of visual acuity impairment in diabetic patients. It is a reflection of already existing more significant and advanced biochemical and pathophysiological processes on the level of retinal microcirculation. The mixed type of diabetic maculopathy was predominant and its onset and severity was in correlation with concurrent diabetic retinopathy. Prevention of retinal changes and sight preservation in these patients, in addition to timely and adequate ophthalmologic treatment, induces multidisciplinary approach since the principal cause of microvascular complications is hyperglycemia in correlation with many risk factors, such as hypertension and dyslipidemia.

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Rezime

KORELACIJA NA DIJABETI^NATA MAKULOPATIJA I STEPENOT NA DIJABETI^NATA RETINOPATIJA

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Edna od retinalnite promeni vo tekot na dijabeti~nata bolest e i pojavata na dijabeti~nata makulopatija ~ija glavna karakteristika e pojava na edem vo predelot na m. lutea. Taa e glavna pri~ina za namaluvawe na vidot i se sretnuva vo okolu 10% od dijabeti~nite bolni.

Celta na trudot e da se odredi zastapenosta na makulopatijata, prevalira~kiot tip na makulopatijata i nejzinata korelacija so aktuelnata dijabeti~na retinopatija.

Materijali i metodi: Vo studijata se analizirani konsekutivni dijabeti~ni bolni so tip II diabetes mellitus, isprateni od drugite oftalmolo{ki centri zaradi tretman vo kabinetot za LFK pri Klinikata za o~ni bolesti vo Skopje. Ispitani se 86 bolni kaj koi se napraveni oftalmoskopski i biomikroskopski pregledi na o~noto dno kako i fluoresceinska angiografija. Gradacijata na stepenot i te`inata na makulopatijata i retinopatijata e napravena spored internacionalnata klasifikacija.

Rezultati: Najdena e visoka zastapenost na makulopatijata kaj ispituvanite bolni (89,5%) {to e rezultat na prethodnata selekcija na dijabeti~nite bolni od mati~nite oftalmolozi. Visokata selektivnost ima odraz i vrz korelacijata na pojavata na dijabeti~nata makulopatija so vremetraeweto na bolesta, kade se voo~uva paralelizam vo nejzinata pojava, no, ova isto taka bi mo`elo da sugerira deka retinalnite mikrovaskularni promeni se javuvaat u{te porano, pred klini~kata manifestacija na dijabetot. Dijabeti~nata makulopatija e najzastapena kaj preproliferativnata i proliferativnata dijabeti~na retinopatija (93,6%

odnosno 95,3%). Isto taka, te{kite formi na dijabeti~na makulopatija, okarakterizirani so prisustvo na golem otok, brojni cvrsti eksudati i so zna~ajni zoni na kapilaren "drop out" na fovealnata kapilarna mre`a, se asocirani so preproliferativnata i proliferativnata dijabeti~na retinopatija. Najzastapeniot tip na dijabeti~na makulopatija e me{aniot tip, kade pokraj eksudativnite karakteristiki prisutni se elementi na ishemija i difuzen "leakage", koj e prisuten vo 56% slu~ai.

Zaklu~ok: Dijabeti~nata makulopatija e samo edna od manifestaciite na dijabeti~nata bolest i e glavna pri~ina za namaluvawe na vidnata ostrina na dijabeti~nite bolni. Taa e odraz na ve}e pozna~ajni i ponaprednati biohemiski i patofiziolo{ki procesi na nivo na retinalnata mikrocirkulacija. Preovladuva me{aniot tip na dijabeti~na makulopatija, a nejzinata pojava i stepenot na te`inata e vo korelacija so konkurentnata dijabeti~na retinopatija. Vo prevencijata na retinalnite promeni i za~uvuvawe na vidot kaj tie bolni, pokraj pravovremen i adekvaten oftalmolo{ki tretman se nalaga multidisciplinaren pristap, bidej}i glavniot imenitel na mikrovaskularnite komplikacii e hiperglikemijata, vo korelacija so pove}ebrojnite rizikfaktori, pred s# hipertenzijata i sostojbata na dislipidemija.

Klu~ni zborovi: dijabeti~na makulopatija, makularen edem, dijabeti~na retinopatija.

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