Original article

Association Between Diverse Diabetic Treatments and Duration of Diabetes Mellitus According to Progression of Diabetic Retinopathy: Experience From a Small Regional Hospital

Ana Bardak [1], Stjepan Kovacevic [2], Bozidar Kovacevic [3], Zeljka Vukovic Arar [3], Sandra Sekelj [3], Dinko Nizic [4], Zvonimir Bosnic [5*]

[1] Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[2] Department of Internal Medicine, General Hospital "Dr Josip Benčević", Slavonski Brod, Croatia
[3] Department of Ophthalmology, General Hospital "Dr Josip Benčević", Slavonski Brod, Croatia
[4] Department of Radiology and Ultrasound Diagnostics, Special Hospital for Pulmonary Diseases, Zagreb, Croatia
[5] Postgraduate Interdisciplinary University Study – Molecular Biosciences, Josip Juraj Strossmayer University of Osijek, Croatia

Corresponding author: Zvonimir Bosnic, zbosnic191@gmail.com

Abstract

Introduction: Research objectives of present study were to examine sex and age-related specifics of diabetic retinopathy according to the therapy approach and duration of diabetes mellitus. The study also aimed to determine the association between the presence of diabetic retinopathy and diabetes duration as a prognostic factor of retinopathy progression in such patients.

Materials and Methods: The study was designed as a retrospective study and included 289 patients with diabetic retinopathy, who were treated at the Department of Ophthalmology of the General Hospital "Dr. Josip Benčević" in Slavonski Brod during the period from 2019 to 2020.

Results: 176 patients were treated with oral antidiabetic drugs (OAD), while 113 patients were insulin-dependent. The median age of patients treated with OAD was 77 years. Diabetic retinopathy was present in 35 (19.9%) patients, of whom 33 (18.8%) had non-proliferative diabetic retinopathy, while 2 patients (1.1%) had proliferative diabetic retinopathy. The median age of the insulin-dependent patients was 79 years. Diabetic retinopathy was present in 54 patients (47.8%), non-proliferative diabetic retinopathy was diagnosed in 51 patients (45.1%), while proliferative diabetic retinopathy was diagnosed in only 3 (2.7%) patients. There was a significant difference between the presence of diabetic retinopathy and diabetes duration ($P<0.001$), as well as between the therapy approach and diabetes duration ($\alpha<0.001$).

Conclusion: Various hypotheses have been proposed to explain the worsening of diabetic retinopathy, and we assume that the therapy approach, duration of diabetes and HbA1c have a significant role in retinopathy progression. Hereby, we emphasize that, although there have been significant advances, there is still a pressing need for a better understanding of a new therapeutic modality, new tools for identifying high-risk patients and continued monitoring in order to intervene effectively before vision loss occurs. Further research is needed to identify and implement the best practices to increase diabetic eye screening rates in the long term.

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Introduction

Diabetic retinopathy (DR) is one of the most frequent complications of diabetes mellitus and it remains a leading cause of vision loss globally. Its aetiology and pathology have been extensively studied for half a century, but unfortunately, there are few therapeutic options and prevention of progression is still the ultimate goal. It affects an estimated 126.6 million people worldwide and it is expected to increase rapidly in the future (1).

Even though many studies, such as The Diabetes Control and Complications Trial (DCCT) and The United Kingdom Prospective Diabetes Study (UKPDS), have confirmed a strong relationship between chronic hyperglycaemia and the development and progression of diabetic retinopathy, there is a lack of understanding of the underlying mechanism leading to the development of microvascular damage (2, 3). According to the WHO, diabetic retinopathy is described as a major cause of 5% of vision loss in the developed world and its prevalence is expected to double by 2030. As stated by the American Diabetes Association, 21% of patients with diabetes mellitus have diabetic retinopathy at the moment of first diagnosis of diabetes, and more than 60% of patients develop DR within 20 years after the diagnosis (4). Microvascular damage slowly accumulates in the retinal blood vessels, leading to retinal ischemia, higher retinal permeability, neovascularization and macular oedema, finally resulting in complete vision loss (5-7). The risk of development and progression of diabetic retinopathy is closely associated with the type and duration of diabetes, blood sugar levels, blood pressure levels, proteinuria and possibly hyperlipidaemia (8). Recent studies suggest that apolipoproteins, inflammatory factors and genetic risk factors could also play a role in the development and progression of diabetic retinopathy (9). An ideal model of screening tools for diabetic retinopathy is based on an annual examination of visual acuity and the eye fundus in all diabetic patients. Adults with type 2 diabetes should undergo an eye screening test at the time of diabetes diagnosis. Annual eye exams are recommended, but if there is no evidence of diabetic retinopathy, eye screening every two years thereafter may be considered (10).

Family medicine physicians have adequate knowledge and awareness of diabetic eye screening guidelines. However, they encounter barriers in ensuring that patients undergo screening due to burdensome and complex tasks they are required to complete during the patient's average 15-20-minute visit to the clinic, as well as due to a lack of access to the patients' eye exam records. Patients should undergo follow-ups by an experienced ophthalmologist using precise eye fundus imaging methods at least once a year. Examination of the eye fundus completed with fluorescein angiography make a gold standard in retinopathy diagnosis and classification (11).

Research objectives of the present study were to examine sex and age-related specifics of diabetic retinopathy according to the therapy approach, duration of diabetes mellitus, as well as accompanying comorbidities. The study also aimed to determine the association between the presence of diabetic retinopathy, diabetes duration and HbA1c as prognostic factors of retinopathy progression in such patients.

Materials and Methods

The retrospective study was conducted on 289 patients treated at the Department of Ophthalmology of the General Hospital "Dr. Josip Benčević" in Slavonski Brod, Croatia during the period from 2019 to 2020. The data were collected from the medical records kept by the Department of Ophthalmology of the General Hospital "Dr. Josip Benčević". The inclusion criteria were the presence of diabetes mellitus and biomicroscope presence of diabetic retinopathy. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical methods

Categorical data were presented by absolute frequency and percentage, while numerical data were presented by the median, minimum, maximum and interquartile range. Differences in nominal variables were tested by the Fisher's exact test, while differences in numeric variables were tested by the Mann–Whitney U Test because of deviations from the normal distribution. All P-values were two-sided. The level of significance was set at $\alpha = 0.05$. IBM SPSS Statistics was used for the statistical analysis (IBM Corp. Released 2015. IBM SPSS Statistics for Macintosh, Version 23.0. Armonk, NY: IBM Corp.).

Results

This study was conducted on 289 patients, who were divided into two groups based on the therapy approach. The first group (N=176) was treated with oral antidiabetic drugs (OAD), while the second group of patients (N=113) was insulin-dependent (Table 1 and Table 2).

Table 1. Characteristics of patients (N = 176) treated with oral antidiabetic drugs

	Frequency	Percentage
Gender		
Male	72	40.9%
Female	104	59.1%
Smoking		
Yes	5	2.8%
No	171	97.2%
Alcohol consumption		
Yes	2	1.1%
No	174	98.9%
Hypertension		
Yes	160	90.9%
No	16	9.1%
Diabetic retinopathy		
Yes	35	19.9%
No	141	80.1%
Non-proliferative diabetic retinopathy		
Yes	33	18.8%
No	143	81.3%
Proliferative diabetic retinopathy		
Yes	2	1.1%
No	174	98.9%

Table 2. Characteristics of insulin-dependent patients (N=113)

	Frequency	Percentage
Gender		
Male	55	48.7 %
Female	58	51.3 %
Smoking		
Yes	9	8.0 %
No	104	92.0 %
Alcohol consumption		
Yes	2	1.8 %
No	111	98.2 %
Hypertension		
Yes	101	89.4 %
No	12	10.6 %
Diabetic retinopathy		
Yes	54	47.8 %
No	59	52.2 %
Non-proliferative diabetic retinopathy		
Yes	51	45.1 %
No	62	54.9 %
Proliferative diabetic retinopathy		
Yes	3	2.7 %
No	110	97.3 %

The median age of patients treated with OAD was 77 years (interquartile range of 71-84), with a minimum age of 50 years and a maximum age of 95 years. The median age of the insulin-dependent patients was 79 years (interquartile range of 71-83), with a minimum age of 47 years and a maximum age of 96 years. Out of 176 patients who received OAD, 35 (19.9%) had diabetic retinopathy, while 141 (80.1%) did not. A total of 113 patients were insulin-dependent, of whom 54 (47.8%) had diabetic retinopathy and 59 (52.2%) did not (Table 3). The OAD group included 72 male patients (40.9%) and 104 female patients (59.1%). Five patients (2.8%) were smokers and 171 patients (97.2%) were non-smokers. Frequent alcohol consumption was reported by 2 patients (1.1%), while 174 patients (98.9%) did not consume alcohol frequently. Hypertension was diagnosed in 160 patients (90.9%), while 16 patients (9.1%) did not have hypertension. Diabetic retinopathy was present in 35 patients (19.9%), while 141 patients (80.1%) were not diagnosed with diabetic retinopathy. Out of 176 patients, 33 patients (18.8%) had non-proliferative diabetic retinopathy, while 2 patients (1.1%) had proliferative diabetic retinopathy (Table 1)

Table 3. Characteristics of patients receiving oral antidiabetic drug therapy (OAD) or insulin depending on the presence of diabetic retinopathy

	OAD	Insulin	Total	P*
Patients with diabetic retinopathy	35 (19.9)	54 (47.8)	89 (30.8)	<0.001
Patients without diabetic retinopathy	141 (80.1)	59 (52.2)	200 (69.2)	<0.001
Total	176 (100)	113 (100)	289 (100)	

Fisher's exact test

The insulin-dependent group consisted of 55 men (48.7%) and 58 women (51.3%). Out of 113 patients, 9 (8.0%) were smokers and 104 (92.0%) were non-smokers. Frequent alcohol consumption was reported by 2 patients (1.8%). Hypertension was diagnosed in 101 patients (89.4%), while 12 patients (10.6%) did not have hypertension. Diabetic retinopathy was present in 54 patients (47.8%), while 59 patients (52.2%) were not diagnosed with diabetic retinopathy. Non-proliferative diabetic retinopathy was diagnosed in 51 patients (45.1%), while the proliferative type was diagnosed in only 3 patients (2.7%).

The groups differed based on diabetes duration. Patients receiving OAD had a median duration of diabetes of 7 years (interquartile range of 4-12 years), with a minimum duration of 6 months and a maximum duration of 35 years. A median duration of diabetes in the insulin-dependent patients was 12 years (interquartile range of 7-20 years), with a minimum duration of 3 months and a maximum duration of 55 years. Patients diagnosed with diabetic retinopathy had a median duration of diabetes of 14 years (interquartile range of 8.5-20 years), with a minimum duration of 0 months and a maximum duration of 20 years. The patients without diabetic retinopathy had a median duration of diabetes of 7 years (interquartile range of 4-12 years), with a minimum duration of 6 months and a maximum duration of 55 years (Figure 1).

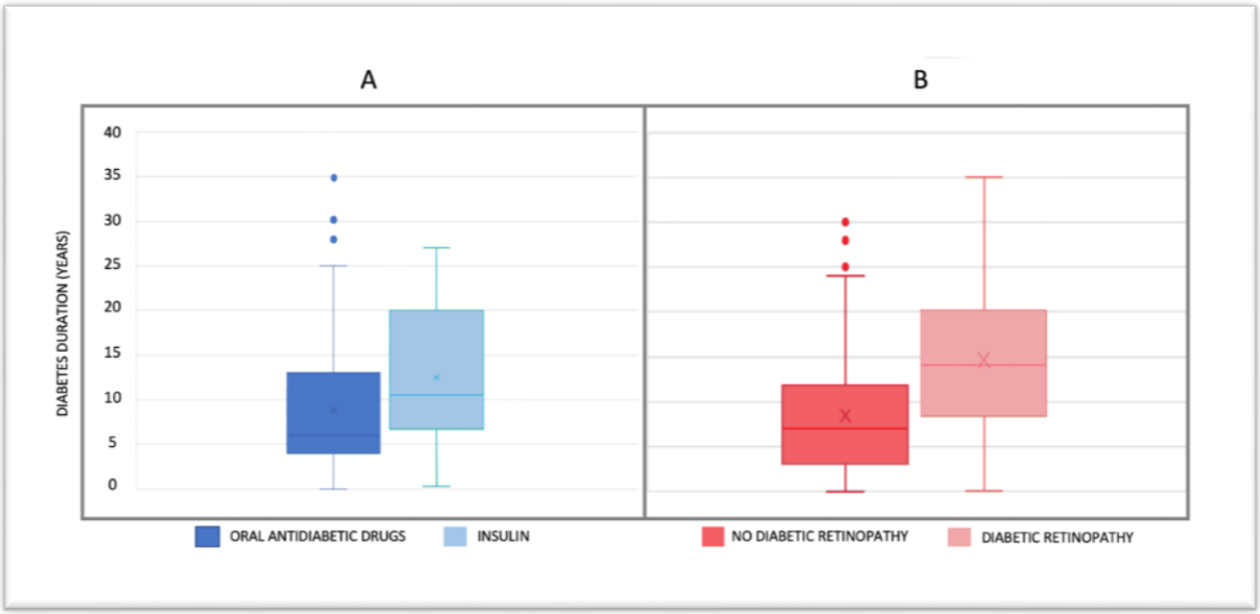

Figure 1. Difference in diabetes duration distribution between patients receiving oral antidiabetic drugs and insulin (A) and between patients with and without diabetic retinopathy (B). p < 0.001 both in Figure 1A and Figure 1B.

Patients diagnosed with diabetic retinopathy had a median duration of diabetes of 14 years (interquartile range of 8.5-20 years), with a minimum duration of 0 months and a maximum duration of 20 years. On the other hand, the patients without diabetic retinopathy had a median duration of diabetes of 7 years (interquartile range of 4-12 years), with a minimum duration of 6 months and a maximum duration of 55 years.

HbA1c concentrations were determined in the patients treated with OAD and insulin. The patients treated with OAD had a significantly lower median concentration of 6.3 mmol/L (interquartile range of 6.1-6.9), with a minimum concentration of 5.5 and a maximum concentration of 7.8 mmol/L. Patients treated with insulin had a median concentration of 7.6 mmol/L (interquartile range of 6.6-8.9), with a minimum HbA1c concentration of 5.5 and a maximum concentration of 12.3 mmol/L (Figure 2).

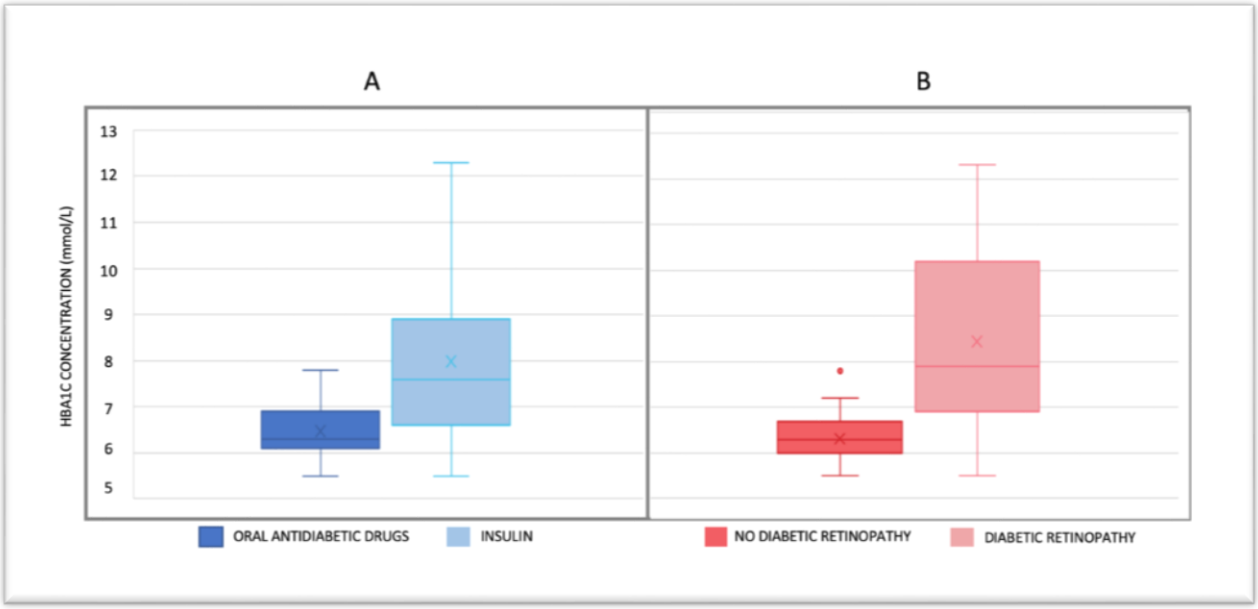

Figure 2. Difference in HbA1c concentration between patients receiving oral antidiabetic drugs and insulin (A) and between patients with and without diabetic retinopathy (B). p < 0.001 both in Figure 2A and Figure 2B.

Discussion

Diabetic eye screening and treatment guidelines are part of the core curriculum for training eye care providers, but the current eye care provider workforce is insufficient to meet the increasing number of diabetic patients. According to epidemiological data, the number of diabetic patients is growing. These patients comprise a large share of eye care provider clinic time, but only one in 20 patients has vision-threatening diabetic eye disease. Our study included 289 patients who suffered from type 2 DM. Patients were divided into two groups according to the therapy approach. There were more patients who used OAD. The majority of the patients using OAD were females who suffered from arterial hypertension, did not consume alcohol and did not smoke. Most of them had no signs of diabetic retinopathy and only two patients had confirmed proliferative diabetic retinopathy (Table 1). In contrast to them, there was a similar number of male and female patients who were insulin-dependent. Most of them suffered from arterial hypertension and half of them had confirmed DR. Only three insulin-dependent patients had proliferative DR. The insulin-dependent patients had more cases of DR confirmed compared to patients who were taking OAD (Table 3). Despite a relatively high prevalence of DR in our study, our results are close to the prevalence of DR reported in the

Region-Specific Information (Europe) and worldwide (Table 3) (12).

Some researchers have pointed out a higher prevalence of DR in patients treated with insulin, suggesting that insulin therapy may be associated with DR and DR severity when compared to the oral antidiabetic drug (OAD) therapy (13). On the other hand, another study, conducted by Gupta et al., has also shown a higher prevalence of DR among insulin users than in patients treated with OAD (52.9% vs 16.3%), discussing how insulin therapy is often started later in the course of the disease, at a stage when glycaemic control is suboptimal for the subject. It was also argued that insulin is simply a marker of disease severity, rather than an independent risk factor for DR, suggesting that starting insulin therapy earlier in the course of the disease might be more beneficial in preventing the development of DR in the longer run (14). In the EURODIAB study, mild forms of non-prolferative diabetic retinopathy (NPDR) were recorded in 25.8%, moderate NPDR in 9.8%, and PDR in 10.6% of insulin-treated patients. The study included 3250 insulin-treated diabetic patients from 13 European diabetes centres, with a mean diabetes duration of 14.7 years. The major factors for vision loss are patient age, diabetes duration, glycosylated haemoglobin and the grade of retinopathy (15, 16).

DM duration is a predictor of diabetic retinopathy (17). Patients with type 1 diabetes develop diabetic retinopathy within five years or less, and only occasionally later, i.e. 27% and 71-90% of patients with diabetes duration of 5-10 and >10 years, respectively. At 20-30 years of diabetes duration, the incidence of diabetic retinopathy increases to 95%. Usually 30-50% of these patients develop proliferative diabetic retinopathy (PDR) (18). In our study, the patients receiving OAD had a median duration of diabetes of 7 years (interquartile range of 4-12 years), while the median duration of diabetes in the insulin-dependent patients was 12 years (interquartile range of 7-20 years). The median age of the patients receiving OAD was 77 years (IQR of 71-84), while the median age of the patients treated with insulin was 79 years (IQR of 71-83). There was a significant difference between the presence of diabetic retinopathy and diabetes duration ($\alpha<0.001$) (Figure 1A). Thus, most of the patients were elderly persons with a comorbidity (e.g. arterial hypertension). Even though the prevalence of DM is relatively high among elderly patients, the incidence of DR and PDR in our study is close to the results of studies conducted in other European countries (12). There are several factors which could explain these observations, some of which are a relatively high quality of life in the last 10 years, newly designed OAD and combinations of OAD, free physical examinations twice or thrice a year and morphological characteristics of the eye structure in elderly persons (posterior vitreous detachment), resulting in slower progression of DR than that observed (19).

Only a few participants in present study consumed alcohol, so alcohol can be excluded as a risk factor and is not directly associated with the presence or progression of diabetic retinopathy (Table 1 and Table 2). Our results are similar to the multicentric study by Lee CC et al., who investigated the association between alcohol consumption and diabetic retinopathy and deterioration of visual acuity in individuals with type 2 diabetes, concluding that alcohol consumption is associated with an increased risk of deterioration of visual acuity, but not with retinopathy in individuals with type 2 diabetes (20). The relationship between cigarette smoking and diabetic retinopathy was examined earlier and data suggest that there is no excess risk of retinopathy in smokers or ex-smokers when contrasted with those who have never smoked. Our study produced similar results due to the fact that a small number of participants consumed cigarettes (Table 1 and Table 2) (21). Landmark multi-centre, randomised controlled trials showed that early identification and proper treatment can prevent the risk of vision loss by 90%, but fewer than 50% of people with diabetes in the USA follow diabetic eye screening guidelines and even lower screening rates (10-20%) have been described (22). Once retinopathy is present, the duration of diabetes appears to be a less important factor than glycaemic control in forecasting progression from earlier to later stages of retinopathy (23). On the other hand, the

link between HbA1c levels and diabetic retinopathy is not conclusive because there are other variables that come into play. In our study, the patients treated with oral diabetic drug therapy had a significantly lower median concentration of HbA1c, without the presence of diabetic retinopathy (Figure 2A and B). Maintaining control of glucose and blood pressure lowers the risk of retinopathy progression and patients should be aware of the importance of maintaining good levels of glycosylated haemoglobin and blood pressure.

Considering a higher prevalence of DM globally, family medicine doctors should improve additional educational programs in diabetic retinopathy screening because multiple workflow and systems-level barriers affect care providers and there is not enough time to follow all diagnostic features in everyday clinical practices (24). The study by Olafsdottir E et al. discusses the benefits of regular screening for diabetes mellitus and diabetic eye disease as the gold standard in preventing diabetic blindness. According to that study, the loss of vision from diabetic retinopathy is uncommon if regular screening is provided and subsequent hospital costs are also lower. The same idea has been confirmed in the study by Bandurska-Stankiewicz E et al., who have confirmed that the incidence of vision loss due to diabetes is significantly lower in the countries which have introduced programs for preventing retinopathy than in those countries which do not have such programs (25, 26). While current evidence indicates that the association between the glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4i) inhibitors and the risk of DR remains uncertain in patients with T2DM, future studies should focus on such types of drugs, especially on the combinations and prevalence of DR, PDR and NPDR in large-scale, well-designed studies (27).

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Once retinopathy is present, the duration of diabetes appears to be a less important factor than glycaemic control in forecasting progression from earlier to later stages of retinopathy. In our study, there is a lack of information about the type of OAD and DR, so in future studies, we will pay more attention to the association of DR, new OAD and combinations of therapy. In addition, opportunities exist in leveraging team-based care approaches, patient self-management programs and emerging telemedicine imaging technologies.

Conclusion

Our study has confirmed the results of previous studies, namely that the risk of development and progression of diabetic retinopathy is closely associated with the type and duration of diabetes and HbA1c concentration. Also, we emphasise that there is still a pressing need for a better understanding of a new therapeutic modality, new tools for identifying high-risk patients and continued monitoring in order to intervene effectively before vision loss occurs. Further research is needed to identify and implement the best practices to increase diabetic eye screening rates in the long term. There is a lack of additional educational programs in primary health care of diabetic retinopathy screening and a lack of large-scale, well-designed studies of diabetic retinopathy occurrence associated with glucose-lowering drugs.

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Competing interests. None to declare.

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Author contribution. Zvonimir Bosnic and Bozidar Kovacevic were responsible for the conceptualisation and design of the study. Stjepan Kovacevic and Dinko Nizic performed the investigation and collected the data. In addition, they were responsible for data validation. Ana Bardak performed the statistical analysis. Zeljka Vukovic Arar and Bozidar Kovacevic provided participants with the data. Sandra Sekelj and Zeljka Vukovic Arar supervised the study. Zvonimir Bosnic and Ana Bardak wrote the manuscript. Bozidar Kovacevic and Sandra Sekelj reviewed and edited the manuscript. All authors have read and agreed on the published version of the manuscript