ASSOCIATION BETWEEN MICROVASCULAR COMPLICATIONS AND GLYCATED HEMOGLOBIN IN PATIENTS WITH DIABETES

Povezanost mikrovaskularnih komplikacija i nivoa glikoziliranog hemoglobin kod pacijenata sa dijabetesom

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Summary

Introduction. The aim of this study was to determine the prevalence of microvascular complications in type 1 and type 2 diabetes mellitus patients in relation to glycated hemoglobin. Material and Methods. This cross-sectional study analyzed the prevalence of microvascular complications in patients with diabetes mellitus registered at the Primary Health Center Banja Luka. Demographic data, duration of diabetes, blood pressure, glycated hemoglobin, dyslipidemia, type of therapy, presence of retinopathy, neuropathy and nephropathy were analyzed. Data collection was done from December 2017 to November 2018. Results. The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. The most common microvascular complication was diabetic neuropathy (24.2%). The mean glycated hemoglobin level in patients with diabetic complications was 7.75 ± 1.66%. Although all participants with complications had unregulated diabetes mellitus (glycated hemoglobin > 7%), a statistically significant difference was found in regard to microalbuminuria (> 30 mg/24 h) and/or proteinuria (> 0.15 g/24 h) and/or decreased creatinine clearance (< 1.5 ml/sec) and their mean glycated hemoglobin (p = 0.025), while for other complications (neuropathy and retinopathy) the same was not confirmed. Multivariate logistic regression analysis confirmed that microalbuminuria and/or proteinuria and/or decreased creatinine clearance (odds ratio = 2.174; 95% confidence interval: 1.040 - 4.543; p = 0.039) as well as elevated diastolic blood pressure (odds ratio = 1.09; 95% confidence interval: 1.024 - 1.162; p = 0.007) were factors associated with glycated hemoglobin > 7%. Conclusion. The most common microvascular complication in patients with both types of diabetes mellitus is diabetic neuropathy with a prevalence of 24.2%. The presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance were associated with glycated hemoglobin > 7% and elevated diastolic blood pressure.

Key words: Diabetes Mellitus; Diabetes Complications; Glycated Hemoglobin A; Diabetic Neuropathies; Diabetic Nephropathies; Diabetic Angiopathies; Primary Health Care; Cross-Sectional Studies

Introduction

Diabetes mellitus (DM) is a chronic non-comunicable disease which has become a global epidemic. It is characterized by a condition of chronic hyperglycemia that may last for years and lead to a series of complications that slowly and quietly endanger the patient’s health [1, 2]. The most common microvascular complications of DM are neuropathy, retinopathy and nephropathy. The International Expert Committee and the International Diabetes Federation (IDF) have introduced glycated hemoglobin

Sažetak

Uvod. Cilj ovog rada je bio ispitivanje učestalosti mikrovaskularnih komplikacija kod pacijenata sa dijabetesom melitus tipa 1 i tipa 2 u odnosu na glikoziliran hemoglobin. Materijal i metode. Studijom preseka ispitivana je učestalost mikrovaskularnih komplikacija kod pacijenata sa dijabetesom melitus, koji su registrovani u Domu zdravlja u Banjoj Luci. Analizirani su: demografski podaci, trajanje dijabetesa, krvni pritisak, glikoziliran hemoglobin, dislipidemija, vrsta terapije, prisustvo retinopatije, neuropatije i nefropatije. Pacari su prikupljeni u period od decembra 2017. do novembra 2018. godine. Rezultati. U istraživanje je bilo uključeno 228 pacijenata i to 132 (57,9%) muškarca i 96 (42,1%) žena. Najčešća mikrovaskularna komplikacija je bila dijabetesesna neuropatija (24,2%), prosečna vrednost glikoziliranog hemoglobin kod pacijenata sa komplikacijama dijabetesa bila je 7,75±1,66%. Iako su svi ispitani sa komplikacijama imali neregulisan dijabetes melitus (glikozilirani hemoglobin>7%), utvrđena je statistički značajna razlika u prisustvu mikroalbuminurije (>30 mg/24 h) i/ili proteinurije (>0,15 g/24 h) i/ili sniženog klirenesa kreatinina (<1,5 ml/sec) i njihovom prosečnom glikoziliranom hemoglobinom (p=0,025), dok za ostale komplikacije (neuropatiju i retinopatiju) isto nije potvrđeno. Multivarijantna logistička regresija potvrdila je da su mikroalbuminurija i/ili proteinurija i/ili snižen klirenes kreatinina (odnos verovatnoća=2.174; 95% interval poverećenja:1,040-4,543; p=0,039) kao i povišen dijastolni krvni pritisak (odnos verovatnoća=1,09; 95% interval poverećenja:1,024-1,162; p=0,007) faktori povezani sa glikoziliranim hemoglobinom>7%. Zaključak. Najčešća mikrovaskularna komplikacija kod pacijenata sa oba tipa dijabetesa je dijabetesesna nepropatija sa prevalencijom od 24,2%. Prisustvo mikroalbuminurije i/ili proteinurije i/ili sniženog klirenesa kreatinina su povezani sa glikoziliranim hemoglobinom>7% i povišenim dijastolnim krvnim pritiskom. Ključne reči: dijabetes melitus; komplikacije dijabetesa; glikozilirani hemoglobin A; dijabetesesna neuropatija; dijabetesesna nefropatija; dijabeteseska angiopatija; primarna zdravstvena zaštita; studija preseka...
A cross-sectional study included patients with both types of DM (T1DM and T2DM), who were registered at the Primary Health Center (PHC) Banja Luka. With a population size of 15,617, an error of 5%, 95% level of confidence, and a confidence interval of 6.44, the estimated sample size of patients with DM was 228. Participants were randomly selected from 20 families with T1DM and T2DM, according to International Classification of Diseases (ICD) [21]. Every third patient was selected from the medical records of patients with DM in accordance with the inclusion criteria.

Inclusion criteria were age 18 to 70, diagnosis of DM according to ICD (T1DM and T2DM), duration of diabetes at least 5 years, and a written consent to participate in the study. Data collection took place from December 2017 to November 2018.

Patients with DM and frequent hypoglycemic episodes who were previously diagnosed with microvascular complications of diabetes were excluded from the study. The study was approved by the Ethics Committee of the PHC Banja Luka.

For the purpose of the research, a checklist was developed for each participant individually. Age, sex, duration of diabetes, blood pressure (BP), HbA1c, dyslipidemia, type of therapy, presence of retinopathy, neuropathy, and nephropathy were analyzed. With regard to age, the participants were divided into 5 groups: 20 to 30 years, 31 to 40 years, 41 to 50 years, 51 to 60, and 61 to 70 years. According to the duration of diabetes, they were divided into 4 groups: duration of diabetes from 5 years to 10 years, from 10 to 15 years, from 15 to 20 years, and over 20 years.

All the participants underwent baseline assessment. Control measurements of BP were performed every 2 months. Control measurements of HbA1c in participants with T1DM were performed every 6 months (a total of 2 measurements), and in participants with T2DM every 6 months (a total of 2 measurements).

The BP was measured three times during each visit to the family doctor using a mercury manometer according to World Health Organization recommendations. The final value of BP was recorded, and it was the mean of the second and third measurement.

The HbA1c and lipids were measured in the central laboratory of the PHC Banja Luka (bioanalyzer Arhitekt c 8000). According to the HbA1c level at the end of follow-up, participants were classified into two groups: participants with HbA1c < 7% and participants with HbA1c ≥ 7%. Dyslipidemia was diagnosed if total cholesterol value was > 4 mmol/l, and/or low-density lipoprotein (LDL) cholesterol > 2.6 mmol/l and/or triglyceride > 1.7 mmol/l [20].

The screening was performed for three basic microvascular complications (retinopathy, neuropathy and nephropathy). The screening for diabetic retinopathy was done by fundus examination performed by an ophthalmologist. A 10 g monofilament Semmes-Weinstein nylon was used to detect neuropathy. The monofilament handling procedure was done in the following way: the examiner first demonstrated the strength of the monofilament touch on each participant’s hand, then told him to close his eyes and proceeded testing the sensations on both
feet. The examined points of pressure are the first metatarsophalangeal joint of the great toe, the dorsum of the great toe, the plantar side of the great toe, and the plantar side of the heel. The participants were asked to say "yes" when they felt the touch. The maximum score was eight. More than four incorrect answers indicated the existence of neuropathy [22].

To confirm neuropathy, the findings of a neurologist during the follow-up period or earlier were taken as well as the findings of electroneurography (ENG).

The presence of nephropathy was detected using microalbuminuria, proteinuria and creatinine clearance in 24-hour urine in the central laboratory of the PHC Banja Luka (biochemical analyzer AU 480). Microalbumin values of 30 – 300 mg/24 h were considered to be the phase of incipient nephropathy-microalbuminuria, and values greater than 300 mg/24 h defined the phase of manifest proteinuria-macroalbuminuria [23]. The value of protein in urine > 0.15 g/24 h and the value of creatinine clearance <1.5 ml/sec, according to the reference values of the central laboratory of the PHC Banja Luka, represented the limit value for diabetic nephropathy. During the research, only 38 participants presented with microalbuminuria, which was not valid for further analysis and for diagnosing nephropathy. Because of that, one of three positive values (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) was monitored.

All analyses were performed using the Statistical package for the social sciences version 25 (SPSS Inc., Chicago, IL, USA). The results were analyzed and presented using descriptive statistics (absolute and relative numbers, measures of central tendency, standard deviation).

Levene’s test was used to assess the equality of variances. Demographic data were analyzed using two samples of the independent Student’s t-test and the Mann-Whitney U test. The Hi square (χ²) test was used to compare categorical variables. Logistic regression was used to identify all factors (microvascular complications, blood pressure, type of therapy) associated with unregulated diabetes (HbA1c greater than 7%). The Kruskal-Wallis test was used to assess the differences in the risk of microvascular complications between the groups based on duration of diabetes. A probability level of p < 0.05 was considered statistically significant.

### Table 1. Presence of microvascular complications in patients with diabetes in relation to the HbA1c level

| Presence of neuropathy | Prisutnost neuropatije |
|------------------------|------------------------|
| YES, n, % | DA n, % | NO, n, % | NE, % | Total, n, % | Ukupno n, % |
| ≤ 7.00 | 20 (36.4) | 64 (37.4) | 84 (37.2) | 168 (100) |
| 7.01+ | 35 (63.6) | 107 (62.6) | 142 (62.8) | 384 (100) |
| Total/Ukupno | 55 (100) | 171 (100) | 226 (100) |

| Presence of retinopathy | Prisutnost retinopatije |
|------------------------|------------------------|
| YES, n, % | DA n, % | NO, n, % | NE, % | Total, n, % | Ukupno n, % |
| ≤ 7.00 | 11 (28.9) | 73 (39.2) | 84 (37.5) | 178 (100) |
| 7.01+ | 27 (71.1) | 113 (60.8) | 140 (62.5) | 300 (100) |
| Total/Ukupno | 38 (100) | 186 (100) | 224 (100) |

| Microalbuminuria and/or Proteinuria and/or decreased CCr | Mikroalbuminuirija i/ili proteinurija i/ili snižen CCr |
|--------------------------------------------------------|------------------------------------------------------|
| YES, n, % | DA n, % | NO, n, % | NE, % | Total, n, % | Ukupno n, % |
| ≤ 7.00 | 29 (26.6) | 33 (42.3) | 62 (33.2) | 124 (100) |
| 7.01+ | 80 (73.4) | 45 (57.7) | 125 (66.8) | 244 (100) |
| Total/Ukupno | 109 (100) | 78 (100) | 187 (100) |

| Sex: Pol | Male | Muški | HbA1c | 7.01+ | 41 (68.3) | 29 (59.2) | 70 (64.2) |
|----------|------|-------|-------|-------|-----------|-----------|-----------|
| Total/Ukupno | 60 (100) | 49 (100) | 109 (100) |

| Female | Ženski | HbA1c | 7.01+ | 39 (79.6) | 16 (55.2) | 55 (70.5) |
| Total/Ukupno | 49 (100) | 29 (100) | 78 (100) |

Legend: HbA1c - glycated hemoglobin; CCr - creatinine clearance; Microalbuminuria (> 30 mg/24 h) and/or Proteinuria (> 0.15 g/24 h) and/or CCr (< 1.5 ml/sec); p - statistical significance
Results

The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. The average age of our participants was 55.8 ± 9.2 years.

The most common microvascular complication was diabetic neuropathy. This study determined the prevalence of diabetic neuropathy in 24.2% and retinopathy in 17% of participants with a statistically significant difference (χ² = 16.770; p < 0.001). Out of the total number of participants, 109 had at least one parameter consistent with nephropathy. According to microalbuminuria (> 30 mg/24 h), 11.9% of participants had a positive result, 67% had a decreased creatinine clearance (< 1.5 ml/sec). The mean HbA1c in patients with diabetic complications was 7.75 ± 1.66% with a statistically significant difference between patients with T1DM and T2DM (U = 3060.500; z = 1.977; p = 0.048).

The participants with unregulated glycaemia showed higher incidence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance (p = 0.025), while the same was not confirmed for other complications (neuropathy and retinopathy) (Table 1).

We analyzed demographic characteristics (sex) in relation to HbA1c and the presence of all microvascular complications and found that there was a statistically significant difference only in patients with microalbuminuria and/or proteinuria and/or decreased creatinine clearance and in women statistically significantly more in the group with HbA1c > 7% (p = 0.022) (Table 1), while there was no statistical significance in regard to other complications. Analyzing microvascular complications in relation to sex, age, duration of diabetes and type of therapy, neuropathy was more frequent among the patients with longer duration of diabetes (p < 0.001), and retinopathy in patients using insulin therapy (p = 0.019) (Table 2).

The parameters of diabetic nephropathy (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) were tested in relation to the duration of diabetes using the Kruskal-Wallis test. The duration of diabetes affected the occurrence of incipient diabetic nephropathy (microalbuminuria) in our participants (p = 0.042) (Table 3).

The univariate regression models showed associations between HbA1c > 7% and the following variables: presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance (OR = 2.492), insulin therapy (OR = 2.215), elevated BP > 130 mmHg and > 80 mmHg (OR=1.833). Multi-

| Variable Promenljiva | Neuropathy Neurupatiya | Retinopathy Retinopatija | Microalbuminuria and/or Proteinuria and/or CCr Mikroalbuminurija i/ili Proteinurija i/ili CCr Microvascular complications/Mikrovaskularne komplikacije | YES/DA (n, %) NO/NE (n, %) P YES/DA (n, %) NO/NE (n, %) P YES/DA (n, %) NO/NE (n, %) P |
|-----------------------|--------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Sex/Pol               | Male/Muški               |                           | 38 (69.1) 94 (54.7) 0.059 26 (68.4) 104 (55.9) 0.155 60 (55) 72 (60.5) 0.404                                                                 |                           |
|                       | Female/Ženski             |                           | 17 (30.9) 78 (45.3)                                                      | 12 (31.6) 82 (44.1)                                                      | 49 (45) 47 (39.5) |
| Age/Doba (Years/Godine) | 18 – 30                  |                           | 1 (1.8) 6 (3.5)                                                          | 2 (5.3) 5 (2.7)                                                          | 4 (3.7) 3 (2.5) |
|                       | 31 – 40                   |                           | 2 (3.6) 10 (5.8)                                                         | 1 (2.6) 11 (5.9)                                                         | 7 (6.4) 5 (4.2) |
|                       | 41 – 50                   |                           | 4 (7.3) 21 (12.2)                                                        | 0.712 6 (15.8) 19 (10.2) 0.674                                           | 12 (11) 13 (10.9) 0.929 |
|                       | 51 – 60                   |                           | 25 (45.5) 73 (42.4)                                                      | 15 (39.5) 82 (44.1)                                                      | 46 (42.2) 53 (44.5) |
|                       | 61 – 70                   |                           | 23 (41.8) 62 (36.0)                                                      | 14 (36.8) 69 (37.1)                                                      | 40 (36.7) 45 (37.8) |
| Duration of diabetes  | 5 – 10 yr./god            | 19 (34.5) 106 (61.6)       | 15 (39.5) 110 (59.1)                                                     | 60 (55.0) 66 (55.5)                                                     |                           |
|                       | 10 – 15 yr./god           | 11 (20) 41 (23.8)          | 10 (26.3) 40 (21.5)                                                      | 23 (21.1) 29 (24.4)                                                      |                           |
|                       | 15 – 20 yr./god           | 13 (23.6) 18 (10.5)        | 0.000 8 (21.1) 22 (11.8)                                                 | 15 (13.8) 16 (13.4)                                                      |                           |
|                       | > 20 yr./god              | 12 (21.8) 7 (4.1)          | 5 (13.2) 14 (7.5)                                                        | 11 (10.1) 8 (6.7)                                                        |                           |
| Type of therapy       | Oral antidiabetic therapy/Oralna antidiabetetsna terapija | 20 (36.4) 89 (52)          | 11 (28.9) 98 (53)                                                        | 49 (45.4) 61 (51.3)                                                      |                           |
|                       | Insulin therapy/Insulinska terapija | 23 (41.8) 44 (25.7)        | 0.056 17 (44.7) 48 (25.9)                                                | 36 (33.3) 31 (26.1)                                                      | 0.479 |
|                       | Combined therapy/Kombinovana terapija | 12 (21.8) 38 (22.2)        | 10 (26.3) 39 (21.1)                                                      | 23 (21.3) 27 (22.7)                                                      |                           |

Legend: CCr – creatinine clearance; Microalbuminuria (> 30 mg/24 h) and/or Proteinuria (> 0.15 g/24 h) and/or CCr (< 1.5 ml/sec); p – statistical significance

| Promenljiva | Neurovascular complications/Mikrovaskularne komplikacije |
|-------------|---------------------------------------------------------|
| Sex/Pol     | Neuropathy Neurupatiya Retinopathy Retinopatija Microalbuminuria and/or Proteinuria and/or CCr |
| Male/Muški  | 38 (69.1) 94 (54.7) 0.059 26 (68.4) 104 (55.9) 0.155 60 (55) 72 (60.5) 0.404 |
| Female/Ženski| 17 (30.9) 78 (45.3) 12 (31.6) 82 (44.1) 49 (45) 47 (39.5) |

Legend: CCr – klirens kreatinina; Mikroalbuminurija (> 30 mg/24 h) i/ili Proteinurija (>0,15 g/24 h) i/ili CCr (< 1,5 ml/s); p – statistička značajnost
variate logistic regression analysis confirmed that microalbuminuria and/or proteinuria and/or decreased creatinine clearance (OR = 2.174; 95% CI: 1.040 - 4.543; p = 0.039) as well as elevated diastolic BP (OR = 1.09; 95% CI: 1.024 - 1.162; p = 0.007) were associated with HbA1c > 7% (Table 4).

**Discussion**

This study determined that the most common microvascular complication in correlation with HbA1c > 7% was diabetic neuropathy with a prevalence of 24.2%. The second microvascular complication in correlation with HbA1c greater than 7% in patients with both types of DM was diabetic retinopathy with a prevalence of 17%. The main predictors of microvascular complications (individual parameters of diabetic nephropathy) were HbA1c > 7%, elevated diastolic BP, duration of diabetes, and insulin therapy.

A recent study conducted in Shanghai, China, found a prevalence of diabetic nephropathy and diabetic retinopathy of 27.97% and 11.33%, respec-
tively, in patients with T2DM with longer disease duration, elevated HbA1c, also high body mass index, high BP and triglyceride levels as possible independent risk factors [24].

A Hussein et al. study of patients with T2DM in Sudan found a prevalence of nephropathy, retinopathy and neuropathy with an incidence of 38.8, 23.9 and 22.5%, respectively, with HbA1c of 7.85% and the most common comorbidity – hypertension [25].

A 12-year longitudinal study from Karachi, Pakistan [26] confirmed that all microvascular complications were significantly high among diabetic patients with duration of diabetes > 10 years, and HbA1c > 7%. A study of Chui et al. in South China revealed a lot of independent risk factors for diabetic retinopathy in patients with T2DM (male gender, higher education level, longer duration of diabetes, higher systolic BP and HbA1c) [27].

This study showed that had HbA1c > 7% was more common in women, so one of the parameters of diabetic nephropathy with statistical significance was present. Also, a statistical connection was established between the duration of diabetes and presence of neuropathy, as well as between the duration of diabetes and microalbuminuria. Therefore, the duration of DM longer than 10 years may be considered as a possible predictor of these two diabetic microvascular complications.

Studies have shown that in addition to HbA1c and its reduction, that is important for delaying and preventing microvascular complications, BP and its good regulation is also an important parameter [28].

Of the analyzed risk factors, high BP was associated with microalbuminuria and/or proteinuria and/or decreased creatinine clearance as well as unadjusted diabetes or HbA1c > 7%. This finding confirms that in patients with diabetes the already established therapy of diabetic nephropathy is at the same time the therapy of hypertension. Among other risk factors (dyslipidemia, age) that were followed in relation to the presence of microvascular complications, showed no statistical significance.

Meta-analysis of Gorst et al. found an association between HbA1c variability with renal and cardiovascular disease in both types of diabetes [29]. The Diabetes Control and Complications Trial found that retinopathy is associated with HbA1c variability in T1DM, while in T2DM it is still debatable depending on the study and diabetic complications [30–32]. Otherwise, many studies have found a strong association between retinopathy and renal outcomes in patients with T2DM and that retinopathy is an independent risk factor for kidney disease in these patients [33, 34]. In T1DM, as many as 95% of patients with diabetic nephropathy also have diabetic retinopathy [23].

The limitation of this study is that only one sixth of our participants had a 24-hour urine analysis for the presence of microalbuminuria and therefore nephropathy could not be diagnosed, so individual parameters (microalbuminuria and/or proteinuria and/or decreased creatinine clearance) were monitored. Even though we followed participants from one PHC, that is the largest in our country, our results could not be applied in general for patients in the Republic of Srpska. Our study showed poor glycemic control in diabetic patients with already present microvascular complications. All healthcare professionals, especially in primary care, should work with diabetic patients to try to prevent or delay the complications of diabetes.

Conclusion

In conclusion, this study confirmed that the most common microvascular complication in patients with both types of diabetes mellitus was diabetic nephropathy with a prevalence of 24.2%. In these patients, the presence of microalbuminuria and/or proteinuria and/or decreased creatinine clearance was associated with glycated hemoglobin > 7% and elevated diastolic blood pressure. Family physicians should perform regular microvascular complications screening tests according to the official clinical guidelines. Furthermore, longitudinal studies exploring the causal relationship between glycemic control and development of microvascular complications are needed.

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