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The glycosylated haemoglobin A1c and albuminuria in patients with type 2 diabetes in the Republic of Srpska: a cross-sectional study

Glikozilirani hemoglobin A1c i albuminurija kod bolesnika sa tip 2 dijabetesom u Republici Srpskoj: studija preseka

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Abstract

Background/Aim. Glycosylated haemoglobin (HbA1c) is currently the gold standard for glucose monitoring in the patients with diabetes. The aim of the present study was to examine the level of success in implementing international guideline targets with regard to glycaemic control in the patients with type 2 diabetes in the Republic of Srpska. This study also aimed to determine the association of albuminuria with the glycaemic control and lipid levels in this patient population. **Methods.** The participating diabetic patients were those registered in the project titled "Estimation of the quality of glycoregulation and presence of vascular complications in the persons with diabetes in the Republic of Srpska." The study was conducted as a cross-sectional study including 1037 patients. HbA1c was determined by a turbidimetric inhibition immunoassay used Roche Diagnostics. Total cholesterol, triglycerides, LDL-C, and HDL-C were determined by reagents from Roche Diagnostics (Roche Diagnostics, Mannheim, Germany) as well as albumin and creatinine in the urine. **Results.** Mean value for HbA1c was 7.35 ± 1.61% (57 ± 18 mmol/moL). The 49.46% of all participants achieved target values of HbA1c (< 7% or 53 mmol/moL) and 40.30% had albumin to creatinine ratio (ACR) < 30 mg/g. When the patients were divided according to HbA1c (with HbA1c < 7%, 519 patients, and HbA1c ≥ 7.0%, 510 patients) the ACR values were different between these groups (39.00 vs. 79.50, $p < 0.001$). We found no significant difference with respect to lipid status between the groups. **Conclusion.** The patients with type 2 diabetes in the Republic of Srpska, in a large percentage, did not meet targets for glycaemic control. Improvements are necessary in the treatment and maintenance of this disease process to ensure achievement of goals in management of diabetes, which in turn would decrease longstanding complications of type 2 diabetes.

Key words:
diabetes mellitus, type 2; glycated hemoglobin a; proteinuria; lipids.

Apstrakt

Uvod/Cilj. Glikozilirani hemoglobin (HbA1c) je trenutno zlatni standard za praćenje glikoregulacije kod bolesnika sa dijabetesom. Cilj našeg istraživanja bio je da se ispita da li je postignut željeni cilj u pogledu kontrole glikemije kod bolesnika sa dijabetesom tip 2 u Republici Srpskoj u skladu sa međunarodnim smernicama i da li neregulisana glikemija utiče na pojavu perzistentne albuminurije i poremećaj lipidnog statusa kod osoba sa tip 2 dijabetesom. **Metode.** Analizirani uzorak su činili bolesnici sa tip 2 dijabetesom koji su bili uključeni u projekat pod nazivom "Procena kvaliteta glikoregulacije i prisustva vaskularnih komplikacija kod osoba sa šećernom bolešću u Republici Srpskoj". Istraživanje je sprovedeno kao studija preseka u 2013/2014, sa učešćem 1037 bolesnika. Za merenje HbA1c je korišten imunoinhibicijski test, Roche Diagnostics. Ukupni holesterol, trigliceridi, LDL-C i HDL-C izmereni su reagensima Roche Diagnostics (Roche Diagnostics, Mannheim, Nemačka) kao i albumin i kreatinina u urinu. **Rezultati.** Srednja vrednost za HbA1c bila je 7,35 ± 1,61% (57 ± 18 mmol/moL). Od svih ispitanika samo 49,46% postiglo je ciljne vrednosti HbA1c (< 7% ili 53 mmol/moL), a 40,30% imalo je normoalbuminuriju, odnosno, odnos albumina i kreatinina (ACR) u urinu < 30 mg/g. Kada su bolesnici podeljeni prema HbA1c (HbA1c < 7%, broj bolesnika 519 i HbA1c > 7.0%, broj bolesnika 510) dobijena je značajna razlika u ACR vrednostima (39,00 *vs* 79,50; $p < 0,001$), ali nije pronađena značajna razlika između ove dve grupe bolesnika u odnosu na lipidni sta-

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tus. **Zaključak.** Kod osoba sa tip 2 dijabetesom, u Republici Srpskoj, u velikom procentu nisu postignute ciljne vrednosti glikemije. Naši rezultati ukazuju na neophodne dodatne mere kojima bi se postigli ciljevi međunarodnih i lokalnih smernica, a kojima bi se smanjile učestale komplikacije tip 2 dijabetesa.

Ključne reči:
dijabetes melitus, insulin-nezavisni; hemoglobin a, glukozilovan; proteinurija; lipidi.

Introduction

Diabetes Mellitus is the most common metabolic disorder and one of the biggest health problems of the 21st century. The estimated worldwide prevalence of diabetes mellitus was 415 million in 2015 and it is expected to rise to 642 million by 2040 [1]. Diabetes requires continuous medical care with multifactorial strategies aimed at preventing and decreasing risks of chronic complications [2]. Chronic hyperglycaemia is tied to long lasting consequences that manifest in various organ dysfunctions, especially kidneys and blood vessels [1]. Diabetes is the most common cause of kidney failure in the world [3–5], and it is estimated that diabetes increases the risk of end-stage renal disease (ESRD) approximately 12-fold [6].

Additionally, diabetes was found to be associated with a 2–4 fold increased risk of myocardial infarction, congestive heart failure, and peripheral arterial disease [7–9]. Many studies have shown a strong link between nephropathy and atherosclerotic cardiovascular disease in patients with type 1 and type 2 diabetes [10, 11].

Glycaemic control is fundamental to the management of diabetes. Several studies have shown the benefit of intensive glycaemic control in reducing the frequency of diabetic microvascular complications, such as retinopathy and nephropathy. The results of long term follow-up of patients with diabetes, who were enrolled in the earlier trials, showed that initial strict glycaemic control led to a reduction in incidence of microalbuminuria and cardiovascular disease outcomes when compared to standard therapies [12–14]. Glycosylated haemoglobin (HbA1c) is currently the gold standard for glucose monitoring in the patients with diabetes and was increasingly adopted as a criterion for diabetes diagnosis.

HbA1c below or around 7% were shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. The American Diabetes Association (ADA) recommends a HbA1c level of less than 7.0% as the standard glycaemic treatment goal [15].

The aim of the present study was to examine the level of success in implementing international guideline targets with regard to glycaemic control in the patients with type 2 diabetes in the Republic of Srpska. This study also aimed to determine the association of albuminuria with glycaemic control and lipid levels in this patient population.

Methods

Subjects

The participating diabetic patients were those registered in the project titled ''Estimation of quality of glycoregulation and presence of vascular complications in the persons with diabetes in the Republic of Srpska." The study was conducted as a cross-sectional study in 2013/2014, including 1,037 patients, age 18 and above, who were randomly selected from the registers for diabetes mellitus type 2 in 13 Health Centres in the Republic of Srpska.

Criteria for participation in the study included that the patients needed to be registered in the population register for diabetes in The Republica of Srpska and in available Health Center registers for family medicine, be at least 18 years old, and had lived in the Republic of Srpska over the year preceding the study. This study excluded pregnant women diagnosed with gestational diabetes and patient whose psychophysical status presented a difficulty in communication.

For the measurement of biochemical parameters, the blood and urine samples were taken in the morning between 7:00 and 10:00 a.m. after 12–14 h of fasting. The patients were diagnosed with albuminuria with an albumin-to-creatinine ratio equal to or greater than 30 mg/g creatinine.

The study was approved by the National Ethics Committee. Written consent was obtained from the participating subjects.

Biochemical analyses

HbA1c, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were determined by reagents from Roche Diagnostics (Roche Diagnostics, Mannheim, Germany) as well as albumin and creatinine in the urine, according to the manufacturer's instructions. Briefly, for HbA1c, anticoagulated whole blood is haemolyzed prior to determination of HbA1c by a turbidimetric inhibition immunoassay, liberated hemoglobin (Hb) in the hemolyzed sample is converted to a derivative having a characteristic absorption spectrum, and measured biochromatically. The instrument calculates the % of HbA1c from the HbA1c/Hb ratio according to a user-selected protocol [16]. The reference values for HbA1c were < 6.5% or 48 mmol/moL, TC < 5.0 mmol/L, HDL-C ≥ 1.16 ♂/1.30♀ mmol/L, LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and albumin-to-creatinine ratio < 30 mg/g. The urine albumin to creatinine ratio (ACR) was used as the index of urinary albumin excretion. Conventionally, subjects with ACR < 30 mg/g were defined as having normal albuminuria, microalbuminuria was defined as ACR ≥ 30 mg/g and macroalbuminuria as ACR ≥ 300 mg/g [17].

Numerous aspects must be considered when setting glycaemic targets. The ADA proposes optimal targets, but each target must be individualized to the needs of each patient and his or her disease factors. The recommendations include blood glucose levels that appear to correlate with achievement of an HbA1c of 7% (53 mmol/moL). The current guideline recommendations for the Republic of Srpska patients with diabetes is HbA1c < 7.0% (53 mmol/moL) to

prevent complications. Reliability of the measurement results was regularly checked through assessment of appropriate controls and application of internal and external quality control principles. HbA1c data were collected and analyzed for the study using percentage values and converted to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values in mmol/mol, which are also cited for the key values reported in the text and tables.

Statistics

All calculations were performed using the SPSS V. 22.0 (IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to test normality. The outliers were identified and omitted using the Tukey's method. The values are presented as median and interquartile range (Q1/Q3) and mean ± standard deviation. The Mann-Whitney *U*-test was used to compare data between the groups. We analyzed different groups according to albuminuria by the ANOVA test. The relations between the variables were determined using the Spearman's rank-order correlation test.

Results

The study sample consisted of 1037 subjects, 44.5% men and 55.5% women, equally selected from rural and urban areas. Average age was 64, the majority was ≥ 65 years old, 47.9% of subjects. The highest percentage were the patients with a diabetes diagnosis of less than 5 years (42.5%). The characteristics of patients with type 2 diabetes were shown in Table 1. Mean value for HbA1c was 7.35 ± 1.61% (57 ± 18 mmol/moL) [the lowest 4% (20 mmol/moL), the highest 14.50% (135 mmol/moL)]. Of all participants, 49.46% achieved target values of HbA1c, < 7% or 53 mmol/moL. The distribution of HbA1c values was shown in Figure 1. Elevated (≥ 5 mmol/L) was evident in 75.60% of subjects, whereas a low level of HDL-C (< 1.15♂/1.29♀ mmol/L) was present in 55.9% of subjects and high LDL-C (≥ 2.60 mmol/L) was recorded in 86.0% of subjects. The high values of TG (≥ 1.70) were recorded in 54.3% of subjects.

The subjects were divided into two groups, those with HbA1c < 7% (53 mmol/moL), 519 subjects, and those with HbA1c ≥ 7.0% (53mmol/moL), 510 subjects and we found that there was a statistically significant difference with respect to albuminuria between the two groups, whereas we found no statistically significant difference with respect to the lipid status between the groups. The values of biochemical parameters in different HbA1c groups are shown in Table 2.

Table 1
Clinical characteristics of patients with type 2 diabetes mellitus

Parameter	Patients (n = 1,037)
Age (years)	64 (58/71)
Gender (female)	55.5%
Therapy	100%
BMI (kg/m^2)	30.00 (27.00/30.00)
Waist circumference, female (cm)	101.50 (94.00/110.00)
Waist circumference, male (cm)	104.00 (98.00/111.00)
Systolic pressure (mmHg)	140 (130/160)
Diastolic pressure (mmHg)	85 (80/90)
HbA1c < 7.0% (53 mmol/moL)	49.46%
Albumin to creatinine < 30 mg/g	40.30%
HbA1c, % (mmol/L)	7.35 ± 1.61 (57 ± 18)

The values are presented as medians and interquartile range (Q1/Q3) and mean ± standard deviation; n – number of patients; ACR – albumin to creatinine ratio; HbA1c – hemoglobin A1c.

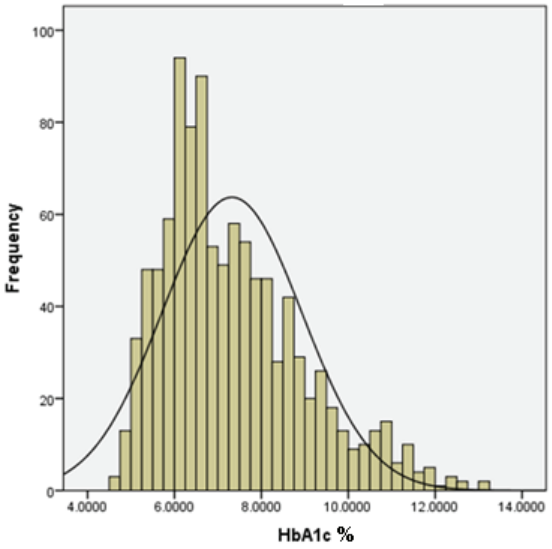

Fig. 1 – Distribution of hemoglobin A1c (HbA1c) values.

Table 2
Parameters in different HbA1c groups in the patients with type 2 diabetes mellitus

Parameter	HbA1c < 7.0% (53 mmol/moL)		HbA1c ≥ 7.0% (53 mmol/moL)		*p*
	n	median (Q_1/Q_3)	n	median (Q_1/Q_3)	
HbA1c (%)	519	6.13 (5.67/6.50)	509	8.25 (7.56/9.33)	< 0.001
or mmol/moL		43 (38/48)		67 (59/78)	
ACR (mg/g)	519	39.00 (10.00/124.75)	510	79.50 (18.00/199.25)	< 0.001
TC (mmol/L)	517	5.76 (4.89/6.66)	516	5.72 (4.93/6.63)	0.738
HDL-C (mmol/L)	520	1.28 (1.07/1.53)	513	1.27 (1.07/1.51)	0.751
LDL-C (mmol/L)	512	3.85 (3.07/4.59)	510	3.72 (3.05/4.51)	0.523
TG (mmol/L)	515	1.82 (1.29/2.52)	512	1.78 (1.31/2.57)	0.640

The values are presented as medians and interquartile range (Q1/Q3). The Mann-Whitney *U*-test was used to compare data between groups. ACR – albumin to creatinine ratio; HbA1c – hemoglobin A1c; TC – total cholesterol; HDL-C – high density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides.

Table 3

Biochemical parameters in different albuminuria groups

Parameters	Groups	n	Median (Q_1/Q_3)	Difference between groups	*p*
ACR (mg/g)	1 (ACR < 30 mg/g)	402	9.00 (6.00/17.00)	1 : 2/1 : 3	< 0.05
	2 (ACR 30–299 mg/g)	508	106.50 (59.00/171.75)	1 : 3	< 0.05
	3 (ACR ≥ 300 mg/g)	115	497.00 (361.00/ 885.00)	1:2	
HbA1c (%) or mmol/moL	1 (ACT < 30 mg/g)	405	6.60 (5.93/7.78) 53 (41/62)	2 : 3	
	2 (ACR 30–299 mg/g)	502	7.20 (6.30/8.50) 55 (45/69)	2 : 1	
	3 (ACR ≥ 300 mg/g)	121	7.43 (6.45/ 8.73) 58 (47/72)	3 : 1	
TC (mmol/L)	1 (ACR < 30 mg/g)	404	5.76 (5.00/6.65)	-	
	2 (ACR 30–299mg/g)	506	5.68 (4.85/6.60)	-	
	3 (ACR ≥ 300 mg/g)	123	5.95 (4.93/ 6.80)	-	
HDL-C (mmol/L)	1 (ACR < 30 mg/g)	404	1.29 (1.08/1.53)	-	
	2 (ACR 30–299 mg/g)	506	1.27 (1.07/1.53)	-	
	3 (ACR ≥ 300 mg/g)	123	1.28 (1.06/ 1.50)	-	
LDL-C (mmol/L)	1 (ACR < 30 mg/g)	400	3.91 (3.18/4.67)	1 : 2	
	2 (ACR 30–299 mg/g)	501	3.68 (2.98/4.44)	2 : 1	
	3 (ACR ≥ 300 mg/g)	121	3.78 (2.98/ 4.57)	-	
TG (mmol/L)	1 (ACR < 30 mg/g)	405	1.87 (1.34/2.52)	-	
	2 (ACR 30–299 mg/g)	502	1.75 (1.24/2.46)	2 : 3	
	3 (ACR ≥ 300 mg/g)	120	1.82 (1.42/2.96)	3 : 2	

The values are presented as medians and interquartile range (Q1/Q3). The ANOVA test was used. ACR – albumin to creatinine ratio; HbA1c – Hemoglobin A1c; TC – total cholesterol; HDL-C – high density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; n – number of subjects.

We subdivided the subjects into three groups with respect to urine albumin concentrations. The group 1 (n = 402) had an ACR < 30 mg/g, the group 2 (n = 508) with albuminuria and ACR > 30–299 mg/g, and the group 3 (n = 115) with ACR ≥ 300 mg/g. We analyzed these groups to determine if differences exist among groups with respect to their lipid statuses and HbA1c values. Biochemical parameters in different albuminuria groups are shown in Table 3.

In our group of patients, there was no correlation between the HbA1c and the ACR index nor with the lipid parameters (results not shown).

Discussion

In this study, we evaluated glycaemic control, albuminuria and the lipid levels in the patients with type 2 diabetes. These are all significant risk factors for complications in these patients. Our data showed that the mean values HbA1c in the patients with type 2 diabetes in the Republic of Srpska (7.35%) were very similar to the values in studies conducted in several other European countries [18, 19]. Also, the prevalence of patients who achieved the target values of HbA1c (< 7%) approaches the reported prevalence in other European countries, i.e., 49.15% vs. 53.6% [19] and 49.15% vs. 55.7% [20]. However, the numbers are still unsatisfactory in striving to achieve the full goals in the prevention of complications in the patients with diabetes. Regardless of advances in the treatment of type 2 diabetes, the studies showed that many patients remain in poor glycemic control [20], which could be attributed to the complex pathophysiology of diabetes as well as noncompliant behaviour of patients with respect to life style changes (nutrition and physical activity) as well as continuation of prescribed therapies. Strategies in following glycaemia and its effects are very important, given that type 2 diabetes is the leading cause of cardiovascular disorders.

The results of our study showed that there was a significant difference with respect to ACR between the groups of patients with the target HbA1c (< 7.0%) and the groups above the target HbA1c values (≥ 7.0 %) ($p < 0.001$). This suggests that the successful therapy, i.e., achieving the target value of HbA1c (< 7.0%), was also successful in reducing microalbuminuria, which is certainly associated with a long-term risk reduction for microvascular complications, including the kidney failure. The results do confirm the knowledge gained from the studies that the patients with type 2 diabetes with higher HbA1c have the higher values of ACR [21].

However, between our two groups, there was no statistically significant difference with respect to the lipid status. We expected a difference between the lipid parameters, given that there was a high presence of pathologic parameters in the lipid statuses of our subjects as well the results of other studies that showed that persistent high levels of albuminuria were correlated with the elevated levels of total serum cholesterol as well as LDL-C, i.e., that albuminuria preceded the development of hypercholesterolemia [22]. We were especially interested in the analysis of the relationship between HDL-C and albuminuria, since many studies showed that these two parameters were implicated in the development of chronic kidney disease [23]. It is interesting that our study did not confirm the results reported in the study by Kim et al. [24] and Sun

et al. [25], where the patients with diabetes and albuminuria had the lower HDL-C values compared to the ones with normal albuminuria. One of the reasons could be that patients were not separated by gender when the analysis of correlation between albuminuria and lipid parameters was done, i.e., with LDL-C and HDL-C that were significantly better in the women. Some studies showed gender differences in the relationship between albuminuria and dyslipidemia [26, 27].

The only statistically significant difference we found was in the values of triglycerides after we subdivided our patients into the groups based on intensity of albuminuria and those results confirmed the results of numerous studies that found that the high TG was associated with ACR in the patients with diabetes [28–30].

This study has limitations. First, the specific types of antihypertensive medication that may influence albuminuria or renal function, such as angiotensin converting enzyme inhibitors or angiotensin II receptor blockers were not taken into account. Second, a number of patients were taking statins, which could have given a skewed picture of the correlation between microalbuminuria and cholesterol (TC, LDL-C and HDL-C). Third, we did not conduct triple measurements of parameters, in different periods of time, due to financial and technical reasons, which could have an influence on data collected.

Conclusion

The patients with type 2 diabetes in the Republic of Srpska, in a large percentage, did not meet targets for glycaemic control. The patients achieving HbA1c < 7% could have reduction of cardiovascular disease risk by reducing their ACR index. Our results do show that there is a large subset of patients with risk factors for complications associated with diabetes, such as the risk of developing renal dysfunction and cardiovascular disease. Improvements are necessary in the treatment and maintenance of this disease process to ensure the achievement of goals in management of diabetes, which in turn would decrease longstanding complications of type 2 diabetes, mortality and costs of treatment.

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