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ORIGINAL ARTICLE

THE EFFECT OF ELEVATED LEVELS OF GLYCOSYLATED HEMOGLOBIN ON PHYSICAL PERFORMANCE IN CARDIAC SURGERY PATIENTS

WPŁYW PODWYŻSZONEGO POZIOMU HEMOGLOBINY GLIKOWANEJ NA WYDOLNOŚĆ FIZYCZNĄ U PACJENTÓW KARDIOCHIRURGICZNYCH

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ABSTRACT

Introduction

The most commonly used biomarker for long-term glycemic control and the diagnosis of diabetes mellitus is glycosylated hemoglobin. Determining its level may provide important information on the risk of complications related to this disease. Research literature review shows that glycosylated hemoglobin may also be prognostic in terms of postoperative outcomes in cardiac surgery patients.

Aim

The aim of this study is to assess the effect of an increased level of glycosylated hemoglobin on physical performance in patients after cardiac surgery.

Materials and methods

109 patients participated in the study, divided into two groups: study – 27 people and control – 82 people. The decisive factor in belonging to the appropriate group was the level of glycated hemoglobin.

Results

Data analysis showed that there were statistically significant differences between the study group and the control group in the mean result of the 6-minute walking test before admission to the ward ($p = 0.005$), in the results of systolic blood pressure measurement before the test ($p = 0.011$), and after performing this test ($p = 0.012$), in the diastolic blood pressure results before ($p < 0.001$), and after the test ($p = 0.001$). The differences were statistically significant also in the heart rate measurement after the 6-minute walk test on admission ($p = 0.019$).

Conclusions

Elevated glycosylated hemoglobin levels may be a factor affecting exercise tolerance in patients after cardiac surgery, which results in reduced effectiveness of cardiac rehabilitation.

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STRESZCZENIE

Wstęp

Najczęściej stosowanym biomarkerem do długoterminowej kontroli glikemii oraz w celu diagnozy cukrzycy jest hemoglobina glikowana. Określenie jej poziomu może dawać istotne informacje na temat ryzyka wystąpienia powikłań związanych z tą chorobą. Przegląd literatury badawczej pokazuje, iż hemoglobina glikowana może mieć również charakter prognostyczny co do wyników pooperacyjnych u pacjentów kardiochirurgicznych.

Cel

Celem niniejszego badania jest ocena wpływu podwyższonego poziomu hemoglobiny glikowanej na wydolność fizyczną u pacjentów po zabiegach kardiochirurgicznych.

Materiał i metody

W badaniu wzięło udział 109 pacjentów, których podzielono na dwie grupy: badaną – 27 osób oraz kontrolną – 82 osób. Czynnikiem decydującym o przynależności do odpowiedniej grupy był poziom hemoglobiny glikowanej.

Wyniki

Analiza danych wykazała, iż pomiędzy osobami z grupy badanej oraz kontrolnej, wystąpiły istotne statystycznie różnice w średnim wyniku testu 6-minutowego marszu przed przyjęciem na oddział ($p = 0,005$), w wynikach pomiaru ciśnienia skurczowego przed testem ($p = 0.011$), a także po wykonaniu tego testu ($p = 0,012$), w wynikach ciśnienia rozkurczowego przed ($p < 0,001$) i po teście ($p = 0,001$). Różnice okazały się istotne statystycznie również w pomiarze tętna po wykonaniu 6-minutowego testu marszowego przy przyjęciu ($p = 0,019$).

Wnioski

Podwyższony poziom hemoglobiny glikowanej może być czynnikiem wpływającym na tolerancję wysiłku u pacjentów po operacji kardiochirurgicznej, co skutkuje obniżoną efektywnością rehabilitacji kardiologicznej.

Słowa kluczowe: rehabilitacja, kardiologia, test marszowy

Introduction

The assessment of the level of glycosylated hemoglobin (HbA1c) in the blood is the most commonly used biomarker for the diagnosis of diabetes mellitus. According to the American Diabetes Association, it is also recommended for monitoring glycemic control in patients with diabetes. It reflects the patient's average blood glucose concentration over the last 3–4 months, which is the average lifetime of the erythrocyte. This is due to the fact that the glycated hemoglobin complex, which is formed from the combination of glucose circulating in the blood with hemoglobin, is removed along with the red blood cells (Halkos *et al.*, 2008; Syed 2011; Kotfis *et al.*, 2019;). Normal HbA1C levels in a healthy person should be around 5% of total hemoglobin. The level of HbA1c of > 6.5% was considered to be the threshold for the diagnosis of diabetes (Syed 2011). In diabetic patients, it is recommended that HbA1c levels be lower than 7%. This is closely related to the risk of developing diabetic complications. The lower the glycated hemoglobin concentration,

the lower the risk of developing these complications (Halkos *et al.*, 2008; Cunningham *et al.*, 2018; Kotfis *et al.*, 2019). Elevated blood glucose levels are often observed in hospitalized patients; therefore, testing the level of HbA1c may be a chance for early detection of diabetes and pre-diabetes in the hospital (Jones *et al.*, 2016; Smulders *et al.*, 2018). Regular HbA1c tests are recommended every 3 to 6 months, depending on the patient's clinical situation (Cha *et al.*, 2016). It is also worth noting that the determination of the HbA1c level does not inform the patient about the daily value of glucose in the blood; therefore, the standard measurement of glucose in the blood is an integral part of the treatment of diabetes (Makris *et al.*, 2011). Compared to the determination of fasting blood glucose, HbA1c is more reproducible and less susceptible to variability. Moreover, it has a prognostic value in relation to future cardiovascular diseases (Ma *et al.*, 2014).

The cardiovascular effect of hyperglycemia is associated with a 2–4 fold increase in the risk of coronary artery disease. The increase in the concentration of free fatty acids and the inhibition of glucose uptake and release result in damage to the function and structure of cardiomyocytes, which, in turn, leads to reduced oxygen transport capacity to cardiomyocytes (Głowacka *et al.*, 2010; Ścibisz *et al.*, 2010). This has an impact on the results of rehabilitation of cardiac surgery patients. In the recovery process, in addition to surgical procedures contributing to the improvement of the blood supply to the heart muscle, an important role, determining both the early and long-term effects of treatment is comprehensive cardiac rehabilitation. The entire recovery process also largely depends on other factors that burden the patient. One of them may be an increased level of glycosylated hemoglobin (Storch-Uczciwek *et al.*, 2007; Zielińska *et al.*, 2009; Pres *et al.*, 2010).

Aim

The aim of this study is to assess the effect of an increased level of glycosylated hemoglobin on physical performance in patients after cardiac surgery.

Material and methods

The research was conducted at the SPSK 2 Cardiac Surgery Clinic of the Pomeranian Medical University in Szczecin in the period from March 2019 to January 2020.

Individuals included in the study were patients who underwent cardiac surgery and then qualified for inpatient cardiac rehabilitation. A total of 109 patients were recruited and divided into two groups: study – 27 people and control – 82 people. The decisive factor in belonging to the appropriate group was the level of glycated hemoglobin. Patients with HbA1c levels higher than 6.5% were the study group, and the control group were those with levels lower than 6.5%.

Data such as diagnosis, comorbidities, baseline fraction, levels of creatinine (Cr), glomerular filtration rate (GFR), C-reactive protein (CRP), creatine phosphate kinase (CKMB), and glycated hemoglobin (HbA1c) were obtained from medical records. In addition, the results of a 6-minute walking test were used to determine physical capacity and the degree of exercise tolerance. In the data analysis, the parameters of blood pressure and heart rate measured before and after the test were also taken into account. Assessment based on the 6-minute walking test was made twice – on the first day of admission to inpatient cardiac rehabilitation and the last day – on the day of discharge.

The first stage of the 6-minute walking test is for the patient to assume a comfortable sitting position in order to rest and normalize vital parameters. The patient's heart rate and blood pressure are measured after 10 minutes. Then, when the 6-minute clock is turned on, the patient has to cover the greatest possible distance, which is measured by the physiotherapist. It is important that the patient walks at his own, free pace. After the time for the test has elapsed, the therapist measures the patient's heart rate and blood pressure again. In the event of any

chest pain, dyspnoea, or imbalance, the test should be discontinued and repeated once the patient's clinical condition is stabilized. It is permissible for the examined person to use a walking aid, in the form of a walker or orthopedic crutches, provided that both tests are performed in the same way.

Cardiac rehabilitation

Comprehensive cardiac rehabilitation was carried out in a stationary mode at the Department of Cardiac Rehabilitation, Department of Cardiac Surgery in Szczecin. The patient's stay in the ward was 3–4 weeks. Rehabilitation was carried out daily, from Monday to Saturday, under the care of physiotherapists. The forms of rehabilitation used included daily patting, as well as breathing exercises using the Trifflo apparatus, which patients performed every hour in the number of repetitions of 3 to 5 deep inhalations and exhalations. Anticoagulation exercises, consisting of simple active movements in the ankle and wrist joints, were prescribed at intervals of 5-minute sessions every hour. Patients also took part in a 20-minute group gymnastics, during which they performed general fitness exercises. An important element of rehabilitation was also systematic training on a cycloergometer. Each patient had an individual training program, selected on the basis of health condition and an exercise test performed on the day of admission to the ward. In addition, each of the patients in their spare time performed lower limb exercises on the rotor at a frequency of 6 times a day for 10 minutes.

Statistical analysis

The statistical analysis was performed using the Statistica 13 licensed program (StatSoft, Inc. Tulsa, OK, USA). The normality of quantitative data distribution was assessed using the Shapiro-Wilk test. Quantitative data were presented as mean, SD and median, and evaluated using the Mann-Whitney U test. Categorical variables were presented as proportions and analyzed using the Chi-squared test or Chi-square test with Yates correction. Univariate and Multivariate logistic regression analysis was performed and presented as odds ratio with 95% confidence interval. Multivariate analysis was adjusted by age, sex, BMI, smoking. The p-value of ≤ 0.05 was regarded as statistically significant.

Ethics and permissions

The study was conducted in accordance with the standards of the Helsinki Declaration. It has been approved by the Bioethics Committee of the Pomeranian Medical University (decision no. KB-0012/43/03/2021/Z).

Results

The characteristics of the subjects divided into patients with glycosylated hemoglobin < 6.5% and ≥ 6.5%, are presented in Table 1. In the analysis of the data, no differences were found between the study group and the control group.

Data analysis showed that there were statistically significant differences between the subjects with glycosylated hemoglobin at a level lower than 6.5% and those with hemoglobin levels higher than 6.5% in the mean result of the 6-minute walking test before admission to the ward (p = 0.005), in the results of the measurement of systolic blood pressure before the test (p = 0.011) and after the test (p = 0.012), in the results of diastolic pressure before (p < 0.001) and after the test (p = 0.001). The differences turned out to be statistically significant also in the heart rate measurement after the 6-minute walking test on admission (p = 0.019).

In the case of measurements made during the 6-minute walking test at discharge from the ward, the differences between the studied groups turned out to be statistically significant only in the case of the test itself (p = 0.016). Detailed results are shown in Table 2.

The assessment of the relationship between the result of the 6-minute walking test and the level of glycated hemoglobin was performed using logistic regression analysis (Table 3).

Table 1. Demographic, disease data, and selected parameters depending on the size of the HbA1c parameter.

		HbA1c < 6.5% (n = 82)	**HbA1c ≥ 6.5% (n = 27)**	**p**
Age [years] (mean ± SD; Me)		67.05 ± 11.28; 68.00	68.14 ± 9.44; 66.00	0.977
Sex (n, %)	male	63 (76.83%)	22 (81.48%)	0.613
	female	19 (23.17%)	5 (18.52%)	
BMI range (n, %)	normal	18 (24.32%)	4 (17.39%)	0.514
	overweight	36 (48.65%)	10 (43.48%)	
	obesity	20 (27.03%)	9 (39.13%)	
BMI (mean ± SD; Me)		27.88 ± 4.35; 27.90	29.15 ± 4.48; 28.44	0.252
Smoking (n, %)		11 (27.50%)	3 (21.43%)	0.655
Medical history				
Heart failure (n, %)		69 (84.15%)	24 (88.89%)	0.546
Arterial hypertension (n, %)		66 (80.49%)	18 (66.67%)	0.138
Renal failure (n, %)		15 (18.29%)	9 (33.33%)	0.102
Arrhythmias (n, %)		18 (21.95%)	5 (18.52%)	0.705
COPD (n, %)		4 (4.88%)	3 (11.11%)	0.252
Kind of operation (n, %)	CABG	48 (58.54%)	17 (62.96%)	0.601
	CABG folded	11 (13.41%)	5 (18.52%)	
	heart valve surgery	13 (15.85%)	4 (14.81%)	
	minimally invasive surgery	3 (3.66%)	1 (3.70%)	
	aneurysm	7 (8.54%)	0 (0.00%)	
Preoperative parameters				
EF [%] (mean ± SD; Me)		45.77 ± 10.40; 50.00	41.92 ± 10.11; 40.00	0.060
CRP [mg/L] (mean ± SD; Me)		5.04 ± 9.97; 1.59	5.12 ± 7.86; 3.14	0.147
Postoperative parameters				
EF [%] (mean ± SD; Me)		45.89 ± 10.34; 45.00	42.96 ± 10.02; 45.00	0.139
CRP [mg/L] (mean ± SD; Me)		249.05 ± 101.31; 264.45	252.05 ± 92.09; 249.84	0.925
GFR [ml/min/m^2] (mean ± SD; Me)		73.27 ± 19.02; 75.00	75.88 ± 22.49; 81.50	0.397
Creatinine [mg/dl] (mean ± SD; Me)		1.06 ± 0.44; 0.98	1.02 ± 0.26; 0.91	0.980

In patients with elevated levels of glycosylated hemoglobin, a statistically significant decrease in the baseline result (OR = 0.994; p = 0.005) was observed in the 6-minute walking test. After regression (adjusted by age, gender, BMI, smoking), a decrease in the distance was confirmed in patients with glycosylated hemoglobin ≥ 6.5% for the baseline 6-minute walking test (OR = 0.991; p = 0.011).

Discussion

The study investigated the relationship between the presence of an increased level of glycosylated hemoglobin and the results of the 6-minute walking test in patients after cardiac surgery incidents.

According to our study, it was found that the increased level of glycosylated hemoglobin has an impact on exercise tolerance in patients after cardiac surgery. Patients with elevated levels of glycosylated hemoglobin obtained lower results of the 6-minute walking test, both before and after rehabilitation, compared to the control group. From the results obtained, it can be concluded that comprehensive cardiac rehabilitation undoubtedly has a beneficial effect for both groups, although patients with increased levels of glycosylated hemoglobin show reduced physical capacity to a greater extent.

Jegdic *et al.* conducted a study aimed at assessing the relationship between

Table 2. Results of the 6-minutes walking test in patients with glycosylated hemoglobin < 6.5% and ≥ 6.5%.

		HgbA1c < 6.5% (n = 82)	**HgbA1c 6.5% (n = 27)**	p
		mean ± SD; Me	mean ± SD; Me	
First 6-MWT distance [m]		**303.09 ± 110.50; 324.50**	**227.56 ± 121.08; 231.0**	**0.005**
Systolic pressure	before	128.15 ± 13.31; 131.00	120.67 ± 13.79; 120.00	0.011
	after	139.68 ± 18.87; 141.00	125.15 ± 30.10; 131.00	0.012
Difference of systolic pressure		11.90 ± 14.37; 10.00	12.26 ± 17.86; 11.00	0.909
Diastolic pressure	before	76.11 ± 10.34; 76.00	68.63 ± 8.74; 69.00	<0.001
	after	77.63 ± 14.48; 78.00	68.22 ± 17.31; 69.00	0.001
Difference of diastolic pressure		3.00 ± 8.40; 3.00	2.46 ± 6.35; 3.00	0.741
Heart rate	before	79.39 ± 11.19; 82.00	77.04 ± 9.65; 76.00	0.302
	after	88.59 ± 13.66; 90.00	82.33 ± 9.56; 83.00	0.019
Difference of heart rate		9.21 ± 11.15; 7.00	5.41 ± 4.88; 6.00	0.081
Last 6-MWT distance [m]		**435.62 ± 102.63; 455.00**	**397.89 ± 97.39; 385.00**	**0.016**
Systolic pressure	before	123.48 ± 13.92; 124.00	121.48 ± 13.89; 123.00	0.619
	after	139.91 ± 18.23; 141.00	142.22 ± 21.59; 143.00	0.619
Difference of systolic pressure		16.93 ± 16.40; 18.00	20.74 ± 13.75; 20.00	0.298
Diastolic pressure	before	70.42 ± 9.22; 70.00	66.70 ± 12.63; 66.00	0.093
	after	74.50 ± 11.97; 74.00	72.00 ± 13.48; 71.00	0.362
Difference of diastolic pressure		4.04 ± 9.84; 3.50	5.29 ± 12.93; 5.00	0.509
Heart rate	before	70.96 ± 10.13; 69.00	70.27 ± 11.12; 65.50	0.483
	after	80.11 ± 13.49; 78.00	77.35 ± 10.54; 75.00	0.431
Difference of heart rate		9.15 ± 7.26; 8.00	7.08 ± 11.66; 9.50	0.890
Difference of 6-MWT distance [m]		**130.55 ± 81.90; 110.00**	**161.85 ± 75.45; 154.00**	**0.056**

Table 3. Multivariate regression analysis for patients with glycosylated hemoglobin < 6.5% and ≥ 6.5%

	HbA1c < 6.5% (n = 82)				**HbA1c 6.5% (n = 27)**			
	p-value	OR	Cl –95%	Cl +95%	p-value	OR	Cl –95%	Cl +95%
No Adjusted								
First 6-MWT distance [m]	0.005	1.006	1.002	1.010	0.005	0.994	0.990	0.998
Last 6-MWT distance [m]	0.100	1.004	0.999	1.008	0.100	0.996	0.992	1.001
Adjusted								
First 6-MWT distance [m]	0.011	1.009	1.002	1.016	0.011	0.991	0.985	0.998
Last 6-MWT distance [m]	0.233	1.005	0.997	1.013	0.233	0.995	0.987	1.003

increased HbA1c levels and reduced physical performance in children with diabetes. 100 people aged 7–17.9 participated in the study. The control group consisted of the same number of healthy people of equal age and sex. The research tool used in the study was the 6-minute walking test. Additionally, the measurements of pulse and saturation were also taken into account. For statistical analysis, the study group was additionally divided into two subgroups: one with HbA1c > 8% and the other with HbA1c < 8%. The results for both groups were worse than the control ($p < 0.001$). The post-test pulse rate

in all subjects was higher than the pre-test pulse rate ($p < 0.001$). The oxygen saturation before the test in the test group was lower compared to the control group ($p < 0.001$), while it decreased in both groups after the test ($p = 0.004$). However, the change in oxygen saturation did not differ between groups ($P = 0.332$) (Jegdic *et al.,* 2013). On the basis of the obtained results, it can be concluded that patients with elevated HbA1c levels were characterized by lower efficiency compared to the control group. The presented results indicate similar conclusions included in the own study, even though the study groups were completely different patients not only in terms of age but also in terms of health condition. Therefore, it may suggest that regardless of age and operations performed, the increased level of glycosylated hemoglobin will be associated with decreased physical capacity.

Stewart *et al.* (2016) conducted a study to assess the physical performance associated with complicated and uncomplicated diabetes using the 6-minute walking test. The study involved 111 people with type 2 diabetes, included in the study group, and 150 healthy people in the control group. The mean results of the 6-minute walking test in diabetic subjects were 376 m, respectively, compared with the control group, which had a mean score of 469 m ($p < 0.001$). In multivariate regression, people with complications of diabetes walked 84 m less, and those without complications – 60 m less than healthy individuals. In the second multivariate analysis, the 6-minute walk distance was found to be 13 meters shorter for each 1% increase in HbA1c. Moreover, in the test group, a higher resting heart rate was observed after the test compared to healthy people in the control group. The oxygen saturation of hemoglobin was higher in the control group than in the diabetic subjects (Stewart *et al.,* 2016). As in the own study, patients from the study group showed a lower level of physical efficiency compared to healthy people.

Nguyen *et al.* (2015) conducted studies aimed at determining the physical capacity of adolescents with good and poor glycemic control. Eight people were qualified to the study group with HbA1c ≤ 7.5%. Another 8 patients were enrolled in the study group with HbA1c ≥ 9.0%. The control group also included 8 healthy people. Patients performed exercises for 7 days under the strict supervision of a therapist. Anaerobic and aerobic muscle functions were assessed with a maximal isometric grip strength test, a Wingate test, and an incremental continuous cycling test until exhaustion. HbA1c levels were also assessed during the study. Statistical analysis showed that the subjects with poor glycemic control showed lower peak oxygen consumption values compared to the control group. Similar dependencies were not found in the people with HbA1c ≤ 7.5% (Nguyen *et al.,* 2015). Accordingly, it can be concluded that the level of glycosylated hemoglobin affects the physical performance of patients, which was also demonstrated in the own study.

The influence of exercises on the blood glucose level in a cardiac patient was also investigated by Denegri *et al.* (2020), who showed that a cardiac rehabilitation program has a positive effect on glycemic control (Denegri *et al.,* 2020).

Physical activity has a significant impact on the correct level of glucose in the serum; therefore, it is recommended for people with impaired carbohydrate metabolism. It is recommended that aerobic exercise should be performed at least 3–4 times a week for 20–60 minutes. The introduction of resistance exercises to training is the next stage that has a positive effect on the patient's condition. According to the research conducted by Seguro *et al.*, resistance training reduces blood glucose levels, systolic and diastolic blood pressure, as well as resting heart rate (Głowacka *et al.,* 2010; Seguro *et al.,* 2019).

The limitation of this study was the small size of the study group, as well as the possible influence of other comorbidities on the test

results. In the course of further research, the number of patients should be expanded.

Conclusions

Elevated levels of glycosylated hemoglobin may affect exercise tolerance in patients after cardiac surgery. Despite the improvement in the results of the 6-minute walk test as a result of rehabilitation in both the control and study groups, people with HbA1c ≥ 6.5% achieved a lower effect. Deterioration of exercise tolerance and reduction of physical capacity results in reduced effectiveness of cardiac rehabilitation.

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