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ASSOCIATION BETWEEN GLYCOSYLATED HEMOGLOBIN AND NEWLY DIAGNOSED HYPERTENSION IN A NON-DIABETIC KOSOVAR POPULATION: A CROSS-SECTIONAL ANALYSIS

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Ключові слова: вітамін D, глюкоза, куріння, гіпертонія

Abstract. Association between glycosylated hemoglobin and newly diagnosed hypertension in a non-diabetic kosovar population: a cross-sectional analysis. Dreshaj Arber, Dreshaj Altin, Veseli D, Sinanaj D., Bresa A., Morina E., Dehari Sh. Diabetes mellitus is a common disease followed by cardiovascular complications, it is a metabolic syndrome with multiple etiology that is characterized by chronic hyperglycemia. Hypertension is a serious health condition that is significantly associated with the risks of heart, brain, kidney, and other diseases. Glycosylated hemoglobin (HbA1c) is diagnostic means of diabetes when fasting (venous) glycemia figures are 126 mg/dl (7.0 mmol/l). The purpose of this study is to focus on the diagnosis, and the treatment of the population with diabetes, identifying the necessary targets to guarantee clinical efficacy. Managing diabetes is challenging, and smoking can complicate it. People with diabetes who smoke often need larger doses of insulin to keep their blood sugar near normal levels. To assess the amount of vitamin D bound to hemoglobin, the study analyzed a number of laboratory parameters in patients with type 2 diabetes. The importance of this study is the estimation of the amount of enzyme-linked immunosorbent vitamin D. Laboratory parameters of diabetic patients were divided into three categories based on increased levels of glycosylated hemoglobin. Vitamin D levels were analyzed in these categories with increased HbA1c values. The influence of smoking

and hypertension on laboratory parameters of diabetic patients was analyzed. The observations were carried out in the form of a database, and the methods that allowed the results for all parameters were followed. The data on the homogeneity of the selected information groups cover 150 patients diagnosed with diabetes mellitus, 40.67% were men, 59.33% were women. Similarly, (in fasting patients), a high OGTT-2-hour glucose level, the hemoglobin test indicates [A1C(HbA1c)] level, cardiovascular disease, and serum vitamin D. Overall, 47.33% of the patients were deficient in vitamin D. Decreased levels of vitamin D were associated with increased levels of glycosylated hemoglobin, while 22% were deficient. As a result, 74.67% of tobacco users had hypertension. Vitamin D deficiency may increase in patients with diabetes, with increased levels of glycosylated hemoglobin.

Реферат. Зв'язок між глікозильованим гемоглобіном і нещодавно виявленою гіпертонією в недіабетичній популяції Косово: перехресний аналіз. Дрешай Арбер, Дрешай Алтін, Веселі Д, Сінанай Д, Бреса А, Моріна Е, Дехарі Ш. Цукровий діабет – це поширене захворювання, що супроводжується серцево-судинними ускладненнями, це метаболічний синдром множинної етіології, що характеризується хронічною гіперглікемією. Гіпертонія – це серйозний стан здоров'я, який значною мірою пов'язаний із ризиками захворювань серця, мозку, нирок та інших захворювань. Глікозильований гемоглобін (HbA1c) є діагностичним засобом виявлення цукрового діабету при показниках глікемії натще (венозної): 126 мг/дл (7,0 ммоль/л). Метою цього дослідження є питання діагностики, а також лікування населення з діабетом, визначення необхідних цілей для гарантування клінічної ефективності. Лікування діабету є складним завданням, а куріння може ускладнити його. Людям з цукровим діабетом, які палять, часто потрібні більші дози інсуліну, щоб підтримувати рівень цукру в крові на нормальному рівні. Щоб оцінити кількість вітаміну D, пов'язаного з гемоглобіном, у дослідженні було проаналізовано ряд лабораторних показників пацієнтів із цукровим діабетом 2 типу. Важливість цього дослідження полягає в оцінці кількості імуноферментного вітаміну D. Лабораторні показники хворих на діабет було розподілено на три категорії на основі підвищення рівня глікозильованого гемоглобіну. Рівні вітаміну D були проаналізовані в цих категоріях з підвищеними значеннями HbA1c. Проаналізовано вплив куріння та гіпертонії на лабораторні показники хворих на діабет. Спостереження проводились у формі бази даних, застосовувались методи, які дозволяють отримати результат для всіх показників. Дані про однорідність відібраних інформаційних груп охоплюють 150 пацієнтів з діагнозом цукровий діабет, 40,67% – чоловіки, а 59,33% – жінки. Таким чином, у пацієнтів натщесерце, високий рівень глюкози OGTT-2 години, тест на гемоглобін вказує на рівень [A1C(HbA1c)], серцево-судинні захворювання та сироватковий вітамін D. Загалом 47,33% пацієнтів мали дефіцит вітаміну D. Зниження рівня вітаміну D було пов'язано з підвищенням рівня глікозильованого гемоглобіну, тоді як у 22% спостерігався дефіцит. У результаті 74,67% споживачів тютюну (із вибірки) мали гіпертонічну хворобу. Дефіцит вітаміну D може збільшуватися у пацієнтів з діабетом при підвищеному рівні глікозильованого гемоглобіну.

This study aims to obtain information on the prevalence and factors associated with type 1 and 2 diabetes in adults aged 35-60 years in the five municipalities studied. Monitoring of patients with diabetes mellitus receiving vitamin D and statistical results in these 150 studied patients. Determination of the self-reported prevalence of diabetes according to sociodemographic factors such as gender, and age and according to lifestyle factors such as smoking, alcohol consumption, and physical activity.

Type 2 diabetes mellitus is a very common disease in Kosovo. According to the office of the World Health Organization in Pristina, there are more than 420 million people affected by diabetes in the world. In poor countries, this disease is very prevalent. About 8% of people in Kosovo suffer from the chronic diabetes. At the Endocrinology Clinic in Kosovo over 90% are patients with type 2 diabetes. Type 2 diabetes dominates both in Kosovo and around the world, within a year, 800-900 patients are treated at the Endocrinology Clinic. Diabetes mellitus, one of the most chronic diseases, appears after cardiovascular diseases, among the chronic diseases is diabetes. Over 60% of samples of diabetes patients have cardiovascular complications, and over 40% have neurological problems.

This is worrisome because these diabetic subjects are predisposed to a foot ulcer, and these subjects may end up in vascular surgery [1, 2]. The economy of Kosovo is very affected by diabetes mellitus. Dealing with such a chronic condition requires a lot of time to treat the disease in the health system of Kosovo. It is a huge financial burden on the health system through medical bills. The loss of working hours due to the morbidity of diabetes mellitus means a reduction in the labor force of the country as a whole [1, 3]. Analytical studies have revealed that an increased risk of diabetes mellitus is associated with worsening vitamin D deficiency [3, 4]. Activation of the vitamin D receptor increases insulin sensitivity [5, 6]. This receptor mediates insulin secretion and protects β -cells against Cy-Ad in association with vitamin D deficiency with duration and glycemic control [7, 8]. Missteps of the polymer at codes 416 and 420 produce the 2 common electrophoretic variants of the protein: Gc1 fast and slow (Gc1f) [9, 10].

The calbindin-D28 K variant affects the active forms of vitamin D in β -cells and then insulin secretion begins. From the monitoring of 794 diabetic samples in Sweden, the results showed that after 17 years, 67% of people with type 1 diabetes mellitus

and 71% of type 2 diabetes mellitus showed symptoms of diabetic retinopathy. Patients with obesity and hyperglycemia who also smoke begin to develop retinopathy between 9-17 years after diagnosis of diabetes mellitus. The smoking-related studies in Finland, which analyzed 41,172 men and 30,700 women over the age of 25, had higher mortality compared to diabetic patients who did not smoke.

According to this study, diabetes mellitus is classified into three groups:

a) Vitamin D deficiency is defined as serum levels of 25-hydroxyvitamin D < 20 ng/ml;

b) Insufficiency of vitamin D in the body is defined as serum 25-hydroxyvitamin D of 20-28 ng/ml;

c) Healthy vitamin D level is defined as serum 25-hydroxyvitamin D > 30 ng/ml.

Glycosylated hemoglobin levels and serum vitamin D levels (n=150) were studied.

Scientific research showed that vitamin D reduces inflammation in the body of diabetes patients, it is a pro-hormone for binding insulin, which is

recommended to be taken in the form of sublimation [11, 12]. Protecting or maintaining vitamin D levels prevents β -cell damage caused by pro-inflammatory cytokines (IL-1 β and IFN- γ) by inhibiting cytokine synthesis [13, 14]. Industrial development reduces people's exposure to sunlight and we are forced to take vitamin D as a supplement. Vitamin D metabolic and immune pathways may be involved in the pathogenesis of diabetes patients at both environmental and genetic levels.

MATERIALS AND METHODS OF RESEARCH

Studies were conducted cross-sectionally to analyze the relationship between newly diagnosed hypertension and HbA1c among non-diabetic Kosovar adults. The data of the sociodemographic study of the participants in the sample were collected using a questionnaire (Table 1). HbA1c was analyzed using the "ichroma II" Apparatus "Diagnostic method side flow immunological analysis based on fluorescence [15, 16].

Table 1

Number of diabetes cases in Peja Regional Hospital, according to municipalities, 2021-2023

Municipality	Cases											
	year 2021				year 2022				year 2023			
	diabetes 1		diabetes 2		diabetes 1		diabetes 2		diabetes 1		diabetes 2	
	M	F	M	F	M	F	M	F	M	F	M	F
Peja	11	5	81	89	12	7	80	92	16	8	109	93
Deçan	7	4	58	78	7	4	57	77	7	4	77	79
Istok	6	7	60	79	7	8	66	80	7	7	68	89
Klina	5	3	67	79	6	4	77	89	6	5	79	91
Junik	5	4	23	35	5	4	27	39	6	4	37	39
	34	23	289	281	37	27	307	377	42	28	370	391
Total	627				748				831			

The Rafshi i Dukagjini extends to a length of 70 km and a width of 43 km. According to the 2011 census, the total population of this region is 228,538 inhabitants. The collection and trading of forest products are the traditional economic acti-

vities of the region, in addition to agriculture, grazing, and forest exploitation. The sample in this study consisted of 5 localities in the region. The sample consisted of 150 studied participants, a sample age over 35 years (Table 2).

Table 2

Statistical presentation of the population with type 2 diabetes

Variables	Subgroup	Frequency (N)	(%)
Gender of DM patients	Males	61	40.67
	Females	89	59.33
Vitamin D status (Classification)	Vitamin D deficiency	71	47.33
	Vitamin D insufficiency	33	22
	Optimal level of vitamin D	46	30.67
Age groups (n=150)	35-45 years	25	16.67
	45-60 years	42	28
	Over 60 years	83	55.33
Total		150	100

The results of microbiological analyses of the samples also showed urinary tract infections and other concomitant diseases of diabetic patients, positive for several types of cyanobacteria (*E. coli*, *Klebsiella*, *Morganella morganii*, *Pseudomonas*, *Staph.*

aureus) (Table 3). Norms of the "WMA Declaration of Helsinki" – paragraphs 7. 10. 12, 13, Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect health and their rights [17, 18].

Table 3

Sensitivity of diabetic patients with positive urine culture/diabetic control (n=150)

	Urine cultures		Total	%
	gender (n)			
	F	M		
<i>Citrobacter species</i>	3	0	3	10.71
<i>E. coli</i>	7	6	13	46.43
<i>Klebsiella</i>	2	2	4	14.29
<i>Morganella Morganii</i>	1	0	1	3.57
<i>Pseudomonas</i>	0	4	4	14.29
<i>Staph. aureus</i>	3	0	3	10.71
Total	16	12	28	100

Data collection is one of the most important stages of the research process. The research project was carried

out in the field, namely the collection of data in the five studied municipalities with diabetes mellitus, so the



results are accurate and reliable. The statistical results were realized with the "Excel" program, which is a program created by Microsoft Office. The statistical results were analyzed and discussed, based on these studied results a comparison was made with the results of other world clinics that treat diabetes.

RESULTS AND DISCUSSION

Statistical analysis

Data were analyzed using SPSS for Windows (version 22.0). Continuous data (including HbA1c) were checked for normality using the Shapiro-Wilk test and found that all data were not normally distributed. The Shapiro-Wilk test tests whether a sample comes from a normally distributed population. The test is sample size biased, so it can give statistically significant results for any large sample.

The results of this study showed that smoking is significantly increases the risk of cardiovascular disease in patients with diabetes. Smokers who use 5 to 12 cigarettes per day are at high risk for cardiovascular disease. Smokers who use more than 16 cigarettes per day have an increased risk of cardiovascular disease and the stroke rate increases by

11.61%-22.12%, respectively. A similar trend is observed with alcohol consumption, increasing the risk of myocardial infarction (more than 18%) compared to heart attack (22.12%) in patients aged 35-60 years. Smoking is the leading cause of type 2 diabetes, with the risk of developing diabetes 30-40% higher for active smokers than for non-smokers.

The risk of type 2 diabetes increases by 16% for every increase of 10 cigarettes smoked per day. The results showed that from 150 patients with diabetes 56.67% were smokers and 74.67% had hypertension. The study shows that these people have erectile dysfunction and according to age it is as follows: 20-30 years old – 5-10%; 40-50 years old – 20-40% and over 50 years old – 50-70%. Diabetic samples (age: ≥ 35 years) consumption of a daily vitamin D dose of 4000 IU does not prevent diabetes (Table 4). Maintaining a vitamin D level of 80 nmol/l or more is known to be adequate for maintaining homeostasis and normal glucose levels in the body. Vitamin D reduces the activation of the NF- κ B enzyme, which is a regulator of genes that have a role in encoding proinflammatory cytokines.

Table 4

Correlation of vitamin D levels/diabetic control. Nine weeks of treatment with vitamin D supplementation did not change mean serum TC, TG, HDL, or LDL cholesterol concentrations versus baseline, (n=150)

Vitamin D status (Classification)	Hemoglobin control A1C (HbA1C)						Cholesterol control		
	good control	%	fair control	%	poor control	%	variable (mg/dl)	before treatment	after treatment
Vitamin D deficiency	11	33,33	16	36,36	20	27,39	T-COL	189.2 \pm 30.1	171.5 \pm 29.12
Vitamin D insufficiency	7	21,21	10	22,73	24	32,88	TAG	225.4 \pm 69.12	199.0 \pm 56.14
Optimal level of vitamin D	15	45,46	18	40,91	29	39,73	LDL-C	106.5 \pm 24.8	101.0 \pm 22.21
Total	33	100	44	100	73	100	HDL-C	41.2 \pm 7.4	37.9 \pm 6.31

Vitamin D regulates calbindin, a cytosolic protein, this protein binds to Ca²⁺, which is found in tissues, including pancreatic β cells. Calbindin has been shown to have the ability to protect against cytokine-induced apoptosis that can cause an increase in cytosolic free calcium.

Protection from cytokine-induced apoptosis is essential for the transmission of the death signal from the cell surface to intracellular signaling pathways

such as: (FasL/FasR, TNF- α /TNFR1, Apo3L/DR3, Apo2L/DR4 and Apo2L/DR5 are now respectively death ligands and receptors). CoR proteins [(Recombinant Cor a 1 (1.0401))], released from steroid/thyroid hormone receptor transcription factor, act as a co-activator protein and have chromatin structures that loosely interact with RNA polymerase 2 receptor.

Smoking causes the development of diabetes mellitus, cardiovascular problems, and increases

insulin resistance. Smoking among women in Kosovo (Kampionet) has reached over 41%, which is a high rate among Kosovar women (Table 5). Recent studies have shown that diabetes mellitus worsens the

metabolic function of glucose hemostasis and increases insulin resistance. It has negative effects on diabetic nephropathy and creates independence with glucose control (Fig.).

Table 5

Distribution of age-variable risk factors/diabetic control (n=150)

Modifiable risk factors		30-41 years	41-61 years	61-70 years	Total	%
Diabetes mellitus	M	12	19	30	61	40.66
	F	21	25	43	89	59.33
Total		33	44	73	150	100
Hypertension	Yes	28	31	53	112	74.67
	No	5	13	20	38	25.33
Total		33	44	73	150	100
Smoking	Yes	17	28	40	85	56.67
	No	16	16	33	65	43.33
Total		33	44	73	150	100

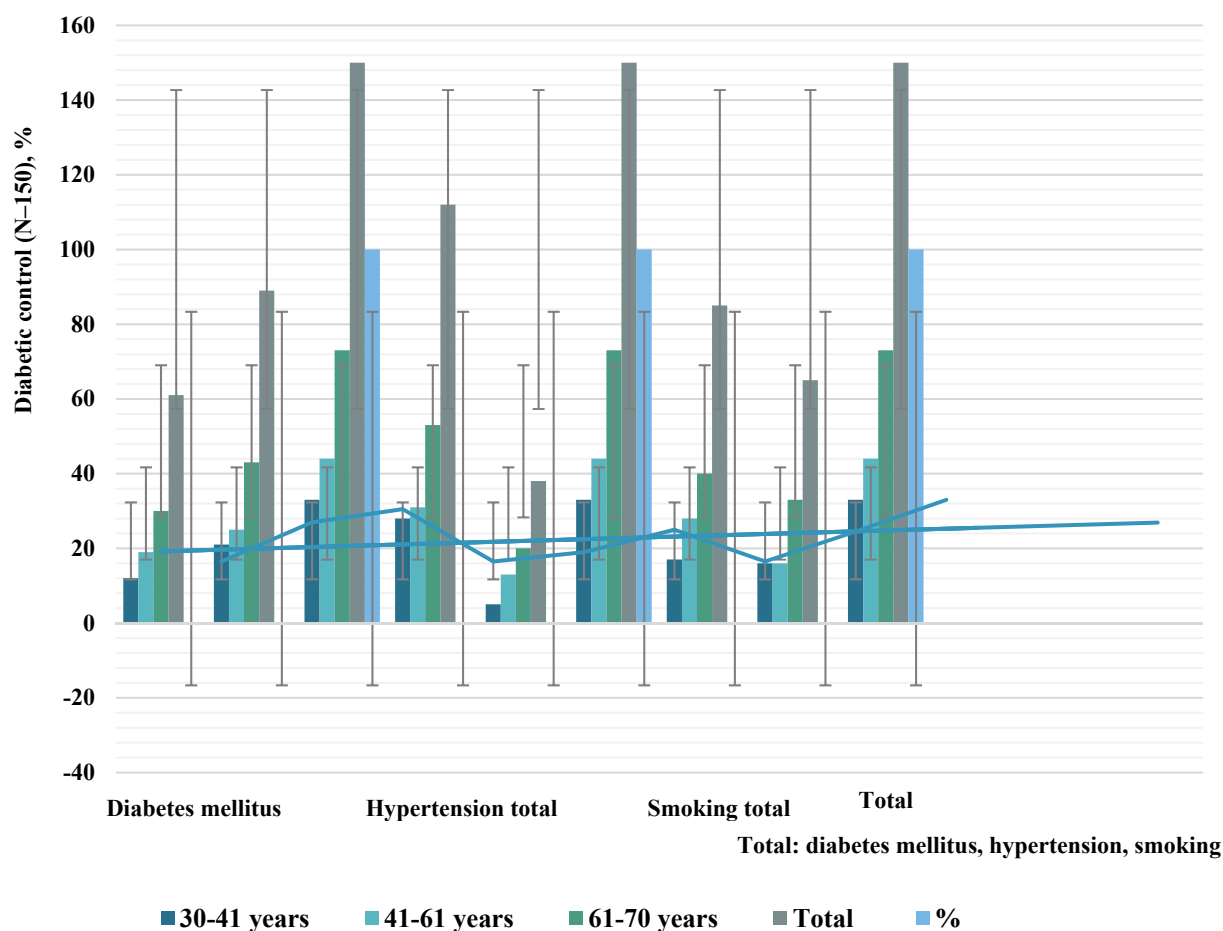
In type 1 diabetes if it lasts 20-25 years, the possibility of diabetic nephropathy is 21%. Extending over 40 years, diabetic nephropathy increases by over 10%, it has been proven that the vulnerability in men is 46%, while in women it is 32%. In diabetic retinopathy 20 years after the onset of diabetes, 90% of patients with type I diabetes and >60% of those with type II diabetes present eye involvement. Diabetic neuropathy is diagnosed in 50% of patients affected by diabetes mellitus.

Diabetes mellitus represents a major health, for social, and economic problem the population in Kosovo, but also throughout the contemporary world, especially in underdeveloped and developing countries. Studies have shown that in diabetic patients who smoke, depending on age, symptoms of arterial hypertension are observed in 112 cases. The number of cases in the study shows that 40.67% are men and 59.33% are women. Research showed that the number of patients with vitamin D deficiency is 47.33%, vitamin D insufficiency – 22%, and optimal vitamin D level – 30.67%. As a result, 70% of patients need vitamin D intake at all ages. Diabetes and high blood

pressure are two diseases that occur in humans and are part of the metabolic syndrome. Among patients with diabetes mellitus aged 30 to 70 years, according to Table 5, the number of cases of hypertension also increases with age, from 25% to 74.67%. And in patients with diabetes who smoke, the risk of increased blood pressure increases from 43.33% to 56.67%.

The most common complications in these patients are diabetic nephropathy, diabetic retinopathy and diabetic neuropathy. If type 1 diabetes lasts 20-25 years, the possibility of diabetes nephropathy is 21%. Diabetic nephropathy increases by over 10%, it has been proven that the vulnerability in men is 46%, while in women it is 32%. In diabetic retinopathy 20 years after the onset of diabetes, 90% of patients with type I diabetes and >60% of those with type II diabetes present with eye involvement. Diabetic neuropathy is diagnosed in 50% of patients affected by diabetes mellitus. Analytical results as for maintaining a normal concentration of vitamin D in the body – about 33.33%, while about 21.21% – vitamin D deficiency, and about 45.46% – the optimal value.





Graphical representation of modifiable risk factors with age/diabetes control

Poor control results is 27.39% and in the optimal level of vitamin D – 39.73%. In patients with vitamin D deficiency, cholesterol levels (mg/dL) before taking vitamin D averaged 189.2 ± 30.1 , and after – 171.5 ± 29.12 . There was no statistically significant difference between these indicators (Table 4). There was no statistically significant difference in cholesterol concentrations between groups when TAG, LDL-C, and HDL-C were analyzed. The mean difference was 13.33% (mg/dL). In patients with diabetes mellitus, whose urine analysis revealed urinary tract infections and other concomitant diseases, positive culture of cyanobacteria was detected in 18.66% of cases (*E. coli*, *Klebsiella*, *Morganella morganii*, *Pseudomonas*, *Staph. aureus*).

Laboratory analyses of these patients (10.66% – female patients and 8% – male) showed that *Escherichia coli* dominates – 46.43%, *Klebsiella* with *Pseudomonas* – 14.29%, and a small percentage of bacterium *Morganella Morganii* 3.57% was isolated (Table 3). These bacteria are the result of consuming contaminated food and water. Eating

contaminated food causes pneumonia and urinary tract infections, 75% to 95% of urinary tract infections are caused by *E. coli*.

Since almost every day we are facing an increase in the number of patients with diabetes mellitus, it is very important to take preventive measures. These measures would be very necessary to achieve positive results as for this disease, which tends to increase continuously.

CONCLUSION

1. Due to the increase in the incidence of diabetes in the Dukadjin Plain region, monitoring over the past three years has shown that in the studied municipalities the average increase in the number of patients was 102 people in 2021-2023. The statistical results show that the number of cases is greater in the females than in males. Studies with diabetes mellitus in smoking patients have shown a significant increase in hypertension cases compared to non-smoking patients.

2. Therefore, educating the population about diabetes is essential for the treatment of diabetes

mellitus in Kosovo. It is essential to provide information to the population on the importance of the type of food we consume and the importance of physical activity. In cases with diabetes mellitus, it is recommended to do the monitoring, first of all examination of the eyes, assess the cardiovascular risk at the time of diagnosis.

3. Monitoring of high arterial pressure of people with diabetes mellitus. Increased blood pressure levels in the study are associated with a wide range of health problems in people with diabetes, especially cardiovascular disease, and eye and kidney damage. In the study, in patients with type 2 diabetes a progressive loss of beta cell function was observed, so insulin remains the only therapy for reducing the level of glucose in the blood.

4. In this study, patients receiving medically recommended vitamin D performed significantly

better than some patients who did not receive enough vitamin D.

Contributors:

Dreshaj Arber – conceptualization, writing of the original draft, writing – review and editing, formal analysis, investigation;

Dresaj Altin – project administration, supervision, validation;

Veseli D – data curation, visualization;

Sinanaj D. – methodology;

Bresa A. – sources;

Morina E. – investigation;

Dehari Sh. – writing – revision and editing, acquisition of funding.

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