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Anemia in Patients with Type 2 Diabetes

Anemija u bolesnika s tipom 2 šećerne bolesti

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Summary

Objectives: The aim of the research is to examine the frequency and types of anemia in patients with type 2 diabetes depending on gender, age, and therapy for the treatment of diabetes mellitus.

Material and methods: The research is a cross-sectional study with historical data. The research used data collected during regular check-ups for patients with type 2 diabetes in primary health care offices in Osijek Health Center from February to June 2022. The collected data were demographic data, data on the duration of diabetes and the used therapy, data on the presence of diabetic nephropathy, fasting glucose values, values of glycosylated hemoglobin, iron, unsaturated and total iron binding capacity, hemoglobin, average erythrocyte volume, average hemoglobin in erythrocyte and average concentration of hemoglobin in erythrocyte.

Results: Anemia was recorded in 19% of the subjects and was usually normocytic normochromic, characterized as mild or moderate. Etiologically, the most prevalent were anemia of chronic disease and mixed anemia. The average age of patients with anemia was 12 years higher than those without anemia. Normocytic normochromic and hypochromic anemia occurred statistically significantly more often in elderly patients, as did mixed anemia. No difference was observed in the frequency of anemia regarding the treatment of diabetes with monotherapy or combined therapy. A significantly higher frequency of anemia was observed in patients who used sulfonylurea derivatives. The first 5 years of metformin treatment were significantly associated with the onset of anemia of chronic disease, and treatment lasting longer than 10 years with the onset of mixed anemia.

Conclusion: Regular screening is essential as a part of routine controls because patients with type 2 diabetes have a high incidence of anemia. This is especially significant for elderly individuals with renal insufficiency and poor disease control, as well as for patients receiving sulfonylurea derivative treatment.

Keywords: Anemia, Type 2 Diabetes mellitus, Diabetic complications, Metformin, Sulfonylurea Derivatives

Sažetak

Cilj istraživanja: Cilj istraživanja jest ispitati učestalost i vrste anemija kod osoba s tipom 2 šećerne bolesti ovisno o spolu, dobi i terapiji za liječenje tipa 2 šećerne bolesti.

Ispitanici i metode: Istraživanje je ustrojeno kao presječno s povijesnim podacima koji su prikupljeni u ambulantama primarne zdravstvene zaštite u Domu zdravlja Osijek od veljače do lipnja 2022. Godine,

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pri redovitim kontrolama bolesnika s tipom 2 šećerne bolesti. Prikupljeni su demografski podaci, podaci o trajanju šećerne bolesti i terapiji, podaci o prisutnosti dijabetičke nefropatije, vrijednosti glukoze natašte, vrijednosti glikoliziranog hemoglobina, željeza, nezasićenog i ukupnog kapaciteta vezanja željeza, hemoglobina, prosječnog volumena eritrocita i prosječnog hemoglobina u eritrocitu te prosječne koncentracije hemoglobina u eritrocitu.

Rezultati: U 19 % ispitanika zabilježena je anemija, najčešće normocitna normokromna, karakterizirana kao blaga ili umjerena. Etiološki su najzastupljenije anemija kronične bolesti i miješana anemija. Prosječna dob osoba s anemijom 12 je godina veća od prosječne dobi osoba bez anemije. Normocitna normokromna i hipokromna anemija statistički značajnije su se češće pojavljivale u osoba starije životne dobi, kao i miješana anemija. Nije uočena razlika u učestalosti anemije s obzirom na liječenje tipa 2 šećerne bolesti monoterapijom ili kombiniranom dijabetološkom terapijom. U osoba koje su koristile derivate sulfonilureje uočena je značajno veća učestalost anemije. Prvih pet godina liječenja metforminom značajno je povezano s nastankom anemije kronične bolesti, a liječenje koje traje dulje od 10 godina s nastankom miješane anemije.

Zaključak: Zbog visoke incidencije anemije u osoba s tipom 2 šećerne bolesti potrebno je vršiti probir u sklopu redovitih kontrola, a posebice u osoba starije životne dobi s bubrežnom insuficijencijom te lošom kontrolom bolesti, kao i u osoba liječenih derivatima sulfonilureje.

Ključne riječi: anemija, šećerna bolest tip 2, komplikacije šećerne bolesti, metformin, derivati sulfonilureje

Introduction

Diabetes mellitus (DM) with vascular complications is one of the main causes of death worldwide.[1] The number of people between the ages of 20 and 79 who were diagnosed with DM increased from 285 million in 2009 to 463 million in 2019, accounting for 95% of patients with type 2 diabetes mellitus (T2DM), according to the 2022 International Diabetes Federation (IDF) reports.[2] Globally, the number of adults with DM is predicted to rise to 783 million by the year 2045, which is posing a serious threat to public health.[3,4] Poor control of glycemic status is extremely important for the control of DM, and is associated with the development of complications that impair functional ability, autonomy, and quality of life, eventually also leading to high mortality.[5]

T2DM is a condition that eventually impairs the operation of nearly every organ in the human body. Therefore, the most significant issue for individuals with DM are chronic complications, and the most prevalent are: diabetic nephropathy, retinopathy, neuropathy, diabetic foot, brain stroke, and coronary artery disease causing myocardial infarction.[6] Anemia can also be one of the many chronic complications of T2DM. According to World Health Organization (WHO) standards, anemia is a common blood condition characterized by a hemoglobin level of less than 130 g/L for males and less than 120 g/L for females. Iron deficiency is the cause of around half of all anemia cases worldwide.[7] Anemia is known to have a major role in the illness, resulting in symptoms such as low energy, breathlessness, lightheadedness, poor appetite, reduced cognitive function, and ability to work, all of which negatively affect the patient's social life. Because of all the above mentioned, patients with anemia typically have a worse quality of life, so we can say that anemia is an unwelcome extra burden for diabetic individuals who already have an increased risk of acute and chronic complications.[8,9]

Anemia is twice as common in patients with T2DM as in non-diabetic patients and has been linked to end-stage renal and cardiovascular diseases (CVD).[10] Moreover, patients with diabetes with lower hemoglobin levels are more likely to require hospitalization.[11] DM is considered to be the leading cause of chronic renal disease (CKD) in Western countries, and anemia as a frequent complication of CKD is occurring in almost half of patients with CKD.[12] However, DM is a risk factor for the development of anemia regardless of the presence of CKD, which is confirmed by the NHANES-III study, according to which patients with diabetes have a 1.7 times higher risk of anemia compared to individuals without diabetes with the same degree of renal damage functions.[13] Anemia is also more frequent in patients with diabetes and normal kidney function and can occur even before the decline of renal function.[14,15] Patients with diabetes have a higher risk and earlier occurrence of anemia[16] compared to patients with the same degree of kidney damage from other etiologies.

Chronic diseases such as DM are often accompanied by mild to moderate normocytic, normochromic anemia, so this is also the case in patients without CKD. The mentioned type of anemia is considered an anemia of inflammation, and we also call it anemia of a chronic disease. Proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) play an important role in its development, and hyperglycemia

is directly related to their increased expression. The above is also associated with other complications besides anemia, especially cardiovascular complications.[17] The erythrocyte lifespan in anemia of chronic disease is reduced from 120 to 80 days. This is explained by the fact that the inflammatory process causes the mononuclear phagocytic system to become hyperactive, which causes the early evacuation of circulating red blood cells (RBCs) from the body. Moreover, a decreased bone marrow response to erythropoietin (EPO) and reduced erythropoiesis due to an inadequate iron supply all contribute to anemia.[18]

Systemic inflammation, inhibition of EPO release, damage to the renal interstitium, and severe autonomic neuropathy, which results in efferent sympathetic denervation of the kidney, affecting the production of EPO and RBCs, are some of the factors proposed as the cause of the earlier onset of anemia in patients with diabetes. Individuals diagnosed with T2DM often have deficiencies in iron, folate, and/or cyanocobalamin, which can lead to various forms of anemia. Certain medications, including metformin, might additionally hinder the absorption of cyanocobalamin, which could lead to a vitamin B12 deficit; however, research in this area has produced inconsistent findings.[19]

Although anemia is a common complication in patients with T2D, it is frequently overlooked and untreated. It can negatively impact the appearance and progression of other diabetes-related complications, which can accelerate the progression of anemia, leading to a vicious cycle.[20] In people with T2DM, anemia is considered a robust and independent predictor of an elevated risk for both macrovascular and microvascular complications associated with the disease and therefore must be considered when conducting routine examinations.[16]

Our study was intended to determine the type and frequency of anemia in individuals with T2DM and to investigate whether there are any differences regarding age, gender, and therapy used for T2DM treatment.

Respondents and methods

The research was organized as a cross-sectional study with historical data and was conducted in Osijek Health Center, in primary healthcare offices, from February 2022 to June 2022. The research was approved by the Ethics Committee of Osijek Faculty of Medicine, J.J. Strossmayer University in Osijek, and carried out according to the principles of the Declaration of Helsinki. Respondents gave written consent to participate in the research. Data was collected through regular controls from the database "Central Health Information System of the Republic of Croatia" (CEZIH). The collected data is anonymous. During the research, the following data were collected from the available medical documentation: age, gender, duration of T2DM, the type of drugs used for the treatment of T2DM, the presence of diabetic nephropathy as a complication of diabetes, values of fasting plasma glucose, glycosylated hemoglobin A1c (HbA_1c), iron (Fe), unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC), hemoglobin (Hb), average volume of erythrocytes (MCV), mean erythrocyte hemoglobin (MCH) and mean erythrocyte hemoglobin concentration (MCHC). The value of TIBC was calculated by summing the values of Fe and UIBC. Anemia was defined by reduced hemoglobin values (Hb < 130 g/L for men and Hb < 120 g/L for women). Hemoglobin values were also used to determine the severity of anemia, so severe anemia was defined as Hg < 80 g/L, moderate anemia as hemoglobin values from 80 to 110 g/L, and mild anemia as Hg > 110 g/L.[21] The values of MCV and MCHC were used for the morphological classification of anemia. Concerning the values of MCV, anemias were divided into macrocytic, in which the MCV is > 97.2, normocytic, with MCV between 83 and 97.2, and microcytic, in which the MCV is < 83. According to the values of MCHC, anemias were divided into hypochromic with MCHC < 320, normochromic with MCHC from 320 to 345, and hyperchromic with MCHC > 345. The etiological classification of anemia into sideropenic anemia, anemia of chronic disease, mixed anemia, anemia of chronic renal insufficiency, and non-specific anemia was also made. Iron values are reduced in sideropenic anemia, anemia of a chronic disease, and mixed anemia. To distinguish sideropenic anemias from the remaining two types, which are characterized by reduced iron values, iron-binding capacity values (UIBC, TIBC) were used. These values are elevated in sideropenic anemia, lowered in anemia of a chronic disease, and in mixed anemia they can be lowered or within the reference values. Transferrin saturation (TSAT) was calculated according to the formula: TSAT = Fe/TIBC to differentiate between anemia of a chronic disease and mixed anemia. Therefore, anemia of chronic disease was determined by decreased iron and TIBC values and normal or slightly decreased TSAT, while in mixed anemia, iron values were decreased, TIBC was decreased or normal, and TSAT was significantly decreased (TSAT < 10%).[22] Normocytic or macrocytic anemia, with iron values within the reference intervals and in the presence of diabetic nephropathy, were classified

as anemias of chronic renal disease.[23] The remaining anemias in which no iron deficiency was observed were classified as non-specific anemias.

Categorical data were represented by absolute and relative frequencies. Differences in categorical data were tested with the χ^2 test and, if necessary, Fisher's exact test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. In the case of normal distributions, numerical variables were described by the arithmetic mean and standard deviation and, in other cases, by the median and the interquartile range. Differences of normally distributed numerical variables between two independent groups were tested by Student's t test. In the case of deviations from the normal distribution, the differences in numerical variables between independent groups were tested with the Mann-Whitney U test. All P values are two-sided. The significance level was set at Alpha = 0.05. For statistical analysis we used the statistical program MedCalc® Statistical Software version 20.109 *(MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022)*.

Results

Seventy-eight subjects (56% women) with T2DM participated in the research. The median age was 71 years, and 19% had anemia. The median value of HbA1c was 6.95% with an interquartile range of 6.3 to 7.9%, while the median value of fasting blood glucose was 7.7 mmol/L with an interquartile range of 6.5 to 9.3 mmol/L. The median duration of diabetes in the subjects was 8 years. No statistically significant difference was observed in the occurrence of anemia regarding fasting plasma glucose values, HbA1c values, and duration of diabetes (Table 1).

According to the morphological classification, the most common anemias were normocytic normochromic (36.84%) and microcytic hypochromic anemias (21.05%). Considering etiology, the most common were unspecified anemia and anemia of chronic disease in 47.37% of cases. All anemias were mild (46.67 %) or moderate (53.33 %).

Subjects with anemia were statistically significantly older than those without anemia (Mann-Whitney U test, P = 0.03) (Table 1).

Table 1 Characteristics of the respondents included in the research
Tablica 1. Osnovna obilježja ispitanika uključenih u istraživanje

	Type 2 diabetes/ *Tip 2 šećerne bolesti*	Subjects without anemia/ *Ispitanici bez anemije*	Subjects with anemia/ *Ispitanici s anemijom*	P*
Number of subjects (N, %)/ *Broj ispitanika (N, %)*	78 (100)	63 (81)	15 (19)	
Age (years)/ *Dob (godine)*	71 (59 - 78)	66 (59 – 77)	78 (70 – 82)	**0,03**†
Duration of type 2 diabetes (years)/ *Trajanje tipa 2 šećerne bolesti (godine)*	8 (4 – 15)	8 (4 – 15)	10 (2,5 – 14,8)	0,97
HbA_1c (%)	6,95 (6,3 – 7,9)	7,1 (6,4 – 7,9)	6,5 (5,8 – 7,7)	0,24
Fasting plasma glucose (mmol/L)/ *Glukoza u plazmi natašte (mmol/L)*	7,7 (6,5 – 9,3)	7,7 (6,6 – 9,3)	7,7 (5,9 – 10,9)	0,89

*Mann-Whitney U test; Bold denotes statistical significance/*Podebljano označva statističku značajnost*
†at the P<0.05 level, higher values are significant in the group of subjects with anemia/†*na razini P<0,05 značajne su više vrijednosti u skupini ispitanika s anemijom*
Values: age, duration of type 2 diabetes, HbA_1c and fasting plasma glucose are expressed as median (interquartile range)/*Vrijednosti: dob, trajanje šećerne bolesti tipa 2, HbA_1c i glukoze u plazmi natašte iskazane su kao medijan (interkvartilni raspon).*

According to the morphological classification, certain types of anemia were also more common in the elderly, namely normocytic hypochromic (Mann-Whitney U test, P = 0.007) and normocytic normochromic anemias (Mann-Whitney U test, P = 0.04). Etiologically, mixed anemia occurred statistically significantly more in elderly people (Mann-Whitney U test, P = 0.04), while no statistically significant difference in the severity of anemia was found depending on the age of the subjects.

Furthermore, 73.3% of patients with anemia were

women, and although microcytic hypochromic and normocytic normochromic anemia were more common in women, no statistically significant difference was observed in the occurrence of individual morphological types of anemia with regard to gender. Etiologically, all types of anemias were more common in women than in men. However, no statistically significant difference was observed in the occurrence of certain etiological forms of anemia, nor in the severity of anemia with regard to gender.

55% of subjects in the study used monotherapy for the treatment of T2DM, while the rest used combined antidiabetic therapy, and 27% of them were treated with insulin therapy (Tables 2 and 3). No statistically significant difference was observed in the frequency of anemia among subjects on monotherapy and combined antidiabetic treatment.

Table 2 Types of therapy of type 2 diabetes in respondents included in the research
Tablica 2. Načini liječenja šećerne bolesti tipa 2 u ispitanika uključenih u istraživanje

	Number of subjects (N,%)/*Broj ispitanika (N,%)*	Total (N,%)/*Ukupno (N,%)*
Oral therapy/*Peroralna terapija*	57 (73)	
Insulin therapy/*Inzulinska terapija*	11 (14)	78 (100)
Combined insulin and oral therapy/*Kombinirana inzulinska i peroralna terapija*	10 (13)	
Combined therapy/*Kombinirana terapija*	35 (45)	78 (100)
Monotherapy/*Monoterapija*	43 (55)	

Table 3 Medicines used in the treatment of type 2 diabetes in respondents included in the research
Tablica 3. Lijekovi korišteni u liječenju šećerne bolesti tipa 2u ispitanika uključenih u istraživanje

	Monotherapy (N,%)/*Monoterapija (N,%)*	Combined with other therapy (N,%)/*Kombinirano s drugom terapijom (N,%)*	Total (N,%)/*Ukupno (N,%)*
Metformin/*Metformin*	28 (47)	32 (53)	60 (100)
Insulin therapy/*Inzulinska terapija*	11 (52)	10 (48)	21 (100)
Dipeptidyl peptidase IV Inhibitors /*Inhibitori dipeptidil peptidaze IV*	2 (7)	25 (93)	27 (100)
Sulfonylurea derivative/*Derivati sulfonilureje*	2 (25)	6 (75)	8 (100)
Glucagon-Like Peptide-1 Receptor Agonists/*Glukagonu sličan peptid-1 receptor agonist*	0 (0)	5 (100)	5 (100)
Sodium-glucose Cotransporter-2 Inhibitors/*Inhibitori suprijenosnika natrija-glukoze 2*	0 (0)	4 (100)	4 (100)

86% of the total number of subjects were treated with oral antidiabetic therapy, and 13% of them had anemia. Most of the subjects were treated with metformin and DPP-4 inhibitors. No statistically significant differences were found in the frequency of anemia depending on using certain types of oral drugs, except in the case of sulfonylurea derivatives. The frequency of anemia was statistically significantly higher in subjects who used the mentioned drug (Fischer's exact test, P = 0.01). Subjects who used sulfonylurea derivatives were mostly treated with combined therapy that included

metformin if it was a dual therapy or metformin and DPP-4 inhibitors if it was a triple therapy. Anemia appeared significantly more often when combined therapy was used, which included sulfonylurea derivatives (Fischer's exact test, P = 0.02).

Furthermore, in patients treated with sulfonylurea derivatives, a statistically significant frequency of normocytic normochromic anemia (Fisher's exact test, P = 0.03) and non-specific anemia (Fisher's exact test, P < 0.001) was observed.

Considering the other therapy used for the treatment of T2DM and whether monotherapy or combined therapy was used in the treatment, no statistically significant differences were observed in the severity of anemia, morphological types of anemia, or etiology of anemia. In subjects treated with metformin, either in monotherapy or as part of combined therapy, no statistically significant differences were observed in the frequency or severity of anemia depending on the length of treatment with metformin. However, normocytic hypochromic anemia occurred statistically significantly more often in subjects in whom metformin was used as antidiabetic therapy for more than 10 years (Fisher's exact test, P = 0.02). Looking at the etiological cause of anemia, in subjects who used metformin in therapy for up to 5 years, anemia of chronic disease was statistically significantly more common (Fisher's exact test, P = 0.04), and in subjects who used metformin in therapy for longer than 10 years, mixed anemia (Fisher's exact test, P = 0.02).

Discussion

In the research that was carried out, the proportion of subjects with anemia, among those suffering from T2DM, was 19%, which is comparable to many other world studies conducted on a similar sample of subjects, with the proportion from 19 to 25%. Some studies showed that the frequency of anemia among patients with T2DM is more than 50%, and the higher incidence may depend on age groups, the severity of T2DM, or the presence of comorbidities in the subjects included in the research. A recent meta-analysis that included almost 20,000 subjects with T2DM worldwide showed that the incidence of anemia is around 27%, and this certainly indicates that anemia is an important public health problem for chronic patients whose health is already impaired by the primary disease, but also frequent complications and comorbidities.[11,16]

The results show no cases of severe anemia in the subjects, but all could be characterized as mild or moderate, which is following other conducted research in which severe anemia in patients with T2DM appeared only exceptionally.[17] Furthermore, morphologically, normocytic normochromic anemia was the most prevalent, followed by microcytic hypochromic anemia, and other studies showed similar results.[24,25] The high prevalence of mild to moderate normocytic anemia could be explained by the anemia of a chronic disease, which can occur in people with T2DM, as shown by other studies.[17] In this study, a part of normocytic anemias could be characterized as anemia of chronic disease, taking into account the etiology, but a part of normocytic anemias due to an unclear etiological cause was recorded as unspecified anemia. The aforementioned is due to the main healthcare institution's laboratory's incapacity to measure additional indicators, like ferritin and TSAT, as part of the routine management of T2DM patients.

Our research did not show statistically significant differences in the frequency of anemias depending on fasting plasma glucose and HbA1c values, although previous studies have shown different results. In some studies, poor glycemic control was associated with a more frequent anemia, while other studies showed lower HbA1c values in people with anemia.[26,27] Given that anemia resulting from iron deficiency raises HbA1c values regardless of how diabetes is regulated, it is highly likely that the outcomes vary depending on the type of anemia that manifests in subjects.[28] On the other hand, hemolytic anemias lead to a drop in HbA1c values due to a shorter life span of erythrocytes and, therefore, the disproportionality of HbA1c values with plasma glucose values.[29] Anemias of chronic disease are also known to have a slightly expressed hemolytic component, so they can also lead to lower HbA1c values. If the anemia is mild, its impact on the above values is negligible; nevertheless, if the anemia is severe, it is advisable to proceed with extra caution when interpreting the HbA1c figure, as an incorrect interpretation may result in insufficient diabetes management.[30]

Furthermore, in our study, the average duration of T2DM in subjects was 11 years, which is in line with research showing that the duration of diabetes longer than 10 years is a risk factor for anemia.[16] It is known that age is a risk factor for the development of anemia, so the results of our study, in which people with anemia and T2DM were significantly older than those without anemia, correspond to other studies conducted so far.[31] In our analysis, several kinds of anemia—namely, normocytic hypochromic and normocytic normochromic anemia—were also more prevalent in the elderly. Etiologically, mixed anemia showed statistically significant increases in older people. In elderly individuals, normocytic anemia is

most likely the result of the interaction between sideropenic anemia and anemia of chronic disease. It is frequently a complex anemia of mixed multiple etiology, involving, in addition to the conditions listed above, age-dependent renal insufficiency, aging of hematopoietic cells, and androgen insufficiency that otherwise stimulates erythropoiesis, as well as other unavoidably occurring conditions of chronic inflammation.[32]

Gastrointestinal symptoms, which can occur as side effects of using metformin, a drug that is still considered the first line of treatment for diabetes but is also used in many other conditions such as prediabetes, insulin resistance, polycystic ovary syndrome, can potentially lead to deficiency absorption of vitamin B12 and consequently the development of megaloblastic anemia.[33] In addition to being a consequence of using metformin therapy, the above can also occur in the case of malnutrition, alcoholism, and other diseases of the gastrointestinal system that inhibit the absorption of vitamin B12, but also in the case of the use of other drugs such as antacids, H2 receptor antagonists, proton pump inhibitors and many others. Furthermore, the insufficiency of the mentioned vitamin is linked to certain age groups, so it is more common in people over 65 years of age, and it also occurs more often in pregnant women.[33,34] Among the 60 patients treated with metformin in our study, 12 had anemia, most often normocytic normochromic. Anemia from a chronic condition was the most common cause in the subjects receiving monotherapy; in the remaining patients, the cause was unknown. In our investigation, we found two cases of macrocytic anemia, both treated with metformin; however, we did not find any evidence of a causal relationship between the metformin treatment and the development of the indicated anemia.

In this study, anemia was more common in the first 5 years of treatment with metformin and after 10 years of treatment, but no statistical significance was observed. However, some previous studies have shown that long-term use of metformin can be associated with vitamin B12 deficiency but also with the occurrence of anemia in general, which does not need to be related to the deficiency of vitamin B12.[35] Anemia of chronic disease appeared significantly more often in subjects treated with metformin in the first 5 years of treatment and mixed and normocytic hypochromic anemia in subjects in whom the treatment lasted longer than 10 years. It can be concluded that the anemias recorded in the group of subjects treated with metformin in our study are primarily the result of chronic disease and/or iron deficiency. At the same time, cobalamin insufficiency may be only a secondary factor that contributed to the development. Nonetheless, new research examining the relationship between iron deficiency anemia and metformin use suggests that metformin may have a pleiotropic effect in individuals with T2DM. Specifically, the study demonstrated that metformin had a protective effect on these individuals and that the incidence of such anemia was lower in the group of people treated with metformin across all subgroups, with the protective effect being particularly noticeable in the subset of those over 65 years old.[36]

In the conducted research, anemia appeared significantly more often in people treated with sulfonylurea derivatives, which is contrary to the results of the A Diabetes Outcome Progression Trial (ADOPT) and The UK Prospective Diabetes Study (UKPDS), which showed that treatment with metformin leads to a more significant decrease in hemoglobin compared to sulfonylurea.[37,38] Anemias in subjects treated with sulfonylurea were more often normocytic normochromic, non-specific etiology, and mild. Research so far has shown that in the treatment of sulfonylurea derivatives, if anemia occurs, it is mild mainly.[39] Aplastic anemia, hemolytic anemia, anemia from acute blood loss, anemia linked to complications like infections, and hemolytic or microangiopathic anemias, in which there is an increased production of erythrocytes, can all be considered differential diagnostic causes of anemia in unspecified anemia in patients treated with sulfonylurea derivatives. Anemia resulting from chronic kidney disease would also be considered in the differential diagnosis; however, as chronic kidney disease was not present in our participants receiving therapy with sulfonylurea derivatives and who had documented anemia, it is ruled out as a possible cause.

Conclusion

Based on the conducted research, it can be concluded that anemia is common in people with T2DM, and in this study, it was recorded in as many as 19% of the total number of subjects and characterized as mild or moderate anemia. Normocytic normochromic anemia is the most common morphological form of anemia, and etiologically, non-specific anemia of chronic disease prevails. The incidence of anemia was higher in older adults, and normocytic normochromic and hypochromic anemia occurred more often in these subjects, while mixed anemia was the most common one regarding etiology. The frequency of anemia did not depend on the gender of the subjects or whether monotherapy or combined therapy was used in the

treatment of T2DM. People who used sulfonylurea derivatives, either as monotherapy or in combination with other therapy, had a higher incidence of anemia, which was characterized as mild, non-specific, normocytic normochromic anemia. Anemia of chronic disease is significantly more common in the first 5 years of metformin used in the treatment of T2DM, while after 10 years of treatment, mixed anemia, morphologically normocytic hypochromic, is the most common. In conclusion, we can say that due to the high incidence of anemia in patients with T2DM, it is necessary to carry out regular screening as part of regular controls, especially in older adults with micro or macroalbuminuria, poor disease control, and reduced transferrin saturation as and in patients treated with sulfonylurea derivatives. Screening is essential at the level of primary health care, with the aim of starting treatment and correcting therapy as early as possible.

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