РАСПРОСТРАНЕННОСТЬ АНЕМИИ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 1 И 2 ТИПА С ПОРАЖЕНИЕМ ПОЧЕК

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Стремительный рост популяции больных сахарным диабетом (СД) в мире приводит к увеличению числа больных с диабетическим поражением почек. Хроническая болезнь почек (ХБП), являющаяся одной из ведущих причин анемии, может выявляться у каждого третьего больного СД.

ЦЕЛЬ. Изучить частоту и тяжесть анемии у больных СД 1 типа (СД1) и СД 2 типа (СД2) с ХБП в сравнении с больными СД1 и СД2 без почечной патологии и недиабетическим поражением почек.

МЕТОДЫ. Обследовано 2015 больных: 807 человек с СД1 (из них 415 человек с ХБП), 1208 человек с СД2 (из них 589 с ХБП) и 244 больных с хроническим гломерулонефритом (ХГН). Критериями исключения явились скорость клубочковой фильтрации (СКФ) <15 мл/мин/1,73 м^2 (5 стадия ХБП) и лечение средствами, стимулирующими эритропоэз (ССЭ), и/или препаратами железа. Анемия диагностировалась при гемоглобине (Hb) <130 г/л у мужчин и <120 г/л у женщин. Стадии ХБП устанавливались в соответствии с рекомендациями KDOQI и KDIGO.

РЕЗУЛЬТАТЫ. Распространенность анемии у больных СД1 и СД2 с ХБП (38,8% и 22,6% соответственно) была значимо выше по сравнению с больными СД1 и СД2 без почечной патологии (16,6% и 11,5% соответственно). Прогрессирование ХБП с 1 по 4 стадию сопровождалось увеличением частоты анемии с 23,3% до 80,0% при СД1 и с 16,9% до 81,0% при СД2 и утяжелением ее степени. Анемия у больных с протеинурией (ПУ) по сравнению с пациентами с микроальбуминурией (МАУ) характеризовалась высокой частотой (53,9% и 29,4% при СД1 соответственно и 34,4% и 17,6% при СД2 соответственно) и более выраженным снижением Hb (у женщин с СД1, у мужчин с СД2). При СД1 с ХБП распространенность анемии была достоверно выше (53,9%), чем при ХГН (19,7%), без различия в степени ее тяжести.

ЗАКЛЮЧЕНИЕ. Наличие диабетического поражения почек увеличивает распространенность анемии у больных СД в 2 раза, тесно связанной со снижением фильтрационной функции почек и усилением выраженности альбуминурии. При диабетическом поражении почек анемия встречается с высокой частотой (в 2,7 раза) по сравнению с недиабетическими гломерулопатиями, но с сопоставимой степенью тяжести при равном уровне снижения СКФ.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; диабетическое поражение почек; диабетическая нефропатия; анемия; хронический гломерулонефрит

PREVALENCE OF ANEMIA IN PATIENTS WITH TYPE I AND TYPE II DIABETES MELLITUS WITH CHRONIC RENAL DISEASE

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BACKGROUND. Diabetes mellitus (DM) is a non-infectious disease with a high prevalence worldwide and is one of the most common causes of diabetic kidney disease (DKD). Anaemia is a well-known complication of chronic kidney disease (CKD) and has been estimated to affect one in three adults with DM.

AIMS. To evaluate the prevalence and severity of anaemia among patients with DKD and to compare the distribution of anaemia among patients with diabetic and non-diabetic CKD.

METHODS. A total of 2,015 patients with DM [n = 807 with type 1 DM (T1DM); n = 1,208 with type 2 DM (T2DM)] and 244 patients with biopsy-proven chronic glomerulonephritis (CGN) were selected. Patients with glomerular filtration rate (GFR) of <15 ml/min/1,73 m2 (stage 5 CKD) and treated by erythropoietin-stimulating agents and/or iron medication were not included. The presence of anaemia was defined as haemoglobin (Hb) of <130 g/l in men and <120 g/l in woman. GFR was calculated using the MDRD formula. CKD stages were defined based on stages 1–4 of CKD by KDOQI and KDIGO guidelines: stage 1 (GFR ≥ 90 ml/

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min/1.73 m2); stage 2 (GFR 60–89 ml/min/1.73 m2); stage 3 (GFR 30–59 ml/min/1.73 m2); stage 3a (45–59 ml/min/1.73 m2); stage 3b (GFR 30–44 ml/min/1.73 m2); stage 4 (GFR 15–29 ml/min/1.73 m2).

RESULTS. Rates of anaemia were higher among patients with DM and DKD (38.8% and 22.6% for T1DM and T2DM, respectively) than diabetic patients without DKD (16.6% and 11.5%, respectively. Prevalence of anaemia by CKD stage increased from 23.3% in stage 1 to 80% in stage 4 among patients with T1DM, and from 16.9% to 81 % among patients with T2DM. The prevalence of anaemia was also higher among protoeinuric patients (53.9% and 34.4% for T1DM and T2DM, respectively) relative to microalbuminuric patients (29.4% and 17.6%, respectively). Anaemia prevalence was significantly greater in DKD due to T1DM (53.9%) than in CGN (19.7), and the rates did not differ based on stages of CKD.

CONCLUSIONS. We found a two-fold higher rate of anaemia among patients with DM and CKD than patients with DM and non-DKD. In addition, we found that the frequency of anaemia depends on renal function (i.e., stage of CKD) and degree of albuminuria. Taken together, anaemia is highly prevalent among patients with T1DM and DKD compared with patients with chronic CGN, without differences in its severity.

KEYWORDS: diabetes mellitus; diabetic kidney disease; diabetic nephropathy; anemia; chronic glomerulonephritis

BACKGROUND

According to the World Health Organization (WHO), anaemia is a global medical and social problem that is detected in 24.8% of the world's population [1,2]. One of the leading causes of anaemia is iron deficiency that is mainly associated with an unbalanced diet and, to a lesser extent, with chronic localised blood loss [3]. In addition, many widespread chronic diseases (rheumatic diseases, tumours and infections) are accompanied by the so-called anaemia of a chronic disease, the pathogenetic mechanisms of which are associated with immune-inflammatory processes affecting erythropoiesis [4].

Among the aetiologies of anaemia is chronic kidney disease (CKD), the prevalence of which has already reached 10%–12% globally [5]. With progressive CKDs, the decrease in production of the main erythropoiesis-stimulating hormone erythropoietin (EPO) by sclerotised kidneys is the main cause of the development of renal anaemia [6,7].

Diabetes mellitus (DM) is a generally-recognised non-infectious disease having an epidemic growth pattern. According to the International Diabetes Federation, in 2015, the number of patients with DM was 415 million (11% of the global population). However, according to forecasts, by 2040, the number of patients with DM may increase by 55% (642 million people), i.e. one in every ten adults on the planet will have DM [8]. The rapid increase in the number of patients with DM is accompanied by a general increase in the number of patients with microvascular kidney complications, such as diabetic nephropathy (DN) or diabetic kidney disease, which is detected in one in three patients with DM [9,10]. According to the results of active screening for the presence of microvascular complications performed by the National Medical Research Center of Endocrinology in various regions of Russia, the prevalence of kidney damage was 40.1% for type 1 DM and 39.3% for type 2 DM [11].

Because DM is a leading factor for the development of anaemia, even in the absence of renal pathology, adherence of renal damage is an additional and significant cause of the increase in the development of anaemia and its increasing severity [12-14]. Currently, less data are available on the prevalence of anaemia in patients with type 1 and 2 DM with kidney damage and they are mostly ambiguous and generally related to the use of different diagnostic criteria for anaemia, and the groups of patients examined were heterogeneous (by diabetes type and presence of CKD) [15-19]. It is of interest to compare the incidence of anaemia in patients with diabetic and nondiabetic glomerulopathy in comparable groups. Therefore, an analysis of the prevalence and severity of anaemia among the Russian population of patients with type 1 and 2 DM with renal damage is important for the planning of diagnostic, therapeutic and prophylactic measures aimed at the timely detection of anaemia and its effective treatment.

AIM

1. Study the prevalence and severity of anaemic syndrome in the Russian population of patients with type 1 and 2 DM with diabetic kidney damage compared to a) patients with type 1 and 2 DM without renal disease and b) depending on the CKD stage and the severity of albuminuria.
2. Assess the incidence and severity of anaemia in patients with diabetic and nondiabetic kidney damage.

METHODS

STUDY DESIGN

1. Overall, 2015 patients with type 1 or 2 DM (one-stage and observational study) were examined to study the epidemiology and severity of anaemic syndrome in patients with type 1 or 2 DM without renal disease and with kidney damage, depending on their filtration function and the severity of albuminuria.
2. Overall, 154 patients with type 1 DM with kidney damage (hereinafter, 'patients with DN') and 244 patients with morphologically verified primary chronic glomerulonephritis (CGN) (retrospective study) were examined to compare the prevalence and severity of anaemia in patients with diabetic and nondiabetic kidney damage.

ACCEPTANCE CRITERIA

1. Criteria for inclusion: a) patients with previously diagnosed type 1 or 2 DM without kidney damage and with kidney damage; b) patients with morphologically verified CGN.
2. Withdrawal criteria: a) glomerular filtration rate (GFR) <15 ml/min/1.73 m^2 (CKD stage 5); b) treatment

with erythropoiesis-stimulating drugs and/or iron preparations; c) insufficient function of the thyroid gland (according to the follow-up monitoring of patients with thyroid gland pathology outpatient card data).

CONDITIONS OF PERFORMING

1. For patients with type 1 or type 2 DM, the study was conducted in different regions of the Russian Federation (five regions) during expeditions of the mobile Diabetes Center with the project Screening of DM complications in the framework of the Federal Target Program Diabetes Mellitus.
2. Catamnesis of patients with CGN was collected on the basis of the Tareev Clinic of Nephrology, Internal and Occupational Diseases, the Sechenov First Moscow State Medical University.

DURATION OF THE STUDY

1. Patients with type 1 or 2 DM underwent a one-stage examination in the project of Screening of DM complications between 2006 and 2007.
2. Patients with CGN were examined and treated in inpatient settings between 1993 and 2001.

DESCRIPTION OF MEDICAL INTERVENTION

1. In patients with type 1 and type 2 DM: a) a sample of capillary and venous blood was collected to determine the value of blood haemoglobin (Hb) and b) a sample of venous blood was collected to determine serum creatinine; a one-time sample of urine (morning portion) and daily urine (urine collected within 24 h) was collected to determine albuminuria.
2. There was no medical intervention in patients with CGN.

PRIMARY STUDY RESULTS

The main parameters evaluated in the study in patients with type 1 or 2 DM were Hb levels, serum creatinine with the calculation of GFR and the severity of albuminuria.

Patients with CGN were evaluated for Hb, serum creatinine and albuminuria, a morphological variant of glomerulonephritis.

ADDITIONAL STUDY OUTCOMES

The frequency and severity of anaemia in patients with nondiabetic renal disease (CGN) was studied.

SUBGROUP ANALYSIS

Of the 2015 patients, 807 (40%) had type 1 DM and 1208 (60%) had type 2 DM. Patients with type 1 and 2 DM were divided into two groups depending on the presence of diabetic kidney damage. There was kidney pathology in 415 patients (51.4%) with type 1 DM and in 589 patients (48.8%) with type 2 DM. In 154 patients with DN (of 415 patients with type 1 DM with kidney damage) and 244 patients with primary CGN, the albuminuria severity reached the degree of proteinuria (PU). Among the patients with CGN, the following morphological variants of glomerulonephritis (GN) were identified: mesangioproliferative GN (104 patients), focal segmental glomerulosclerosis (44 patients), mesangiocapillary GN (34 patients), fibroplastic GN (22 patients), membranous nephropathy (22 patients) and minimum changes (18 patients).

CKD diagnostics in patients with type 1 or 2 DM was performed in accordance with K/DOQI and KDIGO criteria: the presence of any sign of kidney damage with or without a decrease in GFR with a duration of ≥3 months, which was revealed in the study of blood and urine and according to visualising methods of examination, or a decrease in GFR < 60 mL/min/1.73 m^2 for ≥3 months with and without signs of kidney damage [20, 21]. The severity of albuminuria was defined as microalbuminuria (MAU) with loss of albumin in the urine in the morning urine portion of 20–199 μg/ml, in daily urine of 30–299 mg and a urine albumin/creatinine ratio of 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women. The indices of albuminuria less than these values were considered normoalbuminuria (NAU) and those higher than these values were considered PU [22]. GFR was calculated using the MDRD formula [23]. CKD stages were established according to KDOQI and KDIGO classifications: stage 1 (CKD 1) was characterised as signs of kidney damage with normal or increased GFR (≥90 ml/min/1.73 m^2), stage 2 (CKD 2) was characterised withas renal damage with an initial GFR decrease (60–89, GFR > 90 ml/min/1.73 m^2), stage 3 (CKD 3) (30–59 ml/min/1.73 m^2), stage 3a (CKD 3a) was characterised as a moderate reduction (45–59 ml/min/1.73 m^2), stage 3b (CKD 3b) was characterised by a significant decrease in GFR (30–44 ml/min/1.73 m^2) and stage 4 (CKD 4) was characterised by a marked decrease in GFR (15–29 ml/min/1.73 m^2) [20,21]. Anaemia was diagnosed by the absence and presence of CKD according to the same WHO and KDIGO Hb criterion, respectively, as Hb <130 g/l in men and Hb <120 g/l in women [24,25].

METHOD OF REGISTRATION OF OUTPUTS

1. In patients with type 1 or type 2 DM, Hb was determined using a portable photometric device (Hemocue, Sweden) within the framework of a general blood test using a haematology analyser (SYSMEX XE-2100, Japan). Serum creatinine was determined using the analysers Reflatron Plus (Switzerland) and HITACHI (Germany). Albuminuria in a single urine sample was determined using a urine chemistry analyser (AUTON MAXTM AX-4280, Japan) and in 24 h urine using a biochemical analyser (HITACHI, Germany).
2. In patients with CGN, Hb, serum creatinine and albuminuria values as well as information on the morphological variant of glomerulonephritis in patients with CGN were obtained from the medical card of the hospital patient.

ETHICAL EXPERTISE

The study was approved by the Ethical Committee of the Endocrinology Research Center of the Ministry of Health of Russia, Protocol No. 7 of 25.06.2013. The patients were informed of the possible use of their data for scientific purposes during the examination. All patients remained anonymous in the subsequent analysis of the data.

STATISTICAL ANALYSIS

Principles for calculating the sample size were as follows: to study the prevalence and severity of anaemia

Table 1. Clinical characteristics of patients with type 1 and type 2 DM

Parameters	Pateints with Type I DM (n = 807)		Patients with Type II DM (n = 1208)	
	Without CKD (n = 392)	With CKD (n = 415)	Without CKD (n = 619)	With CKD (n = 589)
Gender (male/female) (patients)	167/225	173/242	209/410	250/339
Age (years)	34.4±13.2	36.7±12.6***	57.5±9.6	61.6±9.2***
Duration (years)	11.3±8.9	18.1±8.8***	8.6±6.5	12.4±8.0***
HbAc1 (%)	9.0±2.0	9.1±1.9*	8.2±2.0	8.8±2.0***
BMI (kg/m2)	23.9±3.8	24.0±3.9*	30.9±5.2	30.8±5.2*
SBP (mm Hg)	126.0±17.9	132.5±19.4***	144.5±21.2	151.3±22.4***
DBP (mm Hg)	78.3+9.4	81.1±9.9***	86.1±12.7	88.0±11.5**
GFR (ml/min/1.73 m2)	115.1±32.2	85.9±42.5***	93.7±21.5	80.3±29.3***
CKD stages - 1/2/3/4 (%)	-	45.5/24.4/20.5/9.6	-	37.2/35.0/24.3/3.5
NAU/MAU/PU (%)		5.5/57.4/37.1		8.7/62.6/28.7

Note: data are presented in the form of numerical values, mean values and standard deviation. Significance of differences based on a Mann–Whitney U test **0.05 ≤ p < 0.1, **p < 0.05; ***p < 0.01. Abbreviations: DBP - diastolic blood pressure, BMI - body mass index, MAU - microalbuminuria, NAU - normoalbuminuria, PU - proteinuria, SBP - systolic blood pressure, DM - diabetes mellitus, GFR - glomerular filtration rate, CKD - chronic kidney disease, HbAc1 - glycated haemoglobin.

Table 2. Clinical characteristics of patients with DN and CGN

Parameters	Patients with DN (n = 154)	Patients with CGN (n = 244)
Gender (male/female) (patients)	60/94	133/111
Age (years)	35.8±11.5	31.3±13.2***
Duration (years)	20.5±7.7	2.9±4.1***
HbAc1 (%)	9.2±1.8	-
BMI (kg/m2)	24.0±4.2	23.7±4.0*
SBP (mm Hg)	138.5±20.8	126.8±12.6***
DBP (mm Hg)	83.1±10.1	81.1±8.9*
GFR (ml/min/1.73 m2)	65.7±37.6	76.2±32.2***
CKD stages - 1/2/3/4 (%)	25.3/28.6/26.0/20.1	31.6/33.2/31.1/4.1

Note: data are presented in the form of numerical values, mean values and standard deviation. Significance of differences based on a Mann–Whitney U test *0.05 ≤ p < 0.1; **p < 0.05; ***p < 0.01. Abbreviations: DBP - diastolic blood pressure, BMI - body mass index, SBP - systolic blood pressure, DM - diabetes mellitus, GFR - glomerular filtration rate, CKD - chronic kidney disease, CGN - chronic glomerulonephritis, HbAc1 - glycated haemoglobin.

in patients with type 1 and type 2 DM with diabetic renal disease, the preliminary sample size in each group of patients with type 1 or 2 DM without CKD and with CKD was at least 300 patients (total of 1200 people); to compare the frequency and severity of anaemia in patients with DN and CGN, the preliminary sample size in each group was at least 150 patients, respectively (total of 300 patients). STATISTICA 6.0 statistical package was used for statistical data processing. The arithmetic mean was calculated with a standard deviation and median. The significance of differences was assessed using the nonparametric Mann–Whitney U test. To verify the statistical significance of the differences in frequency indicators, the Pearson nonparametric $\chi 2$ criterion was used. Evaluation of the relationships between the parameters under the study was performed with the use of a Spearman nonparametric correlation analysis. Using the proportional risk model, the relative risk (RR) and the boundaries of its confidence interval (95% CI) were estimated. Correlation/influence coefficients and significance of differences were considered highly significant at $p \leq 0.01$, significant at $p < 0.05$, with a tendency to differ at $p < 0.1$ and insignificant at $p > 0.1$.

RESULTS

STUDY SUBJECTS (PARTICIPANTS)

PRIMARY STUDY RESULTS

Type 1 DM

The prevalence of anaemia in the group of patients with kidney damage was 38.8% (in 161 of 415 patients), which was 2.3 times higher than that in patients with type 1 DM without CKD [16.6% (65 of 392 patients), $\chi 2 = 49.3$, $p < 0.01$)]. The frequency of anaemia in the absence of renal pathology was not significantly different in patients with CKD 1 (23.3%, in 44 of 189 patients) and there was only a tendency to differ ($\chi 2 = 3.7$, $0.05 \leq p < 0.1$). In CKD 2, there was a significant increase in the number of patients with anaemia compared to patients without kidney damage ($p < 0.01$) (Fig. 1). RR of anaemia in patients with renal disease

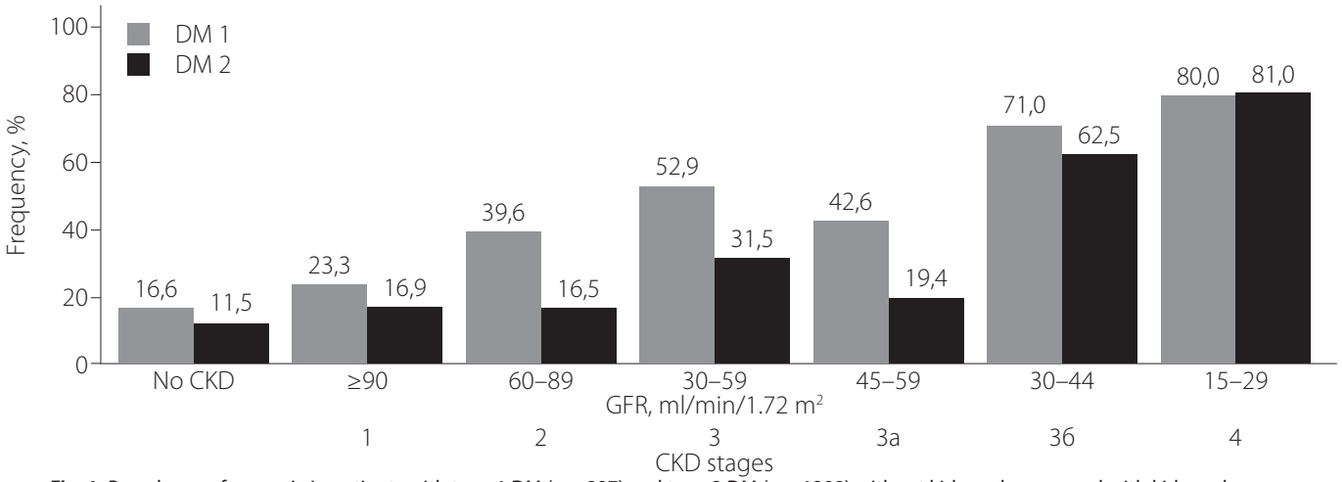

Fig. 1. Prevalence of anaemia in patients with type 1 DM (n = 807) and type 2 DM (n = 1208) without kidney damage and with kidney damage, depending on CKD stage.

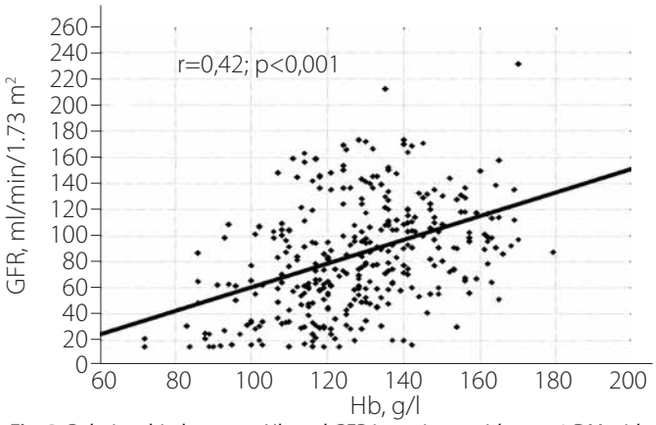

Fig. 2. Relationship between Hb and GFR in patients with type 1 DM with kidney damage (n = 415).

was 2.34 (95% CI 1.82; 3.01) in relation to patients without renal disease.

The prevalence of anaemia was significantly increased in patients with CKD 2 compared to CKD 1 and reached 39.6% (40 of 101 patients) ($\chi2 = 8.5$, $p < 0.01$). In CKD 3, the number of patients with anaemia did not significantly differ from the previous stage and reached 52.9% (45 out of 85 patients) ($\chi2 = 3.3$, $0.05 \le p < 0.1$). However, the prevalence of anaemia was slightly lower with CKD 3a (by 10.3%) [42.6% (23 of 54 patients)] than combined CKD 3, but it increased to 71.0% (22 of 31 patients) with CKD 3b (Fig. 2) and was already comparable to CKD 4 RR of its development and amounted to 4.33 (95% CI 3.16; 5.95) and 4.89 (95% CI 3.73; 6.40), respectively, with an RR of 2.60 (95% CI of 1.78; 3.81) with CKD 3a.

With the onset of CKD 4, anaemia was already detected in 80.0% (32 of 40 patients), which was 1.5 times higher than that of CKD 3 ($\chi2 = 8.4$, $p < 0.01$) (Fig. 1). Dependence on the development and aggravation of anaemia on the level of kidney filtration function revealed the presence of a direct close correlation between Hb and GFR values ($r = 0.41$, $p < 0.01$) (Fig. 2).

The incidence of anaemia in patients with CKD with NAU was higher than that in patients with MAU, accounting for 34.8% (8 out of 23 patients) and 29.4% (70 out of 238 patients), respectively; however, the result was not significant ($\chi2 = 0.3$, $p > 0.1$). When forming a stable PU, more than half of the patients (53.9%, 83 of 154 patients) suffered from anaemia (reliability with respect to MAU: $\chi2 = 23.5$, $p < 0.01$).

Anaemic syndrome in men was accompanied by a more pronounced decrease in Hb with CKD 3 compared to CKD 2 and in women with CKD 4 in relation to individuals with CKD 1; there was a tendency for a difference between the lower Hb value for CKD 4 in men and women compared to that with CKD 1 in men and CKD 3 in women (Table 3). In women with anaemia and with MAU, the Hb value was significantly lower than that with NAU, but it was higher compared to patients with PU, while in men the albuminuria severity did not affect the severity of anaemia (Table 4).

Type 2 DM

Anaemia in the group of patients with CKD occurred in 22.6% of cases (133 of 589 patients), which is two times higher than its frequency in the absence of kidney damage [11.5% (71 of 619 patients) ($\chi2 = 26.5$, $p < 0.01$)]. However, the incidence of anaemia in patients without CKD was

Table 3. Value of Hb (g/l) in patients with type 1 and type 2 DM, depending on CKD stage

CKD stage	Stage 1	Stage 2	Stage 3	Stage 4
Patients with DM type I (n = 161)				
Men	115.7±7.7 (n=11)	117.5±9.6 (n=18)	113.8±8.9$^{(**CKD2)}$ (n=17)	105.7±14.9$^{(*CKD1)}$ (n=14)
Women	110.4±6.9 (n=33)	107.2±10.0 (n=22)	107.7±8.5 (n=28)	99.5±14.3$^{(**CKD1),(*CKD3)}$ (n=18)
Patients with DM type II (n = 133)				
Men	121.7±10.1 (n=23)	116.5±18.3$^{(***CKD1)}$ (n=10)	111.9±12.3$^{(***CKD1)}$ (n=19)	98.0±15.4$^{(***CKD1), (**CKD3)}$ (n=6)
Women	104.1±18.1 (n=14)	109.2±18.5 (n=24)	107.9±10.3 (n=26)	100.9±19.7$^{(**CKD2),(*CKD3)}$ (n=11)

Note: data are presented as mean values and standard deviation. Significance of differences by a Mann–Whitney U test *$0.5 \le p < 0.1$; **$p < 0.05$; ***$p < 0.01$ for a particular CKD stage. Abbreviations: DM - diabetes mellitus, CKD - chronic kidney disease, Hb - haemoglobin.

Table 4. Value of Hb (g/l) in patients with type 1 and type 2 DM, depending on the severity of albuminuria

Severity of albuminuria	NAU	MAU	PU
Patients with DM type I (n = 161)			
Men	117.0±2.6 (n=3)	112.4±11.6 (n=26)	113.8±11.70.474820 (n=31)
Women	116.0±2.0 (n=5)	110.3±6.6(**NAU) (n=44)	103.5±11.7(**NAU),(***MAU) (n=52)
Patients with DM type II (n = 133)			
Men	121.0±7.5 (n=3)	120.2±11.0 (n=29)	108.8±13.2(***MAU) (n=26)
Women	110.0±9.3 (n=7)	107.9±8.4 (n=36)	104.3±10.5 (n=32)

Note: data are presented as mean values and standard deviation. Significance of differences by a Mann–Whitney U test *0.5 ≤ p < 0.1; **p < 0.05; ***p < 0.01 for a particular stage of albuminuria of CKD. Abbreviations: MAU - microalbuminuria, NAU - normoalbuminuria, PU - proteinuria, DM - diabetes mellitus, Hb - haemoglobin.

comparable to its detectability at CKD 1 (16.9%, $\chi2 = 4.2$, $p > 0.1$) (37 of 219 patients) and CKD 2 (16.5%, $\chi2 = 3.5$, $0.05 \le p < 0.1$) (34 of 206 patients). A significant increase in the prevalence of anaemia in patients with renal disease compared to the group of patients without CKD was observed at CKD 3 ($p < 0.01$) (Fig. 1). Anaemia development RR in the presence of kidney damage compared to patients without renal pathology was 1.97 (95% CI 1.51; 2.57).

The prevalence of anaemic syndrome did not differ between CKD 1 and CKD 2 ($\chi2 = 0.01$, $p > 0.1$), and in patients with CKD 3, the detectability of anaemia increased by almost 2-fold compared to CKD 2 (31.5%, 45 of 143 patients) ($\chi2 = 10.8$, $p < 0.01$). In patients with CKD 3a (19.4%, 20 out of 103 patients), the incidence of anaemia was 12.1% lower than that in patients in the combined CKD 3 group, and it increased to 62.5% (25 of 40 patients) at CKD 3b with a corresponding RR of its development, which was closer to that of CKD 4 [5.45 (95% CI 3.94, 7.55) and 7.06 (95% CI 5.22, 9.55), respectively] than at CKD 3a [1.69 (95% CI 1.08, 2.66)]. In CKD 4, there was a rapid increase in the number of patients with anaemia (81.0%, 17 out of 21 patients) ($\chi2 = 19.1$; $p \le 0.01$) (Fig. 1), which was also observed in type 1 DM with CKD, and a direct close association of Hb with GFR was detected ($r = 0.32$; $p < 0.01$).

Anaemia was detected in 19.6% of NAU patients (10 of 51 patients) and in 17.6% of MAU patients (65 of 369 patients), and detection was not significantly different between them ($\chi2 = 0.1$; $p > 0.1$). Anaemia in PU patients was detected significantly more often than in MAU patients and was found in 34.3% of cases (58 of 169 patients) ($\chi2 = 18.3$, $p < 0.01$).

In men with anaemia, as CKD stages increased from 1 to 4, there was a significant decrease in Hb. In women with anaemia, the Hb value for CKD 4 was significantly lower than that at CKD 2 and tended to differ from Hb at CKD 3 (Table 3). Anaemia was more severe in men with PU compared with MAU, while in women, albuminuria severity made no difference in the severity of anaemia.

DIABETIC AND NONDIABETIC KIDNEY DISORDERS

In general, anaemia developed significantly more often in patients with DN than in patients with CGN, accounting for 53.9% (83 of 154 patients) and 19.7% (48 of 244 patients) of patients, respectively ($\chi2 = 50.1$; $p < 0.01$). Among the morphological variants of CGN studied, anaemia was most common in patients with mesangiocapillary GN (35.3%, 12 of 34 patients), which was characterised by a more pronounced immuno-inflammatory component than other primary nephritis cases. While the incidence of anaemia in this group of patients only had a tendency to differ from the high incidence of anaemia in patients with DN ($\chi2 = 3.8$, $0.05 \le p < 0.1$). The detectability of anaemia was significantly lower in other GN variants than in patients with DN: with diffuse fibroplastic GN it was 22.7% (5 out of 22 patients) ($\chi2 = 7.5$, $p < 0.01$), with membranoproliferative GN it was 17.3% (18 out of 104 patients) ($\chi2 = 34.9$, $p < 0.01$), with focal segmental glomerular sclerosis it was 13.6% (6 out of 44 patients) ($\chi2 = 22.4$, $p < 0.01$) and in membranous GN it was 9.1% (2 out of 22 patients) ($\chi2 = 15.5$, $p < 0.01$)

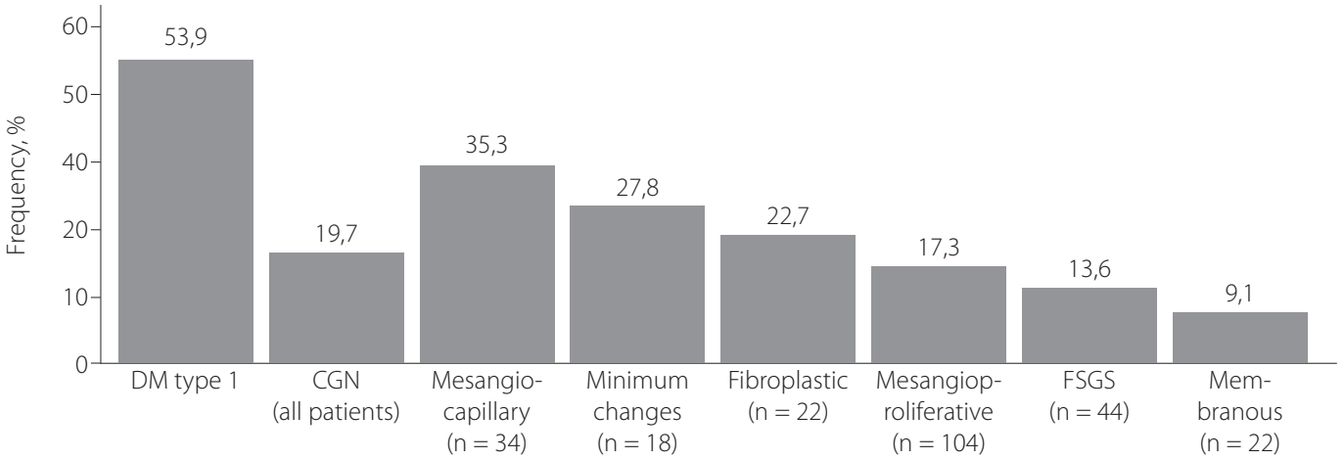

Fig. 3. Frequency of anaemia in patients with type 1 DM with DN with proteinuria (n = 154) and with various morphological variants of primary CGN (n = 244).

(Fig. 3). In our study, the high incidence of anaemia with the disease of minimal changes (lipoid nephrosis) (27.8%, 5 of 18 patients) ($\chi2 = 4.4$, $p < 0.05$) was due to moderate anaemia (Hb to 115.5 g/l) in four women (aged 33.7 ± 15.7 years) with severe nephrotic syndrome and preserved renal function (GFR 115.5 ± 0.6 ml/min/1.73 m^2) and a moderate Hb decrease to 126 g/l in a 24-year-old man with reduced kidney function (GFR 32.9 ml/min/1.73 m^2).

The incidence of anaemia in patients with DN and CGN with GFR corresponding to CKD 1 was 17.9% (7 out of 39 patients) and 14.3% (11 out of 77 patients), respectively ($\chi2 = 0, 3$; $p > 0.1$). As CKD progressed, there was a significant increase in the incidence of anaemia with DN compared to that with CGN: at CKD 2 it was 63.7% (28 of 44 patients) and 17.3% (14 of 81 patients), respectively ($\chi2 = 27.5$, $p < 0.01$); at CKD 3 it was 57.5% (23 of 40 patients) and 26.3% (20 of 76 patients), respectively ($\chi2 = 10.9$, $p<0.01$); at CKD 4 it was 80.6% (25 out of 31 patients) and 30.0% (3 out of 10 patients), respectively ($\chi2 = 8.9$, $p < 0.01$).

In patients with DN with anaemia and CGN, Hb levels did not differ significantly and there were no significant differences in Hb values in men with DN (n = 31) and CGN (n = 23), which amounted to 113.8 ± 11.7 g/l and 117.8 ±7.6 g/l, respectively ($p > 0.1$), and in women with DN (n = 52) and CGN (n = 25) it was 103.5 ± 11.7 g/l and 108.2 ± 8.3 g/l, respectively ($p > 0.1$). In addition, the severity of the anaemic syndrome did not differ between men and women with DN and CGN at comparable CKD stages.

ADVERSE EVENTS

No adverse events were observed during the study.

DISCUSSION

SUMMARY OF THE PRIMARY STUDY RESULTS

The prevalence of anaemia in patients with type 1 or 2 DM with kidney damage was significantly higher (2-fold) than in patients with type 1 or 2 DM without CKD. A reduction in the filtration function of the kidneys and increased severity of albuminuria were accompanied by an increase in the frequency of anaemia and aggravated severity. In patients with diabetic renal disease, the incidence of anaemia was greater than that in patients with nondiabetic renal disease without any distinction in severity.

MAIN STUDY RESULTS

In our study, the prevalence of anaemia among patients with type 1 DM without kidney damage (16.6%) was consistent with Australian data of 315 patients, where the Hb criterion for an anaemia diagnosis was Hb < 130 g/l in men and Hb < 120 g/l in women. In patients with type 1 DM with NAU and a GFR > 60 ml/min/1.73 m^2, the rate of detection was ~17% [16].

In a study by Thomas et al. [17] including patients with type 2 DM without CKD, anaemia was detected in 10% of patients with NAU and a GFR > 90 mL/min/1.73 m^2, which was comparable with our data (11.5%). Their Hb criterion for an anaemia diagnosis was Hb < 130 g/l in men and Hb < 120 g/l in women. In patients with NAU and GFR 60–90 ml/min/1.73 m^2, the authors noted an increase in the incidence of anaemia (15%). In a study by Craig et al. [13] including patients with type 2 DM without pathological albuminuria and a normal GFR value, anaemia was detected in 17.8% of men, which was slightly higher than our results, and in 11.8% of women, although the criterion for an anaemia diagnosis in women was less severe (Hb < 130 g/l in men and Hb < 115 g/l in women). In our study, the incidence of anaemia in men and women with type 2 DM without CKD was approximately the same as that reported by Thomas et al. [17] A small number of patients (62 in total) and a strict age range (55–69 years) in the study by Craig et al. [13] are possible reasons for some result discrepancies.

The leading cause of a more frequent detection of anaemia in patients with type 1 or 2 DM is the formation of diabetic kidney damage, [6,10,26], which was demonstrated in our study. Therefore, we showed that the incidence of anaemia was two times higher in patients with type 1 and type 2 DM with CKD than in patients with no kidney damage. There was also a progressive increase in the number of patients with anaemia as the filtration kidney function decreased from CKD stage 1 to CKD stage 4. The influence of renal pathology on the formation of anaemia in patients with type 1 and type 2 DM was confirmed by the high RR of its development calculated in the presence of CKD. Our RR values were close to the estimates of other authors, which in patients with type 1 and type 2 DM with renal damage reached 2.1 (95% CI 1.4–3.3) [27].

Data are available from a large multicentre US study of the Kidney Early Evaluation Program (KEEP), which examined the prevalence of anaemia at various CKD stages in patients with type 1 or 2 DM with diabetic kidney disease (1,445 patients) or with renal pathology of a different origin (3935 patients) [28]. We could not conduct a comparative analysis of our own results with KEEP data because their frequency of anaemia assessed a combined group of patients with type 1 or 2 DM and they used a different anaemia diagnostic criterion: Hb < 120 g/l in men and postmenopausal women (age > 50 years) and Hb < 110 g/l in premenopausal women (age ≤ 50 years). However, when assessing the incidence of anaemia in the combined group of patients with type 1 and type 2 DM with CKD according to the above criterion, our results (11.5%, 116 out of 1011 patients) were similar to those reported by KEEP (11.6%).

Dobronravov and Smirnov [27] studied the special aspects of anaemia in 1659 patients with diabetic and nondiabetic kidney damage, and they found that the prevalence of anaemia in patients with DN with type 1 DM was more than 50%, which was somewhat higher than our data for type 1 DM (38.8%), and in patients with type 2 DM, the incidence of anaemia was two times higher (approximately 40%) compared to our data (22.6%). Notably, the authors used a single value of Hb < 120 g/l for their anaemia assessment for both sexes, when this value should be Hb < 130 g/l for men. At the same time, a study of anaemic syndrome in patients with DN with type 1 DM with CKD stages 1–5 reported a result similar to our data (41.6%), although anaemia was diagnosed with a higher Hb value for both sexes (Hb < 135 g/l) [19].

The frequency of anaemia in patients with type 1 DM with kidney damage and a GFR of 30–59 ml/min/1.73 m^2 (52.9%) was comparable with the data reported by Thomas et al. [16] who revealed a 5-fold increase in the incidence of anaemia in patients with type 1 DM with a moderate

GFR decline (56%, GFR < 60 ml/min/1.73 m^2) compared to patients with preserved kidney function (10%, GFR > 90 ml/min/1.73 m^2), and the Hb criterion for an anaemia diagnosis was Hb < 130 g/l in men and Hb < 120 g/l in women.

A study of the prevalence of anaemia among the Asian population of patients with type 2 DM, in which 6,325 patients were enrolled, demonstrated anaemia in 1441 (22.8%) patients, 36% of who had CKD. According to our data, anaemia was detected in 22.6% of patients with type 2 DM with renal damage, while in patients with type 2 DM without anaemia, CKD was diagnosed in only 9% [29]. An Australian study conducted by three large medical centres of 2125 patients with type 2 DM revealed that the incidence of anaemia in patients with a GFR of 60–90 ml/min/1.73 m^2 was increased 2-fold compared to patients with a GFR > 90 ml/min/1.73 m^2, similarly for a group of patients with a GFR of 30–60 ml/min/1.73 m^2 compared to patients with a GFR of 60–90 ml/min/1.73 m^2 (the Hb criterion for an anaemia diagnosis was Hb < 130 g/l in men and Hb < 120 g/l in women). However, the increase in incidence of anaemia was not significantly different, which is possibly because the patients were not divided into groups depending on the presence or absence of CKD [17]. In our study, the number of patients with type 2 DM with CKD and anaemia was not significantly different with a GFR ≥ 90 ml/min/1.73 m^2 and a GFR of 60–89 ml/min/1.73/m^2 (16.9% and 16.5 %, respectively), although a significant increase in the incidence of anaemia (1.9-fold) was observed with a GFR of 30–59 ml/min/1.73 m^2 compared to a GFR of 60–89 ml/min/1.73 m^2 (16.5% and 31.5%, respectively).

A study by Bonokdaran et al. [30] included 1962 patients with type 2 DM, and they found a rather low prevalence of anaemia with an Hb criterion for diagnosing anaemia of Hb < 130 g/l in men and Hb < 120 g/l in women, and it was only detected in 7.2% of patients with a GFR > 90 ml/min/1.73 m^2 and in 9% of patients with a GFR of 60–90 ml/min/1.73 m^2. The possible reason for the lower incidence of anaemia compared to our data is the fact that the authors did not clearly specify the presence of CKD in the participants. However, in patients with a GFR < 60 ml/min/1.73 m^2, which a priori referred to patients with CKD, the prevalence of anaemia was 30%, which is closer to our data in the combined group of patients with CKD stages 3 or 4 (37.8%, in 62 out of 164 patients). However, other studies showed a higher prevalence of anaemia in patients with type 2 DM. In the study by Antwi-Bafour et al. [31] in men and women with type 2 DM (54% had kidney failure) with an average GFR of 90.1 ± 1.83 ml/min/1.73 m^2 and 85.4 ± 1.49 ml/min/1.73 m^2, respectively, anaemia was detected in 86.7% of men and 82.9% of women. This high incidence of anaemia can be explained by the 'endemic' component, since the study was conducted in Africa. However, data on the frequency of anaemia in a control group of patients without DM (26% had a decrease in renal function) indicated lower figures for both men and women of 7.1% and 19.4%, respectively.

Notably, the difference in the incidence of anaemia for CKD stages 3a and 3b was quite high, and at stage 3a it was lower by more than 10% than in the combined CKD stage 3 [19]. However, at the onset of stage 3b, the incidence of anaemia was significantly increased, particularly compared to stage 3a, where it was increased by 1.7 times with type 1 DM and by 3.2 times with type 2 DM. The division of CKD stage 3 into two sub-stages was accepted because patients with the GFR level at stage 3a had a high risk of developing cardiovascular complications, while those at stage 3b had a higher risk of renal failure progression to the terminal stage that the risk of death from cardiovascular accidents [20]. A significant increase in the incidence of anaemia at CKD stage 3b may indicate a sharp deterioration in kidney function with a pronounced deficit in EPO production, requiring measures that are more associated with inhibition of renal failure. This can be confirmed by the similar RR of anaemia development at CKD stages 4 and 3b in patients with type 1 DM.

Pathological albuminuria, which is a key sign of damage to the glomerular renal apparatus in patients with type 1 and type 2 DM, is not only closely associated with the rate of renal failure progression, but also with the development of cardiovascular accidents. [32,33] In addition, according to modern outlooks, the severity of albuminuria can indirectly determine the extent of damage to kidney tubulo-interstitial tissues [34], where EPO is formed by peritubular fibroblasts.

In patients with type 1 DM with renal disease, we obtained comparable data from the study by Thomas et al., [16] where the incidence of anaemia was 24% in patients with type 1 DM with MAU and 52% with macroalbuminuria with an Hb criterion for an anaemia diagnosis of Hb < 130 g/l in men and Hb < 120 g/l in women (according to our data these parameters were 29.4% and 53.9%, respectively). The high incidence of anaemia in patients with type 1 DM with CKD with NAU in our study was possibly because out of 23 patients, 21 had stage 3 CKD, 2 had stage 4 CKD, while among the patients with MAU, the number of patients with CKD stages 1 or 2 was much higher than the number of patients with CKD stages 3 or 4 (207 patients and 31 patients, respectively). Our data for patients with type 2 DM with NAU or MAU were slightly higher than those reported by Bonakdaran et al. [30]; the detectability of anaemia in patients with NAU or MAU was only 5.7% and 8.4%, respectively, while the prevalence of anaemia with PU (32.4%) was comparable to our results (34.3%).

One of the best known studies that compared the prevalence of anaemia in diabetic and nondiabetic kidney damage was that of KEEP [28]. According to their results, the frequency of anaemia in patients with type 1 or 2 DM with kidney damage was significantly greater than that in patients with CKD without diabetes. Anaemia with diabetic kidney disease was detected significantly more often than that with nondiabetic kidney pathology, even with an initial decrease in kidney function (GFR 60–89 ml/min/1.73 m^2) it was in 7.5% and 5.0% of cases, respectively ($p < 0.01$), and with a GFR of 30–59 ml/min/1.73 m^2, the prevalence of anaemia was almost three times higher than in the group of patients without DM (22.2% and 7.9%, respectively) ($p < 0.01$) With a further decrease in renal function (GFR < 30 ml/min/1.73 m^2), a significant difference between patients with DM and patients without diabetes was no longer observed (52.4% and 50.0%, respectively), although, according to our results, a significant increase in the frequency of anaemia in patients with DN was observed starting from CKD stage 2. Only a single work made a

comparative assessment of the frequency of anaemia in patients with DM with renal damage and other renal pathology, particularly in comparable groups of 'classical' glomerulopathies, i.e. in patients with type 1 DM with DN and in patients with primary or secondary GN. [27] It revealed that the leading prevalence of anaemic syndrome after patients with DN with type 1 DM (anaemia frequency ≈50%) was with patients with FSHS and mesangiocapillary GN (anaemia frequency ≈40%), and in patients with minimal changes anaemia was also detected considerably (≈20%) (the quoted article did not provide exact figures) [27]. In our work, which included comparable groups of patients with glomerular pathology and with PU, DN or CGN, the detectability of anaemia was significantly higher with DN compared to various morphological variants of CGN.

The high incidence of anaemia detection in patients with diabetic renal disease is because of the nature of the primary disease, which is an independent factor in the development of anaemia [28], and the presence of DM complications, in particular autonomic neuropathy, which adversely affects erythropoiesis [35,36]. In addition, the development of anaemia in patients with DM can be associated with the widespread use of medications that block the renin-angiotensin system in diabetes, in particular, angiotensin-converting enzyme inhibitors [37,38], as well as early damage to the tubulointerstitial apparatus [39] where EPO is produced.

We found that as the filtration function of the kidneys decreased (increase in CKD stage) and albuminuria severity intensified in patients with type 1 or 2 DM and the severity of anaemia increased, which reflects the depletion of EPO production by the kidneys as nephrosclerosis progresses. Contribution of the development and aggravation of anaemia in patients with diabetic renal disease with decreased renal function and severity of albuminuria was demonstrated by Thomas et al. [40] They found that patients with type 2 DM with renal failure and PU, a decrease in Hb was noted at a rate of 1–2 g/dl per year compared to that of patients with NAU and preserved renal function whose Hb value remained stable over 5 years of follow-up. In addition, a decrease in Hb of more than 2 g/dl per year was detected in 50% of patients with type 2 DM with PU, while in patients with NAU or preserved renal function, this was only detected in 10% of patients [41]. In our work, the severity of anaemia was not more pronounced in patients with DN than in those with CGN, although according to Ishimura et al., [42] patients with DM had a significantly lower Hb value than patients without diabetes (9.5 ± 2.1 g/dl and 11.2 ± 2.0 g/dl, respectively) ($p < 0.01$) of the same age and same blood creatinine level. These data were confirmed by a large number of participants in the KEEP study, where patients with type 1 or 2 DM with renal disease had significantly low blood Hb values compared to participants without DM ($p < 0.01$) [28]. The difference in our results is largely because we compared Hb in patients with anaemia that was gender-specific, while the other studies evaluated Hb in patients with anaemia without regard to gender, [42] or data were gender-specific but patients were not divided into groups with or without anaemia (KEEP study) [28].

STUDY LIMITATION

There were no factors that limiting the representativeness of the results obtained.

CONCLUSION

During a one-stage epidemiological study that enrolled 2015 patients with type 1 or 2 DM, it was established that the prevalence of anaemic syndrome was two times higher in patients with type 1 or type 2 DM with renal damage (CKD stage 1–4) than in patients with type 1 or 2 DM without kidney pathology. A statistically significant increase in the number of patients with anaemia with type 1 DM was observed from CKD stage 2, i.e. at the onset of an initial decrease in the filtration function of the kidneys (GFR < 90 ml/min/1.73 m^2), and with type 2 DM it was observed from CKD stage 3, i.e. at the onset of chronic renal failure (GFR < 60 ml/min/1.73 m^2). As CKD stages progressed from 1 to 4, the incidence of anaemia increased from 23.3% to 80.0% with type 1 DM and from 16.9% to 81.0% in type 2 DM, as evidenced by the presence of a close correlation between Hb and GFR values. An increase of albumin excretion in the urine from micro- to macroalbuminuria was accompanied by an increase in the frequency of anaemia, from 29.4% to 53.9% with type 1 DM and from 17.6% to 34.4% with type 2 DM. The severity of anaemia was affected by the level of GFR decrease and severity of albuminuria. In patients with type 1 DM (at the proteinuric stage of kidney damage), the incidence of anaemia was significantly higher (53.9%) than that in patients with nondiabetic kidney damage (from 9.1% to 35.3% for various morphological variants of primary CGN). The severity of anaemia was comparable at different CKD stages in diabetic and nondiabetic kidney pathologies.

ADDITIONAL INFORMATION.

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