Association between Red Blood Cell Count and Renal Function Exist in Type 1 Diabetic Patients in the Absence of Nephropathy

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ABSTRACT

Anemia is a prevalent finding in patients with type 1 diabetes, particularly in those with albuminuria or reduced renal function. We investigated the relationship between red blood cell count (RBC) and renal function in type 1 diabetic patients with normal or mildly impaired renal function and urinary albumin excretion rate (UAE) <30 mg/24 h. Study included 313 type 1 diabetic patients with estimated glomerular filtration rate (eGFR) > 60 mL min^{-1}1.73 m^{-2}, and before any interventions with statins, ACE inhibitors or angiotensin II receptor blockers. UAE was measured from at least two 24-h urine samples. Hemoglobin (Hb), hematocrit (Hct), erythrocytes (E), serum iron and ferritin levels were significantly lower in subjects in the highest quartile of serum creatinine compared to those in lowest quartile (132 vs 148 g/L, 0.39 vs 0.42 L/L, 4.5 vs 4.8x10^{12}/L, 13 vs 18 µmol/L, and 25 vs 103 µg/L, respectively, for all p<0.001). Hb and Hct levels were significantly lower in subjects in the highest quartile of UAE compared to those in lowest quartile (135 vs 140 g/L, and 0.40 vs 0.41 L/L, respectively, for all p=0.03). Finally, those with mildly impaired eGFR had significantly lower levels of Hb, Hct and E compared to those with normal eGFR or hyperfiltrating subjects (133 vs 140 g/L, 0.38 vs 0.41 L/L, and 4.4 vs 4.7x10^{12}/L, respectively, for all p=0.01). We have detected that interplay between RBC and renal function parameters occurs even in type 1 diabetic patients with normal or mildly impaired renal function.

Key words: type 1 diabetes, renal function, anemia, hemoglobin

Introduction

Anemia is a common feature in diabetic patients with chronic kidney disease (CKD) and patients with type 1 diabetes have a 20–50% probability of developing end-stage renal disease[1]. Diabetes itself has been proposed to affect the hematologic system in several ways and nearly a quarter of all diabetic patients have anemia[2,3]. Anemia in diabetic patients develops earlier than in subjects with renal disease from other causes[3–5]. However, it has been demonstrated that anaemia may occur in diabetic patients already in state with mildly to moderate renal insufficiency[4,6]. Declining hemoglobin levels in early kidney disease are more common among those with higher levels of albuminuria[3,7]. Anemia is also more common in patients with impaired kidney function, even in state of normal to mildly increased urinary albumin excretion rate (UAE)[3]. In addition, those with reduced hemoglobin

have higher risk of progressive renal disease and have a more rapid decline in glomerular filtration rate (GFR)[8]. Moreover, recent study demonstrated that anemia is a prevalent finding in patients with type 1 diabetes and represents a significant unrecognized burden[9]. In addition, reduced hemoglobin levels, even within the normal range, identify diabetic patients with an increased risk of cardiovascular morbidity and mortality[10,11]. Treating anemia in early renal disease may slow the rate of decline of renal function[12].

Identification of the determinants of the onset of early diabetic nephropathy is essential for reducing the morbidity and mortality associated with diabetes. Although previous studies demonstrated that anemia is associated with reduced GFR and increased albuminuria in

patients with established renal disease, little is known about the relationship between red blood cell count (RBC) and change in renal function among individuals with normal or mildly impaired renal function. The objective of this study was to investigate relationship between RBC and renal function parameters in type 1 diabetic patients with normal or mildly impaired renal function (eGFR > 60 mL/min/1.73 m², and UAE<30 mg/24 h).

Subjects, Materials and Methods

This study included 313 patients with diabetes mellitus type 1. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years, positive autoantibodies and permanent insulin treatment initiated within 1 year of diagnosis. The study included patients with following characteristics: age of 18–65 years, minimum duration of type 1 diabetes for 1 year, no medical history of liver, renal and cardiovascular diseases, absence of any systemic disease, and absence of any infections in the previous month. Patients were excluded from the study if they took any of the following: lipid-lowering therapy, anti-hypertensive therapy including ACE inhibitor or angiotensin II receptor blockers, and medications that might affect glucose metabolism such as glucocorticoids. Acute and chronic inflammation was excluded on the basis of medical history, physical examination, and routine laboratory tests, including measurement of temperature and urinalysis.

All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed on all study subjects. Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 minutes and expressed in mmHg. UAE was measured from at least two 24-h urine samples and determined as the mean of 24-h urine collections. Patients performed collections on two consecutive days to minimize variability. Normal to mildly increased UAE was defined as a UAE <30 mg/24 h. Those with moderate increased UAE (≥30 <300 mg/24 h) and those with severely increased UAE (≥300 mg/24 h) were excluded from the study. Serum creatinine was measured in fasting blood sample. Creatinine measurements were made on Olympus AU600, by the spectrophotometric Jaffé method. Data on serum creatinine levels, age, sex and race were used to calculate the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which has been shown to be accurate in determining renal function in diabetic patients with normal renal function[13,14]. Those with CKD, defined as the presence of impaired eGFR (less than 60 mL min⁻¹ 1.73 m⁻²), were excluded from the study.

Fasting venous blood samples were collected in the morning between 08:00 and 09:30 hours after an overnight fast for the determination of HbA1c, total, LDL, HDL cholesterol, triglycerides, ferritin, iron, hemoglobin (Hb) and erythrocytes (E). Urinary albumin and HbA1c

was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Cholesterol and triglycerides in serum were measured by an enzymatic colorimetric method. Complete blood count was determined on an automatic blood counter (Advia 120, Siemens Diagnostic Solutions, USA).

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethics committees.

Data are expressed as means ±SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Pearson's correlation coefficients were used to calculate correlations between normally distributed values and Spearman's rank correlation coefficients were used for non-normally distributed values. To investigate the relation between RBC and renal function parameters data were also stratified in quartiles of UAE and serum creatinine according to percentiles. Parameters were also stratified in different groups of eGFR according to stages of renal function, namely in those with mildly impaired renal function (eGFR ≥ 60<90 mL/min/1.73 m²), with normal renal function (eGFR ≥ 90<125 mL/min/1.73 m²), and hyperfiltrating subjects (eGFR ≥ 125 mL/min/1.73 m²). Kruskal-Wallis test was used for calculating the significance of the trend for each variable among the different groups.

TABLE 1
CLINICAL AND METABOLIC CHARACTERISTICS
OF ALL PATIENTS

Variable	Value
Age (years)	34 (18–65)
Duration of diabetes (years)	12 (1–42)
Body mass index (kg/m²)	24 (15–37)
Waist to hip ratio	0.81±0.07
Hemoglobin A1c (%)	7.43±1.63
Systolic blood pressure (mmHg)	120 (79–180)
Diastolic blood pressure (mmHg)	80 (50–100)
LDL cholesterol (mmol/L)	2.8±0.7
HDL cholesterol (mmol/L)	1.7±0.4
Triglycerides (mmol/L)	0.91 (0.3–4.1)
Serum creatinine (μmol/L)	71±14
eGFR (mL min⁻¹ 1.73 m⁻²)	106±16
Urinary albumin excretion (mg/24 h)	11.0 (1.7–29.8)
Erythrocytes (x10¹²/L)	4.66±0.4
Haemoglobin (g/L)	139±16
MCV (fL)	88 (57–124)
Hematocrit (L/L)	0.41±0.04
Ferritin (μg/L)	55 (5–697)
Serum iron (μmol/L)	16 (2–62)
UIBC (μmol/L)	36.3±11.1
TIBC (μmol/L)	53.7±8.0

eGFR – estimated glomerular filtration rate,
MCV – mean corpuscular volume

Level of statistical significance was chosen to be α=0.05. Statistical analysis was performed by statistical package STATA/IC ver.11.1.

Results

The characteristics of the study subjects are listed in Table 1. Mean/median values of BMI, waist to hip ratio (WHR), HDL cholesterol, triglycerides, E, Hb, serum iron, ferritin, serum creatinine, UAE, eGFR as well as blood pressure were within the normal range for patients with diabetes, with slightly elevated HbA1c and LDL cholesterol levels. Association between RBC and parameters of renal function are presented in Table 2. Serum creatinine was significantly associated with Hb, hematocrit (Hct), E, serum iron and ferritin, with Hb showing the strongest correlation (r= –0.42, p<0.001). eGFR was significantly associated with Hb, Hct and E, with Hct showing the strongest correlation (r=0.18, p=0.001). However, UAE did not significantly correlated with RBC. In addition, RBC and renal parameters significantly correlated with various metabolic variables, mainly with parameters included in diagnosis of metabolic syndrome (BMI, WHR, HbA1c, HDL cholesterol, triglycerides and blood pressure). The mentioned correlations were most significant for WHR and HDL cholesterol.

Relationship between RBC among those in the 2nd, 3rd and 4th quartiles of serum creatinine compared to those in quartile 1 are presented in table 3. Stratifying RBC for the degree of serum creatinine, trends across quartiles of serum creatinine for Hb, Hct, E, serum iron and ferritin were statistically significant (all p<0.001). Subjects in the 4th quartile of serum creatinine had significantly lower Hb, Hct, E, serum iron and ferritin levels compared to subjects in 1st, 2nd, and 3rd quartiles. We also explore relationship between RBC among those in the 2nd, 3rd and 4th quartiles of UAE compared to those in quartile 1 (<6.8 mg/24 h). Stratifying RBC for degree of UAE, trends across quartiles was statistically significant only for Hb and Hct (p=0.03) (Table 4).

Relationship between RBC among subjects with normal, mildly decreased renal function or with renal hyperfiltration is displayed in Table 5. Stratifying RBC markers for the degree of eGFR, trends across different groups for Hb, Hct and E were statistically significant (all p=0.01). Subjects with eGFR ≥ 125 mL min⁻¹ 1.73 m⁻² had signifi-

TABLE 2
SPEARMAN CORRELATION ANALYSIS OF ASSOCIATIONS OF RED BLOOD CELL COUNT WITH RENAL FUNCTION PARAMETERS AND METABOLIC PARAMETERS

Variable	Hb	Hct	E	iron	ferritin	creatinine	UAE	eGFR
Duration of diab.	–0.15*	–0.15*	–0.15*	–0.00	–0.13*	0.00	0.14*	–0.29*
BMI	0.16*	0.18*	0.22*	0.09	0.09	0.15*	–0.02	–0.10
WHR	0.52*	0.51*	0.41*	0.24*	0.56*	0.39*	0.01	–0.02
HBA1c	0.00	0.03	–0.04	0.13*	0.07	–0.14*	0.07	0.15*
LDL cholesterol	0.06	0.11*	0.08	0.00	0.07	0.08	0.03	–0.18*
HDL cholesterol	–0.33*	–0.33*	–0.32*	–0.11*	–0.23*	–0.19*	–0.13*	–0.17*
Triglycerides	0.12*	0.14*	0.09	–0.01	0.24*	0.07	0.11*	0.06
Systolic BP	0.18*	0.22*	0.15*	0.15*	0.13*	0.11*	0.09	–0.08
Diastolic BP	0.17*	0.19*	0.16*	0.07	0.19*	0.08	0.23*	–0.01
Serum creatinine	–0.42*	–0.33*	–0.32*	–0.23*	–0.39*			
eGFR	0.11*	0.18*	0.17*	–0.04	0.11			
UAE	–0.03	–0.05	–0.06	0.06	–0.03			

BMI – body mass index, WHR – waist to hip ratio, HbA1c – hemoglobin A1c, eGFR – estimated glomerular filtration rate, UAE – urinary albumin excretion rate, Hb – hemoglobin, Hct –hematocrit, E – erythrocytes, *P<0.05

TABLE 3
QUARTILES OF SERUM CREATININE

	1st quartile (<63 μmol/L)	2nd quartile (≥63<71)	3rd quartile (≥71<80)	4th quartile (≥80 μmol/L)	P for trend
Hemoglobin (g/L)	148±12	142±17	137±17	132±11	<0.001
Hematocrit (L/L)	0.42±0.03	0.41±0.04	0.40±0.05	0.39±0.03	<0.001
E (x10¹²/L)	4.8±0.6	4.7±0.5	4.5±0.4	4.5±0.3	<0.001
Iron (μmol/L)	18 (8–41)	18 (3–46)	16 (2–63)	13 (2–46)	<0.001
Ferritin (μg/L)	103 (8–231)	80 (8–316)	52 (5–697)	25 (8–231)	<0.001

E – Erythrocytes

TABLE 4
QUARTILES OF URINARY ALBUMIN EXCRETION RATE

	1st quartile (<6.8 mg/24 h)	2nd quartile (≥6.8<11.0)	3rd quartile (≥11.0<16.7)	4th quartile (≥16.7 mg/24 h)	P for trend
Hemoglobin (g/L)	140±14	139±16	143±15	135±17	0.03
Hematocrit (L/L)	0.41±0.04	0.40±0.04	0.42±0.04	0.40±0.04	0.03
E (x10^{12}/L)	4.7±0.4	4.6±0.5	4.7±0.4	4.6±0.4	0.07
Iron (μmol/L)	15 (3–46)	17 (3–40)	17 (2–62)	16 (2–46)	0.2
Ferritin (μg/L)	60 (5–335)	52 (8–460)	76 (5–697)	40 (7–374)	0.3

E – Erythrocytes

TABLE 5
LEVELS OF RED BLOOD CELL COUNT DEPENDING ON LEVEL OF ESTIMATED GLOMERULAR FILTRATION RATE

Variable	eGFR≥60<90 mL min^{-1} 1.73 m^{-2}	eGFR≥90<125 mL min^{-1} 1.73 m^{-2}	eGFR≥125 mL min^{-1} 1.73 m^{-2}	P
Hemoglobin (g/L)	133±20	141±14	140±13	0.01
Hematocrit (L/L)	0.38±0.05	0.41±0.04	0.41±0.03	0.001
Erythrocytes (x10^{12}/L)	4.4±0.5	4.7±0.4	4.7±0.3	0.003
Fe (μmol/L)	15 (2–29)	17 (2–62)	14 (3–46)	0.1
Ferritin (μg/L)	33 (7–413)	66 (5–697)	54 (13–194)	0.07

eGFR – estimated glomerular filtration rate

cantly higher levels of Hb, Hct and E than subjects with an eGFR below 125 mL min^{-1} 1.73 m^{-2}.

Discussion

Previous studies documented that anemia is a prevalent finding in patients with type 1 diabetes, especially in those with albuminuria and reduced kidney function, and may contribute to development of CKD in diabetic subjects[1,3–7]. Moreover, anemia is associated with risk of other microvascular complications in diabetes including retinopathy and neuropathy as well as with impaired cognitive functions, increased rates of hospitalization and premature mortality[9,15,16]. On the other hand, the presence and severity of CKD predicts all-cause mortality in type 1 diabetes, and only patients with eGFR >60 mL/min and UAE <30 mg/24 h have no increased risk[17,18].

In the present study we found significant associations between RBC and renal function parameters in type 1 diabetic patients with normal or mildly decreased renal function and UAE <30 mg/24 h. Furthermore, we demonstrated that concentrations of E, Hb, Hct, serum iron and ferritin worsened in parallel with increased in quartiles of serum creatinine and Hb and Hct with increased in quartiles of UAE. In addition, concentrations of E, Hb and Hct were lower in subjects with mildly impaired renal function compared those with normal eGFR or hyperfiltrating subjects. Although previous studies found that significant correlation between RBC and GFR occurs in patients with eGFR < 60 mL/min, we demonstrated significant associations in subjects with normal renal function[6]. In addition, therapy with ACE-inhibitors may cau-

se a small decrease of RBC, but none of our studied patients were treated with ACE inhibitors or angiotensin II receptor blockers[19].

Risk of anemia in diabetes is approximately two to three times that of general population, independently of level of GFR[3]. In type 1 diabetic patients anemia associated with nephropathy is consequence of Epo deficiency and it may be present already in state of normal serum creatinine levels[4]. In type 2 diabetic patients without nephropathy and with UAE < 30 mg/24 h normal increase in Epo production in response to lowering levels of Hb was demonstrated, but without expected reticulocyte response[20]. Microvascular damage and autonomic neuropathy, conditions closely associated with type 1 diabetes, may play role in interstitial fibrosis and consequence impaired function of Epo-producing fibroblasts leading to anemia[21,22]. In addition, reduced sympathetic stimulation of erythropoietin production occurs in diabetic autonomic neuropathy[23]. Severity of this tubulointerstitial injury correlates better with UAE than with GFR[24]. Moreover, declining Hb levels in diabetic patients with early kidney disease are more common among those with higher levels of albuminuria[7]. In this study we also found that Hb and Hct levels were significantly lower in subjects with higher levels of albuminuria.

Although ferritin levels are not an accurate reflection of iron indices in diabetes, levels of ferritin and serum iron worsened in parallel with increasing in serum creatinine in our subjects. Patients with CKD have both absolute and relative iron deficiency[25,26]. Absolute iron deficiency is usually evidenced by a serum ferritin level <100 μg/L, which have majority of our patients. Moreover, only

those in the lowest quartile of serum creatinine (indicating highest GFR) have serum ferritin level > 100 $\mu g/L$. In addition, it has been demonstrated that elevated iron indices are more common in patients with type 1 diabetes, especially in those with poor glycemia and hyperfiltration, which is not confirmed in this study[27,28]. However, our patients with hyperfiltration have higher E, Hb and Hct levels. Hyperfiltration has been suggested as a risk factor for the development of albuminuria and progressive nephropathy[29]. However, recent prospective study including large cohort of type 1 diabetic patients with UAE <30 mg/24 h found that the distribution of estimated GFR in adults type 1 diabetic patients was not significantly different from general population and that type 1 diabetic patients with a higher eGFR were no more likely to develop moderate increased UAE[30].

The present study has a number of potential limitations. First, our study was cross-sectional, which limited our ability to infer a causal relationship between RBC markers and risk for the progression of renal disease in type 1 diabetes. Second, we used estimated GFR rather than more precise measures of kidney function. Third, we did not use sophisticated measures of hematinic parameters such as erythropoietin. Fourth, our analyses were based on measurement of UAE, serum creatinine and eGFR on two consecutive days that may not reflect the relation over time. Fifth, we have not excluded autoimmune gastritis in our patients which may be associated with lower RBC.

In conclusion, anemia is a common finding in type 1 diabetic patients associated with cardiovascular risk and progression of renal disease. Significant associations between RBC and renal function parameters even in type 1 diabetic patients with eGFR >60 mL/min and UAE <30 mg/24 h suggest that the interplay between RBC and renal function exist in the absence of nephropathy. Since progression to chronic renal disease, as a main predictor of all-cause mortality in type 1 diabetes, is likely to occur in majority of diabetic patients, there is a need to further explore the role of risk factors such as anemia.

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POVEZANOST IZMEĐU CRVENE KRVNE SLIKE I BUBREŽNE FUNKCIJE JE PRISUTNA U BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 1 BEZ NEFROPATIJE

S A Ž E T A K

Anemija je česta u bolesnika sa tipom 1 šećerne bolesti, a posebno u onih s albuminurijom ili sniženom bubrežnom funkcijom. Istraživali smo povezanost crvene krvne slike i bubrežne funkcije u bolesnika s tipom 1 šećerne bolesti s normalnom ili blago sniženom bubrežnom funkcijom i razinom albumina u urinu (AU) <30 mg/24 h. Istraživanje je obuhvatilo 313 bolesnika sa tipom 1 šećerne bolesti s urednom ili blago sniženom glomerularnom filtracijom (GF >60 mL/min/1,73 m^2), s AU <30 mg/24 h i bez terapije statinima, ACE-inhibitorima ili blokatorima angiotenzinskih receptora. Razina hemoglobina (Hb), hematokrita (Hct), eritrocita (E), serumskog željeza i feritina je bila značajno niža u bolesnika u najvišoj kvartili serumskog kreatinina u odnosu na one u najnižoj kvartili (132 vs 148 g/L, 0.39 vs 0,42 L/L, 4,5 vs 4,8x10^{12}/L, 13 vs 18 μmol/L, i 25 vs 103 μg/L, p<0,001). Razina Hb i Hct je bila značajno niža u bolesnika u najvišoj kvartili AU u odnosu na one u najnižoj kvartili (135 vs 140 g/L, i 0,40 vs 0,41 L/L, p=0,03). Bolesnici s blago sniženom GF su imali značajno nižu razinu Hb, Hct i E u odnosu na one s urednom GF ili hiperfiltracijom (133 vs 140 g/L, 0,38 vs 0,41 L/L, i 4.4 vs 4,7x10^{12}/L, p=0,01). Rezultati istraživanja ukazuju da povezanost crvene krvne slike i bubrežne funkcije postoji već u bolesnika s tipom 1 šećerne bolesti s normalnom ili blago sniženom bubrežnom funkcijom te AU <30 m/24 h.