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The Erythrocyte Sedimentation Rate is a Simple, Sensitive and Predictive Hematological Index for Non-Septic Diabetic Foot Syndrome: A Cross-Sectional Study

ABSTRACT

Objective: Several studies have found that the hematological index can be considered as a prognostic biomarker of diabetes mellitus. This study aimed to compare the level of the erythrocyte sedimentation rate (ESR) with other hematological indices as a predictive marker of non-infected diabetic foot syndrome (DFS).

Materials and methods: A total of 137 patients with diabetes (53 males and 84 females) and another 30 healthy subjects (10 males and 20 females) were included in this study. The participants were grouped into Group I (healthy subjects, n = 30); Group II (n = 72, type 2 diabetes without clinical evidence of DFS features); and Group III (n = 65, type 2 diabetes with clinical evidence of DFS features (grade 0–2). Hematological indices were determined by a hematology autoanalyzer.

Results: The serum fasting glucose levels were significantly higher among Group III patients compared with Groups I and II. The value of ESR was significantly higher among Group III patients compared with Group II. The ESR and red distribution width (RDW) values increased in tandem with the DFS upgrade. The area under the curve (AUC) of the ESR at a cutoff value of 18 mm/hour was 0.663 with 95% confidence intervals of 0.571–0.755, which was significantly ($p < 0.001$) higher than the AUC of RDW, platelet distribution width, mean platelet volume, and plateletcrit. Also, the area under the curve of the ESR increased as the upgrading of DFS increased.

Conclusions: We conclude that determination of ESR serves as a predictor and discriminator of DFS and its upgrading. (Clin Diabetol 2022; 11; 6: 372–378)

Keywords: type 2 diabetes, diabetic foot syndrome, hematological indices, erythrocyte sedimentation rate, predictive biomarker

Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder caused by pancreatic islet cell dysfunction, resulting in insulin deficiency and impaired glucose metabolism. Several studies found changes in the hematological indices in diabetes and considered these changes as diagnostic and/or prognostic markers.

Among the hematological indices, blood platelets that play a role in atherosclerosis and ultimately cause cardiovascular diseases in people with diabetes were discovered [1]. Diabetes significantly altered platelet indices such as platelet distribution width (PDW), mean

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platelet volume (MPV), and plateletcrit (PCT). PDW is a prognostic indicator for T1D patients with poor glycemic control because it is significantly higher in healthy individuals [2]. The PDW value is significantly lower in T2D complicated with a septic foot compared to healthy subjects [3]. Diabetes-related morphological variations of blood platelets are brought on by glycosylation of platelets due to inadequate glycemic control and endothelial dysfunction [4]. Because of their correlation with vascular complications such as retinopathy, nephropathy, and diabetic foot, PDW and MPV were therefore considered to be predictors of vascular complications in diabetes [5]. MPV measures the average size and volume of the platelets and reflects their activity and thrombogenesis state [6]. Yilmaz and Yilmaz [7] found no evidence of significant changes in the PCT% value in either complications-related or uncomplicated diabetes. A non-specific hematological marker known as the red cell distribution width (RDW) indicates that the red cells are not functioning properly because of changes in their volume and size. Strong evidence links a higher RDW value to a higher risk of cardiovascular disease-related events [8]. Red blood cell deterioration, a shortening of red blood cell life, and an increase in osmotic fragility are all caused by hyperglycemia [9].

RDW is significantly correlated with the duration of diabetes, macrovascular and microvascular complications, and glycemic control [10]. Other studies found a negative relationship between RDW and poor glycemic control [11], as well as a significant increase in the acute rise in serum glucose level, as seen in ketoacidosis complications [12]. Diabetic foot syndrome (DFS) is a pathological entity comprised of peripheral neuropathy, arterial and microcirculatory bed dysfunction, and structural pathological changes in the osteoarticular apparatus of the foot, which leads to the development of ulcerative-necrotic processes and gangrene of the foot [13–16]. It occurs in 25% of diabetes patients and 85% of them have a history of amputation [17]. The erythrocyte sedimentation rate (ESR) is a marker of acute and chronic inflammation [18]. In the non-diabetic septic foot, the ESR level is a non-specific and diagnostic marker at a cutoff level of 45.5 mm/h [19]. In the DFS, the increase in ESR is associated with the infective process [20]. It has been reported that procalcitonin, ESR, and C-reactive protein (CRP) were significantly higher in the infected DFS compared to the non-infected DFS [21]. Therefore, these parameters can predict the occurrence of osteomyelitis and peripheral artery diseases following diabetic foot development with good accuracy and acceptable sensitivity [22]. Another multivariate analysis showed that baseline ESR level was an independent predictor of lower extremity amputations in 89 persons with infected DFS [23]. Moreover, based on the receiver operating characteristic curve analysis, ESR had fair accuracy, in detecting the diabetic foot with osteomyelitis [24]. The value of measurement of ESR in non-infected DFS was not reported in previous studies. Therefore, this study aimed to compare the ESR value with other hematological indices as a predictive marker of non-infected diabetic foot syndrome.

Materials and methods

Ethical approval

The Ethical and Scientific Committee of the University of Sulaimani reviewed and approved this cross-sectional observational study according to the Helsinki guidelines. The patients are free to refuse participation or enroll in the study at any time they wanted. Finally, patients who agreed to participate in this study signed a consent form.

Setting

The present cross-sectional study was performed in the Department of Pharmacology, College of Medicine at the University of Sulaimani in collaboration with Shar Teaching Hospital in Sulaimani city in the north of Iraq through the period of October 1st, 2021 to March 31st, 2022.

Design

Eligible patients were of both sexes and not less than 35 years old. The criteria of inclusion were T2D patients who presented with or without clinical features of diabetic foot syndrome (DFS). The patients were already on oral antidiabetic agents. For grading the DFS, the Wagner-Meggitt classification was used [25]. Our study used the Wagner-Meggitt classification because it is straightforward and satisfies the study's aims. The researchers examined each patient thoroughly. The Wagner-Meggitt classification system has six grades (0–5) of lesions. Grades 0–3 are based on the physical depth of the ulcer, and grades 4 and 5 are based on the extent of gangrene. Grading of DFS was under the supervision of the consultant endocrinologists. The X-ray, as well as specimen culture and sensitivity tests, were done for each patient. Patients with grades 0–2 and negative microbiological testing were included in this study. Patients with a history of blood diathesis, evidence of current infections, chronic rheumatic illnesses, drug intake including non-steroidal anti-inflammatory agents, and smoking were excluded from the study. A total number of 137 patients (53 males and 84 females) with a median age of 55 years old fulfilled the above criteria, and another 30 healthy

Table 1. Characteristics of Participants

Determinants	Group I (n = 30)	Group II (n = 72)	Group III (n = 65)	One way ANOVA analysis		P-value of *post-hoc* Boneferroni test between groups		
				F-value	P-value	Group I versus Group II	Group I versus Group III	Group II versus Group III
Sex (Male:Female)	10:20	35:37	18:47			0.157	0.575	0.012
Age [years]	50.1 ± 6.4	53.4 ± 9.0	56.7 ± 7.8	7.370	0.001	0.194	0.001	0.050
Family history of diabetes	0	48	42					0.801
Duration of diabetes [years]	—	7.78 ± 4.31	10.26 ± 5.65					0.004
Fasting serum glucose [mg/dL]	86.9 ± 8.4	197.1 ± 69.5	226.9 ± 82.3	42.237	< 0.001	< 0.001	< 0.001	0.037
Glycated hemoglobin [%]	4.66 ± 0.29	9.26 ± 1.97	9.64 ± 2.09	84.419	< 0.001	< 0.001	< 0.001	0.659
Grading of diabetic foot ulcers								
Grade 0	0	0	13					
Grade 1	0	0	33					
Grade 2	0	0	19					

The results are presented as a number and mean ± SD. The results were analyzed by using a one-way ANOVA test, and the p-value was calculated by using a two-tail independent two-sample t-test, a *post-hoc* Boneferroni test for continuous data, and a Chi-squared test for categorized data. Group I: healthy subjects, Group II: diabetes without foot syndrome, Group III: diabetes foot syndrome

subjects (10 males and 20 females) was also included. The patients were grouped into:

Group I (n = 30): Healthy subjects served as a negative control group recruited from the same area of the research.

Group II (n = 72): T2D patients without clinical evidence of DFS features.

Group III (n = 65): T2D patients with clinical evidence of DFS features (grade 0–2).

Laboratory investigations

The 12-hour overnight fasting venous blood was drawn from each patient and collected into two series of test tubes, the first portion with anticoagulant (EDTA) test tubes for determination of hematological indices using an automated hematological analyzer (Coulter machine), ESR using the conventional Wintergreen method, and the glycated hemoglobin assay. The second portion was without anticoagulant by which the sera were separated by centrifugation (3000 rpm, for 15 minutes) for determination of fasting serum glucose. Fasting serum glucose and glycated hemoglobin were determined according to the instructions of the manufacturers of the kits. The ratios of granulocyte--to-lymphocyte (GLR), and platelet-to-lymphocyte (PLR) were determined by dividing the absolute number of neutrophils or blood platelets to the absolute number of lymphocytes, respectively.

Statistical analysis

The results are expressed as numbers, percentages, medians, and mean ± SD. The difference between the means of the two groups was analyzed using one-way analysis of variance (ANOVA) with a *post-hoc* Boneferroni test. The area under the curve (AUC) and 95% confidence intervals of RDW, PDW, PCT, MPV, and ESR were determined at a cutoff value of ≥ 12%, ≥ 12%, ≥ 0.2%, ≥ 8fL, and ≥ 18 mm/h, respectively. The cutoff values were adjusted according to the median values of the healthy general population at our laboratories. The odd ratios and 95% confidence intervals of DFS in reference to the patients with diabetes who did not have DFS were calculated for each hematological index. A p-value of ≤ 0.05 is the cutoff level of significance. Excel software (2010) and SPSS 20 programs were used for data analyses.

Results

Table 1 shows the characteristic features of DFS patients, which include a significantly higher proportion of females, a higher mean of age, a longer duration of disease, and a higher mean level of fasting serum glucose. Most Group III patients were presented with grade I (50.8%) followed by grade II (29.2%) and grade 0 (20%). Table 2 shows that patients with diabetes have a significantly higher value of RDW compared with the corresponding value of healthy subjects. The RDW value of Group II patients was not-significantly different from the corresponding value of Group III (Tab. 2). The mean level of the ESR of Group III patients was significantly higher than the corresponding mean levels of Groups I and II (Tab. 2). There were non-significant differences between groups regarding the platelet indices, including PDW, MPV, and PCT (%). The GLR and

Table 2. Hematological Indices and Ratios

Hematological indices	Group I (n = 30)	Group II (n = 72)	Group III (n = 65)	One way ANOVA analysis		P-value of *post-hoc* Boneferroni test between groups		
				F-value	P-value	Group I versus Group II	Group I versus Group III	Group II versus Group III
Red distribution width [%]	11.81 ± 0.81	12.66 ± 1.35	12.62 ± 1.28	5.495	0.005	0.006	0.011	1.000
Platelet distribution width [%]	12.59 ± 1.2	12.26 ± 1.8	12.61 ± 1.69	3.210	0.43	0.190	1.000	0.071
Mean platelet volume [fL]	8.54 ± 0.86	8.53 ± 1.35	8.40 ± 1.03	0.248	0.781	1.000	1.000	1.000
Plateletcrit [%]	0.196 ± 0.051	0.192 ± 0.056	0.205 ± 0.056	0.877	0.418	1.000	1.000	0.575
Neutrophil-to--lymphocyte ratio	2.030 ± 0.65	2.217 ± 1.18	2.509 ± 1.02	2.582	0.079	1.000	0.113	0.299
Platelet-to-lymphocyte ratio	109.7 ± 32.4	111.9 ± 35.9	124.6 ± 47.4	2.214	0.113	1.000	0.288	0.200
Erythrocyte sedimentation rate [mm/h]	11.9 ± 5.5	14.1 ± 11.6	27.9 ± 19.0	20.535	< 0.005	1.000	< 0.001	< 0.001

The results are presented as mean ± SD. The results were analyzed by using a one-way ANOVA test, and the p-value was calculated by using a two-tail independent two-sample t-test, a *post-hoc* Boneferroni test for continuous data, and a Chi-squared test for categorized data. Group I: healthy subjects, Group II: diabetes without foot syndrome, Group III: diabetes foot syndrome

Table 3. Hematological Indices and Ratios According to the Grades of Diabetic Foot Syndrome

Hematological indices	Grading of diabetic foot ulcers			One way ANOVA analysis		P-value of *post-hoc* Boneferroni test between groups		
	Grade 0 (n = 13)	Grade 1 (n = 33)	Grade 2 (n = 19)	F-value	P-value	Grade 0 versus Grade 1	Grade 0 versus Grade 2	Grade 1 versus Grade 2
Red distribution width [%]	12.32 ± 1.0	12.47 ± 1.1	13.09 ± 1.62	1.920	0.155	1.000	0.287	0.276
Platelet distribution width [%]	11.95 ± 1.16	13.08 ± 1.77	12.25 ± 1.69	2.904	0.062	0.115	1.000	0.245
Mean platelet volume [fL]	8.28 ± 1.15	8.61 ± 1.06	8.14 ± 0.87	1.365	0.265	0.995	1.000	0.365
Plateletcrit [%]	0.215 ± 0.037	0.204 ± 0.057	0.199 ± 0.066	0.329	0.721	1.000	1.000	1.000
Neutrophil-to-lymphocyte ratio	2.346 ± 0.749	2.592 ± 1.162	2.477 ± 0.932	0.280	0.757	1.000	1.000	1.000
Platelet-to-lymphocyte ratio	138.1 ± 36.9	118.0 ± 48.8	126.8 ± 51.4	0.863	0.427	0.604	1.000	1.000
Erythrocyte sedimentation rate [mm/h]	19.7 ± 10.6	25.6 ± 19.1	37.5 ± 20.2	4.234	0.019	0.963	0.025	0.081

The results are presented as mean± SD. The results were analyzed by using a one-way ANOVA test, and the p-value was calculated by using a two-tail independent two-sample t-test, a *post-hoc* Boneferroni test for continuous data, and a Chi-squared test for categorized data. Group I: healthy subjects, Group II: diabetes without foot syndrome, Group III: diabetes foot syndrome

PLR were non-significantly higher in patients with diabetes compared with the corresponding values of the healthy subjects (Tab. 2). Moreover, these ratios were non-significantly higher in Group III compared with the corresponding values in Group II (Tab. 2). Table 3 shows the characteristic features of hematological indices in Group III patients according to their presenting grades of DFS. The mean level of RDW was non-significantly higher in grade 2 > grade 1 > grade 0, whereas the PCT (%) was a non-significantly lower in grade 2 < grade 1 < grade 0. The AUC of the ESR is 0.663, which is significantly (p = 0.001) increased compared with

Table 4. Hematological Indices as Discriminators of Diabetes Foot Syndrome

Hematological indices	AUC (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Odds ratio
RDW (≥ 12)	0.530 (0.434–0.622)	75.4	69.4	49.5	57.9	1.35 (0.65–2.93)
PDW (≥ 12)	0.395 (300–0.490)*	53.8	76.4	38.9	36.2	0.361 (0.18–0.77)
PCT % (≥ 200)	0.570 (0.474–0.666)	55.4	45.8	52.2	57.4	1.47 (0.76–3.02)
MPV (≥ 8)	0.490 (0.393–0.587)	66.2	66.7	47.3	52.2	0.98 (0.47–1.95)
ESR (≥ 18)	0.663 (0.571–0.755)**	63.1	31.9	64.1	67.1	3.64 (1.79–7.41)

*p = 0.034, **p = 0.001
AUC — area under the curve; CI — confidence intervals; ESR — erythrocyte sedimentation rate; MPV — mean platelet volume; PCT — plateletcrit; PDW — platelet distribution width; RDW — red distribution width

Table 5. The Area Under the Curve and 95% Confidence Intervals of the Hematological Indices as Discriminators of Diabetes Foot Syndrome

Grades of diabetic foot ulcers	Red distribution width (≥ 12)	Platelet distribution width (≥ 12)	Plateletcrit (≥ 0.200)	Mean platelet volume (≥ 8)	Erythrocyte sedimentation rate (≥ 18 mm/h)
Grade 0	0.404 (0.222–0.586)	0.346 (0.181–0.512)	0.567 (0.396–0.739)	0.337 (0.166–0.507)	0.394 (0.218–0.570)
Grade 1	0.488 (0.347–0.630)	0.676 (0.544–0.809)	0.583 (0.444–0.723)	0.613 (0.475–0.751)	0.444 (0.304–0.585)
Grade 2	0.589 (0.443–0.735)	0.406 (0.253–0.559)	0.347 (0.198–0.496	0.490 (0.334–0.646)	0.649 (0.509–0.790)

The results presented as area under the curve (95% confidence intervals)

the other hematological indices and discriminates the Group III patients from the Group II patients (Tab. 4). The AUC of platelet distribution width is significantly (p = 0.034) decreased in Group III patients (Tab. 4). Group III patients had ESR levels ≥ 18 mm/hour by 3.64 times as many as Group II patients (Tab. 4). The sensitivity and specificity of the ESR at a cutoff value ≥ 18 mm/hour as a discriminator of DFS were 63.1% and 31.9%, respectively. Table 5 shows the AUC of the ESR and the RDW were increased as the grading of DFS increased.

Discussion

The results of this study show that ESR and RDW values are significantly higher in diabetic patients (Groups II and III), and the ESR level is a significantly higher in Group III compared with Group II. A high ESR value significantly discriminated against the grading of DFS at a cutoff of ≥ 18mm/h. The mean ± SD of the age of Group III patients was significantly higher than the corresponding value of Group II, and they had a longer duration of diabetes and a higher serum glucose level. These observations are simply explained on the basis that patients with long-standing diabetes are prone to complications and probably of uncontrolled diabetes [26]. There are no significant differences in the hematological indices between Group II and III except the ESR value, which is significantly higher in Group III patients than the corresponding value of Group II patients. Previous studies showed that a higher value of RDW was observed in patients with diabetes with a longer duration of disease, as shown in our study [27]. Since diabetic complications significantly alter the RDW, hyperglycemia has an impact on changes in red cell indices rather than the DFS [16]. Our findings with the platelet indices showed non-significant differences between the patients with diabetes and the healthy subjects. Walinjkar et al. (2019) [28] study showed significantly higher platelet indices were observed in patients with diabetes and microvascular complications compared with healthy subjects or those without microvascular complications. In the absence of any evidence of infection, Group III patients had a significantly higher ESR value compared with the corresponding values of Group I and Group II patients. Previous research found that a significantly higher ESR value predicted a poor prognosis in the infected diabetic foot [29]. Another study showed that ESR was significantly more precise in the diagnosis of diabetic foot osteomyelitis than magnetic resonance image [30]. In our investigation, which was conducted on diabetic feet that were not infected, the cutoff level of ESR was > 18 mm/h. It has been suggested that the ideal ESR cutoff threshold for predicting osteomyelitis in diabetic feet is > 49 mm/h [31, 32]. This study adds more information that ESR is significantly associated with upgrading of DFS in absence of infection by the evidence of normal plain

X-ray, which is normal. Further analysis revealed that ESR at a cutoff value of ≥ 18 mm/h discriminates DFS from diabetes as well as the upgrading of DFS by the evidence of a significantly higher AUC with an odds ratio of 3.64. The literatures survey did not show any previous studies that demonstrated these findings. The strength of this study is that Group III patients had a grade of 0–2 of DFS which means that there is no frank infection and normal plain X-ray findings. This indicates that a significantly higher level of ESR is not related to the infection.

Conclusions

We come to the conclusion that measuring the erythrocyte sedimentation rate is a quick, accurate, predictive, and low-cost marker that can distinguish between DFS and its upgrading. The erythrocyte sedimentation rate can take the place of other hematological indicators that fluctuate in their calculation and change depending on the severity of the condition, inadequate glycemic control, and the type of complications associated with diabetes.

Conflict of interest

None declared.

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