

Exploring Association of Anemia with Diabetic Foot Ulcer and its Impact on Disease Outcome in a Tertiary Care Hospital

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ABSTRACT

Background: Both short-term and long-term complications are common in people with diabetes, making the disease quite difficult to manage. Among them development of foot ulcer is like a nightmare for diabetic patients. Foot deformities, impairment of microcirculation and concomitant neuropathy all add in the development of these ulcers, that are either delayed to heal or do not heal at all leading to amputation or in extreme cases even death. In addition to these major contributors, concomitant comorbidities like anemia may lead to development of an ulcer or effect it's healing. If anemia identified and treated promptly may enhanced recovery of diabetic foot ulcer patients. We analyzed the effects of anemia on the prognosis of individuals with diabetic foot ulcers (DFUs).

Methods: We prospectively followed 165 diabetic patients admitted to the hospital with DFU until they were either discharged or died. Patient's demographic data, characteristics of the ulcers, duration of diabetes, presence of comorbid conditions, need for blood transfusion and diabetic complications were all taken into account. The appropriate imaging and laboratory tests were conducted. The incidence of anemia and its effect on illness outcome in DFU patients were examined.

Results: Anemia was found in 70% of patients with 38% required blood transfusion. The presence of gangrene, PAD, and an ulcer that had been present for more than a month prior to admission were all significant demographic and clinical predictors of anemia, [p0.008], [p0.00.1], [p0.001] respectively. Comorbidities like proteinuria [p0.003], moderate [p0.002] and severe [p0.00.1] constriction of the blood vessels, previous stroke [p0.012], kidney dysfunction [p0.002] were all significantly linked with anemia. Regarding effect of anemia on disease outcome delayed wound healing [p0.008], osteomyelitis [p0.005], amputation [p0.034] and mortality [p0.008] were all substantially correlated with anemia.

Conclusion: Anemia was seen in majority of patients with DFU. Significant association was found between anemia and worse ulcer outcome in the form of delayed wound healing, osteomyelitis, mputation and mortality. Therefore, it needs to be identified and managed promptly, like other major risk factors such as infection, ischemia and pressure offloading, to promote earlier and complete healing.

Keywords: Exploring, Association, Anemia, Diabetic Foot Ulcer, A Tertiary Care Hospital

INTRODUCTION

Despite worldwide efforts to treat the disease, the number of people who have diabetes continues to rise. Multiple sources project that by 2045, 629 million people will have diabetes¹. Prevalence of diabetes is predicted to grow by 156% across the world, with the highest rates seen in [SSA Sub-Saharan Africa]. In terms of morbidity and mortality, diabetes mellitus [DM] is a big contributor². Diabetes can lead to serious complications including heart diseases, blindness, renal failure, and even amputation of the lower extremities. According to the International Diabetes Federation [IDF], diabetes was the cause of death for almost [4.0] million people aged 25–80 in 2018³. Nearly 4 to 10 percent of patients with DM develop foot ulcers⁴. Foot ulceration has been linked to amputation of 8-21% in the lower extremities⁵. Diabetic foot disease causes significant psychosocial & economic burden⁶. There are a number of causes for DFU. In addition to vasculopathy, other factors that have a role in the DFU development include inadequate glycemic control, changed foot biomechanics, foot deformity, active infection, polyneuropathy, lowered immunity and inflammation⁷. Patient's outcomes may be influenced by these elements as well. Research has shown that people with diabetes are more likely to get anemia than the general population. People with diabetes mellitus (DM) with anemia are at increased risk for cardiovascular disease, stroke, high blood pressure, and kidney disease⁸. Anemia is related with worse results in persons with DFU⁹. However, the correlation between anemia and DFU has only been the subject of a small number of investigations¹⁰.

METHODS

A prospective observational study was conducted at department of Surgery QHAMC Nowshera and Endocrinology department LRH Peshawar between January 2021 and June 2021. Patients over

the age of 18 with DFU, both T1DM & T2DM were included in the study. Ethical approval was obtained from ethical review board of both hospitals. Pregnant women, people with malabsorption disorders, haemoglobinopathy, & those taking iron, folic acid and B12 supplements were excluded. Data was collected on a questionnaire after informed consent. A total of 165 patients were enrolled in the study. Patient's demographic information was collected, including their age, sex, duration of diabetes, type of diabetes & smoking history. Ulcer was graded according to Wagner classification for DFU. Presence of comorbidities like hypertension, heart failure, renal failure, and stroke were taken into account. The relevant investigations like CBC, RFT, HBA1C & imaging studies were done from the laboratory of the hospital. Based on World Health Organization Anemia was described as haemoglobin levels below 12 g/dl in females and below 13 g/dl in males. Loss of pressure sensitivity to 10 gm of "semmes-weinstein monofilament" or "diminished vibration sensitivity" as measured by a 128 Hz tuning fork were used to diagnose peripheral neuropathy. A palpable pulse in the "dorsalis pedis or posterior tibial artery on manual palpation, or significant arterial constriction" of more than 50 % on Doppler ultrasonography, were used to diagnose peripheral arterial disease.

Renal impairment was characterised by proteinuria or an eGFR of less than 90 ml/min.

Statistical Analysis: The latest version of SPSS was used for the statistical analysis. Categorical variables have been transformed into frequencies and percentages. Calculations of mean and standard deviation were made for numerical variables. By utilizing the Chi-Square test for categorical data and the Student t-test for continuous variables, we looked for an uncorrected correlation between anemia and demographic, clinical, and laboratory information. A p-value of 0.05 was taken to indicate statistical significance.

RESULTS

Out of 165 participants 55% were male. Average age was 55.09 years. 90% had diabetes type 2. Average duration of diabetes was 8.05 years. The average ulcer duration before admission was 20 days, ranging from 30 to 75 days. 123 patients (75%) had wound infection. [Table 1] 37% had Wagner grade 04 ulcers. 116 (70%) developed anemia, and 44 needed transfusions.

Table 2 lists demographic and clinical anemia variables. Anemia was common in patients with long-lasting ulcers [OR = 1.89; 95%CI = 1.177-3.04], peripheral artery disease [OR = 2.14; 95%CI = 1.385-3.316], and gangrene [OR = 2.36; 95%CI = 1.522-3.66]. Table 4 shows anemia and DFU results for proteinuria [OR = 2.04; 95% CI = 1.285-3.24], osteomyelitis [OR = 2.01; 95% CI = 1.218-3.34], severe vascular stenosis [OR = 4.15; 95% CI = 1.803-9.56], and stroke [OR = 2.84; 95% CI = 1.24-6.53]. Anemic patients had a reduced likelihood of a favorable outcome (OR=0.52; CI=0.32-0.85). Anemic DFU patients were more likely to die (27.8% vs 17.5%) and have amputations (41.8% vs 30.1%). [OR = 1.67; 95%CI = 1.04-2.69]. Table 5 shows anemia multivariate logistic regression findings. Multivariate study demonstrated that bivariate predictors of anemia acted synergistically.

Table 1: Subject socioeconomic status and clinical features

Variable	Overall
Age (years)	55.09 ± 11.05
Gender [male]	90 [55%]
Type of diabetes (T2DM)	148 (90%)
Duration of diabetes in years	08.05 ± 05.06
Hemoglobin A1C (%)	10.20 ± 01.09
Cigarette smoker	18.90%
Duration of ulcer present before hospitalization (Days)	20 (30–75)
History of Ulcer in past	48.29%
Wound Infection	123 (75%)
Ulcer grade [Wagner]	
Grade 1	08 (5%)
Grade 2	24 (14.57%)
Grade 3	44 (26.5%)
Grade 4	62 (37.57%)
Grade 5	27 (16.36%)
Comorbidities	
Hypertension	125 (75.7%)
Anemia	116 (70%)
Cardiac failure	12 [07%]
Renal impairment	33[20%]
Stroke	16 [10%]

Table 2: Anemia's social and medical causes.

	Anemia		P value	OR	90% C. I for OR
	Yes n [%]	No n [%]			
Age [years]					
<45 [reference]	[45]	13 [55]			
46–70	52 [52]	48 [48]	[0.443]	[1.280]	[0.681–2.409]
≥70	52 [61]	17 [38.6]	[0.083]	[1.877]	[0.921–3.824]
Gender					
Male	50 [52]	43 [45]	[0.981]	[0.995]	[0.646–1.531]
Female	40 [54]	35 [46]			
Type of diabetes					
Type 01	02 [30.8]	05 [70]	[0.105]	[0.371]	[0.112–1.230]
Type 02	88 [55]	73 [44]			
Duration of diabetes					
<10 years [reference]	65 [51]	66 [49]			
10-20 years	25 [62]	15 [37]	[0.053]	[1.670]	[0.992–2.810]
>20 years	01 [38]	02 [57]	[0.680]	[0.726]	[0.159–3.312]
HbA1c					
< 07%	08 [53]	07 [47]	[0.997]	[0.998]	[0.352–2.827]
07%	150 [53.4]	131 [46.6]			
Onset of ulcer					
Spontaneous [reference]	67 [56]	47 [44]	[0.197]	[1.347]	[0.857–2.116]
Traumatic	56 [48.7]	59 [51.3]			
Ulcer duration					
01 month	70 [58]	50 [42]	[0.009]	[1.892]	[1.177–3.042]
<01 month	42 [42.4]	57 [57.6]			
Neuropathy					
Yes	72 [55]	60 [45]	[0.337]	[1.288]	[0.768–2.160]
No	18 [49]	19 [51]			
Peripheral artery disease					
Yes	55 [62]	33 [36]	[0.001]	[2.143]	[1.385–3.316]
No	35 [44]	45 [57]			
Presence of Gangrene					
Yes	113 [63.5]	65 [36.5]	< 0.001	2.361	1.522–3.662
No	67 [42.4]	91 [57.6]			
Wound infection					
Yes	72 [55]	58[45]	[0.327]	[1.289]	[0.776–2.140]
No	19 [49]	20 [51.3]			

Confidence Interval (CI) = Predicted Value minus 90% Odds of Being Wrong (OR) [univariate logistic regression].

Table 3: Relationship between comorbidities and anemia

	Anemia		P value	OR	90% C. I for OR
	Yes n [%]	No n [%]			
Proteinuria					
Yes	38 [63]	21 [35]	[0.003]	[2.041]	[1.285–3.242]
No	48 [46]	52 [53]			
Blood culture					
Positive	48 [59]	18 [41]	[0.131]	1.502	[0.886–2.549]
Negative	45 [49]	47 [51]			
Osteomyelitis					

Yes	30 [65]	08 [34]	0.006	2.018	[1.218–3.342]
No	53 [48]	28 [51]			
Vascular Stenosis					
None	26 [42]	36 [57]			
Mild	20 [49]	40 [50]	[0.263]	[[1.385]	[0.783–2.447]
Moderate	26 [65]	15 [36]	[0.002]	[2.483]	[1.393–4.423]
Severe	13 [74]	05 [24]	[0.001]	[4.154]	[1.803–9.569]
Hypertension					
Yes	51 [51]	45 [46]	[0.770]	[0.938]	[0.608–1.446]
No	40[55]	33 [44]			
Stroke					
Yes	12 [75.0]	04 [23]	[0.014]	[2.846]	[1.240–6.535]
No	78 [52]	75 [49]			
Heart failure					
Yes	08 [74]	03 [24]	[0.050]	[2.607]	[1.002–6.788]
No	81 [51]	75 [43]			
Renal impairment					
Yes	24 [70]	10 [21]	[0.002]	[2.567]	[1.432–4.604]
No	65 [50]	70 [51]			

Confidence Interval (CI) = Predicted Value minus 90% Odds of Being Wrong (OR) [univariate logistic regression].

Table 4: Anemia and foot ulcers as a result of diabetes

	Anemia		[P value]	[OR]	[90% C. I for OR]
	Yes n [%]	No n [%]			
Satisfactory healing					
Yes	20 [21]	27 [35]	[0.009]	[0.525]	[0.324–0.849]
No	70 [78]	51 [65]			
Endpoint					
Died	22 [28]	13 [18]	[0.034]	[1.822]	[1.047–3.171]
Survived	57 [73]	58 [81]			
Amputation					
Yes	33 [42]	21 [30]	[0.036]	[1.668]	[1.035–2.689]
No	04 [23]	14 [70]			

For univariate logistic regression, OR = Crude Odds Ratio, p = likelihood of making a type 1 error, and CI = confidence interval.

Table 5: Findings from a multivariate regression study to identify population-level drivers of anemia

Variable	P value	OR	[90% C. I for OR]
[Ulcer duration 1 month]	[0.504]	[1.217]	0.684-2.164
Presence of PAD	[0.584]	[1.219]	0.600-2.473
Foot gangrene	[0.100]	[1.575]	0.916-2.709
Proteinuria	[0.249]	[1.400]	0.790-2.479
Osteomyelitis	[0.380]	[1.311]	0.716-2.400
Stroke	[0.063]	[2.472]	0.953-6.409
Renal impairment	[0.239]	[1.548]	0.748-3.207
[Moderate arterial stenosis]	[0.352]	[0.586]	0.190-1.806
[Severe arterial stenosis]	[0.541]	[0.723]	0.256-2.042

Peripheral artery disease (PAD) Confidence interval (CI) = Odds ratio (OR) minus the likelihood of making a type 1 mistake (p) multiplied by the odds ratio (OR) from the multivariate logistic regression.

DISCUSSION

Anemia may cause wound healing issues, amputation, and death in DFU patients. Prevalence of anemia in our study population was around 70 % which is close to 85.6% in a study done in BIDE Karachi¹¹. In our study more males than females presented with diabetic foot ulcer & anemia which is similar to other studies¹². Most of the study cohort had poor glycemic control as reflected by mean HBA1C of 10.20 ± 01.09. HBA1C can be affected by a variety of conditions unrelated to DM including anemia¹³. Anemia was more common in those DFU patients with longer duration of diabetes that might be due to chronic metabolic derangements and inflammation associated with the disease, renal impairment was seen as one of the common comorbidities in patients with anemia and DFU as reported in other studies¹⁴. Anemia, which is widespread but generally ignored in people with diabetes mellitus regardless of renal impairment¹⁵.

The finding of high rate of amputation, poor wound healing & mortality in our study group was consistent with a Nigerian study¹⁶. This is owing to the fact that limb ischemia brought on by PAD is often made worse by inadequate oxygen supply to the periphery when anaemia is present. In addition, anemia increases the

production of endothelial adhesion molecules, which results in thrombus formation and further reduces tissue circulation¹⁷. All of them eventually result in limb gangrene and amputation. This explains the significant association of adverse outcome in anemic DFU patients. A study from Brazil also reports these adverse outcomes of wound healing in anemic DFU patients¹⁸.

The limitation of our study is that as the patients coming only to tertiary care hospital were included in study, the results might not reflect the true burden of the disease and cannot be generalized. The inclusion of patients with CKD may also have an impact on the true relation between anemia & chronic inflammation in the research group as the type of anemia and measurement of the inflammatory markers were not examined. In spite of these limitations, the findings of the research give a baseline data on the incidence of anemia and its influence on illness prognosis in DFU patients in our setting. This information should motivate clinicians to take into consideration this co-morbidity when treating patients who have DFU.

CONCLUSION

Our study showed significant association of anemia & DFU. Poor wound outcome were more common in DFU patients who had anemia which means that if it is diagnosed & treated promptly, it can have positive impact on healing. Anemia should be taken in account like other major comorbidities while managing a patient with DFU.

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