

Original Research Article

The importance of HbA1C and erythrocyte sedimentation rate as prognostic factors in predicting the outcome of diabetic foot ulcer disease

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ABSTRACT

Background: The study is to determine the relation between the high HbA1c and ESR as prognostic factors with the severity of the diabetic foot ulcer disease, particularly, in predicting the final outcome in the form of higher incidence of lower extremity amputation (LEA) and/or prolonged hospital stay. The study explored the importance of increased level of serum HbA1c and erythrocyte sedimentation rate (ESR) in determining the final outcome of the disease. It revealed that the severity of diabetic foot ulcer disease is more in patients who had concomitant high levels of baseline HbA1c and ESR on admission.

Methods: This observational study was done in 89 patients who were admitted in the surgical wards of the two teaching hospitals in India. The cohort consisted of patients from the age of 26 to 83 years of age who presented with clinically infected foot ulcers. Routine blood tests were done which include HbA1C on the day of admission and fasting ESR (1st hour) on the next day morning. The standard X-ray plates were routinely taken on the first day for determination of the involvement of underlying bones and soft tissues. The outcome of the diabetic foot ulcer was assessed from the severity of the disease according to Meggit-Wagner classification, the incidence of lower extremity amputation and the duration of hospital stay.

Results: The high levels of baseline HbA1C (more than 7.0%) in blood on the first day of admission was found in all of the 89 patients who were included in this study but the criteria for consideration of high risk was more than 9% which was found in 41 patients. The criteria for consideration of high ESR in this study was set to be 50 mm/h. High ESR of more than 50 mm was found in 63 patients. We had subdivided 31 patients into a High Risk Group whose baseline levels of HbA1C > 9% and ESR > 50 mm/h. The incidence of amputation was 79.31% and 44.44% with HbA1c of more than 9.0% and ESR of more than 50 mm respectively and was considerably increased (83.87%) when both HbA1c and ESR were more than the critical value as set in the study. Similarly, the incidence of prolonged hospital stay of more than 14 days was 58.54% in patients with HbA1C level of greater than 9 %, 51.85% in patients with baseline ESR > 50 mm/h and 93.55% in presence of high levels of both HbA1C (>9%) and ESR (>50 mm/h).

Conclusions: The study observed that the patients who presented with baseline high levels of HbA1C, ESR or both on admission had unfavourable prognosis with increased incidence of lower extremity amputation and prolonged hospital stay than the other patients in the cohort. .

Keywords: Amputation and DFU, ESR and LEA, ESR and Hospital stay, Hospital stay and DFU, HbA1C and Hospital stay, LEA and HbA1C

INTRODUCTION

India is the diabetes capital of the world with a projected 109 million individuals with diabetes by 2035.¹ The disease currently affects more than 62 million Indians, which is more than 7.1% of India's adult population.² India with approximately 42 million cases is ranked first in the list of the ten nations most affected with diabetes.^{3,4} Among diabetes mellitus related complications, foot ulceration is one of the most common, affecting approximately 15% of diabetic patients during their lifetime.^{4,5} More than half of all foot ulcers become infected, requiring hospitalization and 20% of infections result in amputation.⁶ Diabetes is the cause of approximately 66% of non-traumatic lower extremity amputations. This can be attributed to several social and cultural practices such as barefoot walking, inadequate facilities for diabetes care and education, and poor socioeconomic conditions. Limb amputation has a major impact on the individual, not only in distorting body image, but also with regard to loss of productivity, increasing dependency, and costs of treating foot ulcers if patients require inpatient care.⁷ Sporadic qualitative research suggests that diabetic foot ulceration has a profound social impact with patients reporting stigma, social isolation, loss of social role and unemployment.⁸ In India prevalence of foot ulcers in diabetic patients in clinic population is 3%, which is much lower than reported in the western world. Almost 85% of the amputations are preceded by diabetic foot ulcers.^{9,10} Numerous risk factors for the development of foot ulcers have been suggested, the most important being peripheral sensory neuropathy followed by peripheral vascular disease. The proportion of neuropathic, neuroischemic, and purely ischemic lesions in diabetics is 54, 34, and 10%, respectively.¹¹ HbA1C, is an established marker to monitor diabetic status of a patient and is currently being investigated for its association with ulcer healing and progression. It has been observed that ulcer healing rate is significantly slower if the HbA1C levels are high. This observation is especially significant in ulcers located on the foot.¹² Another study by Adler et al. showed high HbA1C levels are a known risk factor for LEA.¹³ In India, it is estimated that approximately 40,000 legs are being amputated every year, of which 75% are neuropathic with secondary infection, which are potentially preventable. It was found that approximately all foot ulcer patients have HbA1C level uncontrolled with 86% of them having HbA1C level of 8.86%.¹⁴ The erythrocyte sedimentation rate (ESR) is an indirect measure of acute phase reactants, which increases in inflammation or infection. ESR was reported to have a useful diagnostic value in detecting diabetic osteomyelitis which is a precursor to amputation. This laboratory parameter is simple and could be routinely performed in developing countries like India where diabetes and its complication are increasingly being encountered. Recent evidence supports the use of ESR for the evaluation of possible osteomyelitis in DFU which may lead to amputation.²⁰

Lower extremity amputation is a multifactorial complication in diabetic patients. The aim of this study was to determine the risk factors associated with amputation in patients with diabetic foot ulcers. The incidence of LEA in diabetic patients has been reported to range from 5.2% to 39.4%. These strikingly different estimates of incidence may reflect variation in the risk factors present in different populations. In Western countries, various studies have reported the risk factors for LEA, but few studies have been done on this topic in India. The detection and control of these risk factors can largely prevent the incidence of amputation and its consequences. The aim of the study was to correlate and compare the severity, prognosis and outcome of the diabetic foot ulcer disease in presence high HbA1C and ESR and to assess and observe the impact of high HbA1C and ESR on LEA and prolonged hospital stay in diabetic patients.

METHODS

Blood samples were taken at the start of hospitalization for the measurement of glucose, haemoglobin A1C (HbA1C), white blood cells (WBC), and fasting erythrocyte sedimentation rate (ESR). The length of stay in the hospital was recorded. HbA1C values greater than 9 percent and ESR of more than 50 mm/h among adult patients allow the opportunity to focus on those patients who are in poor control and at highest risk. We put those patients in a separate group termed as high risk group. In our study, the patients who fulfilled the following criteria were included: the patients were suffering from diabetes mellitus for at least 6 months and on treatment with Insulin during hospital stay. It is important to note that the effectiveness of HbA1C tests may be limited in certain cases like

- In heavy or chronic bleeding, the hemoglobin stores may be depleted with falsely low HbA1C estimation
- HbA1C may be falsely high in iron-deficiency anaemia
- HbA1C test result may be falsely high or falsely low in uncommon variant form of hemoglobin
- A recent blood transfusion or other forms of hemolytic anemia may show variable results.

The following categories of patients were excluded from our study: patients who were acutely ill, patients who were aged less than 18 years of age and patients who were pregnant or lactating. Several classification systems have been proposed and utilized for the assessment of DFU.

There is not one universally accepted classification system. Most systems employ a matrix of grades based upon depth and size of wound. Meggit-Wagner's classification is one of the most widely used and universally accepted grading systems for DFU, consisting of six simplistic wound grades to assess ulcer depth

(Grades 0 to 5).¹⁵ Our criteria for inclusion were patients with DFU of Grade II to Grade IV.

RESULTS

There are no definite guidelines to for using HbA1C as a screening tool; physicians generally consider its elevated value as an indicator of diabetes mellitus. In poorly controlled diabetics, it is 9.0% or above and in well controlled patients it is less than 7.0%.¹⁶ In our study, we divided the patients into four groups depending upon the baseline HbA1C levels: group A (HbA1C level: 7.0 to 7.99%), group B (HbA1C level: 8.0 to 8.9%) and Group C (HbA1C level: greater than 9%) and a separate High Risk Group (HbA1C > 9 % and ESR > 50 mm/h). All 79 patients had HbA1C levels greater than 7.0% with 12 (15.19%) patients in group A, 26 (32.91%) patients in group B, 41 (51.90%) patients in group C and 31 (39.24%) in group D. It was found by Hasan R et al. that approximately all foot ulcer patients have HbA1C level uncontrolled with 86% of them having HbA1C level of 8.86%.

The statistical analysis showed the mean value of the HbA1C for the patients with DFU was 10.5 where 86% of those patients have the HbA1C of 8.86%.¹⁷ Our data showed that 84.81% of patients had baseline HbA1C levels of more than 8.0%. The total number of patients who had LEA was 29; only 2 patients (6.9%) was from group A, 4 patients (13.79%) were from group B, 23 patients were from group C (79.31%) and 26 patients from group D (89.66%).

Although epidemiological studies report positive associations between glycaemia and LEA, the magnitude

of the risk is not adequately quantified and clinical trials to date have not provided conclusive evidence about glucose lowering and LEA risk.

The overall relative risk for LEA was 1.26 for each percentage point increase in HbA1C. Each one percentage point increase in HbA1C was associated with a 26% increase in risk of LEA.¹⁸ Kaplan-Meier survival analysis showed that amputation was independently associated with higher HbA1C values, and the hazard ratio for amputation associated with an HbA1C value of greater than 7.5% was 1.20.¹⁹ Our data showed that the increase in incidence of LEA if far greater than 26% for every 1% increase of HbA1C. The graded association of baseline HbA1C with LEA risk was more significant in female patients with diabetes than male.²⁰ In a study from Costa Rica showed that diabetic patients who had undergone LEA were men with 10 or more years of diabetes and average HbA1C more than 8%.²¹ The number of female patients in our study was 26 (32.91%) out of a total number of 79 patients. Out of total number of 29 amputees, 7 were female patients (24.14%). Among the female patients, 26.92% have underwent LEA.

In a study from Iran, 68% of the patients who underwent amputation were female. The females were found to be at an 8.66 times higher risk of amputation than males.²² This result is consistent with the findings of another study but is inconsistent with the results of Mashaekhi et al and the findings from our study.^{23,24} The prolonged hospital stay of more than 14 days was noted in only 1 (8.33%) patient with HbA1C (7 to 7.9%), 10 (38.46%) patients with HbA1C (8 to 8.9%) and 24 (58.54%) patients with HbA1C > 9%. This result showed that high levels of HbA1C had a detrimental effect on the hospital stay.

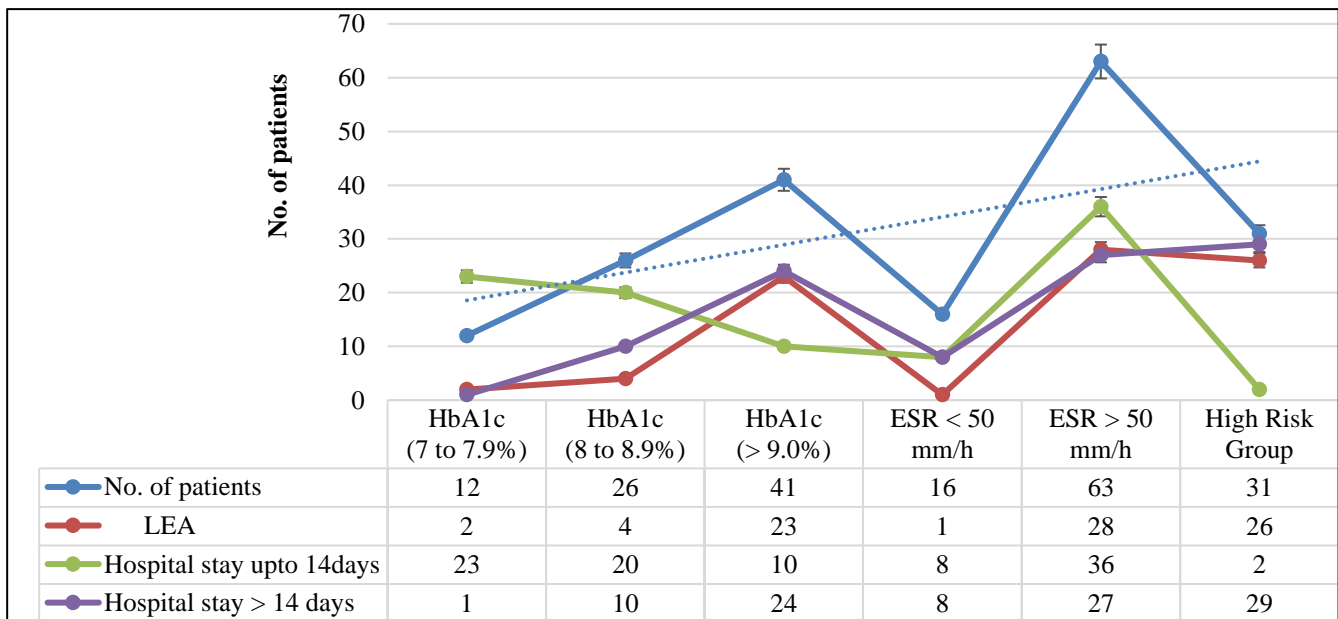


Figure 1: Relative outcome of diabetic foot ulcer disease in relation to risk factors.

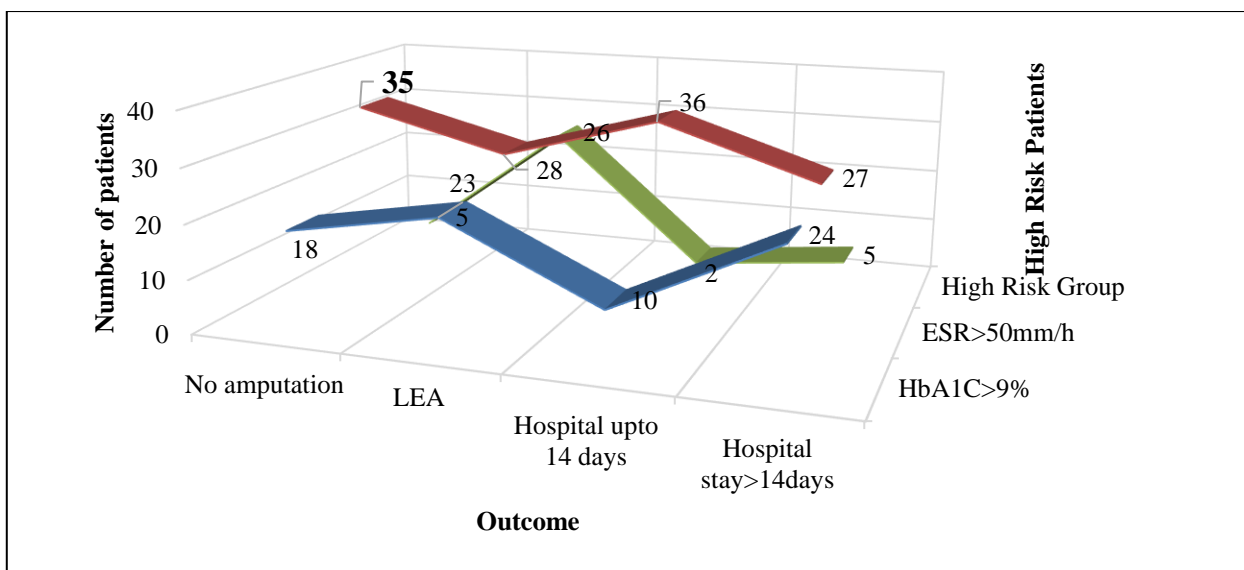


Figure 2: Comparative study of the high risk patients.

Butalia et al showed that an ESR of more than 70 mm/hr significantly increases the probability of osteomyelitis with concomitant increase in amputation.¹⁴ Akinci et al studied acute phase reactants like ESR at admission and found that baseline ESR was significantly elevated in patients who ultimately required amputation.²⁵ These results suggest that ESR is a strong predictor of increased amputation risk. ESR values greater than 54.4 were associated with treatment failure and resulting in LEA.¹⁹ An elevated erythrocyte sedimentation rate may be a better marker of bone infection in the diabetic foot. Armstrong et al found a high ESR in 96% of cases where bone was involved.²⁶

Diabetic osteomyelitis was highest for ESR of more than 70 mm/hr (92%). The various studies shown that an ESR of greater than 70 mm/hr to be the optimal cut off for positive correlation regarding the presence of osteomyelitis with a reported sensitivity of 90 percent and specificity of 94 to 100 percent.^{27,28} Kaleta et al suggested that an ESR level of 70 mm/h might be the optimal cut-off point to predict osteomyelitis with sensitivity of 89.5% and specificity of 100%.²⁹ The cut-off level of 90 mm/h for ESR had fair specificity for the prediction of major amputation.

Retrospective analysis of two series of study indicated that an ESR of more than 70mm/h indicated bone infection with 100% specificity.^{25,30} The sensitivity of this finding was only 28% in one study and was less than 50% in another study.²⁹⁻³¹ Yesil S et al showed that the cut-off level of 90 mm/h for ESR had fair specificity for the prediction of major lower extremity amputations.³² Another study of severe diabetic foot infections reported that the mean ESR in cases with osteomyelitis was only 56 mm/h.³¹

In our study, we divided the patients into two groups: one group with ESR level < 50 mm/h (20.25%) and the other group with baseline ESR level of > 50 mm/h (79.75%). Our study revealed that 28 (44.44%) out of 63 patients who had ESR > 50 mm/h had LEA. On the other hand, only 1 (6.25%) patient had LEA among the patients whose ESR < 50 mm/h. Among the 63 patients who had ESR > 50 mm/h, 27 (42.86%) of them had stayed in the hospital for more than 14 days in comparison to 8 patients (50%) who had ESR < 50 mm/h. In the high risk group, LEA was done in 26 (83.87%) out of 31 patients; and 29 (93.55%) out of 31 patients had hospital stay of more than 14 days. In this study, ESR was a good prognostic factor regarding the outcome in terms of LEA and hospital stay in subgroup of patients who had both baseline levels of HbA1C > 9.0% and ESR > 50 mm/h.

DISCUSSION

A cumulative lifetime incidence rate of diabetic foot ulcers is as high as 25% and are the harbingers of lower extremity amputations. It has been shown from various clinical studies that achieving adequate glucose control ranks foremost in the effective management of diabetic foot ulcers and preventing amputations. Marston et al for the first time in 2006 reported that patients whose HbA1C was high during their study had more severe form of wound infection with higher incidence of amputation.^{32,33} A target HbA1C of less than 7% is acceptable in all diabetic patients and the same is applicable for diabetic foot ulcer patients as well. This study indicates that the progression to the complication of diabetic foot ulcers was strongly correlated to the level of HbA1c as found in a similar study by Mohieldein AH et al.³⁴ The data may suggest the beneficial effect of considering measurement of HbA1C

as a routine test for diabetic patients and maintaining an optimum level of less than 7%. Hb1Ac is the best predictor of outcome and optimization of diabetic control will lead to improved outcome, with less incidence of LEA and amputation. High levels of HbA1c is an important risk factor for LEA in patients with diabetes and supports the strategy for lowering glucose levels to reduce amputation in patients with diabetes.³⁵ Similarly, effective control of hyperglycaemia will result in lesser period of hospital stay. Elevated ESR has been proposed as a useful diagnostic marker of osteomyelitis when combined with clinical data. The present study examined whether or not certain baseline laboratory findings like HbA1C and ESR can predict the risk for overall minor and major lower extremity amputations and concomitant longer hospital stay in patients with diabetic foot ulcer disease. In particular, the potential relationship between baseline levels of HbA1C and ESR with the risk of LEA was evaluated. Multivariate analysis showed that baseline HbA1C and ESR levels were independent predictors of both major and minor lower extremity amputations. Our study tried to correlate the association of increased levels of HbA1C and ESR with the increased risk of LEA and prolonged hospital stay in individuals with diabetes. The current data provide further support for a positive association between the risk of LEA and prolonged hospital stay with baseline levels of HbA1C and ESR. It is important to understand the pathophysiology of diabetic foot ulcer disease and promptly identifying the risk factors for its management is essential. A thorough evaluation of diabetic foot infection involving a multidisciplinary team is recommended to guide treatment regimens and achieve optimal patient well-being. It is also necessary to facilitate consistent communication between health care providers for best patient outcome. Prompt recognition and treatment is mandatory to achieve a goal of maximal limb salvage.

CONCLUSION

The present study showed a strong association between risk of LEA with high levels of HbA1c and ESR in individuals who were suffering from diabetes mellitus. The prompt treatment of hyperglycaemia in patients whose HbA1C remains far above target level of 7% could translate into a large reduction in risk. While amputations occur less frequently than other cardiovascular complications in a long standing diabetic patient, its consequences may be greater. In the absence of conclusive evidence from clinical trials regarding the definite association of LEA with identifiable risk factors, this study tried to provide further epidemiological support for maintaining an optimum level of HbA1C below 7% as a strategy for reducing the risk of LEA and minimizing the hospital stay.

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