

Association between HBA₁C, hyperlipidemia, ankle-brachial index (ABI), and toe-brachial index (TBI) with wound healing in diabetic foot ulcer after angioplasty

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Abstract

Background

Diabetic foot ulcer (DFU) is a serious complication of diabetes that can lead to severe consequences if left untreated. Revascularization with balloon angioplasty is a method of management of peripheral arterial disease, and factors that can affect wound healing are of interest. The aim of the present study was to investigate the association between HBA₁C, hyperlipidemia, ankle-brachial index (ABI), and toe-brachial index (TBI) with wound healing after balloon angioplasty in patients with DFUs.

Methods

Ninety patients with DFUs who underwent balloon angioplasty were included. Baseline HBA₁C, hyperlipidemia, ABI, and TBI were recorded. These were measured once more three months after angioplasty. Then, based on wound healing (satisfactory or failed wound healing) as the outcome measure, patients were divided into two groups and the gathered variables were compared.

Results

The wound healing rate at 3-month follow-up was 62.2% (56 out of 90 achieved healing of ulcer). There was no statistically significant difference between the two groups in terms of gender, age, and body mass index (BMI). Baseline values of HbA1c were significantly higher in those who failed wound healing ($9.6 \pm 1.2\%$ vs. $9.0 \pm 1.2\%$); $P = 0.01$. The average values of ABI (0.77 vs. 0.8; $P = 0.04$) and TBI (0.51 vs. 0.60; $P < 0.001$) were significantly lower in the group with failed ulcer healing. The similar findings were observed at three-month follow-up measurements. There was no significant difference between the groups regarding the frequency of hyperlipidemia.

Conclusion

Baseline and post-angioplasty measures of HbA1c, ABI, and TBI could affect wound healing in patients with DFU and lower limb ischemia undergoing balloon angioplasty.

Background

Peripheral arterial disease (PAD) is an important macrovascular complication in diabetics and may affect half of these patients (1). Limb ischemia and diabetic foot ulcer (DFU) are important consequences of PAD. DFUs may also arise from neuropathy. Approximately 2–3% of patients with diabetes may develop DFUs and the risk of developing foot ulcers in the lifetime of these patients is up to 25%. When PAD exists, the rate of amputation in DFU is four-fold higher than in those without PAD (2). Patients with DFUs

have high mortality and morbidity rates due to infection, gangrene, and amputation (3). High amputation rate and accompanying mortality has converted DFUs to a challenging health issue among diabetics (4).

Treatment options are available for PAD that include bypass surgery and angioplasty (5). However, these interventions may not be performed for all patients and success rates vary among studies (6). There is evidence about the effectiveness and necessity of treating limb ischemia and foot ulcers. Different surgical procedures such as subintimal angioplasty, transluminal angioplasty have been described (7). Angioplasty is an effective method for revascularization of ischemic DFUs (8). Angioplasty and revascularization have been recommended by guidelines when PAD is severe and limb ischemia and foot ulcers develop that are non-responsive to conservative measures (9).

Assessing outcome of the surgical interventions and wound healing is important when planning treatments. Besides technical considerations some variables specific to diabetics are important predictors of wound healing. Appropriate glycemic control and normal HbA1C levels, for example, is an indicator of wound healing (4). Another study showed that improvement in HbA1C is a good indicator for wound healing in diabetics (10). In a study of 85 patients with infected foot ulcers who underwent percutaneous transluminal angioplasty (PTA), among different clinical and laboratory variables, C-reactive protein (CRP) was found as a significant predictor of ulcer healing (9). Another study suggested that gender (male), advanced renal failure, and large ulcers were significant predictors for failure to heal in DFUs (2).

Ankle-brachial index (ABI), systolic pressure at the ankle divided by the systolic pressure at the arm, is a non-invasive method to detect PAD. Measures less than 0.9 could be suggestive for PAD. This factor has been shown in a study to have a significant association with wound healing failure when the values are less than 0.5 (11). Since several factors may have role in determining the outcome of surgical interventions, such as angioplasty, and definitions used to determine wound healing, no consensus exists as what factors may have significant association with intervention success. In a recent systematic review, it was reported that most studies to determine factors associated with wound healing in DFUs have low quality and most focused on ABI and transcutaneous oxygen measurement (TcPO₂) (12). Therefore, we decided to determine the role of four major factors including HbA1C, hyperlipidemia, ABI and TBI in wound healing of DFUs.

Materials And Methods

In this cross-sectional study, patients with DFUs referred to two university hospitals between 2018 and 2019 and were candidates for balloon angiography comprised the study population. Inclusion criteria included patients with DFUs who were candidates for balloon angioplasty with any wound grade in the PEDIS classification. Before angiography, HbA1c, lipid profile (total cholesterol and LDL levels), ABI, and TBI were recorded.

The patients underwent balloon angioplasty during the study period by a single vascular surgeon. Then, the patients were followed for 3 months. After this time, the variables of interest were measured for the

second time. The patients were visited to determine the success of the intervention and wound healing.

The required sample size considering power of 90%, confidence interval of 95%, and wound healing rate of 60% was calculated as 90 patients using the following formula:

Statistical analyses

Descriptive indices including frequency, percentage, mean and standard deviation (SD) were used to express data. In order to compare continuous variables (HbA1c, ABI, and TBI) between the two groups, independent student t test was used. The chi-square test was used to compare the frequency of hyperlipidemia between the groups at baseline and at 3 months of follow-up. In order to compare baseline and 3-month measurements of ABI and TBI, paired t test was used. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off points for HbA1c, ABI, and TBI. To determine the significant factors that have association with wound healing, logistic regression analysis was done, and adjusted odds ratio (OR) were calculated. The significance level was set at 0.05.

Results

A total of 90 patients (62 male and 28 female) with a mean (\pm SD) age of 65.1 (\pm 8.3) years were included. Twenty-four patients (26.7%) had obesity ($BMI \geq 30 \text{ kg/m}^2$).

Good wound healing rate was 62.2% (56 patients). However, wound healing failed in the remaining 34 patients. There was no significant difference between successful healing and failed healing groups regarding gender (71.4% male vs. 64.7% male; $P = 0.5$), mean age (64.5 (\pm 7.9) vs. 66.1 (\pm 9) years; $P = 0.36$), and BMI (25% obese vs. 29.4% obese; $P = 0.74$).

Table 1 presents baseline measurements of HbA1C, ABI, TBI, and hyperlipidemia between the two groups. As observed, baseline mean HbA1c was significantly higher in the group that failed wound healing. ABI and TBI were also lower in this group. However, no difference was seen regarding proportion of patients with hyperlipidemia at baseline between the groups.

Table 1

Baseline measurements of HbA1c, ankle-brachial index (ABI), toe-brachial index (TBI), and hyperlipidemia between successful and failed wound healing groups

	Satisfactory wound healing (N = 56)	Failed wound healing (N = 34)	Total (N = 90)	P value
HbA1c, %	9.0 (\pm 1.2)	9.6 (\pm 1.2)	9.2 (\pm 1.2)	0.01 ^a
ABI	0.82 (\pm 0.1)	0.77 (\pm 0.13)	0.8 (\pm 0.11)	0.04 ^a
TBI	0.60 (\pm 0.11)	0.51 (\pm 0.09)	0.57 (\pm 0.11)	< 0.001 ^a
Hyperlipidemia	36 (64.3%)	19 (55.9%)	55 (61.1%)	0.42*

^a Independent student t test; * Chi-square test

Table 2 presents the measurements made 3 months after angioplasty. Similar to baseline measurements, post-angioplasty HbA1C values were higher in those who failed wound healing. In addition, ABI and TBI were lower in this group.

Table 2

Comparison of post-angioplasty measurements of HbA1c, ankle-brachial index (ABI), toe-brachial index (TBI), and hyperlipidemia between successful and failed wound healing groups

	Satisfactory wound healing (N = 56)	Failed wound healing (N = 34)	Total (N = 90)	P value
HbA1c, %	8.4 (\pm 1)	9.4 (\pm 1.2)	8.8 (\pm 1.2)	P < 0.001 ^a
ABI	0.94 (\pm 0.16)	0.79 (\pm 0.15)	0.88 (\pm 0.17)	P < 0.001 ^a
TBI	0.77 (\pm 0.16)	0.53 (\pm 0.19)	0.68 (\pm 0.18)	P < 0.001 ^a
Hyperlipidemia	29 (51.8%)	14 (41.2%)	43 (47.8%)	0.32*

^a Independent student t test; * Chi-square test

In the group with satisfactory wound healing, ABI and TBI values increased significantly. However, such increase was not seen in the group who failed wound healing (Table 3).

Table 3

Comparison of baseline and post-angioplasty values of ankle-brachial index (ABI) and toe-brachial index (TBI) in satisfactory and failed wound healing groups

Satisfactory wound healing		P value	Failed wound healing		P value	
Baseline	3 months		Baseline	3 months		
ABI	0.82 (\pm 0.1)	0.94 (\pm 0.16)	< 0.001	0.77 (\pm 0.13)	0.79 (\pm 0.15)	0.06
TBI	0.60 (\pm 0.11)	0.77 (\pm 0.16)	< 0.001	0.51 (\pm 0.09)	0.53 (\pm 0.09)	0.10

ROC analyses showed that the greatest area under curve (AUC) belonged to post-angioplasty TBI (AUC = 0.89, P < 0.001) to predict wound healing followed by post-angioplasty ABI (AUC = 0.74, P < 0.001), and post-angioplasty HbA1c (AUC = 0.72, P < 0.001); Fig. 1. Using the Youden Index, the optimal cut-off points for baseline HbA1c, ABI, and TBI were respectively 9%, 0.68, and 0.55. The optimal cut-off values for post-angioplasty HbA1c, ABI, and TBI were 8.7%, 0.72, and 0.6 respectively.

At the next step, a logistic regression model was developed to determine the predictive role of the significant contributors (Table 4).

Table 4

The logistic regression analysis to investigate the significant factors associated with wound healing in diabetic foot ulcer following balloon angioplasty

	B	SE	Adjusted OR	95% CI	P value
Baseline HbA1c < 9%	1.02	0.45	2.78	1.14 to 6.80	0.002
Baseline ABI > 0.68	1.38	0.56	3.98	1.31 to 12.1	0.01
Baseline TBI > 0.55	1.19	0.45	3.3	1.35 to 8.04	0.009
Post-angioplasty HbA1c > 8.7%	1.32	0.46	3.76	1.52 to 9.28	0.004
Post-angioplasty ABI > 0.72	2.13	0.69	8.44	2.15 to 33.15	0.002
Post-angioplasty TBI > 0.60	2.70	0.53	14.95	5.24 to 42.58	< 0.001

The results showed that the odds of satisfactory wound healing was 14.9 times greater for those with post-angioplasty TBI of more than 0.6 and 8.44 times greater in those whose post-angioplasty ABI values were larger than 0.72.

Discussion

Revascularization is an important interventional technique in the management of DFUs. Determining the outcome of this procedure and the factors associated with wound healing, although crucial, has not been evaluated thoroughly. Different factors may play role in the prediction of wound healing. Patient demographic data such as age and gender, early intervention, and tests such as ABI and TBI have been

studied previously to address this question. In this study, we intended to focus on HbA1c levels as well as ABI, TBI, and hyperlipidemia.

According to the current findings, Baseline and post-angioplasty measures of HbA1c, ABI, and TBI all had significant associations with satisfactory wound healing. In the present study, wound healing rate was 62% 3 months after balloon angioplasty. It should be noted that, in general, there is limited information on the factors that can predict wound healing after revascularization techniques (9, 12–14). Additionally, there is great heterogeneity among the studies regarding outcome measure assessment, wound characteristics, follow-up times, tests or variables of interest investigated, and so on. For example, in a multicenter study in Europe involving 1,088 patients with DFUs, 48% of whom had PAD and underwent revascularization treatments, the one-year healing rate was 77% (2). In another large study conducted in Switzerland on 2,511 patients with DFUs, about 50% of whom had PAD and underwent vascularization, wound healing rate was 65% at the median follow-up time of 18 weeks (15). In a systematic review on the effectiveness of vascularization in patients with DFUs and PAD, the overall rate of healing one year after vascularization was 60% (16).

Poor glycemic control is well known to be responsible for a wide range of complications seen in diabetics. Here, we observed that at baseline, mean HbA1c levels were significantly higher in those who did not have a satisfactory wound healing. The findings of previous studies on the association between baseline HbA1c levels and wound healing have been contradictory. Some reports in line with the present study have shown that low levels of HbA1c at baseline are significantly associated with wound healing (17). In contrast to our findings, a previous study on diabetic patients who underwent percutaneous transluminal angioplasty showed that HbA1c levels were comparable between those who needed limb amputation and those with limb salvage (9). There are limited studies that have examined the effect of good glycemic control in the postoperative period on the healing of DFUs. In this regard, the results of the study by Xiang et al. showed that proper glycemic control in the postoperative period to achieve HbA1c levels of 7 to 8%, has a significant relationship with the healing of DFUs (4). But Fesseha et al. concluded that there was no clinically significant association between HbA1c levels during the postoperative period and wound healing in DFUs (18).

We observed that ABI and TBI, especially post-angioplasty measurements of these tests, had significant association with wound healing. The findings showed that both indices increased significantly after the intervention and in addition, the level of both indices was significantly associated with the healing of DFUs. Mean ABI and TBI values in the satisfactory wound healing group were significantly higher. Regarding the effect of angioplasty on these tests, the results of a study by Faglia et al. on patients with ischemic DFUs showed that ABI increased significantly after percutaneous transluminal angioplasty (8).

Conclusion

Baseline and post-angioplasty measures of HbA1c, ABI, and TBI could affect wound healing in patients with DFU and lower limb ischemia undergoing balloon angioplasty.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the ethics committee of Research Deputy of Kermanshah University of Medical Sciences, Kermanshah, Iran (Code: 4000389). The study was designed and carried out according to the guidelines of the Declaration of Helsinki. The details of the study was provided to the participants and informed consent was obtained prior to enrollment.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Competing interests: The authors declare that there is no conflict of interest regarding this manuscript and its contents.

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Figures

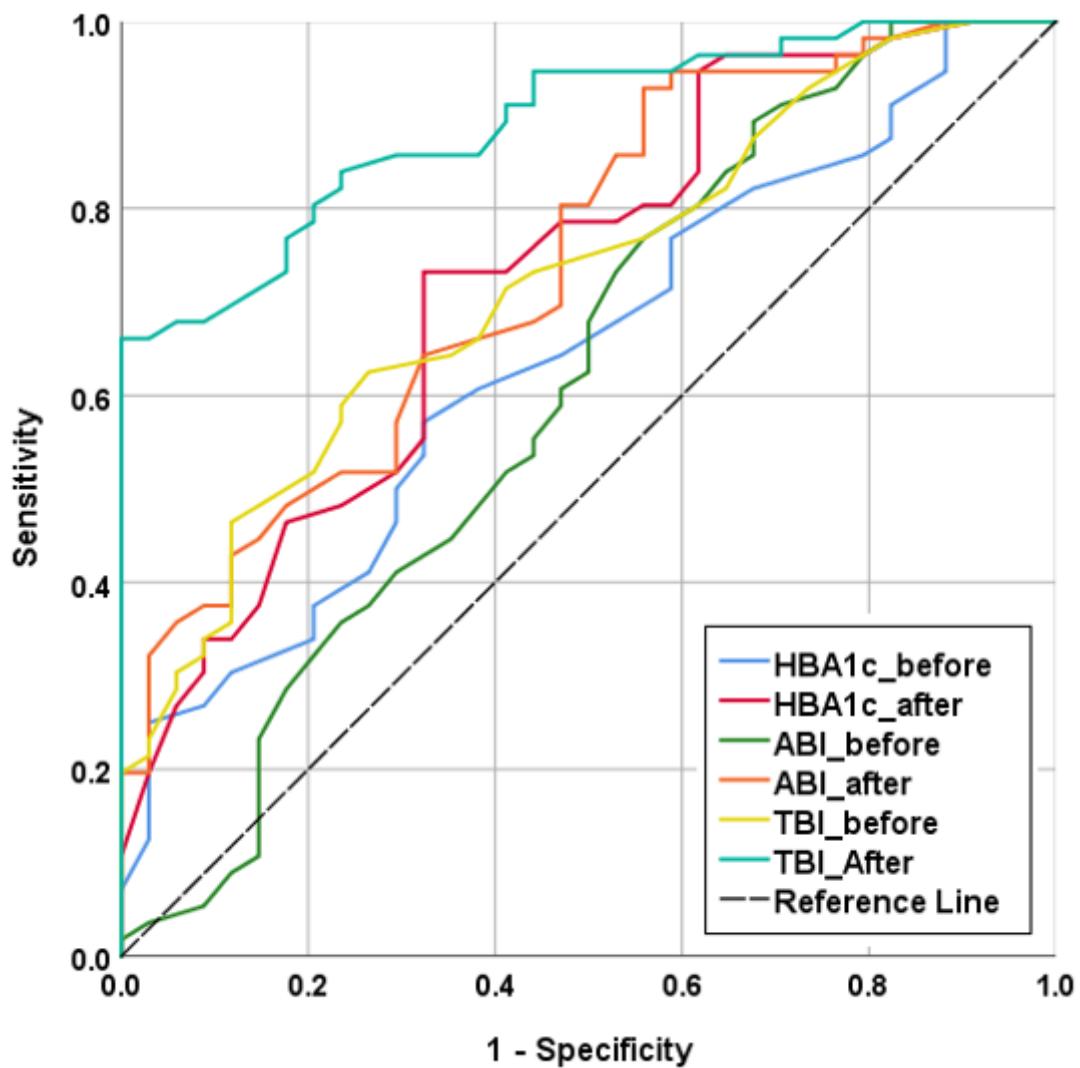


Figure 1

Receiver operating characteristic (ROC) analysis to show function of baseline and post-angioplasty values of HbA1c, ABI, and TBI to predict wound healing