Original Article

Muscle perfusion scan for prediction of anticipated diabetic foot ulceration

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ABSTRACT

Introduction: We evaluated the performance of muscle perfusion scan (MPS) to assess muscle perfusion reserve (MPR) for prediction of incident diabetic foot ulcerations (DFU).

Methods: We recruited 41 diabetic patients without any history of DFU. Five mCi ^{99m}Tc-MIBI was injected intravenously during repetitive dorsal and plantar right foot flexions. Then posterior calves were imaged and the counts of the region of interests (ROI) over the right and left calves were collected. MPR was calculated as the percentage of counts of right calf ROI–counts of left calf ROI / counts of left calf ROI. Six patients did not complete the study, 3 of them due to technical errors. Patients were followed for possible occurrence of DFU for at least 12 months.

Results: During the 563±84 (range: 309-633) days follow up period, 2 patients developed DFU (5.7%). MPR was insignificantly lower in patients who developed foot ulceration in comparison to those without foot ulceration (11.3±0.6 % vs. 63.4±40.8 %; p=0.08). The cutoff at first decile of MPR values (i.e. 16%) discriminated the patients with and without future DFU with accuracy of 92% (OR= 3; p-Value=0.005).

Conclusion: MPS is useful to detect patients with diabetes at risk for future DFU.

Key words: Diabetic foot ulceration; Muscle perfusion reserve; ^{99m}Tc-MIBI scintigraphy

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INTRODUCTION

Diabetic foot ulceration is one of the most devastating complications [1] of the common non-communicable disease, diabetes [2, 3]. The tendency to ulceration and complicated healing of foot ulceration in patients with diabetes (DFU) are attributed to the composition of 3 factors including trauma, malformation and impaired perfusion and innervations [4, 5]. Unfortunately the occurrence of foot ulceration in persons with diabetes who had no history of prior DFU or amputation, is not satisfactorily predictable [5]. Many researchers have tried to find patients with diabetes more susceptible to foot ulceration based on the health characteristics [5], laboratory data [6], and clinical and imaging indices [7]. Such efforts in those without prior DFU were not optimal [5]. Particularly the positive predictive value of clinical stratification systems [7] and clinical screening tests [8] were low. Evaluation of the risk of peripheral vascular disease employing ankle brachial index is challenging in diabetic patients [9, 10] and color doppler sonography [11], transcutaneous oxygen pressure [12] is more useful in prediction of the outcome of the foot ulcers. Use of skin laser thermometer is not encouraging for this purpose and is under debate [13]. ^{99m}Tc-MIBI passes the cell membrane and accumulates in the mitochondria in amounts correlating with the perfusion and metabolism of the tissue. The perfusion and metabolism of the tissue increase by exercise and failure to such enhancement may indicate perfusion failure at cell level [14]. Scintigraphy of muscle and skin perfusion with Technetium ^{99m}Tc-MIBI at rest and after exercise has been used to evaluate the perfusion reserve of the limbs subtracting the perfusion after exercise from perfusion at rest [15]. We speculated that this scan may assist in predisposition of diabetic foot ulceration.

METHODS

From September 2012 to March 2013, 41 patients with diabetes who had normal foot examination and had no history of diabetic foot ulceration were recruited from the diabetes clinic of a teaching university hospital. The study was presented to the diabetic patients and those willing to participate were recruited. The patients with physical disabilities and those with rheumatologic disease including rheumatoid arthritis were not included. Sampling was continued until the required sample size was acquired. These patients underwent muscle perfusion scan with the specification presented in Table 1. In brief the perfusion of the muscle and skin of the left and right legs were imaged after injection of about 5 mCi ^{99m}Tc-MIBI at peak exercise (i.e. active repetitive plantar and dorsi-flexion) of the right foot. Peak flow to the limb is achieved 1 minute after foot exercise which led to the idea behind the timing of MIBI injection after 40 flexions [16]. The total counts of the region of the interests of the posterior images of the calves were used as the muscle perfusion indicator. Muscle perfusion reserve was calculated as the ratio of the increased muscle perfusion of the calf in stressed leg and the muscle perfusion of the resting leg. All the scans and calculation were reviewed and done by a single nuclear physician. Patients were followed for at least 12 months for the occurrence of the foot ulceration. The follow up was done at the patient's last visit to the diabetes clinic and the diagnosis of the DFU was done by one of the authors attending the clinic (i.e. AE). The muscle perfusion reserve (MPR) was compared between persons with and without incident foot ulcer and the optimal cut point of MPR was sought. The analyses were done in IBM SPSS statistics (V19).

Table 1: The method of the muscle perfusion scan.

	Specifications of the method
Exercise	Sitting position; active dorsiflexion and plantar flexion of right foot for 40 times before and 20 times after injection; left foot at rest
Injection	About 5 mCi ^{99m}Tc-MIBI; 1 ml with post injection infusion of 3 ml normal saline at left anti-cubital vein via previously inserted catheter
Gama camera	Double head Forte ADAC (Philips, Milpitas, CA)
Imaging	10 minutes after injection; 64×64 matrix ; low energy collimator; imaging for 2 minutes ; 140 Kev photo-peak with 20% acceptance window
Calculation	$\text{Muscle perfusion reserve} = \frac{\text{Counts of the ROI of the exercising calf} - \text{Counts of ROI of the resting calf}}{\text{Counts of ROI of the resting calf}}$

Table 2: Health characteristics of the participants.

	Female	Male	No DFU	DFU	All
Age	59.3(5.5)	56.6(7.6)	58.1(6.6)	58.5(6.4)	58.1(6.5)
DM_D	12.6(8.2)	11(7.4)	11.5(7.3)	18.5(16.3)	11.9(7.8)
Weight	72.0(12.3)	75.9(12)	73.6(12.5)	74.5(7.8)	73.7(12.2)
Height	157.2(6.7)	172(6.1)†	162.9(9.6)	173.0(9.9)	163.5(9.8)
Waist circumference	97.6(10.1)	97.0(9.2)	97.6(9.9)	94.5(3.5)	97.4(9.6)
SBP	127.6(19.9)	132(15.8)	128.2(17.7)	151.5(14.8)	129.5(18.2)
DBP	75.6(9.5)	79.4(10.1)	77.3(10.1)	76(1.4)	77.2(9.8)
FBS	145.7(46.7)	155.1(44.6)	148.9(46)	162.5(43.1)	149.7(45.4)

Data are mean with standard deviations in parentheses; DFU: Diabetic foot ulceration; †indicates significant difference between male and females. Data of subjects with and without DFU are not statistically different.

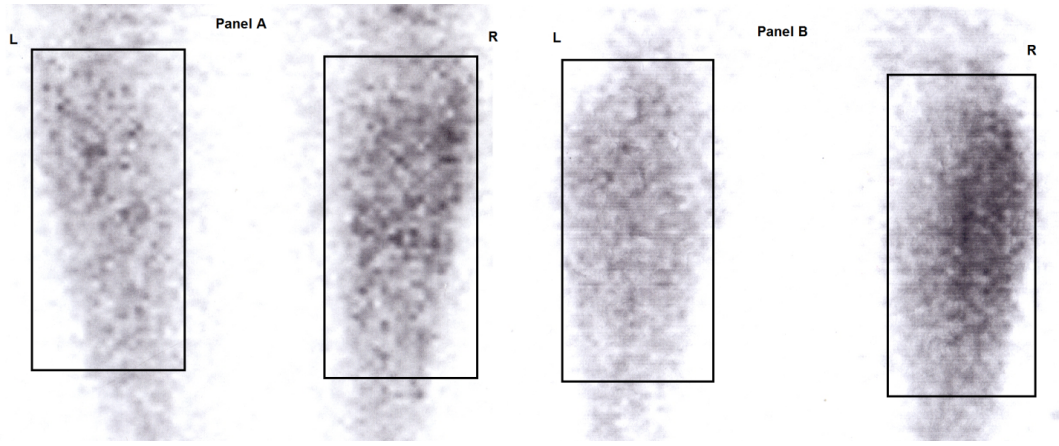

Fig 1. The regions of Interest (ROI) were drawn over the posterior imaging projections of the calf. Panel A, a patient with low exercised to resting ratio; panel B, a patient with high exercise to resting calf count ratio.

RESULTS

Six patients were excluded due to following reasons: one patient had 70% stenosis in popliteal artery in angiography; one turned out to have biopsy proved psoriasis; other was lost to follow up; and the MPS of the last 3 patients were considered technically unreliable and challenging since they were not cooperative during the stress phase of the study (less than required foot exercise) or had negative MPR values. The final analysis was done in the remaining 35 persons with diabetes (15 males). Baseline health characteristics of the participants are presented in Table 2. Distribution of the cardiac risk factors and confirmed diabetes complications were as follow: history of CAD in 12 (34%); hypertension in 13 (37%); hyperlipidemia 24 (68%); smoking 11 (31%); retinopathy 10 (29%); nephropathy 11 (31%); and neuropathy 20 (57%). Average of muscle perfusion reserve of the patients was 60.5±41% (range 4-172%). Patients were followed for 563±84 (range: 309-633) days after the MPS. Two patients developed diabetic foot ulceration (5.7%); one in the left foot and the other in the right foot. A patient, who got ulceration after a burn with boiling water with rapid healing during 10 days, was not included in diabetic foot ulceration case. MPR in patients with diabetes with and without forthcoming foot ulceration were 11.3±0.6% vs. 63.4±40.8% (Figures 1 and 2).

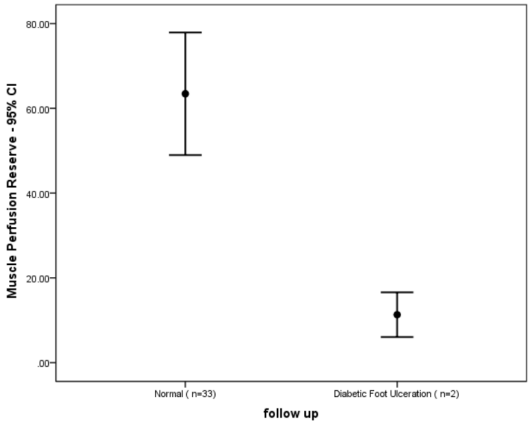

Fig 2. Muscle perfusion reserve in persons with diabetes: comparison between subjects without and with future diabetes foot ulceration (63.4±40.8 vs. 11.3±0.6; P=0.08).

The difference is remarkable but due to few diabetic foot ulceration cases this difference was not found statistically significant (p=0.08). Total counts of the ROI of the exercised limb were 14902.5±5530.8 and 12576.0±3858.0 in patients without and with DFU, respectively. The values of the resting limb were 9280.8±3288.0 and 11308.0±3525.6 in patients without and with DFU, respectively. The first decile MPR value was 16%. This cut point classifies the patient with and without future DFU with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 97%, 66.7%, 100%, and 92%, respectively. In other words if the values of MPR within the first decile are considered abnormal, the persons with abnormal scan are at significantly higher risk for future DFU (OR= 3; Fisher Exact Test p-Value=0.005). The MPR of the patients with arterial stenosis (i.e. evidence of more than 50% stenosis of the superficial femoral artery in ultrasonography) and psoriasis were 43.8 and 13.3, respectively; these data were not included in the final analysis.

DISCUSSION

We found that the patients with lower MPR values were at higher risk for future DFU. In our small scale study with limited follow up period the MPR of patients with forthcoming DFU were among the lowest three MPR values. Our findings are important considering that the currently available methods fail to predict persons with diabetes susceptible to future foot ulceration with reasonable specificities [6]. This study is limited mainly with our small sample size and low occurrence rate of diabetic foot ulceration in persons with diabetes without history of foot ulceration. Additionally DFU has many predisposing factors including neuropathy [17], vascular impairment [18], and inflammation [19]. We did not focused on these confounders because the low sample size prohibited further analyses on additional variables.

The incidence of diabetic foot ulceration during our approximate 2-years follow up was similar to the large scale studies [20]. The positive predictive value of our test was not optimal but superior to other methods [7, 8]. The non-invasive methods to diagnose large vessel disease including dual-mode ultrasound, segmental leg pressure, ankle brachial indices, toe pressures, toe brachial indices , pulse volume recordings, MR-angiography and CT-angiography are not essentially helpful for the prediction of foot ulceration in people with diabetes in terms of occurrence compared to outcome and decision for management [11, 12, 21]. The pathology of the DFU is impaired perfusion secondary to microvascular disease and abnormal innervations of the vessels in addition to the higher rate of traumatic events as a consequence of neuropathy and deformities. We excluded patients with current DFU because the inflammation of the limb with ulcer may confound the baseline low perfusion. The currently available methods to assess microvascular blood flow and prediction of diabetic foot ulcerations are few with overall low accuracies [5-10]. The muscle perfusion reserve can be measured by ^{99m}Tc-MIBI scan [22]. Some researchers showed the usefulness of this scan and the lower MPR values in persons with diabetes [23, 24]. This scan was used successfully in patients with systemic lupus erythematosus [25] and rheumatoid arthritis [26]. For the first time, we documented the use of ^{99m}Tc-MIBI scan and inference of MPR in prediction of DFU. The laterality of the forthcoming DFU is not determined or significant in this test, mainly the overall perfusion reserve of the limbs are assessed. Low MPR indicates high risk for future DFU with no implication for the side.

Study limitations

Low sample size in the DFU group of the study and presence of only two patients in the outcome group prevents valid conclusion. For determination of the perfusion reserve cut-off for prediction of foot ulcer, larger diabetic population and further studies are needed but the cut point of first decile of MPR values was the threshold for prediction of DFU in our study. Also as the SPECT imaging was recently employed for this purpose with capability of discrimination between different muscles [27] we suggest future studies to assess the diagnostic performance of SPECT imaging in this purpose.

CONCLUSION

We believe that muscle perfusion reserve measurement by ^{99m}Tc-MIBI scan may be useful for early detection of microangiopathy and prediction of foot ulceration in type 2 diabetes.

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