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Non-invasive lower limb small arterial measures co-segregate strongly with foot complications in people with diabetes.

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Abstract

Aims: It is unclear how well non-invasive lower-limb vascular assessments can identify those at risk of foot complications in people with diabetes. We aimed to investigate the relationship between a history of foot complication (ulceration or amputation) and non-invasive vascular assessments in people with diabetes. **Methods:** Bilateral ankle brachial index (ABI), toe brachial index (TBI) and continuous wave Doppler (CWD) were performed in 127 adults with diabetes (97% type 2; age 66.08 ± 11.4 years; 55% men; diabetes duration 8.8 ± 7.6 years; 28% on insulin therapy; 31% with foot complication history). Correlations were performed between known risk factors for, and documented history of, foot complications. Regression analysis was used to determine the effect of TBI on the likelihood of a prior foot complication. **Results:** By logistic regression, the likelihood of foot complications history was highest in those with TBI < 0.6 (OR=7.74, $p=0.001$); then longer diabetes duration (OR=1.06, $p=0.05$). HbA1c did not independently predict history of foot complications (OR=1.10, $p=0.356$). **Conclusions:** Likelihood of foot complication in this population was ~8 times higher when TBI was < 0.6 . Such clinical risk profiling was not shown by other non-invasive measures. Prioritising TBI as a measure of lower-limb microvascular disease may be useful to prospectively identify those at risk of diabetic foot complications.

Keywords: microvascular disease, foot complication, diabetes, peripheral arterial disease

1. Introduction

Diabetes is associated with high risk of macrovascular disease in the form of atherosclerosis and also independently with microvascular disease (Association, 2014). In the lower limb, macrovascular changes result in increased incidence, prevalence, severity and progression of peripheral arterial disease (PAD). In the presence of diabetes-related PAD there is a higher likelihood of distal ischaemic ulcer and gangrene, and increased risk of amputation (Jude, Oyibo, Chalmers, & Boulton, 2001). In the foot, microvascular disease is associated with peripheral neuropathy, altered tissue response to injury, impaired wound healing response and plays a fundamental role in the pathogenesis of neuropathic foot ulcers (Chao & Cheing, 2009).

Screening of those at risk of diabetic foot complications requires determination of peripheral neurological and vascular status (Boulton et al., 2008). In addition to screening for neuropathy, non-invasive lower limb vascular assessment is used to identify and/or monitor PAD (Boulton et al., 2008). Current methods for such assessment include investigations of large artery function with the ankle-brachial index (ABI) (ratio of the highest of the dorsalis pedis or posterior tibial pressures and the highest of the left and right brachial pressures) and qualitative assessment with continuous wave Doppler (CWD). CWD permits objective assessment of waveforms and audible signals, specifically whether or not key markers such as systolic forward flow, diastolic flow reversal and diastolic forward flow are present (Poe, 2012). However the extent of the relationship between these measurements and diabetic foot complications may be limited due to the particular contribution of microvascular disease to the development of foot ulceration. Although neuropathic changes can be identified through neurological screening, loss of normal microvascular function and subsequent functional ischaemia are more difficult to identify and remain undetected by large artery assessment techniques.

The toe-brachial index (TBI) (ratio of toe systolic pressure to brachial systolic pressure) is used to assess blood flow at the periphery, usually of the great toe. The TBI is used primarily as an alternative test for diagnosis of lower limb PAD where the ABI is contraindicated (Aboyans et al., 2012). However recent evidence has demonstrated that low toe pressures (used in the calculation of the TBI) are associated with significantly increased risk of non-healing wounds and amputation (Sonter, Ho, & Chuter, 2014). Although an investigation of the relationship between wound healing and the TBI has not been undertaken, these findings suggest that the TBI may be more closely associated with diabetic foot complications including ulceration and amputation than large artery screening techniques.

The aim of this study in people with diabetes, was to investigate the relationship between non-invasive vascular lower limb measures (ABI, CWD and TBI), and a history of lower limb complications including ulceration and amputation.

2. Subjects

Participants were recruited until January 2015 on a volunteer basis from a population attending two University community Podiatry clinics in New South Wales. Ethical approval was granted from the University of Newcastle Human Research Ethics Committee. Participants provided written informed consent prior to their participation. Inclusion criteria were: diagnosis of type 1 or type 2 diabetes confirmed by medical records. Exclusion criteria (n=5) were: contraindications to toe systolic measurement at the hallux, including current injury or ulceration of the hallux or history of a vasospastic disorder, contraindications to brachial pressure measurement including history of mastectomy, or the inability to remain supine for 20 minutes. Demographic data (age, sex, height, weight) and self-reported smoking history were recorded during the testing session. Medical records were used to confirm the diagnosis and duration of diabetes, history of chronic disease including cardiovascular disease,

cerebrovascular disease, hypertension, microvascular disease and evidence of glycaemic control. The most recent blood glucose levels [fasting plasma glucose and haemoglobin A1c (HbA1c)] were extracted. Diagnosis of overt nephropathy from blood chemistry testing was made by an estimated glomerular filtration rate $<60\text{mL/min/1.73m}^2$, urinary albumin-to-creatinine ratio $>25\text{mg/mmol}$ for men and $>35\text{mg/mmol}$ for women (Association, 2014). Retinopathy was considered present if proliferative or non-proliferative changes were present at screening (Association, 2014). Intermittent claudication and rest pain were diagnosed from participant-reported symptoms. Medial arterial calcification (MAC) was diagnosed by an ABI value >1.40 (Aboyans et al., 2012) and was included as a pathological ABI finding. The presence or history and location of foot ulcer and/or previous major or minor lower limb amputation was recorded and verified by medical record and clinical examination where possible. Major and minor lower limb amputation was defined per Nather and Wong (2013) (Nather & Wong, 2013). Ulceration preceding an amputation was included as an amputation only. All participants underwent non-invasive lower limb neurological testing and vascular assessment including CWD assessment and bilateral ABIs and TBIs.

3. Materials and methods

3.1. Equipment

Toe pressures were measured using a 2.5cm Kami-Hadeco[®] inflatable digital cuff (Hadeco, Kawasaki), a PG-21[®] photoplethysmography probe (Hadeco, Kawasaki) and an ERKA[®] aneroid sphygmomanometer (Kallmeyer Medizintechnik GmbH & Co, Bad Tölz). CWD of pedal arteries were performed using an 8Hz Bidop ES-100V3 hand-held Doppler[®] (Hadeco, Kawasaki) and Aquasonic[®] ultrasound transmission gel (Parker Laboratories, New Jersey). These were also used to perform brachial pressures using as required, an adult standard, adult large or adult extra-large inflatable cuff (Liberty Health Care[®], Ashmore) and an ERKA[®] aneroid sphygmomanometer (Kallmeyer Medizintechnik GmbH & Co, Bad Tölz). Size of the

cuff used was determined in accordance with recommendations for cuff width and length (Aboyans et al., 2008). Ankle pressures were measured using the same equipment. All pressure gauges used in this study were newly calibrated. Skin temperature was measured with an infrared skin thermometer (Dermatemp, Exergen, Watertown, MA, USA). PN was assessed using a biothesiometer (Briggate Medical Company) and 10g 5.07 Semmes-Weinstein monofilament (North Coast Medical, California).

3.2. Procedure

Relevant data were extracted from each participant's medical history as described above. Participants were asked to avoid alcohol, exercise and caffeine for two hours prior to participating in the study. Testing was performed with room temperature maintained at 23-25°C. Vascular measurements were taken following 10 minutes of rest with the participant in a horizontal supine position (Chuter & Casey, 2013). Ankle, brachial and toe pressures and CWD were undertaken in a random order pre-determined using a computer generated random allocation function. Skin temperature was measured at the apex of the hallux after 10 minutes of supine rest and prior to each toe pressure measurement to ensure a steady state was maintained. Systolic toe pressure was measured by applying the PPG probe at the distal plantar aspect of the hallux with a cuff placed around the base of the proximal phalanx. The cuff was inflated beyond the point a visual waveform was visible then released until the point of return of the waveform could be seen. CWD and systolic ankle pressure was taken from the posterior tibial artery and the anterior tibial artery (at dorsalis pedis). CWD was performed with the Doppler probe held at 45° to the skin surface with the probe directed against the flow of arterial blood and adjusted to achieve the best audible and visual signals. Ankle pressures were measured using a pressure cuff placed around the lower one third of the tibia, proximal to the malleoli. Brachial pressures were taken with the cuff placed around the upper arm and the Doppler over the cubital fossa. For each pressure measurement the cuff was inflated 20-30

mmHg higher than the last audible Doppler signal and then deflated to the point where the arterial waveform and audible signal returned. The ABI was calculated using the highest of the posterior tibial or anterior tibial artery pressures from each leg over the higher of the two brachial pressures, in accordance with current guidelines (Aboyans et al., 2008). TBI was calculated using the toe pressure from each hallux over the highest of the left or right brachial pressures. CWD tracings were taken from the anterior and posterior tibial arteries of each limb. Arteries were classified as monophasic or multiphasic (bi or triphasic) based on visual and audio data analysis of waveform tracings (Poe, 2012).

Neurological assessments were performed using a 4-site monofilament test and measurement of vibration perception threshold by biothesiometer at the hallux (Boulton et al., 2008). For the monofilament testing, perception of three or less sites in the four-site test were considered abnormal, as was a vibration perception threshold of greater than 25mV (Boulton et al., 2008).

3.3. Statistical analysis

Statistical analysis was undertaken using SPSS version 22. Pearson and Spearman correlation coefficients were calculated to examine the strength of association between measures of each of the lower limb vascular (ABI, TBI and CWD) and neuropathic assessments, with a history of foot complication. Data for the left or right lower limb only were randomly selected for each individual unless there was a history of foot complications when data for the affected leg were used. Where foot complications affected both legs, one leg was randomly selected with associated data. Where previous amputation prevented measurement being taken, data from the contralateral limb were used. Correlation coefficients were interpreted in accordance with Cohen (0.1 denotes poor/weak strength, 0.3 moderate strength and 0.5 strong in strength) with significance level set at $p < 0.05$ (Cohen, 1988). ABI, TBI and CWD were transformed into dichotomous variables (pathology or no pathology) with an ABI cut-off < 0.90 (Aboyans et al.,

2008), a TBI cut-off <0.60 (Suominen, Rantanen, Venermo, Saarinen, & Salenius, 2008), and a monophasic CWD tracing (Schaper et al., 2012) each being considered pathological. Neuropathic status was classified as abnormal if both neurological tests were positive for a deficit (Boulton et al., 2008). Direct logistic regression was performed to determine the effect of diabetes specific risk factors (HbA1c, disease duration) and the TBI on the likelihood of the participants having a history of a foot complication.

4. Results

One hundred and twenty seven participants were recruited to this trial. Participant characteristics are presented in Table 1. Of note, 32% had peripheral neuropathy, and 24%, 38% and 31% had abnormal ABI, TBI and CWD, respectively. Thirty-one percent of the entire study population had a history of foot complications including 9% with amputation, and 22% with ulceration history. These foot complications had on average occurred 1.3 ± 1.7 years prior to the neurovascular assessment.

4.1. Univariate Analysis

By univariate analysis, there was a strong statistically significant correlation between history of foot complication and presence of neuropathy ($r=0.572$, $p<0.01$) and a moderate significant correlation between history of foot complications and a TBI of <0.6 ($r=0.451$, $p<0.01$) (Table 2a). Moderate correlations were found for both diabetes duration ($r=0.333$, $p<0.01$) and the most recently documented HbA1c ($r=0.295$, $p<0.05$) with history of foot complication. There was a weak, non-significant (ns) correlation between history of foot complication and both ABI ($r=0.153$, $p=ns$) and CWD ($r=0.124$, $p=ns$), respectively.

4.2. Regression analysis

The full model containing all the predictors was statistically significant χ^2 (3, $N=127=36.91$, $p<0.0001$) indicating the model could distinguish between those people who did have a history

of a foot complications and those who did not. The model as a whole explained between 23.4% and 33.8% of the variance and correctly classified 77% of the cases. Within the model, only two independent variables reached statistical significance by logistic regression (Table 2b). The strongest likelihood of foot complication was associated with a TBI of <0.6 , followed by increasing diabetes duration. Participants with a TBI of <0.6 were 7.74 times ($p=0.001$) more likely to have a history of foot ulcer or amputation combined. Participants were 1.06 times ($p=0.05$) more likely to have had a foot complication for every year they had diabetes. HbA1C was not an independent predictor of history foot complications.

5. Discussion

This study has identified that, in a community-based, older population with diabetes attending Podiatry services, a low TBI <0.6 is associated with a ~8-fold increase in likelihood of having had a previous foot complication. While the confidence interval for the odds ratio reported is quite wide in this study, the relationship of a low TBI with a previous foot complication, is statistically and clinically, significant. In contrast, large artery screening techniques including CWD and ABI did not show similar links to a history of foot complication.

Consistent with previous research, our study has demonstrated that presence of neuropathy displayed the highest correlation with history of foot complications (Reiber et al., 1999). Prior research involving people with diabetes has shown neuropathy to be present in more than 82% of foot wounds and described as the primary factor in 61-78% of cases (Pecoraro, Reiber, & Burgess, 1990; Reiber et al., 1999). We have also shown through moderate statistically significant correlation in this study, that in a community-based population, a longer duration of diabetes is associated with higher likelihood of a history of foot complication. Longer duration of diabetes has also previously been shown to increase the risk of both neuropathy (Young, Boulton, MacLeod, Williams, & Sonksen, 1993) and development of foot ulceration

(Pham et al., 2000). Boyko and colleagues found that an increased risk of foot ulcer is associated with a higher HbA1c (Boyko et al., 1999). The findings of our study are contrary to this although unsurprising as current HbA1C is unlikely to accurately reflect glycaemic control at the time of the foot complication. In addition to supporting existing findings, this study has demonstrated that, in a community population with moderate incidence of diabetes-related complications, a low TBI <0.60 is associated with an increased likelihood of a previous foot ulcer or amputation.

Our findings of an independent relationship between a low TBI and greater likelihood of foot complication are consistent with research demonstrating low toe pressures are predictive of non-healing and amputation (Sonter et al., 2014). In people with diabetes, the TBI has been demonstrated to be reliable (Sonter, Chuter, & Casey, 2015), to have good diagnostic accuracy for PAD (Chuter, Craike, Johnson, & Casey, 2014), and to be predictive of cardiovascular mortality (Hyun et al., 2014). However, although recommended as an alternative to an ABI for lower limb vascular screening in diabetes cohorts, there has been little investigation into the relationship between the TBI and the history of foot complications in this population. The results of this present study suggest that the TBI may provide additional information relating to risk of foot complications that can be used in conjunction with established methods of non-invasive screening for PAD in people with diabetes. Both the ABI and CWD are methods of large artery screening. Although CWD has been demonstrated to have high diagnostic accuracy for PAD in a diabetes cohort (Tehan, Bray, & Chuter, 2016) the lack of relationship with history of diabetic foot complications found in our present study is unsurprising in the context of the frequently multifactorial nature of diabetic foot complications (Reiber et al., 1999). These often involve several aspects of microvascular dysfunction, especially in marginal foot ulceration and minor amputation which may not be apparent with an assessment of vascular function such as CWD (Armstrong, Lavery, Vela, Quebedeaux, & Fleischli, 1998). The relatively mild

patient phenotype with low prevalence of macrovascular disease of participants in this study and the strong relationship between a low TBI and history of diabetic foot complications indicates more widespread use of the TBI for diabetic foot assessment in the community may be beneficial.

Diabetes-related microvascular disease in the foot is associated with the development of neuropathy and altered skin blood flow through angiopathic changes, including reduced vascular permeability, impaired vascular tone, impaired regulation of blood flow due to autonomic neuropathy, and localised tissue hypoxia (Chao & Cheing, 2009). As a result there is increased risk of unperceived foot injury, limited vasodilatory capacity of capillaries, impaired hyperaemic response to injury and a reduced capacity for tissue to repair (Chao & Cheing, 2009; Hile & Veves, 2003). Although the TBI is not a direct measure of microvascular function, previous research has demonstrated measurement of toe pressures with strain gauge photoplethysmography is correlated with laser-Doppler measurements of microvascular blood flow (Høyer, Sandermann, Paludan, Pavar, & Petersen, 2013). Our findings support a relationship between a low TBI and foot complications associated with microvascular dysfunction, suggesting that a relationship exists between these that is independent of measures of large artery function.

We have demonstrated that TBI of <0.6 is associated with much higher likelihood of a history of foot complication, however the prognostic capacity of the TBI for determining risk of future ulceration or amputation is not yet known. The clinical use of the TBI is also limited as there are widespread inconsistencies in the literature in the cut-offs for diagnosing PAD, ranging from <0.54 - 0.75 (Brooks et al., 2001; Suominen et al., 2008; Williams, Price, & Harding, 2006) and the exact nature of the relationship between the TBI and microvascular dysfunction in the foot is yet to be established. However, based on existing evidence of improved prognostic

capacity for cardiovascular events (Spångéus et al., 2013), evidence of good diagnostic utility for detecting PAD in people with diabetes (Tehan et al., 2016), high reliability (Sonter et al., 2015), and the additional relationship with history of ulceration or amputation that we have identified, these findings suggest the TBI may be a valuable addition to identifying those at risk of diabetic foot complications.

5.1. Limitations

For ABI measures we used the mark of <0.9 as pathological indicating PAD. Research suggests that ABI has limited sensitivity for PAD in the presence of diabetes based around the high likelihood of medial artery calcification (MAC), which can elevate the ABI (Aboyans et al., 2012). Comparisons between ABI and angiography have also found significant associations between presence of MAC and lower ABI, which suggests that MAC has the potential to elevate the ABI into a normal range in the presence of significant PAD, meaning that both pathologies may occur and remain unidentified (Aerden et al., 2011). As we did not use any reference standard for the presence of PAD it is not possible to determine the extent to which the ABI measurements were affected by MAC, however this approach is consistent with clinical practice. Furthermore, we did not investigate the relationship between a post-exercise ABI and previous history of foot complications. Ankle pressure recovery time to pre-exercise levels is typically delayed in people with PAD with a longer delay indicating more advanced disease (Carter, 1972; Laing & Greenhalgh, 1983; Ouriel, McDonnell, Metz, & Zarins, 1982). A post-exercise ABI may be a useful clinical adjunct in patients with intermittent claudication but normal ABI values or to identify a milder form of PAD (Stein et al., 2006). Although there are little data relating to the diagnostic accuracy of the post-exercise ABI for people with diabetes, it is possible this measurement may be more strongly associated with previous history of foot complication than a resting ABI and warrants further investigation.

In addition, this investigation did not consider other methods of assessing microvascular circulation such as laser-Doppler measurement. In addition, it is unknown from our present study if there was a direct relationship between the TBI and microvascular function or if other factors affected both these variables similarly. Further investigation is required to determine the extent of the clinical utility of the TBI for blood flow measurements in people with diabetes.

In this study we excluded potential participants if they had current ulceration or infection of the hallux and this may have affected the results. It may have been possible to include these participants as new research has shown that second digit toe pressures are interchangeable with hallux toe pressures in people with diabetes (Bhamidipaty et al., 2015). Furthermore, ambiguity remains regarding classification of a pathological TBI. Whilst this study has revealed a correlation between prior foot complication and a TBI <0.6 , there may be a need to determine a hierarchy of risk that relates to TBI values.

5.2. Conclusion

Having the capacity to determine the likelihood of foot complication occurring is key to targeting therapy and resources efficiently and to minimise the associated individual and financial burden. This investigation has demonstrated moderate to strong associations between previous foot complication and the presence of neuropathy and greater duration of diabetes. In addition, a TBI of <0.6 is associated with an 8-fold increase in likelihood of previous foot ulceration or amputation. Further investigation of the predictive capacity of the TBI in the development of diabetic foot complications is warranted.

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Author contributions: SL inputted data, drafted the manuscript, contributed to statistical analysis. ST contributed to statistical analysis and drafting of the manuscript. NJ and MB contributed to study design and drafting of the manuscript. IC contributed to drafting of the manuscript and data interpretation. VC conceived the study, collected data, contributed to statistical analysis and drafting of the manuscript. All authors approved the final version of this manuscript.

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Conflicts of interest

All authors declare that there are no conflicts of interests.

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Table legends

Table 1: Participant characteristics

Table 2: Variables examined in association with a history of foot complication

2a: Univariate associations

2b: Associations by multiple logistic regression

Table 1

Participant characteristics

Number	127
Age in years (mean, SD)	66.1 ± 11.4
Men (n)	70
Women (n)	57
Body mass index (kg/m ² ; mean, SD)	27.9 ± 5.7
Type 1:Type 2 diabetes (%:%)	5: 122 (3%, 97%)
Diabetes duration, years (mean, SD)	8.8 ± 7.6
HbA1c % NGSP units (mean, SD) OR IFCC units	8.17 ± 2.07
Insulin therapy alone or combination (n)	37
Oral hypoglycaemics alone or in combination with insulin (n)	115
Diet-controlled diabetes (n)	4
Smoking (n, past or current)	47
Cardiovascular disease (n)	58
Cerebrovascular disease (n)	14
Hypertension	83
Retinopathy	24
Nephropathy	19
Neuropathy	41
MAC (ABI>1.40) (%)	21
ABI (mean, SD)	
Left	1.14 (0.14)
Right	1.15 (0.16)
TBI (mean, SD)	
Left	0.71 (0.18)
Right	0.72 (0.20)
CWD	
Monophasic	39
Multiphasic	88
History of foot complications (n)	
Major amputation	3
Minor amputation	8 (5 digit only, 3 ray [metatarsal and digit])
Foot ulceration	28
Foot re-ulceration	16

NGSP = National Glycohemoglobin Standardization Program, IFCC = International Federation of Clinical Chemistry, MAC = medial arterial calcification, ABI = Ankle-brachial index, TBI = Toe-brachial index, CWD = Continuous-wave Doppler

Table 2

Variables examined in association with a history of foot complication

2a Univariate associations

Variable	<i>r</i>	<i>p</i>
Peripheral neuropathy	0.572	<0.01
TBI <0.6	0.451	<0.01
Diabetes duration	0.333	<0.01
HbA1c level	0.295	<0.05
ABI	0.153	ns*
CWD	0.124	ns

*ns=non-significant statistical result

2b Associations by multiple logistic regression

	Odds ratio	95% CI		<i>p</i>
		Lower	Upper	
TBI	7.74	3.443	21.403	0.001
HbA1c (per 1.0 % increase in NGSP units)	1.103	0.896	1.358	0.356
Diabetes duration (per year)	1.058	0.991	1.121	0.05