Validation of the Diabetic Foot Screening Tool in detecting lower-limb-threatening risk factors in end-stage renal disease patients

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Key words

- Diabetic Foot Screening Tool
- End-stage renal disease
- External validity
- Intraobserver reliability
- Peripheral arterial disease
- Peripheral neuropathy

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This feasibility study investigated the intraobserver reliability and reproducibility of the validated Diabetic Foot Screening Tool to detect evidence of peripheral neuropathy and peripheral arterial disease in a homogenous sample of end-stage renal disease patients on haemodialysis therapy without a concomitant diagnosis of diabetes. Findings suggest that the Diabetic Foot Screening Tool reliably discriminated between end-stage renal disease patients presenting with and those without evidence of lower-limb-threatening risk factors. Further research is needed to determine whether these findings can be applied in the wider context of the haemodialysis population.

Over the past three decades, there has been a dramatic increase in the prevalence of end-stage renal disease (ESRD), which has heightened the global demand for renal replacement therapy. This is of particular importance because dialysis is associated with high economic costs, a reduced quality of life and premature mortality due to a wide range of metabolic complications (Osthus et al, 2012). One of the main challenges facing the chronic kidney disease (CKD) population in Wales is that it currently has the highest incidence of haemodialysis therapy in the UK. The impact of this is compounded by the primary diagnosis of diabetic nephropathy in 28.2% of this population (Rao et al, 2014). This may be attributed to the fact that social deprivation in Wales (48%) is higher than in England (38%) (Diabetes UK, 2008). It is estimated that people living in the most deprived areas in the UK are 2.5 times more likely to develop type 2 diabetes as a consequence of poor nutritional choices and a sedentary lifestyle (Diabetes UK, 2008).

Diabetic nephropathy is a late-stage complication of diabetes mellitus (DM). It has overtaken other primary aetiologies to become the leading cause of CKD in the Western world (Kumar et al, 2014). This raises concerns, as evidence suggests that diabetic nephropathy plays a critical role in the development and progression of peripheral neuropathy (PN) and peripheral arterial disease (PAD) (Nair and Peate, 2014).

The lack of protective sensation in PN exposes the superficial skin to repetitive trauma. Over a period of time, this triggers the formation of callus to protect the integrity of the cutaneous structures on the foot (Lavery et al, 1998). This protective mechanism without adequate offloading can result in focal areas of high pressure that then become susceptible to soft tissue breakdown. Such tissue breakdown often develops into chronic foot ulceration when compounded by concomitant PAD (Pham et al, 1998). This can have a detrimental effect on wound healing potential in the lower limb and may increase the risk of major amputation (Smith et al, 2008). Research has long recognised the internal validity of the Diabetic Foot Screening Tool (DFST) in detecting lower-limb-threatening risk factors (Bower and Hobs, 2009; Murphy et al, 2012), but there is limited evidence to support its external validity in detecting these risk factors in the ESRD population without a concomitant diagnosis of DM.

The external validity of a screening tool to detect risk factors in a defined population may not be

Page points

1. Low test sensitivity or specificity indicates poor predictive validity.
2. The Diabetic Foot Screening tool was investigated to determine its intraobserver reliability and reproducibility in the detection of peripheral neuropathy and peripheral arterial disease.
3. Three repeated measures were conducted on the right foot for the 10-g monofilament, neurothesiometer, pedal pulse palpation and Doppler assessments to determine intraobserver reliability.

Box 1. The standard protocol.

1. After at least 10 minutes resting in a sitting position during dialysis, the couch was reclined and the legs elevated.
2. 10-g monofilament testing on the right foot. Peripheral neuropathy (PN) was established if ≤8/10 test sites were positive. Assessment was repeated three times.
3. Neurothesiometer testing on the right hallux. Vibration perception threshold ≥25 volts confirmed PN status. Assessment was repeated three times.
4. Classification of PN status based on 2 and 3 to establish prevalence data
5. Palpation of pedal pulse on the right foot. Pulses were graded present or absent.
6. Doppler waveform assessment. Right dorsalis pedis pulse followed by right posterior tibial pulse. Waveforms were graded monophasic, biphasic or triphasic. Monophasic waveforms in the dorsalis pedis and posterior tibial pulse confirmed peripheral arterial disease status. Assessment was repeated three times.
7. Classification of peripheral arterial disease status based on 5 and 6 to establish prevalence data.

reproducible in another population. Petrie and Sabin (2009) recommended adopting the principles of test validity to distinguish between populations with and without detectable risk factors with a high degree of accuracy. The two components of test validity are sensitivity and specificity. Test sensitivity is the ability of a test to correctly identify those with the disease (true positive rate), whereas test specificity is the ability of the test to correctly identify those without the disease (true negative rate). Therefore, in a defined population, the sensitivity and specificity of a screening test must be predetermined to minimise the danger of eliciting false positive or false negative results. This can be achieved by evaluating the performance of a screening instrument against a gold standard assessment method.

The gold standard test is often more invasive and expensive than a simple screening test, but has a high degree of accuracy in detecting early signs of disease. Compared to the gold standard, a low test sensitivity or specificity indicates poor predictive validity with a higher risk of false positive or negative results and *vice versa* (Gordis, 2014). The danger with false negative screening in health care is that it often renders the patient ignorant of the potential threat posed by the presenting risk. This can have serious consequences in clinical practice, especially when early signs of lower-limb-threatening complications are missed.

This feasibility study investigated the intraobserver reliability and reproducibility of the validated DFST to detect evidence of PN and PAD in a homogenous sample of ESRD patients on haemodialysis therapy without a concomitant diagnosis of DM.

Methods

Individuals who had been on haemodialysis therapy >3 years were >50 years of age and male were included to ensure the group was homogenous. Patients were excluded if they had a diagnosis of DM (fasting plasma glucose >7 mmol/L [6%] or random serum glucose >11 mmol/L [8.5%]), a pre-existing neurological condition and history of lower-limb amputation, vascular intervention or active foot ulceration. Participants with history of kidney transplant or previous renal replacement therapy with peritoneal dialysis were also excluded.

Ethical approval was granted by the local research ethics committee. Each participant gave informed consent and was allocated a personal identification number to ensure the data were anonymised. The data were initially recorded on paper data collection sheets and then transferred onto an SPSS database.

Foot screening was conducted over the course of two dialysis sessions and followed the protocol in *Box 1*. Potential bias associated with environmental and physiological factors was minimised by screening half the participants during one morning dialysis session and the remainder the next morning. Three repeated measures were conducted on the right foot of each participant to determine the intraobserver reliability of the podiatrist performing the assessments. To control for a potential performance bias, the method and sequence in which the tests were administered was standardised.

Categorical data were summarised using descriptive statistics in the form of frequencies (*n*) and percentages. The prevalence (%) of PN and PAD in this homogenous sample was compared against the prevalence (%) of risk factors reported in

the general haemodialysis population. Intraobserver reliability was recorded in frequencies (*n*) and percentages. Fisher's exact test was performed to establish any statistically significant associations between the binary variables given the small number of participants. $P \leq 0.05$ was considered significant.

Results

Participant demographics

Fourteen male participants were recruited from 57 patients attending the satellite haemodialysis unit at the Cardiff Royal Infirmary Hospital. Of these 14, 12 were screened, one was transferred to a haemodialysis unit in South East Wales and another was notified of an imminent kidney transplant. Participants had a mean age of 68 years (range: 57–79 years) and had been on dialysis for an average of 56 months (range: 39–72 months).

Peripheral neuropathy

The results for the detection of PN are given in *Table 1*. The neurothesiometer detected PN in all six participants, whereas the 10-g monofilament only identified PN in four (67%). The prevalence of PN in this homogenous cohort was 50%. The neurothesiometer detected PN in all six participants whereas the 10-g monofilament only identified PN in four (67%) of the six participants with a vibration perception threshold greater than 25 volts (*Table 1*). There was a significant difference ($P<0.05$) between the two instruments in discriminating between participants with and without evidence of PN.

The intraobserver reliability results are presented in *Table 2*. Intraobserver reliability for the neurothesiometer was estimated at 94% and for the 10-g monofilament it was 100%.

Peripheral arterial disease

PAD was detected in five participants (*Table 3*). PAD was classified in these participants using monophasic Doppler waveforms in the dorsalis pedis and posterior tibial arteries in the right lower limb. Nine out of the 12 participants had absent pedal pulses on tactile palpation. The prevalence of PAD in this homogenous cohort was 42%. Five participants had monophasic Doppler waveforms in both the dorsalis pedis and posterior tibial pulses in the right lower limb, whereas nine out of the 12 participants had absent pedal pulse on tactile palpation (*Table 3*). A Fisher's exact test found no significant difference ($P>0.05$) between the two methods in discriminating among participants with and without evidence of PAD.

Table 1. Detection of peripheral neuropathy.

Instrument	10-g monofilament (≤8/10 sites)	10-g monofilament (≥9/10 sites)	Total (%)
Neurothesiometer (≥25V)	4	2	6 (50)
Neurothesiometer (≤25V)	0	6	6 (50)
Total (%)	4 (33)	8 (67)	12 (100)

Table 2. Intraobserver reliability outcomes for peripheral neuropathy.

Instrument	Assessment 1	Assessment 2	Assessment 3
Neurothesiometer (≥25V)	6	7	6
Neurothesiometer (≤25V)	6	5	6
10g monofilament (≤8/10 sites)	8	8	8
10g monofilament (≥9/10 sites)	4	4	4

The intraobserver reliability Doppler measures are presented in *Table 4*. Intraobserver reliability for the Doppler was 100%. Pulse palpation was not repeated as part of the intraobserver reliability analysis given the subjective nature of the examination.

Discussion

This feasibility study investigated the level of intraobserver reliability and reproducibility of results using the DFST to detect evidence of PN and PAD in a homogenous sample of ESRD participants on haemodialysis therapy without a concomitant diagnosis of DM.

The findings demonstrate that PN was present in 50% of this ESRD sample, which is lower than that estimated in the general haemodialysis population (60%), but could be due to a number of influencing factors (Krishnan and Kiernan, 2007). Cohort bias may explain this discrepancy, as participants were matched for age, gender and length of time on haemodialysis (Jones et al, 2012). Inferential analysis of the categorical outcomes suggests there was a difference between the instruments in discriminating between participants with and without PN. Therefore, the neurothesiometer and 10-g monofilament should be performed together to increase test sensitivity and specificity. This finding is consistent with the strength of evidence

Table 3. Detection of peripheral arterial disease.

Instrument	Tactile pulse palpation		Total (%)
	Pulses present	Pulses absent	
Biphasic Doppler	3	4	7 (58)
Monophasic Doppler	0	5	5 (42)
Total (%)	3 (25)	9 (57)	12 (100)

Table 4. Intraobserver reliability outcomes for Doppler waveform output.

Instrument	Observation 1	Observation 2	Observation 3
Biphasic Doppler	7	7	7
Monophasic Doppler	5	5	5

presented in the literature, which recommends employing both the neurothesiometer and 10-g monofilament to increase the overall sensitivity of PN detection earlier in the natural course of the disease (Gibbons et al, 2010; Mythill et al, 2010; Tan, 2010). The significance is reflected in the descriptive data, which demonstrate a discrepancy between the detection rates of the neurothesiometer (100%) and 10-g monofilament (67%). In terms of these findings, two participants (33%) at risk of developing lower-limb-threatening complications associated with PN would have gone undetected had the 10-g monofilament been used in isolation. However, it could be argued that the variation observed between the instruments may have been due to a host of pathophysiological factors.

The neurothesiometer is considered a valid tool for assessing evidence of large nerve fibre dysfunction; in contrast, the 10-g monofilament examines loss of protective sensation. While large nerve fibre dysfunction and loss of protective sensation are common features of PN in persons with diabetes, it is possible that the pathophysiological mechanisms contributing to PN in the ESRD population have separate causal pathways. This may explain the discrepancy in the descriptive data between the neurothesiometer and 10-g monofilament. Further studies are needed to develop a greater understanding of disease-specific pathways.

Intraobserver reliability of PN screening

The intraobserver reliability measures performed demonstrated that both screening instruments had a high level of reproducibility (100% for the 10-g monofilament and 94% for the neurothesiometer). Over repeated intraobserver reliability measures, the neurothesiometer demonstrated some marginal variability (6%) suggesting that using a single vibration perception threshold reading to establish the presence of large nerve fibre dysfunction could be somewhat misleading. Best practice guidelines recommend that neurothesiometer examination should be repeated three consecutive times to derive a mean vibration perception threshold value before establishing the presence of PN (NICE, 2015). This standard method of assessment was adopted during the feasibility study to detect early signs of PN with the 10-g monofilament. Although people with concomitant diabetes were excluded from the feasibility study, their exclusion did not appear to influence the external validity of the 10-g monofilament in detecting loss of protective sensation. PN screening may, therefore, be effective for monitoring the progression of lower-limb-threatening risk factors in the ESRD population on haemodialysis therapy.

Peripheral arterial disease

Game et al (2006) were the first to propose a temporal relationship between the onset of foot ulceration and the initiation of haemodialysis therapy in the end-stage diabetic nephropathy population. However, the relevance of this temporal relationship in the ESRD population remains undefined. What we know is largely based on evidence from a few published studies that have examined the relationship between haemodialysis and the progression of PAD (O'Hare et al, 2004; Rajagopalan et al, 2006).

Rajagopalan et al (2006) demonstrated a strong and consistent association between haemodialysis duration and the severity of PAD in the ESRD population, suggesting the risk of developing PAD increases with the length of time people are exposed to haemodialysis. The findings from this feasibility study appear to corroborate this finding. Forty-two per cent of participants who had received haemodialysis therapy for >39 months had documented evidence of PAD.

The risk of lower-limb amputation due to complications associated with ESRD represents a significant challenge in routine clinical practice because a large proportion of the haemodialysis

population is not amenable to vascular intervention. Early detection and treatment of PAD may, therefore, have the potential to improve survival outcomes in this population. Further longitudinal experimental studies are required to determine the strength of this inference.

PAD is estimated to feature in approximately 25% of the general haemodialysis population (Rajagopalan et al, 2006), but the prevalence of documented PAD in this homogenous cohort (42%) was 17% higher than estimated in the general haemodialysis population. This variation could be attributed to a number of factors: all participants were male and they had been on haemodialysis for a mean length of 56 months, suggesting that gender and duration of dialysis may contribute to the progression of PAD in the haemodialysis population. Larger-scale studies have reported similar findings (O'Hare et al, 2003; Lancho Casares et al, 2008).

Inferential analysis of the categorical outcomes suggest there was no significant association (P>0.05) between Doppler waveform analysis and tactile pulse palpation, indicating that there was no difference between the abilities of these two methods to discriminate between participants with and without evidence of PAD. This is contrary to findings from an earlier study, which demonstrated that tactile pulse palpation was an unreliable method of detecting PAD in populations at risk of vascular calcification when compared to the gold standard arterial duplex imaging (Williams et al, 2005).

The small number of participants in our study may explain this discrepancy. This issue could have been overcome with the inclusion of a baseline gold standard diagnostic measure to distinguish between the sensitivity and specificity of these two methods in detecting PAD in ESRD. A variation in sensitivity and specificity between the Doppler and pulse palpation may have increased the risk of deriving a false positive or negative result. These methodological limitations could have been addressed by recruiting a larger number of participants to minimise the risk of eliciting a type I or II error.

Intraobserver reliability of PAD screening

The Doppler had a high level of reproducibility (100%), suggesting it was a reliable and reproducible method of detecting PAD. Best practice guidelines recommend early screening for PAD to prevent complications associated with critical-limb ischaemia (Jones and Harding, 2015). It has been proposed that early detection of PAD is of paramount importance in determining the success of evidence-based interventions, such as foot protection education and foot protection programmes in populations at risk of developing lower-limb-threatening complications.

Although participants with concomitant diabetes were excluded from this feasibility study, their exclusion did not appear to influence the external validity of the Doppler in detecting evidence of PAD. Screening for PAD may, therefore, be effective for monitoring the progression of lower-limb -threatening risk factors in the ESRD population on haemodialysis therapy.

Conclusion

Results from this feasibility study demonstrate that the DFST was reliable and reproducible in detecting evidence of PN and PAD in this homogenous sample of ESRD patients on haemodialysis therapy without a concomitant diagnosis of DM. Further research is needed to determine whether these findings can be applied in the wider context of the haemodialysis population. ■

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Article points

1. Neurothesiometer and 10-g monofilament testing followed by pedal pulse palpation and Doppler waveform assessment were carried out on 12 individuals with end-stage renal disease who were on haemodialysis therapy, but did not have a concomitant diagnosis of diabetes.
2. Intraobserver reliability for the neurothesiometer, 10-g monofilament and Doppler waveform assessment was good.
3. Neurothesiometer and 10-g monofilament should be performed together to increase test sensitivity and specificity.

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