Are toe systolic blood pressure and toe brachial pressure index important for persons with kidney failure with replacement therapy?

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Abstract

Introduction

Podiatrists attend dialysis centres to provide wound care and high-risk foot assessment, including peripheral vascular assessment. Persons with kidney failure with replacement therapy (KFRT) have a higher prevalence of peripheral arterial disease (PAD) and medial arterial calcification and are at higher risk of subsequent complications. Therefore, we must understand how toe systolic blood pressure (TSBP) and toe brachial pressure index (TBPI) are utilised in these populations and how the test performs.

Objectives

This thesis reports the results of two studies. The first study was a scoping review that identified the current literature on TSBP and TBPI for persons with kidney failure receiving haemodialysis (HD). The second study was a pilot study that aimed to determine the variability of TSBP and TBPI during HD in persons with kidney failure and whether any observed variability differed between persons with and without diabetes. Finally, future research directions based on the thesis findings are presented.

Methods

The scoping review (Study 1) included a systematic search of electronic databases to identify studies on persons with kidney failure on dialysis with reported TSBP or TBPI values. The pilot study (Study 2) involved the measurement of TSBP and TBPI before HD (timepoint 1), one hour into HD (timepoint 2), and just before the conclusion of HD (timepoint 3). Linear mixed-effects models were undertaken to determine the variability in TSBP and TBPI across the three-time points and whether this variability differed between people with and without diabetes.

Results

The scoping review (Study 1, Chapter 3) describes 16 studies that reported TSBP and TBPI in persons with kidney failure who were undergoing dialysis, and there were only 1,989 participants. Studies had heterogeneous study aims, combined with variable methodology and measurement protocols, and utilised a range of diagnostic thresholds, limiting the studies' direct comparability. Participant ethnicity and socioeconomic status reporting were minimal, which is significant due to known disparities in outcomes between these cohorts. The pilot study (Chapter 4) found a significant reduction in TSBP during haemodialysis but no significant decrease in TBPI during the three time points for all 30 participants. Comparison between participants with and without diabetes showed no significant differences.

Conclusions

The studies included in this thesis have provided an increased understanding of the current literature, including TSBP and TBPI measurement in people with kidney failure receiving HD and the performance of these tests during dialysis, which has the potential to influence clinical practice. The results are clinically important due to the high prevalence of PAD, ulceration, and amputation within this population. The study outcomes highlight the incidence of poor outcomes related to PAD in this population. Future research requires larger studies, with increased reporting on significant measurement protocol variables, for more accurate prevalence and prognostic data. Additionally, further studies may examine the potential of podiatrists to assess for PAD and determine if this will result in modified PAD treatment protocols for this population, which may reduce ulceration, amputation, and related mortality.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements) nor used artificial intelligence tools or generative artificial intelligence tools (unless it is clearly stated, and referenced, along with the purpose of use), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signature:

Date: 19/09/2024

List of Common Abbreviations

ABI	Ankle-brachial index
AUTEC	Auckland University of Technology
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischaemia
DFU	Diabetic Foot Ulcer
DHB	District Health Board
DRLLA	Diabetes-related lower limb amputation
HD	Haemodialysis
KFRT	Kidney failure with replacement therapy
MAC	Medial arterial calcification
NZ	Aotearoa New Zealand
PAD	Peripheral arterial disease
PWD	Persons with diabetes
TBPI	Toe brachial pressure index
TSBP	Toe systolic blood pressure
WIfI	Wound Ischaemia Foot infection threatened limb classification system

List of Co-authored Works Arising from the Research

Parts of the research presented in this MPhil thesis have been published (or submitted) and made available under the CC BY-NC-ND 4.0. deed.

Candidate contribution to co-authored publications	
Chapter 3 Carle R, Tehan PE, Stewart S, & Carroll MR. Use of toe systolic blood pressures and toe brachial pressure indices in people receiving dialysis: A scoping review. 2023. Journal of Renal Care *In review*	Carle, R (80%) Carroll, M (10%) Stewart, S (5%) Tehan, P (5%)
Chapter 4 Carle R, Tehan PE, Stewart S, Semple D, Pilmore A, Carroll MR. Variability of toe pressures during haemodialysis: comparison of people with and without diabetes; a pilot study. Journal of Foot and Ankle Research. 2023,10;16(1):42.	Carle, R (80%) Carroll, M (10%) Stewart, S (5%) Tehan, P (5%)

We, the undersigned, hereby agree to the percentages of participation identified to the chapters above.

Matthew Carroll	
Peta Tehan	
Sarah Stewart	

Conference Presentations Arising from the Research

1. Carle R, Tehan P, Stewart S, Semple D, Pilmore A, Carroll MR. Variability of toe pressures during haemodialysis: comparison of people with and without diabetes; a pilot study. Paper presented at: Renal Society of Australia Conference; May 29-31, 2023; Sydney, Australia.

2. Carle R, Tehan P, Stewart S, Semple D, Pilmore A, Carroll MR. Variability of toe pressures during haemodialysis: comparison of people with and without diabetes; a pilot study. Poster presented at: Diabetes Feet Australia Conference; October 8-10, 2023; Sunshine Coast, Australia.

Awards

1. **Best conference paper:**
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2. **Best conference poster:**
   Diabetes Feet Australia Conference; October 8-10, 2023; Sunshine Coast, Australia.

Ethical Approval

Ethics approval was granted by:

1. The Health and Disability Ethics Committee (HDEC) (**FULL 13482) (Appendix 1)**.
2. Auckland University of Technology Ethics Committee **(22/309) (Appendix 2)**.
3. Locality assessment has been approved by Te Whatu Ora – Te Toka Tumai Auckland **(A+9620 (FULL 13482)) (Appendix 3)**

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Chapter 1: Thesis Overview

Rationale

Persons with kidney failure with replacement therapy (KFRT) are more likely to have foot disease than other populations, especially when this is combined with diabetes [1], and therefore this population is well known to podiatric high risk foot services. Diabetes mellitus (diabetes) is a chronic condition where either the pancreas does not produce enough insulin, or the body is unable to metabolise insulin properly [2, 3]. It is a complex condition which presents as a disturbance of the utilisation of glucose and, subsequently, blood glucose levels, which is caused by malfunction of the pancreatic beta cells, affecting insulin production and release [3]. Over time, diabetes can damage many of the body's systems, including the heart, blood vessels, eyes, kidneys, and peripheral nerves [3]. Foot complications due to diabetes are common, complex, and costly [4, 5], with the most devastating foot complications being diabetes-related foot ulcers (DFU) and diabetes-related lower limb amputation (DRLLA) [6]. Diabetes-related foot ulcers are complicated by peripheral neuropathy (nerve damage) and peripheral arterial disease (blood vessel damage) [4] and are precursors in up to 85% of DRLLA [7, 8].

Important factors related to the progression of DFU to amputation are the extent of peripheral arterial disease (PAD) and the presence of multi-organ disease, including diabetes, heart disease, and chronic kidney disease (CKD) [9]. Diabetes can lead to a deterioration in kidney function in both type 1 and type 2 diabetes [10-12]. Diabetic nephropathy is a major complication of diabetes, increasing morbidity and mortality [13] and can progress with no early symptoms [14]. Diabetes was the primary cause of 46% of all new kidney failure diagnoses in the US in 2016 [15]. End-stage renal disease requires treatment through either kidney transplantation or dialysis. The progression of microvascular kidney damage to kidney failure with replacement therapy (KFRT) in people with diabetes is positively associated with peripheral neuropathy and PAD, which, in turn, is associated with increased risk for DRLLA [13]. Therefore, there is a [1]strong link between KFRT and DRLLA, with a 6.5-10-fold higher risk than the general diabetic population [13, 16]. Both KFRT and DRLLA lead to a decrease in quality of life and an increased risk for premature mortality [16].

Peripheral arterial disease is a circulatory condition that results in partial or complete obstruction of blood flow in arteries, excluding the coronary and intracranial vessels [17]. Lower extremity PAD can present with symptoms of intermittent claudication, which is a pain in the calf muscles with exertion and can progress to pain at rest, which is relieved with dependency [17]. Intermittent claudication only presents in approximately half of persons with PAD [18] and can be masked by peripheral neuropathy, which is prevalent in both persons with diabetes and high uraemia, both of which are frequent in persons with KFRT [19]. Advanced cases of PAD, known as chronic limb-

threatening ischaemia (CLTI), can present as lower limb ulceration of greater than two weeks duration, rest pain, and gangrene, and this is highly correlated with amputation [17, 20]. Peripheral arterial disease is more prevalent in the elderly, persons who smoke cigarettes, persons with diabetes, persons with advanced kidney disease, and persons with hypertension [17]. Peripheral arterial disease reduces blood flow and, therefore, nutrients and oxygen to the extremities, which is primarily caused by atherosclerotic plaques [21]. Atherosclerosis occurs through a complex development of plaque within the intimal layer of the vessels, leading to a narrowing of the artery, and rupture of the plaque formation can cause complete obstruction of blood flow [22]. Medial artery calcification (MAC) is an additional distinct condition that causes reduced blood flow to the extremities and is more prevalent in persons with diabetes and CKD [22]. The pathophysiology of MAC is poorly understood but thought to be due to dysregulation of calcium phosphate homeostasis, resulting in progressive mineralisation and eventual bone formation in the medial layer of the artery [23]. Medial artery calcification results in vascular stiffening, which can cause obstruction of blood flow and present as ischaemic ulceration [24]. Moreover, MAC is associated with poorer outcomes for revascularisation techniques and increased cardiovascular mortality [22]. Persons with PAD are at high risk of cardiovascular mortality, with persons with CLTI at the highest risk [25].

The measurement and monitoring of peripheral blood flow, using non-invasive physiological testing methods, allows for the identification of PAD and appropriate triage and referral to vascular specialists. These physiological tests most commonly include hand-held Doppler waveform analysis, ankle-brachial index (ABI), toe brachial pressure index (TBPI) and toe systolic blood pressures (TSBP), which are supported by multiple best practice guidelines [20, 26, 27]. Timely diagnosis of PAD and effective referral to vascular services may potentially reduce lower limb amputation rates in persons with concomitant diabetes and KFRT by enabling best-practice care [9]. Measurement of TSBP can be obtained chairside with the use of an appropriate handheld Doppler device with a photoplethysmography probe and provides a valuable measure of peripheral blood perfusion [20, 28]. Toe systolic blood pressure <30 mmHg is associated with a 25% increased risk of amputation in persons with a DFU [26]. Toe systolic blood pressure measurements are ideally utilised in conjunction with other testing methods to accurately identify PAD but are also utilised in risk classification systems and useful in predicting wound healing in DFU [20]. A recent systematic review of the reliability of bedside testing of PAD in persons prone to MAC recommended the use of more than one bedside test for PAD diagnosis [29].

In Aotearoa New Zealand (NZ), podiatrists within Te Whatu Ora Health New Zealand (public hospitals) are employed to diagnose and treat persons with active DFU. Additionally, within the northern region of the NZ health service, which includes Counties Manukau District Health Board (DHB), Auckland DHB, Waitemata DHB and Northland DHB, podiatry services have been offered

to people with diabetes whilst attending dialysis for many years. The provision of podiatric assessment and management during dialysis is advocated to reduce the severity of foot complications [30], reduce rates of DRLLA [31], increase the number of patients who can have their feet assessed [32], and ensure rapid access to multi-disciplinary foot clinics [33]. Measuring peripheral vascular status using TSBP and TBPI offers valuable information with respect to the identification and management of PAD in people with diabetes and KFRT. Persons with KFRT without diabetes have a risk of limb loss and injury, which is comparable to those with diabetes [34]. Yet, they are not funded for podiatric care, with the exception of Counties Manukau DHB. Toe systolic blood pressure and TBPI measurement and analysis allowing for PAD identification and monitoring is of benefit to this vulnerable population due to the known relationship between KFRT, PAD and amputations. The Society of Vascular Surgery uses a validated foot ulceration prognosis classification system called the Wound/Ischemia/Foot infection (WIfI), which calculates the grading of wound characteristics and location, level of ischemia, and severity of foot infection. This system specifies that all patients with diabetes should have TSBP measurements taken and that should TSBP and ABI results be in different WIfI vascular grades, TSBP will be the primary determinant of ischemia grade, reinforcing this measure's importance [28]. Low TSBP has also been associated with higher rates of cardiovascular mortality [35].

Non-invasive tests of peripheral circulation play a vital role in the diagnosis, prognosis, and treatment planning for persons with PAD [36], which is especially important for higher-risk populations such as persons with CKD and ESRD. International vascular clinical practice guidelines recommend that PAD should be screened for in persons with CKD to allow for improved medical management [37-41]. The ankle-brachial index is the most accepted reference standard for general populations for PAD diagnosis and is recommended to be used in conjunction with a claudication questionnaire, pulse palpation, and treadmill testing [42]. Medial artery calcification (MAC), which is frequent in persons with KFRT, makes diagnosis for PAD challenging due to increased arterial wall stiffness, which results in peripheral vessels which are non-compressible [29]. Ankle pressures and TSBP are reliant upon haemodynamic changes for accurate results, and MAC can lead to elevated or unreliable results for ABI [29]. Toe systolic blood pressure and TBPI are recommended collaborative tests for PAD diagnosis in persons with diabetes and KFRT, as the toe vessels are less affected by MAC [7, 20, 35]. Regular reviews of these measures are an important strategy for monitoring PAD in populations with KFRT.

Literature describing peripheral vascular assessment on people with diabetes and KFRT whilst dialysing is limited. Kay et al. (2011) reported that TSBP values during dialysis were reduced in people with diabetes, with this reduction in TSBP extending from mid to post-dialysis [43]. There have been a small number of other studies that have investigated peripheral blood flow during dialysis [37-41], with only one related to TSBP variability [43]. Studies comparing ABI to TBPI in

persons with ESRD found that TBPI had higher levels of specificity than ABI, and this result was associated with extensive vascular calcification, which is often present in persons with KFRT [42].

There is limited evidence and guidance relating to performing vascular assessment in people with KFRT despite the need for accurate measurements to allow for accurate identification of PAD and guide wound management strategies. There are no international best practice guidelines for the assessment of PAD for persons with KFRT. Subsequently, there is no consensus on the clinical utility of assessing this high-risk population. This is despite the known and above-stated elevated risk for PAD, amputation, and mortality, which is particularly acute for persons with KFRT [44]. International vascular guidelines recommend measuring TSBP and TBPI in these populations (16, 26), but there is limited guidance provided surrounding the frequency of review and specific treatment plans for people with KFRT [45]. This may relate to the low levels of research relative to health outcomes in the KFRT sector (34). Foot screening programs targeting KFRT populations, including PAD review, have been shown to reduce the rate of major amputation by approximately 17% (35), which offers important evidence for developing future best practice guidelines.

Benefits of the Research

With the paucity of evidence on the benefits and reliability of obtaining TSBP on people with KFRT, there can be a reluctance to obtain and report the results of TSBP. This potentially results in a delay of appropriate referral for PAD.

Research Objectives

1. To review the literature surrounding the assessment of lower limb vascular status using TSBP and TBPI in people receiving dialysis (Study 1).
2. To assess TSBP and TBPI before, during and at the conclusion of a dialysis session (Study 2).

Research Questions

1. What is the current evidence surrounding the use of TSBP and TBPI in people with KFRT?
2. What is the variability of TSBP and TBPI during haemodialysis in people with KFRT?
3. Is there a difference in variability in TSBP and TBPI in people with and without diabetes whilst undergoing haemodialysis?

Thesis Outline

The thesis comprises four chapters. **Table 1** presents an overview of the chapters aligned with the research objectives and questions.

Table 1. Overview of thesis chapters

Chapter 1 Provides the thesis rationale, details the benefits of the research, the research objectives, and research questions	
Chapter 2 Includes an introduction to this thesis, including background on chronic kidney disease, end-stage kidney disease and the relationship between these with poor outcomes for foot disease, alongside background on the importance of assessing lower limb vascular status in persons with KFRT.	
Chapter 3 Presents a scoping review titled “Use of toe systolic blood pressures and toe brachial pressure indices in people receiving dialysis”	Study 1: Research Question 1
Chapter 4 Presents an observational study titled “Variability of Toe Pressures During Haemodialysis: Comparison of People with and without Diabetes; A Pilot Study”	Study 2: Research Questions 2 and 3
Chapter 5 This includes the thesis discussion, an overview of the main findings, future directions, strengths and limitations, and a conclusion.	

Chapter 2: Introduction

Chronic Kidney Disease

Chronic kidney disease is a leading public health problem worldwide, with an estimated global prevalence of 13.4% [46]. It is a non-communicable illness which can lead to early morbidity and mortality, especially due to the known correlation with cardiovascular disease [47]. Chronic kidney disease is defined as abnormalities of kidney structure or function, which are present for >3 months, with implications for health [48]. Chronic kidney disease is diagnosed using an estimated glomerular filtration rate (GFR or eGFR) and classified into 5 stages, with KFRT defined as eGFR of less than 15 mL/min per 1.73m^2 [49] **(Table 2)**.

Table 2. Classification of chronic kidney disease. Adapted from [50].

CKD stage	eGFR/GFR ml/min per 1.73m^2	Description
1	>90	Kidney Damage with normal or increased eGFR
2	60-89	Mildly decreased eGFR
3a	45-59	Mild to moderately decreased eGFR
3b	30-44	Moderately to severely decreased eGFR
4	15-29	Severe decreased eGFR
5	<15 (or Dialysis)	Kidney failure

Chronic kidney disease represents a significant economic health burden, with progression of CKD from stage 3 to stage 4 correlated with a 1.3-4.2 fold increase in treatment costs [51]. Initial symptoms of CKD are rare and can be subtle, which delays diagnosis and appropriate treatment [14]. Early symptoms include changes to the amount and volume of urine passed, changes in the appearance of urine, puffiness in the legs and around the eyes, tiredness, high blood pressure and headaches [52]. As kidney function declines and CKD progresses, disease symptoms may appear, but commonly not until CKD stage 4, and some can remain largely asymptomatic despite minimal kidney function [14].

Pathophysiology of Chronic Kidney Disease

Kidneys are vital to humans due to their involvement in controlling and maintaining internal haemostasis, which is critical for the normal process of most organs [53]. Nephrons are the kidney's basic structural and functional unit, working to filter waste products and ensure haemostasis of substances, including sodium, potassium, and urate, to balance water loss, manage the production of essential hormones, and regulate blood pressure [53]. Nephrons can become damaged through an initial trauma, which elicits a complex process of renal inflammation,

glomerulosclerosis, tubular atrophy, tubulointerstitial fibrosis and capillary refractions [54]. Initial trauma can include proteinuria, high levels of blood glucose, and hypoxemia, which signal inflammatory cells, leading to activation of the renin-angiotensin-aldosterone system (RAAS), which is critical for regulating blood volume, blood pressure and fluid balance [54]. Activation of RAAS increases hypertension, which progressively damages the kidneys [55]. The non-damaged nephrons will initially compensate for this by hyper-filtering, but eventually, they falter, and glomerulosclerosis occurs (hardening of the glomeruli in the kidney) [54]. Additional destructive processes occur concurrently, including the activation, proliferation and loss of intrinsic renal cells and the activation and proliferation of extracellular matrix-producing cells[54, 56]. These, in turn, lead to scarring and fibrosis of the nephrons, replacing the normal architecture of the kidneys[54].

Chronic Kidney Disease and Diabetes

Diabetes is occurring in endemic proportions globally and is a leading cause of CKD [57]. Diabetes-related kidney disease, known as diabetic nephropathy, develops in approximately 40% of persons with diabetes [57]. Diabetic nephropathy, as the primary cause of KFRT, varies markedly across the globe, including Singapore (66.4%), USA (46.9%), Taiwan (46.2%), Canada (37.7%) and the UK (26.5%) and is increasing substantially in low and middle-income countries [58]. Diabetic nephropathy is primarily caused by hyperglycemia [54], which triggers glomerular hyperfiltration and tubular re-absorption of glucose and sodium [59]. Diabetic nephropathy is characterised by slow, long-term, progressive damage to the structure of the kidney, which leads to enlargement of the kidney [60]. In contrast, non-diabetic nephropathy (chronic kidney disease from cause other than diabetes) leads to a reduced size of the kidney [59]. Rigorous control of blood glucose levels is recommended to prevent the progression of CKD [57]. Diabetes is positively correlated with hypertension, the coexistence of both conditions further increasing the risk for progression of CKD to KFRT [61]. Together, these conditions contribute to high morbidity and mortality outcomes from cardiovascular events in diabetic populations [62].

Chronic Kidney Disease and Peripheral Arterial Disease

Chronic kidney disease, even in mild to moderate stages, is known to correlate to 1.5-4 times increased risk of PAD [41], especially in people with diabetes [42] and is a known strong, independent risk factor for the development of PAD [45]. Peripheral arterial disease is a narrowing of the peripheral arteries by atherosclerotic plaque formation and vascular calcification [63]. Peripheral arterial disease occurs in persons with CKD due to a trilogy of processes, including inflammation and oxidative stress, insufficient and abnormal angiogenesis, and uremic toxin buildup [45]. Chronic kidney disease induces inflammation by releasing cytokines, tumour necrosis factor, c-reactive protein and fibrinogen, which induce pro-fibrotic and atherothrombotic processes, inducing atherosclerosis [45]. Vessel inflammation caused by CKD is perpetually amplified,

exacerbating the vascular calcification and medial arterial calcification (MAC) seen within PAD. Medial arterial calcification is a form of vascular calcification which is strongly associated with CKD, KFRT and diabetes, which results in increasing calcification of the medial arterial wall and CLTI [64], of which CKD is a known independent risk factor for [23, 45]. Chronic kidney disease is correlated with defective angiogenesis, which results in reduced development of collateral circulation when vessel damage occurs and contributes to poor outcomes after vascular surgery [45]. Angiogenesis is controlled by proangiogenic mediators, which are deficient in persons with advanced CKD [45]. Additionally, uremic toxins, which build up in persons with CKD and are unable to be removed during dialysis in persons with KFRT, contribute to the development of PAD and are a major risk factor for adverse cardiac events [45]. Uremic toxins accelerate atherosclerosis and can contribute to endothelial dysfunction, such as MAC. Medial arterial calcification is associated with decreased pedal perfusion and poorer outcomes after vascular intervention and independently correlates with major amputation rates [65]. There is a known strong association between albuminuria, which occurs with CKD, and amputations [41]. Peripheral arterial disease can progress to CLTI, which is a severe blockage of the peripheral circulation and is associated with peripheral wound development and lower limb amputations [64]. Chronic limb-threatening ischemia is a severe manifestation of PAD and presents with ischaemic rest pain and/or tissue loss, including ulceration and/or gangrene [45]. Persons with advanced CKD are more likely to present with significant tissue loss and are at higher risk of complications, including wound infections, bleeding complications, and extended hospital stays [45]. Peripheral arterial disease is a known significant contributor to lower limb ulceration and amputation [66, 67].

Chronic Kidney Disease and Peripheral Neuropathy

Chronic kidney disease affects the central and peripheral neurological systems, leading to peripheral neuropathy, which is present in up to 90% of persons undergoing dialysis [68]. Peripheral neuropathy results in loss of protective sensation in the feet, preventing the initial awareness of the development of foot pathology, and is known to worsen with increasing CKD grades and with KFRT [69]. Chronic kidney disease-related peripheral neuropathy typically presents as distal symmetrical sensory neuropathy, and the prevalence and severity are proportional to the duration and severity of CKD [70]. Peripheral neuropathy and associated loss of protective sensation masks intermittent claudication, which can be an early indicator for PAD, potentially delaying diagnosis of PAD [71]. Peripheral neuropathy is a known significant contributor to lower limb ulceration and amputation [68].

Chronic Kidney Disease and Infection Risk

Chronic kidney disease and infection complications are common, with high levels of infection-related hospitalisation noted in this population, especially for those with KFRT [72]. This population

is predisposed to adverse infectious events due to high levels of uraemia, which alters the host defence mechanisms, increasing the risk of infection [72]. Additionally, neutrophils are impaired due to CKD-related malnutrition, iron overload, and other factors. Immunosuppressive drugs, frequently used to treat the underlying cause of kidney disease, can adversely affect immune response [72]. The three most commonly seen serious infectious complications seen by people with CKD are urinary tract infection, pneumonia, and sepsis [72]. In relation to foot wounds, admission rates for sepsis are four times greater in persons with CKD than in non-CKD populations and 10 times higher in KFRT populations compared to non-CKD populations [72]. Regular foot assessments can be a preventive method for reducing lower limb sepsis in dialysis populations [72]. Infection risk significantly contributes to lower limb ulceration and amputation [73, 74].

Kidney Failure

Stage 5 CKD, defined as KFRT, affects approximately 0.1% of the world's population [61]. End-stage renal disease is defined as an irreversible decline in kidney function, which is fatal in the absence of dialysis or transplantation [75]. End-stage renal disease occurs when the estimated glomerular filtration rate is less than 15ml per min 1.73m^2 body surface area [76]. End-stage renal disease is increasing in incidence worldwide [77], attributed to an ageing worldwide population and rising global levels of diabetes and hypertension [78]. Eighty per cent of global ESRD cases are caused by diabetes, hypertension, or a combination of both [79]. Diabetes is the most common cause of ESRD in the developed world [61] and is the primary cause of kidney failure in 44% of NZ patients starting kidney replacement therapy [80]. The incidence of persons beginning renal replacement therapy in NZ has increased from 975 per million population in 2017 to 1054 per million population in 2021 [80]. Diabetes is the main cause of new KFRT in NZ, followed by glomerulonephritis, hypertension, and polycystic disease [80]. Fifty-eight per cent of kidney failure patients in NZ receive HD, with the majority receiving care at a hospital or satellite facilities [80]. The economic burden of progression to ESRD from CKD is vast, with estimations of cost between $20 000 (within Europe)- $100 000 (within the USA) per patient per year [81]. In NZ, this per-patient cost is estimated at $155,712 per year [82]. Li et al. [83] estimating that over 2.3 million persons have died prematurely due to a lack of appropriate renal replacement therapies worldwide.

Kidney Failure with Replacement Therapy and Ethnicity in New Zealand

Inequities of incidence of KFRT are particularly prevalent for the Māori and Pacific populations in NZ compared to non-Māori, non-Pacific populations [80]. There are marked race-related health inequities within NZ, with Māori populations progressing to KFRT and requiring renal replacement therapy at a rate threefold higher than non-Māori populations [80]. Māori and Pacific Peoples represent 60% of dialysis users in NZ, which is projected to increase in the future [82]. Māori and

Pacific Peoples suffer high rates of diabetes and are less likely to access GP services, especially where co-payments are high and appointments have long wait times [82]. Māori are under-represented in NZ renal transplant statistics, especially from live-donor transplants, receiving fewer transplants compared to non-Māori despite proportionally higher dialysis rates [82].

Treatment of Kidney Failure

Treatment for kidney failure encompasses kidney replacement surgery, HD, peritoneal dialysis, or conservative care. The most common treatment for kidney failure worldwide is dialysis, accounting for 78% of the treatments administered for kidney failure. Eighty-nine per cent of persons receiving dialysis receive HD, and 11% receive peritoneal dialysis [77]. Dialysis manages kidney failure by filtering out wastes, toxins and extra fluid from the body [84]. With HD, a person's blood is extracted into a dialyser and is filtered as it moves along a semipermeable membrane, with waste products moving into the dialysate fluid within the dialyser [85]. The filtered blood is then returned to the client. This process is undertaken around three times per week. Peritoneal dialysis involves a catheter inserted into the peritoneal cavity, and dialysate solution is inserted at specified times, allowing for waste products to be filtered via the peritoneal membrane and then eliminated [84]. Other treatments for kidney failure include kidney replacement surgery, which can offer the most successful cure for kidney replacement but is limited by the supply of appropriate kidney donations [83], or conservative care, which includes symptomatic treatment, and end-of-life planning [86].

Kidney Failure Treatment in New Zealand

In NZ, 58% of kidney failure patients receive HD, with the majority receiving care at a hospital or satellite facility [80]. Haemodialysis is associated with high treatment costs and is reported to account for approximately 2-3% of annual healthcare budgets in high-income countries such as NZ [83]. In 2020, 710 people started renal replacement therapy in NZ; of these, 44 (6%) had a kidney transplant, 398 (56%) started HD, and 268 started peritoneal dialysis (38%) [80]. In NZ, the average life expectancy following renal transplant is 15-20 years, and this can be contrasted with life expectancy following HD initiation, which is just 6 years [82].

The Importance of Assessing Lower Limb Vascular Status in Persons with Kidney Failure

Kidney failure with replacement therapy (KFRT) is strongly associated with the risk of lower limb ulceration and amputation [1], combined with high levels of hospital admissions for foot conditions [16]. The pathway to foot ulceration and amputation in persons with KFRT typically involves a

trilogy of risk factors, which include peripheral neuropathy, PAD and increased susceptibility to infection and poor healing [69]. Peripheral neuropathy and previous foot ulceration are major risk factors for developing future foot ulceration in KFRT populations [87]. Amputation rates are 10 times higher for persons with KFRT compared to the non-nephrotic diabetic populations [69]. Thirty-day postoperative amputation mortality for persons with KFRT is high, at approximately 16% compared to 6% for persons with normal renal function [88]. Additionally, HD is a known risk factor for lower limb ulceration, and PAD is significantly associated with ulceration and mortality in persons undergoing HD [89]. The combination of peripheral neuropathy, infection risk factors, and PAD for persons with KFRT is associated directly with high rates of amputation, which has been found to be six times higher than persons with diabetes and no-nephropathy and 150 times higher than the general population [90].

The combination of peripheral neuropathy, infection risk factors, and PAD for persons with KFRT is associated directly with high levels of foot ulceration and amputation. However, this presents an opportunity for optimal care pathways with regular PAD review, allowing for early intervention and prevention programs [45, 91]. There is strong evidence that the provision of foot assessment programs in persons with advanced CKD (stage 4 and above) can reduce ulceration development and amputation rates [13, 31, 64, 92-95].

Environmental Test Conditions for TSBP and TBPI

Toe systolic blood pressures are undertaken regularly by podiatrists and other vascular practitioners to assess peripheral perfusion to diagnose PAD and wound healing capacity [96]. Ideal test conditions need to be observed to ensure the accuracy of this measure [96]. The room temperature should be maintained between 22-24 degrees Celsius, as the effects of peripheral vasoconstriction and dilation outside of these parameters can affect the accuracy of results [97]. The patient must be rested in a supine position, as having the patient seated or legs in dependency can falsely elevate toe systolic blood pressures [98]. Pre-measurement rest time should be 10 minutes supine to allow stabilisation of toe systolic blood pressure [99]. Caffeine, smoking and exercise in the two hours before assessment should be restricted, as these factors affect diagnostic accuracy [96]. Other patient factors which can affect results include essential tremor, reactive hyperaemia, sudden movements, and vaso-neural disorders, including Reynaud's phenomenon [96]. Best practice guidelines endorse TBPI to be used in conjunction with other measurements for PAD diagnosis, including pulse palpation, doppler waveform assessment, ABI and transcutaneous oxygen pressures and recommend advanced imaging with positive results [20, 26]. Toes systolic blood pressures below 30mmHg, in conjunction with tissue loss such as ulceration, necessitates urgent referral to vascular specialists [96].

Ankle Brachial Index in the diagnosis of Peripheral Arterial Disease in persons with Kidney Failure with Replacement Therapy

The ABI is the most accepted physiological test for identifying PAD [35]. It is calculated using the highest systolic ankle pressure divided by the highest brachial systolic pressure [20]. An ABI value of ≤ 0.9 is the accepted diagnostic threshold for identifying PAD. An ABI value ≥1.4 is indicative of calcification [35], and incompressibility of arteries should be considered when ABI is normal in the presence of dampened monophasic waveforms [20]. The ABI is recommended as a first-line test for the identification of PAD [20], as it is quick, inexpensive and requires no special equipment [100]. In mixed populations, the ABI has varying levels of sensitivity and specificity for the diagnosis of PAD at 60-80% and 69-99%, respectively and acceptable levels of intratester and intertester reliability [35]. In diabetic-specific populations, a systematic review of ABI accuracy found high levels of specificity but lower sensitivity in detecting PAD [101]. Ankle-brachial index measurements can be affected by arterial calcification, lower limb oedema and wounds, which may lead to inaccurate results in these persons [35]. No systematic evaluation of ABI accuracy has been undertaken in persons with KFRT.

Toe Brachial Pressure Index for Diagnosis of Peripheral Arterial Disease in Persons with Kidney Failure with Replacement Therapy

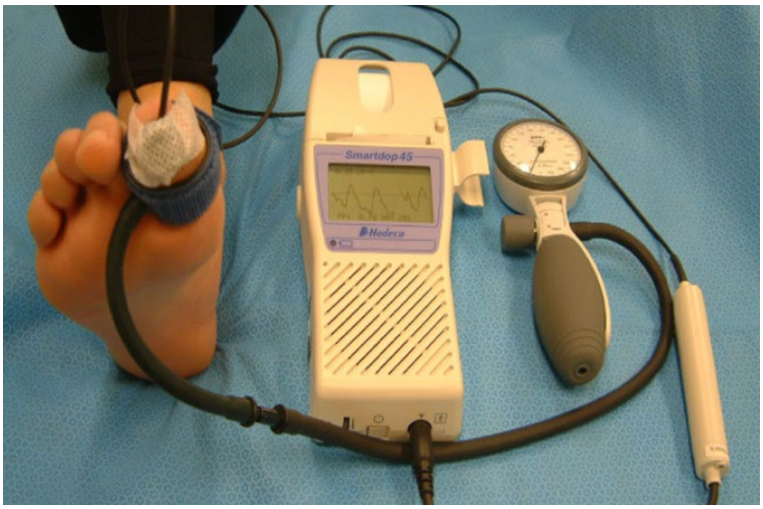
Toe brachial pressure index and TSBP are recommended for use in the presence of incompressible peripheral arteries, which is especially frequent in persons with KFRT [20, 35, 102]. The TBPI has higher sensitivity than ABI for diagnosis of PAD in challenging populations, such as those with diabetes and CKD [35]. The TBPI is calculated by dividing the TSBP into the highest of both brachial systolic blood pressures. There is no universally agreed diagnostic threshold for the identification of PAD using TBPI in international best-practice guidelines, with thresholds varying from >0.6 [103], >0.7 [20, 26, 35] and >0.75 [104].

Toe Systolic Blood Pressures for Prognosis of Ulcer Healing and Ischaemia Grading in Persons with Kidney Failure with Replacement Therapy

Toe systolic blood pressure is determined using a small cuff around either the hallux or second digit, which is attached to a manometer and measured by either Doppler, photoplethysmography or laser Doppler [35]. **Figure 1** demonstrates the setup to obtain a TSBP measurement. Toe systolic blood pressures are typically 20-40mmHg lower than ankle systolic pressures [20]. Results of <30mmHg are diagnostic for severe/advanced ischemia [20, 35] and urgent additional vascular imaging is recommended in the presence of peripheral ulceration [102]. Quantifying TSBP is recommended for the prognosis of diabetic foot ulceration healing, with TSBP ≥30mmHg shown to

increase the probability of wound healing by 25% [102, 105]. International vascular guidelines endorse the WIfI classification system be utilised in the presence of lower limb ulceration, and this is used for stratification of wound healing capacity and amputation risk in high-risk limbs [106, 107]. This system uses either ABI, TSBP or transcutaneous oxygen to determine ischaemia grade, but TSBP is the only obligatory measure, as ABI can be inaccurate in the case of incompressible peripheral vessels due to false elevation of results [107]. If the ABI and TSBP results obtained are within different grades of the WIfI category, TSBP is the principal determinant of ischaemia [26, 106, 107], which elevates its importance as a prognostic indicator of wound healing. Additionally, low TSBP is associated with higher levels of cardiovascular mortality and is recommended to be obtained in patients with CKD and diabetes [35].

Figure 1. Example set up for toe systolic blood pressure measurement



Treatment of Peripheral Arterial Disease in People with Kidney Failure with Replacement Therapy

Medical management of PAD depends on the severity of symptoms and on the development of associated tissue loss, which can signal the progression of PAD to CLTI [35]. Peripheral arterial disease without tissue loss can be treated with education and modification of lifestyle factors, such as smoking cessation, appropriate management of common concomitant diseases such as diabetes, hypertension, and CKD, instigating an exercise program and pharmacological agents [35]. Extensive PAD, which has progressed to CLTI, requires more intensive management, including guideline-directed best medical therapy to reduce cardiovascular risk, endovascular or surgical bypass therapy to improve limb perfusion, in conjunction with local care for infection and wound healing [108]. Surgical vascular interventions, such as revascularisation procedures, performed upon persons with KFRT are associated with a significantly elevated risk of postoperative complications, including death [109]. This increases the importance of early and adequate recognition of PAD, using TSBP and TBPI assessment to enable more intensive treatment of early-stage PAD before progression to CLTI.

Chapter 3 - Use of Toe Systolic Blood Pressures and Toe Brachial Pressure Indices in People Receiving Dialysis; A Scoping Review

Citation

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Preface

Chapter 2 provided insight into the relationship between progressive kidney disease, PAD, and lower limb ulceration and amputation. As noted in Chapter 2, TSBP and TBPI are the most appropriate non-invasive vascular assessment techniques for the diagnosis and monitoring of PAD and for wound prognosis in persons with KFRT [26, 102]. Podiatrists can obtain these measures as they attend HD centres to provide wound care and foot screening for persons with KFRT. Best-practice protocol guidelines for obtaining non-invasive measures of peripheral circulation, including TSBP and TBPI, are not defined for persons with KFRT despite the clear need for accurate results in this high-risk population. The scoping review in Chapter 3 provides foundation work on this subject, presenting all reported information on TSBP and TBPI in persons with KFRT. The findings of Chapter 3 highlight the paucity of studies undertaken on this population, with low levels of participant numbers, high levels of variation in methodology and reporting, and even differing normative thresholds for TBPI. This highlights the need for larger, more methodologically robust studies on this population in the future.

Abstract

Introduction

Current guidelines for non-invasive lower limb vascular testing specify a preference for toe brachial pressure measurement to aid in the diagnosis of peripheral arterial disease populations with high suspicion of peripheral vessel calcification, such as those with kidney failure with replacement therapy.

Objectives

The aim was to identify the current literature on toe systolic blood pressure and toe brachial pressure index for individuals with kidney failure who are receiving replacement therapy.

Design

A scoping review

Methods

MEDLINE, CINAHL, AMED and SPORTDiscus were systematically searched between July 15 and July 30, 2023. The scoping review followed the Arksey and O'Malley framework, with data reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews.

Results

Sixteen studies were included in the review. There was limited data examining the significance of toe systolic blood pressure and toe brachial pressure index during a dialysis session. There were differences in the normative values for toe brachial pressure index values used in the studies and limited reporting on the measurement protocols used to determine toe systolic blood pressure and toe brachial pressure index.

Conclusion

The review found limited data examining the clinical utility of toe systolic blood pressure and toe brachial pressure index in populations receiving dialysis. The use of toe systolic blood pressure and toe-brachial index to identify peripheral artery disease in this population is important. However, there is limited evidence and conflicting information on measurement protocols, reliability, diagnostic accuracy, and prognostic capacity.

Keywords

Chronic kidney disease, kidney failure with replacement therapy, haemodialysis, toe brachial pressure index, toe systolic blood pressure

Introduction

The global prevalence of chronic kidney disease (CKD) has risen considerably over the past 30 years [47]. Accordingly, the global prevalence of kidney failure with replacement therapy (KFRT) has significantly increased in recent decades due to improved KFRT survival rates, higher prevalence of risk factors, demographic changes in populations, and increasing kidney replacement treatments [110]. In 2016, 2.44 million people were treated for kidney failure in 79 countries and regions that reported data, an increase of 43% from 2003 to 2016 [110]. Chronic kidney disease (CKD), even mild to moderate, is associated with an increased risk of peripheral arterial disease (PAD) [111] and is known to have a strong association between increasing levels of albuminuria and lower limb amputations [112], particularly in people with diabetes [20]. People with KFRT often present with high levels of vascular calcification with a distal pattern of arterial disease, which may limit surgical treatment options [20]. Medial arterial calcification (MAC), a form of vascular calcification that leads to the deposition of bone morphogenetic protein in the medial arterial wall, is significantly associated with CKD, KFRT, and diabetes and contributes to the development of chronic limb threatening ischemia [23]. Medial arterial calcification is associated with decreased pedal perfusion, poorer outcomes after vascular interventions, and independently correlates with increased rates of major lower limb amputation [65, 113, 114].

International vascular clinical practice guidelines recommend screening people with CKD for PAD to provide optimal medical care [111]. Non-invasive studies of peripheral circulation play a vital role in diagnosis, prognosis and treatment planning for people with PAD [36]. This is particularly important for higher-risk populations such as people with CKD and KFRT, yet there are no specific best practice guidelines for these populations. Early, appropriate, and ongoing assessment of peripheral circulation serves two purposes. First, it allows detection of early-stage disease, expedites optimal medical treatment, and enables more intensive treatment of early-stage PAD, thereby reducing the likelihood of progression to chronic limb-threatening ischemia [115]. Second, assessing peripheral circulation in severe vascular disease allows for the determination of surgical suitability [116]. This is particularly important since surgical and vascular interventions, such as revascularisation procedures performed upon individuals with KFRT, are associated with a significantly increased risk of postoperative complications, including death [109].

Although the use of ankle-brachial pressure indices (ABI) is a recognised vascular screening test to aid in the diagnosis of PAD [111], the use of ABI in populations with arterial calcification is problematic [117]. Arterial calcification reduces arterial compressibility, leading to higher ABI values and reduced accuracy, which in turn leads to underestimation of PAD severity [111]. As MAC is common in people with KFRT, supplementary testing in addition to ABI is indicated to confirm the diagnosis of PAD, such as toe systolic blood pressure (TSBP) and toe brachial

pressure index (TBPI) [111]. Regular monitoring of TSBP and TBPI is a strategy for monitoring PAD in people with KFRT. Lower TBPI levels are associated with higher cardiovascular mortality and have been shown to be an important indicator of amputation risk [118]. The strong associations between CKD, KFRT and foot ulceration and amputations [119, 120] combined with poor post-amputation survival rates [121] highlight the importance of regular TSBP and TBPI monitoring in people with KFRT.

There is limited evidence for the use of non-invasive vascular assessment techniques in people with KFRT receiving dialysis. This is despite the expected benefits of early PAD treatment and surgical planning for this population. This scoping review aimed to identify the current literature on TSBP and TBPI for people with kidney failure receiving dialysis. Specifically, the review's objectives were to describe the population characteristics, TSBP and TBPI results, and to report the measurement protocols and patient-level factors of studies that reported vascular assessment in people receiving dialysis.

Methods

The framework proposed by Arksey and O'Malley [122] guided the scoping review methodology. This method involves five stages: identifying the research question, identifying relevant studies, selecting studies, charting the data, and collating, summarising and reporting the results [122]. To ensure methodological quality and transparent reporting, this scoping review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews **(Appendix 4)** [123].

Search Strategy

Identifying articles for the scoping review was completed with a comprehensive search of key electronic databases **(Table 3).** The search was conducted between July 15 and July 30, 2023. The electronic databases MEDLINE, CINAHL, AMED and SPORTDiscus were systematically searched from their earliest record (1955 to 2023). Broad-ranging search terms were agreed on by two of the authors (R.C. and M.C.). All titles and abstracts identified from the search were downloaded into EndNote Version X8 (Thomson Reuters, Philadelphia, PA, USA). The articles were cross-referenced, with duplicates removed.

Table 3. Search strategy

Medline search strategy			
a	1	Subject term	exp. Blood pressure determination
	2	Subject term	exp. Diagnostic techniques, cardiovascular
	3	Keyword	"Vascular assessment" **or** "Toe press*" **or** "Toe brach*" **or** TBPI **or** "Toe brachial pressure index" **or** TBI **or** Toe brachial index **or** "Toe systolic press*"
	4	Keyword	Lower extremi* **or** Lower limb* **or** Foot
	5	Combine	1 **or** 2
	6	Combine	3 **or** 4
	7	Combine	5 **and** 6
b	8	Subject term	Hemodialysis **or** haemodialysis **or** dialysis
	9	Keyword	7 **and** 8
CINAHL search strategy			
a	1	Subject term	exp. Blood pressure determination
	2	Subject term	exp. Diagnosis, Cardiovascular
	3	Keyword	"Vascular assessment" **or** "Toe press*" **or** "Toe brach*" **or** TBPI **or** "Toe brachial pressure index" **or** TBI **or** "Toe brachial index" **or** "Toe systolic press*"
	4	Keyword	"Lower extremi*" **or** "Lower limb*" **or** Foot
	5	Combine	1 **or** 2
	6	Combine	3 **or** 4
	7	Combine	5 **and** 6
b	8	Keyword	Hemodialysis **or** haemodialysis **or** dialysis
	9	Combine	7 **and** 8
Sports Discus search strategy			
a	1	Keyword	Blood pressure
	2	Keyword	"Vascular assessment" **or** "Toe press*" **or** "Toe brach*" **or** TBPI **or** "Toe brachial pressure index" **or** TBI **or** Toe brachial index **or** "Toe systolic press*"
	3	Keyword	"Lower extremi*" **or** "Lower limb*" **or** Foot
	4	Combine	2 **or** 3
	5	Combine	1 **and** 4
b	6	Keyword	Hemodialysis **or** haemodialysis **or** dialysis
	7	Combine	5 **and** 6

Scopus search strategy

"Vascular assessment" **or** "Toe press*" **or** "Toe brach*" **or** TBPI **or** "Toe brachial pressure index" **or** TBI **or** "Toe brachial index" **or** "Toe systolic press*" **AND** "Renal dialysis" **or** Hemodialysis **or** haemodialysis **or** dialysis

AMED search strategy

Vascular assessment **or** Toe pressure **or** Toe brachial or TBPI **or** Toe brachial pressure index **or** TBI **or** Toe brachial index **or** Toe systolic pressure Lower extremity **or** Lower limb **or** Foot **AND** Hemodialysis **or** haemodialysis **or** dialysis

Selection Criteria

The first stage of selection involved independent screening of titles and abstracts by two authors (R.C. and M.C.) to identify original studies that included TSBP or TBPI values in people receiving dialysis. The full texts of the selected articles were retrieved and assessed against the following eligibility criteria. Articles were included if they had patients receiving dialysis and included a TBPI, TSBP value or TBPI diagnostic index for PAD diagnosis. Articles were excluded if they were not published in English or were opinion articles, commentary letters, review articles, or non-human studies. Case reports and case series were also excluded because of potential issues with selection bias. Relevant articles were assessed according to the selection criteria, and conflicts were discussed between two authors (R.C. and M.C.) until consensus was achieved. In cases of non-consensus, a third author would be consulted; however, this was not required. Reference lists of all articles that met the inclusion criteria were hand-searched for further potentially relevant articles. If articles met the inclusion criteria but required more specific data, the corresponding authors were contacted for additional information.

Data Extraction

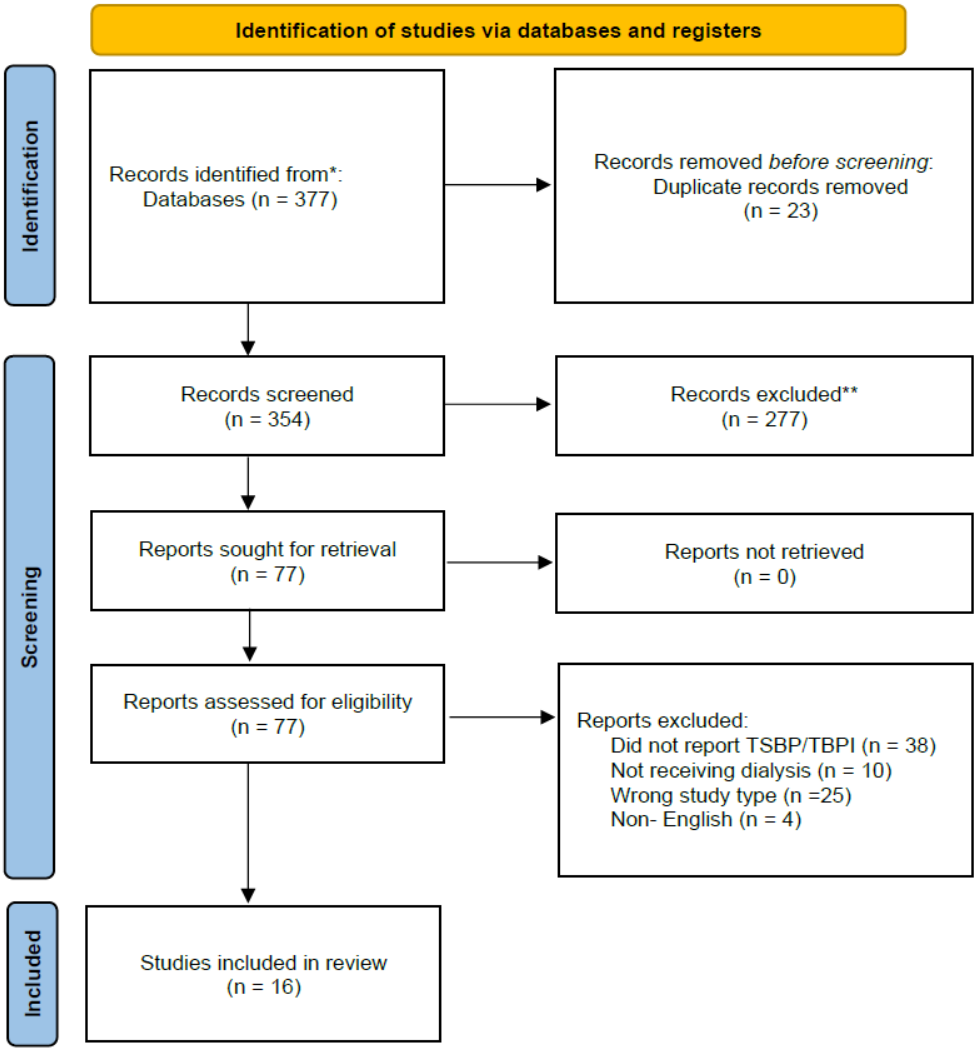
The following information was extracted from all included articles: study characteristics, author's name, year of publication, study design and aim(s). Participant characteristics including sample size, gender, mean age (years), dialysis history, TSBP and TBPI value, the diagnostic threshold for TBPI, the characteristics of TSBP and TBPI measurement protocols, and patient-level characteristics. Articles were then categorised according to their aim: prognostic capacity, prevalence of PAD, diagnostic accuracy, or exploratory.

Results

Selection and Study Characteristics

A total of 354 articles were identified for screening, with 16 articles included for final analysis **(Figure. 2)**. **Table 4** reports the aims, participant characteristics, and dialysis history of the 16 included studies. The included studies were published between 2002 and 2023, with a combined sample size of 1,989 participants (range 15 to 450). Most participants received haemodialysis (86%), and half of the included studies (n=16, 50%) were conducted in Japan.

Figure 2. Search strategy flow chart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table 4. Descriptive information of included papers

Author (year)	Country	Aims of Study (study design)	Dialysis Participants			Sex (M:F)	Age mean, (SD)	Dialysis history mean, (SD)
			Total	HD	PD			
Leskinen [124]	**Finland**	Examine the prevalence of PAD and MAC in patients with CRF. Multi-site, prospective, case-control, cross-sectional.	36	22	14	28:8	50.7 (11.4)	14.4 (15.6 months)
Okamoto [125]	**Japan**	Compare the validity of ABI, TBPI, $TcPO_2$, and SPP in HD patients by comparing to MDCT. Single-site, cross-sectional.	36	36	0	NR	61.9 (10.2)	81.6 (81.6 months)
Huang [126]	**Taiwan**	Determine if there is an association between ABI or TBPI values and peritoneal function in patients undergoing peritoneal dialysis. Single-site, cross-sectional	146	0	146	41:105	48 (11)	50 (34 months)
Shimazaki [127]	**Japan**	1) Demonstrate if SPP or TBPI is more effective for diagnosis of PAD in patients with HD. 2) Compare participants with and without diabetes. Single-site, cross sectional	65	65	0	39:26	63.4 (11.1)	76.9 (88.3 months)
Morimoto [128]	**Japan**	To determine the risk factors of normal ABI and low TBPI in HD patients. Single-site, cross sectional	115	115	0	77:38	54.8 (1.8)	Normal ABI/Normal TBPI 9.2 (0.8 years) Normal ABI/ Low TBPI 12.2 (2.1 years)
Kay [43]	**USA**	To compare the TP, SPP and oxygenation measurement in the lower limbs of diabetic and non-diabetic patients requiring HD. Pilot-study, multi-site, prospective, case-control, cross-sectional, Parallel arm, comparison study	15	15	0	6:9	DM 54-77 (range) No- DM 61-74 (range)	NR
Ohtake [129]	**Japan**	1) Evaluate the arterial calcification score of the arteries of the lower limb quantitatively by MDCT 2) Evaluate the relationship between calcification score and the severity of PAD in HD patients. 3) Evaluate the associating factors for PAD and CLI and compared the predictive power of calcification score with ABI and TBPI for PAD and CLI in HD patients. Single-site, cross sectional	97	97	0	NR	67.8 (12.2)	71.9 (79) months)
Matsuzawa [130]	**Japan**	Assess the prevalence of PAD and risk factors for PAD in patients on HD. Single-site, cross sectional	210	210	0	134:76	66 (11)	9.2 (9.1 years)
Unagami [131]	**Japan**	To investigate the relationship between diastole dysfunction grades, cardiovascular index, ABI, TBPI and aortic calcification area index. Single-site, prospective/ cross sectional	89	89	0	31:58	64 (11)	138 (94 months)
Kaminski [16]	**Australia**	Investigate factors associated with foot ulceration and amputation in a dialysis cohort. Multi-site, cross sectional	450	423	27	291:159	67.5 (13.2)	36.9 (16.6-70.1 IQR) (months)

Ingsathit [132]	**Thailand**	Identify risk factors of PAD in dialysis patients. Single-site, cross sectional	269	212	57	153:116	48.8 (15.1)	52.6 (1.8 months)
Prasad [117]	**USA**	Assess the hypothesis that using the ABI-TBPI score may indicate MAC and PAD in dialysis patients. Single-site, retrospective, cohort	37	NR	NR	37:0	65 (8)	2.9 (3.8 years)
Hishida [133]	**Japan**	Determine if TBPI provides additional prognostic information beyond ABI in patients on HD. Single-site, retrospective, cohort	247	247	0	167:80	66.8 (11.6)	9.5 (8.2 years)
Schembri [134]	**Malta**	Determine the prevalence of foot morbidity among patients on HD. Single-site, prospective, cohort	47	47	0	28:19	67.85 (NR)	43.96 (NR)
Nishimura [135]	**Japan**	Investigate the relationship between ABI, TBPI and cognitive function in patients on HD Single-site, retrospective, cross sectional	100	100	0	67:33	67.9 (11.2)	7.3 (6.8 years)
Carle [136]	**NZ**	1) Determine the variability of toe pressures during HD 2) compare DM to no-DM. Pilot study, multi-site, prospective, cross sectional	30	30	0	16:14	DM Median age 56 (42-78), No-DM Median age 59 (24-79)	DM 3.8 (2.9 years) No-DM 6.2 (4.1 years)
			Total					
			1,989	1,708 (86%)	281 (14%)			

ABI; Ankle Brachial Index, CRF; Chronic Renal Failure, DM; Diabetes Mellitus, F; female, HD; haemodialysis, M; male, MAC; Medial Arterial Calcification, NR; not reported, NZ; New Zealand, MDCT Multi Detector Computed Tomography, PAD; Peripheral Arterial Disease, PD; peritoneal dialysis, SD; standard deviation, TBPI; Toe Brachial Pressure Index, TcPO2; Transcutaneous Oxygen Pressure, SPP; Skin perfusion Pressure.

Toe Brachial Pressure Index

Table 5 shows the TBPI measurement results reported in 94% (n=15) of the studies. Sixty three percent (n=10) of studies reported the TBPI measurement as a mean, median, or percentage. Four defined TBPI categorically as low or pathological. One study [136], documented multiple TBPI measurements on participants.

Toe Systolic Blood Pressure

The four studies reporting mean TSBP values **(Table 6)** varied in their reporting of TSBP (Kay et al. and Carle et al. [43, 136] were the only studies to report the timing in which TSBP occurred in relation to the dialysis session. Shimazaki et al. [127] reported TSBP values categorised by normal or abnormal ABI. Kaminski et al. [137] reported mean right and left TSBP values for all participants.

Table 5. Research papers including TBPI in populations receiving dialysis

Author	Participant numbers		TBPI, all participants, mean (SD)	TBPI, diabetes participants, mean (SD)	TBPI, no-diabetes participants, mean (SD)	Study findings	Categorisation
	DM	ND					
Leskinen [124]	15	21	Low TBPI (<0.6) in 20% of total population	NR	NR	Recommends use of TBPI to evaluate PAD in patients with chronic renal failure.	Prevalence of PAD
Okamoto [125]	15	21	Low TBPI (<0.6) in 21% of total population	NR	NR	Skin Perfusion Pressure is more effective than TBPI for early detection of peripheral occlusive arterial disease.	Diagnostic accuracy
Huang [126]	27	119	0.79 (0.14)	NR	NR	TBPI was not correlated with peritoneal function in patients undergoing PD.	Exploratory
Shimazaki [127]	25	40	NR	**Normal ABI** 0.49 (+-0.14) **Low ABI** 0.37 (+-0.16)	**Normal ABI** 0.64 (+-0.17) **Low ABI** 0.22 (0.0)	Skin Perfusion Pressure had a strong positive correlation with TBPI.	Cross-sectional
Morimoto [128]	NR	NR	Normal TBPI in 78% of population Low TBPI (<0.6) in 22%	NR	NR	Diabetes and high BMI are risk factors for Low TBPI.	Exploratory
Ohtake [129]	38	59	0.67 (0.31)	NR	NR	Arterial calcification below the knee and raised C-reactive protein were independent risk factors for low TBPI, which is associated with PAD and critical limb ischemia	Cross-sectional
Matsuzawa [130]	102	108	Low TBPI (<0.6) in 20.7%	NR	NR	Screening for PAD with TBPI increased diagnostic efficacy	Prevalence of PAD
Unagami [131]	32	57	**Right** 0.66 (0.17) **Left** 0.67 (0.18)	NR	NR	TBPI increased proportionally with diastole dysfunction	Exploratory
Kaminski [16]	180	270	**Right** 0.72 (0.25) **Left** 0.7 (0.26)	NR	NR	52% of the cohort had PAD	Prevalence of PAD
Ingsathit [132]	57	212	0.8 (0.20)	NR	NR	The prevalence of abnormal TBPI was higher than abnormal ABI, which recommends the use of TBPI.	Prevalence of PAD
Prasad [117]	28	9	0.54 (median)	NR	NR	TBPI is an informative predictor of mortality.	Prognostic capacity
Hishida [133]	115	132	0.63 (0.18)	NR	NR	Lower TBPI is independently associated with mortality. Recommend evaluating TBPI in this population.	Prognostic capacity
Schembri [134]	23	24	Pathological TBPI (<0.7) in 40%	NR	NR	High prevalence of foot pathology; recommend podiatry service within the renal unit	Prevalence of PAD
Nishimura [135]	44	66	0.64 (0.18)	NR	NR	TBPI is not recommended to assist diagnosis of mild cognitive impairment	Cross-sectional
Carle [136]	17	13	**Before HD** 0.79 (CI 0.70, 0.87) **1 hour into HD** 0.79 (CI 0.70, 0.87) **End of HD** 0.80 (CI 0.72, 0.89)	**Before HD** 0.79(CI 0.68, 0.9) **1 hour into HD** 0.8 (CI 0.69, 0.91) **End of HD** 0.8 (0.69)	**Before HD** 0.78 (CI 0.65, 0.9) **1 hour into HD** 0.77 (CI 0.64, 0.9) **End of HD** 0.8 (CI 0.69, 0.91)	TBPI is recommended for use during HD.	Exploratory

ABI; ankle brachial index, BMI; body mass index, DM; diabetes mellitus, HD; hemodialysis, NR; not reported, PAD; peripheral arterial disease, PD; peritoneal dialysis, TBPI; toe brachial pressure index.

Table 6. Studies reporting TSBP measurement in dialysis populations

Author	Participant Numbers		TP, all participants, mean (SD)	TP, DM participants, mean (SD)	TP, ND participants, mean (SD)	Study Findings	Categorisation
	DM	ND					
Shimazaki [127]	25	40	**Normal ABI**: DM 73.3 (+-22.7) No-DM 90.2 (+-30) **Low ABI** DM 62.8 (+-26.3) No-DM 37.5 (+-5)	Normal ABI: 73.3 (22.7) Low ABI: 62.8 (26.3)	Normal ABI: 90.2 (30) Low ABI: 37.5 (5.0)	Skin perfusion pressure positively correlated with TP	Cross-sectional
Kay [43]	10	5	NR	During HD: 76.6 (7.1) After HD: 83.9 (8.4)	During HD: 113.5 (10) After HD: 116.3 (12.6)	DM participants had significantly lower TP than ND during and after HD	Exploratory
Kaminski [16]	226	224	L: 93.2(37.7) R: 95.7 (36.6)	NR	NR	52% of the cohort had PAD	Prevalence of PAD
Carle [136]	17	13	**Before HD** 121.50 (CI 105.72, 137.29) **1 hour into HD** 113.17 (CI 97.38, 128.95) **End of HD** 109.56 (CI 93.77, 125.34)	**Before HD** 126.85 (CI 106.07, 147.64) **1 hour into HD** 119.41 (CI 98.63, 140.19 **End of HD** 111.88 (CI 91.10, 132.67)	**Before HD** 116.15 (CI 92.39, 139.92) **1 hour into HD** 106.92 (CI 83.16, 130.69) **End of HD** 107.23 (CI 83.47, 131.00)	TP reduced significantly during HD. Reduced TP during HD may impact healing capacity and may be relevant to the development of lower limb complications	Exploratory

ABI; ankle-brachial index, CI; confidence interval, DM; diabetes mellitus, HD; Haemodialysis, ND; no diabetes, NR; not reported, PAD; peripheral arterial disease, TP; toe pressure.

Prognostic capacity, cross-sectional, prevalence, diagnostic accuracy, and exploratory studies

Prognostic Capacity

Two studies examined the prognostic capacity of TBPI [117, 133]. Both studies found that low TBPI was an important predictor of mortality and recommended the use of TBPI for KFRT populations [117, 133].

Cross-Sectional

Nishimura, Hidaka (138) examined the association between low TBPI and cognitive impairment and found no significant association. Ohtake et al. (2011) examined the relationship between arterial calcification and low TBPI and found below-knee arterial calcification to be a risk factor for low TBPI. Shimazaki, Matsuki (127) found that skin perfusion pressure results strongly correlated with TBPI results for PAD diagnosis.

Prevalence

Five studies examined the prevalence of PAD in individuals with KFRT receiving dialysis [16, 124, 130, 139, 140]. Three studies used a TBPI < 0.6 to represent a diagnosis of PAD [16, 124, 130]. Based on this threshold, the prevalence of PAD in people with KFRT ranged from 30.6% to 52%. Leskinen, Salenius (124) (PAD prevalence 30.6%) defined PAD as either TBPI < 0.6 or ABI < 0.9 or a positive angiogram result. Matsuzawa, Aoyama (130) (PAD prevalence 38.1%) defined PAD as ABI < 0.9 and/or TBPI < 0.6). Kaminski, Raspovic (16) (PAD prevalence 52%) defined PAD as TBPI < 0.6, ABI < 0.9, absence of > 2 pedal pulses or known history of PAD or revascularisation. Ingsathit, Nissaisorakarn (139) reported a PAD prevalence of 11.7% and used an ABPI < 0.9 or > 1.4 to diagnose PAD (prevalence rate 11.7%). In addition, they reported TBPI < 0.6 as “abnormal TBPI” and found this in 29.7% of participants but did not define this population as having PAD. Finally, Schembri and Formosa (140) used a TBPI < 0.7 for PAD diagnosis and found that 40.4% of the 47 people with KFRT had PAD. Furthermore, their prospective study found that the average TBPI was reduced during the 6-month follow-up.

Diagnostic accuracy

One article examined the diagnostic accuracy of TBPI [125, 127]. The study compared skin perfusion pressure and TBPI values with multi-detector row computed tomography [125] as the reference standard for the diagnosis of PAD. Okamoto, Oka (125) found that skin perfusion pressure was more accurate than TBPI in detecting PAD.

Exploratory

Four studies using TBPI [126, 136, 141, 142], were classified as exploratory, and two studies using TSBP were classified as exploratory [43, 136]. There were different focuses and results within the studies. Huang, Chen (126) examined peritoneal dysfunction and found no association between TBPI and peritoneal function. Morimoto, Nakajima (141) examined risk factors for low TBPI and found that diabetes and high body mass index were risk factors for low TBPI. Unagami, Nitta (142) examined diastole dysfunction and found that TBPI increased proportionally to diastole dysfunction. Carle, Tehan (136) examined TBPI variability during haemodialysis, finding that it remained stable, and recommended its use for PAD screening. Kay, Ray (43) and Carle, Tehan (136) examined TSBP variability in people receiving haemodialysis. Kay, Ray (43) found that TSBP decreased during dialysis, but only in people with diabetes. In contrast, Carle, Tehan (136) found that TSBP decreased significantly during dialysis in both people with diabetes and people without diabetes.

Measurement Protocols

Table 7 reports the measurement protocols used in the included studies. Automated measurement devices were used in 93% (n=16) of studies, with only one using a manual device [136]. Resting time prior to measurement was reported in nine studies, with the time ranging between 5 to 30 minutes. Most measurement protocols lacked adequate reporting. Four or fewer studies identified pre-measurement factors known to affect results, such as cuff size and exercise/smoking or caffeine consumption. The time at which data collection occurred in relation to the dialysis session was reported in 16 studies, with six obtaining measurements outside of the dialysis session [125, 127, 128, 130, 131, 135] and four during a dialysis session [43, 133, 136, 137].

Patient Level Factors

Table 8 shows the reporting of patient-level factors. The ethnicity of participants was reported in three articles [117, 136, 137]. Most articles reported age, gender, dialysis history, and co-morbidities.

Table 7. Measurement protocols for obtaining TBPI or TSBP

Author	Measurement device	Time of procedure in relation to dialysis	Single researcher used	Qualification of tester	Blinding of testers	Inter/intra tester testing	Temp of room	Resting time	Resting position	Cuff size used	No exercise before test	No smoking before test	No caffeine before test
Leskinen [124]	Nicolete VasoGuard (Nicolete Vascular Inc, Madison WI).	✗	✓	✗	✗	✗	✗	30 minutes	✓	✗	✗	✗	✗
Okamoto [125]	PPG	Within 6 hours of HD	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗
Huang [126]	Vascular Profiler 1000 (VP-1000) (Colin Corporation, Japan)	✗	✗	✗	✗	✗	✗	10 minutes	✓	✓	✗	✗	✗
Shimazaki [127]	VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan)	On HD-free day	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Morimoto [128]	Form PWV/TBPI (Omron Healthcare)	After HD	✗	✗	✗	✗	✓	20 minutes	✓	✗	✗	✗	✗
Kay [43]	PeriFlux System 5000 (PF5010 + PF5050; Perimed, Sweden)	Before, midway and after HD on 3 separate HD sessions	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Ohtake [129]	ABI-Form (Nippon Colin, Komaki, Japan).	✗	✓	✓	✗	✗	✓	5 minutes	✓	✗	✗	✗	✗
Matsuzawa [130]	Form 3 omron colin	Before HD	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Unagami [131]	VaSera (Fukuda Denshi, Tokyo, Japan)	Before midweek HD	✗	✗	✗	✗	✗	10 minutes	✓	✗	✗	✗	✗
Kaminski [16]	SysToe® (Atys Medical, Soucieu-en-Jarrest, France)	During HD, some on non-HD days	✓	✓	✓	✓	✓	15 minutes	✗	✓	✗	✓	✓
Ingsathit [132]	VaSera VS1500 (Fukuda Denshi, Japan)	✗	✓	✓	✗	✗	✗	10 minutes	✓	✗	✗	✗	✗
Prasad [117]	Unetixs milti-lab series 11 LHS peripheral vascular diagnostic system	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Hishida [133]	Oscillometric device (BP 203RPE III device; Omron Healthcare)	Any time during HD	✗	✗	✗	✗	✓	✗	✓	✗	✗	✗	✗
Schembri [134]	Huntleigh Doppler Assist Vascular Package	✗	✗	✗	✗	✗	✗	15 minutes	✓	✗	✗	✗	✗
Nishimura [135]	VeSera VS-1000 (Fukuda Denshi co. Ltd., Bunkyo, Japan)	3090 minutes before start of HD	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Carle [136]	Handheld doppler/ PPG unit	3 tests done- immediately before HD, 1 hour into HD and in the last 15 minutes of HD	✓	✓	✗	✗	✗	5 minutes	✓	✓	✓	✓	✓
TOTALS	15 automated 1 hand-held	NR: 6/16 During HD: 4 Non-HD days 6/16	4/16	4/16	1/16	1/16	5/16	5 min:2 10min:3 15min:2 20min:1 30min:1 NR:7	12/16	3/16	1/16	2/16	2/16

✗ not reported, ✓ reported, BP; blood pressure, HD; haemodialysis, NR; not reported, PPG; photoplethysmography.

Table 8. Patient level factors

Author	Age reported	Sex reported	BMI reported	Ethnicity reported	Dialysis history reported	Cause of KFRT-Stated	Medications reported	Smoking history reported	Co-morbidities reported	Blood test recorded
Leskinen [124]	✓	✓	✓	✗	✓	✗	✗	✓	✓	✓
Okamoto [125]	✓	✗	✗	✗	✓	✗	✗	✗	✓	✗
Huang, W [126]	✓	✓	✓	✗	✓	✗	✓	✓	✓	✓
Shimazaki [127]	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓
Morimoto [128]	✓	✓	✓	✗	✓	✗	✗	✓	✓	✓
Kay [43]	✓	✓	✗	✗	✗	✗	✗	✗	✓	✓
Ohtake [129]	✓	✗	✗	✗	✓	✗	✓	✓	✓	✓
Matsuzawa [130]	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓
Unagami [131]	✓	✓	✗	✗	✓	✗	✗	✗	✓	✗
Kaminski [16]	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓
Ingsathit [132]	✓	✓	✓	✗	✓	✗	✓	✓	✓	✓
Prasad [117]	✓	✓	✗	✓	✓	✗	✗	✓	✗	✗
Hishida [133]	✓	✓	✓	✗	✗	✓	✓	✓	✓	✗
Schembri [134]	✓	✓	✗	✗	✓	✓	✗	✓	✓	✗
Nishimura [135]	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗
Carle [136]	✓	✓	✗	✓	✓	✓	✗	✓	✓	✗
Totals n (%)	**16/16 (100)**	**14/16 (88)**	**9/16 (57)**	**3/16 (19)**	**14/16 (88)**	**7/16 (44)**	**6/16 (38)**	**11/16 (69)**	**15/16 (94)**	**9/16 (57)**

✗ not reported, ✓ reported, BMI; body mass index, KFRT; Kidney failure with replacement therapy

Discussion

This review investigated studies reporting TSBP and TBPI in populations receiving dialysis and found extremely limited data examining the clinical utility of either measure within populations receiving dialysis. A total of 16 studies investigated TSBP and/or TBPI in this high-risk population, with a total of 1,989 participants. Study aims were highly variable, as were the methodology and outcome measures between studies. Consequently, the reliability, prognostic capacity, and diagnostic accuracy of TSBP or TBPI in people who receive dialysis are yet to be robustly established. Moreover, studies that investigated the variability of TSBP and TBPI measures during dialysis sessions reported contrasting results.

A larger number of the included studies focused on the use of TBPI rather than TSBP. Among the included studies, there was substantial heterogeneity in the diagnostic thresholds used for TBPI, making direct comparison between studies challenging and, furthermore, leaving clinicians without specific guidance on the optimal cut-off in this population. Normative threshold values for TBPI vary amongst international best-practice guidelines from > 0.6 [103], > 0.7 [20], and > 0.75 [26, 143]. Whilst TBPI are used clinically for the identification of PAD and is recommended in multiple guidelines [20, 26, 35, 96], TSBP are also clinically useful in populations with or at risk of PAD. Toe systolic blood pressures are also used as a bedside test to identify PAD, although with less diagnostic accuracy than TBPI [144], but is more commonly used to predict wound healing capacity and amputation risk in people with active foot ulceration or following minor amputation [145, 146]. It is well established that TSBP of < 30mmHg is predictive of amputation risk [20, 147] and are beneficial in determining the need for urgent imaging for revascularisation planning [26]. In people with KFRT, there is a high prevalence of foot ulceration and increased rates of amputation. Therefore, TSBP may be clinically important in identifying the at-risk limb risk, enabling the implementation of optimal medical management and wound prevention programs [120].

This review found a large degree of inconsistency and a low degree of reporting regarding specific measurement protocols despite TBPI and TSBP being a primary outcome measure within the studies. There was limited reporting of test conditions, including room temperature, resting time, and cuff size. Variation in these conditions has been shown to adversely affect the diagnostic accuracy of results of TSBP and TBPI measurements [96, 98, 99]. Patient positioning was not indicated in four studies [43, 125, 135, 137], and this is notable due to the known capacity to influence results obtained [98]. Having participants seated instead of supine increases TSBP results by up to 30mmHg [98], which may significantly impact TBPI results and, therefore, the identification of PAD. Tehan et al. [96] discussed the significance of other additional factors, including controlling patient-dependent variables such as caffeine intake, smoking, and exercising before the test to ensure a reliable and valid assessment. While Tehan et al. [96] advocate for the

consistent reporting of these protocols, it is noted that 13 of the included studies were published before Tehan's recommendations. Automated devices were used in 15 of the 16 studies, which is supported by high levels of interrater reliability in previous studies [148, 149]. Manual devices have been shown to have acceptable reliability but clinically significant margins of error [150]. Eleven studies used multiple researchers for data collection, with only one study [137] ensuring inter and intra-tester testing prior to data collection. Inter-tester reliability for TSBP and TBPI has shown low levels of reproducibility or reliability between clinicians in previous studies, potentially impacting the validity of the results obtained [151]. The review also found limited reporting of data detailing the time at which TSBP and TBPI were obtained in relation to dialysis sessions. This is despite known reductions in intradialytic and increases in interdialytic brachial blood pressures [152], factors that may affect TSBP and TBPI results. Timing of measurements and vascular assessments in relation to the dialysis sessions is also not addressed within best-practice guidelines. Carle et al. (2023) was the only study that reported reducing TSBP during dialysis and related this to reducing intradialytic brachial systolic blood pressure.

The ethnicity of participants was only reported in three studies [117, 136, 137]. Chronic kidney disease and the progression to KFRT are increasing in prevalence worldwide, with wide disparities between different ethnic groups [153, 154]. Indigenous populations worldwide face a disproportionate burden of CKD and KFRT [155-157]. The lifetime risk of kidney failure requiring replacement therapy varies widely. For remote Australian Indigenous populations, the estimated risk of 1 in 5, compared to 1 in 40 for Canadian men, 1 in 60 for Canadian women, and 1 in 13 for American black men [158]. There is a bidirectional relationship between poverty and KFRT, which is a factor in the health disparity between ethnicities in higher-income countries due to the strong link between health access and outcomes [154]. Indigenous populations in Australia, NZ, the United States and Canada all experience KFRT at levels significantly higher than non-indigenous populations, as well as disparities of care, including lower levels of kidney replacement surgery [154]. The US National Institute of Health (the world's largest funder of medical trials) strongly encourages reporting of ethnicity data to aid the elimination of these known disparities [159]. The disparity of ethnic reporting contributes to bias within medical evidence, with understudied efficacy and safety for minority and indigenous populations [160]. The lack of data on ethnic minorities, including indigenous populations, can have negative effects on resource allocation and policy decision-making [161].

This review highlights the limited number of studies investigating the prevalence of PAD in populations undergoing dialysis, with only five studies focused on this, despite the well- known and devastating outcomes that can occur as a result of ESRD and PAD. Although ABI has traditionally been used for prevalence studies for PAD, updated guidelines [20, 26] now specify a preference for TBPI to aid the diagnosis of PAD in populations with high suspicion of peripheral vessel

calcification, such as those with KFRT. Current screening protocols remain unclear, but more robust reporting of methodological detail is required in future studies; for research to accurately reflect PAD prevalence in KFRT cohorts, clarification of the normative value of TBPI for diagnosing PAD through best-practice guidelines is urgently needed. Determining the optimal method for PAD diagnosis in people receiving dialysis is critical to ensure that future prevalence studies are robust. The true prevalence of PAD in KFRT populations is likely underestimated due to the above-mentioned methodological shortcomings and the lack of larger and multicentre studies, with only four studies obtaining data from more than one site [16, 43, 124, 136]. The small number of studies in this review on TSBP and/or TBPI in KFRT populations highlights the lack of studies conducted in populations with KFRT in general. Larger, more powered studies focusing on morbidity, mortality, limb outcomes, including amputations, and quality of life are needed as they may impact service delivery. An international registry or multicentre prevalence study examining PAD in individuals with KFRT and using TSBP and TBPI will allow the allocation of health service resources to this population and consideration of targeted treatment programs. Well-designed and impactful studies can influence health service delivery by targeting areas of economic and health burden, such as populations with KFRT. Funding for research within the renal sector is significantly lower than for other health conditions, such as AIDS, cancer and diabetes [162]. This has resulted in fewer robust clinical trials, randomised controlled trials, innovative research or state-of-the-art clinical trials in this field, and less dissemination of research findings in elite peer-reviewed journals [162]. This is evident from the results of this scoping review. Approximately two-thirds of published medical research is unfunded, and this is directly related to the quality of published research [163].

The results of this review must be considered in light of some limitations. Most of the articles included in this review were cross-sectional. Therefore, it is not possible to imply a causal relationship between TSBP, TBPI and outcomes such as morbidity, mortality, and lower limb amputation rates. The generalisability of the results is also limited because most studies had relatively low participants, and half were conducted in Japan. This scoping review was limited to articles written in English, and therefore, our results can only be generalised to associated populations. Whilst a robust search strategy was used across multiple databases, there may be papers that have not been included.

Recommendations

1. Further clarification on the clinical utility of TBPI and TSBP in populations with KFRT, together with clarifying PAD screening protocols, including the time of assessment. Establishing a clinical pathway to diagnose PAD in people with KFRT accurately is necessary, as this could potentially impact early intervention and prevention programs, thereby reducing the risk of lower limb amputation.

2. Future studies utilising TBPI or TSBP should increase reporting of data relating to ethnicity and Indigenous status with KFRT, due to the known disparities in mortality and morbidity and ensure robust reporting of all measurement protocols to allow for replication.
3. In people with KFRT, accurate PAD prevalence data using TBPI to detect PAD are needed as PAD prevalence statistics are currently based on the ABI, which is known to have reduced sensitivity and is, therefore, likely to miss disease when present.
4. Prospective studies are needed to determine the utility of TSBP and TBPI as predictors of wound healing, revascularisation outcomes, amputation rates, morbidity, and mortality. Further reliability and diagnostic test accuracy studies are also warranted.

Conclusion

The review found limited data investigating the clinical utility of TSBP and TBPI in populations receiving dialysis. Future studies must ensure accurate reporting of measurement protocols and test conditions to improve diagnostic accuracy. Increased reporting of data from Indigenous populations who bear a greater burden of disease must also be a priority to begin to address existing disparities in morbidity and mortality rates. Timely diagnosis of PAD through applying tests such as TSBP and TBPI may enable early identification and subsequent implementation of targeted interventions in people with KFRT, such as preventative foot care, exercise, and smoking cessation programs

Chapter 4 - Variability of Toe Pressures During Haemodialysis: Comparison of People with and Without Diabetes; A Pilot Study

Citation

Carle R, Tehan P, Stewart S, Semple D, Pilmore A, Carroll MR. Variability of toe pressures during haemodialysis: comparison of people with and without diabetes; a pilot study. Journal of Foot and Ankle Research. 2023 Jul 10;16(1):42.

Preface

Podiatrists in Auckland attend HD centres to provide wound care and preventative foot screening, including vascular assessments of the lower limb, including TSBP and TBPI. Providing podiatric care during this time is associated with reduced lower limb amputation rates [93], yet there is little reported data on the effect of HD on peripheral vascular assessments. The review in Chapter 3 illustrated the paucity of information regarding TSBP and TBPI reported on persons with ESRD, despite these measures being preferred over ABI for PAD diagnosis [20, 35], and a clear need for accurate diagnosis in this population with high levels of PAD and lower limb amputation rates [69, 120]. Chapter 4 aims to clarify if TSBP and TBPI should be undertaken whilst undergoing HD or if the mechanism of HD makes these measures an inaccurate reflection of peripheral circulation. This pilot study attempted to answer this by reviewing the TSBP and TBPI at three time points: just before HD, one hour into, and within 15 minutes before the conclusion of one HD session. The results were analysed in 30 people and then further analysed between persons with and without diabetes to allow comparison to the previous study found on this subject [43]. This pilot study should encourage the use of TBPI during HD but found that TSBP reduced significantly during HD.

Abstract

Background

Diabetes, end-stage renal disease (ESRD), and peripheral arterial disease (PAD) are associated with a higher risk of diabetes-related lower limb amputation. Timely identification of PAD with toe systolic blood pressure (TSBP) and toe-brachial pressure index (TBPI) is critical in order to implement foot protection strategies to prevent foot complications in people with ESRD. There is limited evidence describing the effect of haemodialysis on TSBP and TBPI. This study aimed to determine the variability of TSBP and TBPI during haemodialysis in people with ESRD and to determine whether any observed variability differed between people with and without diabetes.

Methods

TSBP and TBPI were taken before dialysis (T1), one hour into dialysis (T2), and in the last 15 minutes of dialysis (T3) during a single dialysis session. Linear mixed-effects models were undertaken to determine the variability in TSBP and TBPI across the three time points and to determine whether this variability differed between people with and without diabetes.

Results

Thirty participants were recruited, including 17 (57%) with diabetes and 13 (43%) with no diabetes. A significant overall reduction in TSBP was observed across all participants ($P < 0.001$). There was a significant reduction in TSBP between T1 and T2 ($P < 0.001$) and between T1 and T3 ($P < 0.001$). There was no significant overall change in TBPI over time ($P = 0.62$). There was no significant overall difference in TSBP between people with diabetes and people with no diabetes (mean difference [95% CI]: -9.28 [-40.20, 21.64], $P = 0.54$). There was no significant overall difference in TBPI between people with diabetes and people with no diabetes (mean difference [95% CI]: -0.01 [-0.17, 03.16], $P = 0.91$).

Conclusion

Toe systolic blood pressure and TBPI are essential to a vascular assessment of the lower limb. TBPI remained stable, and TSBP significantly reduced during dialysis. Given the frequency and duration of dialysis, clinicians taking toe pressures to screen for PAD should be aware of this reduction and consider how this may impact wound healing capacity and the development of foot-related complications.

Background

Diabetes is the most common cause of kidney failure, accounting for 47% of all new end-stage renal disease (ESRD) cases in NZ in 2019 [80].The progression of microvascular kidney damage to ESRD in diabetes is associated with an increased prevalence of peripheral neuropathy and peripheral arterial disease (PAD), which is subsequently associated with an increased risk for diabetes-related lower limb amputations [34]. Foot complications such as ulceration, infection, gangrene and amputation are two-fold more prevalent in persons with ESRD compared to non-nephrotic persons with diabetes [13].

ESRD can lead to uremic neuropathy through an accumulation of dialysable neurotoxins during haemodialysis [164]. Uremic neuropathy is a distal sensorimotor polyneuropathy that leads to a loss of protective sensation in both people with and without diabetes undergoing dialysis [165]. Both uremic and diabetic neuropathy can result in a disruption of the arterio-venous shunting process, leading to capillary circulation being bypassed and vital nutritional and gas exchanges being impaired [166]. This is associated with increased fissuring and infection rates in these populations [166]. There is a strong association between ESRD, loss of protective sensation and diabetes-related lower limb amputation, with a 6.5- to 10-fold higher likelihood than in the general diabetes population [13, 137]. Additionally, lower limb amputation is prevalent in ESRD and diabetes populations, regardless of the presence of both conditions. Both ESRD and lower limb amputation lead to a reduction in quality of life and an increased risk of premature mortality [37]. Foot ulceration and amputation requiring vascular intervention is an expensive burden for taxpayers, with median costs for treatment estimated at $30K NZD per wound [167].

Measurement and monitoring of peripheral blood flow using non-invasive vascular assessments (Doppler waveform analysis, ankle-brachial index, toe-brachial pressure index (TBPI), toe systolic blood pressure (TSBP)) can provide information on the presence and progression of PAD and expedite triage to vascular services, which may reduce the risk of lower limb amputation [31, 42]. TSBP can be measured chairside using a suitable hand-held Doppler, which provides a valuable measure of peripheral blood perfusion [96]. TSBP < 30mmHg (non-pathologic TSBP > 60mmHg) [42] is associated with a relative risk of 3.25 for amputation and non-healing [168]. The TBPI, which compares TSBP to brachial systolic blood pressure, is another important indicator for PAD, with results of ≥ 0.75 making the diagnosis of PAD less likely [102].

There is limited research describing peripheral vascular assessment in people with concomitant diabetes and ESRD during dialysis. Kay et al. [43] reported TSBP values reduced from mid to post-dialysis in persons with diabetes but not in persons with no diabetes. There have been a small number of other studies relating to peripheral blood flow during dialysis, but only one related to

TSBP variability [37-41]. Tsuyuki et al. [42] compared ankle brachial pressure indices to TBPI in people with ESRD and found that TSBP showed a lower level of specificity than the ankle-brachial pressure index, attributing this finding to extensive medial arterial calcification, which is frequently present in ESRD [42]. The sensitivity and overall accuracy of the ankle-brachial pressure index in detecting 50% or greater stenosis in patients with chronic kidney disease have been shown to be 43% and 67%, respectively [169]. In contrast, the sensitivity and overall accuracy for abnormal TBPI detecting 50% or greater stenosis were 77% and 72% for patients with chronic kidney disease. For those with inconclusive ABI, these values for TBPI were 75% and 69% [169]. The authors concluded that TBPI should be used to complement or supplement the ankle-brachial pressure index. Additionally, The American College of Cardiology/American Heart Association recommends using TBPI in evaluating patients with falsely elevated ankle brachial pressure indices, specifically in diabetics and patients with chronic kidney disease, because of the higher prevalence of medial arterial calcification of the calf arteries in these populations [170].
The primary aim of this study was to determine the variability of TSBP and TBPI during haemodialysis in people with ESRD. The secondary objectives were to determine whether observed variability in TSBP and TBPI differed between participants with and without diabetes.

Methods

This cross-sectional pilot study was conducted between October and December 2022. Potential participants were recruited from two community dialysis clinics in Auckland, NZ (Kererū Dialysis Centre and Carrington Dialysis Centre).

Inclusion Criteria

Participants were included if they had ESRD, were on haemodialysis at either the Carrington or Kererū dialysis centres, were between 18 and 80 years of age, tolerated toe pressure assessment, and were able to consent. Participants were excluded if TSBP could not be determined at baseline, revascularisation of both limbs had occurred within the past 3 months, had undergone hallux amputation, or had ulceration that would limit the ability to take a toe pressure measurement. Non-English speakers with no family/friends available for interpretation during the dialysis session were also excluded. Participants were asked to refrain from having caffeine, smoking, or strenuous physical activity two hours prior to data collection, as per the technique paper by Tehan et al. [96].

Recruitment Protocol

Within the two centres, 108 patients were available for recruitment. After a four-week recruitment process, 30 people with ESRD agreed to participate in the pilot study. Recruitment occurred through a non-probability voluntary response sampling method, in which renal case managers

identified potential participants based on the inclusion criteria and then approached patients to determine their interest in participation. The names of potential participants were then passed on to the researcher. The researcher approached the patients during a dialysis session and discussed the protocol, consent processes, and participation date. The prospective participant could opt out at this time or on the day of data collection. This sampling was deemed the most appropriate as the renal case managers have an in-depth knowledge of their clients and would be in the best position to approach those who may be interested; this recruitment method acknowledges that this can be a vulnerable population.

Procedure

TSBP was measured bilaterally according to the protocol described by Tehan [96]. The protocol was modified with regard to the resting time before the initial TSBP measurement. Participants were rested in a 30-degree or lower supine position for 5 minutes prior to assessment, as opposed to the recommended 10 minutes. This protocol was adjusted to cause minimal disruption when participants were preparing for dialysis. Brachial systolic blood pressure was measured on one side only, determined by the presence of fistular or by the participants' preference, using the dialysis machine. This procedure was performed before dialysis (T1), one hour after the start of dialysis (T2), and in the last 15 minutes of the dialysis session (T3). All TSBP readings were taken by R.C., a podiatrist with 18 years of clinical experience.

Demographic and medical history were collected by interviewing participants and reviewing medical records to obtain information on a history of ESRD, hypertension, dyslipidemia, previous stroke, previous heart attack, history of diabetes, history of diabetes-related foot complications, and smoking history. Dialysis notes were reviewed to determine the type of dialysis used, duration of dialysis, interdialytic blood pressure variance, weight change, target weight, completion of a full dialysis session, and urination history. Intermittent claudication was assessed using the Edinburgh Claudication Questionnaire [171]. Foot deformity was assessed using the 6-point scale, with one point assigned for small muscle wasting, hammer/claw toes, bony prominences, Charcot deformity and limited joint mobility [172]. A score of 3 and above indicates the presence of foot deformity [173]. The researcher determined the current callus as minor, moderate or heavy. LOPS was defined by a 10g monofilament assessment over the plantar hallux, first, and fifth metatarsal. If any of these points were absent, the participant was noted as having LOPS [137]. Frailty was self-assessed using two questions derived from the Clinical Frailty Scale [174]. Participants were asked, “Do you go outdoors independently?” and “Do you exercise outside at all?”. If they could not go outdoors independently, they scored 5 or above and were considered frail. If they do go outdoors independently, the self-assessed score was 1 to 4 depending on how often they exercise outdoors (1 = not frail, very fit and exercise often. 2 = not frail. fit 3 = not frail and managing well. 4 = living with very mild frailty, but not dependent on others for daily help). The participant’s

residential address was extracted from hospital notes and entered into the NZ Index of Deprivation [175], which is an area-based measure of socioeconomic deprivation in NZ and was derived from the 2018 census. This is an important indicator because of the relationship between socioeconomic status and mortality in NZ [176].

Statistical Analysis

Demographic and medical data were described separately for each group (diabetes, no diabetes), with n (%) used for categorical data and mean (SD) for continuous data. A linear mixed-effects model was used to determine the variability in TSBP and TBPI across the three time points (T1, T2, T3) (primary aim) and whether this variability differed between people with and without diabetes (secondary aim). Time point (T1, T2, T3) was included as a within-subject fixed effect and participant group (people with diabetes, people without diabetes) was included as a between-subject fixed effect. The interaction effect (time point*participant group) was also examined. Repeated measures between right and left limbs were accounted for by the inclusion of a participant-specific random effect [177]. Mean estimates (adjusted for dependence between right and left limbs) were presented along with their 95% confidences intervals (CI).

A sub analysis assessing the difference in TSBP and TBPI variability between people with and without LOPS was also performed, due to the high number of participants with LOPS, to determine if this was a factor related to TSBP and TBPI. These analyses were also adjusted by participant group (people with diabetes, people without diabetes). All analyses were undertaken in IBM SPSS Statistics 25 with a P value of <5% considered significant.

Results

Participant Characteristics

Thirty participants were recruited, including 17 (57%) participants with diabetes and 13 (43%) with no diabetes. The median age for participants with diabetes was 56 (range 42-78) and 59 (range 24-79) for the no-diabetes participants. Of the participants with diabetes, 10 (59%) were female, and of the no diabetes participants, seven (54%) were female **(Table 9)**. Socioeconomic deprivation, as determined from the participant's address, revealed more participants with diabetes resided in areas of higher deprivation, with 94% being in decile 5 or above, compared to 69% of the no-diabetes participants within this study. Decile 1 represents the least deprived areas; decile 10 represents areas with the most deprivation.

Table 9. Participant characteristics

		PWD	No-diabetes	P-value
Sex (M:F)		10:7	6:7	
Age median (range)		56 (42-78)	59 (24-79)	0.62
Ethnicity, n (%)	Māori	2 (12)	1 (8)	0.72
	European	2 (12)	3 (23)	0.43
	Pacifica	11 (64)	7 (54)	0.56
	Indian	0 (0)	1 (8)	0.26
	Other	2 (12)	1 (8)	0.76
Decile of housing deprivation* above 5, n (%)		16 (94)	9 (69)	0.07
Medical characteristics				
Type 2 diabetes, n (%)		13 (94)	0 (0)	**<0.0001**
Diabetes duration, years, mean (SD)		22 (9)	0 (0)	**<0.0001**
Hypertension, n (%)		13 (76)	9 (69)	0.42
Dyslipidaemia, n (%)		5 (29)	1 (8)	0.15
Smoker, n (%)		1 (6)	2 (15)	0.41
Previous/current heavy drinker, n (%)		2 (12)	1 (8)	0.72
Cerebrovascular diagnosis n (%)		0 (0)	1 (8)	0.85
Cardiovascular event, n (%)		2 (12)	2 (15)	0.78

PWD; persons with diabetes, STEMI; ST-elevation myocardial infarction; NSTEMI; non-ST-elevation myocardial infarction; n, number; %, percentage
*The decile of housing deprivation is based on census information from 2018; decile 1 represents the area of lowest depravity, decile 10 represents the area of highest depravity

Foot Health Characteristics

Foot deformity, minor callus formation, and peripheral neuropathy were more common in participants with diabetes than those with no diabetes. All participants reported low scores on the frailty grade **(Table 10)**.

Table 10. Foot health characteristics

		PWD	No-diabetes	P-value
Foot deformity n (%)		7 (41)	2 (15)	0.14
Current callus	Minor, n (%)	14 (82)	9 (69)	0.41
	Moderate, n (%)	3 (18)	4 (31)	0.41
	Heavy, n (%)	0 (0)	0 (0)	
Loss of protective sensation, n (%)		9 (53)	6 (46)	0.49
Known PAD and known to vascular services (excluding fistular), n (%)		1 (6)	2 (15)	0.39
Revascularisation to lower limb performed, n (%)		0 (0)	0 (0)	
Intermittent claudication, n (%)		0 (0)	1 (8)	0.26
Frailty grade*, mean (SD)		1.8 (1)	1.8 (0.9)	0.88

PWD, persons with diabetes; PAD, peripheral arterial disease; n, number; %, percentage; SD, standard deviation

Hemodialysis Characteristics

General haemodialysis characteristics are presented in **Table 11**. Persons with diabetes were on haemodialysis for a mean of 3.8 years, and persons with no diabetes for a mean of 6.2 years. The aetiology of ESRD in participants with diabetes was attributed to diabetes in 88% of cases and lupus and glomerulosclerosis in 6% of cases. In the no-diabetes participants, the aetiology of ESRD was attributed to lupus (15% of cases), glomerulosclerosis (15%), hypertension (8%), glomerulonephritis (23%), uretic obstruction (8%), and was unknown in 30% of cases.

Table 11. Haemodialysis characteristics

	PWD	No-diabetes	P-value
Haemodialysis duration, years, mean (SD)	3.8 (2.9)	6.2 (4.1)	0.07
Time on dialysis, hours, mean (SD)	4.8 (0.5)	4.7 (0.5)	0.61
Interdialytic weight change, kg, mean (SD)	1.99 (0.9)	2.04 (0.9)	0.91
Peritoneal dialysis before starting HD, n (%)	1 (6)	4 (30)	0.36
Interdialytic systolic blood pressure variation, mean (SD)	40 (21.5)	30 (16.3)	0.16

PWD; persons with diabetes, HD; haemodialysis; n, number; SD, standard deviation; kg, kilograms

Primary Aim: Variability in TSBP and TBPI Over Time

Data showed a significant overall reduction in TSBP (P<0.001) with all participants. There was a significant reduction in TSBP between T1 and T2 (mean difference [95% CI]: -8.34 [-14.22, -2.54], P = 0.006) and between T1 and T3 (mean difference [95% CI]: -11.95 [-17.83, -6.06], P<0.001). No significant difference was found between T2 and T3 (mean difference [95% CI]: -3.61 [-9.49, 2.27], P = 0.17) **(Table 12).** There was no significant overall change in TBPI over time (P = 0.62).

Table 12. Mean toe pressure values and toe brachial pressure index values in PWD and no diabetes

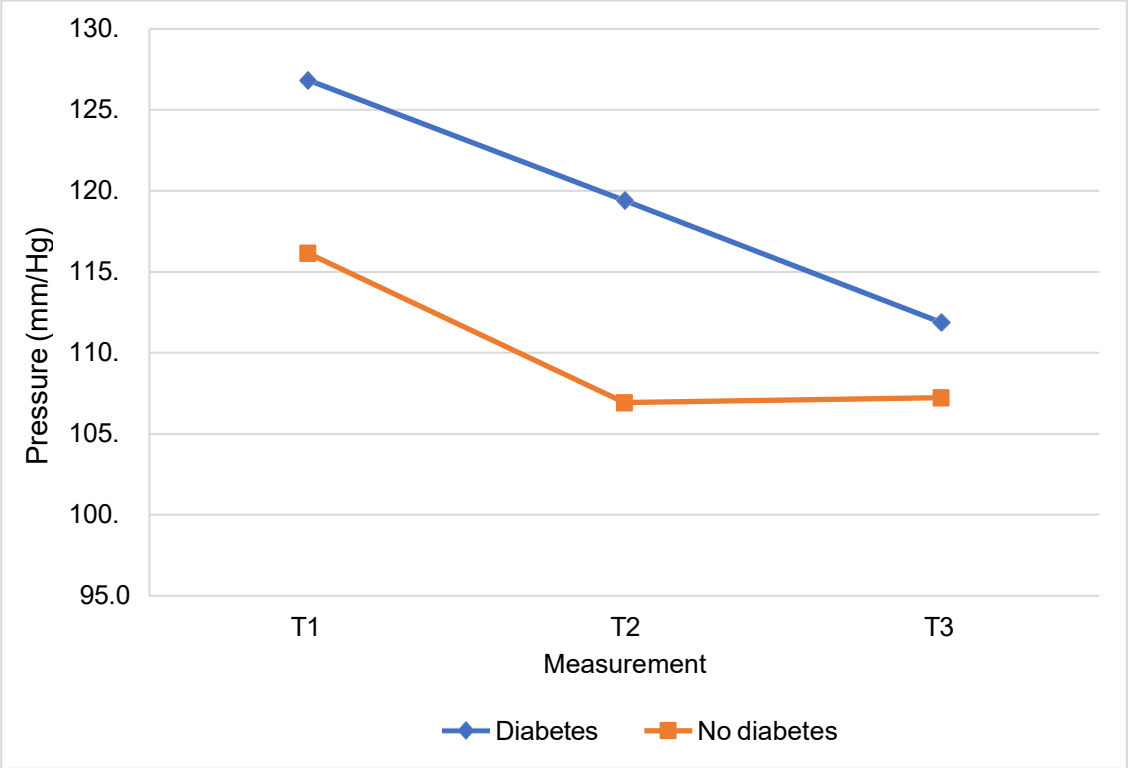
		All participants mean (95% CI)[1]	**PWD** mean (95% CI)[1]	**No-diabetes** mean (95% CI)[1]
Mean toe pressure (mmHg)	**T1**	121.50 (105.72, 137.29)	126.85 (106.07, 147.64)	116.15 (92.39, 139.92)
	T2	113.17 (97.38, 128.95)	119.41 (98.63, 140.19)	106.92 (83.16, 130.69)
	T3	109.56 (93.77, 125.34)	111.88 (91.10, 132.67)	107.23 (83.47, 131.00)
Mean toe brachial pressure index	**T1**	0.79 (0.70, 0.87)	0.79 (0.68, 0.90)	0.78 (0.65, 0.91)
	T2	0.79 (0.70, 0.87)	0.80 (0.69, 0.91)	0.77 (0.64, 0.90)
	T3	0.80 (0.72, 0.89)	0.80 (0.69, 0.91)	0.81 (0.68, 0.94)

PWD, persons with diabetes; T1, pre dialysis measurement; T2, measurement at 1 hour of dialysis; T3, measurement 15 minute prior to conclusion of dialysis, [1]Mean estimates adjusted for repeated measures on right and left feet (random effect)

Secondary Aim: Difference in Variability in TSBP and TBPI between Diabetes and no Diabetes Participants

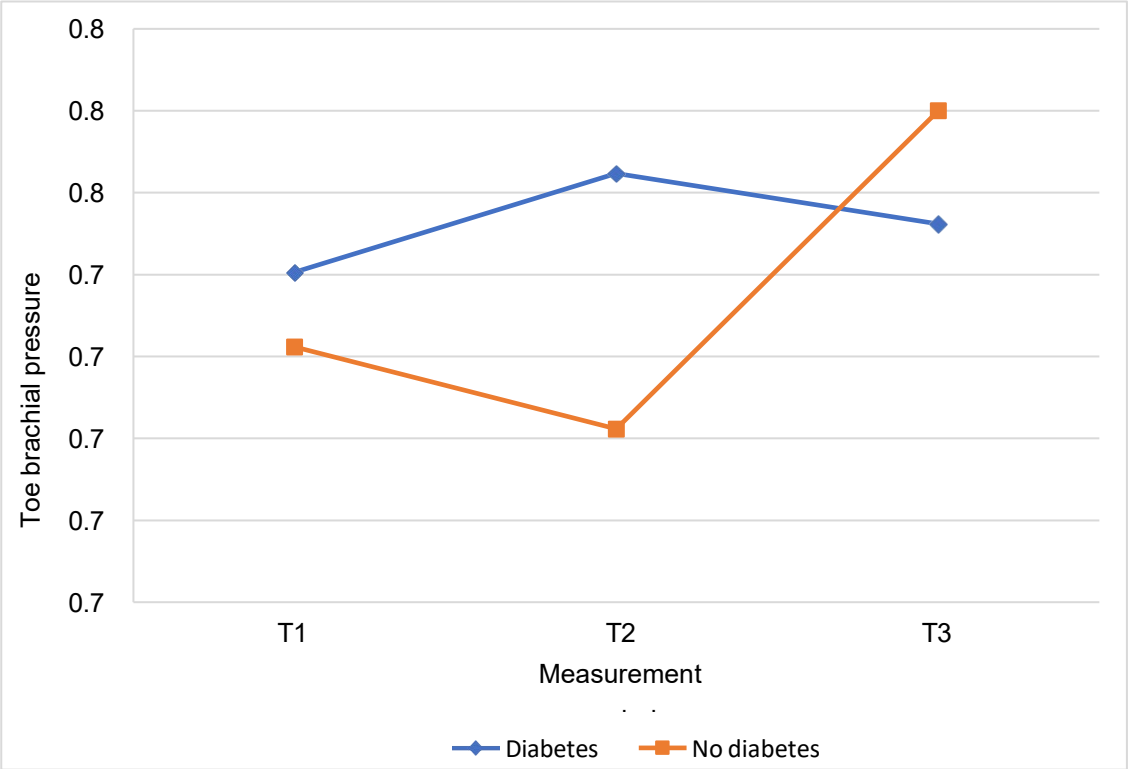
There was no significant overall difference in TSBP between persons with diabetes and persons with no diabetes (mean difference [95% CI]: -9.28 [-40.20, 21.64], P = 0.54). There was no significant difference in TSBP across the three-time points between people with and without diabetes (time point*participant group interaction) (P = 0.39) (**Table 12**). The change in mean TSBP is displayed in **Figure 3**. There was also no significant overall difference in TBPI between people with diabetes and people without diabetes (mean difference [95% CI]: -0.01 [-0.17, 03.16], P = 0.91). There was no significant difference in TBPI across the three-time points between persons with and without diabetes (P = 0.53) **(Table 12)**. The change in mean TBPI is displayed in **Figure 4**.

Figure 3. Mean toe systolic blood pressure between T1, T2, and T3



T1, pre dialysis measurement; T2, measurement at 1 hour of dialysis; T3, measurement 15 minutes prior to conclusion of dialysis.

Figure 4. Mean toe brachial pressure index between T1, T2, and T3



T1, pre dialysis measurement; T2, measurement at 1 hour of dialysis; T3, measurement 15 minutes prior to conclusion of dialysis

Sub-analysis: TSBP and TBPI in Participants with and without Loss of Protective Sensation

The sub-analysis included 15 participants with LOPS and 15 participants without LOPS. There was no overall difference in TSBP or TBPI between people with and without LOPS (P = 0.97, and P = 0.62, respectively) **(Table 13)**. There was no significant difference in TSBP variability across the three-time points between people with and without LOPS (time point*neuropathy interaction) (P = 0.67). However, there was a significant difference in TBPI variability across these time points between people with and without LOPS (P = 0.003). There was no significant difference in TSBP or TBPI variability based on the participant group (diabetes, no diabetes) between people with LOPS (participant group*neuropathy interaction) (P = 0.32, and P = 0.84, respectively).

Table 13. Mean toe pressure and TBPI in participants with loss of protective sensation

		No LOPS mean (95% CI)[1]	**LOPS** mean (95% CI)[1]
Mean toe pressure (mmHg)	**T1**	118.67 (96.42, 140.91)	125.77 (103.52, 148.01)
	T2	113.00 (90.76, 135.24)	115.00 (92.76, 137.24)
	T3	108.23 (85.99, 130.48)	111.50 (89.26, 133.74)
Mean toe brachial pressure index	**T1**	0.77 (0.65, 0.89)	0.80 (0.68, 0.92)
	T2	0.80 (0.67, 0.92)	0.77 (0.36, 0.89)
	T3	0.85 (0.74, 0.97)	0.75 (0.63, 0.87)

LOPS, loss of protective sensation; T1, pre-dialysis measurement; T2, measurement at 1 hour of dialysis; T3, measurement 15 minute prior to conclusion of dialysis
[1]Mean estimates adjusted for repeated measures on right and left feet (random effect)

Discussion

This study presents NZ data related to the assessment of TSBP and TBPI during dialysis. Data showed that TSBP decreased significantly from baseline (T1) to the second (T2) and third (T3) TSBP measurements in both participants with and without diabetes. This contrasts previous data indicating that TSBP was reduced only in persons with diabetes during and after dialysis. [43]. Kay et al. postulated that the differences in TSBP between participants with and without diabetes may have been attributable to the presence of neuropathic sympathectomy [43]. However, no data was provided indicating the prevalence of peripheral neuropathy in the study population.

TSBP decreased during dialysis, and this was reflected by a decrease in participants' brachial blood pressure during dialysis. The phenomenon of dialysis-induced hypotension is thought to be related to the rapid shift in water from the intravascular compartment during haemodialysis, an impaired arginine vasopressin hormone regulation system (which influences optimal plasma

osmolality function) and low vascular tone, which can be present in people with ESRD [178]. Intradialytic hypotension is a common phenomenon during dialysis and was the most common cause of reduced dialysis sessions during the study. While TBPI can remain stable throughout dialysis, less information is available about the specific diagnostic limits of TBPI measurement. The current literature estimates that a TBPI <0.7 could be diagnostic for PAD [179], with Høyer et al. suggesting <0.64 and recommending more large-scale studies to define the diagnostic accuracy of the TBPI for PAD [44]. Despite these criticisms, TBPI has been shown to have higher diagnostic sensitivity than ABI, particularly in the presence of medial arterial calcification, which is positively associated with KFRT [143].

The prevalence of LOPS within the study cohort was lower than previously reported in people with KFRT. Jones et al. estimated that upwards of 60% of people with ESRD have peripheral neuropathy [180]. Uremic neuropathy is a poorly understood side-effect of ESRD, thought to be related to uremic solutes, myoinositol and other molecules leading to a reduction of motor nerve conduction velocity [181]. It is difficult to differentiate between peripheral neuropathy and uremic neuropathy, and either neuropathy may have been present without loss of fine touch perception, which may have resulted in underreporting. Gold standard peripheral and uremic neuropathy assessment involves nerve conduction testing, which was not feasible for this study. LOPS testing through monofilament assessment is recommended in comprehensive foot examinations [182]. Additional neuropathy testing, such as biotheisiometer, tuning fork perception, and reflex testing, may have increased the reported rates of LOPS in this study. Nerve conduction testing would have allowed for more precise peripheral and uremic neuropathy documentation.

In comparing participants with and without LOPS, no significant differences in TSBP were observed at the three time points. However, an interesting finding emerged regarding TBPI, as it consistently decreased throughout the course of haemodialysis in participants with LOPS. This finding was unexpected, considering the stability of TSBP across the time points. This result may be attributed to the variability within the small sample of participants with LOPS, which limits the generalisability of the findings. Nevertheless, this discovery emphasises the need for further investigation into the relationship between TBPI, LOPS, and dialysis.

The study findings should be considered with regard to some limitations. First, the participants were recruited from community dialysis centres. Consequently, people with KFRT in the hospital setting were excluded. Patients dialysing in the hospital setting may be considered medically more unwell than the participants recruited from our study centres. This may explain some of our outcomes, such as the cohort not being classified as frail, the low levels of current PAD, previous ulceration, amputations, and revascularisation present in participants. The hospital dialysis centres were not considered appropriate for data collection due to the tighter turn-around times between

dialysing sessions and space issues in conducting data collection. Second, the resting time prior to the T1 TSBP was reduced from the 10 minutes stated in the Tehan et al. protocol [96] to five minutes to reduce the time burden on dialysis session times. This may have influenced the T1 result, but it was unavoidable given the tight time constraints surrounding dialysis sessions. TBPI has been shown to vary depending on rest time. Sadler et al. found a significant increase in TBPI when the premeasurement rest period was increased from 5 to 10 minutes [183]. Therefore, our initial T1 results may have been lower than expected; future studies should allow for greater resting time if possible.

Future work should consider comparing participants receiving community-based dialysis and hospital-based dialysis. TSBP and TBPI analysis from participants with established PAD, previous amputations, and LOPS would also provide more information on the appropriateness of obtaining these measures during haemodialysis. Additionally, longitudinal studies comparing results with ulceration, amputation, and revascularisation rates could assist in service planning within dialysis settings.

Conclusion

Clinically, the results from this study should encourage the use of the TBPI measurement on people while dialysing. TSBP reduces significantly throughout dialysis, and therefore, clinicians should be aware of this and take this into consideration. This reduction of TSBP during dialysis may impact the healing capacity of people with active ulceration and may also be relevant in the development of lower limb complications.

Chapter 5: Thesis Discussion

Persons with KFRT are at increased risk of lower limb amputation and ulceration due to the strong associations with PAD, peripheral neuropathy, and infection [69, 87]. Peripheral arterial disease in persons with KFRT is associated with lower health-related quality of life, cardiovascular morbidity, and mortality [184]. Accurate diagnosis of PAD in people with KFRT is important as PAD is a known determinant of lower limb amputation risk, all-cause mortality, and cardiovascular events [184]. Toe systolic blood pressure and TBPI are inexpensive, non-invasive testing techniques used to identify PAD [96]. Early identification of PAD through assessment of TSBP and TBPI could allow for the implementation of early and aggressive management regimens with the goal of reducing the development of peripheral ulceration and the subsequent rate of DRLLA.

The scoping review presented in Chapter 3 investigated research question 1 - '*What is the current evidence surrounding TSBP and TBPI in people with KFRT?'*. The review found limited data on the clinical utility of TSBP or TBPI in KFRT populations. Consequently, more data is required to ascertain the prognostic capacity of TSBP and TBPI in relation to PAD diagnosis and wound healing. The review found limited studies investigating the diagnostic accuracy of TSBP and TBPI in people with KFRT. The review showed that clearer and more specific TSBP and TBPI measurement protocols are needed for future studies, including pre-test resting time, resting position, no exercise, caffeine, and smoking before the test, due to the impact of these factors on TSBP results, which may influence TBPI results and subsequently PAD diagnosis. Additionally, consistent reporting of patient-level factors in future studies, including BMI, ethnicity, cause of ESRD, medication, and smoking history, is required to enable replication of study parameters and improve comparability between study cohorts.

Chapter 4 presented a pilot study investigating research question 2, *'What is the variability of TSBP and TBPI during haemodialysis in people with KFRT?*' The pilot study found that TSBP dropped significantly from time point one (before dialysis) to time point two (one hour into dialysis) and from time point one (before dialysis) to time point three (within the last 15 minutes of dialysis). The drop in TSBP may be significant with respect to the effect on wound healing capacity and the initial development of wounds in this population. It is known that TSBP and other additional measurements of peripheral circulation, such as trans-cutaneous peripheral blood flow, have been shown to reduce during HD and in the hours after [38], but no follow-up studies have been conducted on the relationship between these measures and healing rates or studies on interventions to reduce this phenomenon. The pilot study found that TBPI remained stable between the three-time points for all participants, which should encourage the use of this measure during HD.

The pilot study also investigated research question 3, *'Is there a difference in the amount of variability in TSBP and TBPI in people with and without diabetes whilst undergoing haemodialysis?*'. Data showed that TSBP dropped for all participants, with no statistically significant difference between persons with and without diabetes. This finding contrasts with Kay et al. [43], who found that TSBP decreased during HD, but only for persons with diabetes. Additionally, they found no differences between PWD and no-diabetes when comparing transcutaneous oxygenation levels and skin perfusion pressure [43]. The toe brachial pressure index remained stable during HD in both persons with and without diabetes, which may increase the validity of this measure during HD for PAD diagnosis, but larger-scale studies are required. From a clinical perspective, the data presented in Chapter 4 should encourage the use of TSBP and TBPI measurement on persons whilst dialysing.

The reduction in TSBP found in the pilot study may be significant in both ulcer development and prediction of wound healing capacity. However, this role is unknown. Lower limb foot ulcer development is highly prevalent in persons with KFRT due to the trilogy of peripheral neuropathy, PAD, and chronic inflammation [69]. When ulcerations occur in persons with KFRT, there are significant delays in wound healing processes due to poor regulation of essential minerals and enzymes such as zinc, urea, and iron and the high levels of anaemia, which is associated with poor tissue oxygenation [164]. Dialysis is known to cause significant uremic pruritis (itching) and can be an instigator for ulceration, with associated skin dryness and microcirculation delays negatively impacting the healing process [185]. Protein loss is another known adverse outcome of both HD and peritoneal dialysis, which is known to affect wound healing negatively. High levels of infection are a major factor in the delay of wound healing, with known higher levels of local and systemic infection rates in persons with KFRT and poorer outcomes from treatment of infection, resulting in higher hospitalisation rates [186]. Further evidence is required to understand the prognostic value of TSBP in persons with KFRT, as previous evaluations of TSBP have not focused on this high-risk subgroup. Additionally, further research into arteriovenous shunting from the peripheral circulatory system to vital organs which appears to occur during haemodialysis, and the impact of this on wound healing. This phenomenon is noted in hand ischaemia, or 'steal' syndrome, which can occur following brachial access placement and results in tingling, numbness and, in rare cases, gangrene in the hand [187], or additionally highlighted by interdialactyic hypotension, which develops primarily due to reduced blood volume during HD [188].

The pilot study also found that 50% of participants had LOPS. Loss of protective sensation is a known symptom of peripheral neuropathy [194] and was evaluated during this study using 10g monofilament. A sub-analysis between LOPS and no LOPS populations found significant differences in TBPI across the three-time points, with LOPS participants having a reduction in TBPI only. TSBP did not differ significantly through the 3 timepoints between persons with and without

LOPS. The clinical importance of this is unknown, and further investigation is required. Uremic neuropathy is known to be prevalent in 60-100% of persons with KFRT and is thought to result from an accumulation of waste products, presenting as peripheral neuropathy [189]. Uremic neuropathy is a distal, symmetrical, sensorimotor polyneuropathy that typically affects the lower limb, leading to axonal degradation and loss [189]. Even advances in renal replacement techniques have failed to reduce the development of significant neuropathy in persons with KFRT, and the only known treatment for this is kidney transplantation [190]. Additional testing for peripheral neuropathy can also be investigated to allow for accurate diagnosis of this condition.

Strengths and Limitations

This thesis presents novel research investigating an area of clinical practice guided by limited evidence. Strengths of the scoping review include the systematic approach taken, which will ensure an accurate representation of literature and the establishment of a methodology framework for future studies in this area. The data presented in the pilot study demonstrated that TSBP and TBPI are measures that can be obtained whilst people are receiving haemodialysis, allowing for future research to explore the clinical utility of the measures. Limitations noted within the thesis include the pilot study only including 30 participants, and as such, cannot be fully generalised to wider KFRT populations. The pilot study was undertaken in a community HD setting within one city, and as such, the results cannot be generalised to hospital or home-based dialysis populations or peritoneal dialysis populations.

Future Directions

Future Direction 1 - Defining the Role of the Podiatrist

1. This thesis has shown that there is limited evidence investigating TSBP and TBPI in persons with KFRT; consequently, current practice is guided by a low volume of evidence. It is yet to be determined if non-surgical PAD interventions in persons with KFRT are effective in reducing either mortality, ulceration, or amputation rates. A prospective study, with the intervention of exercise, medical management, and smoking cessation programs, could be designed and combined with close podiatry follow-up, including TSBP and TBPI monitoring. Specifically, to observe if podiatric peripheral vascular monitoring and associated expedited referral for treatment reduce the incidence of ulcer development and amputation rates and improve mortality and morbidity through appropriate cardiology referral. Additional non-invasive methods of monitoring peripheral circulation, which podiatrists can undertake, such as skin perfusion testing or laser Doppler review, could contribute to a wider understanding of the effects of haemodialysis and help define the most appropriate vascular testing for this population.

2. The role of podiatrists in identifying PAD has not been thoroughly explored from a health-economic perspective, and as PAD can anticipate the diagnosis of cardiovascular disease, this screening is especially important and appropriate for persons with KFRT. A potential study evaluating the value of early PAD diagnosis, which can be undertaken by podiatrists, with appropriate referral to cardiovascular services upon PAD diagnosis, could validate early appropriate cardiovascular screening and treatment programs, which could allow for reduced mortality rates in this population [191].

3. Research comparing early- and late-stage CKD populations with KFRT populations could clarify if podiatric PAD diagnosis and early intervention are effective in reducing PAD transitioning to CLTI. These results could be related to a cost-benefit analysis examining the costs of expanding the podiatric screening program compared to the costs saved from potential reductions in amputations and ulcerations in persons with KFRT and CKD. This makes it possible to determine whether podiatric care positively impacts health economics.

4. Mixed methodology review examining podiatrists' understanding of the measurement of TSBP and TBPI within their practice is required. An in-depth examination of current practices of podiatrists' knowledge and understanding regarding the clinical utility of TSBP and TBPI will be developed. The initial quantitative practitioner survey will examine the protocol for undertaking TSBP and TBPI, the rationale for the use of these measures, and referral outcomes from TSBP and TBPI results within their clinics. Follow-up qualitative analysis will be undertaken using focus groups or one-on-one interviewing, delving into the beliefs around TSBP and TBPI use. The relationship between TSBP and TBPI to PAD and cardiovascular disease, especially in high-risk populations such as those with advanced kidney disease, requires closer analysis, including analysis of referral beliefs by podiatrists. This will guide further education and training of the podiatric workforce to ensure that the current practice is fit for purpose.

Future Direction 2 - Determination of Diagnostic Thresholds

Clarification of PAD screening protocols is required for persons with KFRT. The diagnostic threshold and accuracy of TBPI for PAD diagnosis need a clear definition. Additionally, clarification is required on the ideal timing and frequency of screening for PAD in people with KFRT. Larger prevalence studies adhering to TSBP protocol guidelines with patient-level factors managed appropriately will allow for the true prevalence of PAD in this high-risk population to be known. The toe brachial pressure index and TSBP are important non-invasive techniques for PAD diagnosis and wound healing prognosis. A large, multi-site study, with consistent and high-quality reporting of

the internationally accepted protocol, will allow for the determination of PAD prevalence levels in ESRD populations.

Future Direction 3 - Diagnostic Accuracy

The stability of TBPI measurement during HD reported in the pilot study should encourage using this measure for diagnosing PAD, but larger studies are required. Toe brachial pressure index could be compared against internationally accepted PAD diagnosis guidelines and further validated against high-quality angiographic imaging methods such as magnetic resonance angiography, computed tomography angiography, or duplex ultrasound imaging [20]. This will allow for the determination of TBPI diagnostic accuracy as a predictor of PAD in KFRT populations.

Future Direction 4 - Loss of Protective Sensation

The pilot study found that in participants with LOPS, TBPI reduced during HD and remained stable in participants without LOPS. This phenomenon requires additional review, which could be investigated with the expansion of the TBPI testing noted within this future direction. Should this finding remain consistent, then review by neurology teams for exploration and explanation is indicated. As found in the pilot study, further neurological testing than monofilament, such as nerve conduction testing or biotheisiometer testing, may show different levels of peripheral neuropathy in KFRT populations, and this should be compared to TBPI stability to understand if more advanced peripheral neuropathy correlates to TBPI reduction during HD and relates to amputation, ulceration, and mortality levels.

Future Direction 5 - Peritoneal Dialysis and Dialysis Setting

The above future directions will benefit from additional studies on sub-groups within KFRT populations, such as those on peritoneal dialysis compared with persons on hospital, community, or home HD. Each subgroup should be evaluated alongside ulceration, amputation, and mortality statistics to determine if there are variations in services, and if marked differences in outcomes are found, this may impact service delivery and renal best practice recommendations. From the scoping review in Chapter 3, we can see that only 14% of study participants were undergoing peritoneal dialysis, meaning little is understood about this population regarding TSBP and TBPI. Information on the above outcomes may guide podiatry and renal collaborations, impact best practice guidelines for renal team planning, and allow for appropriate health economic allocation to areas with greater need.

Future Direction 6 - Ethnicity Considerations for Future Research

Ethnicity and poverty are strongly related to kidney failure, with influences related to genetics, combined with restricted access to new medications, reduced access to healthy foods and wider determinants such as environmental pollution all playing a part in chronic kidney disease progressing to KFRT [192]. Health researchers need a better understanding of how social stratification, such as ethnicity, is associated with social exposures and contributes to health disparities. This confirms the need for research into culturally appropriate care in PAD diagnosis, with a focus on promoting a specific review of ethnic minorities and people of low socioeconomic status in screening and intervention programs, as discussed in future directions 1-4. The above future directions require specific and direct investigation of the outcomes of Māori and other ethnic minorities, as well as for socio-economically disadvantaged populations. As noted in the scoping review of Chapter 3, 81% of studies related to TSBP or TBPI and KFRT did not report ethnicity. This occurs despite international guidelines recommending reporting of ethnicity to reduce the known disparities between ethnic groups [159]**.** Culturally appropriate care and research should be provided in a manner that meets the needs of specific ethnic groups, and this can be achieved through culturally competent consultation, which should be fundamental within research design and consultation [193].

Thesis Conclusion

Toe systolic blood pressure and TBPI are important non-invasive lower limb arterial status measures and have important prognostic capacity for wound healing. The ankle-brachial index is the globally accepted non-invasive test for identifying PAD, but it is potentially inaccurate in persons with KFRT due to known high rates of MAC. Subsequently, TSBP and TBPI are potentially more acceptable measures in this population.

The thesis demonstrated many novel findings related to the measures of TSBP and TBPI in populations receiving dialysis. First, previous research using TSBP and TBPI in populations receiving dialysis varied considerably in methodology, with inconsistent reporting of screening protocols and test conditions and poor reporting of patient-level factors. Consequently, the true prevalence of PAD within KFRT populations is difficult to determine. Second, there is a paucity of literature detailing the prognostic capacity, diagnostic accuracy, and limited exploratory research undertaken on TSBP or TBPI in people with KFRT. Third, ethnicity-based data is underreported in research populations with KFRT despite these populations having a higher burden of KFRT globally. Fourth, the pilot study revealed reduced TSBP, but TBPI measurement remained stable throughout an HD session. Fifth, no significant differences between PWD and no-diabetes were found in either TSBP or TBPI measurements. Finally, for persons with LOPS, the TBPI reduced significantly during the three time points, which contrasted with persons with no LOPS, in which the results were stable.

The thesis has identified numerous pathways for future research to investigate TSBP and TBPI clinical utility in KFRT populations. Notably, research is required to understand the role and potential impact of the podiatrist in the renal care setting and determine the ability of changes in TSBP and TBPI to predict wound healing and lower limb amputation. Additionally, there are significantly poorer health outcomes related to KFRT in Indigenous and economically disadvantaged populations. Therefore, due to Ti Tiriti o Waitangi and the principle of equity that requires the Crown's commitment, there is an urgent need in the NZ health sector to prioritise assessment in this population to achieve equitable health outcomes for Māori.

The findings presented in this thesis should promote the use of TSBP and TBPI during HD for diagnosing PAD. A timely identification may enable optimal management of PAD, for example, through supervised exercise programs, which are an accepted first-line treatment for people with PAD, as well as referrals for smoking cessation and specialist medical review. Podiatrists should be an integral part of HD centres and maintain close relationships with vascular specialists to facilitate rapid referral to these services in the event of progressive PAD, CLTI, or wound deterioration and ultimately provide optimal foot care for this population.

Chapter 6: References

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7. Appendices

Appendix 1

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011
hdecs@health.govt.nz

Ethics reference: 2022 FULL 13482

3 October 2022

Mrs Rachel Carle

90 Akoranga Drive
Nothcote
Auckland
0627
New Zealand

Tēnā koe Mrs Carle

APPROVAL OF APPLICATION

Study title: Variability of toe pressures during haemodialysis: Comparison of persons with and without diabetes.

I am pleased to advise that your application was **approved** by the Central Health and Disability Ethics Committee (the Committee) with non-standard conditions. This decision was made through the FULL pathway.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked about the two groups the researchers are comparing. The Researcher explained they are diabetics undergoing haemodialysis & non-diabetics undergoing haemodialysis. This allows for direct comparison with a study that was done in Canada.
2. The Committee asked if all participants get the same participant information sheet. The Researcher confirmed that all participants get the same participant information sheet.
3. The Committee asked if the half and half diabetic vs non-diabetic groups are feasible to recruit. The Researcher explained they are optimistic they will be able to recruit 20 in each group.
4. The Committee asked if there are any plans to match non-diabetics to diabetics such as gender, age etc. The Researcher explained once they have enough potential participants for the study, they will look carefully at matching characteristics between groups but they must co-operate with the dialysis team.
5. The Committee asked if the researchers will be putting pre-diabetics into the same group as non-diabetics. The Researcher explained the plan is that pre-diabetics would not be recruited.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee which require addressing by the Researcher are as follows.

6. Please amend section D22.1, $50 gift voucher as koha is potentially taxable so make sure that this is an expression of gratitude, not reimbursement for time or effort . researcher will need to discuss this with the university and decide how best to proceed.
7. Please include the length of time that a participant cannot have caffeine before the tests.

The Committee requested the following changes to the Participant Information Sheet and Consent Form (PIS/CF):

8. Please update the ACC statement, the one submitted is out of date.
9. Please add on page 5 that you will not be able to be identified from reports, presentations, or publications.
10. Please amend page 3 of the PIS: change information to be collected to “reviewed”.
11. Please mention the 15-minute interview earlier in the participant information sheet.
12. Please explain where the money is coming from, as your study has no sponsor listed. If there is the grant from the university, please include this.
13. Please change Māori health support to Māori cultural support
14. Please remove yes/no tick boxes unless truly optional on the consent forms.
15. Please remove the bullet point in the consent form about fitting inclusion criteria: that is something the researcher is responsible for, not the participant.
16. Please note that if the GP needs to be informed, please include this first in the participant information sheets or remove this statement.
17. Please remove from the data management plan the statement: no data will be used for commercial purposes & the mention of under ownership rights that information from the study may lead to the development of a commercial product.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study’s sponsor, to ensure that these conditions are met. No further review by the Central Health and Disability Ethics Committee is required.

Standard conditions:

- Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
- Before the study commences at *each given* locality in New Zealand, it must be authorised by that locality in Ethics RM. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

- please address all outstanding ethical issues raised by the Committee
- please update the Participant Information Sheet and Consent Form, taking into account the feedback provided by the Committee. (National Ethical Standards for Health and Disability Research and Quality Improvement, para 7.15 – 7.17).

Non-standard conditions must be completed before commencing your study, however, they do not need to be submitted to or reviewed by HDECs.

If you would like an acknowledgement of completion of your non-standard conditions you may submit a post approval form amendment through the Ethics Review Manager. Please clearly identify in the amendment form that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see paragraphs 125 and 126 of the *Standard Operating Procedures for Health and Disability Ethics Committees (SOPs)*.

After HDEC review

Please refer to the *SOPs* for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 03 October 2023.

Participant access to compensation

The Central Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialed. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation.

Further information and assistance

Please contact the HDECs Secretariat at hdecs@health.govt.nz or visit our website at www.ethics.health.govt.nz for more information, as well as our General FAQ and Ethics RM user manual.

Nāku noa, nā

Mrs Helen Walker

Chair

Central Health and Disability Ethics Committee

Encl: Appendix A: documents submitted

Appendix B: statement of compliance and list of members

Appendix A: Documents submitted

Document Type	File Name	Date	Version
Scientific Peer Review	Peer review		
Other	1 page information sheet		
Other	Data collection Procedure		
Other	Clinical report form		
PIS/CF	Information sheet and consent form		
Protocol	study protocol		
Data Management Plan	Data management plan		
CV for Coordinating Investigator	CV Rachel Carle		

Review Document Type	Review Document File Name	Review Document Version Date

Appendix B: Statement of compliance and list of members

Statement of compliance

The Central Health and Disability Ethics Committee

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008712) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Mrs Helen Walker (Lay (consumer/community perspectives)), Dr Cordelia Thomas (Lay (the law)), Ms Julie Jones (Non-lay (intervention studies)), Ms Sandy Gill (Lay (consumer/community perspectives)), Dr Patries Herst (Non-lay (intervention studies)), Ms Patricia Mitchell (Non-lay (health/disability service provision)), Ms Jessie Lenagh-Glue (Lay (ethical and moral reasoning)), Ms Albany Lucas (Non-lay (observational studies)).

Unless members resign, vacate or are removed from their office, every member of HDEC shall continue in office until their successor comes into office (HDEC Terms of Reference).

http://www.ethics.health.govt.nz

Appendix 2

Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

2 November 2022

Matthew Carroll
Faculty of Health and Environmental Sciences

Dear Matthew

Re Ethics Application: **22/309 Variability of toe pressures during haemodialysis. Comparison of persons with and without diabetes.**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 2 November 2025.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.
8. AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: rachelcarle@hotmail.com; sarah.stewart@aut.ac.nz

Appendix 3

4 October 2022

Te Whatu Ora
Health New Zealand

Mrs Rachel Carle

90 Akoranga Drive
Nothcote
Auckland
0627
New Zealand

Kia ora / Dear Mrs Carle,

Locality approval for research – Te Toka Tumai Auckland

The Research Review Committee Te Toka Tumai Auckland (RRC) would like to thank you for the opportunity to review your study and has given approval for your research project.

A+ 9620 (FULL 13482) Variability of toe pressures during haemodialysis: comparison of persons with and without diabetes

Your locality approval is dependent on the Research Office having up-to-date information and documentation relating to your research and being kept informed of any changes to your study. It is your responsibility to ensure you have kept Ethics and the Research Office up to date and have the appropriate approvals. Te Toka Tumai Auckland locality approval may be withdrawn for your study if you do not keep the Research Office informed of the following:

- Any communication from Ethics Committees, including confirmation of annual ethics renewal
- Any amendment to study documentation
- Study completion, suspension or cancellation

More detailed information is included on the following pages. If you have any questions please do not hesitate to contact the Research Office.

Ngā mihi/Yours sincerely,

Mary-Anne Woodnorth
Manager, Research Office, Auckland City Hospital, on behalf of RRC
Te Toka Tumai Auckland

TeWhatuOra.govt.nz
PO Box 92024, Auckland, 1142
Waea pūkoro: +64 9 307 4949 ext 23854

Te Whatu Ora
Health New Zealand

POST-APPROVAL REPORTING

Your Ethical and Institutional approval is dependent on the Research Office (RO) having up-to-date information and documentation for your research and being kept informed of any changes to your study. This applies even if Te Toka Tumai Auckland is not the main site for the study.

Failure to provide any required reports on progress or changes may result in your locality approval being withdrawn. This will not be reinstated until all issues have been resolved.

All documents / communications must be referenced with the **project number**.

Ethics		
HDEC Annual Progress Report (if study approved by an HDEC)	Use HDEC PAF form, complete and submit **BEFORE** anniversary date of original HDEC approval	• send HDEC approved progress report letter to the RO
Major amendments, design, CI, safety, temporary stops etc. (see HDEC SOP section 11 for definitions)	Complete Te Toka Tumai Auckland amendment form detailing changes, mark up changes in relevant documents. Use HDEC PAF form, complete and submit and obtain HDEC approval	• send fully signed Te Toka Tumai Auckland amendment form to RO – plus • new protocol and PIS-CF • send copy of HDEC approval letter to RO when received
Financial amendments, including changes in study visits, tests, funding etc.	Liaise with research accountant and adjust budget accordingly. If financial amendment is related to a major amendment also follow requirements for a major amendment.	• Send revised budget using template to RO • send fully signed Te Toka Tumai Auckland amendment form to RO

Continued on following page...

Minor amendments	Seldom required. Only report minor amendments that will a) impact resources, b) impact access to services for patients NOT in the study, c) require review of revised legal documents, d) involve new service areas	• If required send fully signed Te Toka Tumai Auckland amendment form to RO
Critical serious adverse event (SAE) reporting	Patients seriously harmed as a result of their participation in a study must be reported to the RO	• Follow SOP for reporting critical SAEs
High risk studies	Studies deemed by RRC to be of high risk must notify locality patient enrolments and SAEs to RRC	• notify RO when new local patients are enrolled in the study • immediately notify RO of any SAEs for local patients • send detailed SAE report to RO when available
Notification of conclusion of study	Complete HDEC PAF form and submit	• Send approved notification of conclusion of study letter to RO • Inform RO if all finance elements also complete
Final Report	Complete HDEC PAF form, upload final report and submit	• Send final report and HDEC approved final report letter to RO • Inform RO when all finance elements also complete

Legal		
Contracts, indemnities, agreements, insurance certificates, etc.	All legal documents must be reviewed and approved before signing. Revise budget where relevant	• Send all legal documents to RO • Send revised budget using template to RO where relevant

All documents must be referenced with the Te Toka Tumai Auckland project number and can be sent via email to: ResearchOffice@adhb.govt.nz.

For further information go to: http://www.adhb.health.nz/health-professionals/research/

Appendix 4

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	15
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	16
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	17-18
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	15 and 18
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N/A
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	18-19
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	19-21
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	21
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	21
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	18-21
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	20
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	20-22

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	21
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	22, 23, 25, 26, 29, 30
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	22, 23, 25, 26, 29, 30
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	22, 23, 25, 26, 2
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	31-34
Limitations	20	Discuss the limitations of the scoping review process.	33
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	34
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	N/A

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.