# An investigation into relationships among neural, vascular and osseous factors in the diabetic foot

*Submitted for the degree of Doctor of Philosophy*

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# Statement of Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

Alex Louise Barwick

# Statement of Authorship

I hereby certify that the work embodied in this thesis contains published papers of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications.

Alex Louise Barwick

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# Contents

# Abstract

The social and financial cost of diabetes and associated lower limb complications is increasing markedly. Interaction between neurological and vascular dysfunction in diabetes are thought to influence bone in the periphery, predisposing to pathology such as Charcot foot, a rare but debilitating joint disease. However, there is a lack of conclusive evidence relating neurological and vascular function to peripheral bone health in people with diabetes. This thesis presents an investigation into relationships among neuropathy, vascular dysfunction and foot bone health in those with diabetes. Such information is useful in the prevention, diagnosis and management of lower limb complications of diabetes.

The research is designed to address two central hypotheses:

- That those with diabetic neuropathy have altered vascular reactivity in the feet
- That neuropathy induced vascular changes in those with diabetes, contribute to a reduction in bone mineral density in the feet

The research includes, firstly, a systematic review of current research related to foot bone strength in people with diabetic neuropathies with a meta-analysis of obtained data. Inconsistent findings were observed among the ten included studies and the meta-analysis was equivocal. Furthermore, the literature was limited by methodological quality and gaps within the literature were observed including the lack of data on foot bones other than the calcaneus prompting the need for further research.

Secondly, two studies developing methodologies required for the research were performed. A reliability study of techniques for assessing post-occlusive reactive hyperaemia at the hallux as a measure of microvascular function was performed. The study found that its measurement in the hallux, using laser Doppler with a probe heated to thermoneutral, is a reliable method of measuring microvascular function for use in research. The most reliable parameters were peak as a percentage of baseline and the index of the area under the curve post-occlusion to pre-occlusion. A reliability study of computed tomography derived densitometry of all tarsal and metatarsal bones was also performed.

The study found that foot bone density can be reliably measured in the tarsals and metatarsals using averaged regions of interest on computed tomography scans. Trabecular bone density was more reliably derived than that of cortical bone. These two methodologies, measurement of post-occlusive reactive hyperaemia at the hallux and bone density measurement in the foot, were used in the final two studies addressing the central hypotheses.

A cross-sectional study was performed to test the hypothesis that those with diabetic neuropathy have altered vascular reactivity in the feet. This approach was taken to examine the complex relationships among diabetic neuropathy types and vascular reactivity in a clinically relevant population, accounting for important confounders in the design and statistical analyses. The study found that the presence of sensory neuropathy was predictive of a slower time to peak perfusion following occlusion.

Finally, a cross-sectional case-control study was performed to test the hypothesis that neuropathy induced vascular changes in those with diabetes, contribute to a reduction in bone mineral density in the feet. The study compares the foot bone density of those with diabetic neuropathy with a diabetes control group. No clear association was demonstrated. Additional analyses were performed to observe potential relationships between subtype of neuropathy and foot bone density, and microvascular dysfunction and foot bone density. No relationships were observed.

These results, limited by the cross-sectional design of the studies, suggest that whilst peripheral neuropathy is associated with altered microvascular function, this may not have an impact on foot bone density in a manner that predisposes to pathology.

# List of Publications, Manuscripts, and Conference Abstracts

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Publications

Barwick, A.L., Janse de Jonge, X. A. K., Tessier, J. W., Ho, A. & Chuter, V. H. *The effect of diabetic neuropathy on foot bones: a systematic review and meta-analysis.* Diabet Med, 2014. 31(2): p. 136-147

Barwick, A., Lanting, S. & Chuter, V. *Intra-tester and inter-tester reliability of post-occlusive reactive hyperaemia measurement at the hallux.* Microvasc Res, 2015. 99(0): p. 67-71

In Press (see Appendix H)

Barwick, A. L., Tessier, J. W., Janse de Jonge, X., & Chuter, V. H. (2016). *Foot bone density in diabetes may be unaffected by the presence of neuropathy.* J Diabet Complications. In Press

Manuscripts under review

'Reliability of computed tomography derived foot bone density measurements in people with diabetes'

'Peripheral sensory neuropathy is associated with altered post-occlusive reactive hyperemia in the diabetic foot'

Conference Abstracts (see Appendix I)

Sydney Diabetic Foot Conference – May 2013 – The effect of diabetic neuropathy on peripheral bone: a systematic review and meta-analysis

NSW Australian Podiatry Association Conference – Sydney, April 2014 – The effect of diabetic neuropathy on peripheral bone: a systematic review and meta-analysis

Australasian Podiatry Council Conference – Dunedin, New Zealand, November 2014 – The effect of diabetic neuropathy on peripheral bone: a systematic review and meta-analysis

Australasian Podiatry Council Conference – Gold Coast, May 2015

Barwick, A., Lanting, S., & Chuter, V. *Intra- and inter-tester reliability of post-occlusive reactive hyperaemia measurement at the hallux. Australasian Podiatry Conference*. JFAR, 2015. 8(2): p. O1

European Association for the Study of Diabetes Conference – Stockholm, Sweden, September 2015

Barwick, A., Tessier, J., Janse de Jonge, X., & Chuter, V. *Initial findings in the relationship between diabetic peripheral neuropathy and microvascular reactivity in the foot. European Association for the Study of Diabetes Annual Meeting.* Diabetologia, 2015. 58(S1): p. S502

# List of Abbreviations

| | |
|---|---|
| AGE | advanced glycated end-product |
| ANS | autonomic nervous system |
| BMD | bone mineral density |
| CAN | cardiac autonomic neuropathy |
| CGRP | calcitonin gene-related peptide |
| CN | neuropathic osteoarthropathy |
| HU | Hounsfield units |
| ICC | Intra-class correlation coefficient |
| LFN | large fibre neuropathy |
| LOA | limits of agreement |
| MRI | magnetic resonance imaging |
| OPG | osteoprotogerin |
| PORH | post-occlusive reactive hyperaemia |
| PRISMA | preferred reporting items for systematic reviews and meta-analyses |
| RAGE | receptor for advanced glycated end-product |
| RANK-L | receptor activator of nuclear factor kappa-B ligand |
| SEM | standard error of measurement |
| SFN | small fibre neuropathy |

| | |
|---|---|
| sRAGE | soluble receptor for advanced glycated end-product |
| VPT | vibration perception threshold |

# List of Appendices