

# **THE EFFECT OF NON-SURGICAL PERIODONTAL INTERVENTION ON PULSE WAVE VELOCITY: A MARKER OF ARTERIAL STIFFNESS AND FUNCTION**

**KOSTAS KAPELLAS**

BOH, BScDent (Hons)

Thesis submitted for the degree of Doctor of Philosophy



**THE UNIVERSITY**  
*of* **ADELAIDE**

School of Dentistry

The University of Adelaide

October 2014

# TABLE OF CONTENTS

|  |      |
|--|------|
| LIST OF TABLES .....   | iv   |
| LIST OF FIGURES .....  | v    |
| PREFACE .....  | vi   |
| ABSTRACT .....   | vii  |
| DECLARATION .....  | viii |
| PUBLICATIONS ARISING FROM WORK CONTAINED WITHIN THIS THESIS .....            | ix   |
| ACKNOWLEDGEMENTS .....   | xi   |
| 1 INTRODUCTION .....   | 1    |
| 1.1 Concepts on atherogenesis.....   | 1    |
| 1.2 Current understanding of aetiology - infection in vascular disease ..... | 3    |
| 1.3 Surrogate markers of cardiovascular disease.....                         | 10   |
| 1.4 Surrogate measures of cardiovascular status .....                        | 13   |
| 1.4.1 Pulse Wave Velocity (PWV).....   | 13   |
| 1.4.2 Flow Mediated Dilatation.....  | 16   |
| 1.4.3 Carotid Intima Media Thickness .....                                   | 19   |
| 1.5 Periodontal intervention studies and cardiovascular events .....         | 22   |
| 1.6 Indigenous Australian health .....                                       | 23   |
| 1.7 Study aims .....   | 25   |
| 1.8 References .....   | 28   |
| 2 GENERAL MATERIALS AND METHODS .....  | 41   |
| 2.1 Project outline.....   | 41   |
| 2.2 Eligibility criteria.....  | 41   |
| 2.3 Study design .....   | 42   |
| 2.3.1 Visit 1: Baseline.....   | 42   |
| 2.3.2 Visit 2: 3-month follow-up.....  | 43   |
| 2.3.3 Visit 4: 12-month follow-up .....                                      | 43   |
| 2.4 Oral assessment .....  | 44   |
| 2.5 Location of recruitment/intervention.....                                | 45   |
| 2.6 Randomisation method .....   | 46   |
| 2.7 Assessment of arterial stiffness .....                                   | 46   |
| 2.8 Blood draw and urine sampling.....                                       | 47   |
| 2.9 Anthropometric measurements.....   | 48   |
| 2.10 Periodontal intervention.....   | 49   |
| 2.11 Data quality control measures .....                                     | 50   |
| 2.11.1 Oral Assessment method .....  | 50   |
| 2.11.2 PWV method .....  | 51   |

|        |  |     |
|--------|--|-----|
| 2.12   | Sample size .....  | 51  |
| 2.13   | Statistical analysis.....  | 53  |
| 2.14   | Data collection .....  | 53  |
| 2.14.1 | Self-Reported.....   | 53  |
| 2.15   | Key variables .....  | 54  |
| 2.15.1 | Dependent variable .....   | 54  |
| 2.15.2 | Independent variables .....  | 54  |
| 2.16   | Study aims and hypotheses.....   | 54  |
| 2.17   | References .....   | 56  |
| 3      | PERIODONTAL DISEASE AND DENTAL CARIES AMONG INDIGENOUS AUSTRALIANS LIVING IN THE NORTHERN TERRITORY, AUSTRALIA.....                    | 58  |
| 4      | ASSOCIATIONS BETWEEN PERIODONTAL DISEASE AND CARDIOVASCULAR SURROGATE MEASURES AMONG INDIGENOUS AUSTRALIANS .....                      | 68  |
| 4.1    | Online Supplement .....  | 70  |
| 5      | EFFECTS OF FULL-MOUTH SCALING ON THE PERIODONTAL HEALTH OF INDIGENOUS AUSTRALIANS: A RANDOMISED CONTROLLED TRIAL .....                 | 82  |
| 6      | THE EFFECT OF PERIODONTAL THERAPY ON ARTERIAL STRUCTURE AND FUNCTION AMONG ABORIGINAL AUSTRALIANS: A RANDOMISED CONTROLLED TRIAL ..... | 94  |
| 6.2    | Online supplement.....   | 106 |
| 6.2.1  | Expanded methods.....  | 106 |
| 6.2.2  | Changes to original study protocol.....  | 107 |
| 6.2.3  | Participant enrolment and allocation .....   | 107 |
| 6.2.4  | Oral assessment methods to measure periodontal status .....  | 107 |
| 6.2.5  | Statistical methods to analyse periodontal parameters .....  | 108 |
| 6.2.6  | Periodontal Intervention .....   | 108 |
| 6.2.7  | Vascular measures .....  | 109 |
| 6.2.8  | Cardiovascular risk assessment .....   | 110 |
| 6.2.9  | Self-reported questionnaire.....   | 111 |
| 6.2.10 | Reproducibility of measurements .....  | 111 |
| 6.2.11 | Sample size .....  | 111 |
| 6.2.12 | Statistical analysis.....  | 112 |
| 6.3    | Validation of carotid-dorsalis pedis PWV with carotid-femoral PWV .....  | 112 |
| 6.3.1  | Methods .....  | 112 |
| 6.4    | Expanded results.....  | 114 |
| 6.4.1  | Periodontal parameters .....   | 114 |
| 6.4.2  | Blood lipids, Asymmetric dimethylarginine (ADMA) & high sensitivity C-reactive protein (hsCRP) .....                                   | 114 |

|       |   |     |
|-------|---|-----|
| 6.5   | Validation of carotid-dorsalis pedis PWV with carotid-femoral PWV .....   | 115 |
| 6.5.1 | Results .....   | 115 |
| 6.6   | Expanded discussion.....  | 116 |
| 6.7   | References .....  | 120 |
| 7     | GENERAL DISCUSSION AND CONCLUSIONS.....                                   | 135 |
| 7.1   | Summary of findings .....   | 135 |
| 7.2   | General discussion.....   | 137 |
| 7.3   | Study Limitations .....   | 140 |
| 7.4   | Concluding statement .....  | 142 |
| 7.5   | Future directions .....   | 143 |
| 7.6   | General overview of periodontal disease/cardiovascular associations ..... | 145 |
| 7.7   | References .....  | 147 |
| 8     | APPENDICES .....  | 150 |
| 8.1   | Manuscripts relevant to thesis .....                                      | 150 |
| 8.2   | Supplementary analysis to Chapter 6 .....                                 | 159 |
| 8.2.1 | Results .....   | 159 |
| 8.2.2 | Stratified analysis by sex .....  | 159 |
| 8.2.3 | Conclusion.....   | 159 |

## LIST OF TABLES

|  |     |
|--|-----|
| <b>Supplement Table 1:</b> Oral Assessment Means Stratified by Quartile Extent PPD $\geq$ 4mm.....   | 70  |
| <b>Supplement Table 2:</b> Baseline Characteristics of Completed versus Lost to Follow-up (Baseline Data Reported).....                        | 122 |
| <b>Supplement Table 3:</b> Periodontal Therapy and Change in Carotid Intima-Media Thickness – Subgroup Analyses.....                           | 124 |
| <b>Supplement Table 4:</b> Periodontal Parameters at Baseline and 12 Months (Complete-Case Analysis).....                                      | 125 |
| <b>Supplement Table 5:</b> Baseline Comparisons of Means Stratified by Sex.....  | 126 |
| <b>Supplement Table 6:</b> Change in Pulse Wave Velocity Stratified by Sex.....  | 127 |
| <b>Supplement Table 7:</b> Baseline-Carried-Forward Analysis.....  | 128 |
| <b>Supplement Table 8:</b> Correlation of Cardiovascular Risk Factors with Carotid-Femoral and Carotid-Dorsalis Pedis Pulse Wave Velocity..... | 129 |
| <b>Appendix Table 1:</b> Change in Anthropometric, Cardiovascular Risk Factors and Metabolic Markers – 3 Months Post-Intervention*.....        | 160 |
| <b>Appendix Table 2:</b> Change in Anthropometric, CVRFs & Metabolic Markers – 3 Months Post-Intervention Limited to Males*.....               | 161 |
| <b>Appendix Table 3:</b> Change in Anthropometric, CVRFs & Metabolic Markers – 12 Months Post-Intervention Limited to Males*.....              | 162 |
| <b>Appendix Table 4:</b> Change in Anthropometric, CVRFs & Metabolic Markers – 3 Months Post-Intervention Limited to Females*.....             | 163 |
| <b>Appendix Table 5:</b> Change in Anthropometric, CVRFs & Metabolic Markers – 12 Months Post-Intervention Limited to Females*.....            | 164 |
| <b>Appendix Table 6:</b> Multiple Imputation of Blood Pressure (3 & 12-months).....  | 165 |

## LIST OF FIGURES

|  |     |
|--|-----|
| <b>Figure 2.1:</b> Study plan flow-diagram. ....   | 43  |
| <b>Figure 6.1:</b> CONSORT flow diagram (3-month PWV n=169) & (Annual cIMT n=168). ....  | 130 |
| <b>Figure 6.2:</b> Periodontal therapy and 12-month change in carotid intima-media thickness. ....                                 | 131 |
| <b>Figure 6.3:</b> Change in PWV [baseline - 3-month] (top panel) & [baseline - 12-month] (bottom panel). ....                     | 132 |
| <b>Figure 6.4:</b> Agreement between carotid-femoral pulse wave velocity and carotid-dorsalis pedis pulse wave velocity. ....      | 133 |
| <b>Figure 6.5:</b> Scatter plot of change in extent PPD $\geq$ 4mm and change in maximum carotid intima-media thickness (mm). .... | 134 |
| <b>Figure 8.1:</b> Change in PWV and blood pressure (baseline to 3-month). ....  | 166 |
| <b>Figure 8.2:</b> Change in PWV and blood pressure (baseline to 12-month). ....   | 167 |

## **PREFACE**

This thesis reports on research work related to the investigation of periodontal treatment on carotid-dorsalis pedis pulse wave velocity that was carried out during my PhD candidature at the school of Dentistry, the University of Adelaide and the Menzies School of Health Research, Darwin, Northern Territory from April 2010 until June 2014.

This thesis is structured in a publication format and consists of eight chapters. The literature review which develops the foundation for the present study aims and hypotheses is presented in Chapter 1. The general materials and methods for this study are presented in Chapter 2 while specific details of methods are further refined in the four manuscripts that are presented in Chapters 3-6 inclusive. Chapters 3-6 have been written as manuscripts for publication and have either been published or accepted for publication. Chapter 7 discusses the main findings of the four manuscripts and places them into context of the wider literature. Attempts to extrapolate the findings into making recommendations for future research are also included within Chapter 7. The appendices comprise the contents of Chapter 8.

Acknowledgements of key personnel and institutions that have assisted in one form or another in the work presented within this thesis have been recorded in pages xii-xiii. Additionally, to conform to journal requirements, acknowledgments of funding bodies and specific highlights to contributors have been made at the end of each manuscript chapter.

## **ABSTRACT**

Cardiovascular disease and periodontitis are highly prevalent diseases that are thought to be associated by chronic inflammation. The aims of the present study were: 1) to determine whether a relationship between periodontal disease and arterial stiffness exists in a sample of Indigenous Australians with periodontal disease; and 2) using a randomised-trial design, determine whether treatment of periodontal disease will result in an improvement in arterial stiffness. Findings presented in this thesis indicate that a positive association between periodontal disease and arterial stiffness exists but that a single session of non-surgical periodontal therapy is insufficient to alter arterial stiffness.



## **DECLARATION**

This work contains no material which has been accepted for the award of any other degree in any university or tertiary institution to Kostas Kapellas and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis (as listed below) resides with the copyright holder of those works.

I also give permission for the digital version of my thesis to be made available on the internet, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the university to restrict access for a period of time.

-----

KOSTAS KAPELLAS

Dated this 20<sup>th</sup> day of June 2014

## **PUBLICATIONS ARISING FROM WORK CONTAINED WITHIN THIS THESIS**

Kapellas, K., Skilton, MR., Maple-Brown, LJ., Do, LG., Bartold, PM., O'Dea, K., Brown, A., Celermajer, DS. & Jamieson, LM. (2014) Periodontal disease and dental caries among Indigenous Australians living in the Northern Territory, Australia. *Australian Dental Journal* 59, 93-99. <http://onlinelibrary.wiley.com/doi/10.1111/adj.12135/abstract>

Kapellas, K., Do, LG., Bartold, PM., Skilton, MR., Maple-Brown, LJ., O'Dea, K., Brown, A., Celermajer, DS., Slade, GD., Jamieson, LM. (2013) Effects of full-mouth scaling on the periodontal health of Indigenous Australians: a randomized controlled trial. *Journal of Clinical Periodontology* 40, 1016-1024. <http://onlinelibrary.wiley.com/doi/10.1111/jcpe.12152/abstract>

Kapellas, K., Jamieson, L., Do, L., Bartold, P., Wang, H., Maple-Brown, L., Sullivan, D., O'Dea, K., Brown, A., Celermajer, D., Slade, G. & Skilton, M. (2014) Associations between periodontal disease and cardiovascular surrogate measures among Indigenous Australians. *International Journal of Cardiology* 173, 190-196. [http://www.internationaljournalofcardiology.com/article/S0167-5273\(14\)00368-4/abstract](http://www.internationaljournalofcardiology.com/article/S0167-5273(14)00368-4/abstract)

Kapellas K, Maple-Brown LJ, Jamieson LM, Do LG, O'Dea K, Brown A, Cai TY, Anstey NM, Sullivan DR, Wang H, Celermajer DS, Slade GD, Skilton MR. Effect of periodontal therapy on arterial structure and function among aboriginal australians: A randomized, controlled trial. *Hypertension*. 2014; DOI:10.1161/hypertensionaha.1114.03359 <http://hyper.ahajournals.org/content/64/4/702.short>

## CONFERENCE PRESENTATIONS FROM WORK ARISING IN THIS THESIS

K. Kapellas, LJ. Maple-Brown, PM. Bartold, A. Brown, LG. Do, K. O’Dea, GD. Slade, DS. Celermajer, LM. Jamieson, MR. Skilton. Oral presentation: Effect of a periodontal intervention on pulse wave velocity in Indigenous Australians with periodontal disease: the PerioCardio randomized controlled trial. World Congress of Cardiology, Scientific Session, Melbourne, Australia 6th May 2014

K. Kapellas, LM. Jamieson. Oral presentation: Is multiple imputation a correct method to assess missing data from an RCT with heavy loss to follow-up? 6th Dental Biostatistics Conference – Methodological Issues in Oral Health Research, Adelaide, Australia 2nd April 2014.

K. Kapellas, MR. Skilton, LJ. Maple-Brown, LG. Do, PM. Bartold, GD. Slade. Oral presentation: Periodontal Outcomes from Single-visit Non-surgical Periodontal Therapy among Indigenous Australians. International Association of Dental Research (IADR) 91<sup>st</sup> General Session, March 23<sup>rd</sup> Seattle, USA 2013.

## CONFERENCE POSTER PRESENTATIONS

K. Kapellas, LJ. Maple-Brown, LM. Jamieson, LG. Do, K. O’Dea, A. Brown, DS. Celermajer, GD. Slade, MR. Skilton. The effect of periodontal therapy on carotid intima-media thickness among Indigenous Australians: A randomised controlled trial. World Congress of Epidemiology, Anchorage, USA 18<sup>th</sup> August 2014.

## **ACKNOWLEDGEMENTS**

I would like to give sincere thanks first and foremost to my three supervisors, Assoc. Prof. Lisa M. Jamieson, Assoc. Prof. Loc G. Do and Prof. Mark Bartold for all their advice, guidance and support during my journey as a post-graduate student. I would also wish, at this point, to specifically acknowledge Prof. Mark Bartold who has supervised me since 2006 in my Oral Health Elective as part of my Bachelor of Oral Health, and then again from 2007 through 2009 where he co-supervised my Bachelor of Science in Dentistry (hons.). Eight years as his student, I now look forward to working with him as a colleague. Additionally, Assoc. Prof. Lisa M. Jamieson has gone above and beyond her supervision requirements to assist me in my work/life balance. Thank you for your persistence and encouragement.

I would also like to thank all the PerioCardio investigators who have assisted in my thesis by revising manuscripts prior to submission for journal review. Without your collective work, the PerioCardio study could not have come to fruition. A special acknowledgment to Dr. Michael R. Skilton is required for his continued assistance and direction into the collection and management of data and manuscript revisions.

I would like to additionally acknowledge the staff at the Menzies School of Health Research, Darwin, Northern Territory which was the location where the PerioCardio study was based. Many thanks go to the directorate and staff from Oral Health Services, NT for providing the clinical facilities to conduct the periodontal interventions, sterilization, consumables and temporary employment to myself for the 2 ½ years I lived in Darwin to collect data for the PerioCardio study. Acknowledgments must also be made to the Department of Corrections and Wurli Wurlinjang who hosted myself and other PerioCardio staff during the data collection process. Rest in peace John Fletcher (former CEO of Wurli) who passed away in 2012.

This thesis could not have occurred were it not for the Divisional Scholarship I received during my candidature and also the University of Adelaide, Faculty of Health Sciences Travel Award that contributed towards the costs of travelling to the USA for IADR presentation and visit to University of North Carolina in 2013.

I would like to also thank Jade Maurer for the specific help she provided from May 2012 to February 2013 that assisted me to develop some very important life strategies.

Finally, I would like to acknowledge and apologise to my parents Andreas and Stavroula and my brother Nick, who have all provided encouraging words in their own special way and have had to deal with my many moods throughout my educational journey.