Institution: University of Birmingham

Unit of Assessment: UoA 3, Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Reducing the global burden of chronic disease through periodontal care

Period when the underpinning research was undertaken: 2002-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Iain Chapple	Professor (Group Lead)	1990–present
Thomas Dietrich	Professor	2007–present
Dr Praveen Sharma	Clinical Lecturer	2011–present
Miss Zehra Yonel	NIHR Doctoral Fellow	2012–present

Period when the claimed impact occurred: 2007–December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Severe periodontitis (sPD) is the 6th most common human disease, affecting 7–11% of adults globally. Periodontitis (PD) shares common inflammatory processes with diabetes, cardiovascular and chronic kidney disease (CKD) and our previous work has shown that PD independently associates with premature death. Furthermore, we have demonstrated that oxidative stress caused by periodontal bacteria entering the blood acts as a causal link between PD and deterioration of systemic diseases such as CKD in a dose-dependent manner. We have clearly **established PD as a global public health and economic burden**. Specifically, we have **shaped guidelines and changed clinical practice** with regard to oral health nationally and internationally for people with non-communicable diseases (NCD), particularly diabetes and cardiovascular disease. We have also had commercial impact, as our **research informed the marketing strategies of multi-national companies** including GSK, Philips, P&G and Unilever. Finally, **we have contributed to better public understanding, learning and participation** on the link between gum disease and general health.

2. Underpinning research

'Periodontal disease' is a general term that describes several gum diseases that affect the tissues and bone that support teeth. Periodontitis (PD) is a specific inflammatory gum disease that affects 40–50% of adults globally, causes tooth loss, and compromises nutrition, speech and overall quality of life. In its most severe form (sPD) it affects 11.2% of adults and is the 6th most common human disease. PD, and most particularly sPD, associate independently with several systemic non-communicable diseases of ageing as well as cardiovascular disorders and all-cause mortality. Strikingly, in global studies PD treatment reduced annual medical costs for Stroke and Diabetes patients by 40% (Jeffcoat *et al*., *Am J Prev Med* 2014;47:166-74) and the economic impact of dental diseases is estimated at $298 billion in direct and $144 billion in indirect treatment costs. This represents 4.6% of global health expenditure and falls within the financial burden of the 10 leading causes of death (Listl S *et al., J.Dent.Res* 2015; 94:1355-1361).

Our ongoing and completed studies (Chapple, Dietrich, Sharma, dePablo, Yonel; R1–R6) have investigated these links at epidemiological, mechanistic and therapeutic intervention levels, spanning the full discovery to translational pipeline. **We have demonstrated that periodontitis is a significant independent risk factor for all-cause and cardiovascular mortality, chronic kidney disease (CKD)** (R3)**, rheumatoid arthritis (RA)** (dePablo *et al*., *J Rheumatol.* 2008; 35: 70–6) **and type 2 diabetes** (T2D) (R2, R3). We unravelled specific biological mechanisms mediated via oxidative stress (R1, R2, R4) in all 4 diseases, and for the first time demonstrated

how and why periodontitis is part of the causal pathway of CKD and cardiovascular disease in CKD, impacting on declining renal function and increasing vascular stiffness of major arteries.
Over 15 years, we have pioneered investigations into oxidative stress (a type of inflammation) in tissues and blood, induced by peripheral blood neutrophils (white blood cells) in response to periodontal bacteria and their products entering the circulation (R1). We have elucidated mechanisms through which periodontitis drives systemic oxidative stress and identified mechanisms of co-morbidity in T2D, CKD and RA (R2, R4, R6).
In diabetes, we demonstrated that **periodontitis, as a co-morbidity with T2D, was associated with additional oxidative stress, reduced pancreatic beta-cell function, elevated blood HbA1C levels** (poorer diabetes control) **and dyslipidaemia** (R2). In cardiovascular disease (CVD), we demonstrated that **periodontitis was an independent and significant risk factor for incident cardiovascular events** (R5). In RA, we demonstrated that periodontitis was a significant risk factor for RA and that periodontitis patients who did not yet have RA exhibited significantly elevated blood titres and higher prevalence of the ACPA autoantibodies that cause RA (R6). **Oxidative stress was found to form a common link** through the production of neutrophil extracellular traps which are a source of ACPA generation (Spengler *et al*., *Arthritis & Rheum*. 2015; 67: 3135–45; Ademowo *et al.*, *Free Rad Biol Med.* 2019; 146: 130–8).
In CKD, we demonstrated that the **presence of periodontitis significantly increased 10-year all-cause and cardiovascular mortality by 9% and 6%**, equivalent to the impact of co-morbid diabetes with CKD (R3). We also demonstrated a significant dose-response relationship between PD and systemic oxidised protein and lipid levels in 770 CKD patients. This led to the discovery of a causal link between periodontitis and kidney failure in CKD acting via oxidative stress (R4).

3. References to the research (indicative maximum of six references)

Research Grants: Our research has been broadly funded by the EU (FP7) (TRIGGER, OPERA, Gums & Joints), UK Charities (CRUK, ARUK, ODRT), NIHR (INSPRIED, RAPiD, SUCCESS). These are collaborative projects (Europe, USA, national) engaging joint medical/dental cohorts.

References:

Oxidative Stress Papers

R1. Matthews, J.B., Wright, H.J., Roberts, A., Cooper, P.R., Chapple, I.L.C. Hyperactivity and reactivity of peripheral blood neutrophils in chronic periodontitis. ***Clin Exp Immunol***. 2007; 147: 255–64. doi: 10.1111/j.1365-2249.2006.03276.x.

Diabetes papers

R2. Allen, E.A., Matthews, J.B., O'Halloran, D., Griffiths, H., Chapple, I.L.C. Oxidative and Inflammatory status in Type 2 Diabetes Patients with Periodontitis. ***J Clin Periodontol***. 2011; 38: 894–901. doi: 10.1111/j.1600-051X.2011.01764.x.

CKD papers

R3. Sharma, P., Dietrich, T., Ferro, C.J., Cockwell, P., Chapple, I.L. Association between Periodontitis and mortality in stages 3–5 Chronic Kidney Disease: NHANES III and linked mortality study. ***J Clin Periodontol***. 2016; 43: 104–113. doi: 10.1111/jcpe.12502.

R4. Sharma, P., Fenton, A., Dias, I.H.K., Heaton, B., Brown, C.L.R., Sidhu, A., Rahman, M., Griffiths, H.R., Cockwell, P., Ferro, C., Chapple, I., Dietrich, T., Oxidative stress links periodontal inflammation and renal function. ***J Clin Periodontol***. 2020 doi: 10.1111/jcpe.13414.

CVD & RA papers

R5. Dietrich, T., Sharma, P., Walter, C., Weston, P., Beck, J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. ***J Clin Periodontol***. 2013; 84(4 Suppl): S70–84. doi: 10.1111/jcpe.12062.

R6. de Pablo, P., Dietrich, T., Chapple, I.L.C., Milward, M., Chowdhury, M., Charles, P.J., Buckley, C.D., Venables, P.J. The autoantibody repertoire in periodontitis: a role in the induction of

autoimmunity to citrullinated proteins in rheumatoid arthritis? ***Ann Rheu Dis*** 2014; 73: 580–6. doi: 10.1136/annrheumdis-2012-202701.

4. Details of the impact (indicative maximum 750 words)

Non-communicable diseases impose a significant health and economic burden. Diabetes affects 415 million adults worldwide, causes >4 million deaths each year and costs $673–$1,200 billion in health spending. Cardiovascular disease is responsible for 17.9 million deaths globally each year.

1. Impact on health policy and practice, by shaping guidelines on oral health in people with non-communicable diseases (NCDs)

A. Changed Policy and Practice for Patients with Diabetes

We directly **influenced the 2019 NHS England (NHSE) Commissioning Standard on Oral Health and Diabetes** for Medical and Dental Practitioners (S1(i-ii)). Our influence is evidenced by references to 4 of our publications in the commissioning standard (S1(i)). Importantly, drawing on our work, the document now incorporates the need for **risk assessing NCDs in dental practices/pharmacies**, something for which we directly advocated (S2(i-ii)).

Chapple advised a NHSE policy implementation group (S1(ii)), and University of Birmingham (UoB) research strongly **informed policy debate**, transformed NHSE thinking and led to a **change in clinical practice** (R2, R3, R4: S1(i), S3, S5)). Acting on UoB research, the standard requires medical practitioners to refer diabetes/pre-diabetes patients for periodontal examination and treatment, and the dental team to risk-assess patients for diabetes to assist early case detection. This draws directly from our studies demonstrating strong public, patient and professional support for this shift in practice (S2(i-ii)). The **commissioning standard** was launched by the Chief Dental Officer (OCDO) with Chapple on 14 November 2018 (Olympia: a record 4,195 attended the event), and drew heavily on our research (e.g. R2, R3; S2 (i-ii)), which was presented by Chapple at the event (S1(ii)). The OCDO confirms this, attesting to "the tremendous impact of fundamental research undertaken by Professor Chapple and Birmingham University's Periodontal Research Group and its translation into public and patient benefit" (S1(ii)).

The International Diabetes Federation (IDF) and European Federation of Periodontology (EFP) **developed joint international guidelines (2018) for medical and dental communities** (S3) at a consensus workshop (Madrid, 2017), co-chaired by Chapple. The importance of the UoB groups' work was highlighted in the guidelines (S3) and recommendations disseminated via a European website (S4(iii)). These are the first published **international guidelines on periodontal care in people with pre-diabetes or diabetes**. They have been disseminated globally with support from Sunstar Foundation, a global oral health foundation present in 100 countries worldwide (S4(i)).

Additionally, **the original EFP-American Academy of Periodontology (AAP) guidelines**, published in 2013 (719 citations 2014–2020) cite our research as a key driver for change. The consensus paper (Chapple lead author) received widespread public media attention (2014–onwards) across Europe, the USA, Canada and beyond (S4(ii-iii)) with 6,451 EFP workshop page views 01-04-2017 to 27-09-2019; Figure 1).

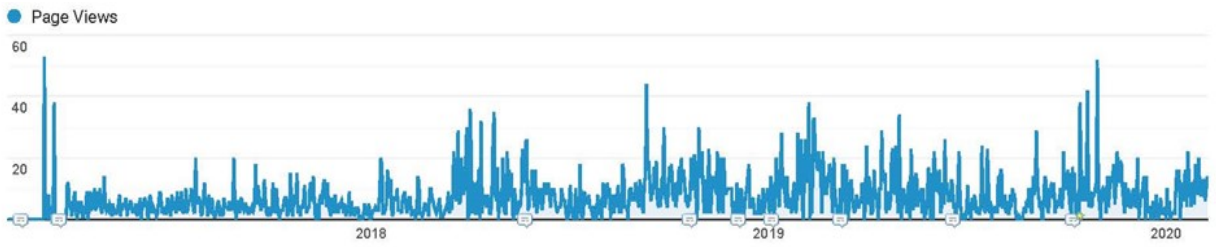

Figure 1 - EFP workshop page views 01-04-2017 to 27-09-2019

B. Changed Policy and Practice for Patients with Cardiovascular disease (CVD)

In 2019, **international guidelines were developed by the EFP and World Heart Federation (WHF)**, drawing on work by Dietrich, Chapple and Sharma (R3, R5; S5). The guidelines provide

recommendations on oral care in people with CVD and heavily cite UoB's portfolio of studies (7 papers) linking PD and NCDs via oxidative stress. In addition, our paper on epidemiological links between PD and incident CVD (R5) directly informed joint **EFP-AAP guidelines** and was key to driving the **EFP-WHF guidelines in 2019**. These recommendations were globally disseminated by Dentaid, a dental health organisation acting in over 70 countries, supporting worldwide uptake for practice change (S6(i)).

C. Changed Practice and Professional Services for Patients with Systemic NCDs

Chapple co-wrote the **EFP manifesto on links between periodontitis (PD) and systemic illnesses (NCDs) (S6(ii)) - the first formal declaration in international dentistry to acknowledge PD as a major public health issue**. It calls directly on experts and individuals worldwide to act in prevention, early diagnosis and effective treatment of gum disease to combat the devastating oral and general health effects for individuals and society. This had been signed by **1255 institutions/organisations/individuals across the world** by September 2019 (Figure 2).

Figure 2: EFP Manifesto signatures: 09-19

2. **Commercial impact through informing marketing strategies**

Our work, permeating through the international guidelines and policy changes, **strongly influenced research and marketing strategies of global companies including GSK, Unilever, P&G and Philips**, for whom Chapple has consulted/lectured to international teams (e.g. (S7(i-ii)). The majority of the developed world uses these companies' products.

GSK declared that our "studies on Chronic Kidney Disease, Rheumatoid Arthritis, Cardiovascular Disease and Diabetes have informed European and global consensus reports and statements that have in turn informed and influenced GSK Oral Health R&D, and our global marketing communication strategies since 2018*"* (S7(i)). These companies now target their research and market their products responsibly with general health as well as oral health benefits (S7(i-ii)).

Philips stated "[...] we have worked with the Periodontal Research Group (PRG) in Birmingham for over 20 years on a variety of topics and on saliva diagnostics and the oral-systemic link in particular. In 2019–2020, we filed 10 US patents with Prof Chapple" (S7(ii)). Philips President announced their interest in the oral-systemic link in a Global Town Hall meeting in autumn 2020.

3. **Shaping public understanding of the link between gum disease and general health**

Chapple's periodontal research group also **raised public awareness and understanding of the impact of PD on general health**. A BBC1 prime-time documentary 'The truth about your teeth' broadcast in the UK (2015) to 2 million viewers, and later in Sweden (2018–2019), increased knowledge from 25% to 90%, demonstrated by a pre- and post-viewing survey (Grant *et al.*, *Res for All*. 2018; 2:122–130) and habits of viewers (S8(i-ii)). Following the EFP-AAP workshop chaired by Chapple (2012), news articles appeared in several major papers in the USA, Spain, Germany and other European countries, as well as video interviews in Canada (S4(ii)). The BMJ invited an editorial by Chapple that the BMJ Editor chose to respond to (S9). Sunstar (Japan) funded a global outreach campaign based upon the IDF/EFP workshop (S4(i)) (2016–2019).

5. Sources to corroborate the impact

Source 1 (i) NHSE – Commissioning Standard: Dental Care for People with Diabetes; Publishing approval number: 000078; Version number: 1.0; First published July 2019, **(ii)** Testimonial from Office of Chief Dental Officer, 2019.
Source 2 (i) Yonel, Z., Sharma, P., Yahyouche, A., Jalal, Z., Dietrich, T., Chapple, I.L.C. *BMJ Open*. 2018; 8: e024503. doi:10.1136/bmjopen-2018-024503, **(ii)** Yonel, Z., Yahyouche, A., Jalal, Z., James, A., Dietrich, T., Chapple, I.L.C. *BMC Public Health*. 2020; 20: 1576. Article
Source 3 (i) Sanz, M., Ceriello, A., Buysschaert, M., Chapple, I., *et al*. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. *Diabetes Res Clin Pract*. 2018; 137: 231–41. doi: 10.1016/j.diabres.2017.12.001; and **(ii)** Maurizio S. Tonetti, Henry Greenwell, Kenneth S. Kornman. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Clin Periodontol*. 2018; 45: 138–49. doi:10.1111/jcpe.12945.
Source 4 (i) Sunstar (Japan - Diabetes), **(ii)** National and International newswires and press releases and video interviews: *Telegraph*, *Mail*, newspapers in Spain, Germany, Portugal, USA, Canada and several other countries; video interviews (EFP; Canada) **(iii)** European Federation of Periodontology (EFP) European Federation of Periodontology
Source 5 Sanz, M., Marco del Castillo, A., Jepsen, S., Gonzalez-Juanatey, J.R., D'Aiuto, F., Bouchard, P., Chapple, I., Dietrich, T., *et al*. Periodontitis and Cardiovascular Diseases. Consensus Report. *Global Heart*. 2020; 15(1):1, and *J Clin Periodontol*. 2020; 47: 268-288
Source 6 (i) Dentaid sponsor of dissemination Joint EFP/WHF/Dentaid project **(ii)** Manifesto EFP Manifesto.
Source 7 (i) Testimonial - GSK global innovation, research investment focus and product development, **(ii)** Testimonial - Philips strategic thinking, investment, research, marketing and development.
Source 8 (i) BBC1 documentary 'The truth about your teeth' (2015) 'The truth about your teeth' (2015)**, (ii)** 'The truth about your teeth', 16:53–22.13 mins and analysis of impact upon public knowledge (re-broadcast in Sweden 2018). >98,000 views 17 December 2020; over 15,000 additional views in Sweden 11 October 2016 and analysis of impact upon public knowledge (re-broadcast in Sweden 2018). 'The truth about your teeth' Sweden 2018
Source 9 Chapple, I.L.C., Time to take periodontitis seriously. The benefits of treatment are likely to exceed the costs. *Brit Med J.* 2014; 348: g2645 (Also Editor's choice in same volume). doi: 10.1136/bmj.g2645.