Dental status as a window to general health

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CHAPTER 1

1

General introduction
and outline of the thesis

GENERAL INTRODUCTION

The history of dentistry is almost as ancient as the history of civilization with the earliest evidence dating from 7000 BC. From the Middle Ages until the 19th century, dentistry was not yet a profession in itself, but an occupation of barbers and the surgeons. They were actually one entity, named barbers surgeon, and were responsible for a range of services relating to care of the body. A barber surgeon performed surgical procedures including amputations, bloodletting and tooth extractions, as well as barbering roles like hair cutting and shaving. Tooth extraction, similar to bloodletting, was used as a therapeutic as well as a prophylactic process, supposed to remove toxins from the body and to balance the "humors". The link between dentistry and general medicine seems historical. However, since the establishment of the first dental college (Baltimore College of Dental Surgery) in 1840, dentistry became a separate entity from medicine.[1] This separation has been maintained by divided education, divergent practices, payment models, and health care policies. Nevertheless, the connection between dental health and general health is in the middle of a revival and its importance is now realized worldwide with major impact on public health.

Remarkable epidemiological and pathological associations between dental status and general health have been reported. Most research focused on the link between periodontitis and cardiovascular disease but also with many other systemic diseases including diabetes mellitus, rheumatoid arthritis, certain cancers, respiratory diseases, cognitive disorders and premature birth.[2] The first study in modern times that found evidence for the association between dental pathology and cardiovascular disease was by Mattila et al. in 1989.[3] This initial study caused a wave of commotion and was leading to the provocative quote "Floss or die".[4] Since then a multitude of studies on this topic have been published, though the fundamental explanations for the associations remained under debate.[5] Most precedent literature tried to find causality between dental pathology and systemic diseases, mainly based on derivative parameters. This thesis provides new insights into this link elaborated in two essential general health conditions: cardiovascular diseases (as the leading cause of global mortality) and COVID-19 (as a recent example of a worldwide pandemic). In this introductory chapter, "dental status" and these two crucial general health conditions are further explicated.

Dental status

Oral diseases are one of the most prevalent diseases globally.[6] The key clinical dental conditions that are considered to be public health priorities include dental caries and periodontitis. Eventually, tooth loss is the ultimate event representing dental pathologies. Tooth loss at a younger age is generally due to caries, and in older ages, it is the final stage of periodontitis. In 2010, 2.3% of the global population, was edentulous (no natural teeth). Prevalence of severe tooth loss (≤9 remaining teeth) reduced between 1990 and 2010, declining from 4.4% to 2.4%. However, this prevalence increases gradually with age, showing a steep increase around the seventh decade of life, associated with a peak in the incidence of severe tooth loss at the age of 65. This older age pattern of tooth loss has not changed during

the past two decades, notwithstanding the gradual decreases in prevalence and incidence within the same period for the whole population.[7]

Dental caries is the primary cause of oral pain and the prevalence of ever having had caries in adults is high, reaching more than 90% of the population.[8] Dental caries is the localized destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates. Physical and biological risk factors for dental caries include inadequate salivary flow and composition, high numbers of cariogenic bacteria, insufficient fluoride exposure, gingival recession and genetic factors. It is a chronic disease that progresses slowly in most people and is initially reversible. In dental caries management, the focus has been around prevention, but tooth restauration and tooth extraction is still widely used.[9]

Untreated caries leads to bacterial invasion of the pulp and root canal. This condition may progress with necrotic root canals and resorption of apical periodontal ligament and surrounding alveolar bone. These peri-apical lesions contain bacteria which can be translocated throughout the body and lodge in various organs.[10]

Periodontitis is the sixth most common human disease, affecting 30-50% and approximately 10% of the global adult population in its most severe form.[11] The global age-standardized prevalence and incidence have remained stable since 1990.[12] Periodontitis is a chronic multifactorial inflammatory disease of the supportive tissues of the teeth. It starts with localized inflammation of the gingiva that is initiated by bacteria in the dental plaque. This gingival inflammation (gingivitis) can be present for years and is considered as a normal and protective host response. Nevertheless, in highly susceptible individuals and with progression age, the host response may show a break in the tolerance to the dental microbiome along and just below the gingival margin. Eventually, due to lack of proper immune fitness, gingivitis may derail in a destructive form of gingival inflammation. This subsequent state is periodontitis, with periods of exacerbation showing progressive loss of alveolar bone and tooth attachment. The inflammation actually creates a favorable ecosystem for pathobionts and a dysbiotic biofilm develops. Although pathogenic bacteria in the dysbiotic biofilm are necessary for periodontitis to take place, a susceptible host is also needed. Consequently, several risk factors for periodontitis have been established, including smoking, diabetes mellitus, socio-economic position, psychosocial factors and genetic predispositions.[13]–[15]

Timely diagnosis of periodontitis is extremely important, since loss of the periodontal tissues is largely irreversible. However, the most prevalent form of periodontitis is painless and it is common to have reached advanced degrees of severity before it is diagnosed. After proper diagnosis and classification, periodontal treatment consists of non-surgical root debridement followed by a surgical treatment phase to further reduce residual deep periodontal pockets. In extreme cases or cases in young individuals, some clinicians opt for adjunctive therapy with systemic antibiotics. Patient education in proper oral hygiene and counselling on control of risk factors for periodontitis, together with a periodontal maintenance programme of 3-4 times a year is important for secondary prevention.[13], [16]

During periodontitis, pathogens in the dysbiotic biofilm trigger immune responses involving both innate immunity as well as adaptive immunity resulting in the production and release of pro-inflammatory molecules. In this regard, it is interesting to notice that inflammation here plays a dual role: Inflammatory response is a physiological reaction aimed at protecting the organism against bacterial infections. However, when inflammation becomes deregulated and chronic, it may lead to an irreversible destruction of the periodontal tissues and becomes the frontline allowing local inflammation to disturb systemic health.[17]

Periodontitis has gained relevance since it has been shown that it can develop into a systemic condition. Unresolved periodontal hyperinflammation may cause, coincide or exacerbate other health issues associated to elevated morbidity and mobility and mortality.[17] Most research in this field focused on the association between periodontitis and cardiovascular diseases, but recent analyses of trial registers showed that even fifty-seven systemic conditions are hypothesized to be linked with periodontitis.[18]

Cardiovascular disease

Cardiovascular disease (CVD) is a cluster of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease and peripheral arterial disease. CVD is the leading cause of global mortality and a major contributor to disability.[19] Acute events of CVD such as myocardial infarction (heart attack), cerebrovascular accident (stroke), and sudden death are mainly caused by an obstruction of the blood vessels. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels, called atherosclerosis. The term atherosclerosis derives from the Greek word for 'gruel' or 'porridge', reflecting the appearance of the lipid material found in the core of the typical atherosclerotic plaque. This underlying pathology, atherosclerosis, is a progressive chronic inflammatory process of the arteries, characterized by a dysfunctional interplay between the immune system and lipids. The observation that inflammatory cells are interspersed in the atheroma was made in the late 1800s, but the contribution of immune cells to all stages of atherosclerosis began to be valued only in the last few decades.[20] Numerous studies have clarified the molecular mechanisms of inflammation in atherosclerosis, and it is widely accepted that both innate and adaptive immune responses play key roles in the initiation and progression of atherosclerosis, leading to clinical manifestations of CVD.[21]

Immune cells, as well as smooth muscle cells, platelets and endothelial cells, drive plaque inflammation through a complex crosstalk of inflammatory mediators. These mediators are activated by risk factor–induced triggers, which are present in the circulation and in the vessel wall, such as shear stress, oxidized lipoproteins and oxidative stress. Without relief from risk factors, the activation of inflammatory processes persists, resulting in a chronic non-resolving inflammation. Inflammation is associated with severity of disease, and complex lesions, which are prone to rupture and cause acute events, are characterized by extensive inflammation.[22]

The relevance of several major risk factors for CVD is now well established, including, but not limited to, smoking, obesity, hypertension, hypercholesteremia, diabetes mellitus and genetics.[23] Because of the multifactorial nature of CVD, its treatment should target all known treatable risk factors. Ideally, primary prevention starts by adopting a healthy lifestyle, reducing exposure to the avoidable major risk factors. Nevertheless, risk factor modification to prevent or even reverse the progression of the atherosclerotic process can provide benefit at any stage of atherosclerotic disease, additionally in the context of secondary prevention.[24]

Consistent epidemiological evidence additionally indicates periodontitis as a risk factor for CVD. The explanation of this association between periodontitis and CVD generally fall into two categories: (a) microbial mechanisms, which through vascular invasion may locally affect the development of the atheroma lesions; and (b) inflammatory and immunologic mechanisms that directly influence the pathobiology of the atheroma lesions.[25] Whether or not treatment of periodontitis is valuable for primary or secondary prevention of cardiovascular disease, have not yet been fully established.[26]

CVD and periodontitis are both complex inflammatory diseases considerably influenced by similar multilevel interactions between metabolic and immune systems. The susceptibility of a host and its associated aberrant immune response is considerably the fundament of this link. In this scope, much more inflammatory diseases and their related complications could be linked. The recent detected, and still ongoing COVID-19 pandemic has significantly increased our focus and perceptions of inflammatory conditions , immune responses and its consequences.[17]

Coronavirus disease 2019 (COVID-19)

At the end of 2019, the novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in China. The later designated coronavirus disease 2019 (COVID-19) rapidly developed in a worldwide pandemic presenting an important and urgent threat to global health.[27] Countries around the world reported 4.2 million deaths from COVID-19 from the beginning of pandemic until the end of July 2021, but the actual number of deaths is probably higher.[28] The most common serious complication of COVID-19 infection, Acute Respiratory Distress Syndrome (ARDS), is characterized by bilateral chest radiographical opacities with severe hypoxemia due to non-cardiogenic pulmonary oedema.[29] Furthermore, COVID-19 does not only affect the respiratory tract, but it also affects other organs with multi organ failure as endpoint. Admission to the Intensive Care Unit (ICU) for mechanical ventilation is predominantly necessary; not primary to cure, but to allow time for the body to recover. Corticosteroids (dexamethasone) can help reduce the length of mechanical ventilation and save lives of patients with severe and critical illness. Nevertheless, approximately one-third of the patients admitted to the ICU with a severe form of COVID-19 eventually die.[30]

The COVID-19 pandemic forced the world to accelerate vaccine and drug development and evaluation at an unparalleled pace. At present, the COVID-19 treatment arsenal is largely represented by antiviral agents (often administered in early stages of disease) and immunotherapeutic agents that modulate the host immune response (often administered in more advanced stages of disease).[31] Moreover, many different public organizations and private companies have worked together to make COVID-19 vaccines available. While the rapidly developed COVID-19 vaccines have provided strong protection against serious illness, hospitalization and death, around 40% of the worldwide population is still unvaccinated until February 2022.[32], [33]

Indication of risk factors for a severe course of COVID-19, such as hospital admission, ICU admission and death, became crucial. Therefore, there was an urgent need for a pragmatic risk stratification tool that allows the early identification of the COVID-19 patients who are likely to be at highest risk of ICU admission and death.[34] Age is one of the main risk factors for morbidity and mortality due to infection with SARS-CoV-2.[35] Additionally, male sex, underlying medical conditions (cardiovascular-, metabolic-, lung- and renal-disease) and obesity are associated with COVID-19 related complications and unfavorable outcomes.[36] It has been hypothesized that poor oral health is associated with the severity of the clinical progression of COVID-19.[37], [38] Consequently, tooth loss, as ultimate sequala of poor oral health and dental pathology, could possibly serve as an easily accessible biomarker for the early identification of COVID-19 patients at risk for a severe disease progression, ICU admittance and even death from COVID-19. Accordingly, also for COVID-19 the dental status could serve as window to general health.

OUTLINE OF THE THESIS

Above it has been outlined that the interface between dental status and general health is fascinating and relevant. Most precedent literature in this field tried to find causality between dental pathology and systemic diseases, mainly based on derivative parameters. This thesis provides new insights into this link elaborated in two essential general health conditions: cardiovascular diseases (as the leading cause of global mortality) and COVID-19 (as a recent example of a worldwide pandemic). Herewith, a more widespread and general statement on this exciting and above all important topic is made.

Therefore, the aim of this thesis is threefold. First, the association between dental status and cardiovascular disease is further investigated using more adequate parameters **(Part I)**. Secondly, the possible link between dental status and severity of COVID-19 is explored **(Part II)**. In the last part, the link between dental status and general health is discussed based on Part I & II **(Part III)**.

Part I – Dental status as a window to cardiovascular disease

Chapter 2 is a review of the literature on the association between periodontitis and atherosclerosis and provides the state of knowledge in this field. The retrospective study presented in **Chapter 3** investigates the association between Coronary Artery Calcium (CAC) scores defined on CT scans and dental pathology seen on dental panoramic radiographs. In **Chapter 4,** a prospective clinical study determines if there is a correlation between the inflammatory burden of periodontitis (quantified by the Periodontal Inflamed Surface Area [PISA] score) and the presence and extent of coronary calcification (investigated by the CAC score). The secondary aims were to study other cardiovascular parameters and CVD risk predictors in relation to periodontitis and dental status. **Chapter 5** describes the effect of periodontal treatment on endothelial function and other cardiovascular parameters after one-year follow-up of the same patients investigated in chapter 4.

Part II – Dental status as a window to COVID-19

In **Chapter 6** the association between alveolar bone loss, tooth loss and severity of COVID-19 is explored in a retrospective study. **Chapter 7** describes the development and external validation of a prediction model for critical outcomes of COVID-19, based on dental status in addition to the established risk factors such as demographic characteristics and other medical condition.

Part III – Dental status as a window to general health

In **Chapter 8** the results of the various chapters of this thesis are discussed and clinical implications and future perspectives are given. **Chapter 9** and **Chapter 10** presents the summary of this thesis in respectively English and Dutch.

References

[1] J. Wynbrandt, *The excruciating history of dentistry: toothsome tales \& oral oddities from Babylon to braces*. Macmillan, 2000.

[2] R. J. Genco and M. Sanz, "Clinical and public health implications of periodontal and systemic diseases: An overview," *Periodontol. 2000*, vol. 83, no. 1, pp. 7–13, 2020.

[3] K. J. Mattila *et al.*, "Association between dental health and acute myocardial infarction.," *BMJ*, vol. 298, no. 6676, pp. 779–81, Mar. 1989.

[4] D. Richards, "Floss or Die?," *Evid. Based. Dent.*, vol. 2, no. 3, pp. 57–58, 2000.

[5] M. Sanz *et al.*, "Periodontitis and cardiovascular diseases. Consensus report," *Glob. Heart*, vol. 15, no. 1, pp. 1–23, 2020.

[6] M. A. Peres *et al.*, "Oral diseases: a global public health challenge," *Lancet*, vol. 394, no. 10194, pp. 249–260, 2019.

[7] N. J. Kassebaum, E. Bernabé, M. Dahiya, B. Bhandari, C. J. L. Murray, and W. Marcenes, "Global Burden of Severe Tooth Loss: A Systematic Review and Meta-analysis," *J. Dent. Res.*, vol. 93, no. July, pp. 20S-28S, 2014.

[8] J. C. Carvalho and U. Schiffner, "Dental Caries in European Adults and Senior Citizens 1996-2016: ORCA Saturday Afternoon Symposium in Greifswald, Germany - Part II," *Caries Res.*, vol. 53, no. 3, pp. 242–252, 2019.

[9] R. J. Lamont and P. G. Egland, "Dental Caries," *Mol. Med. Microbiol. Second Ed.*, vol. 2–3, no. 4, pp. 945–955, 2014.

[10] A. C. Georgiou, W. Crielaard, I. Armenis, R. de Vries, and S. V van der Waal, "Apical Periodontitis Is Associated with Elevated Concentrations of Inflammatory Mediators in Peripheral Blood: A Systematic Review and Meta-analysis.," *J. Endod.*, vol. 45, no. 11, pp. 1279-1295.e3, Nov. 2019.

[11] P. N. Papapanou and C. Susin, "Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both?," *Periodontol. 2000*, vol. 75, no. 1, pp. 45–51, Oct. 2017.

[12] N. J. Kassebaum, E. Bernabé, M. Dahiya, B. Bhandari, C. J. L. Murray, and W. Marcenes, "Global burden of severe periodontitis in 1990-2010: A systematic review and meta-regression," *J. Dent. Res.*, vol. 93, no. 11, pp. 1045–1053, 2014.

[13] D. F. Kinane, P. G. Stathopoulou, and P. N. Papapanou, "Periodontal diseases," *Nat. Rev. Dis. Prim.*, vol. 3, pp. 1–14, 2017.

[14] B. L. Pihlstrom, B. S. Michalowicz, and N. W. Johnson, "Periodontal diseases.," *Lancet (London, England)*, vol. 366, no. 9499, pp. 1809–20, Nov. 2005.

[15] B. G. Loos and T. E. Van Dyke, "The role of inflammation and genetics in periodontal disease," *Periodontol. 2000*, vol. 83, no. 1, pp. 26–39, 2020.

[16] P. N. Papapanou *et al.*, "Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions," *J. Clin. Periodontol.*, vol. 45, no. March, pp. S162–S170, 2018.

[17] M. Martínez-García and E. Hernández-Lemus, "Periodontal Inflammation and Systemic Diseases: An Overview," *Front. Physiol.*, vol. 12, no. October, pp. 1–26, 2021.

[18] P. Monsarrat *et al.*, "Clinical research activity in periodontal medicine: A systematic mapping of trial registers," *J. Clin. Periodontol.*, vol. 43, no. 5, pp. 390–400, 2016.

[19] G. A. Roth *et al.*, "Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study," *J. Am. Coll. Cardiol.*, vol. 76, no. 25, pp. 2982–3021, 2020.

[20] P. Szwed *et al.*, "Infections as novel risk factors of atherosclerotic cardiovascular diseases: Pathophysiological links and therapeutic implications," *J. Clin. Med.*, vol. 10, no. 12, 2021.

[21] J. Moriya, "Critical roles of inflammation in atherosclerosis.," *J. Cardiol.*, vol. 73, no. 1, pp. 22–27, Jan. 2019.

[22] I. Gregersen and B. Halvorsen, "Inflammatory Mechanisms in Atherosclerosis," in *Atherosclerosis*, L. Gianturco, Ed. Rijeka: IntechOpen, 2018.

[23] W. Herrington, B. Lacey, P. Sherliker, J. Armitage, and S. Lewington, "Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease," *Circ. Res.*, vol. 118, no. 4, pp. 535–546, 2016.

[24] P. Libby *et al.*, "Atherosclerosis," *Nat. Rev. Dis. Prim.*, vol. 5, no. 1, pp. 1–18, 2019.

[25] H. A. Schenkein, P. N. Papapanou, R. Genco, and M. Sanz, "Mechanisms underlying the association between periodontitis and atherosclerotic disease," *Periodontol. 2000*, vol. 83, no. 1, pp. 90–106, 2020.

[26] W. Liu *et al.*, "Cardiovascular Disease in People with Periodontitis (Review)," *Cochrane Database Syst. Rev.*, no. 12, 2019.

[27] W. Guan *et al.*, "Clinical Characteristics of Coronavirus Disease 2019 in China," *N. Engl. J. Med.*, vol. 382, no. 18, pp. 1708–1720, 2020.

[28] A. Karlinsky and D. Kobak, "Tracking excess mortality across countries during the covid-19 pandemic with the world mortality dataset," *Elife*, vol. 10, pp. 1–21, 2021.

[29] N. J. Meyer, L. Gattinoni, and C. S. Calfee, "Acute respiratory distress syndrome," *Lancet*, vol. 398, no. 10300, pp. 622–637, 2021.

[30] S. M. Abate, S. A. Ali, B. Mantfardo, and B. Basu, "Rate of intensive care unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis," *PLoS One*, vol. 15, no. 7 July, pp. 1–19, 2020.

[31] F. L. van de Veerdonk *et al.*, "A guide to immunotherapy for COVID-19," *Nat. Med.*, vol. 28, no. 1, pp. 39–50, 2022.

[32] "https://ourworldindata.org/covid-vaccinations." .

[33] C. Huang, L. Yang, J. Pan, X. Xu, and R. Peng, "Correlation between vaccine coverage and the COVID-19 pandemic throughout the world: Based on real-world data," *J. Med. Virol.*, no. January, 2022.

[34] S. R. Knight *et al.*, "Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Development and validation of the 4C Mortality Score," *BMJ*, vol. 370, no. September, pp. 1–13, 2020.

[35] F. Zhou *et al.*, "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *Lancet*, vol. 395, no. 10229, pp. 1054–1062, Mar. 2020.

[36] L. Kim *et al.*, "Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET)," *Clin. Infect. Dis.*, vol. 72, no. 9, pp. e206–e214, 2021.

[37] N. Botros, P. Iyer, and D. M. Ojcius, "Is there an association between oral health and severity of COVID-19 complications?," *Biomed. J.*, vol. 43, no. 4, pp. 325–327, 2020.

[38] N. Marouf *et al.*, "Association between periodontitis and severity of COVID-19 infection: a case-control study.," *J. Clin. Periodontol.*, pp. 0–2, 2021.