Perspective

Chak Kwong Cheng and Yu Huang*

Oral microbiome: a doubtful predictor but potential target of cardiovascular diseases

https://doi.org/10.1515/mr-2023-0015
Received April 26, 2023; accepted June 1, 2023;
published online June 22, 2023

Abstract: Our oral cavity houses various types of microbes including bacteria, protozoa, fungi and viruses, harboring over 700 bacterial species. Oral dysbiosis refers to the imbalance between symbionts and pathobionts in the oral cavity, posing potential threats to host cardiovascular health. Importantly, oral dysbiosis promotes cardiovascular pathophysiology through different mechanisms. Although overgrowth of certain pathogenic bacteria have been indicated in some cardiometabolic diseases, it is still premature to consider oral microbiome as a suitable predictor for non-invasive diagnostic purpose. However, targeting oral microbiome might still provide preventive and therapeutic insights on cardiovascular diseases. Further extensive efforts are needed to deepen our understanding on oral-cardiovascular connection in the context of diagnostic and therapeutic perspectives.

Keywords: cardiovascular diseases; dysbiosis; immune response; inflammation; oral microbiome; periodontitis

Introduction

The oral cavity houses various types of microbes including bacteria, protozoa, fungi and viruses, harboring over 700 bacterial species. These microbes can inhabit both hard surfaces of teeth and soft surfaces of oral mucosa. Oral dysbiosis refers to the imbalance between symbionts and pathobionts in oral cavity, posing potential threats to host health [1]. Oral dysbiosis, which potentially causes periodontitis to subsequently promote systemic inflammation and local vascular inflammation, increases the risks of cardiovascular diseases (CVDs). Numerous CVDs, like hypertensive CVDs, atherosclerotic CVDs, coronary artery diseases (CADs), heart failure, and infective endocarditis, have been validated to be closely associated with oral dysbiosis, both preclinically and clinically [2]. Oral dysbiosis promotes CVD pathophysiology through different mechanisms.

Oral dysbiosis and CVDs

Some common mechanisms by which oral dysbiosis increases cardiovascular risks have been illustrated in Figure 1. During oral dysbiosis and periodontitis, local inflammation in periodontal tissue and permeability of local capillaries are enhanced, therefore bacteria from oral microbiome and bacteria-released toxins can enter the systemic circulation. In a fashion, chronic local inflammation in periodontal tissue promotes the secretion of pro-inflammatory cytokines into systemic circulation. In another fashion, lipopolysaccharide (LPS) on cell walls of Gram-negative bacteria in bloodstream triggers host immune activation, systemic inflammation and increased production of pro-inflammatory cytokines [2]. Moreover, translocation of oral microbes to the intestine aggravates gut microbiome dysbiosis. In case of increased intestinal permeability, gut dysbiosis exacerbates endotoxemia and host immune activation [3]. Dysbiosis of both oral and gut microbiomes result in systemic inflammation and endotoxemia to cause liver dysfunction and even liver diseases (e.g. cirrhosis, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis) [4]. Liver diseases are considered the risk factors for CVDs, where liver disease patients are more susceptible to endothelial dysfunction and arterial calcification, although the detailed mechanisms underlying the causality between liver diseases and CVDs require further study [5]. Ageing is a risk factor for CVDs, where the oral microbiome profiles are largely distinct between aged and young individuals [6], hinting that ageing-associated oral dysbiosis might be partially contributory to cardiovascular pathogenesis. Altogether, the altered immune and inflammatory responses, and endotoxemia contribute to

***Corresponding author: Yu Huang**, Department of Biomedical Sciences, City University of Hong Kong, Tat Chee Avenue, Hong Kong SAR 999077, China, E-mail: yu.huang@cityu.edu.hk. https://orcid.org/0000-0002-1277-6784
Chak Kwong Cheng, Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR, China

the dysfunction and stress in cardiovascular cells (e.g. endothelial cells, vascular smooth muscle cells and cardiomyocytes), increasing cardiovascular risks.

Oral microbiome: a suitable predictor for CVDs?

Numerous preclinical and clinical studies have linked oral dysbiosis to the pathogenesis of different CVDs. Particularly, overgrowth of certain pathogenic bacteria in oral cavity, like *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia* and *Treponema denticola*, are believed to be contributory to pathogenesis of cardiometabolic diseases [7]. However, it is still premature to consider oral microbiome as a suitable predictor for non-invasive diagnostic purpose. A number of obstacles should be overcome to increase the diagnostic insights of oral microbiome in cardiovascular health. Notably, the oral microbiome is highly dynamic over the day. Oral microbiome frequently fluctuates under different activities, such as sleeping, eating, tooth brushing

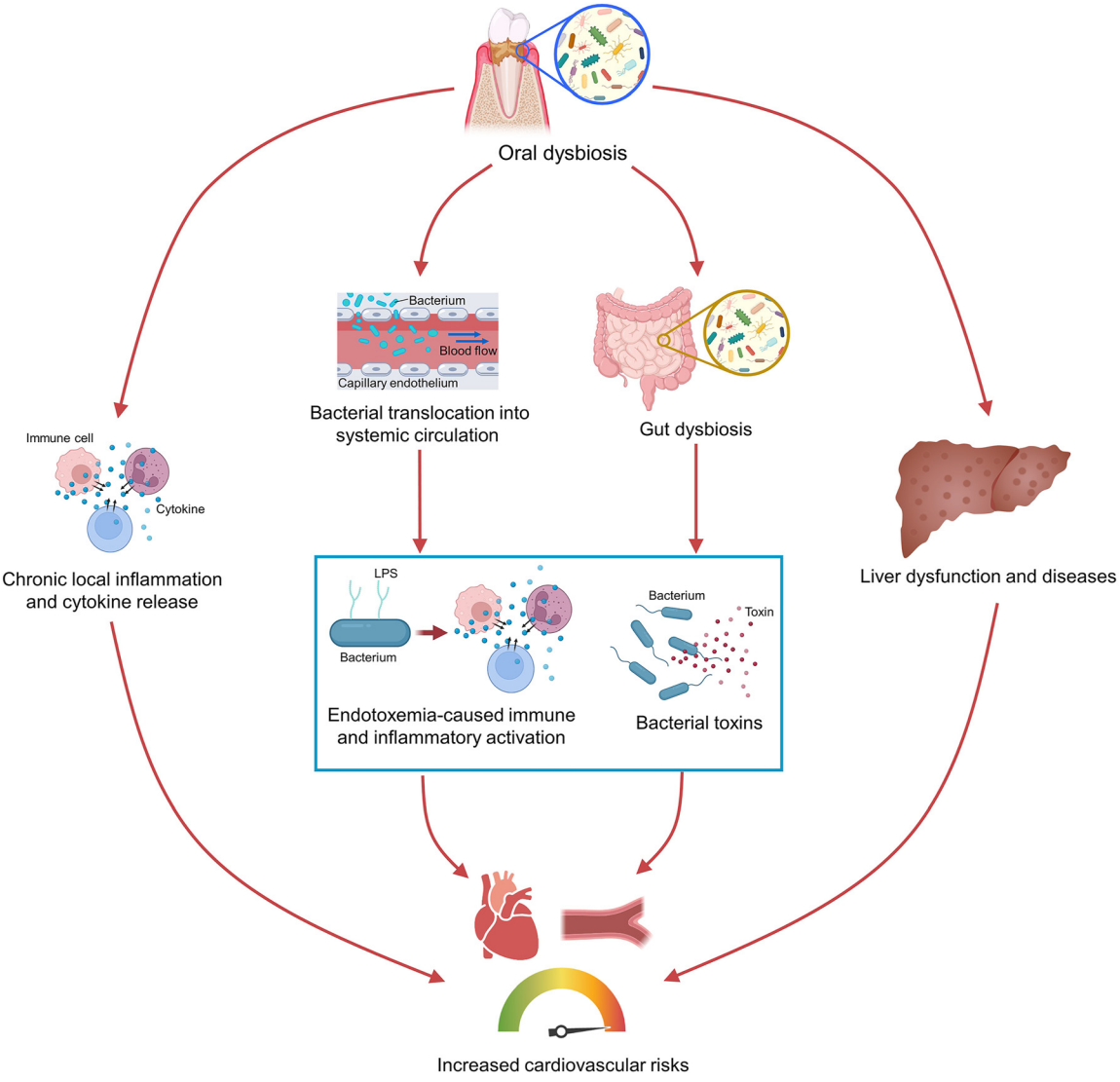

Figure 1: Common mechanisms of oral dysbiosis-promoted cardiovascular pathophysiology. Oral dysbiosis promotes periodontitis pathogenesis, enhancing chronic local inflammation in periodontal tissue, local production of pro-inflammatory cytokines and permeability of surrounding capillaries. Translocation of bacteria from oral cavity to intestine might exacerbate gut dysbiosis. Bacterial translocation from oral cavity and intestine into systemic circulation due to increased vascular and intestinal permeability induces endotoxemia and alters host immune and inflammatory responses. The increased levels of pro-inflammatory cytokines and bacterial toxins trigger dysfunction, inflammation and structural remodeling in cardiac and vascular cells. Oral dysbiosis has been previously shown to be positively linked to pathogenesis of liver diseases, and liver diseases are clinically associated with increased cardiovascular risks.

and exercise. Ageing also greatly alters the oral microbiome of individuals. Oral microbiome profiles of an individual might substantially differ during daytime and nighttime [8]. Whether sampling at a specific timepoint and sampling for multiple times to improve detection accuracy shall be taken into consideration.

Although overgrowth of certain oral microbes, particularly *P. gingivalis*, has been implicated in the pathogenesis of numerous CVDs, their overgrowth cannot specifically predict the occurrence of a particular cardiovascular complication. In other words, overgrowth of certain pathogenic bacteria cannot be used to distinguish different CVDs, but can only imply higher risks for multiple CVDs. Furthermore, overgrowth of certain pathobionts (e.g. *P. gingivalis*) has also been observed in other non-cardiovascular diseases, such as diabetes mellitus and carcinomas [9]. Therefore, we shall not expect a single bacterial strain in oral cavity to be a promising biomarker or predictor in disease diagnosis. Instead, additional to the abundance of single bacterial strain, the abundance of other bacterial strains or other clinical parameters shall be included to improve diagnostic precision. It is postulated that different cardiovascular and non-cardiovascular diseases shall be associated with distinct oral microbiome profiles. However, inconsistency in oral microbiome profiles exists among different clinical studies covering different patient groups, potentially due to individual differences and different research designs. It would be challenging to comprehensively interpret the tremendous amount of oral microbiome data from various databases and studies. The emergence and advancement of artificial intelligence and machine learning technologies shall facilitate researchers to develop prediction models for CVDs in the context of oral microbiome [10]. There is still a long way to go before applying oral microbiome in disease prediction and severity assessment.

Therapeutic insights on oral dysbiosis in CVDs

Although oral microbiome is still not a suitable predictor for CVDs so far, targeting oral microbiome might still provide preventive and therapeutic insights. Notably, personal habits and therapeutic strategies that could restore the ecological balance of oral microbiome and improve oral health are preferred to reduce cardiovascular risks (Figure 2).

Routine oral hygiene maintenance is an important habit in reducing microbial load in oral cavity, lowering the risks of periodontitis for CVD management and prevention. Toothbrushing with fluoride-containing toothpaste, flossing and antiplaque mouthwashes are believed to inhibit dental plaque formation and gingival inflammation. Periodontal treatment might represent a potential approach for lowering cardiovascular risks. In a previous clinical trial, non-surgical periodontal therapy was shown to reduce the plasma levels of systemic inflammation markers (e.g. interleukin-6, fibrinogen and C-reactive protein), and both systolic and diastolic blood pressure in hypertensive patients [11].

Dietary intervention also confers beneficial effects on oral and periodontal health. Consumption of a diet that is rich in fiber and fermentable substrates could boost the levels of end products of microbial fermentation, especially short chain fatty acids (SCFAs), where SCFAs are important regulators of host inflammation, cholesterol metabolism and endothelial homeostasis. Moreover, consumption of micronutrients is beneficial to periodontal and cardiovascular health. Consumption of vitamins (e.g. vitamin A-E, and K) are confirmed to alter oral microbiome, and suppress periodontal inflammation and periodontitis progression [12]. Prebiotics refers to either natural or synthetic food components that stimulate the growth and activity of commensal bacteria in oral and gut microbiome. Meanwhile, probiotics are live microorganisms that confer beneficial effects on host and limit the growth of pathogenic bacteria [13]. Ingestion of prebiotics and probiotics can improve oral microbiome, hence modulating immune and inflammatory responses, both locally and systemically.

Antimicrobial agents can counteract oral dysbiosis through numerous antimicrobial activities, including the disruption on biofilm formation. Although scarce clinical findings have indicated the direct effects of antibiotics on recurrent cardiovascular events, previous studies have implied that oral rinse of 0.12 % chlorhexidine gluconate alleviated infection following cardiac surgery [14], implying postoperative benefits of antibiotic treatment. Similar to gut microbiome, exercise training can also alter oral microbiome, but the detailed mechanism requires further study [15]. In addition, sleep has been linked to alterations in oral microbiome. Recently, chronic sleep deprivation was shown to alter oral microbiome, and cause oral and systemic inflammation in rats [16]. These findings suggested that healthy lifestyles, like regular exercise and sufficient sleep, are beneficial to oral and cardiovascular health. In conclusion, further extensive efforts are needed to deepen our understanding of oral-cardiovascular connection in the context of diagnostic, mechanistic and therapeutic perspectives.

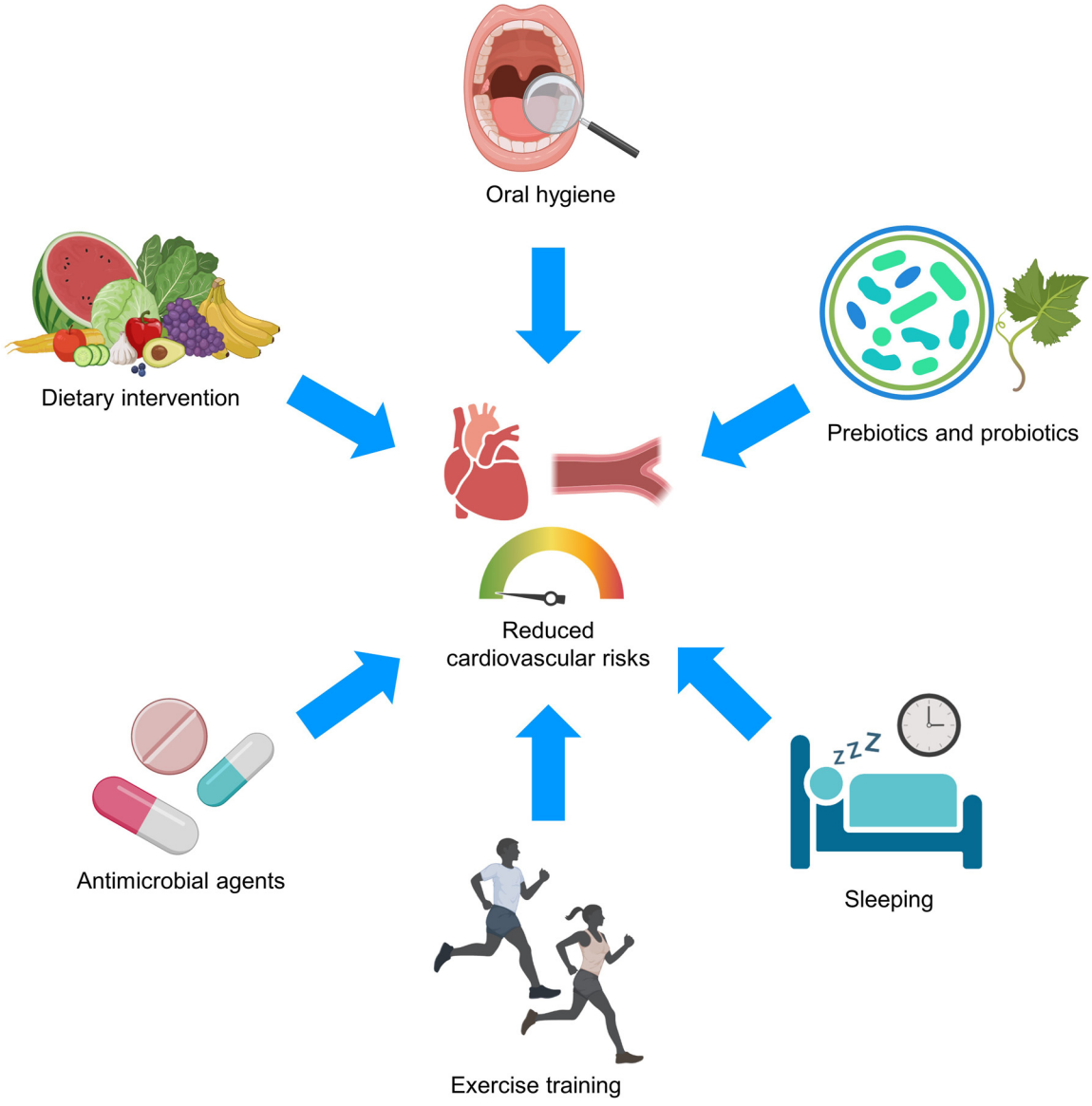

Figure 2: Personal habits and therapeutic strategies to improve oral and cardiovascular health. Maintenance of oral hygiene, dietary intervention, antimicrobial agents, prebiotics and probiotics supplement, exercise training and sufficient sleep are believed to reduce cardiovascular risks via the oral-cardiovascular connection.

Acknowledgments: The authors thank members of the Y. H. group for constructive discussions. Figures were created with BioRender.com.

Research funding: This work was supported by Research Grants Council of Hong Kong (PDFS 2022/23), Health and Medical Research Fund (08190776) and CityU Start-up Fund.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Yu Huang is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and his research group.

Informed consent: Not applicable.

Ethical approval: Not applicable.

References

1. Deo PN, Deshmukh R. Oral microbiome: unveiling the fundamentals. J Oral Maxillofac Pathol 2019;23:122–8.
2. Tonelli A, Lumngwena EN, Ntusi NAB. The oral microbiome in the pathophysiology of cardiovascular disease. Nat Rev Cardiol 2023;20:386–403.
3. Olsen I, Yamazaki K. Can oral bacteria affect the microbiome of the gut? J Oral Microbiol 2019;11:1586422.
4. Acharya C, Sahingur SE, Bajaj JS. Microbiota, cirrhosis, and the emerging oral-gut-liver axis. JCI Insight 2017;2:e94416.
5. Cheng CK, Huang Y. The gut-cardiovascular connection: new era for cardiovascular therapy. Med Rev 2021;1:23–46.
6. Zhou X, Wang B, Demkowicz PC, Johnson JS, Chen Y, Spakowicz DJ, et al. Exploratory studies of oral and fecal microbiome in healthy human aging. Front Aging 2022;3:1002405.

7. Bourgeois D, Inquimbert C, Ottolenghi L, Carrouel F. Periodontal pathogens as risk factors of cardiovascular diseases, diabetes, rheumatoid arthritis, cancer, and chronic obstructive pulmonary disease-is there cause for consideration? Microorganisms 2019;7:424.
8. Carlson-Jones JAP, Kontos A, Kennedy D, Martin J, Lushington K, McKerral J, et al. The microbial abundance dynamics of the paediatric oral cavity before and after sleep. J Oral Microbiol 2020;12:1741254.
9. Olsen I, Yilmaz Ö. Possible role of Porphyromonas gingivalis in orodigestive cancers. J Oral Microbiol 2019;11:1563410.
10. Murugesan S, Elanbari M, Bangarusamy DK, Terranegra A, AlKhodor S. Can the salivary microbiome predict cardiovascular diseases? Lessons learned from the Qatari population. Front Microbiol 2021;12:772736.
11. Vidal F, Cordovil I, Figueredo CMS, Fischer RG. Non-surgical periodontal treatment reduces cardiovascular risk in refractory hypertensive patients: a pilot study. J Clin Periodontol 2013;40:681–7.
12. Santonocito S, Giudice A, Polizzi A, Troiano G, Merlo EM, Sclafani R, et al. A cross-talk between diet and the oral microbiome: balance of nutrition on inflammation and immune system's response during periodontitis. Nutrients 2022;14:2426.
13. Maitre Y, Mahalli R, Micheneau P, Delpierre A, Guerin M, Amador G, et al. Pre and probiotics involved in the modulation of oral bacterial species: new therapeutic leads in mental disorders? Microorganisms 2021;9:1450.
14. Wei J, He L, Weng F, Huang F, Teng P. Effectiveness of chlorhexidine in preventing infections among patients undergoing cardiac surgeries: a meta-analysis and systematic review. Antimicrob Resist Infect Control 2021;10:140.
15. Bryan NS, Burleigh MC, Easton C. The oral microbiome, nitric oxide and exercise performance. Nitric Oxide 2022;125–126:23–30.
16. Chen P, Wu H, Yao H, Zhang J, Fan W, Chen Z, et al. Multi-omics analysis reveals the systematic relationship between oral homeostasis and chronic sleep deprivation in rats. Front Immunol 2022;13:847132.