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Oral Microbiome as the Sixth Vital Sign: A Review of Systemic Connections

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Abstract

The oral microbiome, the complex microbial ecosystem of the mouth, is increasingly proposed as a "sixth vital sign," offering a non-invasive window into systemic health, analogous to traditional metrics like blood pressure and heart rate. This concept is based on the oral cavity's role as both an interface with the environment and a gateway to internal systems. This article reviews the rationale for conceptualizing the oral microbiome as a "sixth vital sign," summarizes the extensive evidence connecting oral microbial dysbiosis (imbalance) to a range of systemic diseases, and critically evaluates the strengths and limitations of this framework. The rationale for this concept rests on the oral cavity's accessibility for sampling, the microbiome's modifiability, and its profound interconnectedness with systemic health. Evidence demonstrates strong associations between oral dysbiosis—particularly stemming from conditions like periodontitis—and numerous systemic disorders. Key mechanistic pathways include the translocation of oral pathogens (e.g., *Porphyromonas gingivalis*, *Fusobacterium nucleatum*) into the bloodstream, the generation of chronic low-grade systemic inflammation, and disruptions via the oral-gut-brain axis. This review details significant links to cardiovascular disease, metabolic disorders (diabetes, obesity), neurological conditions (Alzheimer's disease), autoimmune diseases (rheumatoid arthritis), and various cancers. Despite compelling associations, the "sixth vital sign" concept remains largely metaphorical at present. Its translation into clinical practice is hindered by significant challenges, chiefly the need to establish causality beyond association, the lack of standardized sampling and analytical methods, and the absence of defined "normative" microbial benchmarks. The concept's immediate value is in reinforcing the integration of oral health as an essential component of systemic health monitoring and management.

Keywords: Dysbiosis, Host-microbe Interactions, Oral Microbiome, Systemic Disease, Vital Sign.

Introduction

Vital signs (e.g., heart rate, respiratory rate, blood pressure, body temperature, oxygen saturation) provide immediate, standardised metrics of physiological status and risk (1). In recent years the concept has emerged that the ecosystem of microbes in the oral cavity - the oral microbiome - may serve as an analogous "window" into systemic health (and disease) because the mouth represents both an interface with the external environment and a gateway to internal systems (respiratory tract, gastrointestinal tract) (2).

In this article we have tried to review the rationale for conceptualising the oral microbiome as a "sixth vital sign," summarise the evidence for systemic connections, evaluate the strengths and limitations of this framework, and identify research and implementation priorities.

Oral Microbiome: Ecology, Homeostasis and Dysbiosis

The oral cavity hosts one of the most complex microbial communities in the human body, comprising bacteria (e.g., Streptococcus, Veillonella), fungi, viruses and archaea that inhabit multiple niches (teeth surfaces, gingival sulcus, tongue, mucosa, saliva). In some cases, these microorganisms result in formation of a biofilm, which is a complex community of microbes living together in a protective matrix (3-9).

In health the oral microbiome exists in a dynamic equilibrium (homeostasis), contributing to mucosal defence, nutrient metabolism and prevention of pathogen colonisation. Disturbance of this equilibrium (dysbiosis) occurs via factors such as diet (particularly fermentable sugars), tobacco use, alcohol, salivary flow decline, medications, immunosuppression, poor oral hygiene, and tooth loss (10).

When dysbiosis ensues, pathogenic bacteria may dominate, biofilms become more virulent, local

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inflammation (gingivitis, periodontitis) occurs, and the risk of local disease (caries, periodontal disease) increases. More recently, interest has grown in how these changes may propagate to systemic health via bloodstream dissemination, altered immune responses, or via the oral–gut axis (11).

Why Consider the Oral Microbiome as a "Sixth Vital Sign"?

There are several arguments supporting this framing:

(a) **Accessibility and non-invasiveness**: The oral cavity is easily accessed for sampling (saliva, plaque, swab) unlike many internal organs. Thus, microbial sampling could offer a convenient biomarker of systemic status (12).

(b) **Potential predictive value**: If specific oral microbial signatures precede or reflect systemic disease risk, then measuring them could become part of risk stratification — akin to how elevated blood pressure alerts to cardiovascular risk (12).

(c) **Interconnectedness**: The mouth is both gateway and mirror of systemic health — via the respiratory and gastrointestinal tracts, and via bloodstream. The oral microbiome thus occupies a central position in host-environment interface (7, 8).

(d) **Modifiability**: Unlike many fixed biomarkers (age, genetics), the oral microbiome can be modified via hygiene, diet, antimicrobials, probiotics — offering intervention opportunities (13).

(e) **Holistic health perspective**: Adopting the oral microbiome in vital-sign thinking encourages closer integration between dentistry and systemic medicine.

Nevertheless, it must be emphasised that this concept remains metaphorical at present. For it to become clinically meaningful, we must define normative microbial ranges, standardise sampling/analysis, demonstrate predictive power and cost-effectiveness.

Systemic Connections of the Oral Microbiome

Below we summarise major systemic domains where the oral microbiome (or oral-microbial dysbiosis) is implicated, along with proposed mechanisms and evidence strength.

Cardiovascular Disease

There are numerous associations between periodontal disease/oral microbial dysbiosis and atherosclerosis, coronary artery disease, stroke and hypertension. Review articles highlight key mechanisms:

(a) Translocation of oral pathogens (e.g., *Porphyromonas gingivalis*) into bloodstream from inflamed periodontal pockets to the endothelial activation, oxidative stress, impaired nitric-oxide bioavailability and platelet aggregation (14).

(b) Release of inflammatory mediators (Lipopolysaccharide, cytokines) from oral biofilms into systemic circulation to low-grade systemic inflammation promoting atherogenesis (15).

(c) Molecular mimicry or autoimmunity triggered by bacterial antigens (e.g., heat-shock proteins) leading to vascular damage (16). While these associations are repeatedly observed, demonstrating causality remains challenging.

Metabolic Disorders (Diabetes, Obesity)

The link between periodontal disease and diabetes is well accepted; recent literature emphasises the role of oral microbial dysbiosis in this interplay. Diabetes alters the oral microbial composition (higher glucose in gingival fluid, impaired immunity) promoting pathogenic overgrowth (17). Conversely, periodontal inflammation and dysbiosis may exacerbate insulin resistance via systemic inflammation (18).Obesity and metabolic syndrome have been linked to distinct salivary/oral microbial profiles (reduced diversity, increased pathogens) (19).

Gastrointestinal Disorders & Oral–Gut Axis

Emerging evidence supports an oral–gut axis in which oral microbes may translocate into the gastrointestinal tract (via swallowing or bloodstream) and influence gut microbial composition, barrier integrity and immune responses. *F. nucleatum* (an oral inhabitant) found in gut lesions in irritable bowel syndrome and colorectal cancer. Pathways include enteral route (swallowed saliva with microbes) and hematogenous route (oral microbes entering bloodstream then gut).

Thus, the oral microbiome may influence gastrointestinal disease risk and via gut-derived metabolites affect systemic health (20).

Neurological / Cognitive Disorders

Through processes involving inflammation and oxidative stress, oral microbiome imbalances, also known as oral dysbiosis, are increasingly associated with neurological and cognitive illnesses such as dementia, Parkinson's disease, and Alzheimer's. Toxins and bacteria can enter the bloodstream through chronic oral disorders, pass across the blood-brain barrier, and cause neuroinflammation that harms neurones. Alzheimer's patients' brains have been found to have certain bacteria, such as Porphyromonas gingivalis, which may cause neuronal damage (21).

Mechanisms of Linking the Oral Microbiome with the Neurological Disorders

Systemic Inflammation

When the mucosal barrier is compromised by long-term mouth infections like periodontitis, germs and inflammatory chemicals can enter the bloodstream and cause a systemic inflammatory response that impacts the brain.

Oxidative Stress

Reactive oxygen species (ROS) produced by oral microbial imbalances can lead to oxidative stress, which exacerbates neuroinflammation and neuronal dysfunction.

Oral-Gut-Brain Axis

Oral microorganisms have the ability to go to the gut, where they can cause inflammation that affects brain function and disturb the gut microbiota (gut dysbiosis).

Direct Bacterial Effects

The brain can be directly impacted by certain oral bacteria. For instance, the poisonous enzymes produced by Porphyromonas gingivalis can harm neurones. Another oral bacterium called Treponema denticola has been connected to memory loss in animal experiments.

Blood-Brain Barrier Disruption

Oral dysbiosis-related systemic inflammation can weaken the blood-brain barrier, allowing dangerous substances to enter the brain and injure it (22–28).

Examples of Related Neurological Disorders

Alzheimer's disease (AD)

The pathophysiology of AD is linked to oral bacteria, specifically *P. gingivalis* and *Treponema denticola*, which have been discovered in the brains of AD patients.

Parkinson's disease (PD)

Although the precise processes are still being studied, oral dysbiosis has been connected to PD.

Mild Cognitive Impairment (MCI)

Research indicates that the oral microbiota composition of MCI patients is different from that of cognitively normal people and may be a risk factor for dementia.

Additional requirements

Recent studies point to possible connections between oral dysbiosis and diseases like autism spectrum disorder (ASD), multiple sclerosis, and epilepsy (23).

Autoimmune and Inflammatory Conditions

Mechanisms of oral microbiome contribution to autoimmune and inflammatory responses

Microbial Translocation

Bacteria and their metabolites can enter the bloodstream when the oral barrier is compromised, which can lead to systemic inflammation and an immunological reaction.

Molecular Mimicry

When a bacteria's constituents mimic the body's own proteins, the immune system may unintentionally target the microbe as well as the body's tissues.

Autoantigen Production

Some bacteria have the ability to either manufacture autoantigens themselves or cause the body to do so, which can lead to an autoimmune reaction.

Cytokine Amplification

As seen in Rheumatoid Arthritis (RA), oral dysbiosis can result in an excess of pro-inflammatory cytokines, which can intensify autoimmune reactions and cause tissue damage.

Shared Mechanisms

Inflammatory pathways involving immune cells and pro-inflammatory cytokines like TNF-α and IL-6 are shared by conditions like RA and periodontitis (29-32).

Examples

Rheumatoid Arthritis (RA): Dysbiosis is heavily implicated in RA, with bacteria like *Porphyromonas gingivalis* being specifically linked to the disease. Oral inflammation can promote the creation of autoantibodies, such as anti-citrullinated protein antibodies (ACPAs), which are key markers for RA.

Systemic Lupus Erythematosus (SLE): Changes in the oral microbiome have been linked to SLE, and many patients experience oral lesions like ulcers.
Inflammatory Bowel Disease (IBD): There is increasing evidence that oral dysbiosis can play a role in triggering and worsening IBD conditions like Crohn's disease and ulcerative colitis.
Sjögren Syndrome: Dysbiosis of the oral microbiome is a factor in Sjögren syndrome, which can lead to dry mouth and increase the risk of other oral health issues.
Other conditions: Poor oral health is associated with a higher risk for other autoimmune and inflammatory diseases, including cardiovascular, neurodegenerative, and chronic kidney diseases (29, 31).

Cancer

Through processes like persistent inflammation, the synthesis of carcinogenic compounds, and direct stimulation of tumour growth and invasion, the oral microbiome is associated with cancer. Certain bacteria have been found to be important, including *Fusobacterium nucleatum* and *Porphyromonas gingivalis.* A balanced microbiome may support a healthy immune response, but an unbalanced one (dysbiosis) can encourage cancer by fostering an environment that is pro-inflammatory. The microbiome is being studied for early identification and possible therapeutic approaches**.**

Induction of cancer by microbiome

Chronic Inflammation

One of the main causes of the development of many cancers is chronic inflammation, which can be brought on by an unbalanced oral microbiota.

Production of Carcinogenic Substances

Some oral bacteria can transform salivary nitrate into nitric oxide (NO), which is associated with the development of cancer, or metabolise alcohol from beverages into acetaldehyde, a known carcinogen.

Promotion of Tumour Growth and Invasion

Certain bacteria, such as *F. nucleatum* and *P. gingivalis*, can boost invasion, accelerate tumour growth, and improve the "stemness" of cancer stem cells.

Weakening the Immune Response

Cancer cells can avoid immune surveillance and removal when the body's immune system is suppressed by an unbalanced microbiota (33–35). Table 1 summarizes the important microbial species implicated in systematic disease associations.

Table 1: Microbial Species Implicated in Systemic Disease Associations

Microbial species	Domain of association	Proposed systemic mechanism(s)	References
Porphyromonas gingivalis	Cardiovascular disease, rheumatoid arthritis, diabetes, adverse pregnancy outcomes	Penetration into bloodstream from periodontal pockets; secretion of gingipains; endothelial dysfunction; PAD enzyme citrullination of host proteins (RA)	(36, 37)
Fusobacterium nucleatum	Gut disorders (IBD, colorectal cancer), cardiovascular disease	Oral-gut translocation; promotion of gut inflammation; adhesion/invasion of epithelial cells	(38, 39)
Aggregatibacter actinomycetemcomitans	Rheumatoid arthritis, cardiovascular disease	Leukotoxin A inducing neutrophil hypercitrullination; systemic inflammation	(40–42)
Streptococcus mutans	Endocarditis, cardiovascular disease	Dental biofilm overgrowth; bacteremia during dental procedures; atheroma colonization	(43, 44)
Tannerella forsythia	Periodontitis, cardiovascular disease	Periodontal inflammation, disruption of epithelial barrier, endotoxin release	(45, 46)

Candida albicans	Vulnerable systemic infections, potential role in systemic inflammation	Biofilm co-formation with bacteria; epithelial invasion; immune activation	(47)
Prevotella intermedia	Periodontitis, systemic inflammation, arthritis	Anaerobe dominating in periodontal disease; LPS release; systemic endotoxemia	(48)
Methanobrevibacter oralis	Periodontitis progression, possible systemic links	Methanogenic archaeon; potential modulation of oral biofilm ecosystems; adjunctive role in dysbiosis	(49, 50)

Discussion

The body of evidence linking the oral microbiome to systemic health is compelling. A recurring theme is that oral microbial dysbiosis and periodontal inflammation correlate with systemic disease risk across multiple organ systems (cardiovascular, metabolic, gastrointestinal, autoimmune, neurodegenerative). Mechanistic pathways—although diverse—frequently involve microbial dissemination (enteral or hematogenous), low-grade systemic inflammation, immune modulation and alteration of microbial-host metabolite interactions.

Viewing the oral microbiome as a "sixth vital sign" underscores its potential: easy access, modifiability, integrative potential for systemic health. However, several key challenges must be addressed:

Causality vs Association: Most studies are cross-sectional or observational; few longitudinal studies definitively show that oral microbiome changes precede systemic disease onset. Shared confounders (smoking, poor diet, socioeconomic status) complicate causal inference (51, 52).

Heterogeneity and Standardisation: Sampling (saliva vs plaque vs gingival sulcus), analytical methods (16S rRNA, shotgun metagenomics), definitions of dysbiosis and healthy microbiome vary widely. Without standardisation, translating findings to clinical practice is difficult.

Normative Data Absent: Unlike vital signs (e.g., BP 120/80 mmHg), there is no widely accepted "normal" oral microbiome profile, making thresholds for concern or intervention unclear.

Dynamic Nature of the Microbiome: Oral microbial composition changes with diet, hygiene, medications, salivary flow, dentition status and aging — determining which fluctuations are clinically meaningful vs benign is challenging.

Intervention Evidence Limited: While improving oral hygiene, periodontal therapy and microbial modulation (probiotics, prebiotics) show promise, robust trials demonstrating reduction in systemic disease via oral microbiome modification are scarce.

Implementation and Cost effectiveness: Integrating microbial profiling into routine practice (dental or medical) requires affordable, rapid assays, clinician training, and evidence that monitoring improves outcomes.

Nevertheless, this area offers rich opportunities. Future research can focus on longitudinal cohort studies to establish predictive utility, intervention trials to test causality and benefit, and development of point-of-care microbial assays. Interdisciplinary care models (dentistry and medicine) may help bridge the oral and systemic health divide. If implemented well, the oral microbiome might become part of routine health assessments, especially in high-risk populations (diabetes, CVD, autoimmune disease, pregnancy).

Conclusion

The concept of the oral microbiome as a "sixth vital sign" captures an important shift: recognising the mouth not merely as an isolated organ for eating and speaking, but as a central node in whole-body health. Current evidence robustly supports associations between oral microbial dysbiosis and a wide array of systemic diseases. Nonetheless, translating this into routine clinical practice will require stronger causal evidence, standardised methodologies, normative benchmarks, validated

interventions and cost-effective implementation strategies. For now, clinicians should view oral health — particularly the microbial environment of the mouth — as an integral component of systemic health, and promote oral hygiene, diet and lifestyle interventions accordingly. The next decade holds promise for transforming the oral microbiome from a conceptual window into a standard component of health monitoring.

Abbreviations

LPS: Lipopolysaccharide, PAD enzymes: Peptidyl arginine deiminase

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Author Contributions

All the authors contributed equally.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data are available from the corresponding author upon a reasonable request.

Declaration of Generative AI And AI Assisted Technologies in the Writing Process

The authors used generative AI to assist with language editing and grammatical refinement. The authors critically reviewed and edited the output and maintain complete accountability for the originality and integrity of the published work.

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