The Mouth and its Relationship with Health and Longevity

Raffaele Ambrosio[*], Tiziana Lupoli[**]

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[*] Dentist, neuromuscular gnathologist and posturologist; holder of master's degrees in PNEI and Integrated Care Science, and in Facial Aesthetic Medicine and Therapy; expert and researcher on the extracellular matrix; adjunct professor at various Italian universities; member of the Sipnei Campania coordinating committee and the Sipnei Environment Commission
raffaele.963@virgilio.it
[**] Dentist, expert in oral microbiota; adjunct professor at various Italian universities; holder of master's degrees in PNEI and Integrated Care Science, and in Facial Aesthetic Medicine and Therapy; Mindfulness instructor; member of the Sipnei Campania coordinating committee and the Sipnei Environment Commission.
tizy.lupoli@gmail.com

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Abstract. *The oral cavity is traditionally viewed primarily as the site of mastication, phonation, and the initial phase of digestion. However, recent neuroscientific and microbiological findings indicate that the stomatognathic system constitutes a complex neurosensory and neuroimmunological interface capable of communicating with the central nervous system and numerous organs.*

This paper examines the role of oral health in maintaining systemic health and "healthspan", with particular focus on trigeminal connections, periodontal proprioception, masticatory function, and the oral microbiota.

The natural tooth and the periodontal ligament form a sophisticated proprioceptive unit. Trigeminal afferent signals reach the brainstem, cerebellum, thalamus, and cortex, interacting with circuits involved in arousal, attention, autonomic regulation, and brain plasticity. Tooth loss and reduced masticatory function have been associated with an increased risk of cognitive decline,

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although a direct causal relationship has not yet been proven. At the same time, oral microbiota dysbiosis and periodontitis can contribute to recurrent bacteremia and low-grade systemic inflammation, playing a role in the mouth-heart, mouth-metabolism, mouth-gut, and mouth-brain axes.

The oral cavity can no longer be viewed as an isolated biological compartment. Preserving natural teeth, masticatory function, and oral microbiota balance could be a significant component of strategies for prevention and the promotion of healthy aging.

***Keywords**: trigeminal nerve, vagus nerve, tooth, locus coeruleus, eubiosis, healthspan, longevity, dysbiosis, oral microbiota.*

The Mouth as a Neurosensory Organ: Implications for Neurological Health and Longevity

For many decades, medicine viewed the mouth primarily as the initial segment of the digestive tract and the site dedicated to mastication, phonation, and deglutition. Concurrently, dentistry focused on the prevention and treatment of dental and periodontal diseases, prioritizing functional, aesthetic, and rehabilitative aspects. In recent years, however, advancements in neuroscience, neurophysiology, and integrative medicine have progressively shifted this perspective, highlighting how the stomatognathic system serves as one of the most sophisticated sensory interfaces between the body and the central nervous system.

The mouth is not merely a masticatory organ; it constitutes a complex neurosensory system characterized by an extraordinary density of mechanoreceptors, proprioceptors, nociceptors, and thermoreceptors. These are capable of transmitting a continuous stream of information to the brain – data essential for regulating movement, postural balance, somatic perception, autonomic activity, and, likely, certain higher cognitive functions. This perspective expands the scope of oral health, which can no longer be interpreted solely as the prevention of caries or periodontal disease, but rather as the maintenance of the integrity of one of the body's primary afferent systems.

From an evolutionary standpoint, the stomatognathic system represents one of the most richly innervated regions of the human body. Species survival necessitated the development of a system capable of precisely identifying the texture, temperature, position, and mechanical properties of food prior to swallowing, while simultaneously ensuring airway protection, regulating masticatory force, and controlling phonation. This functional sophistication is made possible by the vast array of sensory information conveyed primarily via the trigeminal nerve.

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The Trigeminal System: An Exceptionally Complex Afferent Network

The trigeminal nerve (5th cranial nerve) constitutes the main sensory pathway of the face and oral cavity. Its three branches – ophthalmic, maxillary and mandibular – collect information from the skin of the face, the oral mucosa, the teeth, the periodontium, the tongue, the temporomandibular joint and the masticatory muscles. The richness of its afferents is such that a considerable part of the cortical somatosensory representation is dedicated precisely to orofacial structures, as demonstrated by Penfield's studies and subsequently confirmed by modern neuroimaging techniques.

Among all the structures of the stomatognathic system, the natural tooth has a unique characteristic: it is suspended within the alveolus by the periodontal ligament, a highly specialized tissue which, in addition to performing a biomechanical function, contains a dense network of extremely sensitive mechanoreceptors. These receptors are able to detect pressure variations of the order of a few grams, allowing almost instantaneous control of the force exerted during chewing. Their function does not simply consist in protecting the tooth from overload, but above all in providing the central nervous system with a continuous flow of proprioceptive information.

The neurophysiological importance of this system is confirmed by the existence of the mesencephalic trigeminal nucleus, an almost unique structure in the entire nervous system. Unlike most sensory pathways, the cell bodies of trigeminal proprioceptive neurons are not located in a peripheral ganglion, but rather within the brainstem. This peculiar anatomical organization testifies to the importance attributed by evolution to the control of the masticatory function and the sensitivity of the oral cavity and suggests the need for a particularly rapid and efficient transmission of information coming from the masticatory muscles and the periodontium (Fig. 1).

From the mesencephalic nucleus, impulses are distributed to numerous structures of the central nervous system: the trigeminal motor nuclei, responsible for controlling the masticatory muscles; the reticular formation, involved in regulating the state of vigilance; the cerebellum, fundamental for motor coordination; the thalamus, main sensory integration station; the somatosensory and motor cortex; the insula and several prefrontal areas involved in attention, motor planning and decision-making processes.

It follows that the occlusal pattern, each chewing act and each swallowing do not represent a simple automatic movement, but rather an extremely complex neurophysiological process that simultaneously involves motor, sensory, cognitive and

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autonomic systems. During a normal day, thousands of chewing cycles generate millions of nerve impulses that reach the brain, contributing to maintaining the activity of numerous neuronal networks; as well as the approximately 1800 swallowing acts (without interposed food, but only saliva) daily and every time the arches come into contact in habitual occlusion.

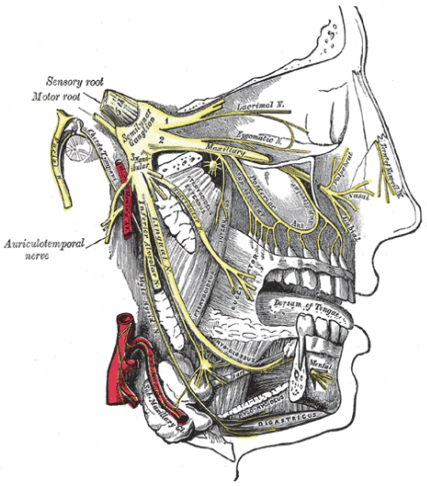


Fig. 1 The trigeminal pathway
The three sensory branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) convey peripheral afferent signals to a primary processing station – the Gasserian ganglion – from which the pathway connecting to the mesencephalic nucleus originates. This is a monosynaptic pathway linking the periphery to the central processing center, a feature that accounts for the immediacy and speed of transmission, as well as the significance of the trigeminal territory within central representation.

The Natural Tooth as a Proprioceptive Organ

Traditionally, the tooth has been described as an anatomical structure composed of enamel, dentin, pulp, and cementum. While morphologically correct, such a description is functionally reductive. Indeed, the tooth should be viewed as a true neurosensory organ, in which the periodontal ligament plays an essential role in transmitting proprioceptive information.

Periodontal receptors enable the discrimination of food consistency, the automatic modulation of mandibular elevator muscle force, and the protection of dental structures against potentially harmful overloading. When a minute foreign object is interposed between the dental arches, the nervous system detects it almost instantly, adjusting muscle contraction with a level of precision rarely found elsewhere in the body. This sensitivity represents one of the most refined expressions of human proprioception.

The loss of a tooth inevitably entails the loss of the receptor system contained within its periodontal ligament. Although implant-based rehabilitation represents a remarkable achievement in modern dentistry, it is well established that an osseointegrated implant cannot fully replicate the natural tooth's proprioceptive function.

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This observation is particularly significant given that the brain maintains its functional organization partly through continuous stimulation from the periphery. As modern neuroscience has demonstrated, cerebral plasticity relies on the constant interaction between sensory inputs and cortical circuits.

Permanently reducing a highly complex afferent input source could, therefore, have consequences extending beyond the mere loss of masticatory function.

Trigeminal Nerve, Locus Coeruleus, and Regulation of Cognitive Functions

In recent years, neuroscience research has progressively expanded the traditional view of the trigeminal system, demonstrating that its functions are not limited to transmitting somatosensory information from the craniofacial region. Indeed, afferent signals from the stomatognathic system reach numerous brainstem structures involved in regulating arousal, attention, and autonomic homeostasis, suggesting that masticatory function may exert effects far broader than mere motor control.

Of particular interest among these structures is the locus coeruleus – a small, pigmented nucleus located in the dorsal pons – which is considered the primary source of noradrenergic neurons in the central nervous system. It gives rise to widespread projections targeting the cerebral cortex, hippocampus, cerebellum, limbic system, and spinal cord, thereby establishing a system for the global modulation of brain functions and the stress axis.

Locus coeruleus activity influences numerous physiological processes, including arousal levels, selective attention, working memory, emotional regulation, synaptic plasticity, the stress response, and pain modulation.

In this context, studies conducted by the group led by Manzoni, De Cicco *et al.* [4, 5, 6] are particularly significant; they proposed a functional relationship between trigeminal afferent input, locus coeruleus activity, and cognitive performance. Using experimental protocols that involved correcting occlusal dysfunctions with customized intraoral devices, the authors observed improvements in certain cognitive parameters, accompanied by changes in pupil diameter – a metric considered an indirect indicator of noradrenergic system activity. The significance of these studies lies not so much in the clinical efficacy of occlusal therapy itself, but rather in demonstrating that altering trigeminal proprioceptive input can influence brain circuits involved in attention and arousal. This innovative perspective warrants further validation through multicenter studies with larger sample sizes, yet it opens up avenues of considerable interest for neurology, neuropsychology, and the medicine of aging.

The pathophysiological hypothesis is biologically plausible. The continuous ac-

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tivity of mechanoreceptors in the periodontal ligament and neuromuscular spindles in the masticatory muscles constitutes a constant source of sensory information directed toward the brainstem. A reduction or alteration in these afferent signals – such as occurs with tooth loss or severe masticatory dysfunction – could, over time, modify the level of stimulation within reticular and noradrenergic networks, potentially impacting cognitive regulation.

Trigeminal Nerve and Autonomic Nervous System

The neurological significance of the mouth extends beyond cognitive functions alone. Indeed, the trigeminal nerve maintains close anatomical and functional links with the autonomic nervous system through connections with the reticular formation, the nucleus of the solitary tract, the nucleus ambiguus, and the dorsal motor nucleus of the vagus nerve.

These interactions form the anatomical basis for the so-called trigemino-autonomic reflexes, which are well-documented in the fields of neurosurgery and maxillofacial surgery. The most well-known of these is the trigemino-cardiac reflex, characterized by the onset of bradycardia, arterial hypotension, apnea, and – in severe cases – transient asystole following the stimulation of specific trigeminal nerve branches during surgical procedures. This reflex clearly demonstrates the capacity of trigeminal afferents to rapidly modulate vagal activity.

From a physiological perspective, these circuits illustrate how the stomatognathic system contributes to the mechanisms regulating autonomic homeostasis. Every act of mastication involves the coordinated activation of somatic and autonomic circuits designed to synchronize respiration, swallowing, salivary secretion, gastrointestinal motility, and cardiovascular responses.

In recent years, some authors have hypothesized that the continuous proprioceptive stimulation resulting from mastication may help maintain the sympathovagal balance, thereby indirectly influencing heart rate variability, cerebral perfusion, and certain neuroendocrine parameters. While available evidence remains limited and often heterogeneous, it suggests that the trigeminal system may serve as a key interface between the somatic and autonomic nervous systems.

This concept is of particular relevance to integrative medicine. Traditionally, the vagus nerve has been considered the primary mediator of autonomic regulation, whereas the trigeminal nerve was described almost exclusively as the sensory and motor nerve of the face. Modern findings, however, indicate that the two systems constantly communicate via shared brainstem networks, contributing to the regulation of inflammation, cardiovascular responses, pain perception, and adaptive processes in response to stress.

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Mastication, Brain Plasticity, and Aging

Mastication is one of the most frequently repeated motor activities throughout a person's life. Thousands of chewing cycles are performed daily, each generating a vast number of afferent impulses directed toward the brainstem, cerebellum, and cerebral cortex. This continuous stimulation may help maintain the integrity of neuronal networks involved in attention, motor coordination, and memory.

Several epidemiological studies have highlighted an association between tooth loss, reduced chewing ability, and an increased risk of cognitive decline. It is important to note that these studies demonstrate an association rather than a causal relationship. Indeed, edentulism also serves as an indicator of general frailty, low socioeconomic status, chronic inflammation, and metabolic disorders – all factors that can independently influence brain health.

Consequently, the loss of trigeminal afferent input may be one of many factors involved in the aging of the nervous system. In this context, preserving natural teeth takes on significance beyond mere chewing function, serving as a strategy to maintain a vital source of sensory stimulation.

This interpretation aligns perfectly with the modern concept of "healthy aging", which holds that maintaining health depends on the integrated preservation of motor, cognitive, sensory, and social functions.

Thanks to its extraordinarily rich neurological connections, the mouth plays a central role in this systemic view of the body.

Preserving natural teeth helps maintain the integrity of the trigeminal system and its central afferent pathways, thereby safeguarding one of the body's key sensory systems. In light of current knowledge, it is plausible to hypothesize that this integrity may contribute – alongside other biological and behavioral determinants – to the maintenance of cognitive function and neurovegetative balance, as well as to healthy aging.

Oral Health as a Determinant of Healthy Aging

For many years, longevity was interpreted primarily as the result of the interplay between genetics, diet, physical activity, and the prevention of chronic diseases. Today, this view appears incomplete. Aging is now considered a systemic process characterized by a progressive loss of biological resilience and a reduced capacity of the organism to maintain homeostasis in the face of environmental stressors. In this context, systems that contribute daily to maintaining the integrity of neurobiological networks are becoming increasingly important.

The oral cavity is one such system.

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Every day, the brain receives a continuous stream of information from the stomatognathic system. Chewing, swallowing, tooth contact, tension in the mandibular elevator muscles, stimulation of periodontal mechanoreceptors, and tongue movements constitute one of the richest sources of afferent information in the entire body. These activities generate millions of nerve impulses reaching the brainstem, cerebellum, thalamus, and cerebral cortex, thereby contributing to the regulation of posture, motor control, alertness, attention, and movement coordination.

Modern biology of aging teaches that the brain maintains its efficiency not only through the absence of disease but also through the continuous stimulation of its neuronal circuits. Sensory deprivation is a major factor contributing to nervous system vulnerability. It is well known that vision loss accelerates the functional decline of certain cortical areas; similarly, hearing loss is associated with an increased risk of social isolation, depression, and cognitive decline. Likewise, a chronic reduction in trigeminal afferent input could – alongside other factors – contribute to altering the balance of neuronal networks involved in cognitive regulation. From this perspective, the natural tooth takes on a significance entirely different from that traditionally ascribed to it by restorative dentistry. It is not merely an element of the masticatory apparatus but a component of a complex neurobiological system capable of providing continuous information to the brain throughout a person's life.

This view also prompts reflection on the value of dental prevention. Preventing caries and periodontal disease should not be viewed solely as a means to avoid pain, infection, or tooth loss, but rather as a strategy aimed at preserving a sensory asset that accompanies the individual throughout their existence. Preserving a tooth means, in fact, preserving its periodontal ligament, its mechanoreceptors, its connections to the mesencephalic nucleus of the trigeminal nerve, and the entire central integration network that relies on it.

Naturally, it would be incorrect to attribute a direct causal role in brain aging processes to tooth loss. Longevity results from a multitude of genetic, epigenetic, metabolic, immunological, environmental, and behavioral determinants. However, integrated medicine teaches us that health emerges from the dynamic interaction between seemingly unrelated systems.

Furthermore, recent literature has highlighted a second level of interaction: the relationship between oral health and systemic inflammation. Periodontal disease is now recognized as a chronic inflammatory condition associated with elevated circulating levels of pro-inflammatory cytokines, such as interleukin-6, TNF-α, and C-reactive protein. These mediators are involved in the processes of inflammaging – the state of chronic, low-grade inflammation that characterizes biological aging and contributes to the development of atherosclerosis, diabetes mellitus, frailty, sarcopenia, and neurodegenerative diseases.

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Therefore, oral health can influence longevity through at least two complementary pathways. The first is immuno-metabolic in nature, involving the control of chronic inflammation and oral microbiota dysbiosis. The second is neurophysiological, involving the maintenance of the integrity of trigeminal afferent pathways and their associated neuronal networks. These two dimensions are not independent; rather, they constantly interact to determine the organism's ability to adapt to the aging process.

This perspective marks a paradigm shift. The mouth is no longer merely the beginning of the digestive tract but serves as a genuine neuro-immunological interface between the environment and the brain. Each natural tooth contributes simultaneously to nutrition, phonation, sensory perception, autonomic regulation, and the maintenance of systemic homeostasis. The loss of this asset entails not only reduced masticatory efficiency but also a decline in the biological complexity of the stomatognathic system.

For integrative medicine, this view opens up particularly interesting prospects. Safeguarding oral health is no longer solely a dental objective; it is now firmly established as a key component of interventions promoting healthy aging.

Current knowledge indicates that the stomatognathic system constitutes one of the richest sensory networks in the human body. Trigeminal afferent signaling, periodontal ligament proprioception, brainstem connections, communication with the autonomic nervous system, and interactions with cognitive circuits suggest that the mouth plays a far more extensive role than traditionally recognized.

Many hypotheses regarding the relationship between masticatory function, brain plasticity, and longevity still require high-quality prospective and experimental studies. However, the body of anatomical, neurophysiological, epidemiological, and clinical evidence is sufficient to propose a new interpretive paradigm: preserving natural teeth is not merely a dental objective but also a strategy for safeguarding a neurological asset.

Every natural tooth is more than just an anatomical element; it is a neurological receptor linked to the brain!

From this perspective, oral health can be considered a determinant of "healthspan" – the length of time spent in good health. This is not because teeth alone determine longevity, but because they help maintain the integrity of a neuro-sensory and neuro-immunological network that constantly communicates with the brain and the entire organism.

Future Perspectives: From Oral Health to Neuro-Prevention

Advances in neuroscience and biology are progressively reshaping our under-

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standing of the relationship between the mouth, the brain, and general health. For decades, dental prevention focused primarily on managing local conditions: caries, infections, periodontal disease, tooth loss, and the restoration of masticatory function. Today, a broader perspective is emerging, one in which maintaining oral health is viewed as integral to safeguarding neurological integrity and promoting healthy aging.

The concept of neuro-prevention stems from the realization that the brain is not an isolated organ but a dynamic system that maintains its efficiency through a continuous dialogue with the body. Sensory information from the periphery plays a key role in maintaining cortical maps, synaptic plasticity, and the functional organization of neuronal networks.

Consequently, preserving natural teeth should be viewed not merely as a way to maintain chewing ability or smile aesthetics, but also as a strategy to safeguard a vital source of neurological stimulation. Each tooth – through its periodontal ligament and associated network of mechanoreceptors – contributes to the ongoing activation of trigeminal pathways that reach the brainstem, thalamus, and cerebral cortex.

In the future, dentistry could play an even more central role in preventive medicine by collaborating with neurologists, geriatricians, psychologists, and rehabilitation specialists to identify early changes in the stomatognathic system that may be linked to reduced sensory stimulation of the brain.

This perspective does not imply a deterministic view in which tooth loss inevitably leads to neurological decline. Brain aging is a complex phenomenon influenced by a multitude of genetic, metabolic, vascular, immunological, environmental, and psychological factors. However, precisely because the brain is a system characterized by plasticity and continuous adaptation, a chronic reduction in sensory stimuli may be one of several elements contributing to the vulnerability of neuronal networks over the course of a lifetime.

A particularly promising area of study concerns the interaction between the trigeminal system, the autonomic nervous system, and stress regulation. Connections linking orofacial afferents, the reticular formation, the locus coeruleus, and vagal nuclei suggest that the mouth may serve as a peripheral entry point for modulating circuits involved in neurovegetative balance. This perspective could open up new avenues of research into chronic stress-related disorders, sleep disorders, age-related cognitive decline, and functional recovery processes following neurological events.

The relationship between oral health and systemic inflammation is also a field of great interest. Reducing the inflammatory burden through the prevention and treatment of periodontal disease could help mitigate “inflammaging” – the state of

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chronic, low-grade inflammation associated with aging that has been linked to numerous chronic diseases, including certain neurodegenerative conditions. Indeed, the mouth constitutes a significant microbial and immunological ecosystem where the balance – or dysbiosis – can have repercussions for the entire body.

From this perspective, a new cultural and clinical model emerges: caring for the mouth means caring for the brain as well. Preventing tooth loss, maintaining masticatory function, managing periodontal health, and preserving trigeminal afferent pathways can be viewed as interventions aimed not only at current quality of life but also at safeguarding future functional reserve.

Indeed, longevity is not merely a matter of living longer; it is about maintaining independence, cognitive abilities, social connections, and overall physical and mental well-being. In this context, oral health becomes a vital component of "healthspan" – the period of life spent in good health.

The Oral Microbiota: From Eubiosis to Dysbiosis

Another aspect to consider regarding the relationship between oral health and systemic health is the oral microbiota.

The oral microbiota represents the second most complex microbial ecosystem after the gut, comprising over seven hundred bacterial species alongside fungal, viral, and archaeal components. It colonizes distinct ecological niches – the dorsum of the tongue, the gingival sulcus, supra- and subgingival tooth surfaces, the buccal mucosa, and saliva – each characterized by specific conditions of oxygenation, pH, and nutrient availability that shape its composition and biofilm structure. Under conditions of eubiosis, the phyla Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria predominate, while genera such as Streptococcus, Actinomyces, Veillonella, and Neisseria act as pioneer colonizers of dental plaque. This balance is maintained by host homeostatic mechanisms – salivary flow, secretory IgA, defensins, and complement proteins in gingival crevicular fluid – as well as by the mycobiotic and viral components, which contribute to horizontal gene transfer and virulence modulation.

Dysbiosis – defined as a loss of diversity and the expansion of pathobiont taxa – is driven by interconnected risk factors: inadequate oral hygiene; smoking; a diet rich in fermentable carbohydrates (which selects for Streptococcus mutans); uncontrolled diabetes; xerostomia-inducing medications (antihistamines, antidepressants, diuretics, muscle relaxants, antihypertensives); chronic immunosuppressive stress; genetic predisposition; and hormonal fluctuations. These factors converge to produce a microbiome dominated by Porphyromonas, Tannerella, Treponema, and Fusobacterium, a state associated with chronic periodontitis. The contemporary

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model of polymicrobial synergy and dysbiosis (PSD) explains this transition not as the effect of a single pathogen, but rather of an organized community in which Porphyromonas gingivalis acts as a keystone pathogen; a similar principle governs dental caries, where S. mutans and an exopolysaccharide secreted by lactic acid bacteria (glucan EPS) generate progressively selective acidic microenvironments.

Systemic Linkage Mechanisms: The Axes

The oral cavity serves as a primary gateway to the bloodstream and the gastrointestinal tract. The first mechanism of systemic linkage is hematogenous bacterial translocation: when the junctional epithelium – physiologically thin – is compromised by periodontal inflammatory processes, bacteria, lipopolysaccharides, extracellular vesicles, and metabolites transiently enter the circulation during chewing, brushing, or dental procedures, resulting in recurrent bacteremia characterized by low intensity but high cumulative frequency. The second pivotal mechanism is low-grade systemic inflammation, marked by chronically elevated levels of IL-6, IL-1β, TNF-α, and C-reactive protein; periodontitis – comparable to a chronic wound due to the extent of ulcerated epithelium – acts as a constant source of immune stimulation, fueling endothelial dysfunction and lipid profile alterations in sites distant from the oral cavity.

The mouth-heart axis is supported by substantial epidemiological and mechanistic evidence: periodontitis is associated with the incidence of atherosclerotic cardiovascular events, a link mediated both by the direct translocation of *Porphyromonas gingivalis* into atheromatous plaques (where bacterial genetic material has been detected) and by the indirect impact of systemic inflammation on endothelial dysfunction, LDL oxidation, and plaque instability. The oral-gut axis is equally significant: the continuous swallowing of oral microorganisms leads to oral-to-intestinal translocation capable of altering the gut microbiota, compromising the mucosal barrier, and contributing to Crohn's disease and ulcerative colitis; it is also implicated in colorectal carcinogenesis via *Fusobacterium nucleatum*, which promotes the recruitment of tumor-infiltrating myeloid cells.

The oral-metabolic axis is supported by a well-established bidirectional relationship between periodontitis and type 2 diabetes mellitus. Chronic hyperglycemia promotes oral dysbiosis through the advanced glycation of tissue proteins, altered neutrophil function, and a compromised mucosal immune response; conversely, the systemic inflammation driven by periodontitis contributes to insulin resistance through the action of proinflammatory cytokines on hepatic, muscular, and adipose insulin receptors, thereby worsening overall glycemic control. Growing evidence also links oral dysbiosis to metabolic syndrome and obesity, suggest-

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ing that the oral microbiota plays a role in modulating appetite via systemically active metabolites and in regulating intestinal permeability.

Systemic Implications

Epidemiological evidence identifies the dysbiotic oral microbiota as a factor in carcinogenesis at distant anatomical sites. Prospective cohort studies have documented that individuals with high antibody titers against Porphyromonas gingivalis face double the risk of pancreatic adenocarcinoma compared to controls, while the abundance of Tannerella forsythia, P. gingivalis, and Fusobacterium nucleatum is significantly higher in esophageal neoplastic tissue than in adjacent healthy tissue.

At a mechanistic level, in oral squamous cell carcinoma, P. gingivalis activates the TLR4-NF-κB pathway – leading to hyperactivation of the JAK1-STAT3 cascade and inhibition of apoptosis – interferes with cyclin regulation and p53, and induces the gingipain-dependent dissociation of the β-catenin destruction complex, thereby promoting the overexpression of oncogenes such as Cyclin D1 and c-Myc.

Nephrology and hepatology have also recently acknowledged the pathogenetic contribution of the oral microbiota. In chronic kidney disease, elevated titers of immunoglobulin G against periodontal pathogens – such as P. gingivalis, Treponema denticola, Selenomonas noxia, Aggregatibacter actinomycetemcomitans, and Veillonella parvula – correlate with the deterioration of renal function; furthermore, large-scale, decade-long cohort studies have documented a 32% to 41% increase in mortality among patients with kidney disease who also suffer from chronic periodontitis.

In the field of hepatology, P. gingivalis infection has been linked to the progression of non-alcoholic fatty liver disease to steatohepatitis, presumably via a mouth-gut-liver axis; in this model, compromised intestinal permeability allows for the translocation of periodontal bacteria and their metabolites – recognized by Toll-like receptors expressed on hepatocytes and Kupffer cells – thereby triggering a chronic hepatic inflammatory response.

This range of organ-system associations finds a useful conceptual parallel in the gut-skin axis [12] – a recently characterized model of bidirectional, microbiota-mediated communication in which metabolites such as short-chain fatty acids and aryl hydrocarbon receptor ligands link gut dysbiosis to chronic inflammatory dermatoses (Fig. 2).

The mouth-brain axis represents the most recently explored area [19], supported by evidence linking chronic periodontitis to neurodegenerative diseases – particularly Alzheimer's – through the translocation of Porphyromonas gingivalis to

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brain tissue (where gingipains, proteases secreted by the bacterium, degrade synaptic proteins and promote beta-amyloid aggregation) and through microglia activation driven by systemic inflammation.

In conclusion, the oral microbiota emerges as a systemic determinant of general health, capable of influencing cardiovascular, gastrointestinal, metabolic, neurodegenerative, oncological, autoimmune, renal, and hepatic conditions through bacterial translocation and chronic low-grade inflammation. Therapeutic prospects are shifting towards species-specific oral probiotics, periodontal maintenance therapy as a form of systemic prevention, engineered bacteriotherapy, prebiotic agents such as arginine, pH-responsive catalytic nanoparticles, and salivary biomarkers predictive of systemic risk.

Integrating these approaches with salivary biomarkers predictive of systemic risk – within the framework of precision medicine – further underscores the need for interdisciplinary training pathways that link dentistry, internal medicine, oncology, nephrology, and hepatology into a truly integrated care model.

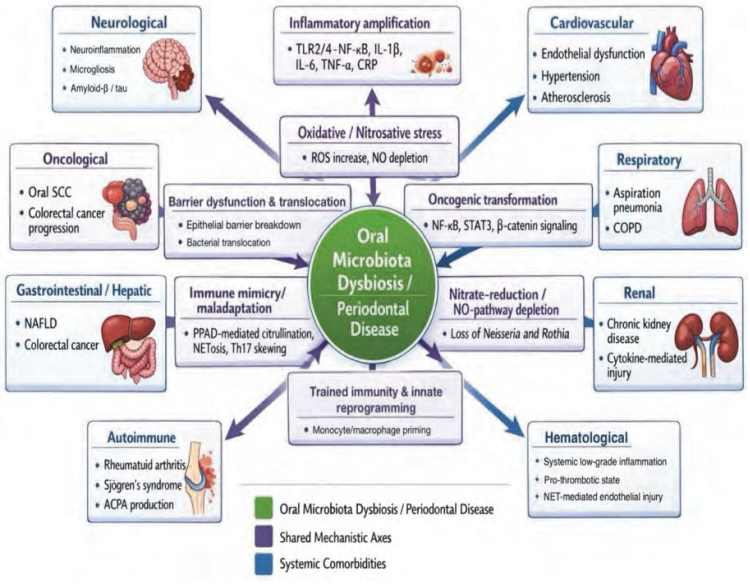


Fig. 2 Clinical effects of oral dysbiosis ***Schematic representation of the local and systemic inflammatory pathways linking oral dysbiosis and periodontal disease to associated comorbidities.***

Conclusions and Therapeutic Prospects

In conclusion, the oral microbiota acts as a systemic determinant of general health, capable of influencing cardiovascular, gastrointestinal, metabolic, neurodegenerative, oncological, autoimmune, renal, and hepatic conditions through bac-

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terial translocation and low-grade chronic inflammation. Therapeutic prospects are shifting towards species-specific oral probiotics, periodontal maintenance therapy as a form of systemic prevention, engineered bacteriotherapy, prebiotic agents such as arginine, pH-responsive catalytic nanoparticles, and salivary biomarkers predictive of systemic risk.

Emerging therapeutic avenues thus extend beyond traditional non-surgical periodontal therapy: fecal microbiota transplantation – while primarily applied to the gut – suggests a principle applicable to modulating the oral ecosystem, just as bacteriotherapy using engineered strains capable of secreting immunomodulatory molecules represents a promising frontier.

Integrating these approaches with salivary biomarkers that predict systemic risk further underscores the importance of strengthening interdisciplinary training pathways to achieve a truly integrated care model.

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