Salivary Short-chain Fatty Acids (SCFAs) Are Viable Predictors of Early Changes in Systemic Health

Bina KASHYAP[1], Eelis HYVÄRINEN[1], Arja M KULLAA[1]

Short-chain fatty acids (SCFAs) are the metabolites identified in both the oral cavity and the gut. They play an important role in the triggering, development and progression of systemic diseases. SCFAs can alter the gut microbial components, intestinal epithelium and host immune system, and are also associated with cancer incidence. Salivary SCFAs, produced by the oral microbiome, are correlated with some oral diseases. The occurrence of systemic diseases associated with gut SCFAs is more clearly defined than oral SCFAs. Salivary SCFAs can enter the bloodstream directly via inflamed gingiva to cause continuous low-grade systemic inflammation. Hence, salivary SCFAs could be an indicator for the early diagnosis of systemic diseases. Furthermore, they provide a basis for understanding the oral-systemic axis driven through salivary SCFAs in the pathogenesis of several diseases.

Keywords: *gut microbiome, oral diseases, oral microbiome, salivary metabolites, SCFAs.*
Chin J Dent Res 2024;27(3):193–202; doi: 10.3290/j.cjdr.b5698392

Oral diseases, including caries, periodontal disease, oral precancers and cancers, are a major concern globally and a serious health burden that has a substantially negative effect on society. The oral cavity is a complex with different niches for the colonisation of micro-organisms including bacteria, fungi, eukaryotes and viruses, that can cause several oral diseases.[1] These niches are predominantly exposed to the saliva and gingival crevicular fluid that hydrate bacteria and provide a medium for nutrient transportation.[2] The oral microbiome maintains a dynamic balance in interbacterial and host-bacterial interactions.[3] Oral dysbiosis is the interaction between the pathogens and the host's immune response, resulting in oral diseases. The microbial diversity and shifts in bacterial composition increase the abundance of pathogenic bacteria and decrease commensal health-associated bacteria. The most common consequences of this oral dysbiosis are oral diseases and infections, such as periodontitis, gingivitis, oral ulcers, oral candidiasis and dental caries.[4] Changes in the oral microbiome have also been observed in connection with metabolic diseases, autoimmune diseases, immunosuppression and pregnancy.[5]

Oral microbes release salivary metabolites as a product of multifactorial interactions between the host, oral bacteria and altered cellular metabolism of the host. Periodontal diseases are initiated and propagated through oral dysbiosis which interacts with the immune defences of the host, leading to inflammation and disease and even systemic inflammation.[6] The relationship between periodontitis and systemic diseases such as cardiovascular diseases, diabetes mellitus, problems during pregnancy, rheumatoid arthritis, chronic obstructive pulmonary disease, pneumonia, obesity, chronic kidney disease, metabolic syndrome and cancer has been previously demonstrated.[7] Furthermore, variation in the oral microbiome is reported to be associated with oral cancer,[8] pancreatic cancer,[9] colorectal cancer[10] and neurodegenerative diseases.[11] Although some relationships involving oral microbiome variations and different diseases have been confirmed, the exact cause of pathogenesis remains unclear.

Salivary metabolites

Homeostasis in the oral cavity is maintained primarily by the saliva's multifactorial defence system. Saliva is

1 Institute of Dentistry, University of Eastern Finland, Kuopio Campus, Kuopio, Finland.

Corresponding author: Dr Bina KASHYAP, Institute of Dentistry, Faculty of Health Sciences, University of Eastern Finland, Kuopio Campus, Kuopio, Finland. Tel: 358-417530854. Email: bkashyap@uef.fi

This study was supported by the Finnish Cultural Foundation.

a complex biofluid consisting of a broad spectrum of components that provides biomarkers of health and disease status. It facilitates diagnosis and prognosis of disease by yielding information on metabolites, proteins, mRNA, DNA, enzymes, hormones, antibodies, antimicrobial constituents and growth factors,[12] and reflects both diseases of the oral cavity and systemic conditions. Salivary metabolites, molecules of a low weight present in the saliva (endogenous or exogenous), often represent a useful tool for the detection of various oral and systemic diseases.[13]

Metabolomic studies have confirmed that micronutrients obtained from dietary sources such as carbohydrates, proteins and lipids are important in regulating energy metabolism and inflammatory responses. The salivary metabolites are studied through different analytical methods such as mass spectroscopy (MS), gas spectroscopy (GS), capillary electrophoresis (CP), high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) spectroscopy. These technologies have helped to reveal how biochemical reactions and their end-products are involved in the pathogenesis of various diseases. The most common salivary metabolites that are quantitatively analysed are amino acids, carbohydrates and organic acids..[14] NMR spectroscopy is used to detect short-chain fatty acids (SCFAs) such as acetate, butyrate, formate and propionate in human saliva samples.[15,16]

Of all the metabolites, acetate, propionate and butyrate have shown pathophysiological changes that reflect disturbances in metabolic pathways in different diseases. Acetate, propionate and butyrate are SCFAs that are produced by saccharolytic and proteolytic oral bacteria and correlate with salivary microbial load.[16] Acetate and propionate are mainly produced by gram-negative bacteria (Bacteroidetes), whereas butyrate is the metabolic product of gram-positive bacteria (Firmicutes). Less than 1% of SCFAs are formed as products from peptide and amino acid fermentation.[17] The release of SCFAs as microbial metabolite has contributed to several oral inflammatory diseases. Table 1 presents salivary SCFAs in different oral diseases.[18-33] SCFAs are also produced by some anaerobic periodontal bacteria and are released from infection sites into the microenvironment.[34] In addition to oral sources, the main SCFAs including acetate, propionate and butyrate are produced in the large intestine by microbial degradation of undigested carbohydrates.[35] Studies from preclinical models have shown that the gut microbiome maintains bidirectional communication with the brain or gut–brain axis via a network of immunological, neuronal and endocrine signalling pathways.[36] The presence of SCFAs in the oral cavity and their communication with the systemic circulations have not been confirmed, despite having overlapping microbiomes with the gut.

SCFAs: a result of oral dysbiosis

Disturbances in the normal symbiotic relationship between the host and its resident microorganisms can increase the risk of disease by changes in the oral environment. Several factors, including smoking, alcohol consumption, socioeconomic status, antibiotic use, diet and pregnancy, can affect the oral microbiome and their metabolites.[37] The oral cavity hosts several microbes distributed at different locations. Oral dysbiosis can lead to the loss of beneficial oral species and pathogen colonisation, either directly or indirectly through immunosuppression, oxygen deprivation, biofilm formation or other potential mechanisms.[38] SCFAs are produced by oral bacteria, as end-products of their metabolism. These fatty acid-secreting bacteria are present in lesions of both dental caries and periodontitis. It has been speculated that these short-chain organic acids assist in cell-to-cell metabolic communication via bacterial colonization. The protective or harmful role of dental biofilm in the oral cavity is still unknown, though it is another source of SCFAs.[39,40]

Salivary lactate, acetate and n-butyrate have been observed in patients with dental caries wherein one or more of the SCFAs reduce the pH and increase the porosity of the dental plaque matrix.[41] In periodontitis, increased salivary metabolites, as acetate, propionate and butyrate are strongly linked to preventing cell division, diminished the ability to repair damage, junctional epithelium degeneration processes and stimulation of inflammatory response with the liberation of cytokines.[23] The presence of these SCFAs is pointed out as a possible indicator of periodontal disease development and progression. In one study, a significant decrease in salivary SCFAs was observed after periodontal treatment.[26] The association of salivary SCFAs with periodontal disease requires further investigation, as it is still unclear whether disease susceptibility is based on the local immune-inflammatory reactivity or oral microbiome, or at systemic metabolic level.

Oral dysbiosis with persistent periodontitis contributes to the development and progression of psychiatric and neurodegenerative disorders, as well as autoimmune diseases.[42] The periodontal pathogens can release or induce pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF)-alpha that accelerate the neuroinflammation involved with Alzheimer's disease.[43] An increased

Table 1 Salivary SCFAs in different oral diseases.

Study	Oral disease	n (C/D)	Saliva	Method	Salivary metabolites (SCFAs)		Oral impact
					Elevated	Decreased	
Fidalgo et al[18]	Dental caries	10/20	USWS	NMR	Butyrate, propionate	NR	Decreased pH and increased porosity of dental plaque matrix
Pereira et al[19]	Dental caries	38/NA	USWS, SWS	NMR	NR	Butyrate	Protein hydrolysis and deglycosylation
Schulz et al[20]	Dental caries	36/21	USWS	LC-MS	Acetic acid, propionic acid,	NR	Dietary factors increase organic acids
Aimetti et al[21]	Periodontitis	22/32	WS	NMR	Acetate, c-aminobutyrate, n- butyrate, propionate	NR	Proteolytic destruction and increased disease severity
Rzeznik et al[22]	Periodontitis	26/26	SWS	NMR	Butyrate	Lactate, acetate	Increased periodontal inflammation and shift in microbial composition
Romano et al[23]	Aggressive and chronic periodontitis	39/61	USWS	NMR	NR	Lactate, acetate, butyrate	Increased prevalence of periodontal bacterial species
García-Villaescusa et al[24]	Chronic periodontitis and glioblastoma	120/10	USWS	NMR	Caproate, isocaproate, butyrate, isovalerate, isoleucine, isopropanol	NR	Increased entry of periodontal pathogens and periodontal pocket formation
Liebsch et al[25]	Periodontitis	909/NA	SWS	UHPLC-MS/MS	Isovalerate	NR	Increased inflammation, cytokine liberation and periodontal pocket formation
Gawron et al[26]	Chronic periodontitis	15/30	USWS	1H-NMR	NR	Propionate, acetate	Shift in microbial colonisation
Citterio et al[27]	Periodontitis after therapy	11/12	USWS	NMR	Isovalerate, lactate.	Acetate, propionate, butyrate	Decreased microbial load after treatment
Kim et al[28]	Periodontitis	92/129	SWS	NMR	Butyrate, isovalerate	Acetate, propionate	Increased periodontal inflammation and increased recolonisation of periodontal pathogens
Sanches et al[29]	TMJ disorder	27/26	USWS	1H-NMR	Acetate, propionate, isovalerate	NR	Increased inflammation and cytokine release
Wei et al[30]	OSCC/leukoplakia	34/69	WS	LC-TOF-MS	Lactic acid, 3-indolepropionic acid	γ-aminobutyric acid	Varied metabolic rates, increased glycolysis and increased occurrence of cancer
Wang et al[31]	OSCC	30/30	USWS	CE-MS	Lactic acid	NR	Altered biochemical process and glycolytic switch
Ishikawa et al[32]	Lichen planus/ OSCC	NA/60	USWS	CE-MS	5-aminovalerate, gamma- butyrobetaine	NR	Tumour progression
Yatsuoka et al[33]	HNC with RT	NA/9	USWS	CE-TOFMS	Gamma-aminobutyric acid (GABA), butyrate, 2-aminobutyric acids	NR	Increased severity of disease

C, control; CE-TOF-MS, capillary electrophoresis time-of-flight mass spectrometry; D, disease; GC/MS, gas chromatography/mass spectrometry; HNC, head and neck carcinoma; LC/MS, liquid chromatography/mass spectrometry; NA, not available; NMR, NMR-spectroscopy; NR, not reported; OSCC, oral squamous cell carcinoma; RT, radiotherapy; SWS, stimulated whole saliva; TMJ, temporomandibular joint; UHPLC-MS/MS: ultra-high performance liquid chromatography and tandem mass spectrometry; USWS, unstimulated whole saliva; WS, whole saliva.

Table 2 SCFA function in a healthy oral environment and during oral dysbiosis.

Condition	Source of SCFAs	SCFAs	Oral microbiome	Dental biofilm	Host immune system	CNS
Healthy oral environment	Carbohydrate, protein, amino acids	Acetate, butyrate, formate, propionate	*Actinomyces spp., Bacteroides spp., Corynebacteria spp., Eubacterium spp., Fusobacterium spp., Haemophilus spp., Megasphaera spp., Neisseria spp., Propionibacterium Prevotella spp., Porphyromonas spp., Rothia spp.*	Antibacterial activity, homeostatic balance	Pro-inflammatory, anti-inflammatory, chemoattractant	Improves synapses, microglial maturation
Oral dysbiosis				Limit commensal microbiota, pathogenic microbiota dominate, homeostatic balance disturbed	Increased inflammation, chronic condition, decrease immunity, increased expression of pro-inflammatory cytokines	Triggers microglia mediated innate immune response, alteration in neurotransmitter production, promotes neuroinflammation, neurodegenerative changes

abundance of *Porphyromonas gingivalis* or *P. gingivalis*, a causative microorganism of periodontitis, was reported in the oral cavity of patients with neurodegenerative diseases.[44] A study on mice has shown brain colonisation due to *P. gingivalis* infection.[45] Also, *P. gingivalis* produces proteases that have neurotoxic characteristics. On the other hand, oral species of phylum *Spirochaetes* and genus *Treponema*, have been shown to cause amyloid plaques in Alzheimer's disease.[45] The pathogenic oral microbes enter the brain tissue through different paths to damage the central nervous system (CNS): haemorrhagic oral treatment, root canal treatment, allows the pathogenic microorganism to cross from periapical lesions into alveolar blood vessels, or via gingival crevices to the capillaries in gingival connective tissues,[46] or oral microorganisms can gain entry to the brain via the trigeminal nerve.[47] The presence of oral microorganisms in the bloodstream and the secretion of cytokines and toxic substances can alter blood-brain permeability.[48] This allows the mobility of microorganisms in the brain to cause damage to the CNS. SCFAs have been shown to have an extensive influence on CNS function, for example causing alterations in neurotransmitter production, mitochondrial function, immune activation, lipid metabolism[48] and gene expression in animal studies, but these lack human evidence and are contradictory. The potential mechanisms of SCFAs produced by the oral microbiome is another research area for investigation. The potential role of SCFAs in a healthy oral environment and oral dysbiosis is outlined in Table 2.[42,49-54]

SCFAs and the gut microbiome

The gut microbiome is modulated by food products, dietary habits and geographical origin. The development of certain diseases has been reported to occur due to alterations in the composition of the intestinal microbiome. Examples of such diseases include heart failure,[55] colorectal cancer,[56] obesity, diabetes,[57] inflammatory bowel disease (IBD)[58] and neurodegenerative disorders.[59] Additionally, studies have shown that the intestinal microbiome is an important source of neurotransmitters,[60] including dopamine, noradrenaline, serotonin, gamma-aminobutyric acid (GABA), acetylcholine and histamine.[36] The gut microbiome degrades dietary products to produce organic acids, gases and large amounts of SCFAs. SCFAs have been studied widely in the intestinal–gut microbiome, where they can modulate cellular activity both extra- and intracellularly. The molecular and metabolic activity of SCFAs has been identified as extracellular activity via SCFA-specific G-protein coupled receptors,[61] intracellular inhibition of histone deacetylases (HDACs),[62] intracellular energy supply for colonic epithelium, substrates for the Krebs cycle,[63] and induction of apoptosis.[64]

SCFAs can activate free fatty acid receptors (FFARs) expressed in the colon, kidneys, sympathetic nervous system, blood vessels, enteroendocrine L cells and immune cells, including lymphocytes, neutrophils and monocytes.[65] In a systematic review of some in vitro studies, the role of SCFAs in human oral epithelial cells via receptor-mediated pathways (FFARs, FFAR3, FFAR2) or inhibition of HDACs by altering DNA transcription was speculated. It was observed that SCFAs can contribute to periodontal destruction and modulation of immune cell migration.[66] There is evidence showing the presence of SCFA receptors in the CNS and peripheral nervous system, thus allowing communication between the gut and brain.[67] Gut-brain communication can occur through direct or indirect effects of the gut microbiome. In direct effects, the metabolites can systemically translocate and diffuse or pass through the blood-brain barrier. Alternatively, in indirect effects,

Table 3 Oral microbiome in gut diseases: a possible mechanism of gut pathogenesis induced by oral bacteria.

Oral bacteria	Targeted cells	Cellular pathways involved	Possible pathologic role
Porphyromonas gingivalis	Epithelial cells	Jak1/Akt/Stat3, PI3K/Akt, Cyclin D, β-catenin, NF-kB, ERK1/2, p38.	Gut dysbiosis, epithelial disruption, antiapoptotic, cell proliferation, immune evasion, tumour invasion
	Neutrophils	Receptor mediated (Toll-like receptors)	Impair action and decrease antibacterial activity
	Dendritic cells	Metalloproteinase and complement system	Increase tissue destruction and compromise host immune system
Fusobacterium nucleatum	Epithelial cells	Wnt/β-catenin, receptor mediated (Toll-like receptors)	Cell proliferation and migration, cell adhesion
	Natural killer cells, T cells	T cell immunoreceptor	Immune evasion
Staphylococcus aureus	Epithelial cells, T cells	NR	Epithelial disturbance, immune activation
Klebsiella pneumoniae	Epithelial cells	Cytoplasmic adaptor protein	Generation of Th cells (type1)
K. aerogenes (K. aeromobilis)			
Campylobacter concisus	Epithelial cells	NR	Epithelial disturbance
Fusobacterium varium	Epithelial cells	NR	Inflammatory cytokine production, cell adhesion and invasion
Atopobium parvulum	NR	NR	Affects hydrogen sulfide detoxification, mitochondrial dysfunction

Akt, protein kinase B; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; Jak 1, Janus kinase 1; NF-kB, nuclear factor kappa- light-chain-enhancer of activated B cells; NR, not reported; PI3K, phosphoinositide 3-kinase; Stat3, signal transducer and activator of transcription 3; Wnt, wingless-related integration site.

the microbes colonise the intestine to release metabolites that are involved in neurological functions. The products generated in the intestine can move via the bloodstream to reach the CNS, where these metabolites act as neurotransmitters or their precursors.[68]

Relations between the oral and gut microbiome

The oral microbiome is the second-largest microbiome in humans after the gut. The gut microbiome shows greater diversity compared to the oral microbiome.[69] Due to the differences between the two, the oral microorganisms that enter the gut through swallowing saliva could change intestinal microbial colonisation. The release of metabolic end-products by the bacteria can accelerate inflammatory changes and affect various tissues and organs in direct or indirect ways.[70] It has been shown that periodontal pathogens, mainly *P. gingivalis*, can survive in the gut, change the composition of the intestinal microbiome, and increase intestinal permeability. The survival of *P. gingivalis* in the gut and the release of metabolites can spread through the bloodstream and affect various sites in the human body. Their role in the development of neuropathology has also been documented.[71] The available data suggest that gut-associated systemic pathology is mediated by periodontal microorganisms (Table 3).[70-72]

A limited number of shared taxa between the oral cavity and the gut are presented in Fig 1. Recently, a

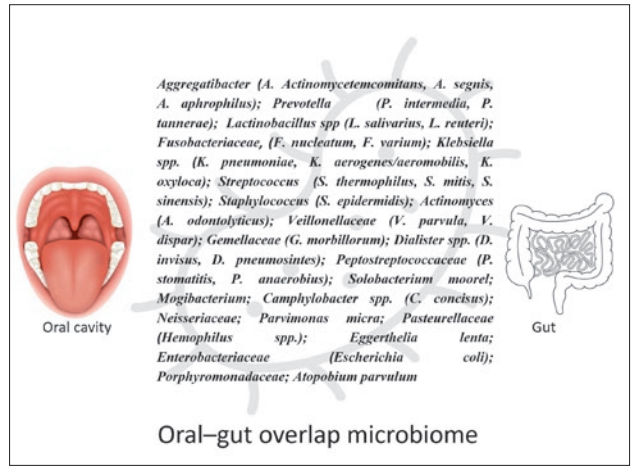

Fig 1 The overlap between the oral and gastrointestinal microbiome, a bridge for the oral-gut axis resulting in several oral and systemic diseases.

subset of 74 species were reported to be transmitted from the mouth to the gut, forming consistent microbe populations along the gastrointestinal tract.[73] The oral mucosa is connected to the gastrointestinal mucosa, and their interrelationships are expected as saliva is ingested every day from the oral cavity to the gut. The oral microbiota affects the gut microbiota through three routes: first, the enteral route, whereby salivary mucins protect the microbiota from gastric acid after swallowing and allow their survival along the gastrointestinal tract; second, the hematogenous route, where-

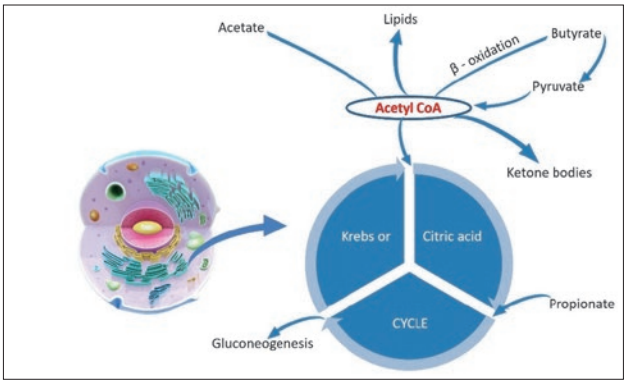

Fig 2 Metabolism of SCFAs. Butyrate absorption negatively regulates pyruvate to produce acetyl-CoA necessary in the Krebs cycle. Butyrate action pushes cell metabolism from glycolysis to β-oxidation. Depending on the metabolic state, acetate and butyrate are converted to acetyl-CoA. SCFAs can enter the citric acid cycle for gluconeogenesis and be utilised to form lipids and ketone bodies.

by oral/dental trauma allows easy penetration of oral microbes through the damaged mucosa and enables oral microbes to spread into the systemic circulation; and third, the immune cell migration route, whereby dendritic cells and macrophages help in the dissemination of oral bacteria from the oral cavity to the gut.[74]

The role of the oral-gut axis in systemic disease has accelerated recently where diabetes and IBD have shown stronger associations between the oral-gut axis and disease progression.[75] In diabetes, Streptococcus salivarius is decreased in the oral cavity as well as in the gut, thereby increasing the abundance of facultative anaerobes including Enterobacteria. The increased *Enterobacteria* drives gut inflammation and impacts diabetes progression. *P. gingivalis* or *Fusobacterium nucleatum* from the saliva of periodontitis patients can increase gut permeability by disturbing the intestinal immune system and assisting disease progression.[75,76] IBD patients have shown oral dysbiosis with different microbial ecotypes exhibiting similar variations as in the gut. Hence, saliva is marked as a convenient tool for risk identification in IBD patients.[77] There is a bidirectional relationship between the oral and gut microbiota; however, there is limited research on the influence of gut dysbiosis on the oral microbiota and the presence of SCFAs receptors in the oral mucosal epithelium.

Metabolism and action of SCFAs

Both exogenous and endogenous SCFAs may be involved in the pathogenesis of different diseases. SCFA provides approximately 10% of the daily calorie requirement and its receptors are present throughout the human body.[78] SCFAs may act as ligands to membrane receptors, thus affecting cell metabolism (Fig 2). Acetate, butyrate and propionate are SCFAs with chain lengths of 1 to 6 carbon atoms. These act on many cell types and regulate important biological processes. Catabolism of different bacteria is the main reason for the different proportions of SCFAs in the human colon.[79] Previous studies on colon epithelium have shown butyrate to be the main substrate, which enhances oxidative phosphorylation within the cell and enhances fatty acid metabolism.[80,81] Butyrate is produced via glycolysis and with a stepwise reduction of acetoacetyl-CoA to butyryl-CoA. The final step in the formation of butyrate from butyryl-CoA involves either the butyryl-CoA: acetate CoA-transferase route or the phospho-butyrate and butyrate kinase pathways.[82] Butyrate and acetate are the substrates for lipogenesis. Acetate is metabolised in muscles and is a substrate for cholesterol and fatty acid synthesis. Several anaerobic bacteria, such as *A. muciniphila* and *Bacteroides spp.*, produce acetic acid through fermentation. Acetate is found in a higher concentration in the proximal colon, where it is absorbed by intestinal epithelial cells and later by the liver via the hepatic portal vein. In the blood, acetate exists as a free acid that is metabolized by several tissues and organs.[83] Propionate is derived from carbohydrate metabolism during glycolysis, mainly through the succinate pathway, and is a precursor for glucose synthesis in the liver.[84] A vitro study has shown that increased secretion of propionate by the intestinal epithelium inhibited hepatocyte adipogenesis and reduced fat deposition in chickens.[85] Several other animal studies have indicated the crucial role played by propionate in lipid metabolism, the nervous system and cardiovascular diseases.[86,87] Thus, the increase and decrease of SCFAs in the colonic epithelium can impair its structure and function.

The importance of SCFAs has been demonstrated and reported in various animal model studies. SCFA metabolism in the liver can directly affect energy status through an imbalance between lipid formation and breakdown, glucose production and catabolism, and cholesterol synthesis and secretion.[88] In another study, SCFAs were shown to promote adipogenesis in the rodent cell model.[89] Acetate or propionate were found to induce significant changes in nuclear receptor expression, leptin secretion and intracellular triglyceride accumulation in the early stage of adipose differentiation.[89] SCFAs were found to mediate glucose metabolism and fatty acid utilisation in skeletal muscle via stimulation through regulators of skeletal muscle metabolism.[90] SCFAs play a dual role as a substrate and as a regulatory factor in lipid metabolism.[90]

Hypothesis

Oral diseases, mainly caries and periodontitis, are well known diseases caused by the oral dysbiosis. Microbial metabolites produced in the oral cavity can enhance the prediction of pathogenesis of oral diseases and, furthermore, provide more consolidated information on several systemic diseases. The salivary metabolites produced by the oral microbiome can be helpful in uncovering the causal relationship between the microbiome and disease at earlier stages. In the present article, the authors propose that salivary SCFAs derived from the oral microbiome and oral infectious diseases constitute a key element for driving oral-systemic alterations to cause numerous diseases. Both saccharolytic and proteolytic bacteria are present in the oral cavity that release SCFAs into saliva. These salivary SCFAs can act in two ways: they can be transferred directly from saliva into the bloodstream via inflamed gingiva, or salivary metabolites are swallowed and transferred via the gut to communicate with other organs. SCFAs as immunomodulators cause low-level systemic inflammation. Salivary SCFAs are the key regulators of oral changes that communicate with systemic conditions much earlier than the gut microbiome. Hence, salivary SCFAs can provide possible advantages as an indicator or diagnostic tool for early diagnosis of systemic diseases (Fig 3).

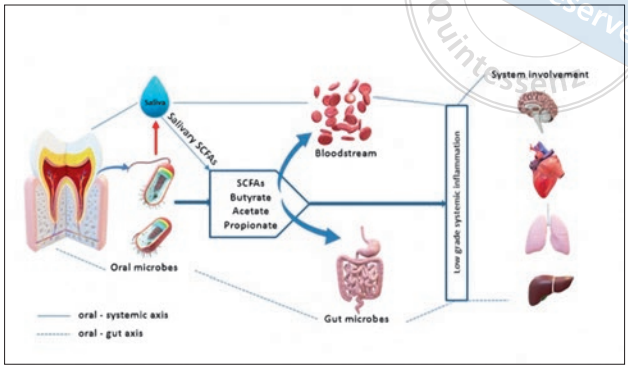

Fig 3 Schematic illustration depicting the paths through which salivary SCFAs produced by the oral microbiome affect systemic health. They are the end-product of oral bacteria and can directly enter the circulating blood and affect systemic health. Salivary SCFAs can be swallowed, which indirectly disturbs the gut microenvironment. The changes in the gut microbiome can further affect systemic health by mediating systemic inflammation. Salivary SCFAs cause low-grade systemic inflammation that can be aggravated via further changes in the oral and gut microbiome.

Conclusion

The two largest known microbial habitats in the human body are the gut and oral cavity. There is growing evidence to support the notion that the oral microbiome can change the gut microbiome through direct translocation of oral bacteria and/or indirectly by oral bacterial byproducts. SCFAs are released by both the oral and gut microbiome. Taken together, the oral–systemic microbiome axis is strongly associated with diseases via SCFAs and could be a predictor of early-stage disease development; however, the presence of SCFA receptors in the oral mucosal epithelium is unclear. The present study provides a basis for further research aimed at understanding the oral–systemic axis driven through salivary SCFAs in the pathogenesis of several diseases. Thus, integrative research on salivary SCFAs is needed to control metabolite-associated diseases and develop novel strategies for precise diagnosis, prognosis and treatment.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Bina KASHYAP contributed to the conceptualisation, study design and manuscript draft; Dr Eelis HYVÄRINEN contributed to the data collection and manuscript review; Dr Arja M KULLAA contributed to the manuscript review, editing and finalisation.

(Received Aug 31, 2023; accepted May 16, 2024)

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