This is a post-peer-review, pre-copyedit version of an article published in Current Oral Health Reports.
The final authenticated version is available online at:https://doi.org/10.1007/s40496-019-0221-7.

Current understanding of the gut microflora in subjects with nutrition-associated metabolic disorder such as obesity and/or diabetes: Is there any relevance with oral microflora?

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Keywords: Oral microflora; Gut microflora; Dysbiosis; Metabolic disorder; Obesity; Diabetes

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Abstract

Purpose of review: The oral cavity is one of the main gateways to the whole body and leads to the gastrointestinal tract. Both oral cavity and gastrointestinal tract have complex ecosystems of microorganisms called microbiota. Recent studies have showed that altered local microbiome in human, such as gut microflora, is associated with various systemic diseases. This review focuses on the association between the microbiota at local sites, such as gut and oral cavity, and the systemic diseases, especially nutrition-associated metabolic disorder, such as obesity and/or diabetes.

Recent findings: The gut microbiota has a potential for regulation in host immune system and metabolisms, such as energy, glucose and lipid, and is therefore an additional contributing environmental factor to the pathophysiology of obesity and diabetes as well as gut infectious inflammatory diseases. In addition, oral microorganisms play important roles as reservoirs for exacerbation of gut diseases and altered oral microbial profiles causing periodontal diseases, one of common oral infectious diseases, has been also associated with several systemic diseases including diabetes.

Summary: It is necessary to consider that impaired oral microbiota, called oral dysbiosis, may affect the metabolic disorders leading to obesity and diabetes in addition to the gut inflammatory diseases via alteration of gut microflora. The relevance of oral microflora to gut dysbiosis leading to nutrition-associated metabolic disorder should be addressed as future investigations.

Introduction

The microbiota, a complex ecosystem of microorganisms mainly consisting of bacteria, has been considered to play important roles in metabolic functions, such as the regulation of several biochemical and physiological mechanisms via the production of various metabolites and substances (1). As the good correlation with the human health, the microbiota has several beneficial activities, such as anti-inflammatory and anti-carcinogenic actions. For instance, over 70% of the microbiota living in the gastrointestinal tract, which is an entry site for nutrients and an encounter site with the immune system, has a mutually beneficial relationship with host (1, 2). However, the alterations of microbiome have been also considered to play critical roles in the cause and development of various systemic diseases, especially metabolic disorder such as obesity and diabetes (1, 3). Moreover, it has been indicated that the disturbance and imbalance in the microbiome result in infectious inflammatory diseases, such as intestinal infectious diseases and periodontal disease, at many sites in human body. Therefore, it has been considered that the microbiota at various sites, such as mouth, gut and skin, in human affects health or disease (2). The mouth is the gateway leading to gut via esophagus as the passageway for food and the microbiota of oral cavity has the second most abundant of microflora after gastrointestinal tract (4). To prevent metabolic diseases caused by the microbiota modifications and to development novel therapeutic strategies for these disorders, the clarification of their pathological mechanisms and the link between the microflora and metabolic diseases is important and required. As two major microbiota in human body, this review focuses on both gut and oral microflorae and provides the current understanding of their association with nutrition-associated metabolic disorder, such as obesity and/or diabetes, and gut inflammatory diseases.

Gut microbiota

The human gut harbors trillions of microbes, which form a symbiotic relationship with the host and play a vital role in both health and disease. This ‘‘gut microbiota’’ makes up bacterial complex community that interacts with each other, and it modulates various biological processes of essential factors in the host for health (5). The diverse of gut microbiota is predominantly composed of four major phyla of bacteria, namely *Firmicutes*, *Bacteroidetes*, *Actinobacteria, and Proteobacteria* (6). Especially, the most popular phyla are the *Firmicutes* and *Bacteroidetes*, which account for 80% of the whole microbiota (7-9). The phylum of bacteria *Firmicutes*, mainly consisted of Gram-positive bacteria, includes the genera *Lactobacillus* (Gram-positive), *Eubacterium* (Gram-positive), and *Clostridium* (Gram-positive). On the other hand, the phylum *Bacteroidetes* formed by Gram-negative bacteria, includes the genera *Bacteroides* and *Prevotella*. The remainder minor proportions are formed by other phyla, such as *Proteobacteria* (Gram-negative, in particular genus *Escherichia*), *Actinobacteria* (Gram-positive, in particular genus *Bifidobacteriium*), *Fusobacteria* (Gram-negative), *Spirochaetes* (Gram-negative), *Verrucomicrobia* (Gram-negative) and *Lentispherae* (Gram-negative) (10-12).

The new critical association of gut microbiota on several metabolisms is found in the last decade. In the recent studies, the biological roles in the gut microbiome, such as modulating juvenile growth (13), maturation of the immune system (14), and modulation of glucose and lipid metabolism (15), have revealed dramatically. Those studies make sure the microbiome participation in homeostatic regulation about different tissues in human body (16). Therefore, the gut microbiota is regarded as a one of main factor for health control and maintenance. However, while the balance of gut microbiota is

disrupted, this alterations can lead to attenuation of immunologic regulation and the development of disease including *Clostridium difficile* infection (17), inflammatory bowel disease (IBD) (18, 19), irritable bowel syndrome (20, 21), asthma (22), obesity (23) and diabetes (24, 25).

Gut microbiota and antibiotic administration

Antibiotics administration inducing disorder of gut microbiota is well-established model in microbiota related disease. *Clostridum difficile*, which is a Gram-positive toxin and spore producing anaerobic bacteria, is a one of the normal gut microbiota and members of *Firmicutes*. *Clostridum difficile* infection (CDI) is a main infectious disease in nosocomial infection (26). During the CDI, *Ruminococcaceae*, *Lachnospiraceae*, *Bacteroides*, and *Porphyromonadaceae* were absent in the patient with diarrhea, compared with healthy control (17). Those changing of microbiota are more pronounced in recurrent CDI patient (27), and recurrent CDI leads to increased abundance of *Proteobacteria*, and decreased abundances of *Bacteroidetes* and *Firmicutes* (28). On the antibiotics administration inducing disorder of gut microbiota, the bio-conversion of primary bile acid to secondary bile acids is regarded as a one of the proposed mechanism. Primary bile acid promotes a germination of *Clostridum difficile* spores, whereas secondary bile acids attenuate vegetating of *Clostridum difficile* growth (29). As a result, there is a significant reduction in microbial bio-conversion of primary bile acid into antimicrobial secondary bile acids, leading to reduced inhibition of *Clostridum difficile* vegetative growth, allowing *Clostridum difficile* outgrowth and colonization of the empty niches, leading to higher susceptibility of host toward CDI (30). The bacterial complex community of gut microbiota is vitally important to providing colonization resistance to

CDI. Therefore, antibiotics administration leads a changing of gut microbiota and increases the risk of CDI (31).

Gut microbiota and gut infectious disease

Similar to the CDI, the condition of gut microbiota also associates with infection of enteropathogenic bacteria. Recent studies investing the relationship between enteropathogenic bacteria and the resident microbiota have developed to illuminate how these pathogens outmanoeuvre the host defenses.

The composition of the gut microbiota is impacted by host diet or lifestyle. Nutrient influences its availability in the gut and changes the composition of the gut microbiota. Pathogenic bacteria compete against commensal bacteria for nutrients and colonization within the gut (32, 33). The members of gut microbiota, such as *Bacterioidetes*, *Firmicutes*, and *Acinobacteria* phyla, break down several complexes of dietary carbohydrates. These gut bacteria produce short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate (34). Those metabolites are also important for not only energy sources that aid host cell differentiation or nutrient absorption by the colonic epithelial cells, but also attenuation of pathogenic bacterial colonization and infection that induce gastrointestinal disease (33, 35). Indeed, regarding enteric food-borne pathogens, such as Enterohemorrhagic *Eschrichia coli* (EHEC), mice fed with acetylated starch or co-infected with *Bifidobacterium spp.,* can produce enough acetate, have increased bacterial acetate levels in their feces, leading the protection against an initial EHEC colonization (36). Also, in *Salmonella enteria* serovar Typhimurium infection, major pathogens of food-borne disease leading gastroenteritis, presence of *Bacterioides* producing the short-chain fatty acid propionate in their feces directly inhibits *S.*

Typhimurium growth and colonization in mice (37).

Therefore, the condition of gut microbiota plays a key role in resistance and tolerance of gastrointestinal infectious disease, and the balance between commensal and potentially pathogenic bacteria is a central element of human health.

Gut microbiota and obesity

Obesity is a consequence of an imbalance of energy intake and energy expenditure. In early studies of germ-free rodents, energy absorption, a capacity to harvest energy from the diet, is clearly increased by exposure to the gut microbiota and this trait is transmissible (15, 38, 39). Interestingly, the colonization of germ-free mice with an obese microbiota caused significantly greater increase in total body fat than that with a lean microbiota, indicating that the gut microbiota is an additional contributing environmental factor to the pathophysiology of obesity by influencing energy intake from the diet and energy storage in the host (39). Regarding the association between gut microbes and nutrient energy adsorption in human, the proportional representation of *Firmicutes* and *Bacteroidetes* correlated positively and negatively with stool energy loss in lean individuals, respectively (40). These changes, an increase in the ratio of *Firmicutes/Bacteroidetes*, were also observed in individuals with obesity compared with in their lean counterparts (41, 42). In addition, recent interesting findings indicate that the gut microbiota may regulate feeding patterns involved in the gut-brain axis via endocrine hormones, including gastric inhibitory peptide, glucagon-like peptide 1, peptide YY, leptin, and cholecystokinin (43-47). Moreover, Kaelberer et al. discovered that there is a direct neural connection from the intestine to the brain in mice (48). In contrast to the energy intake, few reports have investigated energy expenditure and the

gut microbiota. Kocelak et al. reported that resting energy expenditure (REE) expressed on the body surface (kcal/m^2/h) was positively correlated with the total bacterial count ($r = 0.25$, $p < 0.05$), *Bacteroides* count ($r = 0.24$, $p < 0.05$) and *Bacteroides* to *Firmicutes* rate ($r = 0.26$, $p < 0.05$), while negatively with the percentage of *Firmicutes* colonies ($r = –0.24$, $p < 0.05$) in 50 obese and 30 lean healthy weight stable subjects (49). However, none of these correlations were observed in multiple regression analysis. These reports and other reviews suggest that the gut microbiota has a potential for regulation in host energy metabolism (43, 50-52) but their extent in human should be further investigated in more detail.

Gut microbiota and diabetes

In addition to obesity as a metabolic disease linked to an altered gut microbiota, the association between type 2 diabetes, which is the most prevalent endocrine disease worldwide, and gut microbiota as an environment factor has also been focused and some gut microbial markers are suggested to be useful for classifying type 2 diabetes (24, 25). As a result of a cohort study and cross sectional studies of type 2 diabetic patients in China and Europe, the proportion of butyric acid-producing bacteria, including *Roseburia, Clostriiales sp. SS3/4* and *Faecalibacterium prausnitzii*, is low in the intestinal flora of type 2 diabetic patients (24, 25, 53). Possible mechanisms, which involved in the signaling of butyrate and other short chain fatty acid and diabetes, were provided in several reviews (43-46, 54). In addition, the abundance of *Akkermansia muciniphila*, ~~butyrate-producing and~~ mucin-degrading microbe, was ~~enriched~~ reduced in type 2 diabetic patients and negatively correlated with homeostasis model assessment (HOMA) insulin index (24, 53, 55, 56). Recently, Udayappan et al. reported that Gram-negative *Ralstonia pickettii* levels are higher in impaired glucose tolerance patients and type 2

diabetic patients than that of normal glucose tolerance subjects (57). Both *A. muciniphila* and *R. pickettii* could also control the intestinal barrier function in mice (57-59). Impaired intestinal barrier function and subsequent increased endotoxemia are observed in obese and diabetic subjects (60-62). Moreover, an intervention study consisted of a 6-week calorie restriction (CR) in overweight and obese adults revealed that individuals with higher baseline *A. muciniphila* displayed greater improvement in insulin sensitivity markers and other clinical parameters after intervention of the CR, suggesting that *A. muciniphila* is associated with a healthier metabolic status and better clinical outcomes after CR in overweight/obese adults (56). A similar result was drawn in type 2 diabetic patients whom treated by antidiabetic drug, metformin (63). In contrast to the insulin resistance, the regulatory activity of the gut microbiome on insulin secretion was only reported in mice (64). Since both the amount and action of insulin insufficiency are the cause of diabetes mellitus, investigation of their relationship with the gut microbiota, especially in humans, has been much awaited in more detail.

Recently, the modification of the gut microbiota has been attempted to be used in methods of treating obesity and diabetes. Fecal microbiota transplantation is one of treating methods for obesity and/or diabetes that infusing intestinal microbiota from lean donors to recipients with obese and diabetic subjects (65-67). Bariatric surgery is also gathering attention because of its dramatic improvement of metabolic parameters (67, 68). Structural changes of gastrointestinal tract induce changes in the gut environment, therefore, subsequent reconfiguration of the gut microbiota and functional changes may cause after this surgery. Pre- and pro-biotics are traditional approaches for regulating the gut microbiota. However, there is a lack of evidence for the impact of probiotics on fecal microbiota composition in healthy adults or obese subjects (69, 70). Of course

there are some good results (71-73), but the total number of samples, and the quality of methodology should be improved to draw definitive conclusions. These inconsistent results may come from a person-specific gut microbiota which determines resistance to probiotics and its effects (74).

Involvement of oral microflora in gut diseases

The oral cavity is one of the main gateways to the whole body (75). Oral microflora colonizing in oral cavity comprises approximately 700 microbial species and is associated with its complex ecological environment (4, 75). Healthy oral microbiome is maintained by good habitats, such as oral hygiene and food intake, and keeps the oral cavity healthy, but it has been reported that the disruption of good oral ecosystem by various triggers, such as tobacco, alcohol, stress, hormonal alteration, puberty, poor oral care, diabetes and oral inflammatory conditions, leads to dysbiosis and results in various systemic diseases as well as oral diseases (4, 76). Especially, as regards the nutrition, it has been suggested that core oral microbiome may be altered by diet much containing carbohydrate and protein (4). Oral microorganisms living in the oral cavity have been shown to have the interactive roles with human host cells and direct effects on the physiology, metabolism and immune responses in human (4, 76-78). Besides foods, saliva containing oral microorganisms gets into the stomach and intestinal tract, and air goes to the lungs and trachea in one direction via the mouth. Regarding with this concept, it has been considered that predominant members of oral microbiome could spread to the whole body from the mouth and colonize the far areas, such as gut, after reaching to various organs (79). For instance, the association between disturbances of the oral microbiome and various systemic diseases, such as diabetes, gastric ulcer, obesity, cancer, autoimmune diseases, acquired immune deficiency syndrome, endocarditis and

cardiovascular disease, has been reported (4, 80, 81). It has been also reported that the patients with rheumatoid arthritis or IBD have altered oral microbiome (82, 83). Another study has reported that over 50% of the species enriched in the gut microbiota of the patients with liver cirrhosis are buccal origin microbial species, suggesting the invasion of oral microorganisms to gastrointestinal tract (84). In addition to the increasing evidence links the gut microbiota with colorectal cancer, one recent study has shown that a higher abundance of *Fusobacterium* spp. is found in human colonic adenoma tissues and in stool samples from colorectal adenoma and carcinoma patients and *Fusobacterium nucleatum* selectively recruits tumor-infiltrating immune cells, which can promote tumor progression, suggesting Fusobacteria generate a pro-inflammatory microenvironment leading to colorectal neoplasia progression through modulation of the host immune reaction (85). A review article also indicated the association between the domination of *F. nucleatum*, one of late colonizers in oral cavity and periodontal disease-related bacteria, and gut diseases, such as colorectal cancer and IBD (86). Periodontal diseases, one of common oral infectious diseases, are characterized as altered oral microbial profiles with higher levels of periodontal pathogens, such as *Porphyromonas gingivalis*, and disturbed host-microorganism interaction (75) and has been also associated with several systemic diseases such as diabetes, cerebrovascular diseases and atherosclerosis. *In vivo* experiment using mice model demonstrated that oral administration of *P. gingivalis*, one of major periodontal pathogens, alters ileal microbiota related to systemic inflammatory changes (87). Dental caries, another in 2 major oral infectious diseases, is mainly caused by the infection with *Streptococcus mutans*. Regarding the involvement of dental caries-related pathogen in the pathology of gut diseases, it has been reported that the detection frequency of the specific *S. mutans* strains

with collagen-binding protein in oral samples of ulcerative colitis patients was significantly higher than in healthy subjects and increased interferon-γ in liver, where is the target organ for *S. mutans*, is the real trigger of the inflammatory cascade in oral bacteria-induced aggravation of colitis (88). This study finally concluded that the infection with highly virulent specific types of *S. mutans* is a potential risk factor for the aggravation of ulcerative colitis, a major IBD. Moreover, it has been reported that the concomitant reduction of salivary flow and intraoral pH could predispose to intraoral colonization with enterobacterial species, such as *Klebsiella pneumonia*, suggesting that periodontal pocket plays a significant role as a reservoir for enterobacteria to increase the risk of gut colonization (89, 90). These findings have implicated that the relationship between oral and gut ecological systems affects several chronic infectious and/or inflammatory diseases. In this viewpoint, the experiment using susceptible mice demonstrated that multiple antibiotics-resistant *Klebsiella* species colonizing in the gut from the salivary microbiota increase T helper 1 cells and strongly induce gut inflammation (91). Another study demonstrated that *H. pylori*, which is considered to be responsible for gastritis and peptic ulcers and is a risk factor for gastric cancer, was detected frequently in the oral microbiota of subjects with periodontitis, suggesting that periodontal pocketing and inflammation may favor the colonization by this species (92).

Recent findings suggest that oral microorganisms play important roles as reservoirs for exacerbation of gut diseases and understanding of the change in microbial flora may lead to the identification of biomarkers for diagnosing the microbiome-associated diseases (93, 94). Moreover, in recent years, some therapeutic and pharmacologic companies have tried to develop a drug and probiotic bacteria based on oral and gastrointestinal microbiome for the treatment of various diseases instead of antibiotics

having the possibility of generating multidrug resistant microorganisms which is the world-wide problem in the medical field. Regarding the periodontal medicine, a new concept meaning the interplay of oral dysbiosis leading to prolonged chronic inflammatory infectious diseases, such as periodontitis, and gut dysbiosis should be addressed as future investigations.

Conclusions

Microbiome in human has the important roles of homeostatic regulation to maintain human health. The alteration of local microbiome in oral cavity and gut is associated with various systemic diseases. Table 1 summarizes the changes and features in the gut microflora in subjects with nutrition-associated metabolic disorder and oral infectious diseases. The changes of gut microbiota cause several altered metabolisms leading to obesity and diabetes as well as gut infectious inflammatory diseases. In addition, the disturbance of oral microbiota causes oral inflammatory diseases, such as periodontal diseases which is strongly associated with various systemic diseases including diabetes. It has been recently indicated that oral microorganisms play important roles as reservoirs for exacerbation of gut diseases. Therefore, it has been suggested the possibility that impaired oral microbiota, called oral dysbiosis, alters gut microflora having biological and metabolic roles such as energy intake from the diet, and then affects the nutrition associated-metabolic disorders leading to obesity and diabetes in addition to the gut inflammatory diseases. The further investigations focused on the relevance of oral microflora with the nutrition associated-metabolic disorder are should be needed.

Compliance with Ethics Guidelines

Conflict of Interest

All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1 The changes and features in the gut microflora in subjects with nutrition-associated metabolic disorder, such as obesity and diabetes, and with oral infectious diseases, such as periodontal disease and dental caries.

Diseases	**Feature of microbiota**	**Intervention (if any)**	**Changes (Clinical outcome and bacterial colonization)**	**Reference**
CDI (*Clostridum difficile* infection)	Altered fecal bile acid composition in patients with recurrent CDI	Fecal microbiota transplantation	Increased abundance of *Bacteroidetes* and *Firmicutes* Restoration of normal colonic microbial ecology and normal bile acid composition in the colon	28
Enteropathogenic infectious disease	Lethal infection with EHEC (Enterohaemorrhagic *Escherichia coli*)	Orally inoculation of *Bifidobacterium* spp.	Protection of mice against death induced by EHEC infection Inhibition of translocation of ETEC toxin from the gut lumen to the blood	36
	Salmonella Typhimurium intestinal burdens (infection)	Administering of *Bacterioides* to mice	Inhibition of *S. Typhimurium* growth Colonization resistance against *S. Typhimurium* by propionate produced from *Bacteroides*	37
Obesity	Increase in the ratio of *Firmicutes/Bacteroidetes*	Observational study in human and fecal transplantation in mice	*Firmicutes* and *Bacteroidetes* correlated positively and negatively with stool energy loss, respectively.	15, 38, 39-42
Diabetes				

1.	Low in butyrate producing bacteria including *Roseburia, Clostriiales sp. SS3/4* and *Faecalibacterium prausnitzii*.	Observational study and metoformin treatment	Reduction of butyric acid production	24, 25, 53, 63
2.	Low in *Akkermansia muciniphila* and High in *Ralstonia pickettii*.	Observational study	Impaired intestinal barrier function in mice	24, 53, 55-59
3.	*Akkermansia muciniphila*	6-week calorie restriction	Higher baseline *A. muciniphila* displayed greater improvement in insulin sensitivity.	56
Periodontal disease 1	Altered composition of the microflora in the ileum contents (Alteration of the gut microbial ecology)	*P. gingivalis*-orally administered mice	The difference of proportion of Bacteroidetes and Firmicutes (Increased proportion of Bacteroidetes) Induction of inflammatory responses in adipose tissue and liver Induction of insulin resistance Changes in gene expression profiles in the intestine	87

2	The colonization of highly invasive strains of *F. nucleatum* in the intestinal mucosa	Human gut Biopsy from adult patients undergoing colonoscopy for colon cancer screening purposes or assessment of irritable bowel syndrome status or the presence of gastrointestinal disease.	*Fusobacterium* spp. were isolated from 63.6% of patients with gastrointestinal disease compared to 26.5% of healthy controls. 69% of all *Fusobacterium* spp. recovered from patients were identified as *F. nucleatum*. *F. nucleatum* strains originating from IBD patients were significantly more invasive than strains from healthy tissue, suggesting that invasive potential of gut mucosa-derived *F. nucleatum* positively correlates with IBD status	95
Dental caries 1	Transient localization of administered *S. mutans* in the liver (by uptake by hepatocytes and kupffer cells)	Intravenously administration of *S. mutans* serotype *k* strain to dextran sodium sulfate (DSS)-induced colitis mouse model	Aggravation of mouse colitis Increase of inflammatory cytokines, such as IFN-γ, TNF-α and IL-6, in mouse liver tissues	88
	Collagen-binding	Preliminary	Higher detection frequency of the CBP-	

	protein (CBP)-encoding *cnm* gene expressing *S. mutans* in oral samples	screening study of detection frequency of the specific strains of *S. mutans* in human subjects	encoding *cnm* gene expressing *S. mutans* in ulcerative colitis (UC), major inflammatory bowel diseases (IBDs), patients Significantly higher detection frequency of both *S. mutans* serotypes *k* and *f* in UC patients	
	Clinically isolation of *S. mutnas* strains from oral samples of IBD patients	Administration of CBP-expressing *S. mutans* strains from IBD patients in the DSS-colitis mouse model	Aggravation of colitis with mucosal damage and infiltration of inflammatory cells Increase of disease activity index (DAI), including such signs as diarrhea and bleeding Decrease of survival rates	