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The Association between Periodontal Disease and Obesity: Roles of the Dysbiotic Microbiome and Inflammation

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العلاقة بين مرض التهاب اللثة المزمن والسمنة: دور المايكروبيوم الجرثومي والالتهابات

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KEYWORDS

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ABSTRACT

Periodontal disease and obesity are highly prevalent conditions in the developed and developing countries, and recent studies have suggested their association. However, it is not clear whether this association is due to common risk factors or there are underlying molecular and cellular mechanisms linking both conditions. The keystone-pathogen hypothesis holds that administration of the periodontal pathogen *Porphyromonas gingivalis* in the oral cavity of murine models led to low colonisation but transformed the health-associated (symbiotic) microbiota to a disease-causing (dysbiotic) state. This shift causes qualitative and quantitative changes in the oral microbiome and breakdown of the host's homeostatic balance and initiation of periodontitis (Hajishengallis et al., 2011). The second hypothesis suggests the link between periodontitis and obesity is largely based on the oral cavity-gut microbiome connection. Administration of *P. gingivalis* in rodent models altered the composition of the gut microbiome from one of health to disease. These changes resulted in impaired gut barrier function, endotoxemia and inflammation of the liver and adipose tissue (Arimatsu et al., 2014); (Nakajima et al., 2015). This review aims to discuss and assess the available literature in regard to both hypotheses, and the potential mechanisms that are necessary for linking both diseases. In the author's opinion, the available literature partly supports the mechanistic link between obesity and periodontitis through a dysbiotic microbiome and inflammation. This warrant-targeted research to identify the common pathogenic bacteria or other keystone pathogens that drive dysbiosis and orchestrate inflammatory disease for the development of novel diagnostics and treatment modalities.

المخلص

مرض التهاب اللثة المزمن والسمنة من الأمراض السائدة في البلدان النامية والمتقدمة. وتشير البحوث العلمية الحديثة الي وجود علاقة بينهما. غير أنه ليس من الواضح ان كانت أسباب هذا الارتباط هي نفسها عوامل الخطر المشتركة بين الحالتين أو أن هنالك عوامل أخرى خلوية ومناعية مشتركة بينهما. نظرية "الجرثوم الأساسي" اعتمدت على حقن التجويف الفموي لنماذج الفئران بعدد محدود من إحدى البكتيريا المسببة لمرض التهاب اللثة المزمن، حيث نتج عن ذلك تغيير في مجموعة البكتيريا (المايكروبيوم) الداعم للصحة لتتحول الي مايكروبيوم مسبب للمرض. يؤدي هذا التحول الي تغيرات نوعية وكمية في المايكروبيوم الفموي والي اهباز توازن جهاز المناعة وبداية التهاب اللثة. النظرية الثانية تقترح ان العلاقة بين التهاب اللثة المزمن والسمنة سببها التواصل المستمر بين التجويف الفموي والأمعاء، وبالتالي انتقال المايكروبيوم بينهما. عند حقن البكتيريا المسببة لالتهاب اللثة المزمن مباشرة في امعاء نماذج الفئران، نتج عن ذلك تغيرات نوعية وتحول مايكروبيوم الأمعاء من داعم للصحة الي مايكروبيوم مرضي، بالإضافة الي التسبب في ضعف وظيفة حاجز الأمعاء وتسمم الدم والتهابات الكبد والانسجة الدهنية. تهدف هذه الدراسة المرجعية إلى مناقشة وتقييم البحوث العلمية المتاحة بخصوص النظريتين، بالإضافة الي التشابه الخلوي والمناعي الرابط بينهما. في رأينا، ان الدراسات العلمية المتوفرة تدعم جزئيا العلاقة بين مرض التهاب اللثة المزمن والسمنة من خلال المايكروبيوم المرضي والالتهابات. تقترح هذه الدراسة اجراء بحوث علمية تهدف الي تحديد بكتيريا ما إذا كان هنالك مشتركة بين الحالتين او اكتشاف عدد من الجراثيم الأساسية المسببة لتحويل المايكروبيوم الداعم للصحة الي مايكروبيوم جرثومي مرضي والتهابي. سوف تقود مثل هذه البحوث اكتشاف وتطوير طرق حديثة للتشخيص والعلاج.

1. Introduction

In recent decades, much research has focused on the association between periodontitis and metabolic diseases, such as diabetes and obesity. In a systemic analysis review and meta-analysis of 70 studies, (Chaffee and Weston 2010) reported that 41 studies suggested a positive association between periodontitis and obesity. Multiple subsequent systematic reviews showed a positive association between periodontitis and being overweight and obesity in adolescents, young adults and adults (Suvan et al. 2011); (Martinez-Herrera, Silvestre-Rangil, and Silvestre 2017); (Khan et al. 2018). (Arboleda et al. 2019) suggested a positive association with a general direction from obesity to periodontitis. However, most studies were unable to distinguish the bi-directional association between the two conditions. Periodontitis is a polymicrobial inflammatory disease that results from the interaction of microbial challenge from the subgingival microbiota and the dysregulated host inflammatory responses on the tooth supporting tissue or the periodontium (Hajishengallis 2015). This increases the patient's risk of developing diabetes, rheumatoid arthritis and possibly obesity (Genco and Van Dyke 2010); (Lalla and Papapanou 2011). Obesity is defined as a chronic metabolic disorder that is caused mainly by the abnormal accumulation of fat, which is likely to primarily affect the adjacent tissue through lipotoxicity (World Health Organisation 1997). The worldwide increase in overweight and obesity are due to nutritional habits, technological advancements and the interactions of

metabolic, genetic, cultural, social and behavioural factors (reviewed in REF (Kolotkin, Meter, and Williams 2001). Obesity directly affects quality of life with many consequences, such as hypertension, coronary heart disease, stroke, diabetes, osteoarthritis, gallbladder disease, sleep apnoea and gout (Nascimento et al. 2016). There is increasing evidence that a dysbiotic gut microbiome participates in obesity through the development of insulin resistance and low-grade inflammation. Both were driven by Gram-negative bacterial products, namely lipopolysaccharides (LPS) (reviewed in REF (Boulangue et al. 2016).

2. Common Risk Factors for Obesity and Periodontitis

Cross-sectional and longitudinal studies have shown that periodontitis and obesity are risk factors for one another. A meta-analysis of 57 independent studies found that the risk of periodontitis is linked to increased body mass index (BMI). The strength of the association odd ratios were in the range of 1.8–4.4 after adjustment for gender, age, smoking, consumption of alcohol and frequency of tooth brushing (reviewed in REF (Genco and Van Dyke 2010); (Borgnakke et al. 2013). These findings were supported by two important longitudinal studies. The first study was carried out on men for a duration of 40 years and reported that obesity increased the risk of periodontal disease progression, showing a more rapid and significantly increased disease progression in overweight individuals (Gorman, Kaye, Apovian, et al. 2012); (Gorman, Kaye, Nunn, et al.

2012). The second study lasted for five years and was carried out on Japanese individuals (2787 men and 803 women); it showed a direct relationship between BMI and the development of periodontitis (Morita et al. 2011). (Genco et al. 2005) examined the relationship between obesity, diabetes and periodontitis in a population of 12,367 individuals from The National Health and Nutrition Examination Survey. This study proposed a model in which obesity is a risk factor for periodontitis through insulin resistance. In this model, the adipose tissues of obese subjects secrete inflammatory cytokines that inhibit insulin signalling leading to insulin resistance. This in turn contributes to a hyperinflammatory state that sets the stage for periodontal pathogens to initiate disease. (Ritchie 2007) suggested that adipose tissue in obese individuals may act as a reservoir for inflammatory cytokines that increase the likelihood of inflammatory periodontitis being initiated. Similarly, an observational study in 100 obese subjects reported that the association with periodontitis was accompanied by higher levels of the periodontal gingival index, pocket-probing depth, gingival recession and clinical attachment loss (Deshpande NC 2017). Finally, (Winning and Linden 2017) concluded that many observational and prospective studies reported difficulties in interpretation of the association due to multiple compounding factors.

3. Mechanisms of Microbiome Dysbiosis and Inflammation in Periodontitis

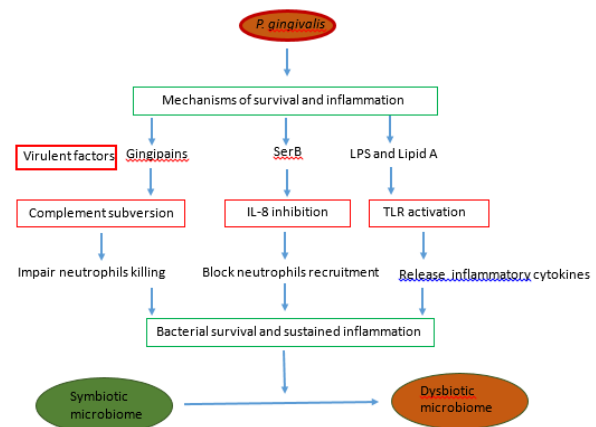
Early studies of periodontitis reported a shift in the composition of subgingival bacteria during progression from health to disease (Socransky et al. 1977); (Hughes et al. 1988). This shift could be attributed to colonisation of pathogenic bacteria that are new to the existing biofilm, leading to microbial changes (dysbiosis) that altered the host–microbiome interaction and induced inflammatory disease (Hajishengallis, Darveau, and Curtis 2012). Further studies have identified specific periodontal pathogens, mostly Gram-negative anaerobic bacteria known as the red complex. The red complex bacteria were strongly associated with active disease and were frequently isolated together and included *P. gingivalis*, *Treponema denticola* and *Tannerella forsythia* (Holt et al. 1988); (Socransky et al. 1998). Recent sequencing methods have identified new species or phylotypes and yet-to-be cultivated microorganisms associated with periodontitis. These include species from the phyla *Bacteroidetes*, *Firmicutes*, *Candidatus*, *Proteobacteria*, *Saccharibacteria*, *Spirochaetes*, and *Synergistetes* (Perez-Chaparro et al. 2014). A recent study reviewed the genome-wide association studies and suggested that the host's genetics may impact the development of a dysbiotic microbiome in the subgingival environment (Zhang et al., 2020).

P. gingivalis is the most studied periodontal pathogen because it is the easiest to grow and to genetically manipulate (Hajishengallis and Lamont 2012). In the mouse model, *P. gingivalis* colonised at low abundance and was able to change the quantitative and qualitative composition of the subgingival microbiome, disrupt the host's innate immunity, and thus was considered a keystone pathogen (Hajishengallis et al. 2011). It was reported that this bacterium evolved strategies to inhibit chemokine induction, to subvert complement, and to impair innate immunity in a way that provided nutrients and protection and, thus, favoured enhanced growth of symbiotic bacteria in the entire biofilm (Hajishengallis 2015).

P. gingivalis produces serine phosphatase (SerB) to disable the gingival epithelium from secreting sufficient interleukin-8 (IL-8) that is important for the recruitment of neutrophils to periodontal tissues. It was shown that *P. gingivalis* persisted in the periodontium, secreted gingipain proteases and exploited the complement component C5aR

involved in cross-talk with the toll-like receptor-2 (TLR2), leading to impaired killing with neutrophils (Wang et al. 2010); (Liang et al. 2011). It was reported that *P. gingivalis* produces two LPS molecules containing distinct glycan repeating units. The first contained O-antigen tetrasaccharide-repeating units (O-LPS) and the second contained anionic polysaccharide repeating units (A-LPS) (Rangarajan et al. 2008). Lipid A is part of LPS and is the most biologically active component in mediating secretion of IL-6 from human gingival fibroblasts and macrophages (Reddi et al. 2008). One species of Lipid A is a 4-acyl-monophosphorelated lipid A moiety that was reported to prevent the activation of the TLR4-dependent pathway important for leukocytes' killing of pathogenic microbes (Darveau et al. 2004). The inflammatory environment containing tissue breakdown and small peptides is a rich source of nutrients that are important for commensal bacterial growth leading to compositional change and destructive inflammation (Gregor and Hotamisligil 2011); (Vreugdenhil et al. 2003). These changes at the periodontal pocket result in higher inflammation and, consequently, bone resorption, leading to eventual tooth loss. In obesity and severe periodontitis, increased levels of common pro-inflammatory cytokines were detected including interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF- α) CRP and leptin. Whereas, IL-1 β was detected only in severe periodontitis (Zuza et al. 2011) (Figure 1). Altogether, these results demonstrate that an inflammatory disease can be caused by qualitative and quantitative changes of the microbiome and dysregulation of the host–microbial interactions that were initiated by a single bacterial species termed as a keystone pathogen

Figure 1. *P. gingivalis* causes inflammation and bone loss through dysbiotic microbiome and dysregulation of the host immune system



Studies have shown that the keystone pathogen *P. gingivalis* secretes several virulent factors including gingipains, serine phosphatase (SerB), LPS and lipid A. These factors are capable of impairing the host's innate immune response, activating inflammatory pathways and, thus, enhancing bacterial survival and inflammation. In doing so, *P. gingivalis* provides protection and nutrients to the standby symbiotic microbiota leading to quantitative and qualitative changes and a microbial shift from symbiosis to dysbiosis. SerB, serine phosphatase; LPS, lipopolysaccharide; IL-8, interleukin-8; and TLR, toll-like receptor.

4. Periodontal Pathogens and Obesity

It has been suggested that certain periodontal pathogens increase the risks of weight gain and obesity in humans. This suggestion was supported by early studies that reported that *T. forsythia* was found in significantly higher numbers in obese individuals with gingivitis, as well as changes in the composition of the salivary microbiome of

obese women (Haffajee and Socransky 2009); (Goodson et al. 2009). Furthermore, bacterial counts of the red complex were found to be significantly higher in overweight and obese individuals independent of periodontitis, although periodontitis was higher in obese individuals. Similarly, the red complex bacteria were identified in higher numbers in the subgingival plaques of obese individuals with periodontal disease, as well as obese individuals with a healthy periodontium compared with non-obese subjects (Matsushita et al. 2015); (Suresh et al. 2017). (Wu et al. 2018) reported a clear distinction between the salivary microbiome of obese and non-obese individuals. Obese individuals harboured significantly more abundant bacteria of the genera *Prevotella*, *Catonella*, *Granulicatella*, *Solobacterium*, *Peptostreptococcus* and *Mogibacterium*. Whereas, the genera *Haemophilus*, *Capnocytophaga*, *Corynebacterium*, and *Staphylococcus* were less abundant, suggesting that these shifts in the salivary microbiome might reflect susceptibility to oral diseases. A recent study showed that patients with cardiovascular disease and obesity exhibited severe periodontitis with increased numbers of periodontal pathogens *P. gingivalis*, *Aggregatibacter actinomycetomcomitans* and *Prevotella intermedia* in their saliva and subgingival plaques (Aoyama 2018).

5. Gut Microbiome Dysbiosis in Obesity

There is a growing interest in the quantitative and qualitative changes in the composition and diversity of the gut microbiome leading to dysbiosis and, thus, predicting metabolic diseases such as obesity. In humans, the gut microbiome can be altered by administration of health-associated bacteria through probiotics or faecal microbiota transplantation (bacteriotherapy) (reviewed in REF (de Groot 2017); (Marotz 2016). Studies in humans and experimental animals have been used to understand the mechanisms involved in the microbial shift of the gut in obesity. Comparisons of gut microbiota in genetically obese mice (*ob/ob*) generated by mutations in the gene responsible for the production of the hormone leptin, responsible for controlling appetite, showed quantitative differences between the phyla *Firmicutes* and *Bacteroidetes*. The ratio of *Firmicutes* to *Bacteroidetes* was positively correlated with obese mice independent of diet (Spor, Koren, and Ley 2011). These observations were supported by a study that showed an increased ratio of *Firmicutes* to *Bacteroidetes* in mice fed a high-fat diet (HFD) and *ob/ob* mutants when both were compared with normal weight mice (Alabdulkarim and Siegel 2005). A causal link between the gut microbiota and obesity was established by transplanting faecal material from co-twins discordant of obesity to germ free mice (GF). The group of GF mice colonised with faecal microbiome from co-twins with obesity showed a significant increase in adipose tissue and body weight compared with the group colonised with the faecal microbiome of normal weight co-twins. Moreover, obese mice co-caged with normal weight mice gained less weight compared with those co-caged with obese littermates (Al-Zahrani 2013). Taken together, these results demonstrate that the shift in gut microbiome in obese and normal weight mice was influenced largely by the diet followed by their co-caging littermates. Furthermore, obesity or normal weight status are highly transferable in GF mice after co-housing that leads to induction of obesity or protection from it in these murine models.

6. Impact of Obesity on the Immune Response

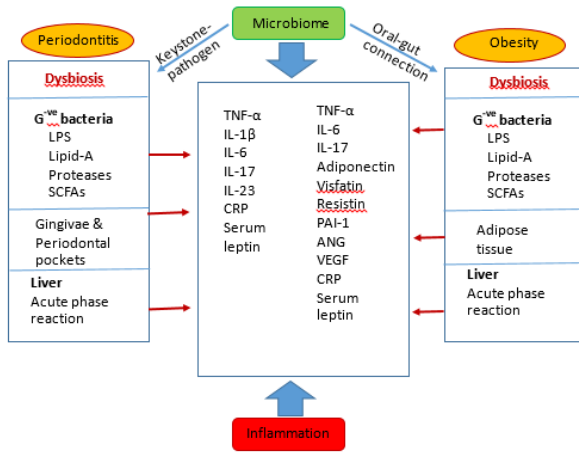
One of the hallmarks of obesity is the induction of low-grade chronic inflammation (Cani et al. 2007). Adipose cells secrete bioactive molecules (adipokines) such as leptin, adiponectin, visfatin and

resistin that are elevated in obese individuals (Luo and Blackledge 2018). These cells also secrete elevated inflammatory cytokines such as TNF- α , IL-6, and other bioactive molecules including inhibitor of plasmogen activator-1 (PAI-1, involved in vascular homeostasis), angiotensinogen (ANG, regulators of blood pressure), vascular endothelial growth factor (VAGF, promoter of angiogenesis) and acute phase C-reactive protein (CRP) (Sales-Peres et al. 2016). Leptin is thought to be a key regulator of innate and adaptive immunity and thus enhances obesity-associated and inflammatory diseases that affect bones and joints (Francisco et al. 2018). It is thought that inflammation is driven by LPS or endotoxin (lipid A) present on the cell surface of Gram-negative bacteria. LPS containing lipid A were able to cross the gastrointestinal mucosa or influence the lipoprotein (chylomicrons) involved in the absorption of cholesterol and triglycerides from the intestines (Neal et al. 2006). Once LPS enter the circulation, they infiltrate the liver and adipose tissues resulting in initiation of innate immune responses (Tanti et al. 2012). Furthermore, LPS activate the CD14 receptor on the surface of macrophages generating a complex that binds to the toll-like receptor-4 (TLR4) that triggers transductional signals and the expression of several inflammatory molecules, such as activator protein P1 (AP-1) and nuclear factor κ B (NF- κ B) (Cani et al. 2007). In addition, LPS are responsible for regulating the nucleotide oligomerisation domain-like (NOD) receptors on the cell surface of macrophages and dendritic cells, which in turn induce NF- κ B (Figure 2). Therefore, LPS is important in the recruitment of effector molecules and components responsible for the activation of the innate immune system and sustaining chronic inflammation (Cani et al. 2008).

The proposed mechanism linking LPS or endotoxemia is that consumption of HFD alters the gut microbiota, leading to increased gut permeability and the continuous release of LPS into the circulation. This mechanism was discovered upon LPS infusion into genetically identical mice, which resulted in a significant weight gain compared with the control counterparts fed the same HFD (Ghanim et al. 2009). In addition, *ob/ob* mice deficient in immunoprotein CD14 and incapable of inducing LPS-mediated inflammation, managed to resist weight gain even when they were fed the same HFD as *ob/ob* mice (Ley et al. 2005).

The oral cavity–gut hypothesis was based on orally administered *P. gingivalis* in mice that resulted in altered gut microbiota composition and modulation of the gut immune system. In this study, the gut metabolites profile was assessed using pyrosequencing and metagenomics analysis. Challenge with *P. gingivalis* caused dysbiosis of the gut microbiome and resulted in the significant increase of bacterial genera *Coriobacteriaceae*, *Gemallaceae* and *Clostridiaceae*, whereas those of *Prevotellaceae*, *Mogibacteriaceae*, *Dorea*, *Butyrivococcus*, *Biophila* and unclassified S24-7 were significantly decreased. Metabolite profile analysis showed that several amino acids in the metabolic pathways relating to the risk of developing obesity and diabetes were significantly elevated in mice challenged with *P. gingivalis*. (Kato et al. 2018). Taken together, *P. gingivalis* was able to cause not only oral microbiome dysbiosis, but also qualitative and quantitative changes in the gut microbiome resulting in altered immune status. This shift resulted in the increased production of certain amino acids absorbed in the systemic circulation through impaired gut barrier function. These findings revealed new insights into the potential mechanisms linking obesity and periodontitis.

Figure 2. Potential mechanistic pathway common to periodontitis and obesity



In both periodontitis and obesity, Gram-negative anaerobic bacteria release virulence factors such as proteases, short chain fatty acids (SCFAS) and cell surface molecules (LPS and lipid A). Host tissues respond by releasing excess cytokines and other molecules resulting in dysregulated immune responses and sustained chronic inflammation. CRP, C-reactive protein; TNF- α tumour necrosis alpha; PAI-1, inhibitor of plasminogen activator-1; ANG, angiotensinogen; and VEGF, vascular endothelial growth factor.

7. Mechanistic Links between Periodontitis and Obesity

A few studies have explored the mechanistic link using experimental animal models on HFD that were challenged with periodontal pathogens. The first study induced periodontitis by oral gavage with *P. gingivalis* and *Fusobacterium nucleatum* on rats fed HFD and a standard diet. The clinical parameters of periodontitis were significantly increased in the rats fed HFD compared with the controls. The study demonstrated that both disorders affect systemic inflammatory and metabolic dysregulation biomarkers, with dyslipidemia, increased glucose and hepatic damage (Spor, Koren, and Ley 2011). The second study induced periodontitis by challenging mice with *P. gingivalis*, *F. nucleatum* and *Prevotella intermedia* followed by feeding them HFD. The mice with periodontitis on HFD showed an increased diversity of periodontal microbiota, which caused higher adaptive immune responses that resulted in insulin resistance (Alabdulkarim and Siegel 2005). The final study used only *P. gingivalis* to challenge mice on HFD and resulted in a significant increase in alveolar bone loss, weak expression of immune response and decreased expression of IL-6, TNF- α and serum amyloid A (SAA). Altered expression of cytokines was confirmed by treating harvested peritoneal macrophages from the mice on HFD with live cells of *P. gingivalis* or its LPS; this resulted in a significant reduction of TNF- α and IL-10. Furthermore, a reduced immune response to *P. gingivalis* resulted in higher bacterial counts in HFD mice compared with lean animals. These elevated bacterial counts could have been caused by the inability of obese mice to mount adequate immune response because of some form of immune paralysis (Amar et al. 2007); (Darveau, Hajishengallis, and Curtis 2012). Similarly, in the keystone-pathogen hypothesis, the inflammation characteristic of chronic periodontitis was driven by altered oral microbiome and *P. gingivalis* activation of TLR-2 and complement component C5aR in neutrophils. This pathway inhibits the host's antimicrobial response (chemokine paralysis) while stimulating an inflammatory response (Darveau, Hajishengallis, and

Curtis 2012).

In obese individuals, circulating endotoxin levels increased by 20% in individuals were associated with a high expression of IL-6 and TNF- α concentration in adipose tissue (Murphy et al. 2013). Altogether, these results demonstrate the important role of LPS derived from Gram-negative bacteria effects in low-grade inflammation observed in obesity. Interestingly, there were similar parallels between the role of LPS-mediated inflammation in mouse models of obesity and periodontitis in terms of activation of CD-40, TLR-2, TLR-4 and NOD receptors leading to the activation of NF- κ B, effector molecules and inflammasome that in turn activated innate immune responses (Hajishengallis 2015).

8. Conclusion

The association between inflammatory mediators in periodontitis and diabetes is well established; however, the link with obesity is not fully understood. The keystone-pathogen and the oral-gut microbiome hypotheses are revealing new insights on the mechanistic links between periodontitis and obesity. This was facilitated by studies of the dysbiotic microbiome in animal models deficient in certain metabolic genes and the impact of periodontal pathogens and HFD on both conditions. Future studies employing genomics, proteomics and transcriptomics are most likely to reveal whether the dysbiotic microbiome is the cause or consequence of periodontitis and obesity. Furthermore, detection of inflammatory biomarkers unique to one or both conditions in saliva, serum or plasma could be used as diagnostics to reduce the risk of development of periodontitis and obesity. Hence, targeting keystone pathogens by periodontal therapy may impact disease progression, especially among overweight and obese individuals.

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Bio

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Joined KFU in October 2015 as a coordinator of the Department of Biomedical Sciences. Research interest on the relationship between oral and systemic diseases. At Queen Mary University of London 1998–2015. Research included: first, analysis of the virulence factors in periodontal pathogens; second, the role of the commensal oral and gut microbiomes in the ontogeny of the innate immune responses. Published over 30 articles in peer-reviewed journals including Nature Immunology, Cell Host and Microbe, Immunity, and Journal of Dental Research.

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