Porphyromonas gingivalis on Biomaterials

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Contributor: Retno Ardhani, Rasda Diana, Bidhari Pidhatika

It was found that *Porphyromonas gingivalis* (*P. gingivalis*) was frequently found at the peri-implantitis site. *P. gingivalis* is a Gram-negative, obligately anaerobic, non-motile, and non-spore-forming bacterium with several virulence factors: hyaluronidase and chondroitin sulfatase enzymes, lipopolysaccharide (LPS) capsule, fimbriae, collagenase, and aminopeptidase.

Keywords: Porphyromonas gingivalis ; surface topography ; dental implants ; subperiosteal implant ; surface roughness ; depth profile

1. Introduction

Subperiosteal implants were first introduced in Sweden in 1942 as an alternative to treat patients with severely atrophic bones [1]. These implants were designed to be placed in between the bone and the periosteum. The main idea was to distribute stress from the prostheses to a large area of bone support [2]. Although, in recent years, subperiosteal implants have been gradually replaced by endosseous implants, for the patient with severely atrophic bones, this type of implant is irreplaceable [3]. In addition, with advanced technology such as computed tomography (CBCT), intraoral scanners, computer-assisted-design/computer-assisted-manufacturing (CAD/CAM) software, and newly discovered materials, the subperiosteal implant has started to regain its popularity [4]. However, the subperiosteal implant has several disadvantages, such as a complex fabrication technique, time-consuming procedures, and a higher risk of postoperative complications [2][5][6]. One of the most common postoperative complications is an infection on the permucosal abutment post. This infection has a clinical characteristic similar to peri-implantitis on the endosseous implant. Once the infection spreads, the option is to perform tissue resection or complete the implant removal [7].

Peri-implantitis is an inflammation around implants and induced progressive bone loss [8]. The effect of peri-implantitis is generally to cause more significant bone loss and more rapid progress than periodontitis [9]. It was found that microorganisms play a vital role in peri-implantitis through biofilm formation [10]. After the implant surface is exposed to the oral environment, the biofilm starts to form in the peri-implant pocket [11]. The biofilm is formed through five stages: (1) reversible cell attachment; (2) irreversible cell attachment facilitated by extracellular polymeric substance (EPS); (3) cells attached on surfaces replicate and form microcolonies; (4) biofilm maturation by forming a three-dimensional structure; (5) detachment of some cells from biofilm and dispersal to propagate and produce biofilm renewal [12]. Overall, biofilm formation happens within 1–2 weeks and reaches its stability after three months [11]. In addition, bacterial infections lead to inflammation, and implant failure can occur at any time during treatment [13][14][15].

To date, to improve the cells and tissue attachment, the implant surface has been modified by both chemical and or physical alteration, which includes creating grooves and roughness [16]. However, implant surface characteristics are crucial not only for tissue attachment but also for biofilm formation. In vitro and in vivo studies reveal that implant surface properties regulate bacterial attachment, physiology, and biofilm formation [12][17]. This is because bacteria can sense chemical signaling and surface-associated mechanical cues. The first clue regarding this phenomenon came in 1981 when Beachy found that different bacteria in the same niche do not interact with the same surfaces. *Streptococcus salivarius*, for example: *S. salivarius* binds to the tongue but not to the teeth, whereas *Streptococcus mutans* acts reversely [18]. Similarly, with *P. gingivalis*, within the same salivary pellicle, the addition of peptide base coating inhibits the attachment of these bacteria. On the contrary, a non-coated implant disk showed a higher number of *P. gingivalis* attached [19].

The effect of topography on bacterial adhesion is like two sides of the same coin, which depends on the size, patterns, and distribution of the topography. For example, some studies suggest that implants with micro-roughness have higher biofilm and bacterial accumulation than more refined surfaces [17][20][21]. At the same time, other studies found the possibility of an antifouling effect from micro-topography by changing the surface wettability [22]. Similar to microtopography, some nanotopography also affects bacterial activity on implant surfaces. Studies showed that

nanotopography could induce bacteria to produce different types of EPS [23]. Nanotopography also affects bacterial membranes. Nanopillars, for example, act like “a bed of nails”, which ruptures bacterial membranes once it is in contact with this surface [22].

2. Porphyromonas gingivalis Structure and Characteristic

Principally, bacterial surface components and their extracellular compounds, such as fimbriae or pili, LPS, and EPS, combined with environmental conditions and quorum-sensing signals, are critical for biofilm formation [24]. Below, researchers will discuss the *P. gingivalis* structure and its significance, especially in biofilm formation.

2.1. Fimbriae

Bacteria, as well as *P. gingivalis*, commonly express their extracellular polymer known as pili or fimbriae, which are similar terms [25]. Fimbriae are considered significant factors in determining *P. gingivalis* virulence, as fimbriae help in bacterial adhesion to the host surface, antibiotic surface, and or in between bacterial cells [26][27][28]. In an in vitro polymerase chain reaction assay (PCR), it was found that the number of fimbriae in a *P. gingivalis* strain is equal to its ability to adhere [27]. A *P. gingivalis* mutant 33277 (MPG1) with minimum fimbriae could not adhere to both epithelial cells or the gingival fibroblast [29]. Fimbriae are also classified into several types based on several classification schemes. The most popular one is a classification based on its morphology and function by Brinton in 1965. Brinton classified six types of fimbriae and then, one year later, Duguid et.al. added a seventh (Type 1 to 6 and F) [28]. However, with *P. gingivalis*, the widely used classification is based on the nucleotide sequences, in which six genotypes of the *fimA* gene have been identified (*fimA* I, Ib, II, III, IV, and V) [30].

P. gingivalis, in general, has two types of fimbriae, which are *FimA* and *Mfa1* fimbriae. The *FimA* fimbriae are composed of *FimA* proteins encoded by *FimA* genes and called the long fimbriae. Similarly, the *Mfa1* fimbriae are composed of the *Mfa1* protein encoded by *Mfa1* genes, and are called the short fimbriae [25][31][32]. These fimbriae help bind specifically to and trigger various host cells, such as epithelial, endothelial, and spleen cells, as well as peripheral blood monocytes in humans, resulting in the release of several distinct adhesion molecules and inflammatory cytokines [25]. In addition, there are several accessory proteins which are incorporated into fimbriae; for example, *Mfa4* which are incorporated into *Mfa1* fimbriae. *Mfa4* mediate the formation of *Mfa1* by promoting the maturation of *Mfa3* and stabilizing *Mfa5* within the cell surfaces; thus they are crucial in biofilm formation [33].

2.2. Capsule

The *P. gingivalis* strain exhibits significant heterogeneity, in which some strains are encapsulated, whereas others are non-encapsulated [34]. Previous studies have reported that the encapsulated strain of *P. gingivalis* has higher virulence than the non-encapsulated one. The capsule plays a major role in evading host immune system activation, reducing phagocytosis, increasing bacterial activity survival ability within the host cells, and boosting its virulence [34][35][36].

2.3. Cell-Wall

In the Gram-negative bacteria, such as *P. gingivalis*, the cell wall is formed from a single layer of peptidoglycan covered by a membranous structure called the outer membrane vesicles (OMVs). *P. gingivalis* expresses protease activity which can be extruded with the OMVs [37]. OMVs enable bacteria and host communication as they can carry molecules involved in immune modulation [38]. *P. gingivalis* OMVs are adherent and small, with the ratio of cells to OMVs at approximately 1:2000 [39].

3. Biofilm Formation

Biofilm is a microbial community attached to the interface enclosed in an EPS that exhibits a distinct phenotype correlated to its gene transcription and growth rate. It is known that the biofilm has been shown to have a specific mechanism for initial attachment to a surface, development, and detachment [40]. Overall, it is believed that biofilm formation begins with bacterial attachment on the surface, which transforms from reversible to irreversible. Adhesive components of bacteria aid this transformation. This attachment then advanced through EPS production, which later entrapped the whole structure. Finally, some bacterial cells escape from the mature biofilm to form new colonies [41]. Once the biofilm is developed, killing the bacteria inside or removing the biofilm from the surface becomes difficult. Bacteria inside the biofilm are packed and resistant to the adverse environment, for example, antibiotics [42]. Hence, interspersing initial bacteria attachment, including their sensing mechanism, is crucial to preventing biofilm formation and related problems [43].

Biofilm formation on the subperiosteal implant is affected by several factors such as (1) oral environment, (2) bacterial properties, and (3) material surface characteristics, including chemical composition, surface free-energy, hydrophilicity, and surface topography (roughness) [17][44]. Higher surface free energy has shown significant correlation to bacterial adherence. Higher surface free energy favours bacterial attachment [45]. In addition, the combination of surface free energy and surface roughness is the major factor and proportional to surface hydrophilicity with low surface energy and smoother-surface-producing higher hydrophobicity [46]. Almost all in vivo studies suggest that a smooth surface reduces the amount of biofilm compared to a rough one. An increase in surface roughness of more than 0.2 µm and or an increase in surface energy promotes biofilm formation, with surface roughness being more dominant [44].

4. Surface Topography

Physical modification of surfaces can provide long-term effectiveness and is environmentally friendly. Thus, the physical modification is believed to be a more promising alternative compared to the chemical modification of surfaces [47]. One of the important parameters in the identification of physical surface properties is surface topography, which refers to both the profile shape and the surface roughness, including the waviness and the asperity or the finish [48].

Furthermore, the most frequently used parameters for characterizing surface topography are average surface roughness (R_a) and root-mean-square surface roughness (R_{rms}), that stands for the average and root-mean-square deviation of height values from the mean line, respectively. However, both R_a and R_{rms} provide no information on the spatial distribution or shape of the surface features. Some researchers have offered new parameters for a more comprehensive characterization of the surface topography, such as summit density (S_{ds}) and developed area ratio (S_{dr}) [47].

In the next paragraph, the surface roughness is presented in R_a or S_a. The average roughness, R_a, provides a general measure of the height of the texture across a surface. It is the average of how far each point on the surface deviates in height from the mean height, while S_a is an absolute value that expresses the difference in height of each point to the arithmetical mean of the surface [49]. In general, surface energy (often presented as water contact angle) changes as the surface roughness changes [50]. However, one should keep in mind that surface chemistry also plays key roles in the changes in surface energy [51][52][53].

5. Subperiosteal Implant Materials and Surface Modification

Material selection in subperiosteal implant placements plays a key role in implant success [54]. In general, like the endosseous implant, subperiosteal implant material is divided into three categories which are metal, ceramic, polymer, and composite [55]. To improve materials properties, surface treatment is commonly applied. The addition of surface treatment improves cell attachment and bacterial debridement. Surface treatment is arguably the most studied topic regarding implant design alteration. There are various types of surface treatment; however, they can be simplified into two types which are chemical and physical. Both of these types showed efficacy in increasing bone attachment and or bacterial debridement [56]. In this section, researchers will discuss the materials used for subperiosteal implants and the various surface modification methods applied.

One of the widely used materials for subperiosteal implants is titanium and its alloys [54][57]. Titanium and its alloys are still a material of choice for dental implants, as they have a high success rate, are durable, and display adequate osseointegration [58]. There are several methods used for titanium surface modification such as sandblasting, acid etching, a combination of both sandblasting and acid etching (SLA), fluoride treatment, calcium phosphate coating, and anodic oxidation [59][60]. Among these methods, sandblasting is one of the most popular. Sandblasting or acid etching or a combination of both can increase surface roughness, increasing the surface area for osteoblast attachments. Hence, it increases bone healing, interfacial stress distribution, and bonding strength [61]. In addition, Alagatu et al. [54], mentioned sandblasting as the best method for titanium and zirconia.

Recently, the popularity of zirconia as an alternative for implant materials has increased. In their review, Alagatu et al. [54] showed that some clinical studies demonstrated that zirconia has better anti-inflammatory properties than titanium. In addition, zirconia is less prone to peri-implantitis than titanium. Zirconia also can be combined with titanium to improve both properties. The addition of zirconia increases implant biocompatibility compared to titanium alone [62]. Several attempts have been made to improve the properties of zirconia such as the addition of hydroxyapatite [63] or calcium phosphate [64], sandblasting [65], acid etching [66], laser treatment [67], and ultraviolet photo-functionalization [68].

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