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MINIREVIEWS

Influence of periodontitis on abdominal aortic aneurysms

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Abstract

Periodontitis is known to be a risk factor for abdominal aortic aneurysm (AAA). However, the influence of periodontitis on AAA development is to be elucidated. This article is to review the relationship between periodontitis and AAA. We focused on the roles of specific periodontopathic bacteria in AAA, matrix metalloproteinases and toll-like receptors in the pathophysiology in the section of experimental analysis. Furthermore, we showed clinical data of periodontitis in patients with AAA. We concluded that periodontal pathogens play a critical role in the AAA development.

Key words: Periodontitis; Abdominal aortic aneurysm; Periodontopathic bacteria; Matrix metalloproteinases; Toll-like receptors

Core tip: This article is to review the relationship between periodontitis and abdominal aortic aneurysm. We showed experimental and clinical data to demonstrate the relationship. We concluded that the infection of periodontal pathogens is critical in the aneurysm development.

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INTRODUCTION

Abdominal aortic aneurysm (AAA) is a common diseases, however, it is life-threatening[1,2]. In AAA development, inflammation enhances a disruption of the lamellar structure of the aortic wall[3]. Pathological examination demonstrated that inflammatory cell infiltration was occasionally observed in human AAA tissue[4,5]. An increased expression of matrix metalloproteinases (MMPs) is also observed in human aneurysm tissue samples[6,7].

Periodontitis is the most common chronic infectious diseases in humans. Pathologically, it is characterized by gingival inflammation and the loss of periodontal support tissue[8]. Periodontopathic bacteria enhance the local immunological inflammation, resulting in the secretion of proinflammatory cytokines and MMPs[9]. This leads to the extracellular matrix destruction of the periodontal tissues[10]. In patients with periodontitis, several inflammatory markers increase[11], meaning that systemic inflammation can be caused by the local periodontal infection.

A strong association between dental and cardiovascular diseases has been demonstrated[12,13]. Especially, periodontal diseases are known to be a significant independent risk factor for cardiovascular disease[14]. Previous studies revealed a deep relationship between periodontal diseases and AAA[15,16]. Clinical investigations demonstrated that some periodontal pathogens accelerated the progression of AAA[17], however, the specific influence

of each periodontal bacterium on AAA was not investigated. Recently, we demonstrated the pathophysiolocial and epidemiological relationship between specific periodontal pathogens and AAA using experimental[18-20] and clinical studies[21,22]. This article reviews the association between periodontitis and AAA.

PORPHYROMONAS GINGIVALIS IS HIGHLY AFFECTED IN SYSTEMIC DISEASES

It is reported that more than 700 bacterial species exist in the oral cavity[23]. Some of them are implicated in the oral disease progression[24]. *Porphyromonas gingivalis* (*P. gingivalis*) is a periodontopahic bacterium that is highly associated with the chronic periodontitis. It is frequently detected in the disease sites, while it is detected rarely in healthy sites[25]. The presence of *P. gingivalis* in a periodontal pocket is a predictable factor for periodontal disease progression[26]. Thus, a reduction of *P. gingivalis* numbers is critical in a resolution of the disease at the affected site[27,28]. Experimental investigation showed that the infection of *P. gingivalis* induced a local inflammatory response and periodontal bone loss[29]. This bacterium has several virulence factors, including cysteine proteinases (gingipains), lipopolysaccharide, capsule and fimbriae[30]. However, the roles of these virulence factors are still to be elucidated.

EXPERIMENTAL MODELS OF PERIODONTOPATHIC BACTERIA INFECTION AND AAA

Recently, we revealed that *P. gingivalis* worsened AAA development in experimental murine AAA models. The model showed that *P. gingivalis* significantly increased the aortic diameter compared to the control mice, while another periodontal bacterium, *A. actinomycetemcomitans* showed no statistical difference. Immunohistochemically, the CD8- and MOMA2-positive cell numbers of *P. gingivalis*-infected mice were significantly higher than control animals. We concluded that *P. gingivalis* could accelerate the progression of experimental AAA[18].

To reveal the pathophysiological mechanism, we focused on MMPs in the animal models. To suppress MMP activity, we used clarithromycin (CAM). We found that CAM administration significantly decreased the *P. gingivalis*-challenged aortic diameter compared to the mice only injected with *P. gingivalis*. Histopathologically, the aortic samples harvested from the *P. gingivalis*-challenged and CAM-treated mice showed less elastic degradation. Furthermore, the plasma levels of MMP-2 in the CAM-treated mice significantly decreased. These findings suggest that MMP-2 is an important factor for developing *P. gingivalis*-accelerated AAA[19].

Next, we analyzed the role of toll-like receptors (TLRs) because they are key receptors of virulence factors of periodontopathic bacteria. To reveal the mechanism, we used TLR knockout mice on *P. gingivalis*-accelerated AAA progression. We found that the *P. gingivalis*-infected TLR-2 knockout mice showed a lower rate of aortic diameter increase compared to the *P. gingivalis*-infected wild-type mice. However, the aortic diameter of the *P. gingivalis*-infected TLR-4 knockout mice statistically increased. Immunohistochemically, the expression levels of MMP-2 in the aneurysmal wall from TLR-2 knockout mice were lower than that from wild-type mice. These findings clarified that *P. gingivalis* accelerated the development of AAA *via* TLR-2 signaling[20].

CLINICAL OBSERVATION OF PERIODONTITIS IN AAA PATIENTS

Based on the animal studies, we surveyed the periodontal conditions in patients with AAA. Firstly, we studied 12 AAA patients and age and sex-matched 24 patients with non-AAA cardiovascular patients. We examined the patients' oral condition and the presence of periodontal pathogens, *P. gingivalis*, *A. actinomycetemcomitans* and *P. intermedia* in oral samples. We revealed that the AAA patients had deeper pocket depth in comparison to the non-AAA patients. However, the existence of periodontal bacteria was comparable between the two groups. In this observation, we concluded that periodontitis might further affect aneurysm progression compared to other cardiovascular diseases[21].

Next, we compared the periodontal condition between AAA and arrhythmia patients. We studied 142 patients with tachy-arrhythmia (TA) and 25 patients with AAA. We examined patients' oral condition and the presence of *P. gingivalis*, *A. actinomycetemcomitans* and *P. intermedia* in the patients' saliva and subgingival plaque. We also measured serum antibody titers against the pathogens using ELISA. We found that the patients with AAA had fewer remaining teeth and deeper pocket depth in comparison to the TA patients. The existence of each periodontal bacterium in their saliva or subgingival plaque and serum antibody titers was comparable between the two groups. We concluded that periodontitis might have a larger affect on aneurysm progression compared to arrhythmia[22].

In these clinical studies, we showed that periodontitis had progressed further in AAA patients compared to patients with other cardiovascular disease. Our result supports the fact that AAA patients had bad oral and periodontal conditions. However, bacterial existence and serum antibody titers were comparable between the groups. This is because other periodontal pathogens may aggravate AAA. A previous study showed that other periodontopathic bacteria were present in AAA specimens[15]. Furthermore, other studies demonstrated that not only *P. gingivalis* but also other periodontal bacteria were frequently detected in aortic aneurysmal walls (Table 1)[31,32]. Therefore, observation of other periodontal pathogens should be investigated to reveal the relationship between periodontitis and AAA development.

Table 1 ***Porphyromonas gingivalis*** **and periodontal bacteria were frequently detected in aortic aneurismal walls**

Ref.	Article and year	Detected bacteria	Samples	*n*
Kurihara *et al*[15]	*Eur J Vasc Endovasc Surg* 2004	*P. gingivalis*, *T. denticola*, *P. intermedia*, *C. rectus*, *T. forsythensis*, *P. nigrescens* and *A. actinomycetemcomitans*	Aortic wall and mural thrombus	32
Marques da Silva *et al*[31]	*J Periodontol* 2005	*A. actinomycetemcomitans*	Aortic wall	56
Nakano *et al*[32]	*Oral Microbiol Immunol* 2009	*P. gingivalis*, *T. denticola*, *A. actinomycetemcomitans*, *S. mutans* and *S. sanguinis*	Aortic wall	86
Delbosc *et al*[17]	*PLoS One* 2011	*P. gingivalis*	Aortic wall	16

In conclusion, AAA may be associated with periodontitis and a specific periodontal pathogen may affect the progression of AAA. Further investigation is needed to reveal the detailed pathophysiology in the relationship between AAA and periodontal pathogens.

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