Effect of Periodontitis on Cardiovascular Manifestations in Marfan Syndrome

Critical Common Role of TGF-β

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Summary

Marfan syndrome (MFS) is a systemic connective tissue disorder that is caused by mutations in the extracellular matrix protein fibrillin-1. While MFS patients are considered to be at high risk of dental disorders and cardiovascular complications, little causal relationship has been provided to date. It is well known that an elevated level of active TGF-β in the plasma is a major manifestation of MFS. TGF-β is known to play a critical role in the development of cardiovascular diseases and its levels were also elevated in the serum and saliva of periodontitis patients. These findings may suggest an association between periodontitis and the cardiovascular complications of MFS. In this article, we review the influence of periodontitis in MFS patients with cardiovascular complications in order to identify critical therapeutic targets of TGF-β. (Int Heart J 2015; 56: 121-124)

Key words: Bacteria, Cardiovascular complications, Connective tissue disorder, Oral diseases, Matrix metalloproteinases

Marfan syndrome (MFS) is an autosomal dominant disorder affecting the connective tissues. Mutations in the fibrillin-1 gene are responsible for alterations of the glycoprotein fibrillin-1, which is a component of the microfibrils in the connective tissue matrices. These microfibrils are present in the suspensory ligament of the lens, skeletal system, lungs, blood vessels, and skin. Thus, MFS is a systemic disease where the localization and degree of symptoms are individually different. Cardiovascular complications, especially aortic dissection or ruptures, are the major cause of morbidity and mortality.

MFS relies on defined clinical criteria (Ghent nosology) that were outlined to facilitate accurate recognition of this genetic syndrome. The Ghent criteria consist of a set of major and minor manifestations in different body systems. Recently, an international expert panel established a revised Ghent nosology that puts more weight on cardiovascular manifestations. In addition to the systemic manifestations, MFS sometimes exhibits characteristic oral features including maxillary protrusion, high palate, crowded teeth, and fragility of the temporomandibular joint. However, the detailed characteristics of the oral features, including periodontitis in MFS, are still to be elucidated.

Periodontitis: An Oral Connective Tissue Disorder

Periodontitis is one of the most common chronic infectious diseases in humans. Pathologically, periodontitis is characterized by gingival inflammation and the loss of periodontal support tissue. Periodontopathic bacteria generate host immunological inflammatory responses, resulting in the secretion of cytokines and matrix metalloproteinases. This leads to the extracellular matrix destruction of the periodontal tissues resulting in connective tissue disorder. In patients with periodontitis, several inflammatory factors increase, meaning that systemic inflammation can be caused by periodontal infection. A strong association between dental disease and cardiovascular diseases has been demonstrated. Periodontal disease in particular has been reported to be an independent risk factor for cardiovascular disease. Previous studies also revealed a strong relationship between periodontal diseases and abdominal aortic aneurysms (AAA). Clinical investigations have demonstrated that some periodontal pathogens accelerated the progression of AAA. Recently, we demonstrated the pathophysiological and epidemiological relationship between specific periodontal pathogens and AAA using experimental and clinical studies.
TGF-β is a Common Critical Factor in MFS, Cardiovascular Diseases, and Periodontitis

It is well known that an elevated level of active TGF-β in the plasma is a major manifestation of MFS, while circulating TGF-β may not be a diagnostic marker in some populations. Chaudhry, et al demonstrated that mutation of fibrillin-1 altered intercellular communication and significantly increased TGF-β protein levels in the extracellular space. TGF-β is a paracrine regulatory molecule involved in several processes. It also enhances collagen production and extracellular matrix remodeling. TGF-β is produced in dimer form in the cells and is bound with latency-associated protein to form a small latent complex. This secreted small latent complex is bound extracellularly to latent TGF-β binding protein to form a large latent complex. In MFS, fibrillin-1 mutation occurs and the large latent complex becomes unable to attach to microfibrils. The latent form is not generated, resulting in an elevated level of serum TGF-β. TGF-β joins to its dimer receptor forming a complex that induces the phosphorylation cascade. (Figure)

TGF-β is known to play a critical role in the development of aneurysms. Many experimental and clinical investigations have been performed in aortic aneurysms to determine the pathophysiological mechanism of TGF-β. The findings indicated a paradoxical role of TGF-β in aneurysmal formation. Although TGF-β promotes the development of thoracic aortic aneurysms (TAAs), it inhibits AAA development. Furthermore, the pathogenic effects of TGF-β have been shown to play an important role in valvular disease and arrhythmia. Thus, a therapy targeting TGF-β appears to be promising for treating a multitude of heart diseases. In periodontitis patients, TGF-β levels were also significantly elevated in serum and saliva compared to controls. It was reported that a periodontal pathogen, Porphyromonas gingivalis, invaded aortic smooth muscle cells and activated TGF-β. TGF-β is known to play a fundamental role in the repair of periodontal tissue. TGF-β stimulates the synthesis of connective tissue matrix components, such as collagen and fibronectin, in periodontal ligament cells. It also inhibits the degradation of matrix proteins by inhibiting the synthesis of matrix metalloproteinases (MMPs) and increasing the synthesis of proteinase inhibitors. Khalf, et al detected high levels of TGF-β in serum, saliva, and gingival crevicular fluid of patients with periodontitis. They also found that TGF-β expression by gingival fibroblasts was significantly enhanced by viable, but not heat-killed, Porphyromonas gingivalis. They concluded that TGF-β is, at least, a marker in the development of periodontitis. On the other hand, Ohshima, et al demonstrated that TGF-β itself enhanced matrix degradation in gingival fibroblasts from patients with periodontitis. Inhibition of TGF-β signaling suppressed the fibroblast-dependent degradation of collagen. These data demonstrated the ability of TGF-β to activate MMPs in gingival fibroblasts, resulting in enhanced matrix degradation. In this respect, TGF-β has a causal role in periodontitis. Therefore, TGF-β significantly affects matrix degradation in periodontal tissue, as shown in studies that demonstrate either stimulation or inhibition of MMPs. These findings support an association between periodontitis and cardiovascular diseases. (Figure)

It is well known that TGF-β function is associated with secondary upregulation with host-derived immune responses and/or primary (genetic) dysregulation. The roles of receptors and signaling have also been reported. Although the role of TGF-β in MFS has been well investigated, the pathophysiological function of TGF-β in periodontitis has not yet been studied in depth. Thus, similarities or differences in TGF-β function in patients with periodontitis and MFS have yet to be elucidated. Further study is needed in the future.

Clinical Observation of Periodontitis in MFS Patients

De Coster, et al reported that severe and frequent oral manifestations were observed in patients with MFS. Local hypoplastic enamel spots, root deformity, abnormal pulp shape, pulpal inclusions, calculus, and gingival indices were frequent findings in MFS patients. Although severe periodontitis is sometimes observed in MFS patients, little information was provided to show its morbidity in MFS patients. Judge, et al showed that individuals with MFS were at high risk of developing dental disorders. However, no report has described the severity and frequency of periodontitis in MFS patients.

Recently, we reported the incidence and severity of periodontitis in MFS patients. Full-mouth clinical measurements, including the number of teeth, probing pocket depth, bleeding on probing, and community periodontal index were recorded in patients with MFS and age- and gender-matched healthy individuals. We found that the MFS patients had periodontitis more frequently than the control subjects. Furthermore, the MFS patients had significantly more severe periodontitis and fewer remaining teeth compared to the controls. We concluded that a high incidence of periodontitis was observed in Japanese MFS patients.

Next, we analyzed periodontitis in cardiovascular disease patients with or without MFS. In this clinical investigation, we analyzed the periodontal condition of the patients and periodontal pathogens. The subjects were MFS patients with car-
diovascular disease and age- and gender-matched non-MFS cardiovascular disease patients served as controls. Full-mouth clinical measurements were obtained and the presence of three periodontal pathogens, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Prevotella intermedia were determined and measured. We found that the MFS patients had a higher incidence of periodontitis compared to the age- and gender-matched non-MFS control subjects. The MFS patients had significantly more severe periodontitis, fewer remaining teeth, and deeper pocket depth compared to the non-MFS controls. Furthermore, the serum antibody titer level against Prevotella intermedia was significantly lower in the MFS patients than in the non-MFS patients.

**Future Perspective**

Previous investigations have shown that TGF-β is a key molecule in MFS. As mentioned above, elevated TGF-β is associated with the development of complications, such as periodontitis and cardiovascular diseases. However, the role of TGF-β in the pathophysiology of oral and cardiovascular manifestation in MFS is still to be elucidated. We speculate that in vivo control of TGF-β may be a promising strategy with which to treat and/or prevent MFS-related complications. Thus, the goal of this field is to establish methodology for controlling TGF-β and related factors to prevent MFS complications. To control them, novel methodologies for specific gene and/or transcriptional regulations are needed. At present, we are interested in the in vivo gene controlling system using siRNA and other methods. New technologies that can control gene expression and transcription in vivo may be available in the coming years.

**Conclusion:** We conclude that TGF-β influences the pathophysiology of MFS. Thus, TGF-β may be a therapeutic target for preventing MFS-related complications, including cardiovascular diseases and periodontitis.

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**Disclosure**

**Conflict of interest:** None to declare.

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