Periodontal disease and chronic wounds: the theory of wound focal infection in a modern context

Author: *Massimo Rivolo*

Periodontal disease is common, is associated with local and systemic infection, and can be responsible for systemic health problems. A scoping review was performed to determine whether chronic wounds pose the same systemic health hazard as periodontal disease. Key words were used to search the PubMed, CHINAL and Cochrane Wounds databases for relevant publications. Studies on oral health were limited and some were very old. Similarities were found between oral infection and chronic wounds, but there was no clear correlation. A 'wound focal infection theory' is postulated to link chronic wounds with biofilm and local infection, but studies are needed to provide evidence to support this theory. If demonstrated, wound focal infection theory could introduce new ways of viewing chronic wounds and how they are treated.

Periodontal disease (PD) affects 20–50% of the global population and is associated with several risk factors, such as smoking, diabetes, age and poor oral hygiene (Nazir, 2017). PD is defined as a chronic inflammatory disease of the periodontium, with periodontal ligament loss or destruction of alveolar bone in the more advanced forms (Nazir, 2017). Oral health is related to the status of the mouth and reflects the health of the entire body (Benjamin, 2010). The World Health Organization (2005) keeps an oral data bank with community periodontal index scores *[Table 1]* for different countries.

In a systematic review and meta-regression, severe periodontitis was the sixth most prevalent condition in the world in 2010 (Kassebaum et al, 2014). PD is a significant risk factor for the development of various diseases including atherosclerosis, subclinical lower-extremity artery disease, cardiovascular disease, stroke/cerebrovascular disease and metabolic/lipid disorders (Chalmers, 2003). Chronic infection of the gums and inflammation due to periodontitis and gingivitis result in bacterial pathogens, antigens and endotoxins entering the bloodstream (Registered Nurses' Association of Ontario, 2008).

Marcaccini and colleagues (2009) found high concentrations of matrix metalloproteinases (MMP) 8 and 9 in the plasma of people with chronic periodontitis. MMPs released from the gums may impact systematic health and these inflammatory markers can stimulate inflammation in other parts of the body. The pro-inflammatory state caused by periodontitis is, therefore, responsible for high levels of MMPs, particularly MMP8 and MMP9, in the circulatory system (Marcaccini et al, 2009). Similar to periodontitis, high levels of MMPs are also seen in chronic hard-to-heal wounds (Caley et al, 2015).

The presence of *Aggregatibacter actinomycetemcomitans*, a typical small Gram-negative organism known to cause PD, has been reported in a chronic heel wound and the authors suggest that the role of this organism in the development of chronic wounds be explored (Böhme et al, 2014). Such future research could demonstrate the role of oral disease in spreading infection to targeted organ(s).

The area of oral surface that may become inflamed is estimated to be equivalent to the palm of a hand. Clinicians would definitely treat a wound of this size to avoid further problems. When it comes to intra-oral infection, however, inflammation is frequently ignored, although infection can be associated with a range of systematic diseases in the same way as a skin lesions (Mohangi et al, 2013). It is common to find

Massimo Rivolo *is Independent Tissue Viability Nurse Consultant, Trained Lymphoedema Specialist, Executive Member of the World Union of Wound Healing Societies*

Table 1. Community periodontal index scores (World Health Organization, 2005).	
Score	Oral state
0	Healthy periodontal conditions
1	Gingival bleeding
2	Calculus and bleeding
3	Shallow periodontal pockets (4–5 mm)
4	Deep periodontal pockets (≥6 mm)

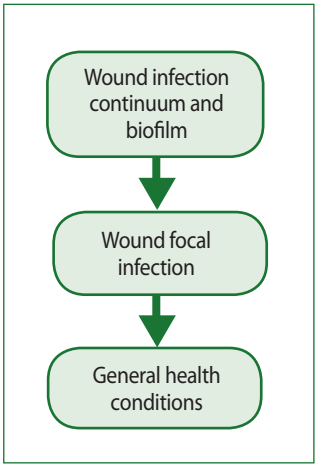

Figure 1. Holistic concept of the impact of wounds on health.

Table 2. Results of the literature search.

Key words used in search	Number of papers found	Relevant papers
PubMed Advanced Search Builder, no limits		
Oral hygiene AND wounds and injuries	561	0
Mouth disease AND wounds and injuries	12,016	1
Periodontitis AND wound and injuries	683	1
Oral hygiene AND infection AND wounds and injuries	75	0
Oral hygiene AND periodontitis AND wounds and injuries	23	0
Oral hygiene AND matrix metalloproteinase AND wounds and injuries	0	0
Oral hygiene AND tumour necrosis factor-alpha AND wounds and injuries	0	0
Oral hygiene AND tissue inhibitors of matrix metalloproteinases AND wounds and injuries	8	1
Periodontal AND infection AND disease	2,960	5
Periodontal disease AND skin ulcers	96	5
CINHAL: Criteria: Full text, references available; Publication type: All; Language: English		
Oral hygiene AND wounds AND metalloproteinases	2	0
Periodontal disease AND skin ulcers AND metalloproteinases	0	0
Periodontitis AND skin ulcers AND tissue inhibitor of metalloproteinase	0	0
Periodontitis AND chronic ulcers AND metalloproteinase	0	0
Cochrane Wounds		
Hand search by subtopic using proteases as a key word	1	0

a palm-sized wound on a leg, but no studies have been published on how a chronic wounds impact general health.

It is clear that oral hygiene and oral disease can impact our general health, but we have not considered whether chronic wounds have a similar effect on our general health. This article aims to examine whether there is a similar correlation between PD/systemic health and chronic wound/systemic health.

Objective

This scoping literature review aimed to map key concepts and identify gaps in existing knowledge about the possible relationship between periodontitis and related circulating MMPs and infection foci. It also aimed to determine whether chronic wounds have the same potential to release endotoxins as PD.

A 'theory of wound focal infection' is hypothesised, developed and postulated in an attempt to reflect evidence from the literature. If it is possible to demonstrate that wounds are a potential reservoir for inflammatory substances, organisms and endotoxins that can effect the entire body, new and interesting ways of thinking open up; we could move from the concept of a wound infection continuum to a deeper and more holistic concept *[Figure 1]*.

Methods

A systematic search of the PubMed, CHINAL and Cochrane Wounds databases was conducted using the following key words: oral hygiene, mouth disease, wounds and injuries, infection, periodontitis, skin ulcer, matrix metalloproteinase, tumour necrosis factor, tissue inhibitors of matrix metalloproteinases, systemic diseases, oral infection, periodontal and atypical wounds. The results of the searches are given in *Table 2*.

Results

Studies on oral health and chronic wounds are limited and some are very old. In 1998, Scannapieco published a position paper on PD about the 'theory of focal infection' stating that the foci of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases, such as arthritis, peptic ulcers and appendicitis. Li et al (2000) highlighted three mechanisms linked with oral infection:

- Metastatic spread of infection from the oral cavity as a result of transient bacteraemia

Box 1. Similarities between oral and wound biofilms.

- Living microbial cells are embedded in an extracellular polymeric substance (Mohangi et al, 2013; Angel et al, 2016)
- Production of matrix metalloproteinases and bacterial proteases (Marcaccini et al, 2009; Serena et al, 2016)
- Can be removed mechanically (Mihai et al, 2015; Bianchi et al, 2016)
- Can reform itself in few hours (Mihai et al, 2015; Bianchi et al, 2016)

- Metastatic injury from the effects of circulating oral microbial toxins
- Metastatic inflammation caused by immunological injury induced by microorganisms.

Periodontal disease is caused by a chronic infection in the mouth with spreading infection via bloodstream due to biofilm. The wound focal infection theory hypothesises the same mechanism, but starting from the wound instead of the mouth *[Box 1]*.

The biofilm is thought to be responsible for PD, with inflammatory response to the local infection caused by colonies of microorganisms and intravascular dissemination of these organisms and endotoxins into the bloodstream (Mohangi et al, 2013). Biofilms on wounds act in the same way, creating a hostile environment for the healing process. Some bacteria or microbes are able to reform biofilm more rapidly than others (Anget et al, 2016). No studies have been published on wound biofilm and the intravascular dissemination of endotoxins/cytokines in the bloodstream as per periodontitis.

An interesting study of a novel, localised drug-delivery system using chitosan poly vinyl alcohol to treat periodontitis showed promising results in oral infection (Wang et al, 2009). Chitosan is a cationic natural polymer used in wound management for its haemostatic, antimicrobial and non-toxic properties and as a vehicle to deliver growth factors to the tissues (Dai et al, 2011). Chitosan can be applied 'from head to toe'. No mention is made in the literature to any effects it might have on MMPs or TIMP activity.

A study of MMPs and TIMPs in chronic leg ulcers showed that the reorganisation and contraction of fibroblast-populated collagen lattices can be mediated by MMPs and TIMPs and their imbalance can be detrimental to the healing process (Cook et al, 2000).

Theory of oral focal infection

This theory was developed in the late 1800s. It resulted in prominent physicians suggesting the removal of all of a person's teeth to treat different conditions, such as allergy, schizophrenia, arthritis deformans and blindness. The theory was later abandoned for being non-scientific and was disregarded for many decades (Kumar, 2013). More recently, periodontal medicine has described and proven the relationship between periodontitis and systemic disease *[Figure 2]*. It is now well known that the subgingival sulcus can harbour many bacterial species and function as a reservoir for pathogens including *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Tropheryma whipplei*. Furthermore, periodontal microorganisms have been found in the tracheobronchial tree, atheromatous plaques, the pancreas and joint cavities, proving that oral infection can metastasise (Kumar, 2013).

Kubota et al (2008) demonstrated that periodontitis can cause an imbalance between MMPs and TIMPs. Increases in MMPs and decreases in TIMPs altered the degradation and synthesis of extracellular matrix. The levels of TIMPs in chronic wounds are generally slightly lower than in acute wounds, demonstrating that an impaired healing can be the result of over-expression of MMPs (Cullen et al, 2009).

A case report by Moutsopoulos et al (2017) describes a patient with leukocyte adhesion deficiency type 1 (LAD1), a rare genetic disorder. This patient had periodontitis and an intractable sacral non-healing wound. The use of ustekinumab, a human monoclonal antibody, blocked the dominant interleukin-23 and interleukin-17 signature — two inflammatory cytokines often detected at inflamed sites in LAD1. Both the sacral wound and the patient's oral condition improved dramatically after three injections. The ulcer had healed 1 year after ustekinumab was first administered. This finding suggests, in the author's opinion, that the immunopathological process (mouth and wound) might play an important role in the healing continuum (Moutsopoulos et al, 2017).

Theory of wound focal infection

The theory of oral focal infection (Kumar, 2013), with its potential to spread contaminants and pro-inflammatory cytokines via the bloodstream, should be expanded to wound infection based on findings such as those by Moutsopoulos and colleagues (2017). Further studies should be undertaken to identify wound behaviour in relation to the subtle and

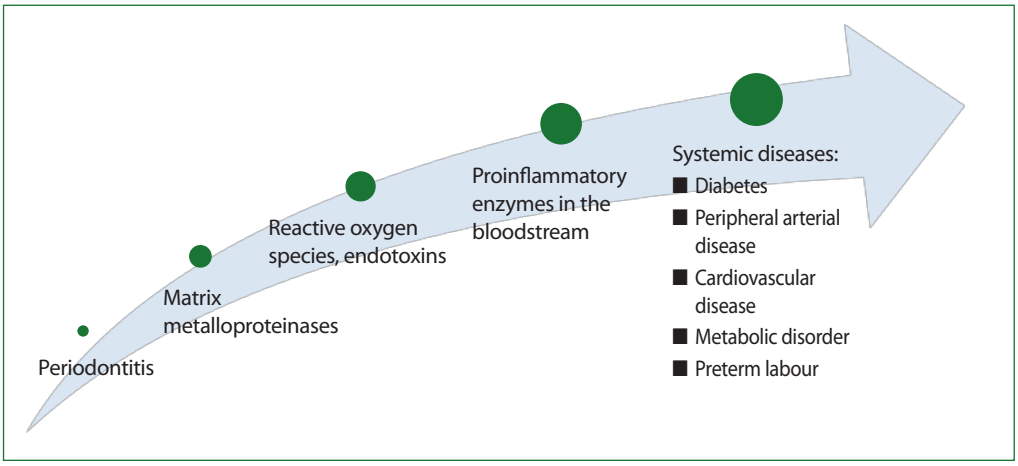

Figure 2. Oral focal infection theory showing the relationship between periodontitis and systemic disease.

continuous release of toxic substances into the body, based on the results from PD research.

Marsh (2006) has described two interesting oral biofilm hypotheses that may be considered in the field of chronic wounds: the community hypothesis and the specific bacterial hypothesis. The specific bacterial hypothesis states that a limited number of microorganisms from the macrobiota are involved in impaired wound healing; while the community hypothesis states that infection can be caused by a pathogenic unit instead of a single microorganism.

Biofilm is a well-recognised issue in many fields, but its role, especially in systemic effects, is not well understood. As with the theory of oral focal infection, wound focal infection should be considered as a potential systemic hazard.

Discussion

Good oral hygiene is fundamental for our health and wellbeing and it should be a core component of strategic health assessment and part of any prevention strategy. In 2007, Dr Halstrom, president of the Canadian Dental Association, encouraged clinicians to 'put the mouth back in the body', as oral diseases and major chronic life-threatening diseases share common risk factors. Periodontitis can release endotoxins, increase circulating MMPs, and has a role in triggering cytokine production and diffusion via the bloodstream. In the same way, chronic wounds might be a reservoir for different endotoxins and microorganisms, and their continuous release into the bloodstream. This relationship may be similar to oral focal infection and further studies should be performed to examine this potential link.

Implication for practice

Wound focal infection could be thought of as a hypothetical theory, wherein a chronic wound enlarges and completes the concept of a local infection and biofilm. The role of this theory must be investigated and its impact on the entire body ecology demonstrated scientifically, as periodontal science did with periodontitis. If demonstrated, wound focal infection theory could introduce new ways of considering chronic wounds. It would also highlight the need to develop strategies to bind MMPs and fight against infection to restore the normal environment and reduce the risk of systemic infection and disease.

WINT

References

Angel D, Black J, Call E et al (2016) *International Wound Infection Institute (IWII): Wound Infection in Clinical Practice.* Wounds International: London. Available at: www.woundsinternational.com (accessed 13.02.2019)

Benjamin RM (2010) Oral health: The silent epidemic. *Public Health Rep* 125(2): 158–9

Bianchi T, Wolcott RD, Peghetti A et al (2016) Recommendations for the management of biofilm: a consensus document. *J Wound Care* 25(6): 305–17

Böhme J, Glaenz TE, Kaiser A, Allmacher C (2014) Cutaneous infection with Aggregatibacter actinomycetemcomitans. *Hautarzt* 65(9): 810–3 [Article in German]

Caley MP, Martins VLC, O'Toole EA (2015) Metalloproteinases and wound healing. *Adv Wound Care (New Rochelle)* 4(4): 225–34

Chalmers JM (2003) Oral health promotion for our ageing Australian population. *Aust Dent J* 48(1): 2–9

Cook H, Davies KJ, Harding KG, Thomas DW (2000) Defective extracellular matrix reorganization by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2, and MMP-2 activity. *J Invest Dermatol* 115(2): 225–33

Cullen B, Gibson D, Harding K et al (2009) MMPs made easy. *Wounds International* 1(1): 1–6. Available at: www.woundsinternational.com (accessed 13.02.2019)

Dai T, Tanaka M, Huang YY Hamblin MR (2011) Chitosan preparations for wounds and burns: antimicrobial and

wound-healing effects. *Expert Rev Anti Infect Ther* 9(7): 857–79

Halstrom W (2007) Let's put the mouth back in the body. *CMAJ* 17(2): 145

Kassebaum NJ, Bernabé E, Dahiya M et al (2014) Global burden of severe periodontitis in 1990–2010: A systematic review and meta-regression. *J Dent Res* 93(11): 1045–53

Kubota T, Itagaki M, Hoshino C et al (2008) Altered gene expression levels of matrix metalloproteinases and their inhibitors in periodontitis-affected gingival tissue. *J Periodontol* 79(1): 166–73

Kumar PS (2013) Oral microbiota and systemic disease. *Anaerobe* 24: 90–3

Li X, Kolltveit KM, Tronstad L, Olsen L (2000) Systemic diseases caused by oral infection. *Clin Microbiol Rev* 13(4): 547–58

Marcaccini AM, Novaes AB Jr, Meschiari CA et al (2009) Circulating matrix metalloproteinase-8 (MMP-8) and MMP-9 are increased in chronic periodontal disease and decrease after non-surgical periodontal therapy. *Clin Chim Acta* 409(1–2): 117–22

Marsh PD (2006) Dental plaque as a biofilm and a microbial community — implications for health and disease. *BMC Oral Health* 6(Suppl 1): S14

Mihai MM, Holban AM, Giurcăneanu C et al (2015) Microbial biofilms: Impact on the pathogenesis of periodontitis, cystic fibrosis, chronic wound and medical device-related infections. *Curr Top Med Chem* 15(16): 1552–76

Mohangi GU, Singh-Rambirich S, Volchansky A (2013) Periodontal disease: Mechanisms of infection and inflammation and possible impact on miscellaneous systemic diseases and conditions. *SADJ* 68(10): 462, 464–7

Moutsopoulos NM, Zerbe CS, Wild T et al (2017) Interleukin-12 and interleukin-23 blockade in leukocyte adhesion deficiency type 1. *N Engl J Med* 376(12): 1141–6

Nazir MA (2017) Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci (Qassim)* 11(2): 72–80

Registered Nurses' Association of Ontario (2008) *Oral Health: Nursing Assessment and Interventions*. RNAO: Toronto, Canada. Available at: https://bit.ly/2TfVoJW (accessed 26.02.2019)

Scannapieco FA (1998) Position paper of The American Academy of Periodontology: periodontal disease as a potential risk factor for systemic diseases. *J Periodontol* 69(7): 841–50

Serena T, Chadwick P, Romanelli M et al (2016) BPA made easy. *Wounds International* 12(4): Available at: www.woundsinternational.com (accessed 13.02.2019) pp3

Wang LC, Wu H, Chen XG et al (2009) Biological evaluation of a novel chitosan-PVA-based local delivery system for treatment of periodontitis. *J Biomed Mater Res A* 91(4): 1065–76

World Health Organization (2005) *Oral Health: Periodontal Country Profiles*. WHO: Geneva, Switzerland. Available at: www.who.int/oral_health/databases/niigata/en (accessed 13.02.2019)