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內文：

***Introduction***

◎ **Rheumatoid arthritis (RA)**

- A systemic **autoimmune** disease ( about **1%** of adult)
- **Chronic inflammation → progressive joint destruction** and other systemic manifestations from
- Inflammation of synovial membrane → invasion into adjacent cartilage matrix → degradation of articular cartilage / bone mechanism unclear
- **MMP**, cathepsins, and osteoclast activation / cytokines like **TNF-α**, IL-1, MCSF involved

◎ **Periodontal disease**

- Gingivitis and periodontitis (**10-60%** in adults)
- Bacterial invaders → **defensive cells** activated and releasing cytokines like IL-1β, **TNF-α**, and IL-6 → production of **collagenolytic** enzymes like **MMPs** → tissue destruction
- Increased risk of atherosclerosis, DM, adverse pregnancy outcome, and **RA**

***Clinical Interelation***

- **Individuals with RA** are more likely to experience **moderate to severe periodontal disease** (prospective clinical trials)
- A **high incidence of RA** in patients with **periodontitis**
- ***A common underlying pathobiology ?***

***Biological Links***

1. Periodontopathic bacteria like *A.a., P.g., B.f., P.i., prevotella melaninogenica, and eubacterium nodatum.* In **synovial fluid of patients with RA, *IgG and IgA*** levels against some of these bacteria found **raised** → *antibodies against periodontopathic bacteria could be important for RA ?*
2. ***Porphyromonas gingivalis* (P.g.)** ~ possess peptidyl arginine deaminase (**PAD**) implicated as a susceptibility factor for RA. Individuals with periodontal infection of *P.g.* are exposed to antigens generated by PAD, leading to **production of rheumatoid factor and local inflammation** of **both gingiva and synovium**
3. **Hsp 70 Ab** of *P.m. and P.i.* found raised in **periodontal tissue as well as synovial tissue** of patients with RA. Hsp 70 expression induced with certain stress-stimulating factors → **pro-inflammatory cytokines** induced in **synovium**
4. Genes on **HLA** region remain the most powerful disease risk genes in the patients of **both RA and periodontitis**. HLA-DR4 antigens (and subtypes) directly associated with **both** diseases
5. **Similar patterns of blood cytokine profile** ~ raised titters of **IL-10, IL-1α,**

**TNF-α, LT-α**, and low titters of auto antibodies to **IL-1α and IL-6** → share **common** underlying **disregulation of the inflammatory and immune response**

6. **Increased levels of IL-1β** found in the **synovial tissue** macrophages of Patient with **RA** and in the **GCF** of patients with **periodontitis**. Recent study demonstrated that the polymorphism of the IL-1 gene affected the cytokine profile in patients of both **periodontitis** and chronic arthritis like **RA**
7. Experimentally induced inflammatory **arthritis** in rats → elevated levels of tissue matrix metalloproteinases **(MMPs), TNF -α, and IL-1β** in **both synovial tissue and gingival tissue**. ( **share common** dysfunction of fundamental inflammatory mechanisms)

*Biological base for linking aspects* → ***therapies that concordantly target the two diseases will be effective in the pathogenesis of both diseases***

***Dual Purpose Therapies Based on Biological Links***

1. ***Tetracyclines*** (and its analogues) ~ broad-spectrum antimicrobial agents for G (+) and G (-) bacteria. (1980s studies)
   - ***Tetracyclines*** **inhibited collagenase** (include **MMPs**). [Enhanced activity of MMP in synovial fluid and fibroblasts of patients with RA.] ***Tetracyclines*** **are useful for RA.** ***Minocycline*** for patients with RA → **significant reduction in disease activity**
   - Tissue destruction in periodontitis ~ partly due to **MMPs**. ***Tetracyclines*** and their analogues ~ useful in Tx. of patients with **rapidly progressive / refractory periodontitis** by suppressing the growth of putative microorganisms & destruction of collagen in gingival, PDL and alveolar bone through **inhibiting MMPs**
2. ***NSAIDs*** ~ **inhibition of cycloxygenase** ( for biosynthesis of prostaglandins)
   - Periodontally diseased tissues have higher prostaglandin levels ( esp. $E_2$ ) → bone resorption. ***NSAIDs*** ~ **preventing inflammation-induced bone loss**. Animal and human studies ~ NSAIDs show unequivocal therapeutic efficacy in **periodontitis**
   - Tx. of RA by NSAIDs → to **reduce pain and inflammation** by inhibiting ***neutrophils and TNF-α*** → contribute to the efficacy of Tx. for RA
3. ***Bisphosphonates*****:** Agents that affect **osteoclast** function
   - A class of drugs are incorporated into the bone and **incapacitate osteoclasts** → inhibiting lysosomal enzyme transport and secretion by osteoclasts. New-generation like ***zoledronic acid*** reduced development of new bony erosions in patients with **RA**
   - Bisphosphonate therapy ~ inhibit bone resorption and increase bone mass, → improves clinical outcome in patients with **periodontitis** → as adjunctive Tx

***Emerging Therapies***

**1.** ***Ornidazole*****:** A synthetic, nitroimidazole with potent **antiprotozoal and antibacterial** activity.
   - Good activity against most of periodontopathic bacteria → drug for Tx of **periodontitis**
   - The usefulness with **RA** → (mechanism not known) reduction in pain and overall reduction in disease activity

- ✓ Well tolerated at a dosage of 500-1000 mg/day with **adverse effects**, such as headache, dry mouth, and nausea

2. ***Chemically modified tetracyclines (CMTs)*:**
   - ◆ To eliminate the antimicrobial properties of tetracyclines
   - ◆ Inhibit synthesis of MMPs. Non antibiotic analogues of ***doxycyclin*** (CMT-3) and ***minocyclin*** (CMT-8) shown to be **potent inhibitors of osteoclastogenesis** in vitro
   - ◆ CMT-8 also shown to exert **anti-inflammatory** effects and modify cell viability by strong apoptosis
   - ✓ CMTs may **reduce tissue breakdown and bone resorption** in **RA and periodontitis**
3. ***Osteoprotegrin (OPG)*:**
   - ◆ OPG **inhibits RANKL* interaction with RANK**
   - ◆ **Interaction** between **RANKL and RANK** has an essential role in the activation of osteoclast and bone resorption
   - ◆ OPG expression is **deficient** in **synovial lining cells** on patients with **RA** and active synovitis and **GCF** in patients with **periodontitis**
   - ✓ OPG may have a therapeutic role in **RA and periodontitis**
4. ***Conjugated linoleic acid (CLA)*:**
   - ✓ Found as an important **inhibitor of osteoclastogenesis** by modulating **RANKL signaling pathway**
   - ✓ Shows **positively influence Ca & bone metabolism**

***Conclusion***

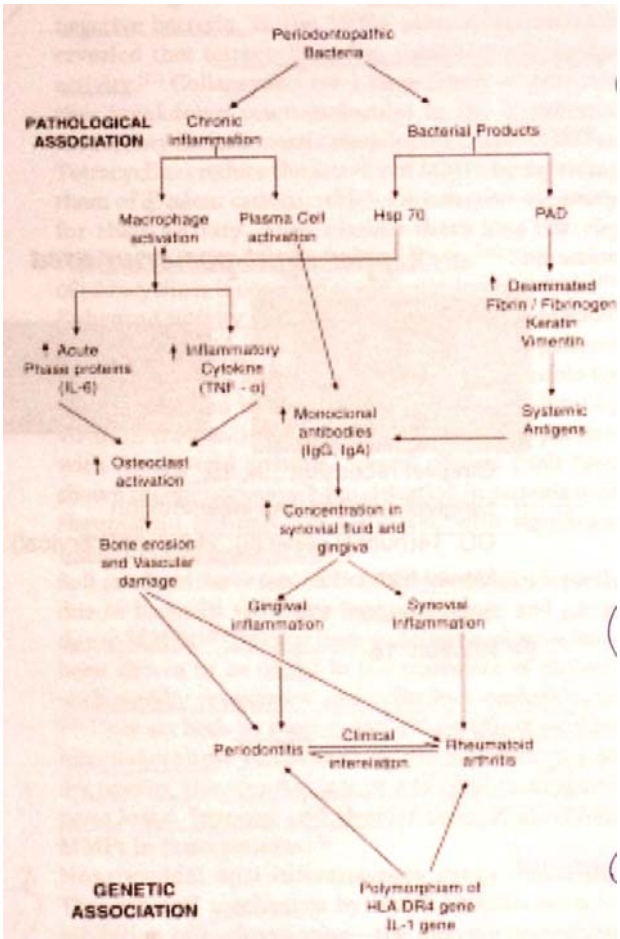
Increase in research evidence suggesting an **association between periodontitis and an increased risk of RA**. Probably the **inflammatory mediators** and **microbial products (endotoxins)** are the likely conduits. **Inhibition of common mediators and effector molecules** such as MMPs can **reduce** the severity of both diseases

Further methodologically rigorous observational studies and therapeutic trials in this area needed

**Table 1: A summary of the effects of drugs that target both rheumatoid arthritis and periodontitis**

| Drugs | Cells affected | Effect | Clinical effect |
|---|---|---|---|
| Tetracyclins | Oral microorganisms and macrophages, fibroblasts | ↓ endotoxins Inhibit lysosomal enzymes, MMPs | ↓ periodontal and joint tissue destruction |
| Bisphosphonates | Osteoclasts | Inhibit lysosomal enzymes | ↓ bone destruction in alveoli and joints |
| NSAIDs | Macrophages | Prostaglandins(PGE2) | ↓ alveolar bone destruction<br>Symptomatic relief in rheumatoid arthritis |
| CMTs | Macrophages, fibroblasts, endothelial cells | Inhibit lysosomal enzymes, MMPs, NO synthesis | ↓ periodontal and joint tissue destruction |
| Ornidazole | Oral microorganisms | - | ↓ periodontal destruction and<br>↓ disease activity in rheumatoid arthritis. |
| Osteoprotegrin | Osteoclasts | Inhibit RANK-RANKL interaction | ↓ bone destruction in alveoli and joints |
| CLA | Osteoclasts | Suppress RANKL signaling | Reduce bone resorption |

CMT - Chemically modified tetracyclins, CLA – Conjugated linoleic Acid, MMP - Matrix Metalloproteinase, NSAID - Non-steroidal anti-inflammatory drugs, NO - Nitric oxide, RANK - Receptor activation of nuclear factor kappa B, RANKL- Receptor activation of nuclear factor kappa B ligand




| 題號 | 題目 |
|---|---|
| 1 | **針對rheumatoid arthritis之治療選擇,下列何種爲非?**<br>(A) Erythomycine之給予<br>(B) Systemic corticosteroid之給予<br>(C) Nonsteroidal anti-inflammatory drugs (NSAIDs) 之給予<br>(D) Severely damaged joint replaced |
| **答案(A)** | 出處：Oral & Maxillary Pathology 2nd edition P.758 |
| **題號** | **題目** |
| **2** | **針對chronic periodontitis,可使用抗生素或藥物作為治療時之輔助,下列何者種藥物最少使用?** |
| | (A) Tetracycline<br>(B) Metronidazole<br>(C) Cepharosporine<br>(D) Nonsteroidal anti-inflammatory drugs (NSAIDs) |
| **答案(C)** | 出處：Oral & Maxillary Pathology 2nd edition P.154 |