Periodontitis, female pathophysiology and systemic diseases in women

Francesco Martelli¹, Piero Nobili², Federico Ronchi², Alberto Zanvit², Roberto Ferdeghini², Antonio Vimercati²

¹ IMI (International Microdentistry Institute), Florence, Italy
AIMOP (Italian Academy of Oral Medicine and Periodontology), Milan, Italy
² ISI - Italian Stomatological Institute, Department of Biological Dentistry, Milan, Italy

KEYWORDS  Periodontal medicine, Gender medicine, Female health.

ABSTRACT

Two concepts are gaining ground in the dental community: the association between periodontal infection and certain systemic diseases, in other words “periodontal medicine”, and the growing awareness and interest in gender differences on the pathophysiology of many diseases, that is “gender medicine”. The aim of this paper is to report the evidence from the literature of the association between periodontitis and certain specific or prevalent systemic diseases in women, in order to evaluate the possible mechanisms involved with the ultimate aim of improving the approach to female oral health. The literature analysed suggests an implication of periodontal disease in many systemic disorders specific to women or with a major impact on them, and reveals the importance of a joint effort by doctors and dentists towards better managing women’s health. In this regard, a gender-specific approach should be applied.

Introduction

Growing attention by the medical community to the potential impact of gender differences on the pathophysiology of many diseases has generated a new branch of medicine: “gender medicine”. Meanwhile, the association between periodontal infection and certain systemic diseases has been demonstrated, and the idea of “periodontal medicine” is gaining ground in the dental community. The aim of this paper is to merge these two new concepts, reporting the evidence from the literature of an association between periodontitis and certain specific or prevalent systemic diseases in women, and trying to evaluate the possible mechanisms involved in order to improve the approach to female health.

Periodontitis is the result of an inflammatory response by the host to a bacterial infection of periodontal tissues. Numerous species of pathogenic bacteria present in sub-gingival plaque can disrupt the normal homeostatic processes, attack the surfaces of the tooth, infiltrate periodontal tissues and organise themselves in the form of biofilm (1) (Fig. 1).

The host’s immune response, triggered by microorganisms and their metabolites, activates the synthesis and release of cytokines, inflammation mediators and metalloproteinases of the matrix, leading to the destruction of the tissues (2) (Fig. 2, 3).

The progression and severity of the disease depend on how much the aggressiveness of the sub-gingival biofilm is countered by the host’s immune response (3, 4), which is further modulated by the genetic and epigenetic context and also environmental factors such as gender, age, smoking and oral hygiene (5, 6) (Fig. 4). It is increasingly clear that, due to bacteraemia and the systemic release of endotoxins, the presence of pathogenic bacteria in periodontal lesions is also correlated to various systemic disorders, including cancer, diabetes mellitus, rheumatoid arthritis, cardiovascular disease, infertility and adverse birth outcomes (7).

From a recent study of nearly 3,000 patients, it appears that periodontitis affects women more than men at a ratio of 3:2 (8) and the literature supports the evidence that, in women, there is an association between periodontitis and puberty, menstruation, pregnancy, use of oral contraceptives and menopause (9-11). Fundamental aspects to consider for understanding the pathogenic mechanisms underlying this association are the periodical and age-related physiological changes in oestrogen and progesterone levels, the tissue distribution of the related receptors and the metabolism of the hormones. The cyclical
reduction in sex hormone levels, leading to increased vasodilation and capillary permeability, makes women transiently more susceptible to periodontitis, and increased levels of progesterone are associated with changes in the bacterial population, especially with an increase in Gram-negative anaerobic bacteria (12). Also oral contraceptives, which act by mimicking pregnancy although with individual variability, are associated with the same gingival disorders and the same generalised osteoporosis that characterise gestation (13, 14). The decrease in levels of progesterone and oestrogen circulating at menopause often cause oral problems, osteoporosis and recurrence of periodontal disease or its worsening if previously existing (15).

Apart from acting on specific target tissues, sex hormones also act on cells of the immune system, adipose, bone and nerve tissues, and gender differences in susceptibility to certain diseases are historically described in the literature (9, 16-18). In basic research and in developing new treatments, the biological differences between the sexes are often not considered and, since periodical age-related hormonal changes make women unstable models, the preference is to study diseases and drugs on males. This lack of interest in specifically female conditions, such as pregnancy and menopause, and the scarce presence of women in clinical trials, can lead to gender disparities in healthcare, and so the development of “gender medicine” is the opportunity to take account of the pathophysiological differences between men and women in modern biomedical research.

Figure 1 Comparison of microbiological analyses prior to periodontal treatment, two months afterwards and 1 year later.

Figure 2 The inflammatory process triggered by microorganisms in subgingival plaque in a situation of dysbiosis with prevalence of pathogenic bacteria.
Infertility and adverse childbirth outcomes

Infertility is a disorder that causes anxiety, depression and stress to many couples of reproductive age all over the world. While not putting life at risk, its negative influence on patients, families and societies makes it a serious problem that, in the West, affects one in six couples, with a 1.9% rate of primary infertility and 10.5% in secondary infertility (19). Infertility is also associated with a high risk of adverse outcomes of pregnancy, such as premature and underweight babies (20). Several risk factors have been identified: drinking alcohol, smoking, drug-taking, mother’s age (young or advanced), low socio-economic level, poor prenatal care, high blood pressure, diabetes, history of previous premature births, multiple pregnancies, infections and chronic inflammation (21). Nonetheless, in half of cases the cause remains unknown and a large number of epidemiological and clinical studies reliably report a possible association between infertility and periodontal problems (22-24), imputed both to the systemic dissemination of oral bacteria and to the high levels of pro-inflammatory cytokines released in circulation, both able to bring about the contraction of myocytes and premature birth.

Supporting the hypothesis that oral bacteria can reach and colonise the maternal-foetal unit and result in infertility and pregnancy problems, P. gingivalis, F. nucleatum and A. actinomycetemcomitans have been found in amniotic fluid or in samples of placenta of women who gave birth prematurely and suffered from periodontitis (23,24) (Fig. 5). Furthermore, metagenomic data confirm similarities between the placental and oral microbiome, and differences with the genitourinary or intestinal microbiome (25) (Fig. 6). Also inflammation mediators induced by periodontal pathogens, whether disseminated by oral lesions or produced by infected endometrial and placental tissues, can cause infertility and pregnancy problems (26).

Several studies suggest a correlation between periodontitis and bacterial vaginosis in women aged over 35 (27) and between periodontitis and endometriosis (28, 29), with a consequent greater risk of infertility in both cases. For endometriosis, a multifactor disease that affects 6-10% of women of reproductive age and which, like periodontitis, originates from an altered immune response and consequent chronic

Figure 3 Quantitative enzymatic analyses of matrix metalloproteinases-8 (MMP-8) before and after periodontal treatment
**Figure 5** Analysis of the vaginal microbiome (Vaginal Path Test, VPT)

**VAGINAL PATH TEST**

<table>
<thead>
<tr>
<th>Nome batterio</th>
<th>Conta batterica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus crispatus</td>
<td>$1.95 \times 10^4$</td>
</tr>
<tr>
<td>Lactobacillus gasseri</td>
<td>$1.12 \times 10^4$</td>
</tr>
<tr>
<td>Lactobacillus jensenii</td>
<td>$3.5 \times 10^3$</td>
</tr>
<tr>
<td>Lactobacillus iners</td>
<td>$1.26 \times 10^4$</td>
</tr>
<tr>
<td>Atoptobium vaginae</td>
<td>$9.5 \times 10^3$</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>$2.48 \times 10^3$</td>
</tr>
<tr>
<td>Megasphera 1</td>
<td>$8.12 \times 10^3$</td>
</tr>
<tr>
<td>Megasphera 2</td>
<td>$1.23 \times 10^4$</td>
</tr>
<tr>
<td>Mobiluncus mulleri</td>
<td>$7.32 \times 10^2$</td>
</tr>
<tr>
<td>Mobiluncus curtisi</td>
<td>$4.2 \times 10^2$</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>$1.14 \times 10^2$</td>
</tr>
<tr>
<td>Mycoplasma genitalium</td>
<td>$0 \times 10^6$</td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td>$4.44 \times 10^3$</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>$3.33 \times 10^4$</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>$3.3 \times 10^2$</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>$3.3 \times 10^2$</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>$3.4 \times 10^2$</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>$1.5 \times 10^2$</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>$4.45 \times 10^3$</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>$6.4 \times 10^2$</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>$7.78 \times 10^3$</td>
</tr>
</tbody>
</table>

Risultati ottenuti mediante tecnica PCR real-time.

**Ratio of saprophytes in the bacterial charge**

- Patogeni (60.5243%)
- Lactobacillus crispatus (16.4363%)
- Lactobacillus gasseri (9.469%)
- Lactobacillus jensenii (2.9501%)
- Lactobacillus iners (10.6204%)

**Commenti**

La paziente presenta...

Biomolecular Diagnostic - Via Nicola Porpora, 5 - 50144 Firenze P.IVA 05029870485
inflammation, a cause-effect relationship has been suggested whereby an altered inflammatory response to periodontal pathogenic bacteria could increase the susceptibility to endometriosis in women suffering from periodontitis (28, 2).

Osteoporosis

In the bone tissue, homeostasis is finely regulated by osteoclastic and osteoblastic activity. If the former becomes excessive, bone resorption exceeds its neoformation, with a consequent decrease in BMD (Bone Mineral Density), degeneration of bone microarchitecture and development of osteoporosis, clinically associated with increased bone fragility and susceptibility to fractures (30) (Fig. 7, 8). BMD is not particularly gender-specific until after the age of 50, when it typically becomes lower in females and the prevalence of osteoporosis and rate of fractures associated with it is twice as high as in males (31). Non-modifiable risk factors are being older, being female, the menopause and genetic makeup, while risk factors that can be modified are the reduction of levels of sex hormones, treatment with drugs, insufficient intake of calcium and vitamin D, a low body mass index, smoking, alcoholism and physical inactivity (32). Pro-inflammatory cytokines have been shown to regulate bone resorption, modulating osteoblast and osteoclast activity, and that oestrogen, by regulating important immunity mediators, has a fundamental role in both inflammation and homeostasis of the bone. In fact, the decrease in oestrogen levels is considered one of the main risk factors for osteoporosis in women (33). Vitamin D also plays an important role and its deficiency, or the presence of polymorphisms in the gene of its receptor, are considered risk factors for osteoporosis (34), immune system disorders, chronic inflammatory diseases and cancer (35).

Osteoporosis and periodontitis are both characterised by bone destruction and share several risk factors, such as advanced age, deficiencies in the sex hormone and vitamin D (or the presence of polymorphisms in the receptor) (36). The association between the two diseases has been studied for decades and much evidence is shown in the literature. For example, menopausal women with osteoporosis are more likely to develop periodontal disease and in more severe form (37) and BMD is an important indicator of this risk (38). In a large-scale population study, an
infertility and post-menopausal hormone replacement (43-45).

Like periodontitis, cardiovascular diseases have multifactor inflammatory characteristics, and some risk factors of the latter (smoking, obesity, type 1 diabetes) coexist in the former (46). In recent decades, many epidemiological studies have considered the existence of a possible relationship between the two diseases (47) and there is a considerable amount of data supporting a link between the prevalence of periodontitis and future cardiovascular problems (48). Recently, for example, a prospective study on a large group of peri-menopausal American women has shown a statistically significant association between prevalence and incidence of periodontal disease and increased risk of developing future cardiovascular diseases (49,50).

Since periodontitis implies infection and inflammation, whose role is also confirmed in cardiovascular diseases (51), among the possible mechanisms involved in this association there are the action of oral pathogens and the consequent inflammation induced by them (52,53). In particular, P. gingivalis is a risk factor for atherosclerosis (54), it can induce the formation of foam cells and platelet aggregation in vitro (55), and in mice it can accelerate the formation of atheromatous plaques following a systemic infection (56).

As cardiovascular disease is the main cause of mortality and morbidity in women, early diagnosis and effective treatment of periodontitis could increase survival and improve their quality of life.
Autoimmunity

This includes a range of systemic pathologies or specific organs that originate from the loss of natural immune tolerance towards self-antigens. The most frequent are Graves’ disease, rheumatoid arthritis, Hashimoto’s thyroiditis, inflammatory bowel disease, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus and Sjögren’s syndrome. Both types of response, cellular and humoral, can contribute to autoimmunity, and their interaction makes the situation more serious (57). Regarding susceptibility to autoimmune disease, several studies have confirmed the importance of the individual genetic structure, of environmental factors such as exposure to infectious agents, elements of diet, chemicals, toxins and stress (58), and the existence of a sexual dimorphism, varying in degree depending on the pathology (59). The last of these can be attributed to the greater female immunological reactivity, both humoral and cellular (60), but also to the action of oestrogens which activate the lymphocytes and the production of immunoglobulins (61), in addition to the X chromosome dosage, epigenetic factors, genomic imprinting and the contribution of microRNAs (62, 63).

Rheumatoid arthritis, the most common autoimmune pathology, is an inflammatory arthropathy that affects 1% of the population, with the highest rate among women. Both types of response, cellular and humoral, can contribute to autoimmunity, and their interaction makes the situation more serious (57). Regarding susceptibility to autoimmune disease, several studies have confirmed the importance of the individual genetic structure, of environmental factors such as exposure to infectious agents, elements of diet, chemicals, toxins and stress (58), and the existence of a sexual dimorphism, varying in degree depending on the pathology (59). The last of these can be attributed to the greater female immunological reactivity, both humoral and cellular (60), but also to the action of oestrogens which activate the lymphocytes and the production of immunoglobulins (61), in addition to the X chromosome dosage, epigenetic factors, genomic imprinting and the contribution of microRNAs (62, 63). Rheumatoid arthritis, the most common autoimmune pathology, is an inflammatory arthropathy that affects 1% of the population, with the highest rate among women.

### Table 1

<table>
<thead>
<tr>
<th>TESTS</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-nuclear antibodies (ANA) (n.v. 1:80)</td>
<td>1:1280</td>
<td>1:640</td>
</tr>
<tr>
<td>C3 (n.v. 0.80-1.52)</td>
<td>0.58 g/L</td>
<td>0.68 g/L</td>
</tr>
<tr>
<td>C4 (n.v. 0.80-1.52)</td>
<td>0.12 g/L</td>
<td>normal</td>
</tr>
<tr>
<td>IgG (n.v. 7.51 – 15.60)</td>
<td>17.00 g/L</td>
<td>normal</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>TESTS</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (n.v. &lt;35)</td>
<td>120 mm/h</td>
<td>108 mm/h</td>
</tr>
<tr>
<td>C-reactive protein (n.v. &lt;0.5)</td>
<td>1.09 mg/dL</td>
<td>normal</td>
</tr>
<tr>
<td>Ra-Test (n.v. &lt;30)</td>
<td>110 U/ml</td>
<td>70 U/ml</td>
</tr>
</tbody>
</table>

### Data

**REPORT (Result)**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient information</td>
<td>Patient information</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Ethnic group: Caucasian</td>
<td>Ethnic group: Caucasian</td>
</tr>
<tr>
<td>Weight: 73kg</td>
<td>Weight: 53 kg</td>
</tr>
<tr>
<td>Foot support: 1</td>
<td>Foot support: 2</td>
</tr>
<tr>
<td>Graph</td>
<td>Graph</td>
</tr>
<tr>
<td>age</td>
<td>age</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

**REPORT (Result)**

<table>
<thead>
<tr>
<th>Data scan: 6.12.2016</th>
<th>Data scan: 2016.09.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site: Right foot</td>
<td>Site: Right foot</td>
</tr>
<tr>
<td>BQI: 140.3</td>
<td>BQI: 50.7</td>
</tr>
<tr>
<td>T-score: 1.9</td>
<td>T-score: -2.9</td>
</tr>
<tr>
<td>T-ratio: 133.6%</td>
<td>T-ratio: 48.3%</td>
</tr>
<tr>
<td>Z-score: 1.6</td>
<td>Z-score: -3.3</td>
</tr>
<tr>
<td>Z-ratio: 125.3%</td>
<td>Z-ratio: 45.6%</td>
</tr>
<tr>
<td>SOS (m/s): 1559.8</td>
<td>SOS (m/s): 1481.5</td>
</tr>
<tr>
<td>BUA (dB/MHz): 151.7</td>
<td>BUA (dB/MHz): 70.8</td>
</tr>
</tbody>
</table>

**Table 1** Table showing how the inflammatory parameters of a young female patient affected by systemic lupus erythematosus (SLE) improve or even normalise after periodontal treatment

**Table 2** Table showing how the inflammatory parameters of a woman aged 45, affected by disabling rheumatoid arthritis, twenty years from the onset of the autoimmune disease, improved or even normalised after periodontal treatment.
Cancer

After cardiovascular disease, tumours are the main cause of female death, and epidemiological and socio-economic evidence reveals its heavy impact both individually and on the community. The most common cancers in women are breast, colon, endometrial, lung, cervix, skin and ovary cancer (81, 82). There are numerous data to back an association between chronic periodontitis and cancer (83, 84), particularly as regards oral-oesophageal, head and neck cancer, pancreatic, lung and breast cancer (85-88). In fact, fundamental to carcinogenesis is an inflammatory microenvironment and periodontitis is typically associated with infection, inflammation, bacteraemia and immune response (89).

Recently it has been shown that menopausal women with a history of periodontitis have a 14% higher risk of developing upper quadrant breast cancer compared to the rest of the population and even 36% higher if formerly smokers (87). Similarly, in another population of menopausal women, a history of periodontitis is associated with a 25% higher risk of developing lung cancer, especially for female former smokers (90) and a similar association is also demonstrated for head and neck cancer (91). In a large prospective study that recently took place, the association between periodontitis and mortality from oral-oesophageal and pancreatic cancer was investigated. Even after all the normalisations for the other risk factors, the IgG levels in serum against P. gingivalis correlated both with the severity of the periodontitis and with the risk of tumours of this type (86). Furthermore, the oral microbiome of patients with pancreatic cancer is different from that of the control subjects (92) and P. Gingivalis has been identified as a specific microbial marker of the risk of developing this type of cancer. These findings suggest the need to further characterise the pathogenic bacteria involved in cancer and show how oral hygiene and the dentist can play an important role in eliminating oral pathogens and thus prevent tumours.

Alzheimer’s Disease

Alzheimer’s disease is a progressive and fatal neurodegenerative disease and a serious geriatric problem worldwide. Clinical signs are cognitive impairment, behavioural changes and communication difficulties (71), while the biochemical signs are the extracellular formation of b-amyloid protein aggregates and intraneuronal neurofibrillary tangles, leading to progressive depressing of synaptic function through to neurodegeneration (72). The early onset form is considered a genetic disease, while the sporadic type is influenced by environmental factors such as age, diet, diabetes, hypertension and a history of head trauma (73, 74). It is also characterised by a strong gender imbalance (two out of three patients are women), partly attributed to longer female life expectancy but also to sex hormones and genetic factors (75).

Several studies have suggested, and sought to clarify, the enigmatic role of periodontal disease as a risk factor for Alzheimer’s disease and vice versa (76, 77). While it is true that people suffering from Alzheimer’s disease may, over time, become less able to take care of their oral hygiene, given the chronic inflammatory nature of both diseases, periodontitis could in turn contribute to the onset of low-grade systemic inflammation and bolster the neurodegenerative process of Alzheimer’s disease (78, 79). If a causal relationship between periodontitis and cognitive impairment were to be demonstrated, then effective periodontal treatment could be beneficial for Alzheimer patients. A study has already yielded promising results in this respect (80). Figure 8

Dual-energy X-ray absorptiometry (DXA) in a young woman with aggressive periodontitis and osteoporosis at the femoral neck.

Cancer

After cardiovascular disease, tumours are the main cause of female death, and epidemiological and socio-economic evidence reveals its heavy impact both individually and on the community. The most common cancers in women are breast, colon, endometrial, lung, cervix, skin and ovary cancer (81, 82). There are numerous data to back an association between chronic periodontitis and cancer (83, 84), particularly as regards oral-oesophageal, head and neck cancer, pancreatic, lung and breast cancer (85-88). In fact, fundamental to carcinogenesis is an inflammatory microenvironment and periodontitis is typically associated with infection, inflammation, bacteraemia and immune response (89).

Recently it has been shown that menopausal women with a history of periodontitis have a 14% higher risk of developing upper quadrant breast cancer compared to the rest of the population and even 36% higher if formerly smokers (87). Similarly, in another population of menopausal women, a history of periodontitis is associated with a 25% higher risk of developing lung cancer, especially for female former smokers (90) and a similar association is also demonstrated for head and neck cancer (91). In a large prospective study that recently took place, the association between periodontitis and mortality from oral-oesophageal and pancreatic cancer was investigated. Even after all the normalisations for the other risk factors, the IgG levels in serum against P. gingivalis correlated both with the severity of the periodontitis and with the risk of tumours of this type (86). Furthermore, the oral microbiome of patients with pancreatic cancer is different from that of the control subjects (92) and P. Gingivalis has been identified as a specific microbial marker of the risk of developing this type of cancer. These findings suggest the need to further characterise the pathogenic bacteria involved in cancer and show how oral hygiene and the dentist can play an important role in eliminating oral pathogens and thus prevent tumours.
Conclusions

Data in the literature suggest that oral pathogenic bacteria may promote the development of systemic diseases through two pathways: systemic dissemination from oral sites to distal tissues and the furthering of local inflammatory phenomena, and/or chronic systemic inflammation induced by bacteriaemia and inflammatory cytokines produced in periodontal lesions that have entered the circulation.

The direct involvement of oral pathogenic bacteria is documented as the prime mover in endothelial dysfunction (93), in the association between periodontitis and rheumatoid arthritis (94) and between periodontitis and Alzheimer’s disease (95). Furthermore, the presence of F. nucleatum and P. gingivalis bacteria is directly correlated to colorectal cancer (96) and to odontogenic and pancreatic tumours (86) respectively.

Systemic inflammation is implicated in endothelial dysfunction (97), in the cognitive impairment typical of Alzheimer’s disease (98) and in molecular mechanisms linked to the development and progression of cancer (99, 100).

Although further investigations aimed at clarifying the mechanisms underlying the association between periodontitis and systemic diseases are necessary and desirable, the hypothesis that periodontal disease is a significant risk factor for many of these disorders is evident (101). It is also increasingly urgent that a gender-specific approach be applied in considering epidemiology and disease progression. The literature analysed in this paper suggests an implication of periodontal disease in many systemic disorders specific to women or with a major impact on them, and reveals the importance of a joint effort by doctors and dentists towards better managing women’s health.

References

57. Mackay IR. Tolerance and autoimmunity. West J Med 2001;174:118-123.
Italian Journal of Dental Medicine vol. 3/1-2018