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Effects of gender on serum biomarkers of systemic inflammation coincident to experimentally-induced periapical lesions

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ARTICLE INFO

Article history:
Accepted 13 September 2010

Keywords:
Periapical lesion
Rat
Inflammation
Cytokine
Gender

ABSTRACT

Objective: The literature suggests that females have less adverse effects to infection than males, due to the protective effects of oestrogen. The purpose of our study is to compare the systemic effects of induced periapical lesions between groups of animals with various serum concentrations of oestrogen.

Methods: To induce periapical inflammation, two molar tooth pulps were exposed in ovariectomized (OVX) and normal female (F) and castrated (Cast-M) and normal male (M) Sprague–Dawley rats (Experimental group, E). Sham-operated control animals from each group were also studied (Control group, C). Twenty-eight days later, serum and maxillas were collected. Serum 17β-oestradiol, testosterone, MMP-9, IL-18, IL-6, TNF-α, and IL-1β concentrations were measured by ELISA. Maxillas were cleaned of residual tissue and digital radiographs were made to verify the presence of periapical lesions. Data were compared by factorial ANOVA, post hoc Tukey, and Pearson correlation tests. Groups were considered to be significantly different when $p < 0.05$.

Results: The serum concentration of IL-18, TNF-α, IL-1-β, IL-6 and MMP-9 was greatest in OVX-E animals, compared to all other groups ($p < 0.001$). F-E rats had significantly higher serum concentrations of these cytokines, compared to F-C. The fold difference in serum concentration of the biomarkers (between E and C groups) was significantly greater in females than males, even though males had higher baseline concentrations of all these biomarkers.

Conclusion: When females are oestrogen-deficient, their systemic response to periapical lesions is significantly greater than males, suggesting that oestrogen is essential in protecting females from the effects of this type of inflammation.

1. Introduction

During the past decade, there have been numerous research studies promoting a re-evaluation of the relationship between the oral and the systemic health of an individual. There is substantial information suggesting that inflammatory diseases release proinflammatory molecules into the systemic circulation, increasing the inflammatory burden within the body and producing a "hyperinflammatory" state.[1] In addition, the interaction between individual inflammatory diseases permits any of them to affect the incidence and severity of the others.[2] A "syndemic" approach to treatment of disease

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doi:10.1016/j.archoralbio.2010.09.008

is required when two or more linked health problems act synergistically to contribute to the burden of disease to an individual.[3] This approach is valid when the diseases have inflammatory characteristics and may be applicable to dental patients with other inflammatory-based diseases, such as atherosclerosis, rheumatoid arthritis, and diabetes mellitus. Opportunities for therapeutic intervention, by disrupting the links between inflammatory diseases are often required for a successful treatment outcome. Thus, it is important to identify the systemic effects of oral inflammation, including periodontitis and periapical inflammation.

The progression of pulpal inflammation to the tooth apex leads to periapical lesion formation with adjacent alveolar bone resorption.[4] These lesions induce both innate and adaptive immune responses by the host.[4] The predominant cell types within periapical lesions are neutrophils,[5,6] macrophages,[7,8] T- and B-lymphocytes,[9,10] mast cells, osteoclasts, osteoblasts, and fibroblasts.[11–14] These cells express a large number of proinflammatory cytokines, including interleukin (IL)-6,[15–18] IL-4,[17,19] IL-1-β,[7,15,16,20–24] IL-1-α,[21,23–27] tumour necrosis factor (TNF)-α,[16,18,21,24,25,28–30] and lymphotoxin-α.[17] These cytokines are likely released into the systemic circulation, since animal models indicate that proinflammatory cytokine concentrations are higher within the serum of animals with periapical lesions.[31]

The concentrations of proinflammatory cytokines are also elevated within both serum and gingival tissues of persons with periodontal inflammation[32] and may contribute to a systemic hyperinflammatory state, which is a risk factor for several types of systemic diseases.[33–35] There are reports of gender differences in the aetiology of periodontal disease, tooth loss, and atherosclerosis, with males having more evidence of periodontal infections and atherosclerosis.[36–38] Data from our previous study indicated that experimental periodontitis in female rats resulted in both higher serum concentrations of C-reactive protein (CRP), IL-6 and TNF-α than within serum from male rats with a similar inflammation.[39] Since gender effects in the systemic response to periodontal disease have been identified, it seems reasonable to expect gender-specific effects in the systemic response to periapical inflammation.

There is evidence for gender differences in the severity of several types of systemic inflammation. Females are known to develop higher antibody responses to various antigens following immunization[40] and sex hormones are reported to regulate T-cell immune function.[41,42] These hormones are able to modulate the activation of macrophages and their production of proinflammatory cytokines,[43–45] which modulate the inflammatory response.[46–49] Females have a 30% lower innate immune response[50] and female animals are more likely to develop a cell-mediated response (rather than a humoral response) after exposure to an infectious agent, compared to males.[51] In general, females produce a more vigorous cell-mediated response to antigens than males, whereas males produce a more intense cell-mediated response to a microbial stimulus.[50]

The role of oestrogens in the modulation of severe inflammation has been reported in vitro[52] and in several clinical studies of trauma and sepsis.[47–49,53] Oestrogen has been reported to have beneficial effects on the severity of systemic inflammation in different trauma models,[47–49,53] including sepsis. There is evidence that these protective effects of oestrogen may be due to its effect on the synthesis and release of plasma proinflammatory cytokines.[47,48,54] In studies that report a gender-based difference in trauma[55,56] and sepsis[57,58] outcomes, there seems to be a survival advantage for premenopausal women, compared to men or post-menopausal women, suggesting a protective role for oestrogen in the pathogenesis of severe inflammation. Animal studies of trauma and sepsis indicate that lower oestrogen levels and/or higher testosterone levels lead to an impaired immune response,[43,47,59–64] which involves the alteration of cell-mediated immunity and cytokine expression.[65]

Recent experimental studies of the gender-specific response to inflammation have utilized a sterile endotoxin challenge. One human study reports that women have a greater increase in serum levels of CRP, TNF-α, and IL-1-β and no differences in IL-6 and IL-10 than men following this type of challenge.[66] Another study, using the identical methodology, reports no differences in serum concentrations of TNF-α, IL-1-β, IL-6 and IL-10 between males and females following a challenge by sterile endotoxins.[67] Similar studies in animals report that females have lower serum levels of these proinflammatory cytokines than males following endotoxin challenge.[50,68,69]

There is recent evidence suggesting a different pattern of association between inflammatory cytokines and matrix metalloproteinases (MMPs) in males and females.[70] In that study, serum concentrations of IL-6 were positively correlated with MMP-9 in males following a myocardial infarction (MI), but not in females following MI. In these females, serum concentrations of IL-6 and IL-18 were positively correlated with MMP-3, but not MMP-9.[70] IL-18 has been associated with the pathogenesis of several diseases, including atherosclerosis.[71] MMP-9 is a critical mediator for tissue remodelling during pathological processes.[72] IL-18 has been reported to initiate the release of MMP-9 by peripheral blood mononuclear cells, which is dependent on the presence of TNF-α.[73] Thus, it is probable that these cytokines and MMP-9 are functionally linked during the pathogenesis of inflammatory diseases, including MI.

There is little information concerning gender differences in the systemic response to periapical lesions. Recently, a study of human patients indicated that previous endodontic therapy was a risk factor for cardiovascular disease.[74] Thus, it seems worthwhile to further investigate the systemic effects of periapical lesions. Since there are gender differences in association between serum concentrations of proinflammatory cytokines and MMPs, it is possible that the presence of periapical lesions could be a risk factor for MI if these lesions produced alterations in the association between proinflammatory cytokines and MMP within serum. Thus, it seemed worthwhile to study the possibility for a gender specific relationship between serum concentrations of TNF-α, IL-1-β, IL-6, IL-18, and MMP-9 in a rodent model to determine whether the presence of oestrogens could alter these relationships. Such information could provide significant new information concerning the potential for periapical infections to be a risk factor to the systemic health of both females and males.