Effect of Oral Infections on Systemic Health

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Immunological mechanisms are known to affect the oral cavity with characteristic pathologic alterations. Infections in general have been suggested to trigger autoimmune diseases such as rheumatic diseases and diabetes and their oral microorganisms such as P. gingivalis may play a role. In The Stockholm Study, the prevalence of autoimmune diseases was investigated and 50 such patients were detected in the database.

Keywords: oral infection ; systemic health

1. Effect of Periodontitis, Inflammatory Markers and Cardiovascular Diseases

Atherosclerosis is the pathology behind life threatening cardiovascular disease outcomes such as heart infarction and stroke. In the Stockholm Study project, an emphasis was placed on these important diseases prevalent in populations. First, a sample of 82 patients with periodontitis and 31 without periodontal disease were examined for oral health parameters, atherosclerosis and its risk factors. Carotid artery ultrasonography was performed where the common carotid artery intima-media thickness (IMT) and lumen diameter were measured, and the intima-media area (cIMA) calculated. The relationship between IMT and cIMA as dependent variables and periodontal disease, age, gender, body mass index, heredity for atherosclerosis, diabetes, hypertension, plasma cholesterol, smoking and education as independent variables, was analyzed using a multiple logistic regression model [1]. The result showed that the mean values of IMT and cIMA were significantly higher in patients with periodontal disease than in those without ($p < 0.001$ in both variables). The regression analysis identified periodontitis as a principal independent predictor of common carotid artery cIMA (OR 5.20; $p < 0.05$) and IMT (OR 4.64; $p < 0.05$). It could thus be concluded that periodontal disease is associated with the development of early atherosclerotic carotid artery lesions [1]. The patients with periodontitis also had significantly higher total cholesterol ($p < 0.01$), low-density lipoprotein cholesterol ($p < 0.05$), and triglycerides ($p < 0.01$) than those without periodontitis. As discussed in more detail below, specific periodontal microorganisms seemed to induce a host response, reflected in increased concentrations of matrix metalloproteinase-8 and -9 (MMP-8 and MMP-9) in gingival pockets as well as in plasma, possibly triggering their up-regulation in blood [2]. These inflammatory markers indicate collagen degradation in tissue level [3] and have been used in studies investigating the associations between periodontitis and systemic health in general [4]. However, when discussing the role of MMPs in general regarding connection with periodontitis, gender differences and smoking habits also need to be taken into account. Virtanen et al. [5] showed in the Stockholm Study material that MMP-13 may have gender implications in periodontitis.

The reason why infections such as oral infections associate with cardiovascular diseases are thought to be the subsequent chronic and often subclinical inflammation that, in turn, triggers pathogenic alterations in the intima of blood vessels leading to lipid and mineral accumulation and then to atheroma formation. C-reactive protein (CRP) is a known serum marker of inflammation, and it has been shown to be associated with atherosclerosis [6]. In the Stockholm Study, however, in the patients examined with carotid artery ultrasonography, this association could not be found. The cIMA and IMT did link to periodontitis as said above, but neither of these variables showed association with CRP values [7][8]. However, as stated above, other elevated inflammatory markers were nevertheless found in the patients with atherosclerosis and periodontitis. Periodontitis was found to predict increased MMP-9 and tissue inhibitor of matrix metalloproteinases (TIMP-1) and their ratio MMP-9/TIMP-1. These values were indeed significantly higher in plasma from subjects with periodontal disease and atherosclerosis when compared with healthy subjects (OR 2.58, 5.53 and 3.41, respectively). Classical atherosclerosis risk factors, such as increased total cholesterol, age, and sex (female), were significant predictors in the model discussed here [9].

Correspondingly, other inflammatory markers such as leukotriene B_4 and cysteinyl-leukotrienes were detected in gingival crevicular fluid (GCF) from subjects with a high dental plaque index (PLI > 0.3), supporting an increased leukotriene formation in periodontitis [10]. Patients with atherosclerotic plaques had significantly elevated concentrations of cysteinyl-

leukotrienes in their GCF when compared with those without visible dental plaque. Thus, the results suggest that increased leukotriene formation may also represent a possible link between periodontitis and atherosclerosis and might be used as risk factor marker for the diseases [10][11].

2. Role of Oral Microorganisms and Poor Oral Health

Obviously, oral microorganisms detected in patients with periodontitis have been of interest in studies regarding the link between oral infections and cardiovascular diseases [12]. In The Stockholm Study, the Söder group has investigated the prevalence of certain periodontal microorganisms in this perspective. GCF samples have been taken to analyze the bacteria Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Tannerella forsythia and Treponema denticola. The prevalence of these bacteria was then statistically analyzed with respect to a number of oral health variables, atherosclerotic risk factors, results from serum analyses, and findings at the carotid ultrasonic examination. The results showed significant differences in the detection of *P. gingivalis* ($p < 0.001$), *P. intermedia* ($p < 0.01$), P. nigrescens ($p < 0.001$) and *T. forsythia* ($p < 0.001$), but also in the levels of MMP-8 and MMP-9 in GCF between patients with and without periodontitis. *T. forsythia* (OR 10.1; $p < 0.001$) and age (OR 5.54; $p < 0.01$) appeared to be the main independent predictors for high MMP-8 in GCF [2].

Earlier analyses of the Stockholm Study cohort showed that poor oral health parameters were associated with premature death of the subjects. Young individuals with periodontitis and missing molars seemed to be at increased risk for premature death by life-threatening diseases, such as neoplasms and diseases of the circulatory and digestive systems [13]. Missing molars indicate earlier dental infections because they are seldom extracted unless there is dental pathology involved.

In addition to gingivitis, derived periodontal disease also apical periodontitis links to cardiovascular diseases. In The Stockholm Study, regression analyses controlled for age, gender, income, smoking and periodontitis, showed apical periodontitis to associate with cardiovascular disease with OR 3.83 (CI 1.18–12.40; $p < 0.05$). These results were from a subsample of 120 patients in that had been radiographically examined for dental pathologies [14].

3. Oral Infections and Cancer

The history of the role of infections in the etiology of malignancies goes back to the year 1911 when American pathologist Peyton Rous detected a virus that caused sarcoma in chicken. This was then verified to be true as late as 1975, even though Rous had received a Nobel Prize for his detection already in 1966. In 1980s, German researcher Harald zur Hausen found out that certain human papilloma viruses can cause cervical cancer. He received the Nobel Prize for these studies in 2008. Further in the 1980s, when Helicobacter pylori was detected by Australian Nobel laureates Barry Marshall and Robin Warren, who received their Prize in 2005, the door was open to investigate the role of also bacterial infections in carcinogenesis [15]. This introduction shows how significant the role of infections is in carcinogenesis, or in malignant transformation in general and that the landmark studies in the area have all been recognized by the Nobel committee.

The Söder group became interested in investigating the role of oral infections in cancer. This development was natural, taking into account the high prevalence of dental infections in populations and the fact that cancer is the second most important cause of death after cardiovascular diseases. Infection-driven inflammations have been estimated to be involved in the pathogenesis of approximately 15–20% of human malignancies [16]. Hence, inflammation caused by infections might be one of the most important preventable causes of cancer and thus controlling the role of oral microbiota is emphasized in this regard [17].

The Stockholm Study provided excellent data for analyzing the associations between poor oral health and malignancies. First, data on breast cancer were published and the results showed that the incidence of breast cancer was 1.75% in subjects who had periodontal disease and/or any missing molars, and 0 in subjects who had periodontal disease but had no missing molars. Of the subjects with periodontal disease and any missing molar in the mandible 5.5% had breast cancer in comparison to 0.5% of the subjects who had periodontal disease but no missing molars (OR 2.36 CI 1.07–5.21; $p < 0.02$) [18] .

When studying the incidence of cancer during the long observation time in the database, it appeared that of the 1390 subjects who underwent clinical oral examination in 1985, cancer had been registered in 71 patients by year 2009. In this material, similarly to the previous study, missing molars associated with cancer with OR 2.62 (CI 1.18–5.78). For comparison, the OR for age was 1.91 (CI 1.06–3.43), respectively [19].

Finally, closer to the etiological agents earlier discussed, a study was created with the hypothesis that certain periodontal microorganisms associate with malignancies. A sample of 99 clinically examined patients of The Stockholm Study cohort was used to investigate the associations between harboring periodontal microorganisms *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia* and *T. denticola*. Here, gingival inflammation emerged statistically as the strongest sign of inflammation (Eigen value 4.11 and Explained Variance 68.44%) in the 2008–2016 Swedish National Cancer Register used. Of the bacteria analyzed, *A. actinomycetemcomitans* showed strong association with malignancy in 32 out of the 99 patients while *P. gingivalis* and *P. intermedia* were more prevalent among patients without malignancy. In principal component analyses, *A. actinomycetemcomitans* was in the strongest component while the second strongest component consisted of a combination of *T. forsythia* and *T. denticola*, respectively [20]. Thus, certain periodontal pathogens indeed seemed to associate with malignancy, but no causality can be drawn from this kind of small-scale investigation.

Taken together, cancer data from The Stockholm Study indicate that oral infections may indeed have a role in carcinogenesis. The putative pathogenic mechanisms that explain the associations detected are similar to those with cardiovascular diseases. Namely, the common nominator is the chronic and often subclinical inflammation caused by oral microorganisms, leading to systemic consequences. Malignant transformation in the cellular level is then one of them [21].

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