**SIALOMETRIC AND SIALOCHEMICAL ANALYSIS IN RHEUMATOID ARTHRITIS PATIENT: A CASE REPORT**

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**ABSTRACT**

Rheumatoid arthritis is a chronic progressive autoimmune disease causing inflammation of the joints and resulting in painful deformity and immobility. Apart from the systemic manifestations there is a profound effect of rheumatoid arthritis on exocrine salivary gland function causing a detrimental effect on the oral health status. Assessing the salivary gland function may be beneficial in understanding the oral health status of the patient in such conditions. This case report is about a 21 year old female patient with a history of rheumatoid arthritis who presented with severely mutilated oral condition. Sialometric and sialochemical analysis were carried out which demonstrated significantly altered salivary gland function. The treatment plan was to augment the salivary function using artificial salivary substitutes and then carrying out the restorative and prosthetic rehabilitation. This article aims to validate the importance of sialometric and sialochemical analysis in treating the underlying etiologic factor prior to any dental procedure, thus providing a definitive and comprehensive management of oral health conditions.

**KEY WORDS:** Oral health, rheumatoid arthritis, sialometry, sialochemistry, salivary gland function.
INTRODUCTION
Rheumatoid arthritis is considered as a chronic inflammatory multisystem autoimmune disease with a spectrum of clinical severity ranging from mild arthritis to crippling joint disorder with internal organ involvement which is associated with considerable morbidity and mortality and may present with extra-articular manifestations including involvement of exocrine lacrimal and salivary glands. Women are about three times more likely to be affected than men and the usual age of onset is between 25 and 50 years. According to the Centre for Disease control, in India more than 20% of total population is suffering from rheumatoid arthritis. Medical complications that may arise due to rheumatoid arthritis and its treatment may affect the oral health status of the patient.

There is a relatively large amount of evidence that the salivary glands are profoundly affected in rheumatoid arthritis. Sullivan et al. has reported from their studies that 58% of rheumatoid arthritis patients had reduced salivary secretion. Morphological studies revealed that the minor salivary glands of rheumatoid arthritis patients were highly infiltrated with lymphocytes and the alterations also included fibrosis, acinar atrophy and lymphoplasma cell sialadenitis. Zhang et al. from their studies demonstrated the presence of anti-salivary duct antibodies in the serum of rheumatoid arthritis patients. Rheumatoid arthritis patient usually manifest a condition called ‘xerostomia’; whereby there is reduced production and secretion of saliva by salivary glands. This altered function of salivary gland has a detrimental effect on the overall oral health status of the patient.

Saliva is also emerging as a diagnostic fluid. Saliva as a diagnostic specimen can give not only the same information as serum testing, but also additional or new information that cannot be obtained from serum. Saliva is a readily available specimen, which can be collected by noninvasive procedures and contains many hormones, drugs and antibodies of interest in screening and diagnosis. This article discusses the importance of salivary function and its compositional analysis in rheumatoid arthritis patient.

PATHOPHYSIOLOGY
The cause of rheumatoid arthritis is unknown, although its etiology appears to be multifactorial as depicted in Fig.1.
Rheumatoid arthritis is believed to be a T-lymphocyte mediated disease in which a sudden influx of T-cells into the affected joint is followed by an increased number of macrophages and fibroblasts, drawn by the release of cytokines, particularly IL-1 and TNF-α. This cytokines release and subsequent migration of cells is thought to be responsible for the chronic inflammation and characteristic destructive changes seen in rheumatoid joints. Synovial joints are composed of articular cartilage, synovial fluid and a synovial membrane. The synovial membrane is the area of the joint infiltrated by the T-cells in a rheumatoid arthritis and is the site of subsequent immune response as shown in fig.2.
The hypertrophied inflamed synovial tissue that covers and extends into the cartilaginous part of the joint with finger like processes is known as *pannus*. Cytokines increase the permeability of blood vessel walls, facilitating the migration of white blood cells into joint spaces that then becomes the site of inflammation. Cytokine release also leads to the proliferation of fibroblasts, synovial cells, increased prostaglandin and matrix degrading protease activity and ultimately the resorption of adjacent bone. IL-1, a cytokine secreted primarily by macrophages, is one of the key mediators of local inflammation, tissue damage, immunologic reactions and bone resorption.[12] TNF-α, another key cytokine that often acts synergistically with IL-1, also promotes the cartilage and bone resorption that leads to pathological joint alterations in rheumatoid arthritis.[13]

Hence, the pathogenesis of rheumatoid arthritis is characterized by prolonged, chronic inflammation of the synovial membrane accompanied by morphological alterations and the recruitment of mononuclear and polymorphonuclear cells into the synovial fluid.[14] However, in recent years it has become clear that, besides the immunological reaction, there is another biological process, based on the injurious activity of free radicals, playing a major role in the pathogenesis.[13,15] The reduction of molecular oxygen to water is accompanied by a large free energy release that can give rise to *Free Radicals* (FR) and/or * Reactive Oxygen Species* (ROS). The most important FR in biological systems are radical derivatives of oxygen. ROS include not only oxygen free radicals but also non-radical oxygen derivatives involved in oxygen radical production. The reactivity and associated toxicity of these may be major contributors to the pathogenesis of several chronic degenerative diseases including rheumatoid arthritis.[13]

**CLINICAL CHARACTERISTICS**

The classic characteristics of this disease are bilateral and symmetric chronic inflammation of the synovium especially affecting small joints of the upper and lower extremities, often leading to the deterioration and eventual destruction of articular cartilage and juxta-articular bone, as well as inflammatory process surrounding tendons, resulting in deformities of the affected joints, a condition known as *synovitis*.[16] Patients with rheumatoid arthritis may also experience systemic manifestations such as fatigue, loss of appetite, weakness and musculoskeletal pain. There is an increased risk of premature mortality due to infections, haematopoietic malignancies, cardiovascular diseases, renal diseases and complications from treatment.[17]
There are extra-articular manifestations as well, including rheumatoid nodules, rheumatoid vasculitis, interstitial lung disease, pericardial disease, episcleritis and scleritis, Felty’s syndrome and Sjogren’s syndrome. Felty’s syndrome is characterized by chronic rheumatoid arthritis, splenomegaly, neutropenia, anemia and thrombocytopenia. Sjogren’s syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia, dry eyes and joint pain. When observed in association with rheumatoid arthritis, it is known as secondary Sjogren’s syndrome. [18]

**ORAL MANIFESTATIONS**

Most patients with rheumatoid arthritis will exhibit some temperomandibular joint involvement during the course of the disease. Involvement of the TMJ results from granulomatous involvement of the articular surface of the synovial membrane, which leads to destruction of the underlying bone. Severe arthritic deterioration of the TMJ may be accompanied by trismus and a high incidence of upper airway obstruction. [19] Patients with longstanding active rheumatoid arthritis may have an increased incidence of periodontal disease, including loss of alveolar bone and teeth. The risk of developing reduced salivary flow increase with the severity of the disease. This xerostomia leads to multiple problems, including difficulty in swallowing food, difficulty in speaking, oral soreness and burning sensation, intolerance to spicy foods, problems in wearing denture, oral candidiasis and increase in caries. Caries in these patients may progress despite excellent home care, use of fluoride and avoidance of cariogenic food. Unexplained dental caries, especially in root and incisal sites, may be the first apparent clinical sign. [20] Cross-sectional studies by R.R Welbury et al. showed significantly increased levels of poor oral hygiene and dental decay in patients with rheumatoid arthritis. [21]

In addition, drugs used for the treatment of rheumatoid arthritis can affect the oral health of the patient. Long-term use of methotrexate and other antirheumatic agents such as gold, D-pencillamine and NSAIDs can cause stomatitis. Cyclosporine may cause gingival overgrowth. [22]

**SALIVA: THE MIRROR OF BODY’S HEALTH**

Saliva serves as a mirror of the body’s health, as it contains proteins, hormones, antibodies and other molecules that are frequently measured in standard blood tests to monitor health and disease. The multifarious components within saliva not only protect the integrity of the oral tissues, but also provide clues to local and systemic diseases and conditions. These
components known as “salivary biomarkers” are being explored as a means of monitoring general health and in the early diagnosis of disease.\[23\] In spite of the relatively large amount of accumulated evidence that the salivary glands are profoundly affected in rheumatoid arthritis, very little has been discussed in the literature about salivary function and compositional analysis. This constitutes a major omission, as such an analysis may contribute in three ways. First, it is well established that, to a large extent, saliva composition represents plasma composition. Such an analysis is easy, non-invasive, cheap and patient-friendly. Secondly, salivary antioxidants play an important physiological role in the oral protective system and may also be important in the gastrointestinal tract after the saliva has been swallowed. Accordingly, if an altered salivary antioxidant profile in rheumatoid arthritis patients accompanies reduction in saliva output there may be further injurious effects. Thirdly, the destructive effect on the salivary glands demonstrated in rheumatoid arthritis patients may be rendered by a free radicals-related process, and thus such an analysis may contribute to the better understanding of the mechanism.\[1\]

CASE REPORT

A 21 year old female patient with a history of rheumatoid arthritis presented with pain in the upper back tooth region since 6 months. On intraoral examination there was deep dentinal caries involving pulp in relation to 17,26,38,36; root stumps in relation to 14,15 and missing 16,37 (Fig.3). There was difficulty in mouth opening (< 30mm). OPG showed bony erosions in relation to mandibular condyles. Patient also reported that although regular home care oral
hygiene practice was followed there was unexplained dental caries with rapid progression. So we decided to analyse the salivary function of the patient (Fig.4).

**Salivary flow rate:** The patient is seated with head slightly down and stimulated saliva was collected in a graduated saliva collection tube for a period of 5 minutes. The salivary flow rate of the patient was found to be 3.5 ml for 5 minutes.

**Salivary hydration time:** lower lip of the patient is everted and is gently blot with a small piece of gauze. Timing the production of droplets of saliva gives an assessment of the hydration time. The hydration time of the patient was 65 seconds.

**Salivary viscosity:** The saliva of the patient was found to be frothy and bubbly suggestive of increased salivary viscosity.

**Salivary pH:** a drop of saliva sample is placed over a pH test strip for 10 seconds, and the colour change is compared with the text chart. The salivary pH of the patient was found to be moderately acidic.

![Salivary Function Tests](image)

**Fig.4: Salivary Function Tests**

**Sialochemistry:** The sialochemical analysis included salivary peroxidase activity, total antioxidant status and uric acid concentration. Automatic analyser unit was used for sialochemical analysis(Fig.5). The salivary peroxidase activity of the patient, normalized to
volume was $840 + 108$ U/ $100\mu l$. The total antioxidant status of the patient was found to be $2.15 + 0.26$ mM /l. The uric acid concentration of the patient was $4.10 + 0.52$ mg/dl.

The results of the salivary function test showed there was an alteration in the salivary gland function of the patient. So, the treatment plan formulated was to perform initial oral prophylaxis to clean the oral cavity, then manage hyposalivation and further restorative and prosthetic rehabilitation. The patient was prescribed artificial salivary stimulants and was instructed to keep her mouth moist always by frequent sipping of water. During the next appointment after a week, the patient was thoroughly examined and revealed an overall improvement in oral hygiene. Further dental procedures such as root canal treatment, restorations and prosthetic rehabilitation were performed in subsequent appointments as shown in Fig.6 and Fig.7.
DISCUSSION

The salivary flow rate of the patient was 3.5 ml for 5 minutes however the normal rate is 5 ml for 5 minutes according to Parvinen et al. The normal hydration time is between 30-60 seconds according to Heintz et al. but, the patient’s hydration time was 65 seconds. Also the patient had viscous and acidic saliva suggesting that there was a significant reduction in salivary gland function. This results points that salivary glands are major target organs of rheumatoid arthritis. The demonstration of rheumatoid arthritis induced alterations in the salivary antioxidant system is novel and its related clinical significance seems to be of paramount importance.

The total salivary antioxidants levels, peroxidase activity and uric acid concentrations increased in the patient. This overall increase in salivary antioxidants may result from the general increase in plasma antioxidants, as demonstrated by Nagler et al.\textsuperscript{1} However, it may also reflect a similar specific response of the salivary glands, i.e. up-regulation of the production of specific salivary antioxidants. It seems that both mechanisms act in concert in pathogenesis of rheumatoid arthritis, in the light of the fact that peroxidase, the most important salivary antioxidant enzyme, is known to be produced specifically in the parotid gland while uric acid, the most important salivary antioxidant molecule, is plasma-borne.\textsuperscript{12}

The fact that the increase in peroxidase was much higher than the increase in uric acid may suggest that the active role played by the salivary glands themselves in fighting oxidative stress-related pathology in the oral cavity of the rheumatoid arthritis patients is of major importance.\textsuperscript{24} However, another explanation for the difference in the levels of increased salivary uric acid vs peroxidase may be based on the specific injurious effect of rheumatoid arthritis on the salivary glands.\textsuperscript{14} Moore et al. found that the uric acid concentration was
profoundly increased only in the severely affected rheumatoid arthritis patients and not in the mildly affected rheumatoid arthritis subgroup. This result may have a very interesting mechanistic significance, as it may be that the pathway of uric acid transduction from the plasma via the parotid parenchymal cells is less sensitive to the injury inflicted by rheumatoid arthritis, while the acinar cellular machinery responsible for producing and secreting peroxidase is more vulnerable.\[^{25}\]

These findings may be of paramount importance in the light of the presumably major importance of the salivary antioxidant capacity in fighting various pathologies in the oral cavity.\[^{10}\] These results suggest that rheumatoid arthritis patients in whom there is both a severe reduction in the salivary flow rate in general and in the total amount of salivary antioxidants secreted into the oral cavity in particular are significantly less well protected. Poor oral health status has a detrimental effect because untreated dental disease and poor gingival health may combine to produce an oral infection which will be a significant risk factor for systemic infection, especially when the patient is immunosuppressed through the use of corticosteroids and disease modifying anti-rheumatic drugs.\[^{21}\]

**CONCLUSION**

From a clinical standpoint, it seems reasonable to conclude that severely affected rheumatoid arthritis patients should be treated both with antioxidants and with saliva substituents and that extra care should be given to the oral cavity. The profound effects of rheumatoid arthritis on salivary gland flow rates and other parameters may also be of great importance in the general diagnosis and evaluation of the disease. Salivary parameters such as salivary flow rate, salivary viscosity, salivary pH and salivary buffering capacity are lower in subjects with high dental caries. Hence, it is recommended that salivary testing be a part of routine diagnosis when treating patients with high dental caries risk.

**REFERENCES**


