

## Clinical Study

# Tumor Necrosis Factor-Alpha in Periapical Tissue Exudates of Teeth with Apical Periodontitis

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Received 20 September 2007; Accepted 4 December 2007

**Aim.** The aim of this study was to determine tumor necrosis factor-alpha (TNF- $\alpha$ ) levels in periapical exudates and to evaluate their relationship with radiological findings. **Methodology.** Periapical exudates were collected from root canals of 60 single-rooted teeth using absorbent paper points. TNF- $\alpha$  levels were determined by enzyme-linked immunosorbent assays. The samples were divided into three groups according to the periapical radiolucent areas. **Results.** Nonparametric Kruskal-Wallis test revealed significant differences between TNF- $\alpha$  concentrations in control group (40,  $57 \pm 28$ , 15 pg/mL) and group with larger radiolucent areas (2365,  $79 \pm 582$ , 95 pg/mL), as well as between control and canals with small radiolucent areas (507,  $66 \pm 278$ , 97) ( $P < .05$ ). **Conclusions.** The levels of TNF- $\alpha$  increase significantly in teeth with periapical pathosis, from smaller to bigger lesions. This research and its results have shown that objective analysis of the TNF- $\alpha$  levels enables establishment of a relationship between different concentrations of TNF- $\alpha$  and different radiological changes.

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## 1. INTRODUCTION

Periapical pathoses of pulpal origin develop in response to microbial irritants in the root canal systems. Bacterial cell wall components react with monocytes, macrophages, other cells of the immune system, as well as with fibroblasts, leading to the production of proinflammatory cytokines, such as IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-8 [1].

Persistent injuries to the dental pulp usually cause irreversible pulpitis and pulpal necrosis. Irritants may be mechanical or chemical, but are most often bacterial. The interaction between these irritants and host defensive cells results in release of numerous mediators that, through the root canal system, are capable of initiating immunologic reactions in periapical tissues resulting in the formation of inflammatory periapical lesions. These reactions include immune response mediated by cells, through the actions of T lymphocytes and cytokines, and humoral immune response mediated by antibodies, activated by B-lymphocyte products [2].

TNF- $\alpha$  is a monocyte-derived protein that has a wide range of proinflammatory and immunomodulatory effects on a number of different cell populations. TNF- $\alpha$  is a cytokine which stimulates bone resorption, prostaglandin synthesis, and protease production by many cell types, including

fibroblasts and osteoblasts. Overproduction or inappropriate expression of TNF- $\alpha$  can lead to a variety of pathological conditions [3]. The local production of PGE<sub>2</sub>, IL1- $\beta$ , and TNF- $\alpha$  has been demonstrated in periapical lesions [4, 5].

TNF- $\alpha$  is a cytokine initially identified as a causative of hemorrhagic necrosis in certain tumors and was later shown to be the same molecule as cachectin, a serum product earlier known as a mediator of wasting in chronic disease. In addition to its diverse bioactivities, TNF- $\alpha$  is the only molecule other than IL-1 that is presently known to have osteoclast-activating function. Although extensive research has been performed in the area of periapical inflammatory mediators, only few studies focused on the role and levels of TNF- $\alpha$  in periapical exudate [6, 7]. The aim of this study was to determine the levels of TNF- $\alpha$  in periapical exudates and to evaluate possible relationships between this cytokine and radiological findings in the involved teeth.

## 2. MATERIALS AND METHODS

The investigation was carried out on 60 subjects of different age and sex. Subjects were divided into three groups according to the radiological findings. Diagnoses were established

according to the clinical and radiological findings. All patients in the certain period were included. The patients with noncontributory medical histories and diagnosed with apical periodontitis were selected for the study as follows.

- (i) Group 1 consisted of 20 subjects whose single-rooted teeth had the diagnosis of chronic apical periodontitis, with dull or absent pain, and size of the lesion <1 cm.
- (ii) Group 2 consisted of 20 subjects whose single-rooted teeth were diagnosed with chronic apical periodontitis, with dull or absent pain, but with the lesion size of >1 cm.
- (iii) Group 3 was control and comprised of 20 subjects whose investigated single-rooted teeth showed symptoms of acute periapical condition accompanied by excruciating pain, necrotic pulp, and radiological thickening of the apical periodontal ligament.

Primary access to the pulp chamber was gained using slow-speed round dental burs, with placement of rubber dam isolation. After determination of the working length, the necrotic pulp was removed and the root canal was enlarged to ISO size 40. The root canal was dried with sterilized paper points. A sterile paper point was inserted into the root canal up to the instrumentation length and held in place for 1 minute to absorb the exudate for the sample [6, 7]. Paper points were immersed into sterile Ependorf vials containing phosphate buffered saline (PBS) and stored at  $-70^{\circ}\text{C}$  until further analysis [8, 9]. The volume of the fluid was calculated from a standard curve and expressed as  $\mu\text{L}$ . Size of the radiolucent area was determined by two independent examiners at the time exudate samples were collected. Periapical lesions were classified as small, when the longer diameter was shorter than 1 cm, while the remaining lesions were classified as large. In the control group, the radiological thickening of the periodontal ligament was present.

Determination of the  $\text{TNF-}\alpha$  levels in supernatant of periapical exudate is based on utilization of monoclonal antibodies specific for  $\text{TNF-}\alpha$  which bind competitively to  $\text{TNF-}\alpha$ . Investigation is based on “sandwich” enzyme immunoassay (EIA).

All subjects were informed of the aims and procedures of research. Within the research, they are guaranteed in respect of their basic ethical and bioethical principles: personal integrity (independence, righteousness, well-being, and safety) as regulated by Nürnberg codex and the most recent version of Helsinki declaration. Only those subjects who gave a written permission in the form of informed consent were included.

### 3. RESULTS

The present study demonstrated the presence of  $\text{TNF-}\alpha$  in all periapical exudate samples. Differences in concentrations of  $\text{TNF-}\alpha$  between control group ( $40, 57 \pm 28, 15 \text{ pg/mL}$ ), the group with large radiolucent areas ( $2365, 79 \pm 582, 95 \text{ pg/mL}$ ), as well as between control and the canals associated with small radiolucent areas ( $507, 66 \pm 278, 97$ ) were statistically significant ( $P < .05$ ). There was also statistically significant difference between the samples with large radiolu-

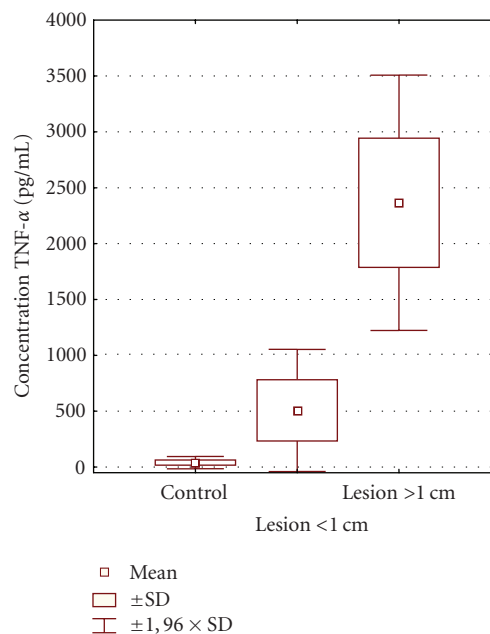


FIGURE 1: Levels of cytokine  $\text{TNF-}\alpha$  in three groups of investigated subjects.

cent areas and small radiolucent areas. EIA data for  $\text{TNF-}\alpha$  were categorized according to radiological diagnosis, using the nonparametric Kruskal-Wallis test (see Figure 1).

### 4. DISCUSSION

Soluble mediators produced and secreted by various inflammatory, immunologically-active, and structural cells, commonly referred to as cytokines, play the leading role in pathogenesis of infectious disease, acting side-by-side with other inflammatory mediators: kinines, vasoactive amines, components of the complement system, and metabolites of arachidonic acid [10].

Secretion of the cytokines is initiated with the purpose of activating immunological response to irritants and increasing local concentrations of inflammatory cells in order to prevent further colonization of bacteria within the tissues. Enhanced reaction of the host to various antigens results in bone resorption and formation of granulomatous tissue, which are the typical features of periapical lesion [10].

In this investigation, levels of the proinflammatory cytokine  $\text{TNF-}\alpha$  in periapical exudate were analyzed due to its leading role in pathogenesis of periapical lesions. Exudates were collected from the root canals using noninvasive methods. These exudates present the inflammatory exudate from the periapical tissues and theoretically contain locally produced and secreted factors [11]. They resulted from the inflammatory response and contain host mediators related in response to the infection [6]. Highest concentrations of  $\text{TNF-}\alpha$  were detected in periapical lesions with large radiolucent areas, while these levels were significantly lower in the periapical lesions with smaller radiolucent areas. In the control group diagnosed as acute periodontitis, which differs in

clinical symptoms from the other two experimental groups, and is characterized by radioloical changes consistent with periodontal ligament thickening, the levels of the investigated cytokine demonstrated the lowest levels. These results show different values from the results obtained by Ataoglu et al. [6]; however, these authors compared the levels of two kinds of cytokines: IL-1 $\beta$  and TNF- $\alpha$ . In the work of Ataoglu et al. [6], IL-1 $\beta$  was detected in all samples of periapical exudates and its levels were significantly higher than TNF- $\alpha$  levels; however, the authors focused their attention only on the TNF- $\alpha$  levels in periapical exudates demonstrated in all tissue specimens with significant differences regarding certain experimental groups. A study by Kjeldsen et al. [12] using ELISA technique also showed significantly higher concentrations of TNF- $\alpha$  in crevicular fluid in patients with chronic adult periodontitis. It is likely that chronic periodontal infection may evoke an immune response that may result in the production of slightly higher levels of TNF- $\alpha$ .

It was proved that TNF- $\alpha$  leads to bone resorption through osteoclast activation and stimulation of the secretion of proteolytic enzymes, plasminogen activator (PA), and matrix metalloproteinases (MMP), which are in charge of destroying extracellular matrix of the bone tissue [13].

The work by Artese et al. [14] showed that there is a small fraction of TNF- $\alpha$ -positive cells within the granuloma with a macrophage-like morphology. Ultrastructural analyses showed that there are some macrophages which have adjusted the extracellular secretion; therefore, these macrophages might be the main source of cytokines in the tissue.

Wang et al. [15] showed that both TNF- $\alpha$  and IL-1 are secreted in the infected rat pulps and periapical lesions. The cells appeared as soon as 2 days following the pulp chamber opening and their numbers increased steadily until the day 30. These findings demonstrate the presence of IL-1 $\alpha$ - and TNF- $\alpha$ -secreting cells in the pulp and periapical tissues immediately following the pulp exposure, which supports the assumption that the abovementioned cytokines play a role in pathogenesis of pulp and periapical pathoses.

In the analysis of TNF- $\alpha$  levels in healthy, symptomatic, and asymptomatic human pulps [16], TNF- $\alpha$  was detected in all vital pulp tissues. The highest concentrations of TNF- $\alpha$ , with regard to clinical classification, were found in symptomatic reversible pulpitis, and the difference was statistically significant in comparison with irreversible asymptomatic pulpitis and healthy pulp. The highest concentrations of TNF- $\alpha$ , with regard to histological classification, were found in histologically confirmed moderate inflammation, followed by severe inflammation, mild inflammation, and finally healthy pulp.

## 5. CONCLUSION

Conclusion can be drawn that cytokine TNF- $\alpha$  could be an objective marker in radiologically confirmed periapical lesions. Presence of TNF- $\alpha$  in this investigation was proved in all clinical samples. The lowest levels were demonstrated in control group, which was characterized by radiological thickening of the periodontal ligament, while somewhat greater

concentrations were found in teeth with periapical radiolucencies of <1 cm diameter; finally, the greatest concentrations were measured in teeth with radiolucent lesions >1 cm, which confirms the relationship between TNF- $\alpha$  and the emergence and development of periapical lesions. Objective analysis of TNF- $\alpha$  levels enables establishment of a relationship between different concentrations of this cytokine and different radiological changes.

## ACKNOWLEDGMENT

This research was supported by a grant from the Ministry of Science and Technology (no.062-0650444-0442 and no.065-0650444-0418), Republic of Croatia.

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## Special Issue on The Changing Concepts of Vesicoureteral Reflux in Children

### Call for Papers

Vesicoureteral reflux (VUR) is considered an enigma of pediatric urology practice, where the management of this salient disease evolved from surgical intervention to observation. Bladder physiology and dysfunction has become the culprit behind VUR, making the diagnosis of primary reflux a historical diagnosis. However, recently the introduction of Deflux and other injectable materials revolutionized the management of VUR in pediatric population. Subsequently, from the moment a child is diagnosed with reflux, pediatric urologists are faced with challenging questions both by parents and peers:

- Do antibiotics have a role in management of VUR?
- If the management of reflux is conservative, do we really need to have this pathology diagnosed? and which radiological modality is better?
- What are the current surgical modalities to treat reflux in 2008?
- What if reflux is not treated, does it cause higher risk of infections in girls at puberty?
- What can the literature tell us? More specifically, do we have enough objective data in the literature on the research and outcome of VUR that will help pediatric urologists make a decision?

Voiding cystourethrogram is recognized as a disturbingly invasive test in pediatrics and sedation, for this test is becoming a routine for children undergoing this test in some centers.

This special issue on the changing concepts of vesicoureteral reflux in children will be focused on addressing most of these questions in an attempt to provide a state-of-the-art foundation for decision making when a urologist is faced with a child who harbors VUR.

The ideal list of topics to be covered is as follows:

- Bladder dynamics, voiding dysfunction and reflux
- Endoscopic treatment: technique
- Intravesical ureteral reimplantation: surgical technique

- Extravesical ureteral reimplantation: surgical technique
- Antibiotics and vesicoureteral reflux
- Diagnostic approach to reflux in 2007
- Outcome of surgical versus medical management of VUR
- Update on reflux nephropathy and ESRD 2nd to VUR
- Relation between Deflux volume and reflux resolution
- Reflux treatment evolution
- Design of study
- VCUG and radiation
- Sedation and VCUG
- Reflux and puberty
- VUR management: state of the art or state of confusion

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## Special Issue on Comprehensive Management of Upper Tract Urothelial Carcinoma

### Call for Papers

Urothelial carcinoma of the upper urinary tract is relatively uncommon, representing only 5% of all urothelial cancers. The 5-year cancer-specific survival for upper tract urothelial carcinoma in the United States is roughly 75% with grade and stage serving as the most powerful predictors of survival. Nephroureterectomy with excision of the ipsilateral ureteral orifice and bladder cuff en bloc remains the gold standard treatment for upper tract urothelial carcinoma, but endoscopic and laparoscopic approaches, are rapidly evolving as standards of care depending on grade and stage of disease. Several controversies remain in management of upper tract urothelial carcinoma including patient selection for endoscopic versus laparoscopic approaches, management strategies of the distal ureter, the role of lymphadenectomy in upper tract urothelial carcinoma, and the value of chemotherapy in upper tract disease.

Aims of this special edition will be to critically review and evaluate controversies in management of upper tract urothelial cancer including: endoscopic management of upper tract urothelial carcinoma, laparoscopic nephroureterectomy and management of the distal ureter, the role of lymphadenectomy in management of upper tract urothelial cancer, and the emerging role of chemotherapy in upper tract disease.

- Endoscopic management of upper tract urothelial carcinoma
- Laparoscopic nephroureterectomy and management of the distal ureter
- Role of lymphadenectomy in management of upper tract urothelial cancer
- Role of chemotherapy in management of upper tract urothelial carcinoma

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## Special Issue on Climate Change and Infectious Disease

### Call for Papers

Virtually every atmospheric scientist agrees that climate change—most of it anthropogenic—is occurring rapidly. This includes, but is not limited to, global warming. Other variables include changes in rainfall, weather-related natural hazards, and humidity. The Intergovernmental Panel on Climate Change (IPCC) issued a major report earlier this year establishing, without a doubt, that global warming is occurring, and that it is due to human activities.

Beginning about two decades ago, scientists began studying (and speculating) how global warming might affect the distribution of infectious disease, with almost total emphasis on vector-borne diseases. Much of the speculation was based upon the prediction that if mean temperatures increase over time with greater distance from the equator, there would be a northward and southward movement of vectors, and therefore the prevalence of vector-borne diseases would increase in temperate zones. The reality has been more elusive, and predictive epidemiology has not yet allowed us to come to conclusive predictions that have been tested concerning the relationship between climate change and infectious disease. The impact of climate change on infectious disease is not limited to vector-borne disease, or to infections directly impacting human health. Climate change may affect patterns of disease among plants and animals, impacting the human food supply, or indirectly affecting human disease patterns as the host range for disease reservoirs change.

In this special issue, *Interdisciplinary Perspectives on Infectious Diseases* is soliciting cross-cutting, interdisciplinary articles that take new and broad perspectives ranging from what we might learn from previous climate changes on disease spread to integrating evolutionary and ecologic theory with epidemiologic evidence in order to identify key areas for study in order to predict the impact of ongoing climate change on the spread of infectious diseases. We especially encourage papers addressing broad questions like the following. How do the dynamics of the drivers of climate change affect downstream patterns of disease in human, other animals, and plants? Is climate change an evolutionary pressure for pathogens? Can climate change and infectious disease be integrated in a systems framework? What are the relationships

between climate change at the macro level and microbes at the micro level?

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## Special Issue on Postradical Prostatectomy Rehabilitation Therapy

### Call for Papers

The use of oral type-V phosphodiesterase inhibitors has been increasingly common over the last several years for the purposes of penile rehabilitation. This edition will provide a current assessment of the evidence supporting this practice. The concerns regarding the true benefit of penile rehabilitation will also be examined.

Topics of interest include, but are not limited to:

- Basic science evidence for the benefits of penile rehabilitation therapy
- Overview of penile rehabilitation therapy
- An appraisal of the peer-reviewed clinical literature on penile rehabilitation therapy
- Experience with penile rehabilitation therapy after robot-assisted laparoscopic prostatectomy

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## Special Issue on Management of Small Renal Masses

### Call for Papers

This special issue aims at summarizing distinct aspects of the management of small renal masses nowadays, focusing on its epidemiology, pathological aspects, prognosis, and mostly the different treatment strategies.

During the last two decades, we all have observed an astonishing increase in the detection of small renal masses, which, generally speaking, we assume to be under 4 cm although there is not a clear cut-off for the definition of a small renal mass. The increase in longevity and medical attention demanded by the population and mainly due to the popularization of sonography among different colleagues, even as a first visitation test in many offices, are some of the classical reasons to justify this phenomenon, but maybe not the unique ones.

All these have led the evolution from radical to partial nephrectomy as the gold standard technique for the treatment of these masses, based on the high percentage of benign masses within this cohort and also the same oncological data when renal cell carcinoma is reported among both techniques.

Then laparoscopy came into scene and partial nephrectomy was finally adopted as a difficult technique but with improved quality of life issues compared to open partial nephrectomy and with the same oncological outcome. While we were attending the slow generalization of this approach, or maybe due to its intrinsic difficulty, we are now receiving many other minimally invasive techniques trying to compete with the previous surgical procedures, namely, radiofrequency, cryoablation, HIFU, and so forth. But, is it necessary to treat all these masses? It is clear that approximately 25% of these masses are not malignant, and there is growing evidence that not all these masses will kill our patients.

This special issue will be focused on the characterization of the present small renal masses and the different management possibilities. We invite authors to present personal experiences, reviews, and opinions around the issue.

The list of topics to be covered is as follows:

- Epidemiology of renal masses
- Incidental diagnosis and clinical symptoms: prognosis aspects

- Histological characterization of small renal masses
- Necropsy studies: incidence of silent renal masses
- Concept of renal adenoma: useful or old term
- Radiology of small renal masses
- Familial syndromes coupling with small renal masses
- Genetic counselling in renal masses
- Potential role of percutaneous biopsy in small renal masses
- Size as a prognostic factor in renal masses
- Multifocality and renal masses
- Watchful waiting in front of a small renal mass
- Importance and limits of ischemia in renal partial surgery: experimental and clinical research
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- Cryoablation
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- HIFU

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## Special Issue on The Human Microbiome and Infectious Diseases: Beyond Koch

### Call for Papers

A century after Robert Koch linked individual cultured microbes to specific diseases (Koch's postulates), it is increasingly apparent that the complex community of microorganisms associated with the human body (the "microbiome") plays a key role in health and disease. The National Institute of Health (NIH) recently announced the Human Microbiome Project and among its goals is to understand the relationship between host-associated microbial communities and disease. Many physicians and researchers, however, have only passing familiarity with the concepts involved in the study and therapeutic manipulation of complex microbial communities. The aims of this special issue are (1) to familiarize the readers with the concepts and methods for the study of complex microbial communities, (2) to demonstrate how changes in the indigenous microbial community can play a role in diseases such as antibiotic-associated diarrhea, bacterial vaginosis, and cystic fibrosis, and (3) to review how probiotics may hold promise for the therapeutic manipulation of the indigenous microbiota. Review articles and original research papers are being sought for this special issue.

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