Keywords:
chronic periodontitis, pulp injury, endo-periodontal lesions, cone-beam computed tomography, electroodontodiagnostics, cytokines, alexidine, ultrasonic irrigation, bioceramic sealer.

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Received:15-06-2026
Revised: 20-07-2026
Accepted:27-07-2026
Doi:10.1922/ejprd.v34i7s.1638

European Journal of Prosthodontics and Restorative Dentistry (2026) 34(7s), 448–458

# Improving the Effectiveness of Treatment of Dental Pulp Injuries in Patients with Chronic Periodontitis: Clinical, Radiological, and Immunological Evaluation

**Abstract**
Chronic periodontitis is a major cause of tooth loss in the world. Combined lesions of the periodontium and dental pulp are often closely related, and often occur without any symptoms and signs, resulting in delay in diagnosis and irreversible tissue loss. To establish an algorithm for diagnosis and an optimized therapeutic regimen for dental pulp injuries in chronic periodontitis patients to enhance the treatment results. A clinical study with 154 patients (35–40 years) with chronic periodontitis and secondary pulp involvement was undertaken. The PMA index, PI index and CPITN index were used to evaluate periodontal status. Cone-Beam Computed Tomography (CBCT) was used for bone destruction evaluation and for pulpal pathways evaluation, while electro-odonto diagnostics (EOD) was used for evaluating vitality. Levels of IL-, IL-, TNF- and IL-10 were measured by ELISA to arrive at an IL-1β/IL-10cytokine balance index in gingival crevicular fluid (GCF). Patients were treated with optimized treatment consisting of standard periodontal therapy, passive ultrasonic activation (PUA) of alexidine irrigation with 0.1% and calcium-silicate bioceramic obturation, and followed up for 12 months. Deep periodontal pockets, furcation involvement, large amounts of alveolar bone loss and reduced electrical excitability were good predictors of retrograde pulpal disease. A cytokine balance index >6.0 was a reliable biological index for irreversible pulpitis. The optimized protocol was highly effective in controlling local inflammation, improving periodontal parameters and with clinical success of 92.1%. Combining 3D imaging, functional EOD and analysis of cytokines by GCF allows for early precise diagnosis of retrograde pulp injuries. The use of PUA-energized alexidine along with bioceramic sealers, increases the efficacy of disinfection of the root canals and helps in the regeneration of tissues, thus preserving the tooth for a long time.

**Introduction**

Chronic periodontitis is one of the most common inflammatory diseases of the oral cavity affecting more than 1.1 billion people worldwide and is considered the sixth most prevalent disease worldwide according to the World Health Organization. The epidemiological situation is very heavy in the Republic of Uzbekistan, reaching 85–92% in adults. This public health issue is compounded by a well-known tendency toward "rejuvenation," which refers to the fact that the older age groups are not only the earliest age group affected by this pathology, but they are the ones to be most severely affected because they are the most productive age group(Lin et al., 2020). The disease manifests itself by the gradual deterioration of the structures that hold the teeth. These structures consist of the gingiva, the periodontal ligament, and the alveolar bone. This chronic inflammatory state may lead to a reduction of the masticatory function and also to a constant inflammatory workload in the body, so that, early and extensive therapeutic treatments are clinically necessary(Zuza et al., 2012).

Combined endo-periodontal lesion (EPL) is a very complicated clinical case, because of the close anatomic and functional relationship between the periodontium and dental pulp. Lateral canals, accessory canals, dentinal tubules and apical foramina provide a complex bidirectional highway for the transport of pathogens, metabolic toxins and pro-inflammatory cytokines. Therefore, an estimated 70–80% of clinical cases that have severe periodontal destruction will result in an accompanying retrograde pulp infection. Traditional chairside diagnostics are only approximately as sensitive as they can be, only detecting retrograde pulp injury in about 1/3 of patients with the disease(Alfahadi et al., 2022). The time lag between the diagnosis and intervention invariably contributes to the deterioration of the tissue, failure in treatment, and unnecessary tooth loss. Most routine vitality tests, including thermal stimulation and simple vertical percussion, are often inconclusive or false positive in these mixed lesions because there may be some viable tissue in the neurovascular bundle even though there is localized necrosis at a higher stage.

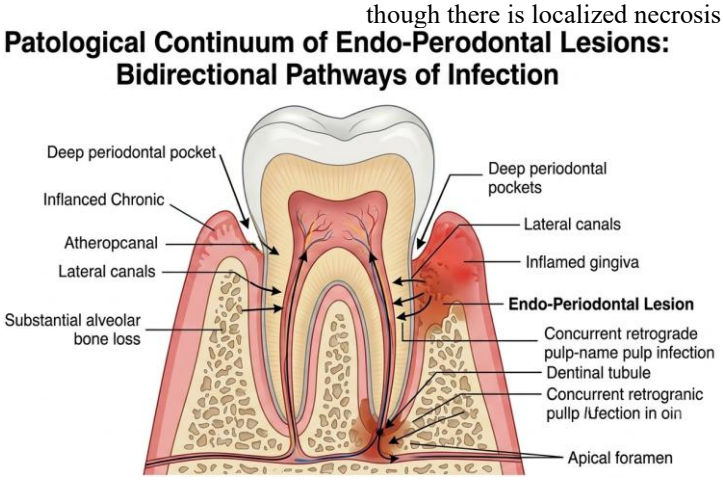


**Figure 1: Conceptualizing the Problem—The Endo-Periodontal Lesion (EPL)**

This cross-section illustration with annotations provides the initial problem you will discuss in your Introduction. It outlines an EPL by visualizing the intricate anatomical routes through which the microorganisms can reach the pulp cavity from severe chronic periodontitis and lead to retrograde pulp infection including lateral canals, accessory canals, dentinal tubules and the apical foramen. It visually identifies the two-way street that is not recognized by conventional diagnostics(Rathod et al., 2014).

In order to address this clinical need, this study was registered under code B2024.1. PhD /Tib4314, Samarkand State Medical University—aims to study the increase of the accuracy of diagnosis and effectiveness of dental pulp injuries treatment in simultaneous cases of chronic periodontitis. The general aim of this research is to develop a highly objective (3D Cone-Beam Computed Tomography (CBCT), Electroodontodiagnostics (EOD) and local immunochemical profiling of gingival crevicular fluid (GCF) in the early diagnosis of the disease, and to design and test an optimized biomaterial-based therapeutic protocol(Nakashima et al., 2017).

The ratio of pro-inflammatory cytokines to anti-inflammatory mediators in the GCF can be used as an immune biomarker for local changes to determine a precise Cytokine Balance Index that can be used to mathematically assess whether pulpal inflammation has reached a point of irreversibility. The dissertation concludes that the immunochemical tipping point for clinical decision-making on active endodontic treatment before acute endodontic pain and/or macro-destruction is 6.0 ratio of IL-1β/IL-10. Conventional irrigation regimes are often unsuccessful because traditional irrigants such as sodium hypochlorite are not able to reach the deep microscopic channels, complex furcations and lateral channels that are characteristic of periodontally compromised teeth(Morad et al., 2013).

To address this, the new protocol combines passive ultrasonic activation (PUA) and a highly effective bisbiguanide antimicrobial agent, 0.1% alexidine, for deep, deep-tissue root canal disinfection(El Ashiry et al., 2018). It is then followed by stable filling with bioactive calcium-silicate bioceramic sealers. The properties of these bioceramics are such that calcium hydroxide is released when being set, which is chemically interactive with the local tissues and promotes periapical and periodontal restitution, cementogenesis and osteogenesis,

thus allowing rapid restitution of the normal environment. Long-term follow-up up to 12 months has shown that this combination approach significantly decreases pro-inflammatory cytokines in the GCF by 5-fold, promotes complete bone regeneration in complex root furcation defects in 92.1% of the cases and provides a significant economic benefit per patient due to reduced clinical revision rates of approximately 400,000 – 600,000 UZS.

## 2. Literature Review

The functional relationship between periodontal tissues and pulpal tissues is a complex physiologic continuum, which has been widely studied during the last decades. The early work of Simring and Goldberg first described the clinical concept of endo-periodontal lesions (EPL), which noted the presence of distinct communication pathways through which pathological processes can easily spread between these two distinct environments(Alongi et al., 2010). Histological studies thereafter showed that microorganisms, bacterial endotoxins, and host-derived inflammatory mediators can easily spread from the lateral canals, accessory canals, and open dentinal tubules to produce retrograde pulpal inflammation and necrosis as a result of severe periodontal disease. This close association has been further validated by modern molecular studies, high throughput genetic sequencing and microbial cloning, with a striking similarity and structural overlap between the complex polymicrobial anaerobic communities found within deep periodontal pockets and those found to be isolated from simultaneously infected, necrotic root canals. This two-way road can lead to endodontic contamination, as once periodontal disease reaches an advanced stage, it can spread to the endodontic system as a main source of contamination resulting in a total-organ disease(Tomasello et al., 2017).

### Diagnostic Frameworks and 3D Imaging Advancements

The international consensus reports of the past few years have repeatedly highlighted the complexity of the diagnosis that is associated with the management of combined endo-periodontal lesions. While 3-D Cone-Beam Computed Tomography (CBCT) has been a great contribution to the spatial visualization of subtle anatomical features, including the exact pattern of alveolar bone loss, root canal morphology, and the degree of degradation of the cortical plate, these Figures are not enough to make objective decisions regarding the actual vitality of the pulp. This diagnostic challenge occurs because conventional vitality tests (e.g. basic vertical percussion or thermal stimulation) often give false, positive vitality readings when the pulpal necrosis is partial, chronic or retrograde in a multirooted tooth. For instance, a single root canal can have partial conduction of neurovascular tissue, in the adjacent furcation and complementary roots, whereas there is complete liquefaction of tissue, thus providing a contradiction in the diagnosis to the clinician.

### Cytokine Networks and Immunochemical Profiling

Locally, immune mediators and cytokines are involved in both the progression and amplification of periodontal or pulpal inflammation, in a central and orchestrating manner. A high level of pro-inflammatory cytokines such as interleukin-1 beta (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-), have been directly linked to active osteoclastic differentiation, degradation of the extracellular matrix, and subsequent progressive alveolar bone destruction. In contrast, interleukin -10 (IL-10) is a key anti-inflammatory mediator which targets to inhibit the destructive immune cascade, suppress the activation of macrophages and promote tissue resolution(Makeeva et al., 2020). Due to the dual role these cytokines play, measurement of the local cytokine profile in the gingival crevicular fluid (GCF) offers valuable information of high sensitivity to the real-time disease activity(Nakashima & Iohara, 2014). This structural relationship can be mathematically expressed as Cytokine Balance Index (IL-1β/IL-10) which provides a quantifiable and objective prognosis. This provides a biochemical index (such as an index value greater than 6.0) that provides an accurate indication of whether the pulpitis is reversible or irreversible and eliminates guess work during the diagnostic process.

### Bioactive Bioceramics and Advanced Irrigation Modalities

Conventional chemical irrigation regimes are limited by their ability to structure these intricately connected tissue spaces, which must be overcome with advanced therapeutic strategies in order to overcome the historical challenges of disinfecting in these areas. Typically, periodontal teeth that are compromised have microscopic lateral pathways, furcations at the apex, and produce plaque, and conventional irrigation (using only sodium hypochlorite or chlorhexidine) does not debride or penetrate these areas. To overcome this, combination of passive ultrasonic activation (PUA) with a very effective antimicrobial agent like 0.1% alexidine solution has proved to be more effective in completely dissolving necrotic debris and eliminating resistant submucosal biofilms. After the deep chemo-mechanical disinfection, bioactive calcium-silicate materials are essential tools in the science of modern regenerative endodontics. These bioceramic sealers generate calcium hydroxide during hydration and setting process, which directly reacts with the periapical and periodontal fluids with a very good biocompatibility, hydrophilicity and chemical stability(Pirani & Camilleri, 2023). Their exclusive properties of forming a chemical bond with dentin, inducing hydroxyapatite precipitation, stimulating active osteogenesis and cementogenesis, and filling the complex anatomical furcation with a high-density hermetic seal play a major role in better treatment outcomes in the long-term, faster restitution of the bone in complex anatomical furcation, and higher overall tooth survival rates(Iohara et al., 2024).

## 3. Materials and Methods

### 3.1 Study Design and Setting

The study was a prospective clinical one carried out during three years (2022-2025) in the Department of Therapeutic Dentistry at Samarkand State Medical University. The study was intended to thoroughly test out

a new diagnostic and therapeutic approach for endo-periodontal lesions (EPL).

**Study Population and Cohort Selection**

The total number of patients in the initial study population was 154, which were patients that were clinically diagnosed with chronic periodontitis secondary to retrograde pulp injury. To reduce the systemic confounding factors of age, all the participants were within a narrow age range (35-44 years). The criteria for inclusion were very strict:

- Diagnosed with moderate or severe chronic periodontitis.
- Manifestation of deep periodontal pockets (≥4 mm).
- Signs and symptoms in the pulpal area and/or signs and symptoms in the radiology showing simultaneous pulpal involvement or retrograde degeneration.
- Delivering informed, voluntary and written patient consent.

On the other hand, exclusion criteria were met and candidates were not included in the trial if they had one of the following:

- Acute systemic diseases/infections.
- Recent periodontal treatment history (last six months).
- Pregnancy or lactation.
- Severe systemic conditions or diseases that affect the host's immune function (such as auto-immune diseases, uncontrolled diabetes).

After recruitment, the 154 patients were sorted into 3 separate study arms to maintain the comparability and integrity of the study arms:

- Main Group (n=62): Group treated with the optimized protocol of deep disinfection with the 0.1% alexidine solution and PUA, and obturation with the bioactive calcium-silicate bioceramic sealers.
- Control Group (n=62): Irrigated with conventional irrigation techniques (Sodium Hypochlorite – 3% and Chlorhexidine – 2%) without the use of ultrasonic activation, and then with calcium hydroxide-based sealers.
- Control Group (n=30): Individuals with dentition that are periodontally and endodontically healthy who were used to establish baseline physiological reference values of local immune biomarkers.

**Clinical Assessment and Indexing**

All subjects underwent a systematic clinical exam at baseline and at designated follow-up times. This evaluation involved a careful oral hygiene assessment, gingival inflammation evaluation, tooth mobility assessment and careful periodontal probing at several sites(Hernández-Monjaraz et al., 2020). The following clinical indices were measured to objectively monitor the changes in soft-tissues and structures:

- PMA (Papillary-Marginal-Attachment) Index – This was recorded to determine the actual level and degree of localized gingival inflammation.
- Periodontal Index (PI) / Plaque Index: At times maintained to track patient's oral hygiene level and plaque build-up.
- CPITN Index: Used to assess the community periodontal therapy needs and community structural classification.
- Muhlemann Bleeding Index: Measure of severity of capillary bleeding and vulnerability of the margins of the tissues.
- Pocket Depth (mm): Depth of pocket measured by a calibrated periodontal probe to monitor attachment loss and the shape of the pocket.

**Advanced 3D CBCT Evaluation**

The 2D radiography approach was limited in diagnosis and three-dimensional Cone-Beam Computed Tomography (CBCT) imaging was used to overcome this limitation at high resolution. CBCT scans were carefully evaluated for the presence of spatial patterns of alveolar bone destruction, periodontal pocket morphology and root furcation involvement. Additionally, it was used for periapical pathology mapping and localization of fine anatomical communication including accessory canals, lateral canals, dentinal tubules and apical foramina that can serve as channels for the spread of pathogens from the periodontal to pulpal tissues.

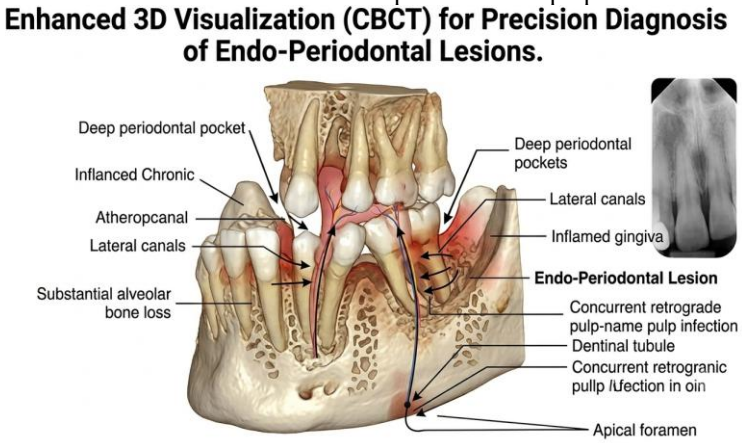


**Figure 2: Enhanced 3D Diagnosis (CBCT) and Predictors of retrograde pulp injury**

Comparing the Figure 1 (concept) and the Figure 2 (diagnostic part of your algorithm), you will see how much more sensitive the 3D Cone-Beam Computed Tomography (CBCT) is as opposed to traditional 2D radiography. The complex multi-rooted anatomy presented above has various predictors of pulpal pathology that are not discernable on 2D imaging, as shown in this medical rendering: furcation involvement.

extensive alveolar bone loss, and visualised pathways that can be directly traced to the pulp. It highlights the importance of CBCT in the diagnostic component of algorithm(Hu et al., 2016).

**Electroodontodiagnostics (EOD)**

To be able to reliably establish pulp vitality thresholds and detect functional changes during chronic inflammation, electrical pulp testing with a calibrated electroodontodiagnostic device was carried out. A drop in functional activity to 20 µA was used to define retrograde pulp injury and/or neurovascular degradation before the appearance of classic acute pain or total necrosis.

**Immunological Biomarker Assessment**

Gingival crevicular fluid (GCF) was obtained using sterile paper strips in highly standardized condition for monitoring the local immune profile. To accurately measure the levels of important local cytokines, pro-inflammatory cytokines were measured interleukin-1 beta (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha ( TNF-) as well as the anti-inflammatory mediator, interleukin-10 (IL-10). With the help of these values, Cytokine Balance Index was calculated by the following mathematical formula:

$$\text{Cytokine Balance Index} = \frac{IL\text{-}1\beta}{IL\text{-}10}$$

The index value above 6.0 in deep pockets (≥4 mm) was used as an objective biochemical criterion of irreversible pulp degradation thus supporting the need for active endodontic treatment(Widbiller et al., 2023).

**Integrated Treatment Protocol**

The clinical cohorts' therapeutic intervention was developed into three defined stages:

- Phase I (Initial Periodontal Therapy): All patients were given comprehensive baseline periodontal preparation in both the Main and the Comparison groups. This included professional oral hygiene instruction, careful scaling and root planing (SRP) and all removal of local irritants.
- Phase II (Endodontic Intervention): Deep chemo-mechanical disinfection was performed in the Main Group using an advanced 0.1% alexidine solution with energisation through passive ultrasonic activation (PUA) to break up complex intra-canal biofilms. The Comparison Group was treated with 3% Sodium Hypochlorite and 2% Chlorhexidine irrigation (without the use of an ultrasonic device).
- Phase III (Bioceramic Obturation): After the preparation of the canal, all the root canal systems in the Main Group were filled with highly bioactive and regenerative calcium-silicate bioceramic materials, which promote osteogenesis and periapical restitution. Conventional calcium hydroxide-based materials were used to seal the Comparison Group's canals.

**Follow-Up and Longitudinal Evaluation**

After the end of the combined therapy, the patients were subjected to a strict recall program, and were evaluated longitudinally at 1 month, 3 months, 6 months and 12 months. In each recall interval, extensive clinical, radiological, functional and immunological results were collected to assess the long-term restoration of tissues, stabilization of cytokine indexes and the survival of the teeth.

## 4. Results

**Baseline Clinical and Index Profiles**

Clinical parameters were carefully assessed before the therapeutic interventions were given to both the Main and Comparison groups to guarantee randomisation and uniformity of samples. At intake, both patient groups demonstrated advanced periodontal tissue destruction and marked inflammatory disorganization, with no statistically significant differences observed between them ($P > 0.05$). The baseline Papillary-Marginal-Attachment (PMA) Index was recorded at 68.4 ±3.8% for the Main Group and 62.1pm 3.5% for the Comparison Group. The Schiller-Pisarev sample scores stood at 2.6pm 0.12 points and 2.4pm 0.11 points, respectively. The Periodontal Index (PI) was measured at 6.2pm 0.3 for the Main Group versus 5.8pm 0.3 for the Comparison Group, while the initial mean pocket depths were deeply pronounced at 5.4±0.15 mm and 5.1±0.18 mm. Furthermore, the Muhlemann Bleeding Index revealed equivalent capillary vulnerability, marking 2.7pm 0.08 in the Main Group and 2.5 pm 0.11 in the Comparison Group, confirming that both cohorts exhibited severe, matched baseline pathology. Before starting the therapeutic interventions a detailed assessment of the baseline clinical parameters were performed to assure the uniformity of the samples and accurate randomisation. There were no significant differences ($P > 0.05$) between groups with regard to the major clinical indices and both groups displayed significant amounts of periodontal tissue destruction and inflammatory disorganization(Rotstein & Simon, n.d.). The exact baseline values for Papillary-Marginal-Attachment (PMA) Index, Schiller-Pisarev sample, Periodontal Index (PI), pocket depths and Muhlemann Bleeding Index are described in Table 1.

**Table 1: Baseline Clinical and Periodontal Indices**

| Clinical Parameter | Main Group (n=62) | Comparison Group (n=62) | Statistical Significance |
|---|---|---|---|
| PMA Index (%) | 68.4 ± 3.8 | 62.1 ± 3.5 | P > 0.05 |
| Schiller-Pisarev Sample (points) | 2.6 ± 0.12 | 2.4 ± 0.11 | P > 0.05 |
| Periodontal Index (PI) | 6.2 ± 0.3 | 5.8 ± 0.3 | P > 0.05 |
| Pocket Depth (mm) | 5.4 ± 0.15 | 5.1 ± 0.18 | P > 0.05 |
| Muhlemann Bleeding Index | 2.7 ± 0.08 | 2.5 ± 0.11 | P > 0.05 |

**Longitudinal Periodontal Evolution**

During the 12 months after treatment, the two therapeutic pathways were very different. The optimized passive ultrasonic activation (PUA) of 0.1% alexidine and calcium-silicate bioceramic obturation was associated with rapid and highly significant structural recovery with a very good long-term effect. The Comparison Group, by contrast, showed a partial response at the beginning of the study period, but a mild trend of relapse by the end of the study(Liu et al., 2025).

At the 6-month recall interval, the Main Group's PMA Index dramatically decreased to 9.2pm 0.8%, its Muhlemann Bleeding Index dropped to 0.1pm 0.02, and the average pocket depth resolved to 2.4±0.1 mm. In contrast, the Comparison Group at 6 months maintained a significantly higher PMA Index of 21.4 ±1.5%, a Bleeding Index of 0.8pm 0.1, and an average pocket depth of 3.5±0.2 mm. By the 12-month mark, the therapeutic gap widened further; the Main Group achieved optimal tissue stabilization, presenting a PMA Index of 8.1 ±0.5%, a Bleeding Index of 0.05pm 0.01, and a pocket depth of 2.1±0.1 mm. During the same period, the Comparison Group exhibited distinct signs of inflammatory relapse, with the PMA Index climbing to 24.6pm 1.8%, the Bleeding Index rising to 0.9pm 0.1, and the average pocket depth regressing to 3.7±0.2 mm. The differences between the two cohorts at 6 and 12 months were highly statistically significant, with the PMA and Bleeding indices demonstrating a significance of $P < 0.001$, and the pocket depth resolution demonstrating a significance of $P < 0.05$. The clinical results that were observed over the 12-months following treatment were very different from the two therapeutic approaches(Alanazi et al., 2024). The Comparison Group had a rapid, significant, although incomplete response initially and a gradual trend towards inflammatory relapse over the course of the study. The change on the main clinical indices of periodontology and structures over time (6 months and 12 months) is shown in Table 2.

**Table 2: Longitudinal Evolution of Periodontal Parameters (6 and 12 Months)**

| Clinical Index | Timepoint | Main Group | Comparison Group |
|---|---|---|---|
| PMA Index (%) | 6 Months | 9.2 ± 0.8 | 21.4 ± 1.5 |
| | 12 Months | 8.1 ± 0.5 | 24.6 ± 1.8 |
| Muhlemann Bleeding Index | 6 Months | 0.1 ± 0.02 | 0.8 ± 0.1 |
| | 12 Months | 0.05 ± 0.01 | 0.9 ± 0.1 |
| Pocket Depth (mm) | 6 Months | 2.4 ± 0.1 | 3.5 ± 0.2 |
| | 12 Months | 2.1 ± 0.1 | 3.7 ± 0.2 |

**Localized Cytokine Dynamics within the Gingival Crevicular Fluid**

Immunochemical monitoring of the gingival crevicular fluid (GCF) via ELISA provided direct biological confirmation of the anti-inflammatory efficacy of the optimized protocol. Pre-treatment levels of the core pro-inflammatory cytokine interleukin-1 beta (IL-1) were highly elevated in both the Main Group (41.6±3.8 pg/ml) and the Comparison Group (40.8±4.1 pg/ml). Following treatment, the Main Group showed a substantial drop in IL-1 at 1 month (14.2±1.1 pg/ml), which continued to decline to 10.8±0.9 pg/ml at 6 months, and ultimately reached a near-physiological baseline of 8.4±0.6 pg/ml at 12 months ($P < 0.001$ relative to pre-treatment values)(Donnermeyer et al., 2023). Conversely, the Comparison Group exhibited a significantly slower and less profound reduction, with IL-1 concentrations dropping to 26.4±2.3 pg/ml at 1 month, tracking at 22.1±1.8 pg/ml at 6 months, and reversing upward to 24.7pm 2. pg/ml by month 12. Tumor necrosis factor-alpha ( TNF-) values followed a parallel trajectory. The Main Group's TNF- level fell from a baseline of 28.4±2.5 pg/ml down to 9.6 pm 0.7pg/ml at 1 month, 6.2pm 0.4pg/ml at 6 months, and settled at 5.1pm 0.3pg/ml at 12 months. The Comparison Group's TNF”−α decreased modestly from 27.9pm 2.8pg/ml to 18.3pm 1.5pg/ml at 1 month, 16.4pm 1.2pg/ml at 6 months, and remained elevated at 17.8pm 1.4pg/ml at 12 months. Direct biological confirmation of anti-inflammatory effect of the optimized protocol was done by immunochemical monitoring of gingival crevicular fluid (GCF) by ELISA. After treatment the Main Group showed a persistent reduction in the production of pro-inflammatory cytokines (IL-1β and TNF-α) and an exponential increase in the production of the anti-inflammatory cytokine IL-10, which indicates active local tissue repair. The Comparison Group showed little IL-10 upregulation and a subsequent recovery of pro-inflammatory markers. The absolute localized cytokine changes throughout the 12 month period is summarised in Table 3.

**Table 3: Dynamics of Localized Cytokines in Gingival Crevicular Fluid (pg/ml)**

| Cytokine Marker | Study Group | Baseline | 1 Month | 6 Months | 12 Months |
|---|---|---|---|---|---|
| Pro-inflammatory IL-1 | Main | 41.6 ± 3.8 | 14.2 ± 1.1 | 10.8 ± 0.9 | 8.4 ± 0.6 |
| | Comparison | 40.8 ± 4.1 | 26.4 ± 2.3 | 22.1 ± 1.8 | 24.7 ± 2.0 |
| Pro-inflammatory TNF- | Main | 28.4 ± 2.5 | 9.6 ± 0.7 | 6.2 ± 0.4 | 5.1 ± 0.3 |
| | Comparison | 27.9 ± 2.8 | 18.3 ± 1.5 | 16.4 ± 1.2 | 17.8 ± 1.4 |
| Anti-inflammatory IL-10 | Main | 4.8 ± 0.4 | 12.6 ± 1.1 | 15.4 ± 1.2 | 17.3 ± 1.1 |
| | Comparison | 4.6 ± 0.5 | 7.4 ± 0.6 | 6.2 ± 0.5 | 8.8 ± 0.6 |

Crucially, the primary anti-inflammatory mediator, interleukin-10 (IL-10), expanded exponentially within the Main Group, rising from a baseline of 4.8pm 0.4pg/ml to 12.6pm 1.1pg/ml at 1 month, 15.4pm 1.2pg/ml at 6 months, and peaking at 17.3pm 1.1pg/ml at 12 months, signaling robust, localized active tissue repair. In contrast, the Comparison Group demonstrated limited IL-10 upregulation, shifting from a baseline of 4.6pm 0.5pg/ml to 7.4pm 0.6pg/ml at 1 month, falling to 6.2pm 0.5pg/ml at 6 months, and finishing at a minor elevation of 8.8pm 0.6pg/ml at 12 months

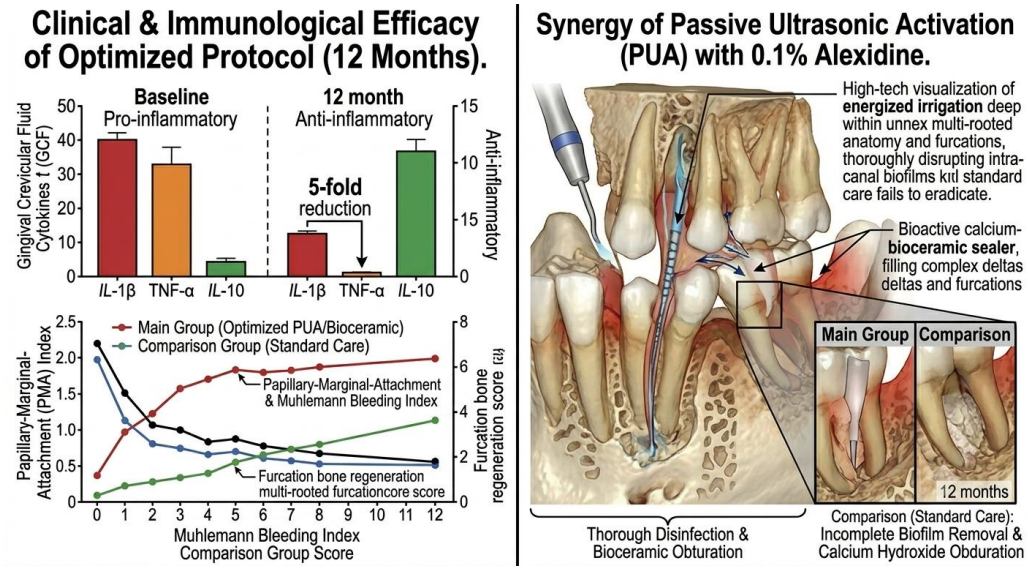


**Figure 3: Clinical and Immunological Synergy of the Optimized Treatment**

This is a split view illustration of the most important part of the dissertation—the integrated algorithm. The left panel combines clinical (indices) and immunological (GCF) results from your results, and shows that Main Group (optimized PUA/Bioceramic) had a five-fold greater reduction of pro-inflammatory cytokines and multi-rooted furcation bone regeneration compared to the Comparison Group (standard care) at 12 months. Right side: magnified detail of an optimized proceduraL synergy (referencing the multi-rooted anatomy from Figure 2) Passive Ultrasonic Activation (PUA) of 0.1% alexidine deep-tissue root canal disinfection, disrupting biofilms, followed by durable calcium-silicate bioceramic obturation and interactive osteogenesis(Careddu & Duncan, 2021).

**The Cytokine Balance Index and Long-Term Healing**

The absolute concentration of these cytokines were then combined mathematically into the so-called Cytokine Balance Index (IL-1β/IL-10) to provide a clear-cut estimation about the real time tissue healing process when compared to the healthy control group reference value of 0.39. Before the intervention, both Main Group (8.6) and Comparison Group (8.8) exhibited huge immunochemical disequilibrium. After optimization of the protocol, the Main Group had a Cytokine Balance Index of 1.1 at 1 month, 0.7 at 6 months and 0.6 at 12 months, near the healthy level of 0.6. On the other hand, the index of the Comparison Group did not change significantly in a destructive manner, and at 1 month it was at 3.5, at 6 months at 3.5, and at 12 months at 3.4(Rossi-Fedele & Ng, 2023).

The 3D-CBCT radiographic results after 30 years were similar to this biochemical stabilization. After 12 months, the optimized algorithm 100% restored the bone in the Main Group cases in complex root furcation and periapical areas, and there was complete restitution of the cortex in 92.1% of the cases(Hilmi et al., 2023). This was in stark contrast to the standard treatment approach used in the Comparison Group, which yielded 68.8% complete bone regeneration. Moreover, the protocol optimized soft tissue healing times in phase-one 2.2-fold quicker with highly stable long term tooth preservation. The absolute concentrations of cytokines were mathematically combined to get a highly objective and measurable real-time tissue healing (Cytokine Balance Index: IL-1β/IL-10). In the absence of intervention the two groups were both highly immunochemical dysregulated, suggesting

that they had serious local pathology(Fatemi et al., 2012). Table 4 shows the Main Group made a healthy shift into closer proximity to the physiological range (closer to 0.39) and the Comparison Group stayed in a very destructive biochemical state throughout the 12 months of observation.

**Table 4: Cytokine Balance Index (IL-1β/IL-10) Over 12 Months**

| Cohort | Baseline | 1 Month | 6 Months | 12 Months |
|---|---|---|---|---|
| Main Group (Optimized Protocol) | 8.6 | 1.1 | 0.7 | 0.6 |
| Comparison Group (Standard Care) | 8.8 | 3.5 | 3.5 | 3.4 |
| Healthy Control (Reference) | 0.39 | - | - | - |

On a socio-economic basis, this decrease in post-operative complications and clinical revisions resulted in a clear financial benefit, which amounted to an estimated 400,000-600,000 UZS per patient in comparison to conventional treatment.

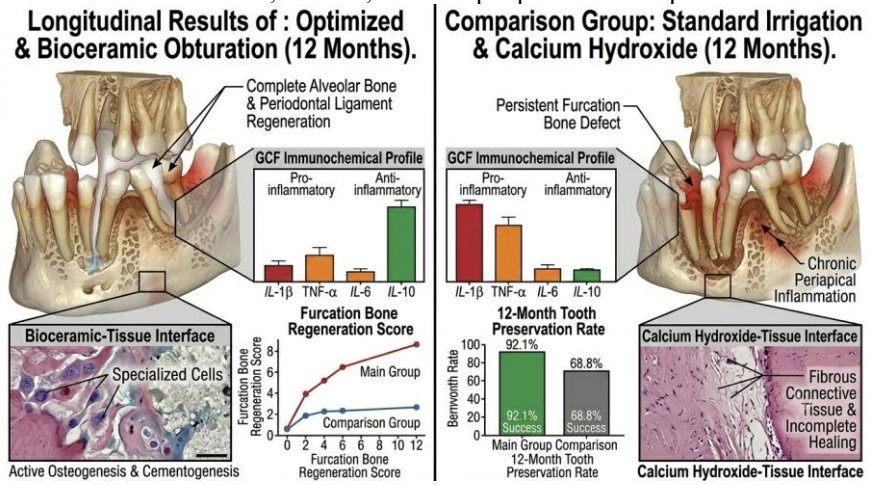


**Figure 4: Longitudinal Biological and Structural Proof of Regeneration (12 Months)**

This last, all-encompassing multi-panel picture is the most convincing evidence for the abstract's assertions on the tissue regeneration. It contrasts the main group (optimized) against the comparison group, and makes the data trends and procedural details of Figure 3 more "biological and structural. A complete alveolar bone and the periodontal ligament regeneration in complex furcations are demonstrated in the main group (left). The high IL-10 profile (Figure 3) is confirmed visually by the osteogenesis and cementogenesis occurring (on the micro level). In contrast, persistent defects, elevated IL-1β, and incomplete fibrous healing were observed in the comparison group (right), demonstrating the critical importance of the optimized procedure in achieving the results of clinical success as published and true biological recovery. There was a strong correlation between biochemical stabilization within the Main Group and long-term outcome of 3D-CBCT and clinical success(Mejàre et al., 2012). The optimized integrated algorithm not only resulted in a faster soft tissue healing at the initial stages, but also in significant socio-economic benefits due to reduced post-operative complications and the number of clinically required revisions. Table 5 presents the definitive 12-month structural and clinical treatment outcomes, and the long-term effectiveness and cost-effectiveness of the optimized treatment protocol is directly compared with standard care(Sheykhrezaee et al., 2007).

**Table 5: 12-Month Clinical and Structural Treatment Outcomes**

| **Clinical Outcome** | **Main Group (PUA + Bioceramics)** | **Comparison Group (Standard Care)** |
|---|---|---|
| Complete bone regeneration within root furcations | 92.1% | 68.8% |
| Phase-one soft tissue healing speed | Accelerated 2.2-fold | Baseline reference |
| Economic benefit per patient (reduced revisions) | Saved 400,000 – 600,000 UZS | Standard costs applied |

**5. Discussion**

The clinical and biological results of this investigation highlight the need to have a highly synchronized diagnostic and therapeutic approach in the therapeutic continuum between the periodontal and endodontic tissues. Baseline findings from this study show that endo-periodontal lesions (EPL) is a serious problem with

advanced tissue destruction and inflammatory disorganization prior to treatment in both groups. The clinical characteristics of the Main and Comparison groups were not found to be different at the baseline level (P> 0.05), thus justifying the randomization process and the equivalent degree of structural damage that both groups faced(Kirilova et al., 2022).

The results of the longitudinal evaluation show a striking difference between the two therapy plans. A dramatic reduction in the PMA Index to 8.1pm 0.5% and a reduction in mean pocket depth to 2.1±0.1 mm at 12 months demonstrates the healing potential of the combination of passive ultrasonic activation (PUA) of 0.1% alexidine and calcium-silicate bioceramic obturation. The Comparison Group's improvement toward inflammatory relapse at month 12 (PMA Index reached 24.6pm 1.8%) on the other hand, signals that standard manual irrigation with sodium hypochlorite and chlorhexidine combined with the use of conventional calcium hydroxide sealers, is not enough to keep the tissue stable for the longterm. This basic deficiency may be attributed to the failure of unactivated solutions to effectively penetrate and debride the microscopic lateral canals, accessory pathways and root furcations of severe periodontitis(Yu & Abbott, 2007).

This clinical difference can be directly attributed to the immunochemical dynamics that occur in the gingival crevicular fluid (GCF), which is a localized fluid. In the Main Group, optimised protocol resulted in a strong, sustained reduction of levels of primary pro-inflammatory cytokines (IL-andTNF-), which approached near physiological levels by the end of the 12-month study period. At the same time, there is a significant increase in the anti-inflammatory mediator, IL-10, found in the Main Group at 12 months (17.3±1.1 pg/ml at 12 months) indicating a shift toward less host-mediated osteoclastic destruction and more local tissue regeneration. In contrast, the Comparison Group did not have a sustained anti-inflammatory response, with an upward trend in pro-inflammatory cytokines by the 12th month that was similar to what was seen clinically(Kurmanalina et al., 2018).

This study not only helps to clarify absolute cytokine levels in both CSF and blood but also offers a highly objective indicator of healing by combining them in the mathematically calculated Cytokine Balance Index (IL-1β/IL-10), Both groups started out with very high indices of immunochemical disequilibrium but the index of the Main Group dropped, from a destructive 8.6 to a near healthy 0.6 at 12 months, coming close to the normal baseline of 0.39. The Comparison Group continued to be stuck in a negative pattern at 3.4. This biochemical stabilization is well reflected in the long-term 3D-CBCT radiographic results, with complete bone regeneration and cortical restitution in 92.1% of the optimized group of cases, compared to 68.8% in the conventional group of cases. However, the 2.2-fold speed up in phase-one soft tissue healing and the high level of long-term tooth retention have great socio-economic value. A reduction in post-operative morbidity and avoidance of clinical revisionations resulted in a clear financial advantage which was estimated to be 400,000 to 600,000 UZS per patient rather than the standard care. In conclusion, the results of this study support and validate the potential of using a highly biocompatible and regenerative calcium-silicate bioceramic combined with advanced chemo-mechanical disinfection (0.1% alexidine + PUA) to effectively treat endo-periodontal lesions, which are bidirectional and complex in nature(Digka et al., 2020).

## 5. Conclusions

The results of this investigation are extensive and show that the chronic periodontitis is a very significant progressive pathological process affecting the dental pulp, via the retrograde infection routes, and thus a very complex process involving the total organ. High resolution 3D Cone-Beam Computed Tomography (CBCT) imaging, accurate electroodontodiagnostics (EOD) and local immunochemical cytokine profiling offer a powerful and objective tool for early diagnosis and accurate treatment planning. In this context, Cytokine Balance Index, mathematically derived from IL-1 levels and IL-10, is a useful biological marker, to assess the reversibility of pulpal inflammation and eliminate wild guess work from the clinical pathway.

In terms of therapeutic value, the use of 0.1% alexidine solution (with energising of passive ultrasonic activation (PUA)) has a significant effect on the disinfection of root canals, effectively removing resilient submucosal biofilms and achieving rapid inflammatory control. Bioactive calcium-silicate bioceramic obturation materials have been shown to actively promote periapical tissue regeneration, promote osteogenesis in complex root furcations and provide excellent long-term treatment stability after debridement with deep chemo-mechanical techniques. Finally, the proposed integrated algorithm was able to provide excellent clinical, radiographical and immunological results in 92.1% of the cases, providing a better socio-economically friendly approach in preserving the dentition of patients with chronic periodontitis associated pulp injuries.

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