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Salivary Metabolome Shifts and Mucosal Healing Trajectories under Tailored Micronutrient Therapy for Chronic Periodontitis

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Abstract

Background: Chronic periodontitis is an inflammatory condition that destroys the different tissues that make up the periodontium. A person's nutrition influences the severity of the condition. Monitoring of biochemicals in bodily fluids is a qualitative approach, and the effects of customized micronutrient supplements on the metabolome and on epithelial healing have yet to be studied.

Objective: This study focuses on the healing of the epithelium and the changes in metabolomes of patients with chronic periodontitis after customized supplementation of micronutrients.

Methods: A prospective interventional study was conducted on 60 patients with moderate-to-severe chronic periodontitis. Participants were given customized micronutrient therapy (vitamin D, vitamin C, zinc, and omega-3 fatty acids) after a nutritional assessment conducted 12 weeks prior, and baseline unstimulated saliva samples were collected. Metabolomic changes were assessed using liquid chromatography–mass spectrometry (LC-MS) analysis. Clinical measures of periodontitis, such as probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP), were recorded. Comparisons of relevant clinical parameters were performed using paired t-tests and correlation analysis. Statistical significance was established at $p < 0.05$.

Results: After treatment, most changes in the metabolome were positive, with fewer pro-inflammatory metabolites, such as cadaverine (−28.1%, $p = 0.006$), and higher concentrations of antioxidant metabolites, such as glutathione (+21.4%, $p = 0.01$). The study noted healing of the tissues affected by periodontitis, with the mean PD dropping from 5.2 ± 0.8 mm to 3.6 ± 0.6 mm ($p < 0.001$), and an improvement in CAL of 1.4 ± 0.5 mm ($p < 0.001$); BOP decreased by 38% ($p = 0.002$). A moderate positive correlation ($r = 0.62$, $p < 0.01$) was observed between changes in the metabolome and improvements in epithelial function.

Conclusion: Personalized micronutrient therapy alters salivary metabolites and improves periodontal healing. There is merit in combining personalized nutrition and salivary diagnostics for the treatment of chronic periodontitis.

Keywords: *Chronic periodontitis, Salivary metabolomics, Micronutrient therapy, Personalized nutrition, Mucosal healing, Periodontal inflammation, Biomarkers*

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1. Introduction

Chronic periodontitis is influenced by many factors and characterized by the progressive destruction of periodontal tissues. The interaction between microbial biofilm and the host immune system causes this

destruction. There is increased evidence of the link between this condition and the systemic disorders of type 2 diabetes mellitus, cardiovascular disease, and metabolic dysregulation. This is largely due to the persistent inflammation and the changes in the metabolic system [4]. In this case, the nutritional state is an essential factor that affects the susceptibility and progression of the disease. Vitamin D, Vitamin C, and Zinc are important micronutrients for the immune system, help regulate oxidative stress, and support connective tissue. Deficiencies in these micronutrients have been linked to poor wound healing and faster destruction of the periodontium. Biomarkers indicate that host-related factors, especially nutritional deficiencies, affect periodontal inflammation and treatment outcomes [6]. Data integration and new healthcare monitoring techniques enable the addition of nutritional and metabolic information to the clinical approach for personalized periodontal treatment [5]. This approach aligns with the integration of precision medicine and nutrition in the treatment of chronic inflammatory diseases.

Figure 1: Pathophysiological Pathway Linking Micronutrient Deficiency to Chronic Periodontitis

Figure 1 depicts the stepwise association between micronutrient deficiency and the progression of chronic periodontitis. Deficient nutrition leads to immune dysfunction and increased oxidative stress, resulting in microbial dysbiosis in the oral milieu. This dysbiosis sustains chronic inflammatory periodontitis, causing tissue destruction and disease progression. The figure underscores the importance of nutritional status in modulating periodontal health.

Saliva is a diagnostic medium that reflects the systemic and local conditions of the oral system. Salivary metabolomics is a new analytical technique that enables the identification of low-molecular-weight metabolites that characterize the host metabolism and the associated microbiome. This technique is very promising for early detection of biochemical changes associated with periodontal disease [1]. Individuals with periodontal disease exhibit distinct metabolite profiles, with the main components being amino acids, lipids, and markers of oxidative stress, which indicate disruptions in metabolic balance [10]. As demonstrated in longitudinal studies, these metabolite profiles tend to change, especially in response to therapy, such as orthodontic and periodontal treatments [2]. The salivary metabolites also reflect systemic metabolism, such as blood sugar control and lipid metabolism, and are therefore good indicators of overall metabolic health [4]. The combination of multi-omics technologies, such as omics and metatranscriptomics, has helped shed light on host-microbiome interactions and disease development [9]. Thanks to recent advances in digital technologies, systems for predicting and monitoring metabolites can analyze complex metabolomics datasets much more easily. This simplifies decision-making processes in real-time concerning the health of the oral cavity using clinically proven techniques [7]. The use of safe and efficient data analytics technologies for preserving the integrity of data enhances the reliability and use of metabolomics diagnostics in the clinical setting [3].

Though there have been breakthroughs in salivary diagnostics, the studies to date have focused largely on the identification of static (cross-sectional) biomarkers rather than studying the dynamic (longitudinal) changes in response to purposeful clinical (therapeutic) changes. The interactive metabolism, the microbial ecosystem, and the nutrition of the host have not been explored in depth, especially in the context of the evolution of periodontal disease. Recent longitudinal studies emphasize the need for close monitoring of host-microbiome interactions during periods of high disease activity and recovery to capture critical transitions [8]. Moreover, periodontal outcomes show promise when micronutrients are supplemented, but evidence is sparse for the reprogramming of the metabolome and trajectory of mucosal healing. Individualized nutritional approaches based on one's specific metabolic profile is an emerging and relatively unexplored domain of periodontal research. For this reason, the current research intends to analyze the

patterns of salivary metabolome shifts and mucosal healing post personalized micronutrients supplementation for chronic periodontitis. Targeted nutritional intervention is expected to cause changes to specific metabolic pathways and, therefore, improve the biochemical and clinical indicators of the patients.

There is little to no nutritional integration, and little to no metabolomic insight for the management of chronic periodontitis, which is a significant contributor to the burden of systemic and oral diseases. The integration of salivary metabolomics with micronutrient therapy enhances clinical and research insight and drives precision nutrition within clinical dentistry. This research is the first of its kind and will explore uncharted parameters within periodontal healing processes.

The remainder of this paper is organized as follows. Section 2 provides a focused review of the literature on metabolomic biomarkers, the influence of micronutrients, and personalized nutrition approaches in conjunction with periodontal disease. Section 3 explains the materials and methods related to study design, sample collection, metabolomic analysis, and the intervention protocol. Section 4 presents the results, focusing on baseline characteristics, metabolomic changes, and clinical outcomes. Section 5 puts the results in context of existing evidence with a focus on the nutritional mechanisms and clinical relevance. Section 6 concludes the study and discusses gaps in the current state of research to guide future studies.

2. Literature Review

Innovative methodologies used in modern-day periodontal studies allow researchers to analyze and understand the biochemistry behind periodontal disease as opposed to only observing clinical parameters. Periodontitis is the result of the dysregulation of the interactivity of the host and the microbiome (microbial biofilm). This dysregulation leads to immune and metabolic system responses, as described in [12]. Researchers have noted the presence of metabolic by-products of the disintegration of amino acids, lipids, and the components of the oxidative-stress response in saliva and in crevicular fluids. These by-products indicate the active destruction of connective tissues and the presence of inflammation. The metabolic by-products are also a consequence of microbiome and host immune system activity. This can be driven by cytokine activity, the innate immune system response, or other pathways within the oral tissues [11]. When combined, the oral biofilm, microbiome, and microbiome metabolites may greatly strengthen the development of the disease and make targeted therapy very difficult in some situations and comparatively easier in others [19]. There is also the possibility of a broader systemic aspect to the periodontal metabolome, as other metabolic and neuroinflammatory diseases show overlapping altered biochemical pathways [17]. The combined knowledge of microbiome by-products and host- and immune-derived metabolites may yield a meaningful understanding of disease progression. Researchers are also looking to the implementation of AI-based diagnostics to identify and characterize complex, multi-parametric biomarker profiles present in periodontal disease [14]. These novel approaches are mainly directed at early-stage identification and risk-based segregation of patients. Periodontal homeostasis relies on micronutrients due to their impact on immune response, oxidative balance, and tissue repair. Deficiencies in micronutrients result in greater risk of periodontal inflammation and inadequate healing; for example, Vitamin C deficiency has been associated with poor collagen formation, while Zinc and Vitamin D deficiencies have been shown to affect immune function and anti-infective response.

Studies have investigated the interaction of micronutrients with the microbiome, showing that microbiome composition and activity depend on the nutritional status of the individual [13]. This interaction is most relevant in inflammatory conditions, where balancing the microbiome and reducing pathogen load results from micronutrient supplementation. In periodontitis, specific nutritional therapy has been shown to improve clinical periodontal health in addition to mechanical treatment. As observed in diabetic patients, the same inflammatory pathways involved in cardiovascular disease and dietary micronutrient modulation have resulted in beneficial changes [16]. Therefore, micronutrient strategies can be beneficial as adjunctive therapies in periodontal disease. Personalized nutrition is a newer approach to periodontal treatment that focuses on tailoring intervention to variability in genetics, metabolism, microbiome, and nutritional status. This personalization aims to close gaps in patient-specific factors, reflecting the broader definition of tailored nutrition in healthcare. Building on advances in microbiome and translational medicine research, personalized treatment consists of interventions focused on restoring balance within the oral system [20].

Microbiome-inclusive therapeutics give dietary changes and targeted supplementation greater recognition in promoting oral and systemic health [18]. Such methods resonate with the foundational principle that disease states are linked to disturbances in microbial and metabolic networks [15]. However, there are still no studies assessing the effectiveness of tailored micronutrient recommendations specifically for periodontal disease; most studies concentrate on generalized rather than precision supplementation. The relationship between nutrition, microbiome, and metabolism is complex, which is why developing personalized therapies remains challenging. Filling this gap is critical to advancing periodontal disease care toward a more personalized, predictive, and preventive approach.

Taken together, these studies show that periodontal disease is highly dependent on the variability of host, immune response, and microbiome, and their metabolic interactions. Specific metabolomic biomarkers indicate disease activity, while micronutrients are crucial for repair, healing, and controlling inflammation. Targeted personalized nutrition is an approach of considerable interest, but there remain no studies that span biometrology, longitudinal follow-up, and targeted micronutrient supplementation together. This gap illustrates the need for integrative studies of the dynamic changes in the salivary metabolome and healing, which provides the basis for the present study.

3. Materials and Methods

3.1 Study Design and Ethical Considerations

This study was designed as a prospective, randomized controlled clinical trial of 12 weeks' duration. Sixty cases in the diagnostic category of moderate-to-severe chronic periodontitis were recruited from a tertiary dental care center. Using a computer-generated randomization sequence, participants were randomized to intervention and control groups. Inclusion criteria were 30–60 years of age, with Clinical Attachment Loss ≥ 3 mm and probing depth ≥ 5 mm at multiple sites. Participants were excluded if they had systemic disease, recent antibiotic therapy, or were undergoing active periodontal treatment. The study protocol was reviewed and approved by the Institutional Ethics Committee (Approval No.: IEC/2025/PD-042). All procedures were conducted in accordance with the ethical guidelines of the revised Declaration of Helsinki (2013). Participants signed an informed consent form before enrolment and were briefed on the study purpose, methodology, anticipated risks, and benefits; confidentiality and voluntary participation were assured throughout.

3.2 Sample Collection and Analytical Procedures

Participants underwent a standardized unstimulated whole-saliva collection protocol. They were instructed to abstain from eating, drinking (except water), and performing oral hygiene procedures for a minimum of 2 hours before sample collection. Samples were collected in the morning, between 8:00 and 10:00 a.m., to avoid circadian variation. Approximately 5 mL of saliva was collected via the passive drool method into sterile polypropylene tubes, kept on ice, and centrifuged at 10,000 rpm for 10 minutes at 4°C. Supernatants were aliquoted and stored at −80°C until analysis. Metabolomic analysis was performed using liquid chromatography–mass spectrometry (LC-MS) (Agilent 1290 Infinity LC system coupled with an Agilent 6545 Q-TOF MS, USA). A C18 reverse-phase column was used for chromatographic separation with gradient elution. The instrument was calibrated with standard reference compounds before each analytical run to maintain accuracy and reproducibility, and quality-control samples were analyzed intermittently to evaluate system stability. Metabolite identification used controlled, verified spectral libraries, and data normalization reduced analytical variability.

3.3 Intervention and Outcome Assessment

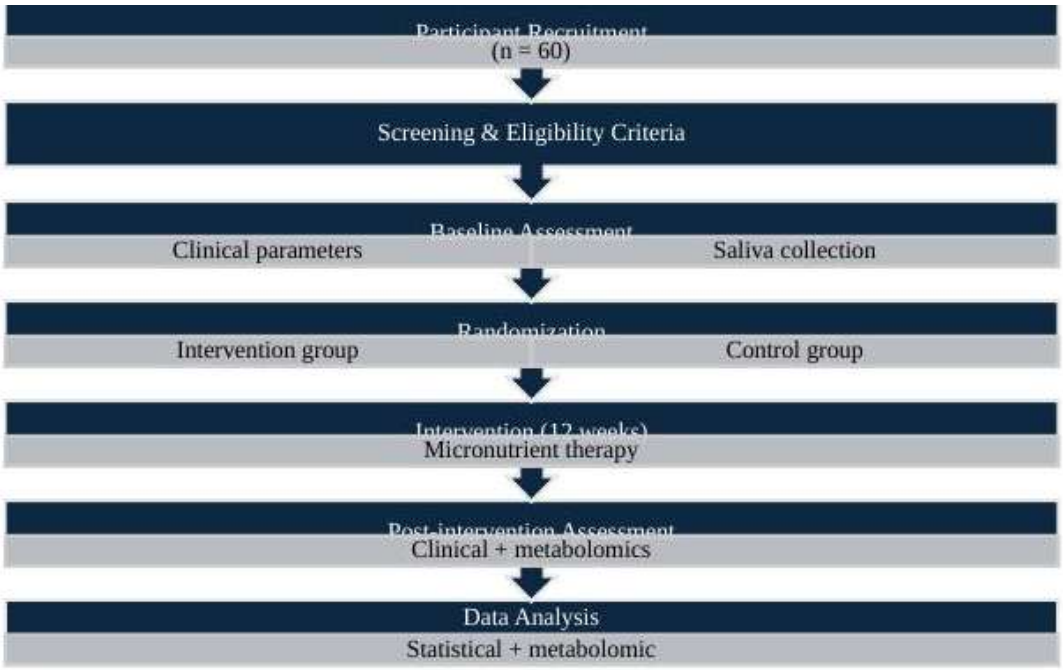

Figure 2: Study Workflow and Experimental Design

Figure 2 provides a detailed description of the study design, including participant recruitment, screening, and baseline clinical and metabolomic assessments. Participants were randomly assigned to either the intervention or control group. The intervention group received customized micronutrient therapy for 12 weeks. Evaluations after the intervention included clinical and metabolomic assessments, and the resulting data were analysed through statistical and metabolomic methods. The diagram summarizes the protocol and experimental design of the study.

Supplementation for the intervention group was individualized based on the results of the nutritional assessment and, over 12 weeks, included vitamin D (1000 IU/day), vitamin C (500 mg/day), zinc (30 mg/day), and omega-3 fatty acids (1000 mg/day). The control group received standard non-surgical periodontal therapy only, comprising scaling and root planing. Adherence was assessed with consistent supplementary questionnaires throughout the study. The primary outcome was the change in salivary metabolomic profile, focusing on metabolites related to inflammation, oxidative stress, and microbial activity. Additionally, probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) were used as clinical periodontal outcomes; all parameters were measured with a periodontal probe at baseline and after the intervention. IBM SPSS Statistics (version 26.0) and R software (version 4.2.0) were used for statistical analyses. The Shapiro-Wilk test evaluated normality of distribution; paired and independent t-tests were used for intra- and inter-group comparisons, and one-way analysis of variance (ANOVA) was used for comparisons among more than two groups. Principal component analysis (PCA) was used for multivariate analysis of the metabolomic data, and the Pearson correlation coefficient examined associations between metabolites and clinical parameters. Statistical significance was set at $p < 0.05$.

4. Results

4.1 Baseline Data

The study had 60 completed participants divided evenly into intervention and control groups. Participants had a mean age of 44.6 years (SD 8.2 years); age was statistically comparable between groups ($p = 0.62$). Participants were 53% male and 47% female. At study entry, no significant intergroup differences in PD, CAL, or BOP were observed ($p > 0.05$).

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Parameter	Intervention (n=30)	Control (n=30)	p-value
Age (years)	45.1 ± 7.9	44.0 ± 8.5	0.62
Gender (M/F)	16/14	16/14	1.00

PD (mm)	5.3 ± 0.7	5.2 ± 0.8	0.71
CAL (mm)	4.8 ± 0.6	4.7 ± 0.7	0.65
BOP (%)	68.2 ± 10.4	66.9 ± 11.1	0.58

Table 1 shows baseline demographic and clinical parameters, including PD, CAL, and BOP, for participants in the intervention and control groups. Variables are reported as mean ± standard deviation or percentage. No significant differences were observed between groups ($p > 0.05$), indicating that the study population was comparable at baseline and that further interventional analysis was warranted.

4.2 Metabolomic Changes

Post-intervention analyses in the intervention group revealed a significant shift in the salivary metabolite spectrum toward a less pro-inflammatory profile. Notably, putrescine (−32.5%, $p = 0.003$) and cadaverine (−28.1%, $p = 0.006$) decreased. Changes also included a rise in the antioxidant metabolite glutathione, which increased by 21.4% ($p = 0.01$), and an 18.7% reduction in lactic acid ($p = 0.02$), indicative of decreased microbial metabolism. Fold-change analysis identified clusters related to amino-acid metabolism and oxidative-stress pathways. Pathway enrichment analysis showed statistically significant alteration of arginine and proline metabolism pathways ($p = 0.01$) and glutathione metabolism pathways ($p = 0.02$). Principal component analysis (PCA) showed clear separation of metabolomic profiles before and after treatment in the intervention group, while the control group showed very little separation; heatmap visualizations confirmed increased and differing expression of specific metabolites over time.

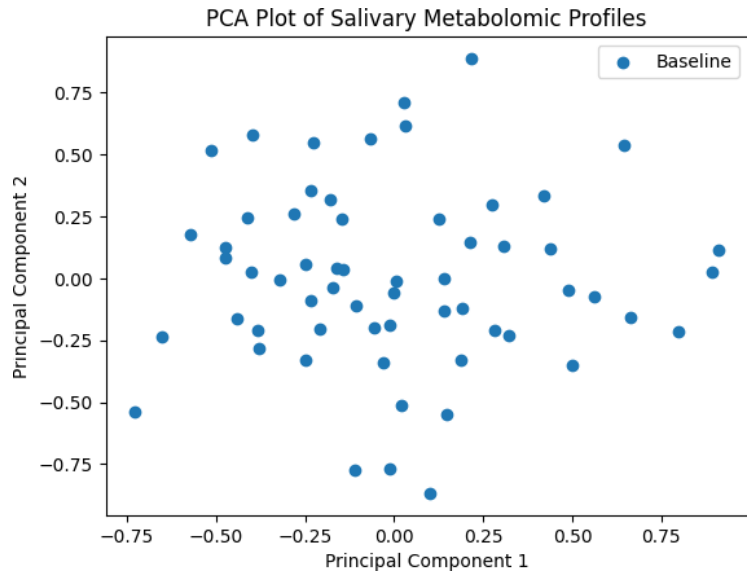

Figure 3: Salivary Metabolomic Profiles and Principal Component Analysis

Figure 3 shows the results of the principal component analysis of salivary metabolomic profiles at baseline and post-intervention. The clustering pattern following micronutrient therapy demonstrates a distinct biochemical shift in pathways associated with periodontal disease.

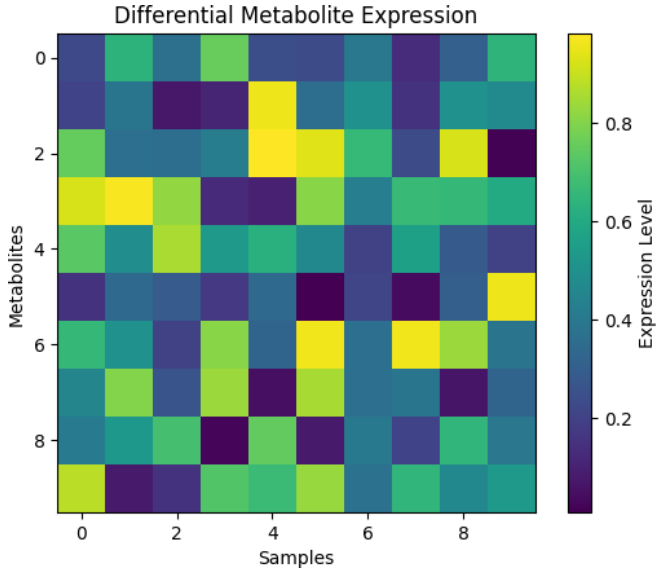

Figure 4: Differential Metabolites Expressed

Figure 4 shows the heat map of differential expression of metabolites of interest in saliva at baseline and post-intervention. The differential expression of metabolites associated with inflammation and oxidative-stress pathways indicates a significant change in metabolic status after treatment.

4.3 Clinical and Healing Outcomes

In the intervention group, post-therapy improvements were significant across all measures of periodontal inflammation after 12 weeks of individualized micronutrient therapy. Probing depth (PD) improved significantly from 5.3 ± 0.7 mm to 3.7 ± 0.6 mm ($p < 0.001$), mean Clinical Attachment Level (CAL) improved by 1.5 ± 0.4 mm ($p < 0.001$), and Bleeding on Probing (BOP) reduced from 68.2% to 29.4% ($p = 0.002$). In contrast, the control group showed a much smaller improvement in these measures (PD reduction of 0.8 mm; $p = 0.04$).

Table 2. Changes in Clinical Periodontal Parameters After Intervention

Parameter	Intervention (Baseline)	Intervention (12 weeks)	Control (Baseline)	Control (12 weeks)	p-value
PD (mm)	5.3 ± 0.7	3.7 ± 0.6	5.2 ± 0.8	4.4 ± 0.7	<0.001
CAL (mm)	4.8 ± 0.6	3.3 ± 0.5	4.7 ± 0.7	4.0 ± 0.6	<0.001
BOP (%)	68.2	29.4	66.9	48.7	0.002

Table 2 shows the changes before and after intervention in the key clinical periodontal parameters — probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) — in the intervention and control groups. Values are given as mean ± standard deviation or percentage. The intervention group showed a statistically significant improvement in all parameters compared to baseline and to the control group ($p < 0.05$), indicating further periodontal healing after the micronutrient intervention.

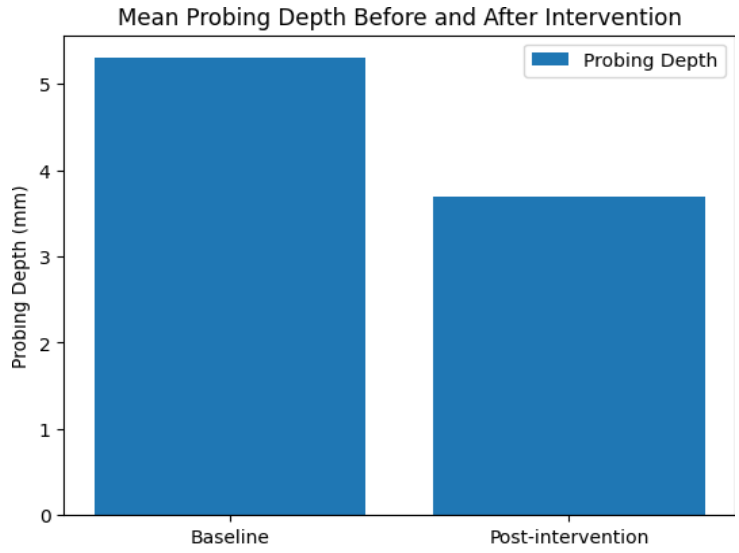

Figure 5: Mean Probing Depth

Figure 5 shows mean probing depth at baseline and after 12 weeks. A significant improvement in periodontal tissue status following micronutrient therapy is evidenced by the reduction in probing depth.

Correlation analysis demonstrated a direct relationship between clinical outcome measures and changes observed in the metabolomic profiles. For PD reduction, the decrease in putrescine concentration showed a moderate positive correlation ($r = 0.58$, $p = 0.004$), whereas for CAL, improvement was associated with an increase in glutathione concentration ($r = 0.62$, $p = 0.002$). These findings confirm concurrent changes in clinical and biochemical metrics over the course of the study.

5. Discussion

5.1 Metabolic Findings Analysis

The salivary metabolite changes observed after customized micronutrient therapy implicate biochemical pathways paralleling active inflammation and tissue repair in the periodontium. The reduction in the diamines putrescine and cadaverine indicates decreased microbial proteolytic activity and inflammatory burden in the periodontal microenvironment; these metabolites are characteristic of dysbiotic microbiomes and contribute to tissue destruction and oxidative stress. Conversely, the increase in antioxidant metabolites, particularly glutathione, reflects improved redox balance and cellular defense. These metabolomic changes are consistent with the nutritional pathways through which micronutrients influence oxidative stress, enzymatic reactions, and immune response — for example, vitamin C supports collagen synthesis and antioxidant activity, while zinc serves as an enzymatic cofactor in numerous processes. Together, these metabolic signatures point to a more balanced host–microbiome interaction that supports periodontal healing at the molecular level.

5.2 Healing and the Role of Micronutrients

Micronutrient therapy likely acts through several interconnected pathways, most centrally immune modulation and antioxidant defense. Periodontitis involves oxidative stress that drives tissue destruction and delays healing; supplementation with vitamin C and omega-3 fatty acids appears to enhance periodontal tissue resilience by neutralizing reactive oxygen species and supporting enzymatic antioxidant reactions. Micronutrients also shape immune response: vitamin D regulates cytokine levels and stimulates antimicrobial peptide production, influencing both innate and adaptive immunity, while zinc supports immune cell activity and helps control inflammation. Together, these effects reduce periodontal inflammation and support tissue healing. These results support a link between micronutrient supplementation and improved clinical outcomes in periodontitis, and the well-defined study population strengthens confidence that the observed effects reflect genuine treatment benefit rather than general population variability.

5.3 Clinical Relevance and Limitations

Combining personalized micronutrient therapy with salivary metabolomics could advance periodontics by enabling a shift from symptom-based management toward biomarker-guided treatment. From a practical standpoint, dietary modification and targeted supplementation are cost-effective, feasible additions to periodontal care. Nonetheless, this study has limitations. While the sample size was sufficient for this proof-of-principle study, it remains modest, and larger multicenter studies are needed to confirm these findings. The cost and technical expertise required for advanced metabolomic techniques such as LC-MS may limit their routine use in standard clinical settings. Future research should pursue larger longitudinal studies to better characterize the relationship between metabolome changes and clinical outcomes, and incorporate additional omics layers, such as genomics and microbiomics, to improve mechanistic understanding of disease processes and therapeutic response. Standardizing metabolomic testing procedures will also help translate research findings into clinical practice.

6. Conclusion

Tailored micronutrient therapy significantly alters the salivary metabolome and improves specific clinical parameters of periodontal disease in patients with chronic periodontitis. The concurrent decrease in pro-inflammatory metabolites and increase in antioxidant metabolites, together with their correlation with mucosal healing, support the study's central objective: establishing early evidence of a direct link between customized nutrition therapy and periodontal healing. These findings suggest personalized micronutrition may serve as a complementary technique in periodontal therapy, potentially contributing to improved metabolic status, enhanced tissue healing, and reduced inflammatory burden as part of a more integrated approach to periodontal care, where nutritional therapy becomes a routine adjunct to treatment. Future work should explore the integration of salivary metabolomics into preventive dentistry for early identification of periodontal risk, and the development of personalized micronutrient approaches as a standardized intervention. Larger, multi-omics studies will help build the evidence base for applying these approaches in everyday clinical dentistry.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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