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Original Scientific Paper

CHANGES IN SALIVARY PROTEOME WITH REGARD TO PAIN-RELATED PROTEINS FOLLOWING FIXED ORTHODONTIC APPLIANCE PLACEMENT

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SUMMARY – Orthodontic tooth movement relies on the application of force that drives bone resorption and formation. As saliva reflects these processes and harbors proteins of diagnostic and prognostic value, we studied these changes in patients with malocclusion. This study sampled the proteomes and evaluated the intensity of experienced pain related to the apparatus placement in ten male patients with malocclusion on day 0, 30 and 60 of orthodontic therapy. A prospective shotgun proteomic pilot study identified 947 proteins, and demonstrated a shift in the salivary proteome during orthodontic therapy. Gene enrichment analysis revealed hemostasis, but also platelet activation, signaling, aggregation and degranulation as prominent processes occurring 30 days post appliance placement, while proteins related to antimicrobial resistance were detected throughout the observed tooth movement period. Our research indicated an increased expression of proteins related to the immune and protective response to foreign bodies and pathogens, cellular and tissue injury, and biomechanical stimuli associated to bone remodeling. While a direct linkage between the alteration of the proteomic profile and the direction of painful perception was not identified, all results suggest a well-coordinated yet complex occurrence involving a multitude of biologically active signaling pathways and molecules.

Key words: *Saliva; Proteomics; Fixed orthodontic appliance; Pain perception*

Introduction

Orthodontics as a specialized branch of dentistry is dedicated to the examination, therapeutic intervention, and prophylaxis of malocclusion, teeth misalignment, and irregular bite patterns. Orthodontic tooth movement (OTM) denotes orchestrated application of controlled forces through orthodontic appliances to affect repositioning of teeth. This dynamic process involves targeted remodeling of the contiguous bone and supportive structures, ultimately facilitating attainment

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of the desired alignment for the dentition[1]. Orthodontic therapy, implemented through the use of fixed braces or removable devices, typically spans a duration ranging from months to years. Anchoring of teeth is accomplished through the utilization of metal braces affixed to a replaceable wire, pivotal in orchestrating three distinct movement phases, i.e., initial, lag, and postlag. The initial phase begins promptly following the application of force to the tooth, typically manifesting within one to two days of therapy commencement[2]. During this phase, discomfort reaches its peak approximately 24 hours post-treatment, gradually diminishing in intensity by the second or third day[3]. Subsequently, the lag phase ensues, characterized by minimal to negligible tooth movement. The culmination of the process is marked by the postlag phase during which the rate of tooth movement accelerates[4]. The majority of OTM occurs in the postlag phase as a direct result of bone remodeling due to mechanical pressure of the fixed orthodontic apparatus[5]. The postlag phase of movement lasts as long as the force is being applied to the teeth. This comprehensive approach to orthodontic therapy underscores the nuanced progression through these defined phases for optimal and enduring treatment outcomes. OTM triggers the release of a diverse array of specific molecules, a phenomenon integral to comprehending the intricate biological processes governing the remodeling of periodontal tissues in the course of orthodontic treatment. Various molecules, such as cytokines, growth factors, and enzymes, play pivotal roles in mediating the cellular and molecular events associated to tooth movement. Research on biomarkers in OTM has expanded to include analysis of saliva, as it offers a noninvasive and easily accessible medium for monitoring physiological changes[6]. Saliva has important protective roles in the process of feeding where it serves as a lubricant and contains several enzymes which are important in food digestion, and it has an important protective role of the oral cavity. Collection of saliva is cost-efficient, noninvasive and not stressful for the patient, making it a viable substitution for blood sampling[7]. However, the composition of saliva is very dynamic, reflecting its adaptability to internal and external influences in the oral environment. Salivary protein secretion is regulated by neurological mechanisms, and the amount of protein released is contingent upon the specific stimulus. Proteins released from the salivary glands undergo extensive enzyme modifications, underscoring the complexity of the salivary proteome[8]. This inter- and intra-individual variability in composition can in turn represent a major drawback in its clinical use[9]. Contributing factors include individual genetic influences on the saliva make up and production[10]. Physiological aspects related to age and gender, but also dietary habits, circadian rhythms, medication usage, (oral) health conditions, environmental elements, and collection methods also contribute to this variability[11-13]. Recognizing this inconsistency is crucial for interpreting salivary biomarkers, diagnosing oral and systemic conditions, and tailoring personalized healthcare strategies.

Although there is a significant overlap in salivary and plasma proteomes, saliva contains many unique proteins that are not present in peripheral blood. Therefore, the analysis of salivary proteomes holds promise for discovery of important modulators of OTM[14]. Our research provides an overview of the proteomic shift during the fixed orthodontic therapy in time and hints at the possibility of identifying salivary proteins which might precede pain during OTM.

Ethics

This research was approved by the Ethics Committee of the School of Dental Medicine, University of Zagreb (No. 05-PA-30-13-12/2022). Agreement forms were signed by the participants' parents or legal guardians. All procedures were performed in accordance with ethical standards of the institutional or regional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983[15].

Subjects and Methods

We conducted a prospective observational pilot study that included 10 underage study participants with diagnosed malocclusion. All patients were required to meet the following criteria: male gender, healthy, not undergoing any other therapy, between the age of 12 and 14 years, and with an indication for fixed orthodontic therapy. Exclusion criteria were local or systemic disease development during the follow-up period,

failure to keep follow-up appointments, and patients who willingly drop out from the study; however, no patients were excluded during this pilot study. Fixed orthodontic appliance consisted of self-ligating metal brackets glued to the teeth and a removable steel wire attached to the brackets.

Saliva samples were obtained at three different time points, i.e., day 0 (before the beginning of therapy, control group), day 30 (thirty days from the beginning of therapy, after first wire adjustment), and day 60 (sixty days from the beginning of the fixed orthodontic therapy, after second wire adjustment) (Fig. 1). Saliva samples were obtained from each patient and placed immediately at -20 °C and later stored at -80 °C. This paper aimed to follow the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[16].

Sample collection and storage

The participants provided saliva samples at previously determined time points. Participants refrained from eating or drinking at least 60 minutes before the appointment. Prior to spitting into a clean Petri dish, the participants 'collected' saliva in their mouths for at least 60 seconds. The process was repeated several times to accumulate approximately 1.5 mL of saliva *per* sample.

Measurement of pain intensity

Each patient held a 'pain diary' in which they stated the level of pain experienced for seven days after placement of the fixed orthodontic appliance and seven days after each orthodontic adjustment. Visual analog scale (VAS) was used to measure the pain level daily throughout the 7-day periods. VAS is a commonly used tracking tool for pain measurement in clinical studies using subjects' self-reports of pain. Pain levels from each time point were measured and marked on the scale from no pain to the worst possible pain.

Sample analysis

The collected saliva samples were centrifuged for 10 minutes at 14000 g to remove food residue, cellular debris and/or other aggregates, and stored at -80 °C until use. Samples from individual time points were pooled using 500 µL of saliva *per* study participant, and 250 µL of sample pool *per* time point were used

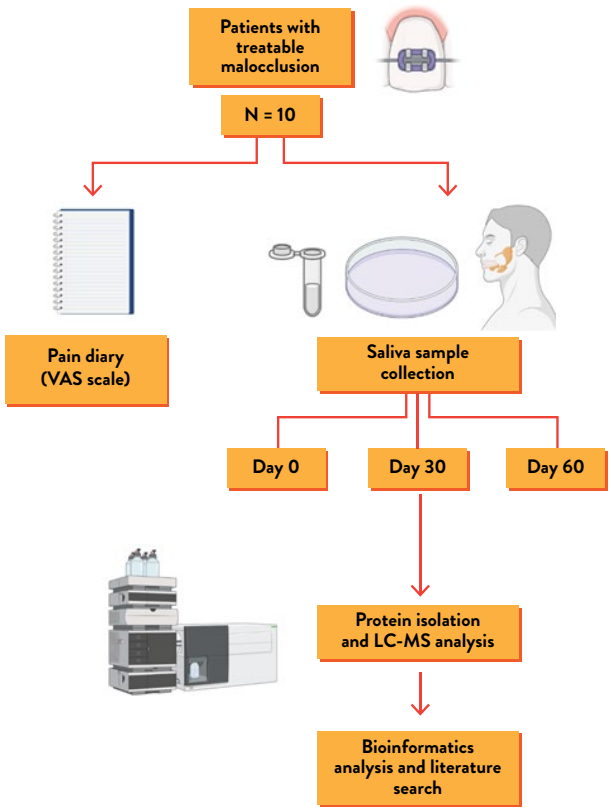

Fig. 1. Study outline. Ten patients with treatable malocclusion gave saliva samples at three different time points, i.e., day 0 (before the beginning of therapy; control group), day 30 (thirty days from the beginning of therapy), and day 60 (sixty days from starting the fixed orthodontic therapy). Each patient kept a 'pain diary' for the first seven days after the start of orthodontic therapy. Visual analog scale was used to assess the sensation of pain after each orthodontic adjustment. After protein isolation and liquid chromatography-mass spectrometry (LC-MS) analysis, the identified proteins were further analyzed.

for further analysis. Proteins were precipitated by adding 1 mL of ice cold acetone and incubated at -80 °C for 60 minutes. After centrifugation at 16000 *g* for 15 minutes, the supernatant was removed and the protein pellet air-dried for 30 minutes. The pellet was dissolved, and the containing proteins denatured in 8 M urea. Protein concentration was determined using the BioRad RC Protein Assay Kit II (Bio-Rad Laboratories, CA, USA), according to the manufacturer's instructions.

Samples containing 40 µg of protein were further processed in 10 kDa cut-off centrifugal filter units. Alkylation was performed in dark for 20 minutes using 55 mM iodoacetamide, and tryptic digestion overnight at 37 °C using 0.8 µg of trypsin (Worthington, TPCK treated). Digested peptides were eluted, acidified and then purified/concentrated using C18 micro-columns StageTips[17]. Peptides from individual sample pools were analyzed in technical duplicates utilizing a nanoLC EASY-nLC™ 1200 System (Thermo Fisher Scientific, Germering, Germany) in a 60-minute long gradient of acetonitrile (0-80%) in 0.1% formic acid on a 75 µm × 250 mm reversed-phase chromatography column. Mass spectrometry was performed on Thermo Scientific Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer (Thermo Fisher Scientific, Bremen, Germany). Full MS scans (m/z from 350 to 1800) were acquired by an Orbitrap analyzer at a resolution of 70,000, using internal 'lock mass' calibration. The top 12 ions were chosen for fragmentation (MS2), recorded at a resolution of 17,500 (Fig. 1).

Statistics

Experimental MS data were processed using the Thermo Scientific Proteome Discoverer software version 2.4. The protein lists obtained were further processed using gene enrichment analysis, which included analysis of relevant biological pathways. Gene enrichment analysis was performed using the FunRich 3.1.3 software. The analysis software used the protein ID as an input to identify the majority of protein isoforms in each group. Peptides that matched multiple isoforms were included in the analysis. The software determined significance of the results by calculating the p-values using the hypergeomic test and Bonferroni correction considering $p \leq 0.05$ as a significant value. The isolated proteins were then analyzed for biological processes and pathways.

Results

A total of 947 human proteins were identified in the saliva samples which were collected on day 0 (control), day 30 and day 60 post orthodontic appliance

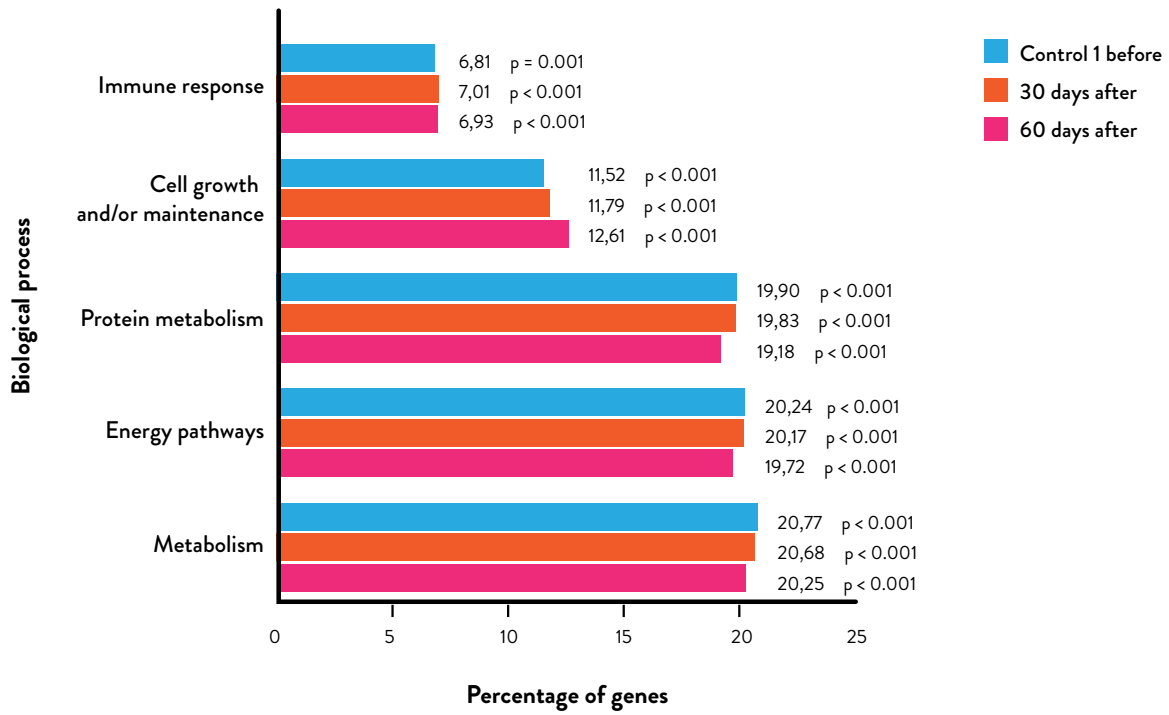

Fig. 2. Relevant biological processes significantly associated to the isolated proteins in each study group.

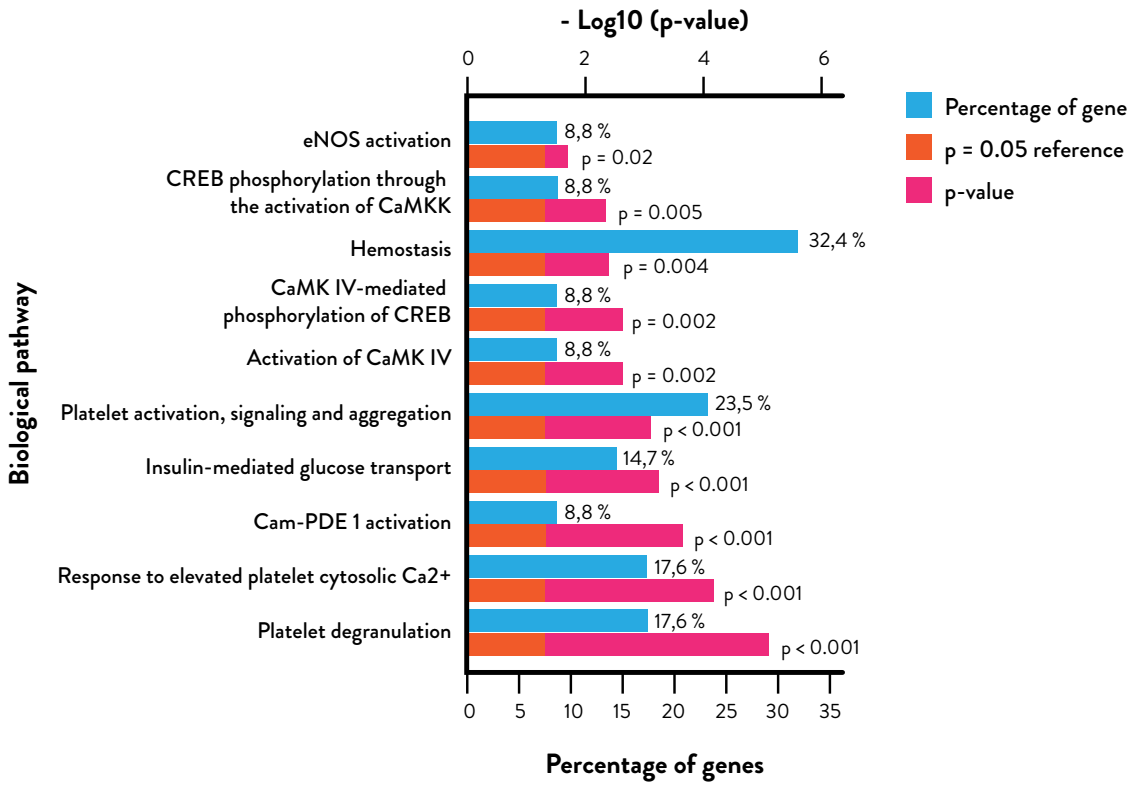

Fig. 3. Percentage of genes shown in certain biological pathways after 30 days of treatment.

placement. We identified several significant pathways related to immune response, cell growth, and maintenance, metabolism, and energy pathways (Fig. 2).

Analysis of relevant biological processes showed a substantial proportion of proteins involved in modulating the immune response, cell growth/maintenance and metabolism, among others (Fig. 2). Gene enrichment analysis of biological pathways revealed that among other significant pathways, hemostasis, platelet activation, signaling, aggregation and degranulation were associated to the larger proportions of identified proteins at 30 days post orthodontic appliance placement (Fig. 3). Hemostasis showed the highest ratio of associated proteins (32.4%) among other pathways.

After placement of the fixed orthodontic appliance, several proteins were found to be increased in their expression intensities. Compared to control samples (day 0), thirty days after placement of the orthodontic device we recorded an increased expression of calponin-2 (1.9-fold increase), carbonic anhydrase isozyme VI (1.40-fold increase), cyclic dependent kinase CDK11 (1.7-fold increase), cystatin SN (1.80-fold increase), S100A9 (2.2-fold increase) and statherin (not expressed in control samples). Sixty days after placement of the orthodontic device as compared to control samples, we saw increased expression levels of S100A16 (1.8-fold increase) and zymogen granule protein 16 homolog B (ZG16B) (1.5-fold increase). Finally, BPI fold-containing family B member 1 (BPIFB1) was found to have an increased expression as compared to controls throughout the measured course of orthodontic treatment (2.6-fold and 1.8-fold increase on days 30 and 60, respectively) and statherin was expressed exclusively after 30 days of treatment.

Pain levels were visibly higher on the first few days after orthodontic appliance placement or adjustment and then gradually decreased (Fig. 4). The highest levels of pain were recorded on day 1 (first day of the orthodontic treatment). Clear links between the isolated proteins and pain response could not be established.

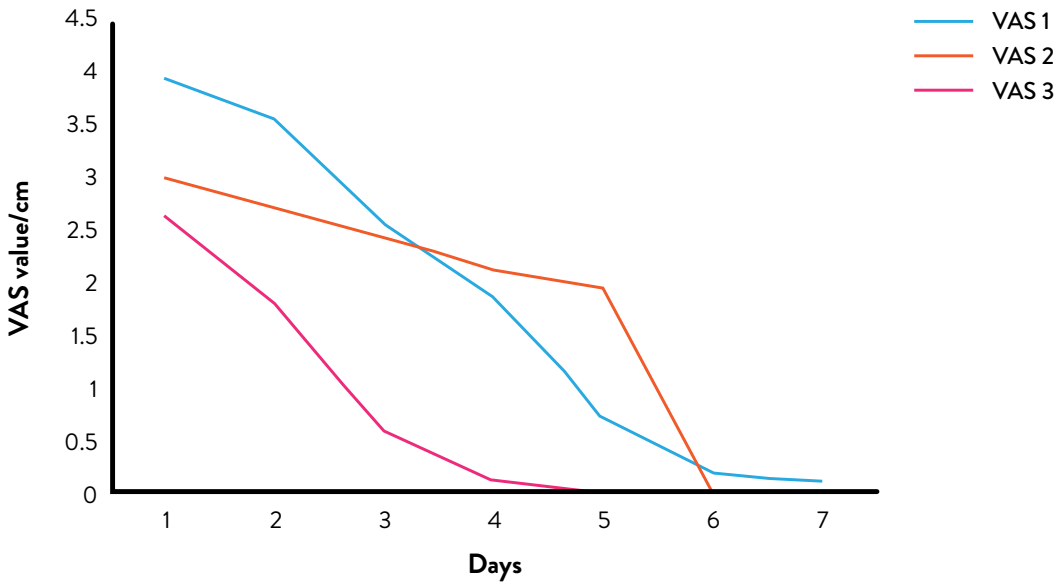

Fig. 4. Median pain intensity measured by visual analog scale (VAS) at three time points: VAS 1 line (day 1-6 following orthodontic appliance placement); VAS 2 (day 31-37 following orthodontic appliance adjustment); and VAS 3 (day 60-66 following orthodontic appliance adjustment).

Discussion

We conducted a prospective shotgun proteomic pilot study in order to observe a shift in the salivary proteome at discrete time points during orthodontic therapy. Among the proteins with modulated expression levels resulting from placement of the orthodontic appliance, proteins related to antimicrobial defense were detected. As the oral cavity is home to a large and diverse microbiome, a range of antimicrobial peptides (AMPs) exist in the oral mucosa that modulate innate immunity and influence microbial colonization[18]. Increased levels of an AMP member, BPIFB1, were identified 30 and 60 days after placement of the fixed orthodontic device. As its functions are related to innate immunity, binding and modulating cellular responses to lipopolysaccharides, its elevated expression could be related to its antimicrobial function[19]. Increased levels of calponin-2 were noticed after device placement, which could be related to developing and healing bone tissues. Calponin-2 plays a vital role in the regulation of osteogenic differentiation in mesenchymal cells, and its increase may be an indicator of biomechanical advancements during orthodontic therapy[20]. Identified isozyme VI, a well-known secreted form of salivary carbonic anhydrase (CA VI) was previously confirmed in saliva, tears, and milk of mammals, as well as enamel organs of rodent teeth, although its physiological roles remain largely unknown[21,22]. A rise in salivary CA VI levels was observed 30 days following placement of a fixed orthodontic appliance, hinting its role in modulating the biomechanical and physiological changes that occurred during adaptation to the biomechanical forces. We also identified increased expression levels of cyclin-dependent kinase 11 (CDK11) in the saliva post device placement. Its role is in the regulation of apoptotic signaling, while its inhibition has been shown to lead to cancer cell death and apoptosis[23]. The cystatin superfamily of potent cysteine peptidase inhibitors has been identified in low concentrations in human and rat saliva. Nonetheless, we detected elevated levels of cystatin SN 30 thirty days following placement of a fixed orthodontic appliance. Its function is still unknown, but might be related to the regulation of salivary gland development, immunomodulation, and protection from ingested food[24]. Protein family members S100-S100A8 and S100A9 stimulate

leukocyte recruitment and cytokine secretion and are expressed on monocytes, macrophages and neutrophils. S100 proteins are known to play a critical role in cell proliferation, differentiation, migration, and apoptosis, and are associated to various brain pathologies[25]. Additionally, their increase in saliva was previously associated to periodontitis[26]. In this study, elevated levels of S100A9 protein were observed 30 days after device placement, and of S100A16, 30 and 60 days after orthodontic device placement. A significant increase was observed in ZG16B expression 60 days after therapy placement. In a study that used whole saliva to search for salivary biomarkers of oral chronic graft-*versus*-host disease, clear reduction in ZG16B was observed[27]. Increased levels of statherin, a protein that inhibits the nucleation and growth of calcium phosphate minerals was observed 30 days after therapy placement. As it is related to the maintenance of tooth integrity, it could have a protective role in responding to the biomechanical force applied[28]. Proteins related to pathways modulating the immune response, cell growth and maintenance, protein metabolism, energy pathways, and metabolism were upregulated in the analyzed samples when compared to day 0 controls. However, no significant difference was observed between the examined groups in relation to the biological processes at the three different time points. This could be due to the variability of saliva and the sampling time that did not cover the first 24 h after placement or adjustment of the fixed appliance and therefore, we consider it as a limitation of this study. The presence of proteins that could be directly linked to pain was not confirmed, and the reason may be adaptation of the body to therapy and sampling time that did not cover the first period after placement of the fixed orthodontic appliance. However, our results are in agreement with previous research utilizing VAS analyses, which indicate that the acute painful stimulus is strongest in the first few days after placement of a fixed orthodontic appliance[29].

Our study had several limitations. The restricted size of our sample may have inadequately represented the entirety of the salivary OTM proteome, particularly those associated with pain perception. Consequently, our identification efforts may have been biased toward prominent regulators, potentially overlooking less conspicuous yet pivotal modulators. Another limitation stems from the analysis of pooled samples and absence of the assessment of interindividual variability. Specifically, saliva samples collected from boys undergoing treatment with a fixed orthodontic appliance, along with those from untreated control subjects, were aggregated based on temporal parameters. This pooling methodology precluded characterization of interindividual variability within the proteomic signals.

In conclusion, this prospective shotgun proteomic pilot study observed shifts in the salivary proteome during orthodontic therapy. Despite its inherent analytical challenges, saliva as a biological fluid revealed dynamic proteome changes within two months of orthodontic appliance placement. The increased presence of proteins associated to antimicrobial defense mechanisms, immune response, protection against foreign bodies, cellular and tissue injury, and biomechanical stimuli sheds new light on how therapeutic oral devices can impact saliva composition over time. A direct link with painful sensation was not demonstrated, although it is possibly integrated through all the aforementioned processes, which could not be observed separately in this experimental approach.

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Sažetak

PROMJENE U PROTEOMU SLINE U ODNOSU NA PROTEINE POVEZANE S BOLI NAKON POSTAVLJANJA FIKSNOG ORTODONTSKOG APARATA

I. Jelić, R. Novak, S. Hrkač, G. Salai, M. Močibob i *L. Grgurević*

Ortodontski pomak zuba oslanja se na primjenu sile pomoću ortodontskog aparata, koja zatim potiče resorpciju i stvaranje kosti. Proteinski sastav sline odražava ove procese te može sadržavati potencijalne dijagnostičke i prognostičke biljege pa je cilj istraživanja bio ispitati proteom sline u pacijenata s malokluzijom. Uzorkovan je proteom sline pacijenata te procijenjen intenzitet doživljene boli povezane s postavljanjem aparata u deset muških pacijenata s malokluzijom 0., 30. i 60. dana od početka primjene ortodontske terapije. Prospektivnom proteomskom studijom identificirano je 947 proteina koji odražavaju promjene u proteomu sline tijekom ortodontske terapije. Analiza obogaćenja gena otkrila je hemostazu, ali i aktivaciju, signalizaciju, agregaciju i degranulaciju trombocita kao važne procese koji se događaju 30 dana nakon postavljanja ortodontskog aparata, dok su proteini povezani s antimikrobnom rezistencijom otkriveni tijekom cijelog promatranog razdoblja pomicanja zuba. Istraživanje ukazuje na povećanu ekspresiju proteina povezanih s imunosnim i zaštitnim odgovorom na strana tijela i patogene, staničnu i tkivnu ozljedu te biomehaničke podražaje povezane s procesom koštane pregradnje. Iako izravna veza između promjene proteomskog profila i percepcije boli nije utvrđena, rezultati ukazuju na dobro usklađen, ali složen proces koji uključuje mnogo biološki aktivnih signalnih putova i molekula.

Ključne riječi: *Slina; Proteomika; Fiksni ortodontski aparat; Percepcija boli*