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REVIEW

The Role of Inflammatory Biomarkers (IL-1, IL-6, TNF-α, and Alpha-Amylase) in Saliva on Post-Odontectomy Swelling: A Rapid Review

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Background: Odontectomy is a commonly performed surgical procedure in the oral cavity and has several possible postoperative complications, including swelling. In addition to clinical examination, post-odontectomy swelling can be identified by utilizing saliva samples to analyze inflammatory biomarkers. The purpose of this study was to determine the role of inflammatory biomarkers IL-1, IL-6, TNF-α, and alpha-amylase in saliva on post-odontectomy swelling.

Methods: A rapid literature review of clinical studies was conducted using the PRISMA framework. Article searches were performed on six databases (PubMed, ScienceDirect, SpringerLink, Cochrane Library, and EBSCOhost) using boolean operators and hand searching on Google Scholar.

Results: Ten articles met the inclusion criteria. A risk of bias assessment was conducted using the JBI critical appraisal tools. Seven articles analyzed alpha-amylase, two articles analyzed TNF-α, and one article analyzed IL-1, IL-6, and TNF-α simultaneously to see the swelling or inflammation that occurs post-odontectomy. These four biomarkers were examined before, immediately after, or up to several days after the procedure. Significant elevations in biomarkers including IL-1, IL-6, TNF-a, and alpha-amylase are seen in the majority of articles. Post-procedure alpha-amylase elevation was observed along with swelling, pain, and fear associated with the odontectomy procedure. Increases in IL-1, IL-6, and TNF-α were observed due to tissue manipulation during the procedure that initiated the production of these proinflammatory cytokines.

Conclusion: Inflammatory biomarkers IL-1, IL-6, TNF-α, and alpha-amylase in saliva play a role in post-odontectomy swelling, as their levels increase the intensity of swelling or inflammation also tends to rise. These biomarkers contribute to swelling through mechanisms involving immune cell recruitment, increased vascular permeability, and acute responses to pain and stress. Although it is constrained by the lack of relevant research, this review provides recommendations for further research into the most pertinent salivary biomarkers for identifying post-odontectomy swelling.

Keywords: inflammatory biomarkers, saliva, odontectomy, swelling

Introduction

In the oral cavity, saliva has multiple roles including lubrication, bolus formation, antibacterial properties, and wound healing.[1,2] Saliva is secreted by three pairs of major salivary glands, namely parotid glands, submandibular glands, and sublingual glands, as well as various minor salivary glands which contain many biomarkers. Salivary biomarkers can vary depending on a person's health status, especially because systemic changes, diseases, or inflammation can also affect salivary biomarker concentration.[3–6] Therefore, saliva is one of the preferred non-invasive specimens for diagnosis due to its ease of use and safety. The contents in saliva that are often used as biomarkers include proteins, DNA, mRNA, inorganic ions, and metabolites.[4,5] Several inflammatory mediators are also used as biomarkers to detect pathological conditions or therapeutic responses.[4]

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Inflammatory mediators are upregulated in response to harmful stimuli, such as infection or tissue injury, as part of the body's immune defense mechanism. Cytokines, a type of inflammatory mediator, are responsible for the initial recognition of inflammatory stimuli and for regulating the initiation, maintenance, and resolution of inflammation that is triggered through tissue damage or infection.[7] IL-1, IL-6, and TNF-α are among the most often used cytokines as oral cavity inflammation biomarkers because they are crucial in triggering other inflammatory chain components.[8] Apart from cytokines, another common inflammatory biomarker in the oral cavity is alpha-amylase, an enzyme component found in saliva whose synthesis is controlled by the autonomic nervous system.[8–10]

One of the common inflammatory responses that occurs in the oral cavity is post-odontectomy swelling. Odontectomy is a common surgical procedure in the oral cavity that involves tooth removal through tissue incision or flap elevation, and often accompanied by alveolar bone reduction. It is typically indicated for impacted or difficult-to-extract teeth.[11–13] This procedure has several postoperative complications that may occur with an incidence range of 2.6% to 30.9%.[11,14] The most common complications include pain, swelling, trismus, ecchymosis, hematoma, and infection.[11]

Swelling is a frequent clinical manifestation of inflammation following odontectomy, caused by tissue injury during the procedure and factors associated with the release of inflammatory mediators.[14,15] According to Nurfuadah et al around 54% of patients experience post-odontectomy swelling, with swelling being the most common consequence noted on the first day after the precodure.[16] To assess swelling, clinicians typically perform a craniometric clinical examination using specific anatomical landmarks on the extraoral surface to measure changes in facial dimensions.[17] This examination is performed by manually measuring the distance from the tragus to the pogonion, the tragus to the corner of the mouth, and the lateral angle of the cantus to the mandibular angle in millimeters (mm).[17–20] This examination should be conducted prior to the procedure and repeated two to seven days postoperatively to evaluate the presence of post-odontectomy swelling.[20] Intraoral examination methods, such as inspection, palpation, and measurement of intraoral swelling size, may also be used to evaluate soft tissue inflammation.[21] However, post-odontectomy swelling is most commonly assessed using craniometric clinical measurement.[17] Craniometric clinical measurement is more sensitive for assessing extraoral swelling after mandibular odontectomies, as extraoral swelling is less frequently observed following maxillary odontectomies. This is due to the maxilla's thinner bone and greater vascularity, which facilitate easier extractions and faster healing, whereas the mandible's denser bone and lower vascularity lead to more trauma and noticeable swelling.[22] Furthermore, because this method is insufficiently sensitive, only swelling visible to the operator's eyes can be considered swelling, raising the chance of unrecognized swelling.[23] In addition to clinical examination, identifying the presence of inflammation in the oral cavity can be done by utilizing saliva samples.[15,24] The advantages of this saliva examination include a simple and easy-to-perform sampling procedure, as well as more comprehensive results for describing the inflammation present.[4–6,23]

Several studies have associated the inflammatory biomarkers IL-1, IL-6, TNF-α, and alpha-amylase in saliva with post-odontectomy swelling. Gutiérrez-Corrales et al investigated the association between alpha-amylase levels and post-odontectomy swelling, while Al Shehhi et al examined the inflammatory response of cytokines IL-1, IL-6, and TNF-α during surgical tooth extraction.[24,25] Although an increasing number of studies have explored inflammatory biomarkers in saliva, no review to date has specifically synthesized the role of IL-1, IL-6, TNF-α, and alpha-amylase in relation to post-odontectomy swelling. Furthermore, the clinical assessment commonly used to evaluate swelling, such as craniometric clinical measurement has limited sensitivity and is inherently subjective, which increases the risk of inaccurate or undetected swelling. This emphasizes the need for an alternate approach that is more sensitive and objective. Thus, this review is intended to fill this knowledge gap by collecting the current scientific literature focused on salivary inflammatory biomarkers, in particular IL-1, IL-6, TNF-α, and alpha-amylase in post-odontectomy swelling with attention to their expression pre- and post-operatively, as well as how they might advance possible models for improved diagnostic approaches.

Materials and Methods

This research was conducted as a rapid review, a type of evidence synthesis that uses simplified and accelerated methods to summarize findings on a particular topic. By streamlining certain steps of the systematic review process, rapid reviews aim to provide timely and resource-efficient evidence for quick decision-making.[26]

Research Questions

Identification of research questions was carried out using the PICO framework which includes:

- Population (P): patients undergoing odontectomy procedures to extract impacted third molar teeth
- Intervention (I): examination using saliva samples to identify the value of inflammatory biomarkers (IL-1, IL-6, TNF-α, and alpha-amylase) in saliva post-odontectomy
- Comparison (C): examination of the value of inflammatory biomarkers (IL-1, IL-6, TNF-α, and alpha-amylase) in saliva before the odontectomy procedure
- Outcome (O): the level of inflammation or swelling after odontectomy.

Search Strategy and Eligibility Criteria

Article searches were conducted on six databases, including PubMed, ScienceDirect, Scopus, SpringerLink, Cochrane Library, and EBSCOhost as well as hand searching on Google Scholar. The search was conducted using boolean operators by combining the operators "OR" or "AND". The keywords used in this study were ("odontectomy" OR "extraction impacted third molar" OR "tooth extraction") AND ("salivary biomarkers" OR "IL-1" OR "IL-6" OR "TNF-α" OR "alpha-amylase") AND (inflammation OR swelling OR edema).

The inclusion criteria for this study were articles that discussed the relevance of the role of inflammatory biomarkers (IL-1, IL-6, TNF-α, and alpha-amylase) in saliva to swelling post-odontectomy, articles with research types such as randomized controlled trial, quasi-experimental, cohort, case-control, and cross-sectional, articles published in English or Indonesian in the last 10 years and available in full-text or open access. The exclusion criteria were articles that were review studies, conceptual or narrative articles without empirical data, and articles not published in English or Indonesian more than 10 years ago.

Data Collection and Data Items

The literature search and analysis were conducted from October 2024 to January 2025 through a series of stages: identification through database searches, removal of duplicates, screening based on titles and abstracts, full-text assessment for eligibility according to the inclusion criteria, and evaluation of the risk of bias. Literature screening was carried out with the PRISMA instrument and the included articles will be presented in the form of two tables. The first table presents the study characteristics, including the author's name, year of publication, country, article title, research methods, and research results. The second table presents the characteristics of inflammatory biomarkers in saliva, including the author (year of publication), type of biomarker, saliva sampling or analysis method, clinical method for identifying swelling, monitoring interval, and interpretation of biomarker values.

Results

Study Selection

The initial search was conducted using six databases and predetermined keywords to obtain a total of 398 articles, including 47 articles identified through PubMed, 187 articles identified through ScienceDirect, 46 articles identified through Scopus, 72 articles identified through SpringerLink, 9 articles identified through Cochrane Library, 32 articles identified through EBSCOhost, and 5 articles identified through hand searching on Google Scholar. Articles were screened for duplication using Mendeley Reference Manager, and a total of 341 articles were collected. The next step involved screening based on the relevance of the article's title and abstract, resulting in 24 articles being obtained. Full-text reading was then carried out and 10 articles were obtained that met all eligibility criteria for review (Figure 1).

Risk of Bias Assessment

Risk of bias assessment was conducted using the Joanna Briggs Institute (JBI) critical appraisal tools[28–30] by answering several questions with yes (Y), no (N), unclear (UC), or not applicable (N/A) based on each research method. This risk of

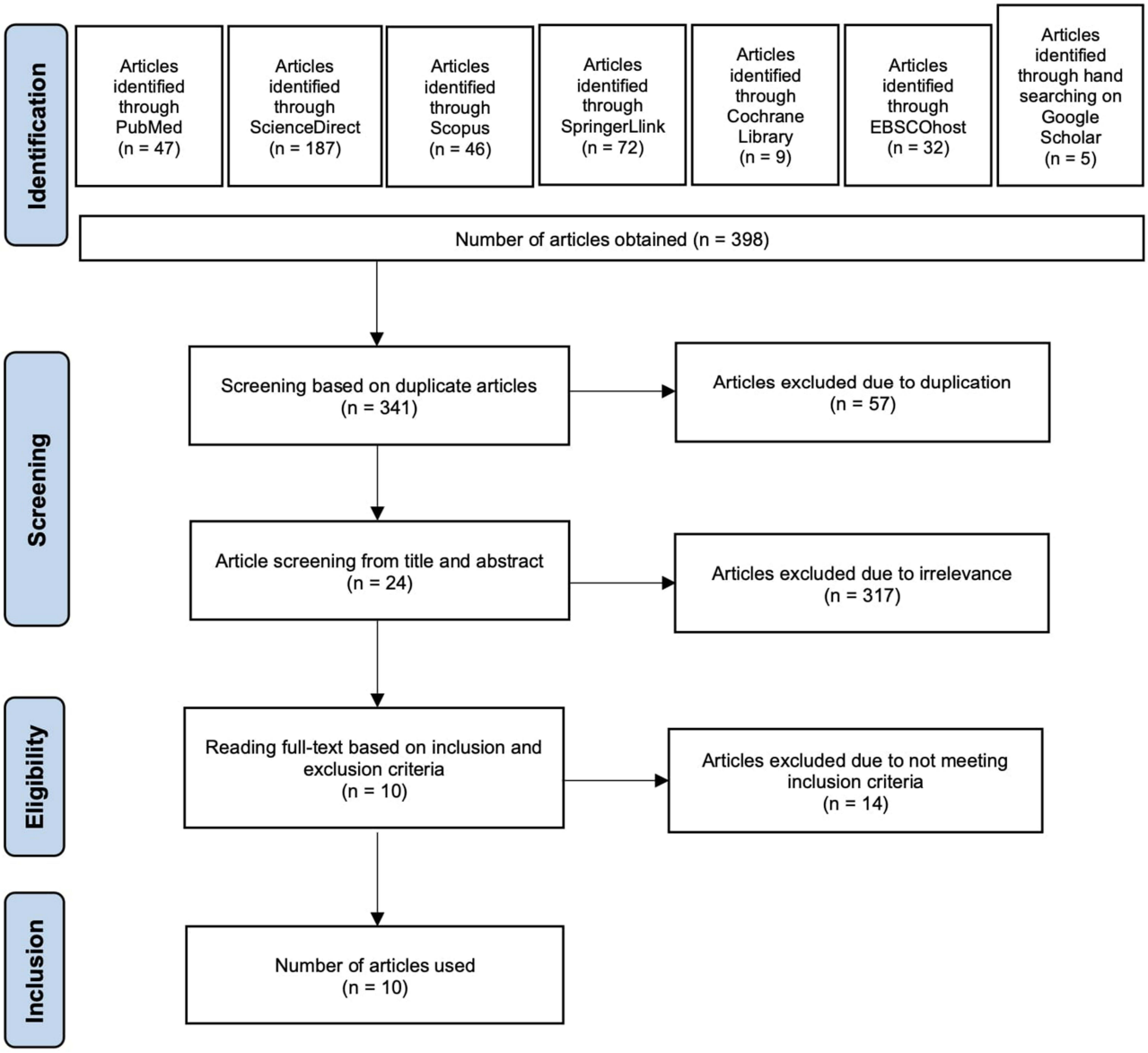

Figure 1 Article Selection and Screening Process through PRISMA. PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.[27]

Table 1 JBI Critical Appraisal Tool for Randomized Controlled Trials

Article Author	Domain and Question Items													% Yes	Risk
	Selection and Allocation		Administration of Intervention				Assessment, Detection, and Measurement of the Outcome			Participant Retention	Statistical Conclusion Validity				
	1	2	3	4	5	6	7	8	9	10	11	12	13		
Ruth et al[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Yusa et al[32]	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	92.3%	Low

Table 2 JBI Critical Appraisal Tool for Quasi-Experimental Studies

Article Author	Domain and Question Items									% Yes	Risk
	Temporal Precedence	Selection and Allocation	Confounding Factors	Administration of Intervention	Assessment, Detection and Measurement of the Outcome			Participant Retention	Statistical Conclusion Validity		
	1	2	3	4	5	6	7	8	9		
Sulfiana et al[33]	Y	Y	Y	Y	Y	Y	UC	Y	Y	88.9%	Low
Wulansari et al[34]	Y	Y	Y	Y	Y	Y	UC	Y	Y	88.9%	Low

Table 3 JBI Critical Appraisal Tool for Cohort Studies

Article Author	Question Items											% Yes	Risk
	1	2	3	4	5	6	7	8	9	10	11		
Gutiérrez-Corrales et al[24]	N/A	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	81.8%	Low
Muhajir et al[15]	Y	Y	UC	Y	UC	Y	Y	Y	Y	N/A	Y	72.7%	Low
Al Shehhi et al[25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	90.9%	Low
Surin et al[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	90.9%	Low
Chandini et al[36]	N/A	Y	Y	Y	Y	Y	Y	N	Y	N/A	Y	72.7%	Low
Jumaah & Al-Adili[37]	Y	Y	Y	Y	UC	Y	Y	Y	Y	N/A	Y	81.8%	Low

Notes: The risk of bias was categorized as high if the study obtained up to 49% "yes" responses, moderate if it ranged from 50% to 69%, and low if it exceeded 70%.

bias assessment is presented in (Table 1) for articles with randomized controlled trials research methods, (Table 2) for articles with quasi-experimental research methods, and (Table 3) for articles with cohort research methods. The risk of bias assessment stated that all ten articles had a low risk of bias and were eligible for inclusion in this review.

Table 4 Study Characteristics

No	Author Name	Year of Publication	Country	Article Title	Research Methods	Research Result
1.	A. Gutiérrez-Corrales, E. Campano-Cuevas, G. Castillo-Dalí, M.-Á. Serrera-Figallo, D. Torres-Lagares, J.-L. Gutiérrez-Pérez.[24]	2017	Spain	Relationship between salivary biomarkers and postoperative swelling after the extraction of impacted lower third molars	Prospective-cohort study	Alpha-amylase concentration were significantly correlated with the inflammatory process that occurred post-odontectomy, particularly in samples taken 2 hours and 7 days post-procedure. These biomarker changes are suggestive of the initial inflammatory response of extraction, having reached peak levels at 2 hours, suggesting activation of the immune response early in the extraction process.
						Alpha amylase concentration was relevant after odontectomy (P<0.05).

(*Continued*)

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Table 4 (Continued).

No	Author Name	Year of Publication	Country	Article Title	Research Methods	Research Result
2.	Idawati Muhajir, Harmas Yazid Yusuf, Lucky Riawan.[15]	2018	Indonesia	Correlation between swelling post odontectomy in lower third molar with the increase of concentration alpha amylase saliva	Prospective-cohort study	Salivary alpha-amylase concentration was significantly correlated with swelling post-odontectomy, as identified through facial dimension measurements in Class IIa, IIb, and IIc impactions ($P < 0.05$). The findings suggests that the inflammatory reaction will accelerate the increase in alpha-amylase concentration in saliva while also increasing salivary flow velocity.
3.	Yousuf Ibrahim, Al Shehhi, Noha M. Elemam Mohammed Amjed Alsaegh.[25]	2024	Uni Emirat Arab (UEA)	The response of salivary proinflammatory biomarkers to tooth extraction in individuals with type II diabetes mellitus	Prospective-cohort study	In the DM group, TNF-α concentration decreased 2 hours after extraction and increased again after 2 days, whereas in the non-DM group, it increased after 2 hours and decreased after 2 days. This study demonstrated that TNF-α is a contributor to swelling following extraction as it promotes inflammation, angiogenesis, and activation of immune cells needed for wound healing. Reduced TNF-α concentration may lead to suppressed inflammatory and healing responses, which may lead to prolonged resolution of swelling, particularly in type II diabetes.
						IL-6 concentration increased 2 hours after extraction in both groups. On the second day, it continued to increase in the DM group, while it decreased in the non-DM group. This study indicates that IL-6 regulates both inflammation and tissue proliferation following extraction, making it essential for timely wound healing; impairment in its signaling pathway may result in delayed healing.
						IL-1β concentrations decreased in both groups 2 hours post-extraction and increased on the second day post-extraction. This study indicates that IL-1β plays a role in the early inflammatory response of extraction wounds; however, its persistent elevation, as observed in chronic diabetic wounds, may impair healing.
4.	Melisa Ruth, Cahya Y. Hasan, Rahardjo, Rustamadji.[31]	2020	Indonesia	Effects of 15 mg meloxicam administered before odontectomy on pain, facial edema, trismus, and expressions of TNF-α following odontectomy of impacted mandibular third molar	Randomized controlled trial	The group given meloxicam showed less swelling, pain, and lower TNF-α concentrations than the placebo group (p=0.000).
						Swelling and pain increased on the first day and decreased by the third day after odontectomy.

(*Continued*)

Table 4 (Continued).

No	Author Name	Year of Publication	Country	Article Title	Research Methods	Research Result
						The concentration of TNF-α in saliva is related to the intensity of inflammation that occurs. This study shows that TNF-α plays a key role in post-extraction inflammation, with higher levels strongly associated with increased pain and moderately with facial edema, which in turn contributes to reduced mouth opening.
5.	Sulfiana, Harmas Y., Yusuf, Lucky Riawan.[33]	2021	Indonesia	Efficacy of natrium diclofenac gels application after odontectomy of lower third molar by assessment of swelling based on the level of alpha amylase and imunoglobulin-g: Research	Quasi-experimental study	There was a difference in swelling between the groups given sodium diclofenac gels and those not. ($p<0.05$).
						Alpha amylase concentrations changed along with swelling identified through facial dimension measurements. ($p<0.05$)
						An increase in alpha-amylase concentration was observed 2 hours post-procedure, peaking on day three and decreasing again by day seven.
6.	Harpindo Yusa, Cahya Yustisia Hasan, Bambang Dwirahardjo.[32]	2022	Indonesia	Effect of pre-operative 40 mg oral methylprednisolone on post-odontectomy facial swelling, intraoral redness, pain and level of TNF-α	Randomized controlled trial	The group given methylprednisolone experienced less swelling, pain, intraoral redness, and lower TNF-α concentrations than the placebo group ($p=0.000$).
						The decrease in TNF-α concentration in saliva showed a correlation with a decrease in swelling, pain, and intraoral redness ($p<0.05$). This study demonstrates that higher TNF-α concentration is associated with increased facial swelling, while greater intraoral redness correlates with higher pain scores.
7.	Wanvipa Surin, Piyanart Chatiketu, Nuntouchaporn Hutachok, Somdet Srichairatanakool.[35]	2022	Thailand	Pain intensity and salivary α-amylase activity in patients following mandibular third molar surgery	Prospective-cohort study	Pain identified using a visual analog scale (VAS) was significantly correlated with salivary alpha-amylase concentration ($p < 0.05$). This study demonstrates that tooth extraction triggers pain, which leads to increased alpha-amylase activity. This highlights its role as a biomarker of acute stress and pain response, with levels decreasing as the pain diminishes.

(*Continued*)

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Table 4 (Continued).

No	Author Name	Year of Publication	Country	Article Title	Research Methods	Research Result
8.	Dr. R.C.P Vijaya Chandini, Dr. Shayan Ghosh, Dr. Shubham Sharma, Dr. Akanksha Kumari, Dr. Vidhi Rathi, Dr. Pallavi Srivastava.[36]	2022	India	Correlation between salivary amylase a biomarker and postoperative pain after third molar surgery	Prospective-cohort study	Patient-reported pain and salivary alpha-amylase concentrations were higher before the procedure than after odontectomy. These findings suggest that changes in salivary alpha-amylase concentrations can reflect the patient's pain level before and after odontectomy.
						Alpha-amylase concentration did not increase after odontectomy.
9.	Falah Hasan Jumaah, Sahar Shakir Al-Adili.[37]	2022	Iraq	Evaluation of salivary alpha-amylase level in patients undergoing surgical extraction of impacted lower wisdom teeth	Prospective-cohort study	The concentration of alpha-amylase in saliva increased 48 hours after odontectomy but was not significant.
10.	Daisy Wulansari, Jenadi Binarto, Indra Hadikrishna, Endang Syamsudin.[34]	2018	Indonesia	The influence of relaxation music therapy with binaural beat effect on salivary alpha amylase enzyme as an indicator of dental anxiety in patient who will undergo surgical odontectomy	Quasi-experimental study	The concentration of alpha-amylase in saliva decreased significantly in the group given the intervention to reduce dental anxiety ($p<0.05$). This study shows that dental anxiety activates the autonomic nervous system, leading to increased salivary alpha-amylase levels.

Table 5 Characteristics of Inflammatory Biomarkers in Saliva

No	Author (Year of Publication)	Types of Inflammatory Biomarkers in Saliva	Saliva Sampling or Analysis Methods	Clinical Identification Methods of Swelling	Monitoring Interval	Interpretation of Biomarker Values
1.	Gutiérrez-Corrales et al, (2017)[24]	Alpha-amylase, IgA, total protein	Passive saliva collection using auto aspiration pipette tip. Total protein was analyzed using coomassie plus (bradford) assay, alpha-amylase was analyzed using kinetic method with amylase assay, IgA was analyzed using ELISA.	n/a	Before, immediately after, 2 hours after, and 7 days after odontectomy.	There was an increase in alpha-amylase concentration 2 hours post-procedure and a decrease 7 days post-odontectomy.
2.	Muhajir et al, (2018)[15]	Alpha-amylase	Cocoro meter placed under the tongue.	Measure the distance between the tragus to the corner of the mouth, tragus to pogonion, and lateral canthus to the angle of the mandible using 4.0 silk yarn.	Swelling was seen before, 1 day after, 3 days, and 7 days after odontectomy.	There was an increase in alpha-amylase concentration at 2 hours post-procedure, reaching a peak at 3 days post-procedure and decreasing again at 7 days post-odontectomy.
					Alpha amylase was seen before, 2 hours after, 3 days and 7 days after odontectomy.	

(*Continued*)

Table 5 (Continued).

No	Author (Year of Publication)	Types of Inflammatory Biomarkers in Saliva	Saliva Sampling or Analysis Methods	Clinical Identification Methods of Swelling	Monitoring Interval	Interpretation of Biomarker Values
3.	Al Shehhi et al, (2024)[25]	TNF-α, IL-6, IL-1β, IFN-γ	Spitting with luminex multiplex assay analysis.	n/a	Before the procedure, 2 hours after, and 2 days after extraction.	There was a decrease in TNF-α 2 hours after extraction in the DM group and an increase 2 days after extraction.
						There was an increase in TNF-α 2 hours after extraction in the non-DM group and a decrease 2 days after extraction.
						There was an increase in IL-6 2 hours after extraction in the DM group and continued to increase 2 days after extraction.
						There was an increase in IL-6 2 hours after extraction in the non-DM group and a decrease 2 days after extraction.
						IL-1β decreased in both groups 2 hours post-extraction and increased on the second day post-extraction.
4.	Ruth et al, (2020)[31]	TNF-α	Spitting with ELISA analysis.	Measure three facial lines and average them, namely the distance from the tragus to the pogonion, the tragus to the corner of the mouth, and the lateral angle of the canthus to the angle of the mandible with a measuring tape.	Before the procedure, 1 day, and 3 days after odontectomy.	TNF-α concentrations increased on the first day after odontectomy and decreased on the 3rd day after odontectomy.
5.	Sulfiana et al, (2021)[33]	Alpha-amylase, IgG	n/a	Measure the distance between the tragus to the corner of the mouth, tragus to the mental, and lateral canthus to the angle of the mandible.	Before the procedure, 2 hours after, 3 days, and 7 days after odontectomy.	There was an increase in alpha-amylase concentration at 2 hours post-procedure, peaking on day 3, and decreasing again on day 7.
6.	Yusa et al, (2022)[32]	TNF-α	Spitting with ELISA analysis.	Measure three facial lines and average them, namely the distance from the tragus to the pogonion, the tragus to the corner of the mouth, and the lateral angle of the canthus to the angle of the mandible with a measuring tape.	Before the procedure, 1 day, and 3 days after odontectomy.	TNF-α concentrations increased first day after odontectomy and decreased 3 days after odontectomy.

(*Continued*)

Table 5 (Continued).

No	Author (Year of Publication)	Types of Inflammatory Biomarkers in Saliva	Saliva Sampling or Analysis Methods	Clinical Identification Methods of Swelling	Monitoring Interval	Interpretation of Biomarker Values
7.	Surin et al, (2022)[35]	Alpha-amylase	Passive saliva collection using sterile plastic pipette was analyzed using coupled enzymatic colorimetric assay.	n/a	Before the procedure, immediately after the anesthesia wears off, 1 day and 7 days after the odontectomy.	Alpha-amylase concentrations before the procedure in the symptomatic group were significantly higher compared to the asymptomatic group.
						On the first day after the procedure, the alpha-amylase concentration in the asymptomatic group increased sharply, while in the symptomatic group it decreased.
						On the 7th day in both groups there was a decrease in alpha-amylase concentration.
8.	Chandini et al, (2022)[36]	Alpha-amylase	Passive saliva collection using auto-aspiration pipette tip using kinetic method analysis with amylase assay.	n/a	Before the procedure and immediately after odontectomy.	The concentration of alpha-amylase in saliva before the procedure was higher than after the procedure, associated with pain felt before the procedure also being higher than after the procedure.
9.	Jumaah & Al-Adili (2022)[37]	Alpha-amylase	Passive drooling method with ELISA analysis	n/a	Before the procedure, 48 hours after, and 7 days after odontectomy.	There was an increase in alpha-amylase concentration at 48 hours post-procedure and a decrease at 7 days post-odontectomy.
10.	Wulansari et al, (2018)[34]	Alpha-amylase	Cocoro meter	n/a	Before the procedure and 20 minutes after the procedure.	Alpha-amylase concentration is influenced by patient dental anxiety, as seen by a significant decrease in concentration in the group given intervention with the aim of relaxation.

Characteristics of Study and Inflammatory Biomarkers in Saliva

The included articles were published within the last ten years. The earliest article included was published in 2017, and the most recent article was published in 2024. A total of ten articles were included, consisting of six cohort studies, two randomized controlled trials, and two quasi-experimental studies. The results of the article selection can be seen in (Table 4 and Table 5).

Discussion

Salivary biomarker analysis has emerged as a valuable approach for the early detection of both oral and systemic diseases. It has been used to identify oral diseases, including periodontitis, caries, and oral cancer, as well as systemic diseases such as diabetes mellitus, cardiovascular disease, viral infections, and cancers.[38] More recently, salivary biomarkers have been analyzed for the identification of postoperative swelling following odontectomy. Among the four biomarkers reviewed, alpha-amylase is the most widely utilized salivary biomarker for detecting inflammation after odontectomy.[15,24,33–37] Other studies have used salivary TNF-α to identify post-procedure inflammation.[25,31,32] IL-1 and IL-6 in saliva have also been used to identify inflammation.[25] These studies identified post-odontectomy swelling by

collecting saliva samples at multiple time points, including before the procedure (baseline), immediately after surgery, and on postoperative days 1, 2, 3, and 7.

Alpha-Amylase

Alpha-amylase in saliva increases in response to acute inflammation after surgical procedures such as odontectomy. This happens as a result of autonomic nervous system dysregulation, which is connected to psychological stressors such as procedure-related pain or anxiety.[39] A study by Gutiérrez-Corrales et al compared alpha-amylase concentrations before, immediately after, two hours, and seven days post-odontectomy.[24] This study also examined other biomarkers, including total protein and immunoglobulin A (IgA). The authors reported that only alpha-amylase had a significant effect on the inflammatory response. The increase in alpha-amylase concentration in saliva started immediately after the procedure and increased significantly at two hours after the procedure. This suggests alpha-amylase reacts to the acute inflammatory process after odontectomy.[24] Acute inflammation is the body's immediate response to injury that can occur within hours in association with inflammatory mediators that capture the stimulus.[40] The results also indicated that alpha-amylase significantly decreased by the seventh day post-procedure, suggesting that the inflammation had begun to resolve.[24] The swelling following odontectomy generally subsides within seven days.[19]

The increase in alpha-amylase concentration two hours after, followed by a decrease on the seventh day, was also observed in the studies by Muhajir et al and Sulfiana et al that analyzed alpha-amylase concentrations before, two hours after, three days after, and seven days after odontectomy.[15,33] These findings suggest that alpha-amylase concentration increased two hours after odontectomy, peaked on the third day, and decreased slowly on the seventh day after odontectomy. The peak increase in alpha-amylase three days after the procedure is in line with the healing phase of the extraction socket which usually occurs within 48 to 72 hours after tooth removal. This phase involves the recruitment, migration, differentiation, and proliferation of numerous inflammatory mediators to initiate new tissue formation.[40] Research conducted by Jumaah & Al-Adili also reported an increase in alpha-amylase concentration at 48 hours post-procedure, followed by a decrease at seven days post-procedure.[37]

The correlation of changes in alpha-amylase concentration in saliva with swelling identified by clinical examination to see facial dimensions was observed in studies conducted by Muhajir et al and Sulfiana et al[15,33] Muhajir et al classified impacted third molars as Ia, Ib, Ic, IIa, IIb, or IIc.[15] A significant correlation was found between post-odontectomy swelling and increased alpha-amylase in class IIa, IIb, and IIc impactions compared to class Ia, Ib, and Ic impactions. This positive correlation suggests an increase in clinically measured facial swelling corresponds with an increase in salivary alpha-amylase concentration. Class I third molar impaction refers to the condition where there is sufficient space between the mandibular ramus and the distal side of the second molar for the third molar to erupt. In contrast, class II impaction indicates limited space, smaller than the mesiodistal width of the erupting third molar. Class II impactions need more extensive tissue manipulation than Class I due to decreased accessibility of the impacted tooth, resulting in higher surgical trauma, a heightened stress and inflammatory response, and, as a result, more substantial postoperative swelling.[41] Sulfiana et al also reported a significant correlation between swelling and alpha-amylase concentration before, two hours after, three days after, and seven days after odontectomy.[33] This study compared swelling with facial dimension measurements, alpha-amylase concentration, and IgG concentration in groups that were given diclofenac sodium gel intervention and those that were not. The authors reported that swelling corresponded with changes in alpha-amylase concentration in both groups, regardless of intervention. These findings suggest that changes in alpha-amylase concentration in saliva can describe an inflammatory response, specifically swelling post-odontectomy, which is linked to elevated autonomic nervous system activity or a stress response that may arise in response to tissue injury.

Other signs of inflammation that commonly occur after odontectomy, such as pain, are also associated with alpha-amylase. Surin et al found a strong correlation between changes in salivary alpha-amylase concentration and patient-reported pain.[35] The study categorized patients into symptomatic and asymptomatic groups. Before odontectomy, the symptomatic group had significantly higher alpha-amylase levels compared to the asymptomatic group. This is likely because discomfort experienced by symptomatic patients prior to the procedure triggers the autonomic nervous system, stimulating the adrenal medulla to release norepinephrine and adrenaline that activate the acinar cells of the salivary glands, leading to increased alpha-amylase secretion. In the asymptomatic group, alpha-amylase concentrations

significantly increased on the first postoperative day compared to pre-odontectomy levels, while in the symptomatic group, they decreased.This is explained by the fact that the symptomatic group underwent the procedure as a treatment for pre-existing discomfort, whereas the asymptomatic group, having not experienced prior stress, was newly exposed to a stressor during and after the procedure. In both groups, alpha-amylase concentration declined by the seventh postoperative day, alongside reductions in patient-reported pain. Pain levels were assessed using a Visual Analog Scale (VAS), and a significant decrease was observed on day seven compared to earlier days. Chandini et al also compared patient pain using VAS and analysis of alpha-amylase concentration in saliva.[36] The study found that alpha-amylase levels were significantly higher before the procedure than after, aligning with VAS scores, which were also higher preoperatively. These findings suggest that changes in salivary alpha-amylase concentrations can reflect the patient's pain level before and after odontectomy.

Alpha-amylase concentration in saliva can also reflect dental anxiety in patients undergoing odontectomy. Wulansari et al conducted a study where participants were divided into two groups: one group received a relaxation music intervention, while the other group did not.[34] In the control group, alpha-amylase concentration before the procedure and 20 minutes afterward showed no significant change. In contrast, the intervention group experienced a significant decrease in alpha-amylase concentration. This finding suggests that fear or anxiety related to dental procedures, specifically odontectomy is associated with elevated salivary alpha-amylase concentration.

Pain and fear activate the autonomic nervous system via signals to the hypothalamus, triggering the sympathetic response. This leads to acetylcholine release, which stimulates chromaffin cells in the adrenal medulla to produce norepinephrine and epinephrine, resulting in increased salivary alpha-amylase levels.[34,42,43] Although salivary alpha-amylase is a promising biomarker for assessing stress-related inflammatory responses, it is important to realize that salivary alpha-amylase elevation is influenced by its multifactorial contribution.

TNF-α, IL-1, and IL-6

Another inflammatory biomarker found in saliva that is associated with post-odontectomy swelling is TNF-α. While alpha-amylase primarily reflects how a human responds to stress, TNF-α is a proinflammatory cytokine that is directly involved in tissue inflammation. The correlation between swelling identified through clinical examination of facial dimensions and changes in salivary TNF-α concentration was observed in studies by Ruth et al and Yusa et al[31,32] In a study by Ruth et al participants were divided into two groups: one receiving meloxicam and the other receiving a placebo, to evaluate pain, swelling, trismus, and TNF-α concentration following odontectomy.[31] TNF-α concentration in both groups increased on the first-day post-procedure and decreased by the third day. This pattern paralleled changes in facial dimensions, which increased on the first day and decreased by the third day, suggesting a significant correlation between TNF-α concentration and swelling. Additionally, the increase in TNF-α was also associated with pain intensity, as measured by VAS. Yusa et al similarly assessed swelling post-odontectomy by comparing TNF-α concentration in saliva with clinical facial measurements.[32] Participants were divided into methylprednisolone and placebo groups to observe swelling, intraoral redness, pain, and TNF-α concentrations. TNF-α concentration increased significantly on the first-day post-odontectomy, corresponding with clinically observed swelling, and decreased on the third day, aligning with reduced facial swelling. The study also reported a strong correlation between TNF-α concentration, pain, and intraoral redness. TNF-α experiences a peak increase in the first few days after tissue injury due to its key role in the wound-healing process.[44] Both Ruth et al and Yusa et al observed that TNF-α levels peaked on the first day post-odontectomy.[31,32] This increase is linked to elevated vascular permeability, which leads to the accumulation of fluid and proteins in the tissue, contributing to swelling.[45] These findings indicate that TNF-α concentration in saliva has a role in swelling post-odontectomy.

The increase in TNF-α related to the inflammation that occurs was also seen in the study of Al Shehhi et al.[25] Samples were collected before, two hours after, and two days after the tooth extraction procedure by dividing two different groups, including a group with type II diabetes mellitus (type II DM) and a control group of individuals without type II DM. TNF-α in the control group increased significantly two hours after the procedure, while in the type II DM group, a significant increase in TNF-α was seen two days after the procedure. This is related to the healing process of extraction sockets in DM individuals being slower when compared to non-DM individuals.[46]

Hyperglycemia experienced by diabetic patients will continuously damage cells or tissues, thus slowing the formation of new tissues and implicating a prolonged inflammatory phase.[47] This hyperglycemia condition will produce glycation end-products (AGEs) that will be captured by receptors and cause the production of proinflammatory cytokines, such as TNF-α, to be more abundant and longer retained at the injury site.[25] Endotheliopathy or impaired endothelial lining in diabetic patients is also associated with a prolonged wound-healing phase. This condition causes microvascular or macrovascular changes that lead to reduced production of growth factors that play a role in the angiogenesis process so that the supply of nutrients or oxygen to the injury site is inhibited and also slows down the wound growth process.[47] The increase in TNF-α after odontectomy is initiated by tissue injury during the procedure which plays a role in the socket healing process by promoting angiogenesis, stimulating cell proliferation and differentiation, and increasing the immune response to remove debris and pathogens from the wound site. TNF-α is required for the delivery of immune cells to the site of injury, but excessive TNF-α production can lead to prolonged inflammation.[25,45,48,49]

Research by Al Shehhi et al not only analyzed TNF-α but also other inflammatory biomarkers in saliva, including IL-1 and IL-6.[25] IL-6 levels increased in both the type II diabetes mellitus (DM) group and the control group two hours after the procedure. However, by the second day, IL-6 levels continued to rise in the DM group, while they declined in the control group. In contrast, IL-1, particularly IL-1β, decreased in both groups two hours post-procedure but increased again by the second day. IL-1β serves an important role in immune responses as a proinflammatory cytokine and is the most frequently detected subtype of IL-1 in saliva. Its salivary concentration has been assessed as a noninvasive biomarker in many studies of both local oral inflammatory conditions and systemic inflammatory conditions.[50,51] These findings suggest that IL-1β and IL-6, as proinflammatory cytokines, reflect a prolonged inflammatory response in the DM group compared to the non-DM group.

IL-1 is known to be associated with extraction socket healing after odontectomy. Its production increases in response to tissue injury and acts as a chemotactic agent, recruiting immune cells to the site of inflammation. Acute inflammation often occurs during this process, typically presenting as swelling caused by increased vascular permeability and fluid accumulation in the affected area.[25,52] The overexpression of IL-1 can prolong the inflammatory phase and impair wound healing, as observed in the DM group.[25,53] In addition to IL-1, IL-6 activity is also linked to post-odontectomy socket healing. Similar to IL-1, IL-6 expression is triggered by tissue damage and initiates the inflammatory response. Although IL-6 plays a critical role in promoting tissue repair, persistently elevated IL-6 levels can lead to prolonged inflammation and delayed healing, particularly in diabetic patients.[25,54,55] IL-1 is early in the initiation of the inflammatory response through stimulating the production of additional cytokines and recruiting immune cells to the site of injury, while IL-6 has both a role in promoting the inflammatory response and also in repairing tissue.[45]

The increase in proinflammatory cytokines in saliva is associated with the acute inflammatory process that initiates socket healing following odontectomy. The body's initial response to the socket formed after the procedure is blood clot formation. The resulting tissue injury triggers the release of damage-associated molecular patterns (DAMPs), which activate toll-like receptors (TLRs), subsequently stimulating immune cells to release proinflammatory cytokines such as IL-1, IL-6, and TNF-α. The release of these cytokines induces vasodilation and increases tissue permeability, leading to swelling. These cytokines also recruit additional immune cells to the injury site to phagocytize necrotic tissue and eliminate foreign substances from the socket. This inflammatory response facilitates the transition to the tissue repair phase, ending the acute inflammatory phase and initiating the proliferative stage, which involves fibroblast recruitment and angiogenesis. During this stage, proinflammatory cytokines begin to be replaced by anti-inflammatory cytokines, resulting in a decrease in salivary proinflammatory cytokine concentrations a few days after the procedure. Granulation tissue subsequently forms and develops into woven bone. Finally, during the remodeling stage, mature bone is formed and completes the socket healing process.[25,40,45]

Biomarker Analysis Methods

Changes in the concentrations of inflammatory biomarkers in saliva, such as alpha-amylase or the three proinflammatory cytokines, IL-1, IL-6, and TNF-α, can be detected using various analytical methods. Alpha-amylase was analyzed using enzyme assay, ELISA, or a cocoro meter, depending on the study, while the analysis of IL-1, IL-6, and TNF-α was performed using either ELISA or Luminex assay. To perform the analysis, a reliable assay is needed to detect the biomarker. Several

factors need to be considered, such as the sensitivity and specificity of the test. Sensitivity refers to a test's ability to correctly identify true positives, while specificity refers to its ability to correctly identify true negatives.[56]

Jumaah & Al-Adili utilized ELISA to evaluate alpha-amylase, while Ruth et al used it for evaluating TNF-α.[31,37] ELISA is an immunological test used to detect and measure the presence of antigens in a sample that can be detected quantitatively using a device such as a luminometer or spectrophotometer.[57] ELISA has become a widely used immunoassay because of its excellent sensitivity and specificity in test results.[58] The high sensitivity of ELISA comes from enzyme amplification, which allows detection at low analyte concentrations. Its specificity is based on exact antibody-antigen interactions, which correctly identifies the target.[59]

In addition to using ELISA, there are three articles that analyze alpha-amylase in saliva using enzyme assay.[24,35,36] An enzyme assay is an analytical method used to detect the presence and measure enzyme activity in a sample by utilizing the enzyme's ability to catalyze certain chemical reactions. The results are based on the accumulation of reaction products or substrate reduction during the enzymatic reaction, which can be observed through changes in color or light intensity of the sample at a certain wavelength using a spectrophotometer.[60]

The cocoro meter is also often used to analyze alpha-amylase, as demonstrated in the studies by Muhajir et al and Wulansari et al[15,34] The cocoro meter is a portable biosensor device that can measure alpha-amylase activity in saliva quickly and accurately. Its main advantage is that it offers a portable alternative for field-based analysis to measure the concentration of alpha-amylase in saliva using a biosensor device and disposable strips that are placed under the tongue for 15 seconds without the need for laboratory analysis methods.[61,62] Cocoro meter can produce analysis with 94% accuracy in less than a minute.[63] Alpha-amylase catalyzes the breakdown of starch into maltose, maltotriose, and larger oligosaccharides. This makes the reaction products of alpha-amylase easier to measure, allowing analysis using a portable cocoro meter device that performs colorimetric detection.[62,64] Based on that, all three methods can be used to analyze alpha-amylase in saliva, ELISA can be used to detect inflammatory biomarkers in saliva with high sensitivity and specificity, enzyme assay can be used with simpler steps than ELISA, and cocoro meter offers a faster analysis time and easier process with high accuracy.

In order to analyze the three proinflammatory cytokines, Ruth et al used ELISA to specifically analyze TNF-α, while Al Shehhi et al used Luminex assay to simultaneously analyze IL-1, IL-6, and TNF-α.[25,31] The Luminex assay is used for the detection and quantification of cytokines and can analyze multiple cytokines in a single test with accuracy comparable to the ELISA method.[65] Based on this, both methods can be used to analyze cytokines in saliva, but when analyzing multiple cytokines simultaneously, the Luminex assay is preferred.

Limitations and Suggestions for Further Research

This study was conducted with consideration of the limited availability of relevant articles in the selected databases that specifically addressed the role of salivary inflammatory biomarkers, IL-1, IL-6, TNF-α, and alpha-amylase in post-odontectomy swelling. Moreover, a limitation of this review is the outcome specificity, as most of the included studies did not focus exclusively on swelling, but also investigated related factors such as pain, anxiety, and intraoral redness. Therefore, further clinical trials are recommended to provide a clearer understanding, especially by directly comparing clinical examinations with saliva sample examinations that analyze inflammatory biomarkers IL-1, IL-6, TNF-α, and alpha-amylase to detect swelling that occurs. Further research should address the limitations of this review by utilizing a wider range of databases, expanding the publication year range, including studies published in other languages, and employing broader and more commonly used search keywords. Systematic review and meta-analysis methods are recommended to enhance the scope and reliability.

Conclusion

The literature review concluded that the salivary inflammatory biomarkers IL-1, IL-6, TNF-α, and alpha-amylase demonstrated significant association with post-odontectomy swelling, as indicated by increased levels corresponding to greater swelling intensity. Among these biomarkers, alpha-amylase is most frequently used due to its rapid responsiveness to inflammation, its ability to reflect pain and anxiety through autonomic nervous system activation, and the practicality of its measurement using portable and accessible tools. TNF-α contributes to post-odontectomy swelling by

increasing vascular permeability, leading to fluid and protein accumulation in the tissue. Meanwhile, IL-1 and IL-6 contribute to post-odontectomy swelling by promoting immune cell recruitment and increasing vascular permeability, leading to fluid accumulation at the injury site. These biomarkers can be accurately measured using several established analytical methods, with ELISA being the most commonly applied, while enzyme assays and the cocorometer offer simplified and portable alternatives for clinical or field-based use. Overall, salivary biomarkers show promising potential for improving the clinical monitoring of post-odontectomy swelling.

Disclosure

The authors report no conflicts of interest in this work.

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