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Literature Review

High-Fat Diet and Salivary Gland Alterations: A Scoping Review

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KEYWORDS

Inflammation, oxidative stress, saliva composition, saliva secretion.

ABSTRACT

Introduction: Obesity is a growing global health concern, largely driven by high-fat diet (HFD) consumption, which promotes adipose tissue accumulation and increases metabolic disorder risk. Beyond systemic effects, obesity may impair salivary gland function, which is essential for maintaining oral homeostasis. However, evidence regarding the effects of HFDs on salivary glands remains fragmented and inconsistent. This scoping review aimed to map the literature on HFD-induced salivary gland alterations and elucidate the underlying biological mechanisms.

Review: The review followed PRISMA-ScR guidelines. Relevant studies were identified through comprehensive searches of PubMed and Scopus and screened using predefined eligibility criteria. Twenty-two studies were included. HFDs affected four major aspects of salivary gland physiology: reduced antioxidant and digestive enzyme activity; altered salivary proteins, including mucin and IgA; increased inflammatory biomarkers and oxidative stress; and morphological and functional changes, including reduced salivary secretion, fibrosis, vacuolization, inflammatory infiltration, and lipid accumulation. However, some studies reported no significant changes, suggesting that responses may vary according to gland type, HFD exposure duration, and metabolic status.

Conclusion: HFD consumption induces oxidative stress, inflammation, and structural and molecular alterations in salivary glands, potentially contributing to salivary dysfunction. Further longitudinal and translational studies are needed to clarify the underlying mechanisms and clinical implications.

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INTRODUCTION

Obesity is increasingly recognized as a global health crisis, with projections indicating that nearly 3.3 billion adults may be affected by 2035, an increase from 2.2 billion in 2020. This represents a rise in prevalence from 42% of adults in 2020 to over 54% by 2035. Among individuals aged 5–19, the prevalence is anticipated to escalate from 22% (430 million) to more than 39% (770 million) by 2035.[1] Obesity is characterized by an increase in body fat deposition, which can be attributed to genetic and environmental factors, including a high-energy diet and a sedentary lifestyle.[2,3] A chronic imbalance between caloric intake and energy expenditure is the primary cause of obesity.[4] The consumption of foods high in fat contributes to the accumulation of adipose tissue, thereby increasing the risk of obesity and various associated complications.[5]

Obesity is linked to a wide array of health risks, including type 2 diabetes mellitus (T2DM), metabolic syndrome, cardiovascular disease, cognitive decline, and non-alcoholic fatty liver disease.[6–8] Additionally, obesity has implications for various exocrine organs, notably the salivary glands. Research has demonstrated that individuals with obesity often experience diminished saliva production, compositional changes, and heightened oxidative stress, which can lead to dental caries and periodontal disease.[9–13]

Saliva is a crucial physiological fluid that sustains homeostasis within the oral cavity. The secretions from the salivary glands are abundant in fluids, ions, and proteins, which serve to protect teeth and oral tissues. Additionally, saliva contains antimicrobial agents such as immunoglobulins, lysozyme, lactoferrin, and peroxidase, which can inhibit bacterial metabolism, suppress proliferation, or directly eliminate microorganisms.[14] Furthermore, saliva contributes to the initial digestion of carbohydrates, facilitates the formation and swallowing of food boluses, and possesses a buffering system that maintains pH levels, thereby safeguarding teeth against erosion and damage.[15,16] The major salivary glands, specifically the parotid, submandibular, and sublingual glands, are responsible for saliva production, and their functional integrity is essential for both oral and systemic health.

Numerous experimental investigations have demonstrated that a high-fat diet (HFD) can influence the function and structure of the salivary glands through various mechanisms. Research conducted by Maciejczyk et al and Zalewska et al indicates that prolonged exposure to HFD elevates oxidative stress and inflammation, induces insulin resistance, and disrupts autonomic nervous system regulation, which is integral to saliva secretion.[17,18] These alterations have the potential to impair enzyme and saliva protein production, reduce saliva flow rate, and provoke histological changes in glandular tissue. However, the findings in the literature are inconsistent. Several studies have documented decreased antioxidant enzyme activity, diminished saliva flow, and notable histopathological changes following HFD exposure.[17–20] Conversely, other studies have reported no significant changes in functional or histological parameters, despite evidence of molecular dysfunction.[21,22] These discrepancies are likely attributable to variations in study design, duration of dietary exposure, type of gland examined, and biomarkers assessed.

To date, no comprehensive review has specifically mapped the evidence regarding the impact of high-fat diets (HFD) on the salivary glands. The extant literature predominantly addresses the systemic consequences of HFD, while the salivary aspects remain fragmented. However, understanding the changes in saliva and salivary glands

induced by HFD is crucial, given its implications for oral health and its relationship to broader systemic diseases. A deeper understanding of these alterations is also essential for supporting broader initiatives that strive to advance good health and overall well-being.

In light of this context, the present scoping review seeks to systematically map the extant literature concerning the impact of high-fat diets (HFD) on salivary glands, with a particular focus on elucidating the biological mechanisms that underpin these effects. The review primarily concentrates on molecular expression, including genes, enzymes, and biomarkers of inflammation and oxidative stress, as well as histological alterations in salivary gland tissue, as evidenced in animal-based experimental studies.

REVIEW

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines; however, this review was not registered.[23] A scoping review design was employed to delineate the parameters utilized in evaluating alterations in salivary gland secretion and function attributable to a high-fat diet. Consequently, the research question addressed is: How does a high-fat diet affect salivary gland secretion and/or function in rodent models?

The primary studies were sourced from the electronic databases PubMed and Scopus. The search strategy employed two principal concepts to identify relevant medical subject headings (MeSH), utilizing the keywords "high-fat diet" and "salivary gland". The keywords employed for the term “high-fat diet” were (“high-fat diet” OR “high-fat diets” OR “diets, high fat” OR “high fat diet” OR “high fat diets”) AND for “salivary gland” were (“sublingual” OR “submandibular” OR “parotid” OR “saliva” OR ‘salivary’ OR “salivary secretion” OR “salivary dysfunction” OR “secretory dysfunction”). All keywords were searched within the title, abstract, and article fields. Boolean operators were employed in the search process, utilizing "OR" for keywords and subjects within the same concept, and "AND" to connect the main concepts.

The literature search was conducted in the PubMed and Scopus databases on 5 June 2025. The search results were extracted from both databases, and duplicates were identified using Rayyan software. Two reviewers, DF and VF, conducted an independent screening of the results based on titles and abstracts. After acquiring the full texts of the identified studies, one reviewer organized the relevant articles. Both reviewers then independently evaluated the full texts to verify their alignment with the established criteria. In cases where the reviewers' assessments differed, a third reviewer, HG, was consulted to mediate and resolve the discrepancies

The criteria for inclusion in this review were as follows: (1) in vivo experimental studies utilizing rodent models, specifically rats or mice; (2) original research articles assessing the impact of a high-fat diet on salivary gland secretion or function; (3) studies accessible in full-text format; and (4) publications authored in English. The exclusion criteria encompassed the following: (1) observational studies conducted on human subjects; (2) research involving non-rodent animal models or in vitro systems such as cell cultures; (3) secondary literature, including systematic reviews, scoping reviews, narrative reviews, meta-analyses, editorials, commentaries, and conference abstracts; and (4) articles that did not report parameters related to saliva secretion or salivary gland function.

During a thorough review process, 166 studies were initially sourced from the PubMed and Scopus databases. These studies were imported into the Rayyan software, where 71 duplicate entries were identified and removed, resulting in 95 distinct articles. Two reviewers then conducted a screening of these articles based on titles and abstracts, leading to the exclusion of 73 studies that did not meet the inclusion criteria. The full texts of the remaining 22 articles were subsequently assessed for eligibility, with detailed reasons for exclusion recorded for each study. The study selection process is summarized in a PRISMA flow diagram (Figure 1).

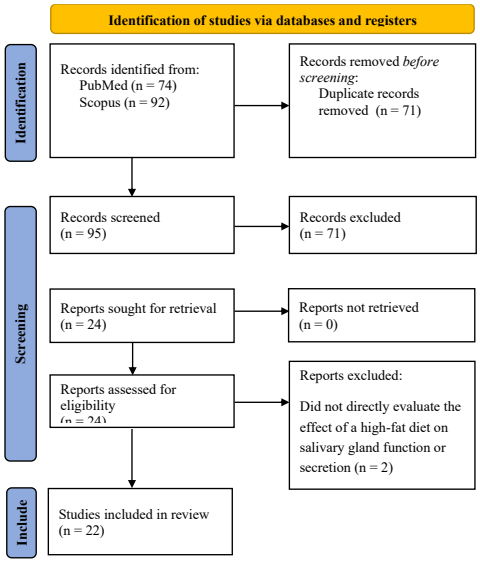

Figure 1 PRISMA flowchart of the study selection process

According to the review findings, 22 studies employing mouse models were published between 2008 and 2024. These studies investigated the impact of a high-fat diet (HFD) on salivary gland secretion and/or function by examining various parameters, including (1) saliva composition, (2) biomarkers of inflammatory and oxidative damage, (3) alterations in salivary gland function, and (4) histological changes in the salivary glands. A summary of the article characteristics and principal findings is presented in Tables 1, 2, 3, 4, 5, and 6.

Table 1. Data characteristics and main results of saliva enzyme composition

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Zalewska et al. (2014)	Wistar rats; male; young adults; 273 (240–286) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	5 weeks	ELISA; colorimetric assay	↑ SOD2 and CAT; ↓ Px
Lasisi et al. (2018)	Rats; sex not reported; approximately 3–4 weeks	Not reported	15 weeks	ELISA	↓ α-Amylase
Żukowski et al. (2018)	Wistar rats; male; 4 weeks; 345 (326–364) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Colorimetric assay	↓ SOD1 and Px
Maciejczyk et al. (2021)	Rats; male; age not reported; 537 ± 36.52 g	Not reported	8 weeks	Spectrophotometric assay	↓ SOD, GPX, and Px

Zalewska et al. (2019)	C57BL/6 mice; male; age not explicitly reported; 37.88 ± 0.63 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	Colorimetric assay	↓ CAT and Px
Zalewska et al. (2020)	Mice; sex, age, and weight not reported	Not reported	6 weeks	Spectrophotometric assay	↓ SOD and Px
Huang et al. (2023)	Mice; sex not reported; 5 weeks postnatal; weight not reported	Not reported	30 weeks	Western blot	↓ α-Amylase
Lungruammint et al. (2024)	Wistar rats; male; 7–8 weeks; increased body weight	Carbohydrate: 763.04 kcal; fat: 308.16 kcal; protein: 1414.40 kcal; cholesterol: 90 kcal	12 weeks	HPLC assay	↓ SOD2 and GPX4

Note: HFD, high-fat diet; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; SOD, superoxide dismutase; SOD1, superoxide dismutase 1; SOD2, superoxide dismutase 2; CAT, catalase; GPX, glutathione peroxidase; GPX4, glutathione peroxidase 4; Px, peroxidase. ↑ indicates an increase; ↓ indicates a decrease. Values are presented as reported in the original studies.

Table 2. Data characteristics and main results of saliva protein composition

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Zalewska et al. (2014)	Wistar rats; male; young adults; 273 (240–286) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	5 weeks	BCA assay	↓ Protein concentration in parotid glands
Kołodziej et al. (2017)	Wistar rats; male; age not explicitly reported; 407.7 (376–450) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	BCA assay	↓ Protein concentration in parotid and submandibular glands
Lasisi et al. (2018)	Rats; sex not reported; approximately 3–4 weeks; weight not reported	Not reported	15 weeks	ELISA; Biuret method	↑ Leptin; significant differences in salivary IgA and total protein
Żukowski et al. (2018)	Wistar rats; male; 4 weeks; 345 (326–364) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	BCA assay	↓ Protein concentration in parotid and submandibular glands
Zalewska et al. (2019)	Wistar rats; male; 5 weeks; 345.4 ± 15.7 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	BCA assay	↓ Protein concentration in parotid and submandibular glands
Zalewska et al. (2021)	Wistar rats; male; 4–5 weeks; 350.4 ± 10.32 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	10 weeks	ELISA	↓ Protein concentration in parotid and submandibular glands
Yamamoto et al. (2021)	Wistar rats; male; 7 weeks; similar weight gain	Fat: 220 g/kg	70 days	ELISA	↓ IgA flow rate in saliva
Zalewska et al. (2022)	Wistar rats; male; age not explicitly reported; 395.9 ± 34.85 g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	6 weeks	ELISA	↓ Protein concentration in parotid and submandibular glands
Huang et al. (2023)	Mice; sex not reported; 5 weeks postnatal; weight not reported	Not reported	30 weeks	Western blot	↓ MUC20 and MUC13
Zalewska et al. (2014)	Wistar rats; male; young adults; 273 (240–286) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	5 weeks	BCA assay	↓ Protein concentration in parotid glands

Note: HFD, high-fat diet; BCA, bicinchoninic acid; ELISA, enzyme-linked immunosorbent assay; SigA, secretory immunoglobulin A; IgA-FR, immunoglobulin A flow rate; MUC13, mucin 13; MUC20, mucin 20. ↑ indicates an increase; ↓ indicates a decrease. Values are presented as reported in the original studies.

Table 3. Data characteristics and main results of inflammatory parameters

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Jitjiroi Itthichaicharoen et al. (2017)	Wistar rats; male; age not explicitly reported; 607.50 ± 12.50 g	Standard rat diet with casein (250 g/kg), lard (310 g/kg), cholesterol (10 g/kg), vitamins (60 g/kg), DL-methionine (3 g/kg), yeast powder (1 g/kg), and sodium chloride (1 g/kg); lard was the major fat source	16 weeks	Monoclonal antibody assay	↑ TNF-α
Kołodziej et al. (2017)	Wistar rats; male; age not explicitly reported; 407.7 (376–450) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	RT-PCR	↑ TNF-α, IL-6, and IL-1β
Zalewska et al. (2019)	C57BL/6 mice; male; age not explicitly reported; 37.88 ± 0.63 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	Arraystar Mouse LncRNA Microarray V4.0 (Agilent) and RT-qPCR	↑ TNF-α and IL-2
Zalewska et al. (2019)	Wistar rats; male; 5 weeks; 345.4 ± 15.7 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	RT-PCR	↑ TNF-α and IL-1β
Zalewska et al. (2021)	Wistar rats; male; 4–5 weeks; 350.4 ± 10.32 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	10 weeks	RT-PCR	↑ TNF-α and IL-1β
Lungruammint et al. (2024)	Wistar rats; male; 7–8 weeks; increased body weight	Carbohydrate: 763.04 kcal; fat: 3080.16 kcal; protein: 1414.40 kcal; cholesterol: 90 kcal	12 weeks	Western blot and RT-PCR	↑ Protein expression of p-NF-κB p65, total NF-κB, TNF-α, IL-1β, IL-6, IL-10, and gene expression of IL-22 and Ifng
Jitjiroi Itthichaicharoen et al. (2017)	Wistar rats; male; age not explicitly reported; 607.50 ± 12.50 g	Standard rat diet with casein (250 g/kg), lard (310 g/kg), cholesterol (10 g/kg), vitamins (60 g/kg), DL-methionine (3 g/kg), yeast powder (1 g/kg), and sodium chloride (1 g/kg); lard was the major fat source	16 weeks	Monoclonal antibody assay	↑ TNF-α

Note: HFD, high-fat diet; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, reverse transcription quantitative polymerase chain reaction; TNF-α, tumor necrosis factor-alpha; IL, interleukin; NF-κB, nuclear factor kappa B; Ifng, interferon gamma. ↑ indicates an increase. Values are presented as reported in the original studies.

Table 4. Data characteristics and main results of oxidative stress parameters

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Kołodziej et al. (2017)	Wistar rats; male; age not explicitly reported; 407.7 (376–450) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Colorimetric assay (AOPP); spectrophotometric assay (PC)	↑ AOPP and PC
Itthichaicharoen et al. (2017)	Wistar rats; male; age not explicitly	Standard rat diet with casein (250	16 weeks	HPLC-based assay kit	↑ MDA

	reported; 607.50 ± 12.50 g	g/kg), lard (310 g/kg), cholesterol (10 g/kg), vitamins (60 g/kg), DL-methionine (3 g/kg), yeast powder (1 g/kg), and sodium chloride (1 g/kg); lard was the major fat source			
Żukowski et al. (2018)	Wistar rats; male; 4 weeks; 345 (326–364) g	Carbohydrate: 20.1% kcal; fat: 59.5% kcal; protein: 20.1% kcal	8 weeks	TOS (commercial kit); AOPP (colorimetric assay); 4-HNE (ELISA); OSI calculation	↑ TOS, AOPP, 4-HNE protein adducts, and OSI
Zalewska et al. (2019)	C57BL/6 mice; male; age not explicitly reported; 37.88 ± 0.63 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	AGE (fluorimetric assay); AOPP (colorimetric assay); LOOH (bichromatically); MDA (colorimetric assay)	↑ AGE, AOPP, LOOH, and MDA
Zalewska et al. (2019)	Wistar rats; male; 5 weeks; 345.4 ± 15.7 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	MDA (TBARS); NO (colorimetric assay); H_2O_2 (Amplex Red-horseradish peroxidase); NO and peroxynitrite (colorimetric assay); nitrotyrosine (ELISA)	Higher MDA and NO in the parotid gland; higher H_2O_2 in the submandibular gland
Zalewska et al. (2020)	Wistar rats; male; age not explicitly reported; 380.9 ± 30.42 g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Nitrosative and oxidative stress assays	↑ NO, peroxynitrite, nitrotyrosine, and H_2O_2
Maciejczyk et al. (2021)	Wistar rats; male; age not explicitly reported; 537 ± 36.52 g	Not reported	8 weeks	Not reported	↑ 4-HNE
Zalewska et al. (2021)	Wistar rats; male; 4–5 weeks; 350.4 ± 10.32 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	10 weeks	TBARS	↑ MDA
Zalewska et al. (2022)	Wistar rats; male; age not explicitly reported; 395.9 ± 34.85 g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	6 weeks	TAC and TOS (colorimetric assays); OSI (TOS/TAS × 100%)	↓ TAC; ↑ TOS and OSI
Lungruammint et al. (2024)	Wistar rats; male; 7–8 weeks; increased body weight	Carbohydrate: 763.04 kcal; fat: 3080.16 kcal; protein: 1414.40 kcal; cholesterol: 90 kcal	12 weeks	HPLC assay	↑ MDA

Note: HFD, high-fat diet; AGE, advanced glycation end products; AOPP, advanced oxidation protein products; H_2O_2, hydrogen peroxide; LOOH, lipid hydroperoxide; MDA, malondialdehyde; NO, nitric oxide; OSI, oxidative stress index; PC, protein carbonyl; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TOS, total oxidant status; 4-HNE, 4-hydroxynonenal. ↑ indicates an increase; ↓ indicates a decrease. Values are presented as reported in the original studies.

Table 5. Data characteristics and main results of salivary gland function changes

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Kołodziej et al. (2017)	Wistar rats; male; age not explicitly reported; 407.7 (376–450) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Pilocarpine-stimulated salivary secretion; saliva collected using cotton balls and quantified by weight	↓ Stimulated salivary flow rate by 45%
Itthichaicharoen et al. (2017)	Wistar rats; male; age not explicitly reported; 607.50 ± 12.50 g	Standard rat diet with casein (250 g/kg), lard (310 g/kg), cholesterol (10 g/kg), vitamins (60 g/kg), DL-methionine (3 g/kg), yeast powder (1 g/kg), and sodium chloride (1 g/kg); lard was the major fat source	16 weeks	Saliva collected for 10 min after pilocarpine administration	No significant difference in salivary flow rate
De Carvalho et al. (2017)	ICR mice; female; age not specified; weight not reported	Fat: 55%	3 months	Western blot	↓ Adiponectin and TH (sympathetic innervation)
Lasisi et al. (2018)	Rats; sex not reported; approximately 3–4 weeks; weight not reported	Not reported	15 weeks	Visual assessment of salivary pooling; stopwatch-based salivary lag time; salivary flow-rate measurement; IHC	No significant differences in salivary lag time, salivary flow rate, M3 receptor, Na^+/K^+-ATPase, or aquaporin-5 expression
Żukowski et al. (2018)	Wistar rats; male; 4 weeks; 345 (326–364) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Unstimulated and pilocarpine-stimulated salivary flow-rate measurements	↓ Stimulated salivary flow rate
Zalewska et al. (2019)	C57BL/6 mice; male; age not explicitly reported; 37.88 ± 0.63 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	8 weeks	Pilocarpine-stimulated salivary flow-rate measurement	↓ Stimulated salivary flow rate; no significant difference in unstimulated salivary flow rate
Zalewska et al. (2020)	Wistar rats; sex not reported; age and weight not reported	Not reported	6 weeks	Pilocarpine-stimulated salivary flow-rate measurement	↓ Stimulated salivary flow rate; no significant difference in unstimulated salivary flow rate
Zalewska et al. (2020)	Wistar rats; male; age not explicitly reported; 380.9 ± 30.42 g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	Pilocarpine-stimulated salivary flow-rate measurement	↓ Stimulated salivary flow rate; no significant difference in unstimulated salivary flow rate

Yamamoto et al. (2021)	Wistar rats; male; 7 weeks; similar weight gain	Fat: 220 g/kg	70 days	Bulk RNA-seq	↓ TH and pIgR
Huang et al. (2023)	Mice; sex not reported; 5 weeks postnatal; weight not reported	Not reported	30 weeks	Pilocarpine-stimulated salivary flow-rate measurement; 100 µg/mL pilocarpine hydrochloride (0.5 µg/g body weight)	↓ Stimulated salivary flow rate; altered expression of multiple salivary-gland-related genes, including Aqp2, Bsnd, Clcnka, Hcn2, Kcnj2, Kcnj8, Slc2a4, Tmem158, Adamts2, Adamts10, Col2a2, Emd, Adrb1, P2rx3, Efna4, Rab17, and Snca
Lungruammint et al. (2024)	Wistar rats; male; 7–8 weeks; increased body weight	Carbohydrate: 763.04 kcal; fat: 3080.16 kcal; protein: 1414.40 kcal; cholesterol: 90 kcal	12 weeks	RT-PCR	↓ AQP5

Note: HFD, high-fat diet; IHC, immunohistochemistry; TH, tyrosine hydroxylase; pIgR, polymeric immunoglobulin receptor; AQP5, aquaporin-5; RT-PCR, reverse transcription polymerase chain reaction; RNA-seq, RNA sequencing. ↑ indicates an increase; ↓ indicates a decrease. Values are presented as reported in the original studies.

Table 6. Data characteristics and main results of salivary gland histological changes

Author (Year)	Experimental model	HFD composition	Intervention duration	Analytical method	Main findings
Pissicler et al. (2003)	Wistar albino rats; male and female; 8 weeks; weight not reported	Standard chow supplemented with cholesterol (1.63%), cholic acid (0.41%), and sunflower oil (16.3%)	3 months	H&E staining	↑ Intracellular lipid droplets in parotid and sublingual glands; serous acinar cells predominantly affected; submandibular gland showed partial resistance to lipid accumulation; acinar cell disarrangement, cytoplasmic vacuolization, nuclear irregularity, fibrosis, cellular infiltration, vascular dilation with hemorrhage, dark-stained irregular nuclei, and intracellular vacuoles/lipid droplets
Selim et al. (2013)	Rats; male; 5–7 months; weight not reported	Carbohydrate: 50–52%; fat: 30% of calories from buffalo fat; protein: 18–20%; vitamins and minerals: 1–2%; 210 kcal/100 g/day	3 months	H&E staining	Degenerative vacuolar changes in parotid and submandibular glands; more severe vacuolization in parotid glands
Kołodziej et al. (2017)	Wistar rats; male; age not explicitly reported; 407.7 (376–450) g	Carbohydrate: 20.1% kcal; fat: 59.8% kcal; protein: 20.1% kcal	8 weeks	H&E staining	Degenerative changes characterized by vacuolization in parotid and submandibular glands; more severe vacuolization in parotid glands
De Carvalho et al. (2017)	ICR mice; female; adult; age and weight not reported	Fat: 55%	3 months	Oil Red O and H&E staining	No major histological changes; acinar and ductal cells appeared normal with few signs of inflammation
Lasisi et al. (2018)	Rats; sex not reported; approximately	Not reported	15 weeks	H&E staining	Submandibular and sublingual glands showed normal lobular architecture with densely packed

	3–4 weeks; weight not reported				acini and well-developed secretory duct systems; no significant histological changes in the submandibular gland
Kikuchi et al. (2020)	Sprague–Dawley rats; male; initially 3 weeks; 444.32 ± 63.22 g	Carbohydrate: 7.5%; fat: 60%; protein: 24.5%	10 weeks	H&E staining	No lipid deposition observed in the submandibular gland
Al-Serwi et al. (2021)	Sprague–Dawley rats; male; 8–10 weeks; weight not reported	Corn oil (>98% ω-6 polyunsaturated fatty acids); carbohydrate: 50%; fat: 21.4%; protein: 17.5%; fiber: 3.5%; ash: 4.1%	12 weeks	H&E staining	↓ Acinar cell number; vacuolization; lipid deposition; ultrastructural damage
Yamamoto et al. (2021)	Wistar rats; male; 7 weeks; similar weight gain	Fat: 220 g/kg	70 days	H&E staining	No significant histological changes in salivary glands compared with controls
Liu et al. (2021)	C57BL/6J mice; male; 4 weeks; approximately 80.5% greater weight than controls	Fat: 60% kcal	16 weeks	H&E staining	Acinar atrophy and ductal enlargement in submandibular gland tissue; no lipid accumulation in submandibular gland tissue
Zalewska et al. (2021)	Wistar rats; male; 4–5 weeks; 350.4 ± 10.32 g	Carbohydrate: 20% kcal; fat: 60% kcal; protein: 20% kcal	10 weeks	H&E staining	Vacuolization in both parotid and submandibular glands; more pronounced in the parotid gland
Kandeel et al. (2022)	Rats; male; adult; 150–200 g; approximately 80.5% greater weight than controls	20% animal fat + 1% cholesterol added to standard animal diet	6 weeks	H&E staining	Disturbed architecture, congested blood vessels, inflammatory cellular infiltration, acinar cells with cytoplasmic vacuoles, and vacuolated ducts
Huang et al. (2023)	Mice; sex not reported; 5 weeks postnatal; weight not reported	Not reported	30 weeks	H&E staining	Salivary glands were not obviously affected in obese mice compared with controls; no significant changes in acini or ducts
Lungruammint et al. (2024)	Wistar rats; male; 7–8 weeks; increased body weight	Carbohydrate: 763.04 kcal; fat: 3080.16 kcal; protein: 1414.40 kcal; cholesterol: 90 kcal	12 weeks	Picrosirius Red staining and ImageJ analysis	↑ Fibrosis in the submandibular glands

Note: HFD, high-fat diet; H&E, hematoxylin and eosin; ω-6, omega-6 polyunsaturated fatty acids. ↑ indicates an increase; ↓ indicates a decrease. Values are presented as reported in the original studies.

A high-fat diet (HFD) is consistently linked to diminished activity of salivary and antioxidant enzymes, although the specific patterns vary across different studies. Research by Maciejczyk et al and

Lungruammit et al has demonstrated significant reductions in superoxide dismutase (SOD), glutathione peroxidase 4 (GPX4), and peroxidase in mice subjected to an HFD.[18,19] This is likely attributable to increased reactive oxygen species (ROS) resulting from excessive mitochondrial fatty acid oxidation, which leads to oxidative stress and glandular dysfunction.[24–27] A reduction in GPX4 is correlated with elevated lipid peroxidation and decreased expression of aquaporin 5 (AQP5), which impacts saliva secretion.[27]

Żukowski et al.[30] reported a decrease in superoxide dismutase (SOD) and peroxidase (Px) activity in the parotid glands, along with a reduction in Px activity in the submandibular glands,[28] indicating an impaired redox balance. An excess supply of fatty acids under a high-fat diet (HFD) enhances mitochondrial electron leakage and reactive oxygen species (ROS) generation, thereby promoting oxidative damage and metabolic dysfunction in the salivary glands.[29,30] Conversely, Zalewska et al.[24,31] observed a reduction in Px activity but an increase in SOD2 and catalase (CAT) activity, suggesting a compensatory antioxidant response that varies depending on the enzyme type and gland location.

Subsequent research has associated reduced levels of antioxidant enzymes with insulin resistance, ceramide accumulation, apoptosis, glutathione depletion, and compromised glandular function.[32–35] Furthermore, a high-fat diet (HFD) diminishes α-amylase activity,[22,36] which may affect carbohydrate digestion and colonic fermentation and potentially exacerbate metabolic imbalances.[37] In summary, the available evidence suggests that oxidative stress may contribute to HFD-associated salivary dysfunction through multiple molecular alterations.

In addition to alterations in enzyme activity, numerous studies have demonstrated that a high-fat diet (HFD) markedly affects the synthesis and secretion of salivary proteins. Huang et al.[36] reported that diet-induced obese (DIO) mice subjected to an HFD exhibited diminished production of MUC20 and MUC13, which was associated with the downregulation of genes encoding extracellular matrix components, membrane receptors, and transport-related proteins. These molecular alterations suggest compromised exocrine function, resulting in reduced stimulated salivary flow and mucin content.[10,11,13]

In their study, Zalewska et al.[17] reported a decrease in total protein levels in the parotid and submandibular glands of rats subjected to a high-fat diet (HFD), which is likely a consequence of ongoing protein glycation. This process diminishes the functional surface area of the glands, thereby impeding secretion. Complementing these findings, Kołodziej et al.[38] documented a 35% reduction in parotid and a 10% reduction in submandibular protein concentrations in HFD-induced insulin-resistant (HFD-IR) mice, attributing these changes to insulin resistance and altered metabolic regulation sensitivity. The negative correlation observed between plasma free fatty acids (FFA) and submandibular protein concentration, coupled with histological evidence of glandular vacuolization and neurotransmission disruptions, further corroborates this mechanism.

Zalewska et al.[24,39] further correlated the reduction in protein concentration with an increase in reactive oxygen species (ROS) and a decrease in antioxidant capacity, resulting in protein oxidation, organelle damage, and diminished synthesis. These alterations may contribute to the progression of oral diseases under conditions of metabolic stress. Additionally, a high-fat diet (HFD) influences immune and regulatory salivary proteins. Yamamoto et al.[40] reported a decrease in IgA-FR levels in rats fed an HFD compared to those on a low-fat diet,

suggesting that sympathetic activity modulates IgA secretion.[41] Conversely, Lasisi et al.[22] observed elevated salivary leptin levels in HFD-induced obese mice without significant changes in total protein or IgA levels.

In conclusion, both Żukowski et al.[28] and Zalewska et al.[17,32] have corroborated significant reductions in total protein levels within the parotid and submandibular glands following exposure to a high-fat diet (HFD). This phenomenon is attributed to impaired protein synthesis, dysfunction in exocytosis, insulin resistance, and apoptosis of acinar cells.

Inflammation serves as a critical mechanism connecting high-fat diet (HFD) exposure to dysfunction in salivary glands. Numerous studies have demonstrated that HFD induces both systemic and localized inflammatory responses within salivary tissues. Lungruammmit et al reported elevated levels of p-NF-κBSer536, total NF-κB, TNF-α, IL-1β, IL-6, IL-10, IL-22, and Ifng in the submandibular glands of mice subjected to HFD, indicating a robust activation of inflammatory signaling pathways. Similarly, Zalewska et al.[19,32] observed increased levels of TNF-α and IL-2 in animal models on an HFD, while Ittichaicharoen et al.[21] emphasized that prolonged HFD consumption activates the TNF-α/NF-κB pathways and Caspase-3 expression, thereby promoting apoptosis in acinar cells.

Zalewska et al.[33,42] demonstrated a significant increase in IL-1β and TNF-α levels within the mitochondrial fraction of the parotid and submandibular glands in mice subjected to a high-fat diet (HFD), thereby providing evidence of inflammation at the subcellular level. Similarly, Kolodziej et al.[38] reported that HFD induces inflammatory activation in adipocytes and macrophages, characterized by elevated expression of TNF-α, IL-6, IL-1β, and MCP-1, which facilitates the recruitment of M1 macrophages.

In accordance with these findings, Zalewska et al.[33,43] verified increased levels of IL-1β in the salivary glands and mitochondrial fractions of rats on a high-fat diet (HFD) compared to control groups. These results collectively imply that HFD persistently triggers inflammatory pathways through NF-κB signaling, proinflammatory cytokines, and apoptosis-related processes, resulting in inflammation and dysfunction of the salivary glands.

The consumption of a high-fat diet (HFD) consistently induces oxidative stress in salivary glands by disrupting the equilibrium between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the antioxidant defenses. Lungruammit et al.[19] reported a significant increase in malondialdehyde (MDA) levels in the submandibular glands of mice fed with an HFD, indicating lipid peroxidation and oxidative damage. This finding is consistent with the report by Tóthová et al.[44], who identified MDA as a well-established biomarker of oxidative stress.[45,46]

Zukowski et al.[28] reported elevated levels of TOS, AOPP, 4-HNE, and OSI in the salivary glands of rats subjected to a high-fat diet (HFD), which were attributed to excessive mitochondrial reactive oxygen species (ROS) generation.[29,30] Similarly, Zalewska et al.[32] identified increased levels of AGE, AOPP, LOOH, and MDA, suggesting enhanced mitochondrial lipid peroxidation. These effects were observed to persist after 16 weeks of HFD exposure, even in the absence of changes in saliva flow rate.[21,38]

The study conducted by Zalewska et al.[33] similarly identified elevated MDA levels within the mitochondrial fraction of the parotid and submandibular glands in rats subjected to a high-fat diet (HFD). In the subsequent year, Zalewska et al.[17] demonstrated a significant reduction in total antioxidant capacity (TAC), alongside notable increases in

total oxidant status (TOS) and oxidative stress index (OSI) in the homogenates of the parotid and submandibular glands of HFD rats. TAC serves as a crucial indicator of antioxidant defense, as it represents the body's overall antioxidant capacity. TOS, which indicates the total oxidant content in a sample, showed an expected increase in concentration within both salivary glands of HFD rats.[47] Furthermore, a high-fat diet resulted in elevated levels of 8-isoP, 4-HNE, AGE, and AOPP in the homogenates of the parotid and submandibular glands of HFD rats compared to controls. Isoprostanes may disrupt the structural integrity and fluidity of mucosal cell membranes, potentially impairing membrane receptor function and contributing to oxidative tissue injury.[48] Additionally, isoprostanes have been reported to modulate neurotransmitter release in several cell types, which may impair neural regulation of salivary gland function and contribute to reduced saliva secretion.[49]

Kołodziej et al.[40] identified the parotid gland as more susceptible than the submandibular gland, exhibiting greater increases in advanced oxidation protein products (AOPP) and protein carbonyls (PC) under conditions of insulin resistance.[38] In alignment with these findings, Maciejczyk et al reported elevated levels of salivary 4-hydroxynonenal (4-HNE), which were correlated with body weight and carbohydrate metabolism, thereby linking oxidative stress to inflammation.[18,47,50,51]

Moreover, Zalewska et al.[52] emphasized the impact of mitochondrial dysfunction by identifying increased levels of NO, peroxynitrite, nitrotyrosine, and H_2O_2 in the parotid and submandibular glands of HFD rats. The mitochondrial electron transport chain (mETC) is acknowledged as the principal source of reactive oxygen species (ROS),[53,54] and disruptions in this system have been correlated with salivary gland dysfunction in various disease states.[32,43,55] The rise in H_2O_2 can also result from the activity of the NADPH oxidase isoform NOX4, which tends to increase in response to high glucose and free fatty acid concentrations.[56–59] The accumulation of ROS subsequently triggers signaling pathways such as NF-κB, leading to the release of inflammatory cytokines, cellular damage, and apoptosis. Additionally, research by Zalewska et al.[17,43] indicates distinct oxidative stress patterns between the parotid and submandibular glands. Specifically, MDA and NO concentrations were elevated in the parotid gland, whereas H_2O_2 production and the redox ratio were higher in the submandibular gland.

High-fat diet (HFD) has been shown to decrease total antioxidant capacity (TAC), elevate oxidative biomarkers such as total oxidant status (TOS), oxidative stress index (OSI), advanced glycation end-products (AGE), advanced oxidation protein products (AOPP), and 4-hydroxynonenal (4-HNE), and induce mitochondrial dysfunction. These findings corroborate the role of oxidative stress as a central mechanism underlying HFD-induced damage to the salivary glands.

Huang et al.[36] reported that exposure to a high-fat diet (HFD) in diet-induced obese (DIO) mice resulted in the decreased expression of 212 genes within the salivary glands. These genes are primarily associated with the secretory pathway, extracellular matrix, membrane channels (Aqp2, Bsnd, Clcnka, Hcn2, Kcnip2, Kcnj8, Slc2a4, Tmem158), and protein trafficking (Rab17, Snca). This downregulation led to impaired exocrine function, as evidenced by reduced production of MUC20, MUC13, and α-amylase, along with decreased stimulated saliva flow and mucin content. These findings are consistent with previous observations in obese rats and humans, which have demonstrated reduced saliva secretion and protein concentration.[10,11,13]

Invariably, Zalewska et al.[17] identified a significant reduction in both stimulated and unstimulated saliva secretion in high-fat diet (HFD) rats, while Kołodziej et al.[38] documented a 45% decrease in stimulated salivary flow in insulin-resistant (IR) mice. Zukowski et al.[28] also observed impaired protein synthesis and secretion, particularly within the parotid gland, which is the primary contributor to stimulated saliva. Although the weight of the parotid gland increased in HFD rats, there was a marked decrease in stimulated secretion, attributed to acinar apoptosis and diminished regenerative capacity.[32,60] Similar findings were reported by Zalewska et al.[52,61] in subsequent studies, where only stimulated flow was affected. Chronic exposure to a high-fat diet may irreversibly reduce stimulated secretion through mechanisms such as fat accumulation, alterations in neurotransmission, and decreased sensitivity of muscarinic receptors.[24,28,32,38]

In contrast, Ittichaicharoen et al.[23] reported no significant difference in salivary flow despite metabolic alterations, suggesting the presence of compensatory mechanisms.[21] Salivary flow is regulated by intracellular calcium concentrations within acinar cells; therefore, researchers evaluated calcium regulation by measuring calcium transients.[62,63] The results indicated intracellular calcium dyshomeostasis in HFD mice. This finding was unexpected, as intracellular calcium transients and mitochondrial dysfunction were observed in the salivary glands, yet salivary secretion remained unaffected. The lack of differences in intracellular calcium levels between HFD and ND mice suggests that acinar cells can maintain salivary secretion at a comparable rate. This consistency is further supported by the observation that AQP5 protein expression did not significantly change in the HFD group. Consequently, the authors conclude that a compensatory mechanism preserves salivary secretion function, specifically the degree of transient intracellular calcium dysfunction that is insufficiently severe to disrupt secretion, along with the maintenance of mitochondrial dynamic balance, ensuring adequate ATP production to support normal salivary secretion.[21] Similarly, Lasisi et al.[21] found no significant differences in flow rate, M3R, Na^+/K^+-ATPase, or AQP5 expression between obese and control mice, consistent with previous findings.

Variations among studies may arise due to differences in diet duration, gland type, and metabolic severity. De Carvalho et al.[64,65] demonstrated that a 3-month high-fat diet (HFD) increased body weight without affecting submandibular gland mass, while it decreased adiponectin and tyrosine hydroxylase (TH) levels, suggesting impaired sympathetic innervation and reduced protein secretion via adrenergic pathways. In alignment with these findings, research by Yamamoto et al.[40] also indicated that a high-fat diet reduced TH levels in the submandibular glands of rats. TH is a rate-limiting enzyme in catecholamine synthesis and serves as a crucial marker of sympathetic nerve activation. Its decreased expression is associated with reduced pIgR expression in the submandibular gland (SMG) and diminished levels of IgA FR in saliva.

Lungruammit et al.[19] further demonstrated the presence of fibrosis and a reduction in AQP5 expression in the submandibular glands of rats subjected to a high-fat diet, which correlates with diminished saliva flow. AQP5, a crucial water channel involved in acinar secretion, is also associated with lipid metabolism, the regulation of oxidative stress, and the pathophysiology of diabetes.[26,66–69] A decrease in the expression of the antioxidant enzyme GPX4 exacerbates lipid peroxidation and further downregulates AQP5, thereby aggravating glandular dysfunction.[26,27]

Research investigating the histological impacts of a high-fat diet (HFD) on salivary glands has yielded diverse findings. Selim et al.[20] identified that a 3-month HFD resulted in fibrosis, mononuclear infiltration, vascular dilation, pyknotic nuclei, vacuolization, and lipid droplet accumulation in parotid acinar cells. These inflammatory and degenerative changes may hinder nutrient diffusion and cellular function.[70,71] Lipid accumulation, corroborated by electron microscopy, mirrors findings in other organs such as the liver, kidneys, and pancreas.[72–76] Reactive oxygen species (ROS)-induced lipid peroxidation likely exacerbates these effects by disrupting protein synthesis and secretory granules.[77,78] Similarly, Al-Serwi et al.[79–81] reported degeneration in the submandibular and sublingual glands, characterized by reduced acinar cells, vacuolization, and decreased serous granules, indicating impaired enzyme and mucin secretion.

In contrast, Huang et al.[36] observed a reduction in mucus secretion without any structural damage to the acini or ducts after 30 weeks of a high-fat diet (HFD). Meanwhile, de Carvalho et al.[64] and Pisiriciler et al.[72] reported either an absence of lipid deposition or only mild intracellular lipid accumulation, predominantly in the parotid and sublingual glands. Kołodziej et al.[38] documented increased vacuolization and lipid-related enlargement in the parotid glands compared to the submandibular glands, which aligns with the greater susceptibility of parotid tissue to fat deposition.

Lungruammit et al.[21] identified fibrosis in the submandibular glands, which correlated with decreased AQP5 expression,[19] while Liu et al.[29] described acinar atrophy and ductal dilation without lipid deposition.[26] In contrast, Yamamoto et al,[40] Kikuchi et al,[82] and Lasisi et al.[22] reported no significant histopathological changes or lipid accumulation following 10–15 weeks of HFD.

However, Kandeel et al[83] identified degenerative characteristics, including congested vessels, acinar and ductal vacuolization, and inflammatory infiltration after six weeks of a high-fat diet (HFD), which are consistent with diminished salivary function and xerostomia associated with obesity.[12,80,84] Similarly, Zalewska et al. [33] and Kołodziej et al.[38] reported significant vacuolization in parotid glands, further highlighting their susceptibility to lipid-induced degeneration.

This scoping review effectively delineated consistent evidence concerning the effects of a high-fat diet (HFD) on salivary gland dysfunction and saliva composition. The findings fundamentally suggest that HFD induces molecular, cellular, and functional dysregulation within the salivary glands, which can be encapsulated by two primary mechanisms: oxidative stress and chronic inflammation. The majority of studies consistently report a significant reduction in the activity of salivary and glandular antioxidant enzymes, such as SOD, GPX4, and Peroxidase, which are unable to counteract the increased ROS production resulting from mitochondrial fatty acid oxidation.[18,19,28] This redox imbalance not only results in direct damage, as indicated by elevated levels of MDA, AOPP, and 4-HNE,[28,32,38,45,46] but also activates inflammatory pathways, characterized by increased pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and NF-κB activation,[19,32,42,43] ultimately leading to acinar cell apoptosis.[32] Mechanistically, this critical reduction in GPX4 is directly associated with increased lipid peroxidation and decreased expression of AQP5 (Aquaporin-5),[27] an essential water channel.[26,66] This establishes a crucial link between oxidative stress and impaired salivary secretion. Variations in enzymatic responses (e.g., decreased Px but increased SOD2 and CAT) highlight the presence of compensatory mechanisms that

likely depend on the phase of metabolic disease and the specific glandular location.[24,31]

The consequences of this molecular dysregulation manifest as exocrine dysfunction. Most studies indicate a reduction in salivary levels of proteins and digestive enzymes, such as α-amylase, which is associated with the downregulation of secretory genes and the inhibition of anabolic processes due to high-fat diet (HFD)-induced insulin resistance.[17,22,36,38] This finding is corroborated by histological evidence of acinar cell apoptosis, vacuolization, and fibrosis.[19,32,38] Functionally, the stimulated salivary flow rate is most susceptible to metabolic disturbances, consistent with the dominant role of the parotid gland in stimulated secretion.[17,28,38,52] However, this review also identifies a contradiction in salivary flow findings; some studies reported no change, potentially indicating temporary compensatory mechanisms, such as the maintenance of intracellular calcium transients and AQP5, during the early to intermediate phase of HFD exposure.[21,22,82] These discrepancies are likely influenced by the duration of HFD intervention, the specific gland type investigated, and the severity of insulin resistance attained.[64] Furthermore, the findings of reduced salivary protein concentration negatively correlating with plasma Free Fatty Acid (FFA) levels and morphological changes, such as vacuolization, further reinforce the hypothesis that salivary glands are sensitive target organs for systemic metabolic dysfunction. This is also supported by the reduced expression of genes such as Aqp2, Slc2a4, and Adrb1.[20,36,38] Collectively, these findings are illustrated in Figure 2, which summarizes the proposed mechanism by which HFD contributes to salivary gland dysfunction.

This review has several limitations. The literature search was limited to PubMed and Scopus because access to Web of Science was not available during the review process; therefore, relevant studies indexed exclusively in other databases may have been missed.

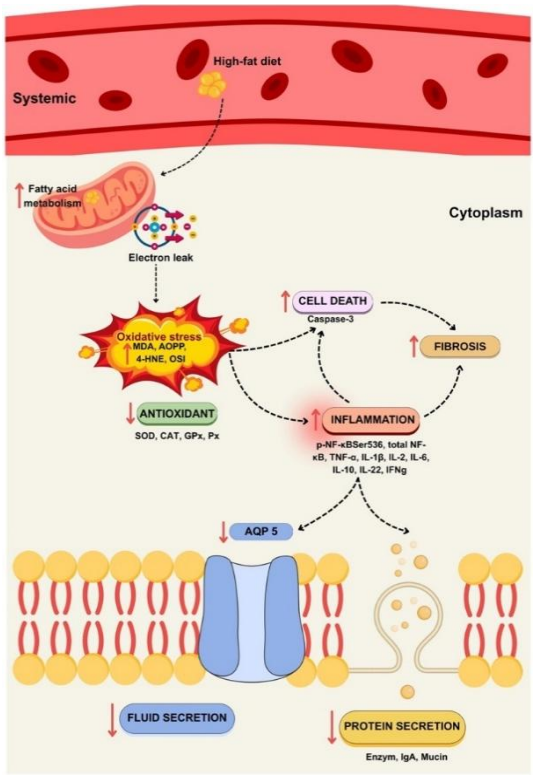

Figure 2. Proposed mechanism of salivary gland dysfunction induced by high-fat diet (HFD)

CONCLUSION

A high-fat diet (HFD) induces a series of pathological alterations in the salivary glands. Excessive fat consumption elevates the production of reactive oxygen species (ROS) and activates inflammatory pathways, thereby instigating oxidative stress and chronic inflammation. This condition directly impacts acinar and ductal cells, resulting in modifications in gene expression, enzyme activity, and the levels of critical proteins such as α-amylase, aquaporin-5 (AQP5), and secretory immune proteins.

A reduction in antioxidant capacity, coupled with an increase in oxidative biomarkers (MDA,

AGE, AOPP, 4-HNE) and proinflammatory cytokines (TNF-α, IL-1β, IL-6), accelerates cellular damage and disrupts secretory function. Structurally, these changes manifest as fibrosis, vacuolization, inflammatory cell infiltration, and lipid accumulation within glandular tissue. Ultimately, the accumulation of these processes impairs salivary gland function and structure, characterized by decreased secretion, alterations in saliva composition, and diminished protective capacity of saliva in the oral cavity. This condition heightens an individual's susceptibility to oral and systemic health disorders. Future research should encompass longitudinal analyses in animal models with varying durations of dietary exposure to differentiate between early and chronic changes, as well as translational studies in humans to validate the clinical relevance of a high-fat diet's effects on salivary function.

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