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The Role of AQP5 and CASP3 in the Pathogenesis of Submandibular Gland Acinar Cell Atrophy in Malnutrition

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ABSTRACT

Background: Malnutrition can impair the function and integrity of submandibular acinar cells, but the molecular mechanisms involving Aquaporin-5 (AQP5) and Caspase-3 (CASP3) in submandibular acinar cell atrophy are not yet fully understood. ***Objective:*** This systematic review aimed to synthesize and evaluate the scientific evidence regarding the effects of malnutrition on AQP5 expression and function in submandibular acinar cells, the role of CASP3 and apoptosis in acinar cell changes or atrophy, and the relationship between these mechanisms in malnutrition-associated submandibular acinar cell atrophy. ***Methods:*** The literature search, selection, and reporting processes were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A total of 15 articles that met the inclusion criteria were narratively analyzed based on their molecular focus and relevance to the research objectives. ***Results:*** The synthesis showed that AQP5 is an important component of water transport and salivary secretion, particularly through the regulation of its distribution and trafficking to the apical membrane of acinar cells. Meanwhile, CASP3 is a major component of the execution phase of apoptosis, contributing to acinar cell loss and potentially to acinar cell atrophy. ***Conclusion:*** AQP5 and CASP3 are involved in distinct processes that may converge in the impairment of acinar cell function and integrity. Findings from submandibular acinar cells and supporting studies on acinar tissue indicate that pathological environmental changes, metabolic stress, impaired membrane transport, and cell death may affect the function and structural integrity of acinar cells under chronic conditions.

Keywords: AQP5; CASP3; submandibular gland; malnutrition; good health and well-being

INTRODUCTION

Malnutrition is a health problem that can disrupt children's growth and development and affect the function of many organs, including oral health. In children with stunting, malnutrition can cause changes in saliva, such as a decreased flow rate and pH, increased viscosity, and reduced buffering capacity [1], [2], [3], [4], [5]. These changes may be related to disturbances in the submandibular gland, particularly the acinar cells that produce saliva. Nutrient deficiency can impair cell maintenance and survival, so that in the long term it can lead to structural changes and acinar cell atrophy [6], [7], [8], [9].

One of the proteins involved in salivary secretion is Aquaporin-5 (AQP5), a water channel found mainly in the apical membrane of acinar cells. AQP5 helps regulate the movement of water during saliva formation, so changes in its expression or function can affect salivary secretion [10], [11], [12]. In protein malnutrition, reduced salivary secretion has also been reported to be associated with decreased AQP5 expression in the submandibular gland [8].

Besides impaired secretion, malnutrition can also affect the number of acinar cells through apoptosis. Caspase-3 (CASP3) is one of the main proteins in apoptosis and directs cells toward programmed cell death. Increased apoptotic activity in the salivary glands can reduce the number of acinar cells and subsequently affect the structure and function of the gland [13], [14], [15].

Based on this, it is important to understand the relationship among malnutrition, changes in AQP5, and CASP3-mediated apoptosis in the development of submandibular gland acinar cell atrophy.

Therefore, this systematic review was conducted to examine and summarize the scientific evidence on the effect of malnutrition on AQP5, the role of CASP3 in acinar cell apoptosis, and the relationship of both with structural changes and the occurrence of submandibular gland acinar cell atrophy.

METHODS

This study used a Systematic Literature Review (SLR) approach to identify, analyze, and synthesize scientific evidence on the molecular mechanisms linking malnutrition to submandibular gland acinar cell atrophy, particularly through AQP5 and CASP3. This approach was used to obtain a systematic overview of the available research findings. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure that article identification and selection were transparent. The data analyzed were secondary data derived from research articles relevant to the focus of the review [16].

The literature search was conducted in Scopus and Crossref using Publish or Perish (PoP) software. PoP was used as a tool to search and collect article metadata from both sources. The search was limited to articles published between 2021 and 2026 to obtain relevant and relatively current literature. The search strategy used a combination of keywords and the Boolean operators AND and OR, as follows: ("malnutrition" OR "undernutrition" OR "protein malnutrition" OR "nutritional deficiency") AND ("submandibular gland" OR "salivary gland") AND ("acinar cell" OR "acinar atrophy") AND ("AQP5" OR "Aquaporin-5" OR "CASP3" OR "Caspase-3" OR "apoptosis")

The research question was formulated using the PICO framework (Population, Intervention/ Exposure, Comparison, and Outcome). The Population/Problem (P) component covered the submandibular gland or acinar cells under malnutrition, while the Intervention/Exposure (I) was malnutrition or nutrient deficiency. The Comparison (C) component was normal nutritional status or a control group, and the Outcome (O) covered changes in AQP5, CASP3/apoptosis, secretory function, and structural changes or acinar cell atrophy. This framework was used as the basis for determining the search focus and article selection criteria.

The inclusion criteria were: 1) primary research articles; 2) published between 2021 and 2026; 3) addressing malnutrition or nutrient deficiency; 4) involving the submandibular gland, salivary glands, or acinar cells; 5) evaluating AQP5, CASP3/ apoptosis, or structural and functional changes of acinar cells; 6) available in full text; and 7) written in English or Indonesian. The exclusion criteria were: 1) articles irrelevant to the research focus; 2) studies that did not provide appropriate empirical data; 3) reviews, editorials, comments, or other non-research publications; 4) articles without an available full text; and 5) duplicate articles. These criteria were applied consistently at the screening and eligibility stages to determine eligible studies. Thus, only articles with substantive relevance that met the methodological requirements were included in the review.

At the identification stage, 1,000 articles were obtained from the Scopus and Crossref searches through PoP. After checking for duplicates, 180 articles were removed, leaving 820 articles for screening. Based on title and abstract screening, 650 articles were excluded as irrelevant to the research focus, so 170 articles proceeded to full-text assessment. At the eligibility stage, 155 articles were excluded for not meeting the inclusion criteria, leaving 15 articles that met all criteria and were included in the final analysis [17]. This is presented in Figure 1, the PRISMA 2020 flow diagram, summarized below.

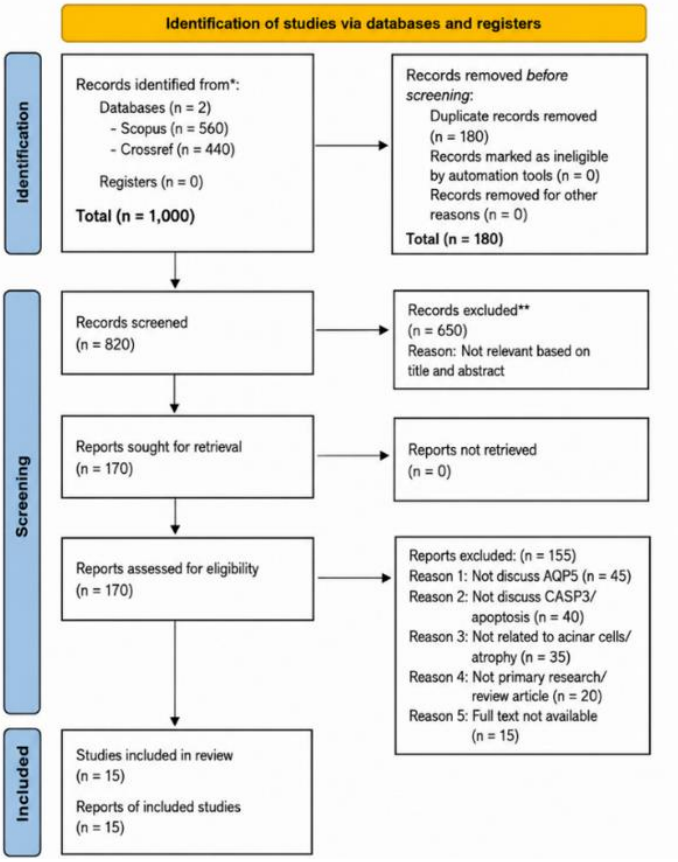

FIGURE 1: PRISMA 2020 flow diagram.

Data from the 15 selected articles were extracted systematically using predetermined components. The information collected included: 1) author and year of publication; 2) study design; 3) characteristics of the subjects or study model; 4) malnutrition condition; 5) AQP5 parameters; 6) CASP3/apoptosis parameters; 7) acinar cell changes or atrophy; and 8) main findings. These data were used to compare characteristics and results across studies. Extraction was also performed to identify patterns of relationship among malnutrition, changes in AQP5, apoptosis/CASP3, and structural changes of acinar cells.

The methodological quality and risk of bias of the 15 included articles were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. The JBI instruments were selected and adapted to the design

of each article to ensure that the quality assessment was relevant. The assessment covered the selection of subjects or samples, the suitability of the research methods, the measurement of variables and outcomes, the control of confounding factors, and the appropriateness of the analysis and reporting of results. The JBI results were used as a consideration in assessing the quality of evidence and interpreting the synthesis results of each study. The risk of bias results of the 15 selected articles are as follows:

TABLE 1: Risk of bias assessment results.

No.	Study	Risk of bias
1	Xu et al. (2024)	Low risk
2	Chen et al. (2023)	Low risk
3	Takeyasu et al. (2024)	Low risk
4	Manhas et al. (2024)	Moderate risk
5	Rump et al. (2022)	Low risk
6	Golnarnik et al. (2026)	Low risk
7	Sakai et al. (2026)	Low risk
8	Tiffner et al. (2022)	Moderate risk
9	Wu et al. (2024)	Low risk
10	Yuan et al. (2026)	Low risk
11	Storey (2024)	High risk
12	Korpela et al. (2022)	Moderate risk
13	Yildiz & Hartavi (2025)	Low risk
14	Keshara et al. (2026)	Low risk
15	Desai et al. (2024)	Low risk

Based on Table 1, the predominance of studies with a low risk of bias indicates that most of the evidence used in this systematic review has adequate methodological quality to support the synthesis on AQP5, CASP3, apoptosis, and acinar cell changes. Studies with a low risk of bias, especially Xu et al. (2024) and Chen et al. (2023), provide stronger support for the involvement of AQP5 in the secretory function of the submandibular gland, while studies evaluating CASP3 and apoptosis support its role in cell death mechanisms. Studies with a moderate or high risk of bias can still be used as supporting evidence, but their interpretation should be cautious, particularly because some studies used cell or tissue models other than the submandibular gland. Thus, risk of bias strengthens the interpretation of results when considered together with the suitability of the study model, so that evidence from studies with a low risk of bias was prioritized in explaining the mechanisms of AQP5 and CASP3 in acinar cell atrophy.

After obtaining the risk of bias results, data were analyzed using a thematic synthesis approach. The findings were grouped by the mechanistic focus studied: 1) the relationship between malnutrition and changes in AQP5 and secretory function of the submandibular gland; 2) the role of CASP3 and apoptosis in the loss or alteration of acinar cells; and 3) the relationship of AQP5 and CASP3 with structural changes or atrophy of acinar cells. The results of each group were compared to identify similarities, differences, and consistency of findings across studies. All findings were then integrated to provide an overview of the molecular mechanisms that may link malnutrition to submandibular gland acinar cell atrophy.

RESULTS

A total of 15 articles met the inclusion criteria and were used as the basis for the synthesis in this systematic review. The characteristics of the studies analyzed included author and year of publication, study design, research focus, and main findings related to AQP5, CASP3, apoptosis, acinar cell function, and glandular structural changes. This information is summarized in Table 2 to provide an overview of the studies that form the basis of the evidence synthesis in this systematic review.

TABLE 2: Characteristics of studies included in the systematic review.

No.	Author (year)	Study design	Research focus	Main findings
1	Xu et al. (2024)	Experimental, *in vitro*	AQP5 and salivary secretion	Impaired trafficking of AQP5 to the apical membrane reduced salivary secretion, showing the importance of AQP5 in acinar cell secretory function.
2	Chen et al. (2023)	Experimental, *in vitro*	AQP5 and gland hypofunction	TGF-β1 decreased AQP5 expression and protein secretion, showing a relationship between AQP5 changes and reduced secretory function.

No.	Author (year)	Study design	Research focus	Main findings
3	Golnarnik et al. (2026)	Experimental, *in vitro*	Oxidative stress and metabolic response	Oxidative stress caused changes in metabolic responses and the redox system in submandibular acinar cells.
4	Sakai et al. (2026)	Single-cell RNA sequencing	Molecular profile of acinar cells	Showed changes in gene expression in submandibular acinar cells related to cell maintenance and function.
5	Storey (2024)	Case report	Submandibular gland atrophy	Showed submandibular gland atrophy in a chronic pathological condition.
6	Rump et al. (2022)	Molecular/ genetic study	Regulation of AQP5 expression	The AQP5-1364A/C polymorphism was associated with changes in AQP5 promoter methylation that may affect AQP5 expression.
7	Wu et al. (2024)	Experimental, *in vitro*	CASP3 and apoptosis	Apoptosis induction accompanied by increased CASP3 supports the role of CASP3 as an executioner caspase in apoptosis.
8	Manhas (2024)	Computational modeling	Ca^{2+} dynamics and acinar cell function	Showed the importance of Ca^{2+} dynamics and organelle interactions in regulating acinar cell function.
9	Tiffner et al. (2022)	Mechanistic report	Ca^{2+} signaling and cell function	Ca^{2+} signaling through ion channels plays a role in various cellular processes related to cell function and survival.
10	Keshara et al. (2026)	Experimental, *in vitro*	Acinar cell specification	Identified molecular mechanisms regulating acinar cell specification and development.
11	Desai et al. (2024)	Experimental, *in vitro*	Acinar cell proliferation	GNAS activation affected acinar cell proliferation through PKA-dependent and PKA-independent mechanisms.
12	Korpela et al. (2022)	Observational/ histopathological	Fibrosis and acinar atrophy	Fibrosis and chronic inflammation were found together with acinar cell atrophy.
13	Yildiz & Hartavi (2025)	Experimental, *in vivo*	Acinar cell changes and survival	Showed changes in acinar cell responses under pathological tissue conditions.
14	Yuan et al. (2026)	Experimental/ molecular	CASP3 and apoptosis	CASP3 was involved in apoptotic mechanisms under cell injury.
15	Takeyasu et al. (2024)	Experimental, *in vitro*	Ion transport and salivary secretion	SGLT1 activity helped maintain Cl^- currents and supported secretory function of submandibular acinar cells.

Based on these study characteristics, the studies included in the systematic review provide evidence on acinar cell secretory function, AQP5 regulation, apoptosis/CASP3, and structural tissue changes. Studies that directly used submandibular gland cells or tissue provide the main evidence on AQP5 mechanisms, ion transport, cellular responses to stress, and glandular changes, whereas studies using other objects provide supporting information on apoptosis mechanisms, CASP3, and acinar cell maintenance. The findings of all studies were then mapped according to their contribution to the three objectives of the systematic review, namely changes in AQP5, the role of CASP3 and apoptosis, and the relationship of both mechanisms with changes and atrophy of submandibular gland acinar cells. This mapping is presented in Table 3 as the basis for the thematic synthesis in the Discussion.

TABLE 3: Mapping of studies by research objective focus.

Focus	Articles	Synthesis of main findings
Effect of malnutrition on AQP5 expression and function in the submandibular gland and acinar cells	Rump et al. (2022); Chen et al. (2023); Xu et al. (2024); Takeyasu et al. (2024); Golnarnik et al. (2026); Sakai et al. (2026)	Disturbed cell conditions and changes in the physiological environment can affect the expression, distribution, or function of AQP5 as well as membrane transport mechanisms in submandibular acinar cells. These changes may lead to impaired salivary secretion.
Role of CASP3 and apoptosis in changes or atrophy of submandibular gland acinar cells	Korpela et al. (2022); Wu et al. (2024); Storey (2024); Takahashi et al. (2025); Yuan et al. (2026)	CASP3 activation is an important part of the apoptosis mechanism. Increased apoptosis and loss of acinar cells can contribute to structural changes and a decrease in the number of secretory cells, leading to atrophy.

Focus	Articles	Synthesis of main findings
Relationship of AQP5 and CASP3 in the molecular mechanisms underlying malnutrition-related submandibular acinar cell atrophy	Chen et al. (2023); Xu et al. (2024); Wu et al. (2024); Storey (2024); Takahashi et al. (2025); Golnarnik et al. (2026)	AQP5 is mainly related to water transport and salivary secretion, whereas CASP3 is related to apoptosis and cell loss. Integrating both mechanisms suggests that impaired secretory function and increased acinar cell loss can proceed as two complementary pathways in the development of atrophy.

Based on the mapping in Table 3, the studies included in the systematic review show that the three research foci are interrelated in explaining changes in the function and structure of submandibular gland acinar cells.

Evidence on AQP5 mainly shows its role in maintaining water transport and salivary secretion, while evidence on CASP3 shows its involvement in apoptosis and cell loss. Meanwhile, research on metabolic changes, cellular stress, and acinar cell maintenance provides a basis for understanding the conditions that can affect the survival and function of secretory cells. Thus, the mapping results serve as the basis for synthesizing the molecular mechanisms among nutritional disturbance, AQP5 changes, apoptosis through CASP3, and submandibular gland acinar cell atrophy.

DISCUSSION

Effect of Malnutrition on AQP5 Expression and Function in the Submandibular Gland and Acinar Cells

The synthesis shows that changes in submandibular gland function under nutritional disturbance are related to changes in the secretory mechanisms of acinar cells, with Aquaporin-5 (AQP5) as one of the main components of water transport. Acinar cells are the main secretory unit of the salivary glands, so changes in their function and maintenance can affect salivary secretory capacity. Various studies show that AQP5 plays a direct role in salivary secretion through water transport and trafficking to the apical membrane of acinar cells [18], [19], [20].

The most specific evidence on the role of AQP5 in the submandibular gland was reported by Xu et al. (2024), who showed that cholinergic stimulation triggers the movement of AQP5 from intracellular vesicles to the apical membrane of acinar cells. Conversely, disruption of the SNAP23 protein inhibited this trafficking and reduced salivary secretion. This finding indicates that AQP5 function is determined not only by the amount of protein expressed but also by its distribution and movement to the apical membrane, which is required to maintain secretory activity [20].

This mechanism is relevant to malnutrition because the secretory function of acinar cells depends on the coordination of water, ion, and cellular energy transport. Takeyasu et al. (2024) showed that the activity of sodium-glucose cotransporter-1 (SGLT1) helps maintain Cl^- currents that support fluid secretion, while Manhas (2024) emphasized the importance of Ca^{2+} regulation in secretory function. Thus, disturbances of metabolism and cellular homeostasis that can occur in malnutrition may affect the secretory function of the submandibular gland.

The relationship between a pathological environment and changes in AQP5 is also supported by Chen et al. (2023), who showed that exposure to TGF-β1 decreased the expression and membrane distribution of AQP5 in human submandibular gland cells, accompanied by reduced secretory function. In addition, Rump et al. (2022) reported that AQP5 expression can be regulated by epigenetic mechanisms through promoter methylation. These findings show that changes in AQP5 function can occur through various mechanisms, at both the protein and gene regulation levels.

Besides AQP5, metabolic homeostasis also plays an important role in maintaining acinar cell function. Studies by Golnarnik et al. (2026) and Sakai et al. (2026) showed that changes in metabolic responses, redox regulation, and gene expression can affect the condition of submandibular acinar cells. Overall, the available evidence indicates that AQP5 is an important component of the secretory function of submandibular acinar cells through water transport and trafficking to the apical membrane. Changes in AQP5 expression, distribution, or function may contribute to decreased secretory function under disturbed cellular homeostasis, including conditions related to malnutrition.

Role of CASP3 and Apoptosis in Changes or Atrophy of Submandibular Gland Acinar Cells

The synthesis shows that apoptosis is an important mechanism in the loss of acinar cells during regressive processes or atrophy of the salivary glands. If apoptosis is excessive or persistent, the number of secretory cells can decrease, reducing the functional capacity of the gland. This concept is supported by various studies showing that changes in cell number and condition are an important part of the tissue atrophy process [15], [21], [22].

In the submandibular gland, atrophy is characterized by a reduction of acinar components and changes in tissue structure. Storey (2024) reported a case of bilateral submandibular gland atrophy associated with chronic sialolithiasis, showing that chronic disturbance can cause loss of tissue components and end in atrophy. This finding shows that atrophy is the end result of long-standing disturbances of homeostasis in the gland.

The involvement of apoptosis in atrophy is reinforced by Takahashi et al. (2025), who showed that apoptosis plays a role in eliminating acinar cells during

regressive processes of the salivary glands. Thus, the decrease in acinar cell number is caused not only by shrinkage of cell size but also by increased cell death and elimination. Studies of pancreatic acinar tissue also show that atrophy, inflammation, and tissue damage can occur together in chronic pathological conditions [21], [23].

At the molecular level, CASP3 is one of the main executioner caspases in the apoptosis pathway. CASP3 activation triggers the cleavage of various cellular proteins, leading to morphological changes and cell elimination. Although the studies by Wu et al. (2024) and Yuan et al. (2026) did not use submandibular acinar cells, both provide strong evidence that CASP3 plays an important role in the execution phase of apoptosis. In addition, the regulation of apoptosis is influenced by various cellular factors, including Ca^{2+} homeostasis and the response to cellular stress [18], [24].

In the context of malnutrition, an imbalance between cell survival and cell death can occur because energy and nutrient deficiency disrupts metabolism, protein synthesis, and organelle function. These conditions can increase cellular stress and trigger apoptosis through CASP3 activation. Therefore, CASP3 and apoptosis can be regarded as important components contributing to acinar cell loss and decreased secretory capacity in submandibular gland atrophy, although evidence directly linking malnutrition to increased CASP3 in submandibular acinar cells still requires further research.

Relationship of AQP5 and CASP3 in the Molecular Mechanisms Underlying Malnutrition-Related Submandibular Gland Acinar Cell Atrophy

Based on the synthesis results, AQP5 and CASP3 have different molecular functions but can contribute to the same disturbance in acinar cells, namely decreased function and cell loss. AQP5 plays a role in water transport and salivary secretion, whereas CASP3 plays a role in the execution phase of apoptosis. The secretory function of acinar cells itself depends on the coordination of water, ion, and Ca^{2+} transport and energy metabolism [18], [19], [20].

Under malnutrition, disturbances in nutrient and energy availability can disrupt cellular homeostasis. As a result, secretory function can decline through changes in the expression, distribution, or trafficking of AQP5, while prolonged cellular stress can activate apoptosis pathways involving CASP3. Both processes can potentially cause dysfunction of the remaining cells while also reducing the number of acinar cells. The role of AQP5 in secretory function is supported by Xu et al. (2024), who showed that impaired AQP5 trafficking inhibits salivary secretion in submandibular acinar cells. Chen et al. (2023) also reported that a change in the pathological environment was accompanied by decreased expression and membrane distribution of AQP5 as well as reduced secretory function. These findings show that changes in AQP5 have direct consequences for submandibular gland function.

On the cell loss side, Takahashi et al. (2025) showed that apoptosis plays a role in regressive processes and atrophy of the salivary glands, while Storey (2024) described submandibular gland atrophy resulting from chronic disturbance. In addition, various studies show that CASP3 is a main component of the apoptosis execution pathway and contributes to cell elimination, so it can be linked to the reduced acinar cell population.

Overall, the available evidence indicates that AQP5 and CASP3 lie on two different molecular pathways that can converge in the mechanism of acinar cell atrophy. AQP5 is related to impaired secretory function, whereas CASP3 is related to cell loss through apoptosis. Under malnutrition, disturbed metabolic homeostasis may affect both pathways simultaneously, thereby reducing the function, secretory capacity, and integrity of the acinar tissue of the submandibular gland.

CONCLUSION AND RECOMMENDATIONS

Based on the results of this systematic review, malnutrition potentially disrupts the homeostasis and function of submandibular gland acinar cells through changes in secretory mechanisms and cellular metabolic conditions. AQP5 plays an important role in water transport and trafficking to the apical membrane that supports salivary secretion, whereas CASP3 acts as an executioner caspase in apoptosis that can cause loss of acinar cells. Thus, impaired AQP5 function and increased apoptosis through CASP3 may contribute to decreased secretory capacity and structural changes of the gland toward atrophy.

Future studies are recommended to use malnutrition models directly in the submandibular gland or acinar cells, measuring AQP5 expression and distribution, AQP5 trafficking, CASP3 activation, apoptosis, and acinar cell morphological changes simultaneously. Such studies are needed to clarify the temporal and mechanistic relationships among nutritional disturbance, changes in secretory function, apoptosis activation, and the development of acinar cell atrophy, and to determine whether changes in AQP5 and CASP3 are interrelated mechanisms or two pathways that contribute in parallel to gland damage.

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