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Implication of serum and salivary albumin tests in the recent oral health related epidemiological studies: A narrative review

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ABSTRACT

Albumin is the most abundant protein in human serum and a specific amount of albumin also can be found in the saliva. It has several physiological functions such as blood colloidal osmotic pressure, antioxidant activity, binding and transporting of endogenous and exogenous substrates. We conducted an electronic search across several databases such as PubMed, Scopus, Cochrane, Embase and Science Direct using the relevant MeSH terms and keywords like "albumin", "serum albumin", "salivary albumin", "oral health" "dental caries" and "epidemiology". Only the epidemiological studies published between 2010 and 2023 were included. After the application of the inclusion criteria, a total of 51 studied were included in this narrative review. Serum and salivary albumin tests have been used in various aspects of oral health as a diagnostic and prognostic factor. Some of the results point out to a pattern of association while some of them are inconclusive and even contradictory. This narrative review discusses the role, significance and impact of albumin in epidemiological oral health related studies including the categories of periodontal health and disease, dental caries, oral function and hypofunction, nutrition and malnutrition, tooth loss and its treatment, diabetes and cancer. In addition, it offers a short manual for the researchers on when, where and how to use albumin tests in planning their study designs whether investigating an association or measure them as a covariate.

1. Introduction

Albumin, found in human serum at concentrations of 35–55 g/L, is the most abundant protein in vertebrate blood plasma. The liver produces 10–15 g of albumin daily, constituting 10 % of total protein synthesis, with a serum half-life of 15–20 days. Albumin levels are higher in the extravascular area than in the intravascular zone. Albumin makes 28 "journeys" throughout the lymphatic system over a person's lifetime (Azzazy and Christenson, 1997). After release by liver hepatocytes, albumin enters circulation through the liver, bone marrow, small intestine, and pancreatic endothelial pores. The kidneys and gastrointestinal tract usually catabolise only 6 % and 10 % of the albumin, respectively, leaving a balance of 84 % or 9 g/day between the skin and muscles (Levitt and Levitt, 2016).

Albumin produces 80 % of blood colloidal osmotic pressure and performs numerous important functions. Many endogenous chemicals bind to albumin (Rosenoer et al., 2014). Albumin transports copper, zinc, calcium, and other ions (Evans, 2002). Most drugs and toxins bind to albumin (Bteich, 2019) and are transported to the target tissues or biotransformation sites to determine their toxicokinetics. This protein may also dictate the half-lives of warfarin and ibuprofen (Quinlan et al., 2005). Many experimental solid tumours retain albumin in their tissues (Heneweer et al., 2011). Albumin retention and accumulation in the tumour interstitium make it a promising therapeutic carrier for targeted cancer therapy (Kratz, 2008).

Albumin transports bilirubin, a haeme breakdown byproduct, to the liver for excretion (Merlot et al., 2014). Albumin serves as an antioxidant, while oxidised albumin is an oxidative stress marker in diabetes,

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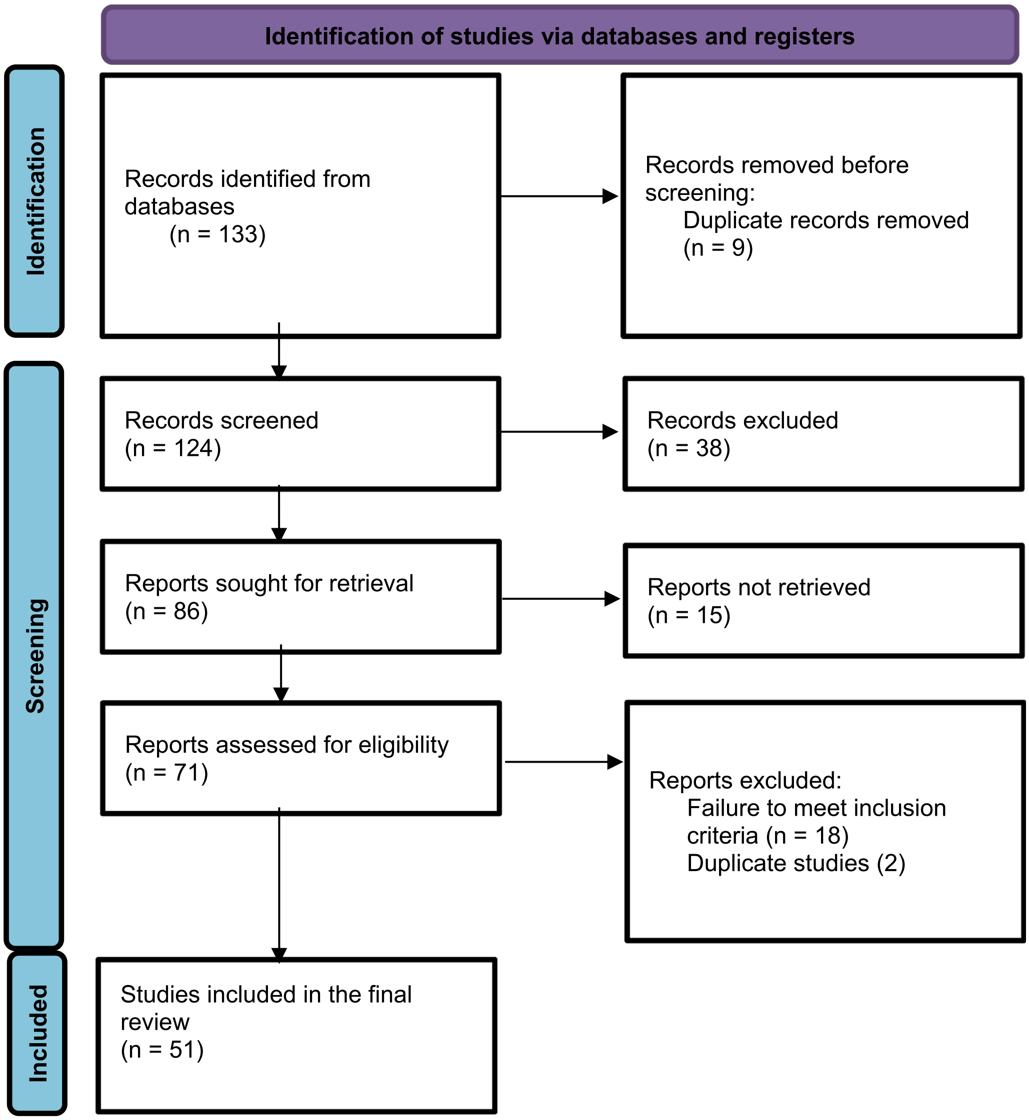

Fig. 1. PRISMA flowchart of the studies selection process.

renal, and liver disease patients (Roche et al., 2008).

Serum albumin level has long been used as a nutritional tool for diagnosing and predicting degenerative, inflammatory, and malignant disorders. A level below 35 g/L indicates hypoalbuminaemia, now considered a risk factor and predictor of morbidity and mortality regardless of age, sex, medical conditions, or polymorphisms. Several studies have examined the serum albumin levels in infections and cancers (Yang et al., 2016). Lower albumin concentrations were associated with worse outcomes in chronic obstructive pulmonary disease COPD, pancreatitis, coronary vascular disease, and all intensive care admissions (Gunen et al., 2005). Mortality risk in haemodialysis patients can be calculated using C-reactive protein and albumin levels (Hwang et al., 2015). During the coronavirus pandemic, an inverse correlation between disease severity (Aziz et al., 2020), COVID-19 mortality (Violi et al., 2021), and serum albumin level was noted. The anticoagulant and antioxidant capabilities of albumin might explain this association.

In most diseases, albumin level, a negative acute-phase reactant, is decreased (Levitt and Levitt, 2016). Low serum albumin is associated with poor health owing to its importance in normal health (even small variations in its concentration can reduce its benefits) and its role as an indicator of various illnesses, even in seemingly healthy individuals (Soeters et al., 2019).

Serum and salivary albumin tests have been used to assess various aspects of oral health, such as periodontitis, dental caries, oral function, nutrition, tooth loss and its treatment, diabetes, and cancer. Albumin levels are considered by dental and oral health researchers for diagnosis and prognosis; results vary, with some indicating a relationship and others being inconclusive or conflicting. To our knowledge, there have been no previous reviews on the role of albumin in oral health. This narrative review aimed to 1) evaluate albumin's role, significance, and influence in epidemiological dental and oral health research since 2010; 2) offer researchers a brief guide on when and how to apply albumin testing in association or covariate studies; and 3) address the necessity and utility of checking serum and salivary albumin concentrations under specific conditions.

2. Methodology

In September 2023, an electronic search was conducted across several databases such as PubMed, Scopus, Cochrane, Embase and Science Direct were searched using the relevant MeSH terms and keywords such as "albumin", "serum albumin", "salivary albumin", "oral health" "dental caries" and "epidemiology". To ensure maximum coverage, a further search was conducted on Google Scholar and the reference list of the previously identified records. Article published between 2020 and 2023 that fulfilled the objective of the study were selected (n = 133).

Table 1
Selected studies on serum/salivary albumin levels in periodontal health and disease.

Author, year (References)	Sample description and size	Study design	Exposure	Outcome	Type of studied albumin	Findings	Albumin significance*
(Ebersole et al., 2013)	80 participants (30 healthy and 50 adults with chronic periodontitis).	Case-control	Salivary biomarkers: Albumin, interleukin-1β, TNF-α, IL-6, PGE2 and MMP-8	Distinguishing healthy periodontium from chronic periodontitis	Salivary albumin	Salivary albumin, IL-6, IL-1β, and MMP-8 were considerably higher while IFN-α was reduced in periodontitis cases compared with healthy people.	Yes
(Verhulst et al., 2019)	156 patients (≥18 years of age)	Cross-sectional	Self-reported oral health and salivary biomarkers (albumin, MMP-8, chitinase and protease activities)	Periodontitis	Salivary albumin	Albumin level was increased in patients with severe periodontitis.	Yes
(Iqbal et al., 2015)	50 healthy patients classified in two groups: healthy and patients clinically diagnosed as AgP.	Cross-sectional	Laboratory blood investigations (WBC, neutrophil, lymphocyte and platelet count). Serum proteins (total protein, albumin and globulin).	AgP	Serum albumin	Patients with AgP had elevated blood parameters and decreased serum protein levels including albumin.	No
(Gopinath et al., 2019)	90 participants were split into two groups: healthy and chronic periodontitis.	Case-control study	Salivary albumin levels	Healthy periodontium and chronic periodontitis	Salivary albumin	Chronic periodontitis patients had higher salivary albumin levels than individuals.	Yes
(Shaila et al., 2013)	120 subjects grouped as controls, gingivitis and periodontitis.	Case-control study	Total salivary protein, albumin, buffering capacity, pH and flow rate	Comparison between normal, gingivitis and periodontitis	Salivary albumin	In gingivitis and periodontitis, albumin and salivary total protein were higher than in healthy participants.	Yes
(Nagao and Tanigawa, 2019)	47 LC patients were separated into high and low red complex bacteria groups.	Cross-sectional	Number of red complex periodontal pathogens	Liver cirrhosis	Serum albumin	LC patients were more likely to have red complex bacteria, which causes periodontal disease. One major risk factor between groups was the albumin level.	Yes
(Grønkjær et al., 2016)	110 LC patients	Cross-sectional	Periapical radiolucency	Liver cirrhosis	Serum albumin	Individuals with periapical radiolucency had decreased albumin levels.	Yes

* Reported statistical significance, AgP: aggressive periodontitis, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, IFN-α: interferon-α, MMP-8: matrix metalloproteinase-8, PGE2: prostaglandin E2, LC: liver cirrhosis.

Only the epidemiological studies were included. All the *in-vitro* and animal studies were excluded. After removal of the duplicates, the inclusion criteria were applied to yield 71 records for eligibility. Furthermore, 20 reports were excluded mostly due to failure to meet the exact inclusion criteria. Finally 51 papers were included in the narrative review. Fig. 1 shows the flowchart of the study selection process.

3. Serum and salivary albumin tests in recent oral health-related epidemiological studies

3.1. Periodontal disease

Chronic periodontitis is caused by a wide variety of bacteria. Periodontal injury can result from pathogen products and host reactions to plaque bacteria and chemicals. Periodontitis may cause systemic inflammation and raise the risk of many diseases (Iqbal et al., 2015).

Biomarkers, including serum and salivary albumin, have been used to study periodontal health and disease. Table 1 summarises the selected articles and their conclusions. Most practitioners can distinguish established periodontitis from a healthy periodontium, but the clinical presentation still makes the diagnosis of early periodontitis challenging (Ghiabi and Weerasinghe, 2011). Owing to its increased frequency, comorbidities, and high treatment costs, periodontitis development and progression should be screened and diagnosed early. Several researchers have used serum and salivary albumin levels to distinguish periodontitis and gingivitis from healthy gums. Among these, one promising screening tool that uses a quick and easy oral rinse protocol has shown good specificity and sensitivity (Verhulst et al., 2019).

Natto et al. reviewed the most common chronic periodontitis classifications and variables worldwide. The least-studied variables in 351 studies were albumin and creatinine (Natto et al., 2018). A meta-analysis of five controlled trials found no significant differences in albumin and IL-6 levels after 3 or 6 months of nonsurgical periodontal therapy in haemodialysis patients (Yue et al., 2020). In a multicentre trial of 11,160 patients under general anaesthesia, perioperative oral management significantly improved serum albumin levels (Yamada et al., 2021). A meta-analysis of salivary markers of periodontal disease found that smokers had higher salivary albumin levels (Noh et al., 2022). In liver disorders where liver proteins like albumin decrease, low serum albumin levels have been linked to periapical periodontitis (Grønkjær et al., 2016). Moreover, red complex periodontal pathogens and liver cirrhosis are associated with serum albumin as independent covariates (Nagao and Tanigawa, 2019).

As mentioned in the introduction, serum albumin levels decrease in most diseases. Similarly, periodontal disease patients exhibited lower serum albumin levels than healthy individuals. Interestingly, in periodontitis cases, salivary albumin levels increased. The exact mechanism remains unknown, but it is hypothesised that chronic periodontitis decreases the liver's albumin production capacity, leading to increased albumin infiltration into saliva in response to local irritation. Salivary proteomics may also elevate owing to local bacterial plaque inflammation. In conclusion, serum/salivary albumin, along with other markers, can be used to diagnose and prognosticate periodontitis, especially in its early stages.

3.2. Dental caries

Dental caries are caused by an interaction between cariogenic

Table 2
Selected studies on serum and salivary albumin levels in dental caries.

Author, year (References)	Sample description and size	Study design	Exposure	Outcome	Type of studied albumin	Findings	Albumin significance*
(Yoshihara et al., 2007)	266 persons followed-up for annual examinations for 6 years.	Longitudinal	Serum albumin concentrations	Root caries	Serum albumin	Lower serum albumin was significantly associated with root caries lesions.	Yes
(Hegde et al., 2014)	80 participants (20–30 years old) were distributed into four groups: control group, pulpal caries, dentinal caries, and enamel caries.	Cross-sectional	Serum and salivary albumin levels	Dental caries	Serum and salivary albumin	When compared to the control groups, caries-prone patients had lower serum and salivary albumin levels.	Yes
(Schroth et al., 2013)	266 subjects: 122 caries-free controls and 144 preschoolers with S-ECC.	Case-control	Serum albumin Vitamin D, calcium and parathyroid hormone	S-ECC	Serum albumin	Children with S-ECC exhibited significantly lower levels of albumin, vitamin D, and calcium than the group without caries.	Yes
(Mungia et al., 2008)	811 dentate volunteers, aged 35–75, were separated into four age groups.	Cross-sectional	Salivary components including albumin, IgA, lactoferrin, lysozyme, mucin, cystatin, mucin, $K+$, $Ca + 2$, $Na+$, and Cl.	Dental caries (measured by DMFT)	Salivary albumin	Caries, age, and salivary proteins including albumin were significantly correlated.	Yes
(Jha, Jha et al., 2021)	266 child participants (S-ECC group and caries-free groups)	Cross-sectional	Serum albumin, Vitamin D3, hemoglobin, ferritin, $Ca++$ and TRH.	S-ECC	Serum albumin	Serum albumin, Vitamin D3 and $Ca++$ concentrations were significantly deficient in S-ECC youngsters compared to caries-free group.	Yes
(Rafieian Kupaei et al., 2013)	108 patients aged 13–19 years categorized in 3 groups of mild, moderate and severe dental caries.	Cross-sectional	Salivary albumin levels	Dental caries evaluated by DMFT	Salivary albumin	No statistical significance between the groups.	No
(Khandelwal and Palanivelu, 2019)	60 healthy adults (18–40 years) categorized according to DMFT	Cross-sectional	Salivary albumin levels	Dental caries	Salivary albumin	With lower salivary albumin, caries incidence increased.	Yes

* Reported statistical significance, S-ECC: Severe-early childhood caries, IgA: Immunoglobulin A, DMFT: Decayed, missed and filled teeth, TRH: Thyrotropin-releasing hormone.

bacteria, the oral microenvironment, and the host's reaction. Several hereditary and environmental factors influence tooth decay. Salivary proteomics are a contributing factor. Salivary glycoproteins retain and remineralise hydroxyapatite microcrystals (Devarajan and Somasundaram, 2019). Vitorino et al. (2005) found a significant correlation between high phosphopeptide levels and the absence of caries, demonstrating their importance in tooth integrity. Cystatin, statherin, histatin, and proline-rich pellicle proteins are too large to enter enamel pores; instead, they remain linked to hydroxyapatite, facilitating mineral penetration for remineralisation and preventing their outflow. This stabilises the hydroxyapatite crystals of the enamel (Devarajan and Somasundaram, 2019). Albumin has a molecular weight similar to that of protective pellicle proteins. This may explain why individuals with higher albumin levels have lower caries levels.

In an epidemiological study, 18.6 % of children with severe-early childhood caries had hypoalbuminaemia and were 3.6 times more likely to have low albumin concentrations (Schroth et al., 2013). Caries-prone patients had lower blood and salivary albumin levels than the control group, although only salivary albumin levels were significantly different (Hegde et al., 2014). In Mungia et al. (2008) reported a significant association between albumin levels and dental caries. This conclusion supported two longitudinal studies by Yoshihara et al. (Yoshihara et al., 2007) and (Yoshihara et al., 2003) that linked serum albumin levels to dental caries. A thorough analysis of salivary biomarkers for caries detection revealed that salivary albumin affects dental plaque inflammation and disease severity. Furthermore, salivary albumin levels are negatively correlated with dental caries, with lower levels resulting in more caries (Alamoudi et al., 2022). However, cross-sectional research on 13–19-year-olds found no difference (Rafieian Kupaei et al., 2013). In contrast to periodontitis patients, dental caries patients have lower serum and salivary albumin levels. The key findings of the selected epidemiological studies are listed in Table 2.

Conversely, albumin is found in the demineralisation zone of white opaque enamel caries, suggesting that inhibits remineralisation (Shore et al., 2000). Perez et al. found serum albumin in the hypomineralised enamel of 6-year-old molars, suggesting that albumin entrapment worsens the disease. A comparison of chalky and hard-white enamel revealed a dose–response relationship between albumin and clinical hardness (Perez et al., 2020). A comparable study found that albumin and other proteins were overexpressed in molar and incisor hypomineralisation-infected enamel, indicating that albumin may hinder hydroxyapatite crystal formation (Mukhtar et al., 2022).

In conclusion, tooth caries and albumin levels may be associated. However, the correlation's nature, direction, and degree is unclear. Further research is required to understand this relationship and its underlying mechanisms.

3.3. Oral function and hypofunction

Oral hypofunction or oral frailty is a recent concept concerning basic oral function in older adults. Physical performance and oral function deteriorate in people aged ≥70 (Iinuma et al., 2012). Oral hypofunction is a complex issue caused not only by aging but also by numerous diseases. Oral hypofunction is diagnosed by measuring seven parameters: oral hygiene, oral dryness, tongue pressure, tongue-lip motor strength, occlusal force, mastication ability, and swallowing (Kugimiya et al., 2021).

Oral hypofunction directly affects malnutrition in older age groups. Several studies have investigated oral hypofunction by using an integrated serum albumin test as a representative measure of nutritional status. A strong association between oral frailty and lower albumin levels has been reported, emphasising the importance of oral function

Table 3
A list of selected studies on the serum/salivary albumin levels used in oral health researches related with nutrition and malnutrition.

Author, year (References)	Sample description and size	Study design	Exposure	Outcome	Type of studied albumin	Findings	Albumin significance *
(Motokawa et al., 2021)	509 community-dwelling elders	Cross-sectional	Chewing ability	Nutritional status (undernutrition was examined by serum albumin levels.)	Serum albumin	Chewing ability was closely associated with undernutrition measured by serum albumin as well as nutrient and food intake.	Yes
(Poisson et al., 2016)	159 consecutive inpatients with the mean age of 85	Cross-sectional	Dysphagia (assessed by using the water test) and oral health status.	Nutritional status (malnutrition indicated by: BMI, MNA or serum albumin)	Serum albumin	Poor oral health significantly correlated with malnutrition. Dysphagia and candidiasis were strongly associated with albumin, but not BMI, salivary flow, or posterior occluding pairs.	Yes
(Ohshima et al., 2020)	880 hospitalized patients (median age: 76 years)	Cross-sectional	OAG (A scale including eight items: swallowing, voice, oral mucosa, tongue, lips, saliva, teeth and gingiva)	Hypoalbuminemia	Serum albumin	Hypoalbuminemia was linked to poor oral health in hospitalized individuals.	Yes
(Okada et al., 2010)	200 subjects (mean age: 76)	Cross-sectional	Chewing ability and anthropometric measurements	Nutritional status	Serum albumin	Chewing ability and anthropometric parameters associated with serum albumin. Age, chewing skill, grip strength, and sex predicted serum albumin.	Partial
(Johansson et al., 2015)	108 participants, 54 diagnosed as having EDs	Case-control	Eating disorders	Salivary biochemical composition	Salivary albumin	Albumin and total protein were considerably greater in ED patients.	Yes
(Inui et al., 2017)	532 participants 50–79 years old community-dweller adults	Cross-sectional	Oral conditions (number of teeth and xerostomia)	Dysphagia	Serum albumin	Oral dryness and tooth count were linked to dysphagia, but not serum albumin.	No
(El Osta et al., 2022)	103 individuals, 70 years or older diagnosed with dementia	Cross-sectional	Number of PFUs	Anthropometric malnutrition measured by MUAC	Serum albumin	MUAC was associated with serum albumin level and the number of PFUs.	Yes
(Abe et al., 2021)	102 patients (65.6 ± 9.8 years) who have underwent surgery for OSCC.	Longitudinal	PNI (measured by serum albumin and blood lymphocyte count).	Overall and disease-free survival	Serum albumin	Patients with a higher PNI (including serum albumin levels) had higher chances of survival compared to the lower group of PNI.	Yes

* Reported statistical significance, PNI: Prognostic Nutritional index, MUAC: mid-upper arm circumference, DMFT: Decayed, missed and filled teeth, OAG: Oral Assessment Guide, BMI: Body mass index, PFUs: Posterior functional units, MNA: Mini nutritional assessment, OSCC: Oral squamous cell carcinoma, ED: Eating disorder.

and suggesting that the deterioration of oral function in frail elderly people impairs their nutritional intake (Watanabe et al., 2017; Watanabe et al., 2018; Iwasaki et al., 2020; Kugimiya et al., 2021). Thus, in community-dwelling older persons, maintaining overall dental health and function may help prevent malnutrition (Iwasaki et al., 2020). Conclusively, serum albumin level is a useful tool for monitoring the systemic and nutritional effects of oral function in older age groups.

3.4. Nutrition and malnutrition

Serum albumin levels have been utilised as a traditional nutritional indicator, although recent studies have questioned its validity (Merlot et al., 2014). Nevertheless, it can still determine nutritional status and systemic illness severity. Therefore, it has been used in research studying various aspects of oral and dental health. The important findings of the selected epidemiological studies are presented in Table 3.

Hypoalbuminaemia is also associated with poor oral health in hospitalised patients (Ohshima et al., 2020). Additionally, geriatric chewing skills and anthropometric measures are associated with serum albumin levels (Okada et al., 2010). Anthropometric malnutrition is related to serum albumin and posterior dental functional units in the older adults with dementia, emphasising the relevance of the dental criteria for malnutrition (El Osta et al., 2022). Older people's chewing ability is closely linked to undernutrition as determined by serum albumin (Motokawa et al., 2021), and salivary albumin was significantly greater in eating disorder (ED) patients than in controls (Johansson et al., 2015). Although the difference was difficult to explain, the authors observed that ED patients had more parotid gland swelling than controls.

Albumin level was significantly associated with dysphagia in elderly French people (Poisson et al., 2016), but serum albumin level was not associated with dysphagia in middle- and older-aged Japanese participants. Following oral squamous cell cancer resection surgery, serum albumin levels have been linked to overall survival (Abe et al., 2021). Lower posterior dental functional units and serum albumin levels have been associated with an increased risk of Alzheimer's disease (Popovac et al., 2021). Nutritional status and inflammation may link periodontal status to COPD and its progression (Terashima et al., 2017).

COVID-19 did not affect the oral health of older Japanese patients who underwent total hip or knee arthroplasty. However, serum albumin levels were lower, suggesting that the pandemic likely reduced the dietary quality (Matsuda et al., 2022). Similarly, the pandemic did not affect the serum albumin levels or oral health in older gastric cancer patients (Matsuda et al., 2021).

Thus, serum albumin level is a useful tool to assess oral health and nutritional status and their effects.

3.5. Tooth loss

Dental caries, periodontitis, and trauma can all lead to tooth loss. Nutritional studies have linked tooth loss with serum albumin levels. For instance, a reduced tooth count has been linked to low masticatory competence in males and females, as well as low serum albumin and BMI

Table 4
A list of selected studies on serum/salivary albumin levels in tooth loss and its treatment.

Author, year (References)	Sample description and size	Study design	Exposure	Outcome	Type of studied albumin	Findings	Albumin significance*
(Okamoto et al., 2019)	3134 participants (median age: 71 years)	Cross-sectional	Tooth loss, masticatory ability	Nutritional indices (serum albumin and BMI)	Serum albumin	Low tooth number was linked to poor mastication in both men and women. Decreased masticatory skill was linked to decreased female albumin and BMI.	Partial
(Felix Gomez et al., 2022)	10,481 individuals: 3,519 denture users and 6,962 controls.	Cohort/Case-control	Using dentures	Nutritional status	Serum albumin	Denture wearers had lower serum albumin and calcium. Among denture wearers, pre-post analysis revealed decreased serum albumin, calcium and creatinine.	Yes
(Yoshihara et al., 2013)	554 dentate subjects followed-up for 5 and10 years.	Longitudinal	Serum albumin levels	10-year tooth loss	Serum albumin	Long-term missing teeth were negatively linked with baseline serum albumin levels. Elderly hypoalbuminemia increases 5- and 10-year tooth loss.	Yes
(McKenna et al., 2012)	44 patients aged over 65 years participated: 21 underwent conventional treatment and 23 underwent functionally orientated treatment.	Randomized controlled clinical trial	Tooth replacement	Nutritional status evaluated by MNA and hematological markers including albumin	Serum albumin	The only nutritional parameter that improved significantly for both groups after therapy was MNA. No significant changes were seen across groups in haematological testing, including albumin.	No
(Hirotomi et al., 2015)	569 subjects (mean: 70 years) examined after 5-year follow-up.	Cohort	Number of teeth	5-year mortality	Serum albumin	After adjusting for relevant variables, patients with 20 or more teeth had a considerably reduced death risk than those with 19 or less. No significant albumin difference existed across groups.	No
(Ioannidou et al., 2014)	2,749 of CKD patients classified based on oral health status.	Cross-sectional	Tooth loss	Serum albumin,	Serum albumin	Serum albumin was the least in fully edentulous group without dentures. Tooth loss significantly affected serum albumin, protein, and calorie intake.	Yes
(Miura et al., 2020)	191 patients who underwent esophagectomy classified according to tooth loss and followed-up for 3 years.	Longitudinal	Tooth loss	Three-year overall survival after esophagectomy	Serum albumin	Fewer tooth loss improved overall survival. Tooth loss, clinical T stage, and preoperative serum albumin independently predicted the outcome.	Yes
(Nomura et al., 2020)	666 subjects aged 80 years followed for 20 years	Longitudinal	Serum albumin levels, number of remaining teeth, and self-assessed chewing ability	Mortality	Serum albumin	Serum albumin and self-assessed chewing skills independently influenced male mortality.	Yes
(Nakamura et al., 2019)	2049 individuals aged ≥50 years	Cross-sectional	Number of remaining teeth	Nutrient intake and serum albumin levels	Serum albumin	Fewer remaining teeth were linked to lower serum albumin and nutrition intake.	Yes

* Reported statistical significance, CKD: Chronic kidney disease, MNA: Mini Nutritional Assessment, BMI: Body mass index.

in females (Okamoto et al., 2019). Older persons with baseline hypoalbuminaemia show a high tooth loss rate after 5 or 10 years (Yoshihara et al., 2013). Self-assessed chewing ability and serum albumin levels are independent risk factors for mortality in older adults (Nomura et al., 2020). Furthermore, having fewer remaining teeth is associated with low serum albumin levels and low nutrient intake (Nakamura et al., 2019). In a large study of 2,749 chronic kidney disease patients, the fully edentulous group without dentures exhibited the lowest serum albumin levels, and tooth loss significantly affected serum albumin, protein, and energy intake, indicating that tooth loss is strongly associated with malnutrition.

Gomez et al. showed that denture wearers had lower serum albumin, calcium, and creatinine levels than controls, and completely edentulous denture wearers had even lower values (Felix Gomez et al., 2022). However, another study reported that prosthodontics did not improve serum albumin levels, although the small sample size of 44 patients may have obscured this finding (McKenna et al., 2012).

Several studies have linked tooth loss with mortality (Österberg et al., 2008; Hirotomi et al., 2015; Miura et al., 2020). For example, in a 5-year cohort study, patients with 20 or more teeth had a considerably lower mortality rate than those with fewer teeth, and each surviving tooth had increased longevity by 4 %. However, the serum albumin levels were similar between the groups (Hirotomi et al., 2015). In contrast, a 3-year study of esophageal cancer patients who underwent oesophagectomy indicated that those with less tooth loss survived better. Tooth loss, clinical tumour stage, and pretreatment serum albumin levels independently predict this correlation (Miura et al., 2020). Table 4 presents important findings from the selected studies.

According to the aforementioned and other studies, a bidirectional association exists between tooth loss and malnutrition, as represented by serum albumin measurements. Further research with larger sample sizes, including serum albumin testing, is required to determine how tooth replacement affects malnutrition correction.

Table 5
Selected studies on the serum/salivary albumin levels in oral health status of patients with cancer and premalignant lesions.

Author, year (References)	Sample description and size	Study design	Exposure	Outcome	Type of studied albumin	Findings	Albumin significance *
(Keinänen et al., 2021)	159 surgically treated OSCC patients followed-up for 3 months	Retrospective	Albumin, CRP/ albumin ratio and CRP.	3-month mortality	Serum albumin	CRP/albumin, not albumin, was higher in 3-month mortality group than in those who survived.	Partial
(Soutome et al., 2021)	53 cancer patients followed up for 1–2 years after treatment for cancer.	Retrospective	Cancer treatment	Dental caries and periodontal disease	Serum albumin	Albumin results were not significant before and after treatment.	No
(Maruyama et al., 2012)	50 primary head and neck cancer patients divided by serum albumin concentrations.	Case-control: high and low albumin groups	Serum albumin levels	Periodontal condition measured by PD, CAL, percentage of BOP and percentage of sites with plaque accumulation.	Serum albumin	The decreased serum albumin group had greater CAL and CRP than the normal group.	Yes
(Metgud and Patel, 2014)	45 subjects separated into three groups of 15: normal, oral pre-malignancy and oral cancer patients.	Cross-sectional	Serum and salivary albumin levels	Pre-malignancy and oral malignancy	Serum and salivary albumin	Compared to healthy people, blood albumin declined and salivary albumin increased in oral pre-malignancy and malignancy cases.	Yes
(Nobuhara et al., 2022)	1,926 patients with colorectal cancer: 808 patients received perioperative oral care and 1,118 did not receive care.	Case-control	Perioperative oral care	Postoperative site infection	Serum albumin	The oral care group had significantly fewer surgery site infections than the control group. Lack of perioperative dental care, low albumin, rectal malignancy, and blood loss were independent risk variables in multivariate analysis.	Yes
(Ahmad et al., 2022)	75 patients divided into 3 groups of 25 individuals: control, chewing tobacco habit without OSF, chewing tobacco habit with OSF.	Case-control	Serum albumin level	OSF	Serum albumin	Serum albumin was significantly reduced in patients with chewing tobacco habit with OSF compared to the control group.	Yes
(Dawood and Hasan, 2013)	33 patients with oral tumors aged 15–75 compared with healthy controls.	Case-control	Serum and salivary albumin	Oral tumors	Serum and salivary albumin	Compared to the control group, patients' serum albumin decreased and salivary albumin increased significantly.	Yes

* Reported statistical significance, OSCC: Oral squamous cell carcinoma, CRP: C-reactive protein, CAL: Clinical attachment loss, PD: Probing depth, BOP: Bleeding on probing, OSF: Oral submucous fibrosis.

3.6. Diabetes

Diabetes mellitus (DM) is a metabolic condition characterised by hyperglycaemia. DM promotes hyperglycaemia by decreasing insulin secretion and altering insulin activity. In oral health, diabetes increases the risk and severity of gingivitis, periodontitis, dental caries, salivary flow reduction, candidal infections, taste disturbances, ulcers, and delayed healing (Kudiyirickal and Pappachan, 2015).

DM increases the non-enzymatic condensation of carbohydrates, lipids, proteins, and nucleic acids, thereby generating advanced glycation end (AGE) products. AGEs are glycotoxins that disrupt cell structure and function and cause cytotoxicity. Owing to its abundance in the plasma, albumin is also sensitive to glycation; hence, it may predict DM risk, even in euglycaemia (Freitas et al., 2017). Therefore, a portion of the healthy plasma albumin undergoes glycation. Some studies suggest 10–20 % proteins glycation in normoglycaemic blood, rising to 40 % in diabetic blood. AGEs alter protein structure and function, making them immune system targets through autoantibodies. Antibodies against serum albumin have been detected in DM and atherosclerotic patients (Kudiyirickal and Pappachan, 2015).

Albumin reaches the mucosal secretions through saliva. Several studies have compared the serum and salivary albumin levels of DM patients to those of healthy individuals. Salivary albumin levels in diabetes patients vary; some show higher concentrations (Gheena et al., 2011; Shahbaz et al., 2015), while others show a decrease compared to controls (Hasan and Abdulsattar, 2015; Tabatabaei et al., 2021). Aberrant serum protein binding to the salivary glands and basement membranes increases the permeability and migration of albumin, other proteins, IgG, and IgA from the exocrine glands into tissues. Permeability of the basement membrane is common in diabetes (Abd-Elraheem and Mansour, 2017).

A study on serum albumin and root caries in type II diabetes found no significant link, whereas hypoalbuminaemia was strongly correlated with tooth number, with a 7 % decrease in the probability of missing extra teeth (Marlow et al., 2011). Periodontal therapy significantly decreases glycated haemoglobin levels but does not modify serum albumin levels. However, periodontal therapy significantly lowers urine albumin levels, a marker of diabetic renal disease (Hayashi et al., 2017). Glycated serum albumin reflects a 2-week glycaemic state, with substantial correlation between salivary and serum glycated albumin levels. Therefore, the salivary albumin test can replace the serum glucose test because it is non-invasive and less frequent than the finger-prick method, thus reducing diabetes care's invasiveness and expense (Aihara et al., 2023).

Salivary parameters, including albumin level, may assist in evaluating the general metabolic condition of DM patients. Further research is required to make these tests comparable to blood tests. However, the serum and salivary albumin levels of DM patients vary from those of healthy individuals, perhaps owing to the vast range of symptoms and the complexity of its mechanism in diverse populations.

3.7. Cancer and pre-malignancy

Serum albumin levels are lower in cancer patients than in healthy individuals, and baseline concentrations predict survival in various malignancies (Gupta and Lis, 2010). A multicentre research of 1,926 colorectal cancer patients indicated that oral care improved post-operative site infections. The oral care group had a considerably poorer outcome than the control group, and lower blood albumin levels were independent risk factors (Nobuhara et al., 2022). According to a meta-analysis of four studies, a low preoperative CRP/albumin (CAR) ratio was associated with a higher overall survival rate following surgery in oral squamous cell carcinoma OSCC patients (Lu et al., 2023). CAR, but not albumin, may predict the 3-month mortality in patients undergoing OSCC surgery (Keinänen et al., 2021).

Serum albumin levels decline and salivary albumin levels increase in oral pre-malignancy and malignancy cases compared to healthy individuals, suggesting that albumin may assist in the diagnosis and prognosis of oral cancer (Metgud and Patel, 2014). Chewing tobacco users with oral submucous fibrosis had lower serum albumin levels than controls (Ahmad et al., 2022). In oral cancer patients, serum albumin levels are lower and salivary albumin levels are higher than those in healthy controls (Dawood and Hasan, 2013). Serum albumin levels and clinical attachment loss, a marker of periodontitis, are associated with head and neck cancer (Maruyama et al., 2012). Serum albumin levels before and after cancer therapy did not indicate that the therapy worsened periodontal disease or dental caries (Soutome et al., 2021). Table 5 summarises the recent publications in this domain.

These data suggest that serum albumin level can predict cancer survival. Salivary albumin may also help distinguish oral premalignant from malignant patients. Cancer patients also exhibit increased serum and decreased salivary albumin levels.

4. Conclusion

This article reviewed the implications of serum and salivary albumin levels on various aspects of oral health such as periodontal health and disease, dental caries, oral function, nutrition and malnutrition, tooth loss and its treatment, diabetes, and cancer. Some studies searched for an association between the oral condition and albumin levels, whereas others used these tests as confounders while investigating another association. In diseases, a pattern of decrease in serum and increase in salivary albumin levels is observed compared to healthy states. However, mixed results have been reported. Currently, albumin levels are not been studied in detail in the oral health setting, indicating the need for additional high-quality research.

Serum and salivary albumin, together with other markers, can be used as diagnostic and prognostic biomarkers to assess the presence and severity of periodontitis, particularly during initial stages of the disease. There seems to be an association between dental caries and albumin levels; however, the exact nature and extent of this correlation remain unclear. In addition, serum albumin level is a useful tool for monitoring the systemic and nutritional effects of oral function in older age groups. Moreover, the serum albumin level is a good indicator of the interaction between oral health and nutritional status. The existing literature suggests that there is a bi-directional association between tooth loss and malnutrition represented by serum albumin measurements. In diabetes, salivary parameters, including albumin levels, can be used as supplementary tools to assess the general metabolic condition of patients. Finally, sufficient evidence supports the role of serum albumin levels in predicting cancer survival, and salivary albumin may be a promising diagnostic tool for differentiating between oral premalignant and malignant cases.

CRediT authorship contribution statement

Mohammed Khalid Mahmood: Conceptualization, Writing – original draft, Writing – review & editing, Methodology, Resources. **Handren Ameer Kurda:** Data curation, Investigation. **Balen Hamid Qadir:** Visualization, Methodology. **Herve Tassery:** Supervision, Project administration. **Romain Lan:** Supervision, Project administration. **Delphine Tardivo:** Supervision, Project administration. **Mohammed Aso Abdulghafor:** Visualization, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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