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ORIGINAL RESEARCH

MORPHOFUNCTIONAL FEATURES OF THE ORAL MUCOSA AND ITS REGENERATIVE POTENTIAL IN THE AGE ASPECT

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ABSTRACT

Background: Because they are considered biocompatible, tough and look great, zirconia crowns are commonly used instead of metal-ceramic restorations. The advantage of monolithic zirconia is that it does not include a veneer which can easily chip in bilayered restorations. Cementation technique can affect the toughness of the material. The purpose of this study was to compare between the fracture strength of monolithic and bilayered zirconia crowns cemented with either resin or glass ionomer cements.

Methods and Materials: Sixteen monolithic zirconia crowns and Sixteen bilayered zirconia crowns were fabricated using CAD/CAM technology and formed two groups called Group A and Group B. Each group was split into two new subgroups (eight each) dependent on the type of used cement, naming the subgroups with AR and BR groups for the adhesive resin cement and AG and BG groups for the glass ionomer cement. All crowns were prepared by air-abrasion and cemented onto epoxy resin dies, after which they were thermocycled (5,000 times, from 5°C to 55°C). Strength at fracture was determined on a universal testing machine and the types of fracture failure were explored using a scanning electron microscope.

Results: The fracture strength was much higher in monolithic zirconia crowns than in bilayered crowns, no matter the cement used. The average fracture strength was 2541 ± 349 N for AR, 2578 ± 339 N for AG, 1557 ± 418 N for BR and 1691 ± 526 N for BG. There were no major differences between adhesive and conventional cements used in crowns of the same type ($p > 0.05$). Even so, there were significant differences ($p < 0.001$) between crowns made from solid material and those made from two layers. Analysis of failures showed that monolithic crowns suffered major fractures, but the layer-separation problem arises with bilayered crowns.

Conclusion: The fracture resistance of monolithic zirconia crowns exceeded that of bilayered zirconia crowns, with this advantage noticeable regardless of the cementation method. Both adhesive resin and glass ionomer cements worked well clinically. For posterior restorations that are best suited to strong crowns, monolithic zirconia may be recommended.

Keywords: aging of the oral mucosa, oral aging, regeneration of the mucous membrane, age-related features of the mucous membrane, oral mucosa

INTRODUCTION

Modern dentistry faces a significant challenge—the rapid increase in elderly patients, which requires revising traditional treatment approaches. Recent advances in aging biology have provided new insights into age-related changes in the oral cavity, which are complex and progressive. The oral mucosa in the elderly undergoes physiological transformations: the epithelial layer thins, cellular renewal activity decreases, and protective properties change. Over time, these processes create a favorable environment for various pathologies.

Epidemiological data show a clear correlation between age and the frequency of dental diseases—older patients exhibit more pronounced and diverse oral lesions. Each case requires an individualized approach, considering not only local manifestations but also overall health. Treating elderly patients with multiple chronic conditions is particularly challenging, as it requires balancing treatment efficacy and safety.

Modern clinical guidelines emphasize the importance of preventive measures and gentle treatment techniques aimed at preserving natural teeth and maintaining quality of life. Interdisciplinary collaboration between dentists and other specialists is increasingly important for developing comprehensive care programs for elderly patients. These changes in gerontological dentistry open new opportunities for improving the dental health of the growing elderly population.

The oral mucosa (OM) is a highly specialized tissue consisting of three layers: epithelium, lamina propria, and submucosa [1, 2]. It serves as the first line of defense against external pathogenic influences and performs multiple functions, including barrier, sensory, secretory, immune, and thermoregulatory roles [3–5]. The OM has a high regenerative capacity, essential for recovery from daily mechanical and physiological damage. The epithelium and shedding of its outer layer ensure constant renewal. Newly formed cells maintain mucosal balance, while the removal of surface cells eliminates microorganisms. The protective function is also linked to specialized immune cells [5].

This systematic review presents the morphofunctional features of the OM, highlights the characteristics of its protective barrier, and examines its regenerative capacity in the context of aging. Special attention is given to the mechanisms underlying mucosal regeneration. The review also explores molecular factors in mucosal protection. Two key questions are addressed:

1. Are there structural differences in the OM between young and elderly individuals?
2. Does age affect the regenerative potential of the OM?

The aims of the study: To analyze available data on the structure, function, and regeneration of the OM in the age aspect.

METHODS

The methodology of this study complies with the PRISMA guidelines for systematic reviews and meta-analyses.

Data Sources:

Publications were searched in four electronic databases (PubMed, ScienceDirect, Google Scholar, and eLibrary) from 2014 to 2025.

Search strategy

The following keywords were used in the search (in Russian and in English): the structure of the oral mucosa, oral epithelium, intercellular junctions, epithelial barrier, wound healing, mucosal regeneration, saliva, immunological aspects of regeneration, influence of factors on regeneration, aging of the mucous membrane, aging of the oral mucosa, oral microbiome, regenerative potential of the mucous membrane. In addition, the bibliographic sources of the found publications were studied and suitable studies were additionally manually selected from them.

Data collection

The search was performed by five independent researchers and was last updated on March 25, 2025. Two independent reviewers (DAM & TGT) reviewed the titles and abstracts of each study to determine its compliance with the established inclusion and exclusion criteria. There were no restrictions on the language of publications.

Potentially eligible studies underwent a full-text review, and discrepancies between reviewers were resolved through discussion. First, articles obtained from the database search were identified; then, articles were selected, excluding duplicates and those not relevant to certain descriptors, by screening titles and abstracts; after this step, an eligibility check was performed with full text reading, excluding articles that did not meet the previously established criteria; finally, relevant articles were included in the review.

Inclusion criteria

The publications present the results of in vitro and in vivo studies, including: randomized controlled trials, controlled clinical trials, observational studies, multicenter studies, comparative studies, and literature reviews. The research included the results of studying the structure of the oral mucosa in the age aspect, the aging of the oral mucosa, the processes of wound healing of the mucous membrane in normal and pathological conditions, the influence of various factors on the regenerative abilities of the mucous membrane, changes in the regenerative potential of the oral mucosa with age.

There were no restrictions on minimum quality, minimum sample size, or number of patients.

Exclusion criteria

Publications were excluded from the review if: the age of the subjects was under 18; descriptive works without clearly structured results and conclusions; studies with insufficient information to extract data; letters to the editor; comments; unpublished works.

The effectiveness was assessed by summarizing the relevant data on the results obtained in the course of individual studies.

Data extraction

Six reviewers (DAM, TGT, EGM, MDS, GLS, NDG) extracted data from the included studies using a standardized data extraction form. Reviewers identify and document the threats to the validity of each study due to faulty execution or poor measurement. Discrepancies in data extraction were resolved by discussion.

Quality assessment

The effectiveness was assessed by summarizing the relevant results obtained in the course of individual studies. The aim of the study was to systematize information about the oral mucosa and its regenerative potential in the age aspect.

Data synthesis and analysis

The results of this review were reported following the PRISMA guidelines. A narrative synthesis of the findings was provided. Six independent reviewers (DAM, TGT, EGM, MDS, GLS, NDG) the texts, selecting texts that met the inclusion criteria. The year of publication, study methodology, population (number of patients, mean age of patients), study results, outcome.

Effect measures

The effectiveness was evaluated by synthesizing relevant outcome data extracted from selected studies. The outcome was to systematize information of the features of the structure, functioning and regeneration of the oral mucosa in the age aspect.

Risk of bias

The form collects information needed to monitor the status of screening, reviewing and summarizing each article by 4 reviewers. Developing tables that summarize the body of evidence. The form captures detailed descriptive data about the intervention and evaluation. Classifying other key characteristics of the intervention and assessing the quality of the study's execution. Reviewers identify and document the threats to the validity of each study due to faulty execution or poor measurement. This information is used as a criterion for continued inclusion of the study in the body of evidence for intervention.

Following the study design, it has identified domains rating the certainty of evidence: risk of bias, inconsistency and publication bias. To assess the risk of bias, each individual criterion was considered to have a low risk of bias, a high risk of bias, or an uncertain risk of bias (lack of information or uncertainty related to potential bias). Discrepancies between authors were resolved by consensus.

Clinical outcome

In the literature review, information of the features of the structure, functioning and regeneration of the oral mucosa in the age aspect.

Results of the search

Based on the criteria, 66 publications were selected and included in the systematic review. The research included the results of studying the structure of the oral mucosa in the age aspect, the aging of the oral mucosa, the processes of wound healing of the mucous membrane in normal and pathological conditions, the influence of various factors on the regenerative abilities of the mucous membrane, changes in the regenerative potential of the oral mucosa with age.

RESULTS

Initially, 8,052 publications were screened by date, title, and abstract. Duplicates were removed, leaving 5,874 unique publications. After reviewing titles, abstracts, and conclusions,3,298 publications were excluded for irrelevance. The selection process is illustrated in Figure 1.

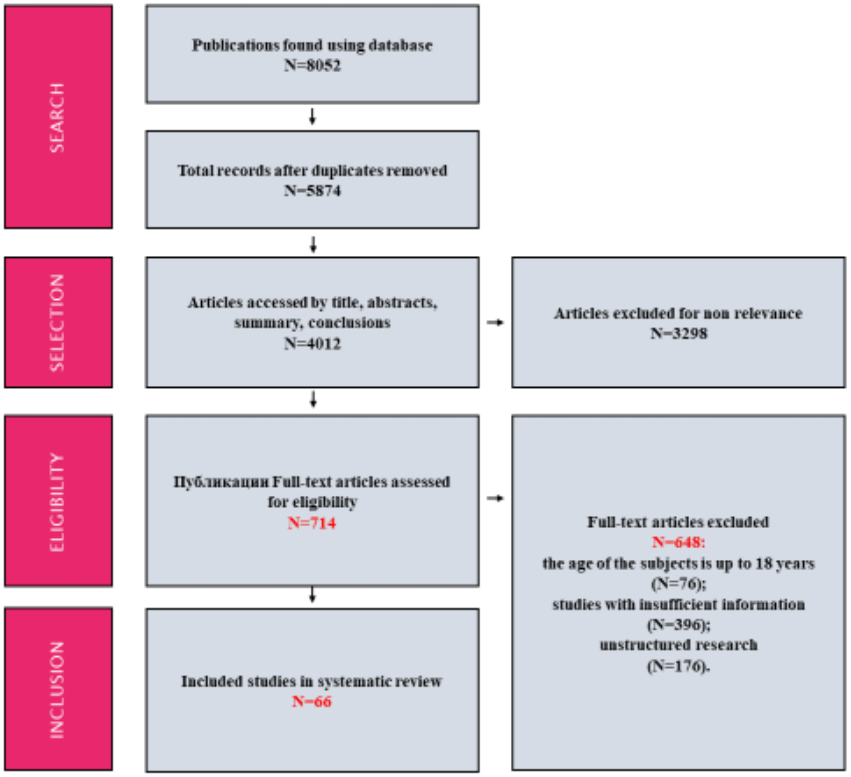

Figure 1. Criteria for selecting publications

Disagreements on inclusion were resolved through discussion. Based on the criteria, 66 publications were selected for the systematic review.

DISCUSSION

The oral mucosa exhibits remarkable heterogeneity, reflecting its adaptation to a variety of functional loads. According to classical works [5,6], histologists distinguish three main types of mucosa: masticatory, lining, and specialized, each of which has unique structural characteristics. These differences are especially noticeable when analyzing multilayer epithelium, represented by three forms: non-keratinized, orthokeratous (complete keratinization) and parakeratous (incomplete keratinization).

Areas subject to intense mechanical stress, such as the hard palate and gums, are covered with chewing mucosa. Orthokeratous epithelium prevails here, firmly connected to the underlying tissues by dense collagen fibers, which

provides resistance to abrasion. In contrast, the lining mucosa located on the cheeks, soft palate, lips, and bottom of the oral cavity is formed by a non-corneal epithelium supported by elastic connective tissue, which allows the tissues to stretch freely with jaw movements. The parakeratous type, characteristic of areas with moderate stress (for example, areas of the cheeks along the line of teeth closure), is an intermediate variant with partial keratinization. Interestingly, about half of the oral cavity area is covered by keratinizing forms of epithelium, while 30% is occupied by non-keratinizing, and the remaining 20% is occupied by teeth [3,7–9].

A special place is occupied by the specialized mucous membrane of the back of the tongue, combining elements of keratinized and non-keratinized epithelium. Its surface forms a complex relief due to the lingual papillae, which perform mechanical and sensory functions, and taste buds are integrated into this structure, providing chemoreception. The rate of epithelial cell renewal varies depending on the location: proliferation occurs more intensively in the lining areas than in the chewing areas. This dynamic is supported by the active cell division of the basal layer, which allows the mucosa to recover quickly despite constant mechanical and microbial influences [3,7–9].

The mucous membrane of the mouth is exposed to frequent mechanical effects of solid food, temperature factors, biting, exposure to microorganisms, etc. As a result, one of the main functions of the oral mucosa is protective. It is provided largely due to the unique architectural integrity of the multilayer epithelium, where epithelial cells are connected by tight junctions (TJs) (occlusal junctions), gap junctions and anchor junctions (desmosomes and adhesive junctions); and also due to the constant renewal of the multilayer epithelium, its excellent regenerative ability [10,11,12,13]. The production of cells in the deeper layers of the epithelium is balanced by the loss of cells from the surface. There is a rapid purification of surface cells, which acts as a protective mechanism, limiting the colonization and invasion of microbes adhering to the surface of the mucous membrane [8].

The problem of regeneration of the oral mucosa is currently an important problem of modern dentistry and carries a number of important issues, how does the healing process occur normally and in pathological conditions of OM, what factors influence it; what changes occur in OM with age, as well as the features of its regenerative potential in the age aspect.

Mucosal repair includes hemostasis, inflammation, proliferation, and remodeling [14].

Immediately upon damage to the OM and rupture of blood vessels, the coagulation cascade is activated to prevent blood loss and ensure temporary sealing of the wound. The opened extracellular matrix causes the activation of circulating platelets, which further triggers the hemostatic cascade. Platelets, surviving keratinocytes, and fibroblasts produce biologically active substances such as vasoactive mediators and chemotactic signals that release proteases, cytokines, and growth factors to quickly trigger the inflammatory phase, attracting immune cells to the area of damage. Blood vessels constrict to prevent bleeding, and platelets clump together to form platelet plugs, which strengthen by polymerizing fibrin, forming a fibrin clot and closing the wound. Fibro-fibronectin clots provide support as a temporary matrix for the extracellular matrix and allow epithelial cells and fibroblasts to migrate to the wound area [15,16].

The inflammation phase occurs almost immediately after blood clotting and lasts 2-4 days [17]. It is aimed at removing dead tissues from the damaged area and preventing infection by pathogenic microorganisms. Damage-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP) in the wound bed trigger Toll-like receptor (TLR), multiligand receptor (RAGE), and inflammasome signaling pathways, leading to a cascade of cytokine and chemokine release by resident cells, which marks the beginning of the inflammatory phase in within a few hours of injury. Neutrophils, monocytes, macrophages, mast cells, and T-cells penetrate the wound bed in response to chemokine gradients and trigger an immune response against potential pathogens [18]. As early as 4 hours after injury, keratinocytes, fibroblasts, Langerhans cells and resident macrophages begin to phagocytize the formed dead cells. Primary keratinocytes and fibroblasts of the oral cavity produce more interleukin 8 (IL-8, also known as CXCL8) after stimulation by early inflammatory mediators such as tumor necrosis factor alpha, interferon gamma, interleukin-1 beta (TNF-α,

IFN-γ, IL-1β), in addition, keratinocytes increase expression ICAM-1 (adhesion molecules used by neutrophils to facilitate extravasation and migration to the damaged area), which promotes a faster influx of immune cells into the damaged area and thus accelerates wound healing [19,20].

The proliferation phase includes several processes, such as angiogenesis, proliferation and differentiation of fibroblasts into myofibroblasts (formation of granulation tissue) and proliferation of epithelial cells (re-epithelialization) [17]. During the proliferation phase, which lasts from several hours to several days after injury, endothelial cells, fibroblasts, and epithelial cells migrate to the wound surface for tissue regeneration. Well-vascularized and loose granulation tissue formed by fibroblasts and endothelial cells provides the wound surface with structural support and nutrition. Meanwhile,

epithelial cells repair the wound surface epithelium during proliferation, migration, and differentiation [21]. Stagnation of blood in the damaged area leads to hypoxia and triggers an angiogenic reaction. Cells in the hypoxic wound bed secrete various pro-angiogenic factors, such as hypoxia-induced factor 1a (HIF-1a) and vascular endothelial growth factor (VEGF), which stimulate the proliferation and migration of endothelial cells, resulting in the formation of a large number of permeable vessels that provide granulation tissue with nutrients and immune cells. During wound healing, angiogenesis is accompanied by the creation of a dense but poorly organized capillary bed, which eventually shrinks to a normal density and capillary architecture [22].

In wounds of the oral cavity, there is a lower level of infiltration of macrophages, neutrophils and T cells with less secretion of inflammatory cytokines, including interleukin-6 (IL-6) and other factors produced by keratinocytes. These data suggest that attenuation of the inflammatory response is a key feature of wound healing. The epithelium of the mouth has a lower expression of transforming growth factor beta-1 (TGF-β1), a proinflammatory and profibrotic cytokine, which is known to promote the formation of hypertrophic scars during wound healing [23]. A smaller number of immune cells in a healthy oral mucosa can cause a weakened immune response upon injury, suggesting that the mucosa is inherently less sensitive to inflammation, and may explain its higher healing ability [24,25,26].

Keratinocyte migration and proliferation are key processes during re-epithelialization, as they are less prone to differentiation and instead preferentially adopt a proliferative and migratory phenotype.

Oral keratinocytes exhibit accelerated migration (2.6 times faster than skin keratinocytes) and higher proliferation, independent of the influence of

underlying connective tissue, which is their innate feature [27].

In addition, oral fibroblasts produce more hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) (both are known inducers of keratinocyte migration and proliferation) [28,29].

The oral mucosa is constantly washed with saliva, which contains epidermal growth factor (EGF), which accelerates re-epithelialization, and fibroblast growth factor (FGF), which acts on fibroblasts, increasing their renewal and promoting wound healing. Saliva also contains histatins, hydrogen peroxide, lactoferrin and lysozymes, antimicrobial peptides and mucins, which provide essential antimicrobial protection and can promote wound healing by stimulating fibroblast proliferation and migration, accelerating keratinocyte renewal and releasing growth factors [23,30,31,32,33].

Histatins, in particular histatin-1, promote cell adhesion and migration in oral keratinocytes, gingival fibroblasts, epithelial cells outside the oral cavity, and endothelial cells. This is especially important because histatin-1 promotes the phase of re-epithelialization and angiogenic reactions, enhancing the migration of epithelial and endothelial cells [34,25,35,36].

Nerve growth factor (NGF) and its various precursor forms are secreted by the salivary glands into human saliva, and are also produced by a multitude of cells in the tissues of the oral cavity. The main forms of NGF in human saliva are forms of pro-nerve growth factor (pro-NGF), rather than mature NGF. NGF receptors associated with tropomyosin kinase A (TrkA) and neurotrophin p75 receptor (p75NTR) are widely expressed in human oral soft tissue cells, including keratinocytes, endothelial cells, fibroblasts and leukocytes, as well as in ductal and acinous cells of all types of salivary glands. NGF is involved in most stages of the oral wound healing process: repair, cell survival, apoptosis, cell proliferation, inflammation, angiogenesis, and tissue remodeling [37].

While keratinocytes migrate and multiply, restoring the epithelial barrier, granulation tissue is formed. Fibroblasts and endothelial cells begin to secrete fibronectin to create a dense fibrillar network that ensures cell migration to the wound surface. It was found that more fibronectin, fibronectin ED-A, and chondroitin sulfate are expressed in OM, and less elastin is expressed [38]. A dense network of fibronectin at the wound site is necessary for the formation of a mature collagen matrix I/III [39]. In the initial stages of wound healing, the main type of collagen produced is collagen III, followed by the production of collagen I to increase the strength and elasticity of tissues [39,40].

In addition to the fibrous proteins that form the structural basis for cells, the extracellular matrix contains many matrix proteins (such as glycoproteins and proteoglycans) that promote the matrix's interaction with cells and regulate various cellular reactions such as adhesion, migration, and cell proliferation [40].

As soon as the wound is covered with new epithelium and the balance between the body and microbes is restored, the inflammation is suppressed by anti-inflammatory cytokines. Macrophages switch from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype and secrete growth factors, matrix metalloproteinases (increased expression of MMP1, MMP2, MMP3, and MMP10), and tissue metalloproteinase inhibitors (TIMPs), stimulating fibroblast-mediated remodeling of the extracellular matrix [18]

Human OM fibroblasts have higher proliferation and weaker contractility, and also exhibit delayed aging due to their long telomere length. An embryonic or fetal phenotype associated with a long telomere may be the

reason that wounds on the mucous membrane heal with less scarring [23]. Regarding the properties of cell adhesion, fibroblasts of the oral mucosa demonstrate higher adhesion to vitronectin and collagen types I and IV, and are very sensitive to transforming growth factor beta (TGFb1), the main profibrotic cytokine expressed during healing. TGFß1 increases the rate of proliferation, as well as collagen synthesis [38].

There is increasing evidence that the oral mucosa may contain a population of progenitor cells or "stem-like" cells, known by various names, including progenitor cells of the mucosal lamina proper, stem cells, and mesenchymal gum stem cells, which may contribute to reducing scarring observed during wound healing [41]. The ability of the oral mucosa to recover quickly without scarring is determined not by any one feature, but by key external and internal factors present at all stages of the wound healing process, which are crucial for improving the final result [42,43,44]. Human stem cells obtained from the oral cavity have a plasticity and ability to proliferate 30-50% higher, as well as a more pronounced immunoregulatory effect compared to bone marrow stem cells. Due to their potential for differentiation, mesenchymal stem cells derived from oral tissues are promising for tissue engineering and regenerative medicine [45,46,47].

Tissue remodeling (the contraction phase, «maturation») is the last and longest phase of tissue healing; it consists of collagen synthesis and degradation to align newly formed collagen bundles along tension lines and can last from several weeks to several months [17].

Adaptive mechanisms that ensure not only effective restoration of tissue integrity, but also the prevention of chronic processes against the background of constant microbial colonization are described in detail in studies [48,49]. The integration of these systems makes it possible to maintain the functionality of the dental apparatus even under regular mechanical stress, demonstrating the amazing resistance of the complex ecosystem of the oral cavity. Depletion of reserves, reduction of biodiversity, and gradual specialization within the oral ecosystem eventually lead to a significant decrease in its ability to cope with everyday tasks [50].

On the one hand, some studies show that there is no evidence to support that age is a factor in poor wound healing. However, there is evidence that wound healing is slower in the elderly than in the young; the number of fibroblasts decreases with age, which is associated with their proliferative activity [41]. In addition, elderly people exhibit an altered inflammatory response characterized by a steady increase in the level of pro-inflammatory cytokines such as IL-6 and TNFa, and a decrease in the level of growth factors. This combination leads to a high level of TGF-β, which may play a role in the transformation of acute wounds into chronic ones by suppressing re-epithelialization [35]. Accelerated and progressive aging is also associated with delayed infiltration of macrophages and T cells into the wound area and decreased macrophage function [26,27]. Microcirculation disorders and hypoperfusion, characteristic of aging tissue, contribute to the weakening of the inflammatory response and interfere with the physiological angiogenic phase as a whole, and reduced extracellular matrix production and increased expression of matrix metalloproteinases, especially MMP-2, leads to disorders in the remodeling phase [51].

From a clinical point of view, the oral mucosa in the elderly may not differ from the oral mucosa in young people. However, its appearance may change due to various factors affecting the oral cavity over a long period of time. The balance of the various ecological niches of the oral cavity is the result of a large number of interrelated factors [50]. Local factors include mechanical stimuli, salivation insufficiency, and ear diseases. Systemic risk factors include metabolic disorders such as chronic nutrient deficiencies, including vitamins and trace elements, as well as endocrine dysfunctions, in particular diabetes mellitus. No less significant are cardiovascular disorders, for example, arterial hypertension and ischemic conditions, which provoke a deterioration in peripheral blood circulation, which directly affects tissue trophism. Pathologies of the gastrointestinal tract, accompanied by impaired nutrient absorption and dysbiosis, also contribute to the destabilization of oral homeostasis. Prolonged use of pharmacological agents with a xerostomicor ulcerogenic effect potentiates structural changes in the epithelium. The use of tobacco and alcohol not only disrupts microcirculation, but also suppresses local immunity, creating prerequisites for chronic inflammation. Improper oral hygiene, expressed in irregular or inadequate procedures, contributes to the accumulation of bacterial plaque. The synergy of these factors leads to a cumulative effect: for example, the combination of vitamin deficiency and smoking accelerates mucosal atrophy, and hyperglycemia while taking certain medications exacerbates xerostomia [52-55]. Sex hormones play a role in the physiological healing of wounds. In addition, there are sexual features of wound healing in the elderly: the healing of acute wounds in older men is much slower than in older women due to the positive regulatory effect of estrogen on wound healing [51].

During the aging process, progressive atrophic processes develop in the integumentary epithelium of the OM. The thickness of the epithelial layer is significantly reduced: in the lip area — from 500 to 300 microns, cheeks — from 700 to 400 microns, on the back of the tongue — from 800 to 500 microns. The

cells of the basal layer undergo structural metamorphoses — their shape becomes low-prismatic, the nuclei decrease in size, acquiring a pyknotic appearance, which is accompanied by a decrease in the content of DNA, RNA and dehydrogenase activity. These changes reflect the suppression of proliferative and metabolic functions, and the smoothing of epithelial scallops disrupts the histological architecture of tissues [56,57]. Visually, OM loses its pink hue, becoming grayish-white due to increased keratinization of the multilayer squamous epithelium. In parallel, there is a decrease in the number of cellular elements and fibrous structures in the underlying connective tissue. Elastic fibers undergo sclerosing and thickening, while collagen fibers undergo hyalinization, losing their order and increasing in diameter. This leads to a decrease in the elasticity and mobility of the mucosa, making it rigid and vulnerable to mechanical influences. The vascular system of the OM also undergoes age-related degeneration: the walls of the vessels become sclerosed, the capillary loops of the gums become less pronounced, and part of the anastomoses is obliterated. The formation of vascular-free zones, recorded during histological analysis[58], exacerbates trophic disorders. Against the background of general tissue dehydration, the mucosa becomes thinner and loses moisture, which is manifested by increased sensitivity and susceptibility to mechanical influences, as well as delayed repair. Even minor injuries, such as denture friction, in elderly patients with concomitant chronic diseases often provoke the formation of painful decubital ulcers, characterized by prolonged healing. Age-related changes create prerequisites for the development of specific pathologies: cracks in the corners of the mouth, candidal lesions, allergic reactions, lichen planus and lichenoid changes. These conditions, which occur in the elderly 3-4 times more often than in the young [59,] are associated with the combined effects of reduced local immunity, impaired microcirculation, and chronic tissue hypoxia.

In patients with complete adentia, age-related transformations of the oral mucosa become more pronounced. Each anatomical region exhibits unique patterns of degeneration reflecting local features of tissue organization. Progressive thinning of the epithelial layer is observed in the buccal region, mainly due to the reduction of the thorny and basal layers. The cells decrease in size, their nuclei become hyperchromic, and the epithelial scallops lose their relief, which disrupts the structural integrity of the mucosa. Molecular studies have revealed a critical decrease in the expression of the SIRT3 and SIRT6 genes in the buccal epithelium. These genes encode sirtuins, proteins that play a key role in protecting cells from oxidative stress and slow down the development of age—related pathologies [60]. Their deficiency exacerbates the processes of cellular aging, creating a vicious circle of degenerative changes. In the gum mucosa, despite the relative preservation of the epithelial layer, other pathological processes are noted. Fibrous changes are accompanied by fragmentation of nerve endings, the density of which decreases by 40-50% with age. Unlike the buccal region, the mucous membrane of the hard palate shows a paradoxical thickening with a simultaneous loss of density, which is associated with the restructuring of the connective tissue stroma. Sclerotic processes prevail here: collagen fibers thicken and are replaced by fatty inclusions, and the number of vessels and cellular elements is reduced by 30-35%. The histological picture is complemented by the appearance of extensive vascular-free zones and areas with a complete absence of cellular elements. These changes are aggravated by trophic disorders, which is especially noticeable in patients with prolonged adentia.

The sensitivity of the oral cavity, defined as the distinction of touch points, does not change significantly with age. Only a slight decrease in sensitivity was observed in people over 80 years of age. Different areas of the oral mucosa exhibit varying degrees of permeability. Increased keratinization is associated with decreased permeability (e.g., hard palate), and decreased keratinization is associated with increased permeability (e.g., the floor of the oral cavity). An in vitro study was conducted showing that the permeability of the cell membranes of the epithelial cells of the oral cavity increases with age [56.] It has been found that tactile sensations in the mouth (i.e., sensitivity and spatial acuity) and perception of warm but not cold stimuli worsen with age, especially after 80 years [19].

The oral microbiota influences wound healing by secreting lipopolysaccharides that support the homeostasis of oral mesenchymal stem cells through the microRNA-21/Sp1/telomerase reverse transcriptase pathway (Su et al., 2018). Bacteria can accelerate wound healing, having a positive effect on the immune response, granulation tissue, and collagen formation [44,61]. It has been proven that aging is one of the factors affecting the structure of the oral microbiota and its sensitivity to various viral, fungal, or bacterial infections [62,63]. Older people may have a higher bacterial diversity than younger and middle-aged people [52]. For example, Liu et al. (2020) examined the microbial composition in three areas of the oral cavity (gum fluid, back of tongue, and saliva) and concluded that the alpha diversity of bacteria decreases with age, while beta diversity tends to increase [64]. Willis et al. (2022), on the other hand, comparing saliva samples in different age groups, they concluded that in middle age the composition of the oral

microbiota is most homogeneous, while in old age there is increased microbial diversity due to low-abundance taxa [65]. The oral microbiome depends on the niche and varies depending on the age group, and also provides new insight into the possible relationship between changes in the oral microbiome and age-related diseases. Studying the age-related features of microbial communities in various parts of the oral cavity can open up new opportunities for microbiome-based diagnosis, new directions in preventive medicine, and offer innovative treatment methods [66].

CONCLUSION

In the context of global demographic aging, an in-depth study of age-related transformations of the oral mucosa is of particular scientific and practical importance. The tissue structures of the oral cavity, being a kind of reflection of systemic age-related changes, undergo a complex transformation requiring detailed morphofunctional analysis.

Modern research reveals a paradoxical feature: despite its apparent accessibility for visual observation, the oral mucosa remains one of the least studied organs in the gerontological aspect. Meanwhile, her age-related changes are systemic in nature:

- progressive atrophy of the epithelial layer;
- reduction of the vascular network;
- reduction of regenerative potential;
- changes in the qualitative composition of saliva and microbiota.

The clinical significance of these transformations cannot be overestimated. Firstly, they create the pathogenetic basis for the development of a number of diseases and conditions (atrophic glossitis, xerostomia, leukoplakia, candidal lesions, lichen planus and others). Secondly, they modify the pharmacodynamics of local medicines, requiring correction of therapeutic approaches. Thirdly, they affect the processes of oral sensory perception, significantly changing the quality of life of elderly patients.

Of particular relevance is the study of the molecular mechanisms of aging of the oral epithelium, such as activation of senescent phenotypes, disruption of intercellular communications, changes in the profile of cytokine secretion, dysregulation of apoptosis.

A promising direction is the development of «age-adapted» diagnostic algorithms and therapeutic protocols that take into account the specifics of the metabolism of the aging oral mucosa. This is especially important in light of recent data demonstrating a link between the condition of the oral epithelium and the risk of developing age-related systemic diseases.

Thus, an in-depth study of the gerontological aspects of the morphofunctional state of the oral mucosa is a strategically important area located at the junction of clinical dentistry, gerontology and fundamental medicine. Further research in this area will not only improve the quality of dental care for elderly patients, but also, possibly, reveal new aspects of the general biological mechanisms of aging.

Authors' Contributions:

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T.G. Tsagaraeva (TGT) – data collection/analysis, writing;
I.S. Kopetsky (ISK) – research concept/design, editing, final approval;
E. G. Mikhailova (EGM) – data collection/analysis;
M. D. Stavitsky (MDS) – data collection;
G. L. Stepanyan (GLS) – data collection;
O.Yu. Guseva (OYG) – analysis;
Yu.L. Vasil'ev (YLV) – supervision, editing;
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None declared

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