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Review Article

Prospects for the Use of Short Peptides in Dentistry

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Received: March 13, 2025; **Published:** May 22, 2025

Abstract

The article presents the results of forty years of research on the use of Khavinson peptides in dentistry. The use of short peptides in the complex treatment of dental pathology contributed to the enhancement of reparative processes and, as a result, reduced rehabilitation time and complications after medical interventions in the oral cavity.

Keywords: *Khavinson Peptides; Short Peptides; Dental Pathology*

Introduction

Research on the role of peptides in regulating key body functions occupies a leading position in both fundamental science and clinical practice [8,10,25,28]. Although the first studies in this field began more than 100 years ago, peptide research remains a crucial area in modern pharmacology.

The first studies on the application of peptide bioregulators in dentistry were conducted as early as the 1980s [9]. However, the clinical use of peptide bioregulators, developed by V. Morozov and V. Khavinson, began in the 1970s in Russia. The primary distinction of Khavinson peptides from other short peptides is their ability to regulate gene activity and protein synthesis at the cellular level, thereby enhancing the body's reserve capabilities and reducing mortality, as proven in experimental and clinical studies. Clinical experience with Khavinson peptides has demonstrated the high efficacy of this class of substances in various diseases and pathological conditions of the oral cavity. Additionally, these peptide drugs significantly enhance the effectiveness of existing rehabilitation methods following exposure to extreme factors (trauma, radiation exposure, intoxications, infections, psycho-emotional overloads) and in the prevention and treatment of age-related pathology [14,16,18,27,28].

It is known that the pathogenesis of many oral diseases is characterized by a combination of metabolic disorders in periodontal tissues, impairments in microcirculation, and changes in local immunity. Therefore, the use of peptide bioregulators in the complex therapy of patients with dental pathology has been pathophysiologically justified. Studies on the biological properties of peptides have previously established that these substances are directly involved in tissue-specific gene expression regulation and biosynthesis. As a result of peptide

regulation, the accumulation of pathological changes in cells (DNA damage, mutations, malignant transformations, etc.) decreases, and reparative processes aimed at restoring cellular homeostasis are enhanced [15,17,20].

Moreover, short peptides have the ability to maintain the morphology and function of oral hMSCs for extended periods. Studies have shown that Khavinson short peptides AEDG and KED reduce the mRNA expression of p16 and p21 by 1.56-2.44 and 1.82-3.23 times, respectively, in stem cells of two types (hMSCs: human periodontal ligament stem cells (hPLSCs) and human gingival mesenchymal stem cells (hGMSCs)). These results were confirmed through immunofluorescent visualization. Therefore, short peptides can be used as additional substances in culture media to slow down the expression of aging markers during long-term stem cell cultivation, facilitating large-scale *in vitro* expansion, which is essential for the clinical application of stem cell therapy [4,23].

Furthermore, peptide bioregulators can regulate immune and neuroendocrine mechanisms of interaction between organs and systems in individuals of different ages. At the molecular-cellular level, the key immunomodulating effects of short peptides include stimulating the differentiation of thymocytes into T-lymphocytes, stem cells into precursors of T- and B-lymphocytes, and enhancing IL-2 mRNA synthesis in lymphoid cells. Additionally, peptides activate the immune response of T-lymphocytes and macrophages, promote their proliferation, and reduce apoptosis levels [11,16].

Given the pathogenesis of oral diseases, several peptide drugs are used in dentistry, including immunomodulators and reparative agents (thymus peptides), chondroprotectors (cartilage tissue peptides), angioprotectors (vascular peptides), and geroprotectors (pineal gland peptides).

It is known that treating maxillofacial injuries in elderly and senile patients is a complex problem in surgery and dentistry. This is primarily due to decreased functional activity of the immune system and the presence of severe comorbid conditions and age-related changes. Reduced reparative functions in such patients are usually associated with low fibroblast levels, low alkaline phosphatase activity in leukocytes, and a high amount of necrotic tissue. This explains why, with age and reduced reparative functions, the effectiveness of complex therapy decreases. Experimental studies on the thymus dipeptide Lys-Glu (Vilon) in animals with purulent incised-contused wounds provided a basis for using Khavinson's peptide in the comprehensive treatment of elderly patients with maxillofacial injuries and chronic generalized periodontitis [22,29].

The Lys-Glu dipeptide (Vilon) was obtained through directed chemical synthesis based on amino acid analysis of the complex thymus drug Thymalin, considering its immunoactive and physicochemical properties [29]. Lys-Glu is a fragment of peptides such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, interferon, splenin, splenopentin (SP-5), thymosin 1, thymosins 4, 7-14, thymopoietin I, thymopoietin II, motilin, parathyroid hormone, and somatoliberin.

To evaluate the effect of the Lys-Glu dipeptide on reparative processes and periodontal tissues, a study was conducted involving 269 patients with maxillofacial injuries and chronic generalized periodontitis. Patients in the main group received the dipeptide at a dose of 10.0 mg for 10 days as part of complex therapy.

The use of the Lys-Glu dipeptide improved immune system function by stimulating leukocyte and macrophage activity. The cytological pattern of wound surfaces shifted from degenerative-necrotic and degenerative-inflammatory to regenerative types, leading to shorter wound epithelialization periods. As a result of a rapid reduction in local and systemic inflammatory reactions, recovery times in the main group were reduced by 4.3 ± 0.35 days compared to the control group. Additionally, the use of Vilon in patients with decompensated diabetes mellitus led to a significant 15% reduction in blood glucose levels by the end of treatment, which also promoted improved reparative osteogenesis. At the same time, a good effect was noted in 76.4% of patients [19]. Optimization of tissue regeneration processes under the influence of the dipeptide (Lys-Glu) contributed to the reduction of periodontal pocket depth, elimination of inflammation of the

gingival margin mucosa in a shorter period compared to conventional treatment in elderly and senile patients with chronic generalized periodontitis, leading to the elimination of periodontal dysfunction. Thus, according to the authors, the inclusion of the dipeptide (Lys-Glu) in the treatment regimen for generalized periodontitis in elderly and senile individuals is justified [3].

According to several authors [2,26], the use of the therapeutic and prophylactic oral gel "VIVAX DENT" (manufactured in Russia) containing a complex of short peptides Lys-Glu (thymus peptides), Ala-Glu-Asp-Gly (vascular peptides), Lys-Glu-Asp (cartilage and bone tissue peptides) contributed to a 0.8- and 0.9-fold reduction in the epithelialization and regeneration times of the deep layers of the lamina propria of the oral mucosa in patients with acute and chronic traumatic lesions of the oral mucosa compared to similar patients in the control group. The study involved 615 patients diagnosed with acute or chronic trauma of the oral and lip mucosa (prosthetic bed damage, flat leukoplakia).

Furthermore, the use of the dental gel with a peptide complex contributed to the qualitative restoration of the deep layers of the oral and lip mucosa, as determined by scanning methods. The application of Khavinson® peptides in the gel did not leave poorly distributed conglomerates on the oral mucosa surface, did not cause adverse side effects, and in 35% of cases, positively influenced the elimination of *Candida* fungi mycelium from the prosthetic bed mucosa in elderly patients. Therefore, according to the authors, to optimize rehabilitation and improve the quality of life of elderly patients, considering degenerative processes in the mucosal tissues and age-related changes in oral and lip mucosa microcirculation, as well as a decrease in local immunity, it is advisable to use a therapeutic and prophylactic oral gel containing a complex of thymus, vascular, cartilage, and bone tissue peptides.

The influence of thymus and pineal gland peptides in the complex therapy of periodontitis was also studied [13,21]. A clinical and laboratory study was conducted on 118 patients aged 60 - 75 years with moderate (36 patients) and severe (82 patients) periodontal disease in the exacerbation stage. All patients received conventional comprehensive treatment: surgical (removal of dental deposits, curettage of periodontal pockets) and therapeutic (use of antiseptics or antibiotics if necessary). The patients were divided into three equivalent groups. The control group consisted of 36 patients who received only conventional treatment. In the first main group, in addition to standard treatment, patients received thymus peptides (thymogen) at a dose of 1.0 ml submucosally in the gingiva daily; the treatment course consisted of five injections. The second main group received pineal peptides (epitalamin) at a dose of 10.0 mg daily submucosally in the gingiva; the course consisted of five injections.

Assessment of cellular and humoral immunity parameters in all patients with generalized periodontitis indicated significant disturbances in the T-cell immune link, manifested by a decrease in T-lymphocyte subpopulations and impaired functional activity. Additionally, there were disruptions in nonspecific resistance parameters, including a reduction in peripheral blood neutrophils, decreased expression levels of specific neutrophil receptors, and impaired phagocytosis.

The use of Khavinson® peptides as part of comprehensive therapy contributed to positive changes in the studied immunological parameters, with normalization of phagocytosis, an increase in neutrophil count in the blood, and restoration of their functional activity. The use of the thymus peptide drug (thymogen) contributed to the normalization of IgM levels, an increase in neutrophils, and an improvement in the neutrophil phagocytic index, indicating enhanced neutrophil functional activity. A more pronounced immunostimulatory effect was noted with the use of the pineal peptide drug (epitalamin). The restoration of humoral and cellular immunity under the influence of thymus and pineal peptides led to the elimination of bacterial microflora that sustained inflammatory foci in periodontal pockets. Moreover, bulbar microscopy and gingival microcapillaroscopy data showed an increase in blood flow velocity, a decrease in erythrocyte aggregation in capillaries, a reduction in bleeding index, and resolution of local inflammatory processes under the influence of thymus and pineal peptides. Periodontal pocket depth decreased, teeth with grade I mobility stabilized, grade II mobility reduced to grade I, and grade III mobility improved to grade II. The papillary-marginal-alveolar and periodontal indices significantly decreased.

Thus, the results of using thymus and pineal gland peptide drugs in patients with generalized periodontitis indicate their normalizing effect on nonspecific resistance parameters, cellular and humoral immunity, which correlates with positive clinical manifestations and contributes to a twofold reduction in treatment duration.

Based on the study results, the authors proposed a method for the comprehensive treatment of elderly patients with generalized periodontitis, which, in addition to standard treatment, includes the administration of thymogen for mild to moderate disease and epitalamin for periodontitis of varying severity, including severe cases. The proposed treatment method significantly improved periodontal and vascular tissue conditions, as well as immunological parameters in elderly patients, enhancing treatment effectiveness, including long-term outcomes, resulting in tooth preservation and maintained masticatory function [13].

For individuals who have recovered from COVID-19 and require dental rehabilitation through prosthetic restoration on artificial supports, optimizing mucosal immunity is crucial for dental implant survival. The clinical and laboratory study results indicate that all patients who have recovered from COVID-19 exhibit signs of immune decline and increased inflammatory responses in the oral cavity. These patients showed a significant decrease in secretory immunoglobulin A with a simultaneous increase in pro-inflammatory cytokines in mixed saliva [12,14]. The use of immunomodulatory thymus peptide drugs (Thymalin and Thymogen) led to a reduction in overall inflammation in the oral cavity by normalizing the balance of pro-inflammatory and anti-inflammatory cytokines, shifting towards lower concentrations of pro-inflammatory cytokines (IL-1β, TNFα, IL-8, and IL-6) in patients' mixed saliva. Additionally, an increase in sIgA synthesis, the main component of antibacterial mucosal immunity, was observed, which is pathogenetically important both for preventing inflammatory processes after dental implantation and for preventing peri-implantitis. Therefore, the authors recommend that patients who have recovered from COVID-19, especially those with periodontal and oral mucosal issues, use immunomodulatory thymus peptide drugs Thymalin and Thymogen before dental implantation. These peptides contribute to the normalization of oral mucosal immunity [1].

The effect of a peptide bioregulator of cartilage and bone tissues was studied in patients with temporomandibular joint (TMJ) disorders [6,7]. The study involved 86 patients aged 60-89 years with partial or complete tooth loss who had various TMJ diseases, including dysfunction, arthrosis, and arthroso-arthritis. The control group consisted of 24 patients who underwent adequate and rational prosthetic dental rehabilitation, as well as the standard functional and pharmacotherapy commonly recommended in dental practice. The main group of patients, in addition to prosthetic treatment and conventional pharmacotherapy, received a peptide bioregulator of cartilage and bone tissue as a dietary supplement (Sigumir) at a dosage of 1 capsule twice a day for one month.

The use of the peptide bioregulator Sigumir significantly improved treatment outcomes for elderly and senile patients with TMJ disorders (dysfunction, arthrosis, arthroso-arthritis). The positive therapeutic effect in the main group occurred 40% faster than in the control group. Under the influence of Khavinson's peptides, pain disappeared, as did pathological sound phenomena (clicking and crunching) in the TMJ area, which was confirmed using an electronic phonendoscope-stethoscope.

Dynamic observations over 12 months in patients with TMJ disorders demonstrated that a comprehensive treatment and preventive approach-including rational dental prosthetics, functional and pharmacotherapy, and the use of the peptide bioregulator of cartilage and bone tissue (Sigumir)-allowed for faster pain relief, increased mouth opening amplitude, and improved chewing function. Moreover, patients in the main group not only experienced shorter treatment durations but also showed no recurrence of TMJ disorders within a 12-month follow-up period.

Further studies confirmed the chondroprotective effect of cartilage and bone tissue peptides. For instance, when studying the effect of the complex peptide preparation for cartilage tissue (Kartalax) on reparative osteogenesis of the jaws after surgical treatment of chronic periapical odontogenic infection foci, a pronounced positive clinical effect was observed. Clinical and radiological studies confirmed the effectiveness of this peptide in enhancing reparative osteogenesis in elderly and senile patients [24].

Conclusion

Forty years of experience with Khavinson's peptides have demonstrated their high efficacy in dentistry. Due to their immunomodulatory, chondroprotective, angioprotective, and geroprotective properties, short peptides have shown significant effectiveness in treating various oral diseases and pathological conditions. The use of short peptides in the comprehensive treatment of dental pathologies has contributed to enhanced reparative processes, leading to shorter rehabilitation periods and fewer complications after medical interventions in the oral cavity.

Furthermore, Khavinson's peptides significantly improve the effectiveness of existing rehabilitation methods after exposure to various extreme factors (trauma, radiation, intoxications, infections, and psycho-emotional stress), as well as in the prevention and treatment of age-related pathologies.

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Volume 8 Issue 6 June 2025

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