MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt24S108

# Major approaches of inflammatory processes and peri-implant infections in the cellular and molecular scenario of mesenchymal stem cells, exosomes, and microRNAs: a systematic review

**Danilo Martins Paladino[1,2*], João Antônio Figueiredo Vidoto[1,2], Rafael Bertelli Lopes[1,2], Fábio Alarcon Idalgo[1,2], Alvaro José Cicareli[1,2], Elias Naim Kassis[1,2]**

[1] UNORTE - University Center of Northern São Paulo, Dentistry Department, São José do Rio Preto, São Paulo, Brazil.
[2] UNIPOS - Post Graduate and Continuing Education, Dentistry Department, São José do Rio Preto, São Paulo, Brazil.

*Corresponding author: Danilo Martins Paladino.
Unorte/Unipos - Postgraduate and continuing education,
Sao Jose do Rio Preto, Sao Paulo, Brazil.
E-mail: danilo_paladino@hotmail.com
DOI: https://doi.org/10.54448/mdnt24S108
Received: 01-09-2024; Revised: 02-27-2024; Accepted: 02-29-2024; Published: 03-01-2024; MedNEXT-id: e 24S108

## Abstract

**Introduction:** Bone diseases are denoted by fractures, osteoporosis, and osteoarthritis that affect a large number of individuals, with a rising prevalence of osteopenia for 64.3 million American individuals and osteoporosis for 11.9 million by the year 2030. Dental implants are not free from possible complications with consequent failure, the causes of which are still the subject of debate in the dental scientific community. In particular, peri-implant infections are multifactorial pathological conditions characterized by inflammation of the peri-implant mucosa with or without progressive loss of supporting bone. Specific expression profiles of microRNAs (miRNAs) extracted from peri-implant tissues are predictive of specific clinical outcomes of dental implants and can be used as biomarkers in implant dentistry for diagnostic and prognostic purposes. **Objective:** It was to address the main approaches to inflammatory processes and peri-implant infections and dental implants in the cellular and molecular scenarios of mesenchymal stem cells, exosomes, and microRNAs, emphasizing the main biomarkers in the therapeutic control of harmful dental implant processes. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from October 2023 to January 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 138 articles were found, 44 articles were evaluated in full and 34 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 26 studies with a high risk of bias and 24 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with X2=67.9%>50%. It was concluded that specific expression profiles of miRNAs extracted from peri-implant tissues are predictive of specific clinical outcomes of dental implants and can be used as biomarkers in implant dentistry for diagnostic and prognostic purposes. Studies have shown that many of the miRNAs extracted from the implant's peri-crevicular fluid were common to those detected in soft tissues taken from the same peri-implant sites. Evidence suggests that exosomes derived from adipose-derived stem cells exhibit similar functions to those cells, with low immunogenicity and no tumorization. Insufficient bone volume directly impacts the placement of dental implants. Adipose-derived stem cells can accelerate bone healing when combined with dental implants. An increase in the concentration of exosomes with negative expression of miRNA-21-3p and miRNA-150-5p may be related to the development of peri-implantitis.

**Keywords:** Dental implants. Inflammatory processes. Peri-implant infections. Mesenchymal stem cells. Exosomes. microRNAs.

## Introduction

In the context of problems in dental implant processes, bone diseases are denoted by fractures,

osteoporosis, and osteoarthritis that affect a large number of individuals, especially the elderly. Without intervention, the prevalence of osteopenia is projected to increase to 64.3 million American individuals and that of osteoporosis to 11.9 million by the year 2030 [1].

Even with existing prevention and treatment methods, the incidence and mortality of bone diseases are still gradually increasing, creating a significant financial burden for societies around the world. To prevent the occurrence of bone diseases, slow their progression, or reverse the injuries they cause, new alternatives or complementary treatments need to be developed [1,2].

In this scenario, despite the high percentages of success, dental implants are not free from possible complications with consequent failure, the causes of which are still the subject of debate in the dental scientific community. In particular, peri-implant infections are multifactorial pathological conditions characterized by inflammation of the peri-implant mucosa with or without progressive loss of supporting bone, such as peri-implantitis or peri-implant mucositis [1,2].

Still in this aspect, the development of genomics and epigenomics, microRNAs (miRNAs) are small endogenous sequences of non-coding RNAs (ncRNAs) responsible for the specific regulation of gene expression in a post-transcriptional manner [2]. They are involved in biological processes such as immunoinflammatory response, bone metabolism, cell replication, and apoptosis [3]. They are already widely used for early diagnosis, prognosis, and personalized therapies for oncological and genetic diseases, but are still little explored in implant dentistry [4].

Based on this, it was demonstrated that specific expression profiles of miRNAs extracted from peri-implant tissues are predictive of specific clinical results of dental implants and can be used as biomarkers in implant dentistry for diagnostic and prognostic purposes [2,5,6]. The detection of biomarkers in various biological fluids can be a predictable substitute for traditional tissue biopsies for diagnosis and prognosis of inflammatory processes, and it has been demonstrated that peri-implant disease can be effectively evaluated by analyzing peri-implant tissues in crevicular fluid (PICF) of the peri-implant pocket [7]. As literary support for this, a study demonstrated that many of the miRNAs extracted from PICF were common to those detected in soft tissues taken from the same peri-implant sites [8].

In addition, mesenchymal stem cells (MSC) mediate the homeostasis and regeneration of tissues and organs, making decisions about whether to remain quiescent, proliferate, or differentiate into mature cell types, mainly through the production of exosomes and microRNAs. These decisions are directly integrated with the energy balance and nutritional status of the organism. Metabolic byproducts and substrates that regulate epigenetic and signaling pathways are considered to have instructive, rather than bystander, roles in regulating cell fate decisions [9].

In this sense, the quiescent state of stem cells is characterized by an inherently glycolytic metabolism, followed by a transition to favor mitochondrial oxidative phosphorylation during differentiation [10-13]. However, increasing evidence suggests that metabolism during quiescence, activation, and differentiation may vary between tissues, integrating signaling cues and metabolic inputs with the release of exosomes and microRNAs as important metabolic messengers in the organism [14-16].

Therefore, the present study aimed to address the main considerations of inflammatory processes and peri-implant infections and dental implants in the cellular and molecular scenarios of mesenchymal stem cells, exosomes and microRNAs, emphasizing the main biomarkers in the therapeutic control of harmful dental implant processes.

## Methods

### Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 01/16/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 01/16/2024.

### Data Sources and Research Strategy

The literary search process was carried out from October 2023 to January 2024 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Dental implants. Inflammatory processes. Peri-implant infections. Mesenchymal stem cells. Exosomes. microRNAs"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

### Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-

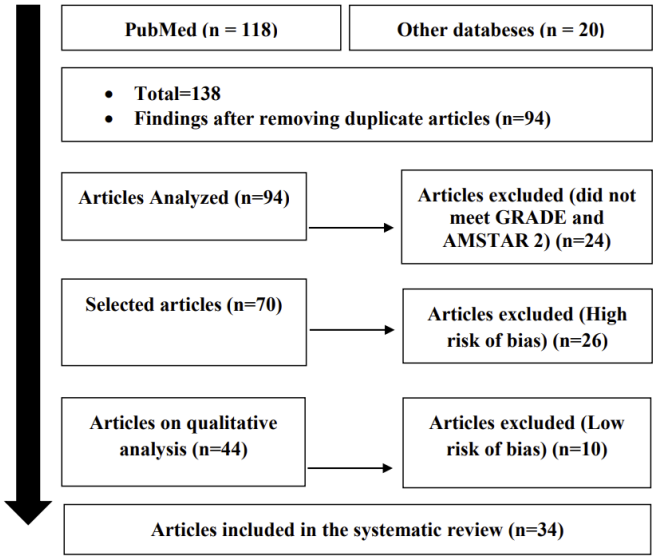
analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

## Results and Discussion

### Summary of Findings

A total of 138 articles were found that were subjected to eligibility analysis, with 34 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2$=67.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 26 studies with a high risk of bias and 24 studies that did not meet GRADE and AMSTAR-2.

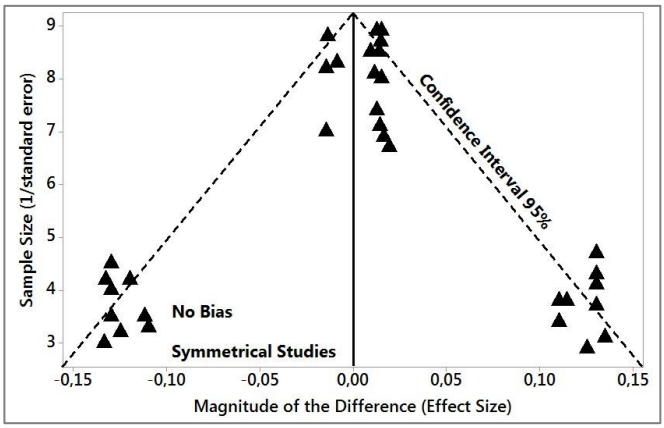
Figure 1. Article selection and exclusion process.




Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=34 studies).




Source: Own authorship.

### Major Approaches and Outcomes

Based on the main considerations of inflammatory processes and peri-implant infections and dental implants in the cellular and molecular scenarios, MSC are pointed out as an alternative for cell therapy and human tissue engineering, since it was found that they present a high degree of plasticity, with the capacity for self-renewal and differentiation into specialized progenitors, in addition to being the major producers and regulators of exosomes and microRNAs [17].

In this aspect, MSC are primordial mesodermal cells present in all tissues and are capable of differentiating in vitro and in vivo into different cell types. Its therapeutic potential is mainly explained by the production of bioactive molecules, which provide a regenerative microenvironment in injured tissues [18]. MSC secrete a cascade of cytokines and growth factors with paracrine, autocrine and endocrine activities, such as Il-6, Il-7, Il-8, Il-11, Il-12, Il-14, Il-15, factor macrophage colony stimulator, Flt-3 ligand and Stem Cell Factor (SCF), leukemia inhibitory factor, granulocytic colony-stimulating factor (G-CSF) and granulocytic-macrophagic colony-stimulating factor (GM-CSF). These factors, when conjugated, can produce a series of responses from the local immune system, stimulating angiogenesis and inducing the proliferation and differentiation of mesenchymal stem cells in the desired tissue [19].

In addition, MSC induce the expression of junction proteins and increase microvascular integrity and the production of nitric oxide (NO) by macrophages [18]. The stromal vascular fraction (SVF) originating from

MSC is a heterogeneous mixture of cells, including fibroblasts, pericytes, endothelial cells, blood cells, and adipose-derived stem cells (ADSC).

In addition, exosomes are extracellular vesicles with a diameter of 40-100 nm and a density of 1.13-1.19 g/mL, containing proteins, mRNAs, miRNAs, and DNAs. Exosomes change the biochemical characteristics of recipient cells through the delivery of biomolecules and play a role in cellular communication. These vesicles are produced from body fluids and different types of cells. Evidence suggests that ADSC-derived exosome (ADSC-EXO) exhibits ADSC-like functions with low immunogenicity and no tumorization [20]. However, the composition of exosomes differs based on their sources [21]. Exosomes also contain heat shock proteins (Hsp70 and Hsp90), which facilitate the loading of peptides into MHC I and II [22–24].

Regarding miRNA, ADSC-exosomes prominently feature miR-1, miR-15, miR-16, miR-17, miR-18, miR-181 and miR-375 [25]. Additionally, various cytokines such as Tumor Necrosis Factor-α (TNF-α), Granulocyte Macrophage Colony Stimulating Factor, Interleukin (IL)-2, IL-6, IL-8, IL-10, IL-15, IL-1β, are expressed in exosomes [26]. Based on this, normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals. The main force in this process are osteoblasts and their precursors [27]. Osteoblasts can produce new bone along with biomaterials and can initiate the release of biological signals that guide bone formation and remodeling.

These biological signals attract bone-forming cells to the receptor site. Growth factors and other proteins are some biological signals that may be involved in bone formation and tissue remodeling. Furthermore, through chemotaxis, there is migration of bone-forming cells to the area of application, as the stimulation of cell migration occurs in response to chemical stimuli [28].

In this sense, monocytes, macrophages, and endothelial cells contribute to bone remodeling, either through contact with osteogenic cells or through the release of soluble factors such as cytokines and growth factor [28]. In the skeletal system, TNF-α stimulates bone and cartilage resorption and inhibits the synthesis of collagen and proteoglycans. IL-1 induces the expression of a wide variety of cytokines. LIF and IL-6 are two such molecules that are known to stimulate the differentiation of mesenchymal progenitor cells into the osteoblastic lineage, they are also potent antiapoptotic agents for osteoblasts. In bone, the main sources of IL-6 are osteoblasts and not osteoclasts. Prostaglandin E2 (PGE2) is also directly related to the expression of the cytokine IL-6 [29,30].

Given this, it is noteworthy that insufficient bone volume directly impacts the placement of dental implants. ADSC can accelerate bone healing when combined with dental implants. A study carried out by authors Du et al. (2019) [31] identified the ideal conditions for the placement of dental implants. Exosomes derived from 3T3L1 preadipocytes (3T3L1-exo) were purified and characterized. It was confirmed that 3T3L1-exo improved the osteogenic differentiation of 3T3L1 preadipocytes. Furthermore, microRNA (miR) expression profiles of 3T3L1-exo and 3T3L1 preadipocytes were sequenced and compared. The results of further analysis demonstrated that miR-223 expression was reduced in 3T3L1-exo-stimulated 3T3L1 preadipocytes compared to unstimulated cells. This finding suggested that 3T3L1-exo promoted 3T3L1 bone formation by decreasing miR-223 through a competitive mechanism.

The authors Chaparro et al. (2021) [32] analyzed the diagnostic utility of extracellular vesicles (EVs) and microRNAs (miRNA-21-3p, miRNA-150-5p, and miRNA-26a-5p) in peri-implant crevicular fluid (PICF) of individuals with healthy peri-implant mucositis and peri-implantitis implants. A total of 54 patients were included in the healthy, peri-implant mucositis and peri-implantitis groups. PICF samples were collected, and subpopulations of EVs were isolated and characterized by nanoparticle tracking analysis and transmission electron microscopy. The expression of miRNA-21-3p, miRNA-150-5p, and miRNA-26a-5p was quantified by qRT-PCR. PICF samples show the presence of EVs delimited by a bilayer membrane, according to morphology and size (<200 nm). The concentration of PICF-EVs, microvesicles, and exosomes was significantly increased in peri-implantitis implants compared to healthy implants. The expression of miRNA-21-3p and miRNA-150-5p was significantly downregulated in peri-implantitis patients compared to peri-implant mucositis sites.

Furthermore, a systematic review study carried out by the authors Delucchi et al. (2023) [33] evaluated that some inflammatory biomarkers collected from peri-implant crevicular fluid (PICF) (collagenase-2, collagenase-3, ALP, EA, gelatinase b, NTx, procalcitonin, IL-1β and several miRNAs) appear to be correlated with the process of peri-implant bone loss, assisting in early diagnosis. Also, miRNA expression demonstrated a predictive potential of peri-implant bone loss that could be useful for hostdirected preventive and therapeutic purposes.

Finally, several studies have demonstrated that exosomes participate in intercellular communication and play a fundamental role in osseointegration. Authors Zhang et al. (2021) [34] found that exosomes can promote osteogenic differentiation and mineralization of

cells. Through RNA sequencing and genetic analysis, differentially expressed microRNAs were found that target signaling pathways that may be related, such as mTOR, AMPK, Wnt, etc., and thus provide a reference for the mechanism of osteoimmune regulation of osseointegration of the implant. The study further elucidated the mechanism of implant osseointegration provided new insights into the effect of exosomes on implant osseointegration, and provided reference for the clinical improvement of implant osseointegration and implant success rate.

## Conclusion

It was concluded that specific expression profiles of miRNAs extracted from peri-implant tissues are predictive of specific clinical outcomes of dental implants and can be used as biomarkers in implant dentistry for diagnostic and prognostic purposes. Studies have shown that many of the miRNAs extracted from the implant's peri-crevicular fluid were common to those detected in soft tissues taken from the same peri-implant sites. Evidence suggests that exosomes derived from adipose-derived stem cells exhibit similar functions to those cells, with low immunogenicity and no tumorization. Insufficient bone volume directly impacts the placement of dental implants. Adipose-derived stem cells can accelerate bone healing when combined with dental implants. An increase in the concentration of exosomes with negative expression of miRNA-21-3p and miRNA-150-5p may be related to the development of peri-implantitis.

## Acknowledgement

Not applicable.

## Ethical Approval

Not applicable.

## Informed consent

Not applicable.

## Funding

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

## Similarity check

It was applied by Ithenticate@.

## Peer Review Process

It was performed.



## References

1. Delucchi F, Canepa C, Canullo L, Pesce P, Isola G, Menini M. Biomarkers from Peri-Implant Crevicular Fluid (PICF) as Predictors of Peri-Implant Bone Loss: A Systematic Review. Int J Mol Sci. 2023 Feb 6;24(4):3202. doi: 10.3390/ijms24043202.
2. Menini M, Pesce P, Baldi D, Coronel Vargas G, Pera P, Izzotti A. Prediction of Titanium Implant Success by Analysis of microRNA Expression in Peri-Implant Tissue. A 5-Year Follow-Up Study. J. Clin. Med. 2019;8:888. doi: 10.3390/jcm8060888.
3. Chaparro A, Atria P, Realini O, Monteiro LJ, Betancur D, Acuña-Gallardo S, Ramírez V, Bendek MJ, Pascual A, Nart J, et al. Diagnostic potential of peri-implant crevicular fluid microRNA-21-3p and microRNA-150-5p and extracellular vesicles in peri-implant diseases. J. Periodontol. 2021;92:e11–e21. doi: 10.1002/JPER.20-0372.
4. Menini M, De Giovanni E, Bagnasco F, Delucchi F, Pera F, Baldi D, Pesce P. Salivary Micro-RNA and Oral Squamous Cell Carcinoma: A Systematic Review. J. Pers. Med. 2021;11:101. doi: 10.3390/jpm11020101.
5. Menini M, Dellepiane E, Baldi D, Longobardi MG, Pera P, Izzotti A. Microarray expression in peri-implant tissue next to different titanium implant surfaces predicts clinical outcomes: A split-mouth study. Clin. Oral. Implant. Res. 2017;28:e121–e134. doi: 10.1111/clr.12943.
6. Menini M, Dellepiane E, Pera F, Izzotti A, Baldi D, Delucchi F, Bagnasco F, Pesce P. MicroRNA in Implant Dentistry: From Basic Science to Clinical Application. Microrna. 2021;10:14–28. doi: 10.2174/2211536610666210506123240.
7. Akram Z, Abduljabbar T, Abu Hassan MI, Javed F, Vohra F. Cytokine Profile in Chronic Periodontitis Patients with and without Obesity: A Systematic Review and Meta-Analysis. Dis. Markers. 2016;2016:4801418. doi: 10.1155/2016/4801418.
8. Menini M, Pesce P, Pera F, Baldi D, Pulliero A, Izzotti A. MicroRNAs in Peri-implant Crevicular

Fluid Can Predict Peri-implant Bone Resorption: Clinical Trial with a 5-Year Follow-up. Int. J. Oral. Maxillofac. Implant. 2021;36:1148–1157. doi: 10.11607/jomi.9040.

9. Chacón-Martínez CA et al. Hair follicle stem cell cultures reveal self-organizing plasticity of stem cells and their progeny. EMBO J. 2017, 36, 151–164.
10. Rodríguez-Colman MJ. et al. Interplay between metabolic identities in the intestinal crypt supports stem cell function. Nature, 2017, 543, 424.
11. Snoeck, H.W. Mitochondrial regulation of hematopoietic stem cells. Curr. Opin. Cell Biol. 2017, 49, 91–98.
12. Zheng, X. et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. Elife, 2016, 5, e13374.
13. Flores A et al. Lactate dehydrogenase activity drives hair follicle stem cell activation. Nat. Cell Biol. 2017, 19, 1017–1026.
14. Rinschen MM. et al. Identification of bioactive metabolites using activity metabolomics. Nat. Rev. Mol. Cell Biol. 2019, 20, 353–367.
15. Agathocleous, M. et al. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature, 2017, 549, 476–481.
16. Shapira SN, Christofk HR. Metabolic Regulation of Tissue Stem Cells. Trends Cell Biol. 2020 Jul;30(7):566-576. doi: 10.1016/j.tcb.2020.04.004.
17. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, Deans RJ, Keating A, Procko DJ, Horwitz EM. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 2006, v. 8, n. 4, p. 315-317.
18. Zuk PA, Zhu M, Ashjian P. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell; 2002, 13: 4279–4295.
19. Caplan AI, Buder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. Trends Mol Med; 2001, 7: 259-64.
20. Thery C, Boussac M, Veron P, Ricciardi-Castagnoli P, Raposo G, Garin J, et al., Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles, J. Immunol. 2001, 166:7309–7318.
21. Baharlooi H, Nouraei Z, Azimi M, Moghadasi AN, Tavassolifar MJ, Moradi B, Sahraian MA, Izad M. Umbilical cord mesenchymal stem cells as well as their released exosomes suppress proliferation of activated PBMCs in multiple sclerosis. Scand J Immunol. 2020 Dec 18:e13013. doi: 10.1111/sji.13013. Epub ahead of print. PMID: 33338274.
22. Mears R, Craven RA, Hanrahan S, Totty N, Upton C, Young SL, et al., Proteomic analysis of melanoma-derived exosomes by two-dimensional polyacrylamide gel electrophoresis and mass spectrometry, Proteomics. 2004, 4:4019–4031, https://doi.org/10.1002/pmic.200400876.
23. R Gastpar, M Gehrmann, MA Bausero, A Asea, C Gross, JA Schroeder, et al., Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells, Cancer Res. 2005, 65:5238–5247, https://doi.org/10.1158/0008-5472.can-04-3804.
24. W Xu, Z Yang, N Lu. From pathogenesis to clinical application: insights into exosomes as transfer vectors in cancer, J. Exp. Clin. Cancer Res. 2016, 35: 156,https://doi.org/10.1186/s13046-016-0429-5.
25. H. Valadi, K. Ekstrom, A. Bossios, M. Sjostrand, J.J. Lee, J.O. Lotvall, Exosomemediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, Nat. Cell Biol. 2007, 9:654–659, https://doi.org/10.1038/ncb1596.
26. B. Zhang, L. Shen, H. Shi, Z. Pan, L. Wu, Y. Yan, et al., Exosomes from Human Umbilical Cord Mesenchymal Stem Cells: Identification, Purification, and Biological Characteristics, 016, p. 1929536, doi.org/10.1155/2016/1929536.
27. Zhuang G, Mao J, Yang G, Wang H. Influence of different incision designs on bone increment of guided bone regeneration (Bio-Gide collagen membrane +Bio-OSS bone powder) during the same period of maxillary anterior tooth implantation. Bioengineered. 2021 Dec;12(1):2155-2163. doi: 10.1080/21655979.2021.1932209.
28. Mesimäki K, Lindroos B, Törnwall J, Mauno J, Lindqvist C, Kontio R, Miettinen S, Suuronen R: Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. Int J Oral Maxillofac Surg 2009, **38** : 201-209.
29. Zotarelli Filho IJ, Frascino LF, Greco OT, Araujo JDD, Bilaqui A, Kassis EN, Ardito RV and Bonilla-Rodriguez GO. Chitosan-collagen scaffolds can regulate the biological activities of adipose mesenchymal stem cells for tissue engineering. J Regen Med Tissue Eng. 2013; 2:12.

http://dx.doi.org/10.7243/2050-1218-2-12.

30. Egido-Moreno S, Valls-Roca-Umbert J, Céspedes-Sánchez JM, López-López J, Velasco-Ortega E. Clinical Efficacy of Mesenchymal Stem Cells in Bone Regeneration in Oral Implantology. Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2021 Jan 21;18(3):894. doi: 10.3390/ijerph18030894.
31. Du W, Su L, Zhang N, Wang H. Exosomes derived from preadipocytes improve osteogenic differentiation, potentially via reduced miR-223 expression. Mol Med Rep. 2019 Feb;19(2):951-958. doi: 10.3892/mmr.2018.9760.
32. Chaparro A, Atria P, Realini O, Monteiro LJ, Betancur D, Acuña-Gallardo S, Ramírez V, Bendek MJ, Pascual A, Nart J, Beltrán V, Sanz A. Diagnostic potential of peri-implant crevicular fluid microRNA-21-3p and microRNA-150-5p and extracellular vesicles in peri-implant diseases. J Periodontol. 2021 Jun;92(6):11-21. doi: 10.1002/JPER.20-0372.
33. Delucchi F, Canepa C, Canullo L, Pesce P, Isola G, Menini M. Biomarkers from Peri-Implant Crevicular Fluid (PICF) as Predictors of Peri-Implant Bone Loss: A Systematic Review. Int J Mol Sci. 2023 Feb 6;24(4):3202. doi: 10.3390/ijms24043202.
34. Zhang T, Jiang M, Yin X, Yao P, Sun H. Mechanism of Exosomes Involved in Osteoimmunity Promoting Osseointegration Around Titanium Implants With Small-Scale Topography. Front Bioeng Biotechnol. 2021 Jul 15;9:682384. doi: 10.3389/fbioe.2021.682384.