Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) 2023 24(10):853-867
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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Review
https://doi.org/10.1631/jzus.B2200702

Current status and future prospects of stomatology research

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Abstract: Research in stomatology (dental medicine) continues to expand globally and is oriented towards solving clinical issues, focusing on clarifying the clinical relevance and potential mechanisms of oral–systemic connections via clinical epidemiology, oral microecological characterization, and the establishment of animal models. Interdisciplinary integration of materials science and tissue engineering with stomatology is expected to lead to the creation of innovative materials and technologies to better resolve the most prevalent and challenging clinical issues such as peri-implantitis, soft and hard tissue defects, and dentin hypersensitivity. With the rapid development of artificial intelligence (AI), 5th generation mobile communication technology (5G), and big data applications, "intelligent stomatology" is emerging to build models for better clinical diagnosis and management, accelerate the reform of education, and support the growth and advancement of scientific research. Here, we summarized the current research status, and listed the future prospects and limitations of these three aspects, aiming to provide a basis for more accurate etiological exploration, novel treatment methods, and abundant big data analysis in stomatology to promote the translation of research achievements into practical applications for both clinicians and the public.

Key words: Stomatology; Dental medicine; Systemic disease; Material; Innovative technique

1 Introduction

With the advancement of science and technology, stomatology now plays at least four roles: promoting oral health, providing oral health care, treating oral diseases, and rehabilitating oral functions. Etiology is the premise of a breakthrough in the treatment of disease, including oral diseases. As the mouth is an integral part of the body, oral diseases are usually directly or indirectly related to systemic factors. Many early studies focused only on oral problems and ignored the influence of the whole system, but the direction has been changing in recent years. Exploring the association between oral and systemic diseases can help clinicians make correct and timely diagnoses. In addition to etiology, dental therapy is expanding into other newer areas. The development of stomatology has been accelerated greatly since the turn of the twenty-first century by various new concepts, techniques, and materials. Additionally, the ongoing integration of dental medicine with clinical medicine and biomedical engineering has deepened the notions of the digitalization, functionalization, and individualization of oral care. The rapid development of "intelligence" has led to an increasingly close relationship between dentistry and the Internet. With the help of big data devices and artificial intelligence (AI), the clinical, educational, and research aspects of dentistry will be further advanced. Stomatology research worldwide is on the rise, and it will need to make breakthroughs and innovations in several directions in the future to better serve patients. In this review, we summarize three aspects that are of most interest to dentists based on our clinical experience and the relevant literature review: the connection between oral health and systemic health or disease, the research and development of new technologies and materials at the nexus of medicine and industry, and the advancement of information-based dental medicine or stomatology. The three parts complement each other and together are indispensable for promoting the development of dentistry research.

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Received Dec. 29, 2022; Revision accepted Mar. 27, 2023; Crosschecked July 31, 2023; Published online Aug. 7, 2023

2 Understanding the association between oral diseases and systemic diseases facilitates the early detection and effective prevention of systemic diseases

Clinical epidemiology has demonstrated that oral diseases contribute to the development of several systemic diseases such as diabetes mellitus (DM), atherosclerosis, and Alzheimer's disease (AD). Also, oral manifestations or symptoms are frequently the first signs of systemic diseases such as inflammatory bowel disease (IBD), leukemia, and rheumatoid arthritis (RA). Microbial high-throughput sequencing can be used to accurately identify oral pathogens in systemic diseases and perform functional assays. Modelling of oral disorders in established animal models of systemic diseases can enable better visualization of these interconnections and facilitate mechanistic investigations. Therefore, a deeper understanding of the association is essential to promote oral and systemic health.

2.1 Clinical epidemiology associates oral–systemic connections

The World Health Organization (WHO) has focused on the significance of oral health for the general populace as a major public health issue for decades, in an effort to increase awareness of oral health and encourage the proactive prevention and treatment of oral disorders. Clinical epidemiology has demonstrated the objective rules, distribution characteristics, and susceptibility factors of oral–systemic connections.

Various oral diseases, such as caries, periodontal disease, dental trauma, oral mucosal disease, and malocclusion, lead to a reduction or loss of masticatory function, negatively impacting general health by impairing oral function and resulting in gastritis, enteritis, and other digestive system diseases. Additionally, oral disease-related inflammation can spread to other adjacent tissues and structures, and more severe inflammation can break through the barrier of the oral mucosa and periodontal ligament to enter the blood circulation, causing focal or systemic infection. Moreover, an imbalance of oral microorganisms indirectly affects the health of the entire body (Kilian, 2018). Oral disorders are known to have the potential to cause disease or disease progression in the nine primary systems of the entire body (Casamassimo et al., 2018). The interactions of periodontitis with diabetes (Matsha et al., 2020), caries, and digestive system diseases (Marruganti et al., 2021) are among the best-known examples.

At the same time, certain systemic conditions can produce specific oral reactions. For example, the first manifestation of leukemia might be gingival haemorrhage (Angst et al., 2020), and 5%–50% of patients with Crohn's disease have oral aphthous ulcers (Rogler et al., 2021). This is because systemic diseases often cause a systemic inflammatory response. Inflammatory factors reach the oral cavity through blood circulation and can easily cause oral diseases. Also, systemic diseases reduce the immunity of the host, making the host susceptible to specific oral diseases. For example, diabetic patients are less resistant to infection and are more likely to react to periodontal pathogenic bacteria than healthy normal individuals, and thus more likely to develop periodontitis. In addition, patients with systemic diseases are often under greater stress or have poor lifestyle habits, and these external factors can also make patients susceptible to oral diseases. The interactions are illustrated in Fig. 1.

Currently, the oral–systemic connections have not received sufficient attention, making it challenging to promptly identify and treat patients suffering from systemic diseases in a timely manner through the control of oral diseases. Through clinical epidemiology research, we will eventually unite the fields of dental medicine with clinical disciplines, link clinical treatment with scientific research, and further confirm that the link between systemic diseases and oral diseases. It will facilitate early detection, diagnosis, and treatment, leading to significant improvements in oral and general health.

2.2 High-throughput sequencing promotes the identification of oral–systemic connections

High-throughput sequencing (HTS) is a powerful technique for analyzing the composition and function of microbial communities without relying on culture technology, and can directly and comprehensively evaluate the gene sequences of microorganisms (Krishnan et al., 2017). More than 700 microorganisms have been identified in the human oral cavity, including bacteria, viruses, fungi, and archaea (Paster et al., 2006). These microorganisms are intricate, diverse, and informative, and their richness and diversity are influenced by various factors such as genetics, oral hygiene, diet, and lifestyle (Gao et al., 2018).

Oral microbes are attached mainly to the surface of oral structures in the form of a plaque biofilm, which is particularly stable and resistant to external disturbances under normal conditions. Planktonic organisms are another type of microbes present in saliva. They form a relatively stable balanced microecological environment together with the normal structures of the oral cavity (Zhang et al., 2018). Any qualitative or quantitative changes in this environment will result in localized inflammation or diseases, such as caries, endodontic periodontal disease, periodontitis, oral mucosal disease, and oral squamous cell carcinoma (Table 1). More importantly, with the implementation of the "Human Microbiome Project" (Turnbaugh et al.,

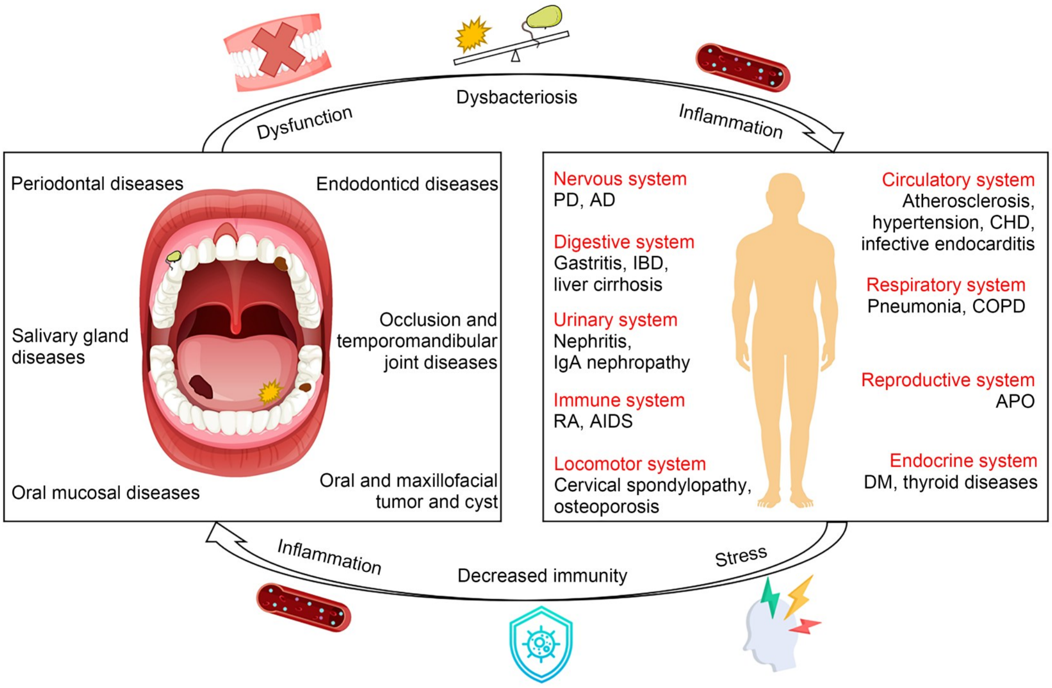

Fig. 1 Association of oral diseases with systemic diseases. Oral diseases induce or promote systemic diseases through three main pathways (affecting the physiological function of oral cavity, causing an imbalance of oral flora, and producing inflammatory responses). Systemic diseases promote the progression of oral diseases through three main pathways (producing an inflammatory response, decreasing host immunity, and producing greater mental stress). AD: Alzheimer's disease; AIDS: acquired immune deficiency syndrome; APO: adverse pregnancy outcome; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; IBD: inflammatory bowel disease; IgA: immunoglobulin A; PD: Parkinson's disease; RA: rheumatoid arthritis.

Table 1 Dominant microbes detected in oral diseases

Oral disease	Oral pathogens	Reference
Dental caries	*Streptococcus* spp., *Lactobacillus* spp., *Actinomyces* spp., and *Veillonella* spp.	Belda-Ferre et al., 2012
Periapical periodontitis	*Fusobacterium nucleatum*, *Porphyromonas endodontalis*, *Tannerella forsythia*, *Parvimonas micra*, *Propionibacterium*, *Porphyromonas gingivalis*, and *Prevotella intermedia*	Shang et al., 2013
Periodontitis	*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Peptostreptococcus*, *Parvimonas micra*, *Filifactor alocis*, *Synergiste*, and *Fusobacterium nucleatum*	Costalonga and Herzberg, 2014
Oral squamous cell carcinoma	*Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Streptococcus* spp., *Gemella*, *Capnocytophaga*, and *Prevotella melaninogenica*	Mager et al., 2005
Oral lichen planus	*Porphyromonas*, *Fusobacterium*, *Leptotrichia*, *Lautropia*, *Solobacterium*, *Candida*, and *Aspergillus*	Li et al., 2019
Oral leucoplakia	*Fusobacterium*, *Leptotrichia* spp., and *Campylobacter concisus*	Lin et al., 2021
Recurrent aphthous ulcers	*Porphyromonadaceae*, *Veillonellaceae*, *Lachnoanaerobaculum*, *Cardiobacterium*, *Leptotrichia*, *Fusobacterium*, and *Malassezia*	Hijazi et al., 2015

2007) or other initiatives, many studies have demonstrated the tight connection between oral microbes and systemic disorders such as atherosclerosis, DM, IBD, RA, and AD (Table 2). Their findings indicate that equilibrium of the oral ecosystem is critical for the maintenance of human health, although there is still debate over the cause-and-effect relationship between oral microbiota dysbiosis and systemic diseases.

2.3 Animal modelling reveals the specific molecular mechanism of oral–systemic connections and high-throughput sequencing promotes the identification of oral–systemic connections

Animal modelling of the oral–systemic connections visually reproduces the process of oral diseases and systemic diseases. Thus, using animal modelling to explore the specific molecular connections could

Table 2 Association between systemic diseases and oral dominant microbes

Systemic disease	Samples	Methods	Results	References
Atherosclerosis	Oral cavity and carotid intima	16S rRNA sequencing and PCR	*Porphyromonas gingivalis*, *Streptococcus*, *Veillonella*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *Neisseriawere* were detected in atherosclerotic plaques.	Haraszthy et al., 2000; Koren et al., 2011
DM	Oral cavity and subgingival biofilm	16S rRNA cloning and sequencing	DM patients presented higher percentages of total clones of *TM7*, *Aggregatibacter*, *Neisseria*, *Gemella*, *Eikenella*, *Selenomonas*, *Actinomyces*, *Capnocytophaga*, *Fusobacterium*, *Veillonella*, and *Streptococcus* genera, and lower percentages of *Porphyromonas*, *Filifactor*, *Eubacterium*, *Synergistetes*, *Tannerella*, and *Treponema* genera.	Casarin et al., 2013
IBD	Saliva	16S rRNA sequencing	Bacteroidetes were significantly increased and Proteobacteria were significantly decreased in the salivary microbiota of IBD patients. *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, *Veillonella*, and *Gemella* were found to contribute greatly to dysbiosis in IBD patients.	Said et al., 2014
RA	Oral cavity saliva	Multiplexed 454 pyrosequencing and metagenomic shotgun sequencing	*Lactobacillus salivarius*, *Atopobium*, *Leptotrichia*, *Prevotella*, and *Cryptobacterium curtum* were more abundant in RA patients, while *Corynebacterium* and *Streptococcus* were less abundant.	Scher et al., 2012; Zhang et al., 2015
APO	Placentas, amniotic fluid, and subgingival plaque	PCR	*Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been found in the placenta of women with preeclampsia. *Porphyromonas gingivalis* could indicate the threat of premature labor.	Barak et al., 2007; León et al., 2007
AD	Pieces of frontal lobe cortex and plasma	PCR and ELISA	*Treponema* and *Treponema pallidum* were detected in the brain tissue of AD patients. Higher expression of antibodies (IgG) to *Actinomycetes*, *Porphyromonas gingivalis*, and periodontal pathogen and TNF-α was detected in the serum of AD patients than in controls.	Riviere et al., 2002; Kamer et al., 2009
Lung cancer	Saliva	16S rRNA sequencing and quantitative PCR	*Veillonella* and *Capnocytophaga* were higher in saliva samples from lung cancer patients.	Yan et al., 2015
Pancreatic cancer	Oral mouthwash samples	16S rRNA amplification and sequencing	*Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were associated with a higher risk of pancreatic cancer; Fusobacteria and Leptotrichia phyla were associated with decreased pancreatic cancer risk.	Fan et al., 2018
Colorectal cancer	Oral mouthwash samples	16S rRNA sequencing	*Treponema denticola* and *Prevotella intermedia* were associated with an increased risk of colorectal cancer.	Yang et al., 2019

AD: Alzheimer's disease; APO: adverse pregnancy outcome; DM: diabetes mellitus; ELISA: enzyme-linked immunosorbent assay; IBD: inflammatory bowel disease; IgG: immunoglobulin G; PCR: polymerase chain reaction; RA: rheumatoid arthritis; rRNA: ribosomal RNA; TNF-α: tumor necrosis factor-α.

help us to find effective interventions. Oral diseases are strongly related to numerous systemic diseases, and the use of animal models of systemic diseases for dental medicine is an important future trend (Table 3).

DM is one of the most prevalent systemic diseases, with 90% of cases being type II DM (T2DM) and a minor fraction being type I DM (T1DM). Patients with DM experience change in the physicochemical characteristics of their teeth, including enamel hypoplasia, diminished peritubular dentin, and increased density of dentin tubules (Saghiri et al., 2020). The administration of streptozotocin (STZ) is currently the most commonly used animal model to induce T1DM or T2DM for the observation and study of oral disease (Srinivasan et al., 2005). It has been shown that the extraction of the first molar of T2DM mice induced by a high-fat diet (HFD) with STZ significantly slowed the healing of alveolar bone, and decreased the expression of osteogenic Runt-related transcription factor 2 (RUNX2), osteocalcin (OCN), angiogenic platelet endothelial cell adhesion molecule-1 (PECAM-1, also known as CD31), and vascular endothelial growth factor (VEGF) in the alveolar bone (Shen et al., 2021). $Lepr^{db}$ mutant mice are another mouse model of T2DM that exhibits loss of leptin receptor activity. Compared to normal mice, the oral microflora of $Lepr^{db}$ mutant mice had a markedly different composition, with higher concentrations of the bacteria Enterobacteriaceae, *Aerococcus*, *Enterococcus*, and *Staphylococcus*, all of which are intimately associated with the development of periodontitis (Xiao et al., 2017). In addition to periodontal changes, the diabetic mice had dental tissue lesions. STZ-induced T1DM mice showed a decrease in enamel microhardness after 12 weeks of induction and a substantial decrease in dentin microhardness after 20 weeks (Saghiri et al., 2022). Similar results were observed in diabetic rats, in which the thickness of enamel and dentin was significantly reduced, but mineralization density was not abnormal, thus increasing the rate of caries (Abbassy et al., 2015). Compared to nondiabetic db/+ mice, diabetic db/db mice have more severe

Table 3 Some animal models of oral–systemic connections

Classification	Species	Methods	Stomatology-related phenotypes	References
T2DM	Mouse	HFD and injection of STZ	Decreased osteogenic and angiogenic capacity after tooth extraction	Shen et al., 2021
		db/db mice	Increased periodontitis-related microbial composition/higher severity of dental caries	Sano et al., 2011; Xiao et al., 2017
T1DM	Mouse	Injection of STZ	Decreased microhardness of enamel and dentin	Saghiri et al., 2022
	Rat	Injection of STZ	Significant decrease in the thickness of enamel and dentin surfaces	Abbassy et al., 2015
Hypertension	Rat	Spontaneously hypertensive rat	Decreased alveolar bone/salivary hypofunction	Elias et al., 2006; Uchibori et al., 2020
RA	Mouse	Injection of methylated BSA	Alveolar bone loss	Bingham and Moni, 2013
		Injected with type-II college	Inhibited osteogenic function, increased osteoclast activity and adipogenesis function of alveolar bone	Park et al., 2011
	Rat	Injection of mycobacterium cell wall in complete Freund's adjuvant	Increased periodontal bone loss and tooth mobility	Ramamurthy et al., 2005
Crohn's disease	Mouse	SAMP mice	Spontaneous alveolar bone resorption	Pietropaoli et al., 2014
AD	Mouse	AβPP/PS1 transgenic mice	Exacerbated learning and memory impairment, augmented Aβ and neuroinflammatory responses	Qian et al., 2021
	Rat	Periodontally inoculated SD rats with *Porphyromonas gingivalis*	Increased alveolar bone resorption, memory deficits, pro-inflammatory cytokine production, and changes in astrocytic morphology	Díaz-Zúñiga et al., 2020

AD: Alzheimer's disease; AβPP/PS1: amyloid-β (Aβ) protein precursor/presenilin 1; BSA: bovine serum albumin; HFD: high-fat diet; RA: rheumatoid arthritis; SAMP: SAMP1/YitFc; SD: Sprague-Dawley; STZ: streptozotocin; T1DM: type I diabetes mellitus; T2DM: type II diabetes mellitus.

caries and periapical inflammation, with pathological manifestations such as destruction of dentin tubules with dentin caries, and in more extreme cases, pulp necrosis or periapical inflammation with bone resorption (Sano et al., 2011).

A spontaneously hypertensive rat (SHR) model has been established by repeating multiple generations of mating in hypertensive Wistar-Kyoto (WKY) rats, which gradually lose alveolar bone even when local irritants are removed (de Medeiros Vanderlei et al., 2013), resulting in lower bone density, higher receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) ratio, and more tartrate resistant acid phosphatase (TRAP)-positive osteoclasts in SHR alveolar bone (Bastos et al., 2010). The teeth of rats in the SHR group move more easily than those of healthy rats (Uchibori et al., 2020) and local periodontal ligation leads to more severe periodontal inflammation and a higher probability of eventual tooth loss (Leite et al., 2005). In dental tissues, SHRs have decreased salivary flow and reduced tooth mineralization, and are more susceptible to dental caries (Elias et al., 2006).

The clinical manifestation of RA is aggressive inflammation of the joints, and lesions are also manifested in the temporomandibular joints. A chronic Ag-induced arthritis (AIA) mouse model has been created via injection of methylated bovine serum albumin (BSA). It exhibits marked alveolar bone resorption with a significant increase in the number of osteoclasts and expression of inflammatory factors (Bingham and Moni, 2013). Mice induced with collagen, in addition to enhanced osteoclastic activity, also appear to have reduced osteogenic capacity and enhanced lipogenic differentiation (Park et al., 2011). A similar phenotype was obtained by injecting *Mycobacterium* cell walls in complete Freund's adjuvant into the joints of rats (Ramamurthy et al., 2005).

SAMP1/YitFc (SAMP) mice, a substrain of AKR/J mice, which is a mouse model of Crohn's manifestation of IBD (Matsumoto et al., 1998), spontaneously develop periodontal manifestations (Pietropaoli et al., 2014).

Systemic diseases affect oral health, and oral homeostatic imbalance can also have an impact on other diseases. The association between AD and periodontitis is well established, with periodontitis accelerating AD cognitive decline. Injection of *Porphyromonas gingivalis* lipopolysaccharide into periodontal tissue in amyloid-β protein precursor (AβPP)/presenilin 1 (PS1) (5XFAD) transgenic mice, along with periodontal ligation, worsens learning memory dysfunction and enhances neuroinflammation in mice (Qian et al., 2021). *P. gingivalis* injection with K1/K2-type *P. gingivalis* caused localized alveolar bone resorption, memory deficits, and AD-like changes in astrocyte morphology in Sprague-Dawley (SD) wild-type rats (Díaz-Zúñiga et al., 2020).

Animal models of systemic diseases could pave the way for the oral treatment of systemic diseases. Performing procedures such as tooth movement, tooth extraction, and periodontal ligation in models facilitates the observation of oral lesions. The final treatment administered in the models can also help to determine the efficacy of medications or treatments for oral lesions caused by systemic diseases.

3 Innovative materials and technologies enhance solutions to several clinical challenges

The development and application of innovative materials and technologies are establishing better clinically oriented research systems, thereby overcoming several clinical challenges such as peri-implantitis, soft and hard tissue defect repair, and dentin remineralization. Numerous bottlenecks in scientific research on stomatology, such as stem cell behavior regulation, osteoimmunology modulation, and bionic mineralization improvement, are being overcome through the cross-fertilization of material science, tissue engineering, and stomatology, as well as interdisciplinary cooperation of stomatology with medicine, industry, or research.

3.1 Cell-sheet engineering promotes implant osseointegration

Osseointegration is one of the most important elements in the success of dental implants. However, the healing time for conventional implant insertion in the alveolar bone is currently three months, with a modest osseointegration rate and a long implant treatment period. In addition, patients with diabetes and osteoporosis have a significantly higher implant failure rate than healthy patients. The renewal of tissue engineering is an integral part of the development of stomatology, and currently the most interesting aspect is the application of cell-sheet engineering technology. This novel tissue engineering technique allows for cell transplantation without scaffolding while preserving the extracellular matrix and intercellular connections. Various types of temperature-controlled, mechanical scratching, light-, electric-, and pH-controlled systems are commonly used for cell-sheet technology. With the further development of tissue engineering, new systems such as light-, electric-, and pH-controlled systems have emerged to compensate for the shortcomings of mechanical scratching and temperature-controlled types that are prone to cellular damage. Their combination with new implant materials provides a new approach to implant surface modification. The most important materials for dentists are photosensitive biomaterials. Photosensitive treatment is the most commonly used treatment in dentistry and has been widely applied in daily clinical work, such as laser therapy, photodynamic therapy, and the application of light-curing materials. Its mechanism of action has been elucidated by scientific research. Hong et al. (2013) used light-controlled cell-sheet technology mediated by titanium dioxide (TiO_2) nanodots combined with dental implants to create cell sheet–implant complexes. After 20 min of exposure to 365-nm ultraviolet (UV) light, the hydrophilicity of the TiO_2 nanodots changed, and more than 90% of cells could be detached from the substrate surface. Cheng et al. (2015, 2016) have used this method to construct mouse preosteoblast cell sheets and mouse embryonic fibroblast cell sheets. Wang Y et al. (2017) developed rat bone marrow mesenchymal stem cell (BMSC) sheet–implant complexes using light-controlled cell-sheet technology, and found that these complexes had higher alkaline phosphatase activity and osteogenic performance. Light-controlled BMSC sheet–implant complexes can promote the formation of bone tissue around the implant and prevent the occurrence of poor healing and inflammation. Therefore, these implant complexes have the potential to become important means of promoting implant osseointegration. Na et al. (2018) reported that the transplantation of adipose stem cell sheets induced by near-infrared sources into back skin wounds in mice to accelerate wound healing and promote skin regeneration. In addition, photobiomodulation technology could activate the expression of antiapoptosis, antioxidation, and gene amplification products by irradiating the wound with light of various wavelengths through a light-emitting diode (LED) or laser, releasing nitric oxide, reactive oxygen species, and intracellular calcium (Poyton and Ball, 2011). This treatment alleviated pain and inflammation, modulated immune antiapoptosis, and promoted wound healing and tissue regeneration (Arany, 2016). Guillaume-Gentil et al. (2011b) prepared substrates by depositing alternating layers of cationic and anionic poly-layers on a conductive indium tin oxide surface. The results showed that placenta-derived MSCs could easily adhere to the substrate surface, the pH dropped to 4.0, and the cell membrane could be completely separated within 2–3 min. However, this technique must be used with caution for pH-sensitive cells, and it is difficult to precisely control the local or overall pH. Guillaume-Gentil et al. (2011a) also found that the electrochemical dissolution of polyelectrolyte monolayers and multilayers could be locally controlled by insulating micropatterns formed by photolithography on transparent indium tin oxide electrodes. However, the electrochemical dissolution of the polyelectrolyte coating resulted in changes in local pH which were unfavorable for cell growth.

Overall, photoresponsive biomaterials promote implant surface modification and modulate stem cell behavior through photochemical and photobiological reactions to achieve more stable implant osseointegration, breaking the bottleneck of restoration and regeneration of oral and maxillofacial soft tissue defects. Photosensitive tissue engineering technology is still in its infancy in the field of stomatology. The application of the technology is not widespread because of the impact of light on the cell survival rate and cell-sheet integrity, the effect of long-term light on thermal cell killing, and other issues (Jing et al., 2019). Continuous optimization of the existing light-controlled cell-sheet technology is needed to demonstrate its biological safety and cell activity. At the same time, potential light response materials must be constantly developed and updated to allow for the repair of refractory oral and maxillofacial soft and hard tissue defects.

3.2 Physical and component modifications of materials modulate osseointegration via osteoimmunology

The term "osteoimmunology" refers to the specific interaction between immune cells and bone cells (Tsukasaki and Takayanagi, 2019). One of the most critical problems in the fields of dentistry and tissue engineering is the host immune system response triggered by bone implant materials. A deeper understanding of osteoimmune mechanisms of the peri-implant environment will facilitate the development of innovative implant materials to promote osseointegration and battle peri-implantitis, improving the success rate of oral implants.

With the development of osteoimmunology, it has been discovered that the physical properties of biomaterials (e.g., their shape, roughness, porosity, pore size, hydrophilicity, and surface charge) have impacts on the immune response (Hench and Thompson, 2010). Surface modification of biomaterials using various methods can achieve more stable osseointegration between the material and the host bone tissue (Table 4). In addition, the biomaterial surface can be functionalized to release small soluble molecules or bioactive factors to modulate the immune response by creating a bioactive material surface. For example, magnesium ions can induce osteogenesis in the bone marrow space by activating the Wnt signaling pathway, causing BMSCs to differentiate into the osteoblast lineage (Hung et al., 2019). Strontium ions can induce macrophage polarization for osteogenesis and angiogenesis (Yu et al., 2022). Currently, enhancing the bone repair capacity of bone implant materials through the addition of bioactive components is a successful strategy.

Clinically, the repair of jaw deformities is a more serious and challenging issue than the repair of dental deformities. Therefore, researchers should continue to work to create multifunctional bone implant materials with excellent osteogenic efficacy and the capacity to control the immune microenvironment, drawing on the experience of implant osseointegration. Furthermore, the management of the immune microenvironment of stem cell differentiation has significant scientific and translational medical implications for the regenerative repair of jaw defects. Therefore, management of the immune microenvironment should receive as much attention as the direct regulation of stem cell osteogenic differentiation in the research and development of bone implant materials. However, most current studies reflect only the in vitro situation, and only a few consider biomaterial-mediated osteoclastogenesis in vivo. Moreover, there are few published studies on the role of immune cells other than macrophages in bone remodeling processes. Further studies are needed to elucidate the exact interactions between different immune cells and bone-forming cells to provide efficient strategies to modulate bone immune responses and viable options for surface modification and the design of bone biomaterials.

3.3 Bionic mineralization-combined bonding technique: a fresh approach to repairing dental tissue defects

The bionic mineralization-combined bonding technique offers a fresh perspective for repairing dental tissue defects by occluding and mineralizing dentin tubules. The technique overcomes the drawbacks of conventional dentin hypersensitivity desensitization therapy, such as insufficient mineralization and strength and recurrence.

Dentin hypersensitivity (DH) is a common clinical disorder with a prevalence of 3%–98% in the

Table 4 Immunomodulation of osseointegration of titanium implant by altering biomaterial properties

Methods	Mechanisms	References
Change the porosity and pore size	Larger porosity and pore size reduce the inflammatory response and facilitate osseointegration.	Taniguchi et al., 2016; Wang et al., 2016
Change the titanium surface particle roughness	As the roughness increases, macrophages become more malleable on the material surface and are more likely to secrete inflammatory factors such as IL-6 and TNF-α.	Refai et al., 2004
Change the hydrophilicity and hydrophobicity of materials	A hydrophilic TiO_2 film surface promotes M2-type polarization of macrophages, and decreased hydrophobicity can lead to lower IL-6 and TNF-α levels.	Hotchkiss et al., 2016
Nanomorphology	Nanomorphs regulate endogenous bone morphogenetic protein expression and signaling pathways to induce osteoblast differentiation and downregulate MCP-1, IL-6, and IL-8 expression.	Castro-Raucci et al., 2016

IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; TiO_2: titanium dioxide; MCP-1: monocyte chemotactic protein-1.

population (Splieth and Tachou, 2013). Despite the efficacy of desensitizers in managing DH symptoms, when DH is associated with dental defects, the tissue defects cannot be restored. Furthermore, it is unclear from the available research whether the application of desensitizers followed by filling the defect with bonding resin will reduce the subsequent bonding performance and lead to filling loss or even secondary caries. In addition, it is difficult to avoid the recurrence of DH once the desensitizer function is terminated.

Biomimetic mineralization of dentin refers to the in vitro simulation of the biomineralization process of dentin. The core of biomineralization is the orderly deposition and growth of inorganic mineral nano-precursor phases under the regulation of organic substances to obtain an organic-inorganic composite structure resembling that of natural dentin (Wang HR et al., 2017). Amorphous calcium phosphate (ACP) is the most popular bioactive material. It is a nanoparticle precursor phase that is essential for the biomineralization of dental hard tissues. However, most ACP carriers used in conventional desensitizer systems, whether solutions, gels, or pastes, have the drawback of a limited contact period with tooth tissue. They are unable to provide a constant and steady source of calcium and phosphorus to induce dentin mineralization. As a result, the idea of biomimetic mineralization, which involves mixing an auxiliary mineralizing substance with a bonding agent, was developed. This method promotes the self-restoration of demineralized teeth by allowing the mineralizing material to cling to the target area for an extended period, thereby enhancing the action time with the tooth. Its application to dentin remineralization in combination with bionic analogues and ACP is still in its early stages. In certain investigations, bonding agents have been used as ACP carriers, and loaded ACP nanoions can remineralize demineralized dentin without impairing the bonding performance. For example, Wu et al. (2017) synthesized Si-containing ACP particles (Si-ACP) stabilized with poly(aspartic acid) (PAsp) and loaded Si-ACP with a self-etching bonding agent. They found that the Si-ACP-containing bonding agent could continuously release calcium and phosphate ions and promote the intra- and extra-fibrillar remineralization of type I collagen and demineralized dentin. Shi et al. (2019) investigated the PAsp-ACP-loaded self-etching adhesive, which could effectively occlude dentin tubules while having strong biocompatibility and resistance to abrasion and acid.

However, the strategy remains in the proof-of-concept phase. To achieve structural and functional proximity to natural dentin, efforts must be made to address the issues of the lengthy bionic mineralization process, the disorderly arrangement of crystals and fibers, the ongoing supply of calcium and phosphorus ions necessary for mineralization, the maintenance of long-lasting drug concentrations, and the stability of the material mechanical properties.

4 AI, 5G, and big data techniques create a new paradigm of clinical treatment, education, and research

The development of AI, 5th generation mobile communication technology (5G), and big data techniques has contributed significantly to the transformation of medical models and service delivery systems (Li et al., 2021; Zhu et al., 2023), including those of dental medicine. In the face of complicated oral diseases, long-term care of chronic disease courses, increasingly vast amounts of disease data, and other issues, it is possible to transcend the conventional medical perspective, develop a more robust and standard oral health management program, and accurately satisfy the varied demands of clinical treatment, education, and research in the area of stomatology (Fig. 2).

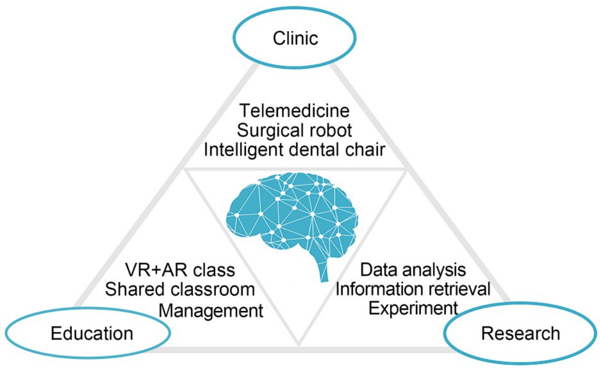

Fig. 2 AI, 5G, and big data techniques in the clinical treatment, medical education, and research management of stomatology. AI: artificial intelligence; AR: augmented reality; 5G: 5th generation mobile communication technology; VR: virtual reality.

4.1 Innovative techniques make dental practice more intelligent, precise, and personalized

AI decision support systems can swiftly provide diagnosis and treatment suggestions. AI models can identify disease-related factors that were previously ignored, thereby improving the sensitivity and specificity of early prevention, early diagnosis, and treatment of oral diseases. AI can also assist physicians in improving the efficiency and quality of treatment if an oral–systemic connection exists (Shan et al., 2021). The use of 5G technology for remote diagnosis, in conjunction with 5G haptic sensory devices, remote imaging, and other equipment, helps significantly to overcome discontinuous, ambiguous, and nonsynchronous information transmission, making diagnosis considerably more efficient (Ahad et al., 2020). It should be noted that a 5G technology-based remote surgery robot for oral and maxillofacial surgery can achieve highly immersive visual–haptic interaction (Mohan et al., 2021). This provides great convenience for patients with limited mobility or those with oral diseases in remote areas, and strengthens nationally graded diagnosis and treatment. Currently, the traditional dental chair, the treatment computer, the auxiliary examination department, and doctors all work independently, so much of the disease-related data obtained, such as digital dental model scan information and microscopic root canal image photos, cannot be retrieved in a timely manner at the chairside, greatly decreasing the dentist's efficiency. When 5G technology is used, it is possible to effectively interoperate the hardware and software components of medical equipment. A new generation of smart dental chairs has gradually emerged on the market in recent years. The comprehensive management platform of those chairs based on 5G+medical internet of things (IoT) technology helps to overcome the limitations of the traditional dental chair. It is possible to collect data, monitor and manage dental equipment, and resolve the present technical challenges in the sharing and supervision of dental medical information. Health regulatory agencies can simultaneously conduct real-time supervision through the cloud.

Big data permit the sharing of patient data within the hospitals and across various medical institutions by aggregating multiple examination reports of each patient to create personal files. Doctors can collect information about health problems of patients without being constrained by time or space, allowing for consistent and precise disease diagnosis, treatment, and prevention.

4.2 Innovative techniques can reform the model of stomatological education

Intelligent education is a brand-new concept in the era of information technology that provides a fresh perspective and ideas for the development and reform of stomatological education (Masters, 2019). Students often cannot clearly observe the teacher's operation during the clinical learning process due to the special structure of the oral anatomy and limited vision. However, virtual reality+augmented reality (VR+AR) technology can present teaching content in three-dimension (3D) form in front of students in real time, which can enhance the experience of VR (Kwon et al., 2018). For example, when preparing cavities and full crowns, the hardness and physiological structure of teeth can be simulated, allowing students to better master their operation skills. At the same time, the maxillofacial region's anatomical structure can be exhibited using VR+AR technology. The muscles, nerves, and blood vessels can be clearly oriented, demonstrating a layer-by-layer progressive relationship. In addition, the emergence of virtual labs based on VR technology can provide medical students with disease models, not only alleviating the existing resource shortage but also increasing the opportunities for hands-on practice. However, VR+AR necessitates extremely high network bandwidth and latency. Fortunately, 5G technology emerged at the appropriate time and is perfectly suited to this approach. In the future, cloud-computing systems based on 5G and big data technologies will be able to manage dental education accurately and intelligently by optimizing the teaching curriculum and examination format. At the same time, the development of smart classrooms makes it possible for students from all over the world to study in the "same classroom" and attend high-quality courses worldwide, maximizing the sharing of educational resources.

4.3 Innovative techniques propel research on stomatology to a new level

At present, "AI+5G+big data" are widely used in various fields, and it is expected that their integration with dental medicine will propel research to a new level. AI brings new vitality to life science research. For example, AI can forecast a 3D protein model (Zaid et al., 2012), and speed up the creation of novel medications (Gupta et al., 2021). Researchers will be relieved of arduous and repetitive work thanks to AI-based research robots that can independently conduct more than 700 experimental tasks, such as weighing medications and calculating ratios, using a predetermined algorithm and program (Zhong et al., 2018). Schwendicke et al. (2021) presented a consented checklist for planning, conducting, and reporting of AI studies. AI can provide solid advice for the conceptualization and planning of dental research. Conducting research design according to this checklist can improve the robustness, comprehensiveness, and transparency of research. Big data and 5G+IoT technologies will aid in the effective management of scientific research results, big data retrieval, and analysis, so that the results can benefit clinicians and the public.

While AI stomatology shows great advantages, there are also some potential challenges. For instance, there are significant issues that must be addressed in the near future regarding how to appropriately govern the ethical and moral dangers of AI. In addition, with the increase of network communication speed, personal privacy leakage and other security issues also must be constantly optimized and enhanced.

5 Summary

In summary, we have presented a brief assessment of the current status and promising trends in stomatology (Fig. 3). The significance of oral health for systemic health has been elucidated from several perspectives. Bioinformatics and animal model development allow for a more thorough understanding of disease mechanisms and thus a more targeted strategy for the early prevention of systemic diseases. The application of innovative materials and technologies has greatly facilitated the progress of dentistry, not

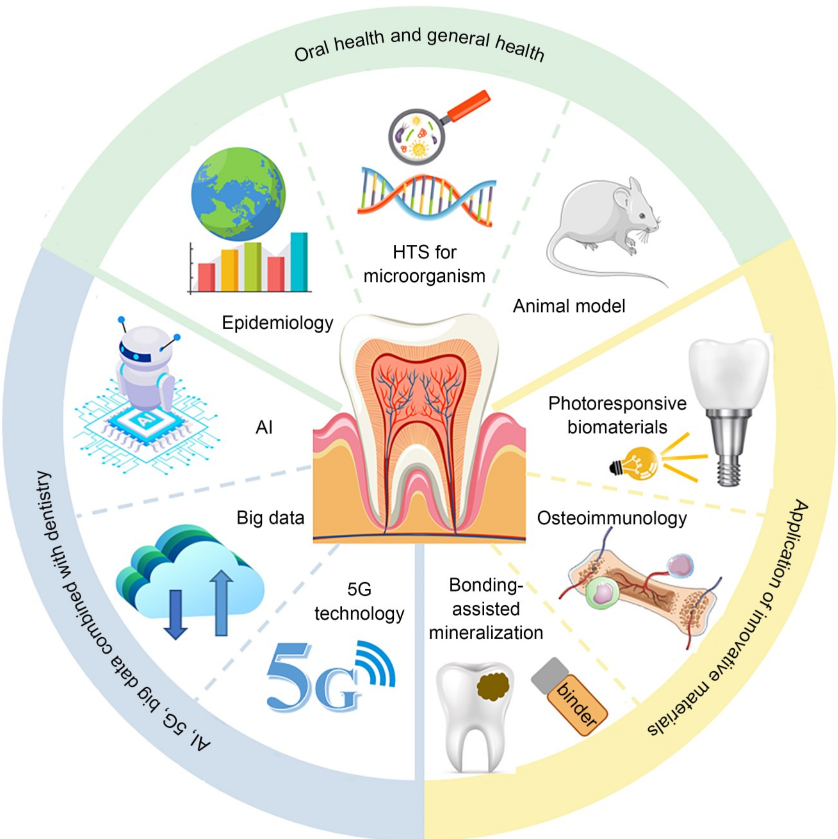

Fig. 3 Innovative trends in stomatology (the connections among oral health and systemic health or disease, the research and development of new technologies and materials at the nexus of medicine and industry, and the advancement of information-based dental medicine). AI: artificial intelligence; 5G: 5th generation mobile communication technology; HTS: high-throughput sequencing.

only in compensating for the shortcomings of existing treatment technologies, but also in elucidating the mechanisms related to osteoimmunology and achieving in-depth research on disease progression. The advent of the information era has helped to reform the medical paradigm, with intelligent devices and concepts leading to individualized care. Although considerable progress has been made in stomatology research, many challenges remain to be addressed. First, research on the mechanisms of oral–systemic diseases is confined mostly to oral diseases leading to systemic diseases, while systemic diseases leading to oral manifestations or aggravating pre-existing oral diseases are the most clinically relevant. Animal models for both mechanisms above are still immature. Second, although the integration of dentistry, materials science, and tissue engineering has pushed dental research to new heights, many studies are still at the experimental stage and clinical trials have yet to be conducted, so the biosafety of new approaches still needs to be tested. Finally, due to the unevenness of economic development worldwide, the popularity of new technologies such as AI and 5G varies greatly from country to country and region to region. Future studies need to explore various aspects to accelerate the transformation of scientific research results into clinical applications that will benefit the majority of patients.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 81991500 and 81991502).

Author contributions

Qianming CHEN constructed the idea of this review, and drafted and revised the manuscript. Yahui WANG and Jing SHUAI involved in data compiling, and manuscript editing, revision, and submission. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Qianming CHEN, Yahui WANG, and Jing SHUAI declare that they have no conflict of interests.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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