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www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com
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Advanced Materials and Modern Production Technologies: Current Developments

Preface

In today's rapidly advancing scientific and technological landscape, the disciplines of metallurgy and materials engineering offer innovative solutions across a wide range of fields, from industrial production and energy technologies to aerospace and defense industries and advanced materials. The design of new materials, the enhancement of the performance of existing materials, and the development of sustainable production methods in line with evolving needs are increasing the importance of this field every day. Prepared within this context, [Book Title] aims to create a comprehensive reference source for researchers, academics, graduate students, and industry professionals by bringing together current scientific studies in the field of metallurgy and materials engineering. The chapters in this book have been prepared with contributions from expert researchers in the field and cover many important topics such as advanced engineering materials, characterization techniques, production technologies, surface engineering applications, nanomaterials, composite systems, additive manufacturing methods, sustainable materials technologies, and current research approaches. Each study aims to present the latest developments in the relevant field while also shedding light on future research. Prepared with the aim of sharing scientific knowledge and strengthening interdisciplinary collaborations, we believe this work will contribute to the body of knowledge in the field of metallurgy and materials engineering and will be a valuable resource for readers. We would like to thank all the chapter authors who contributed to the preparation of the book, the reviewers who contributed to the evaluation process, and all stakeholders who provided support during the publication phase. Our greatest hope is that this work will contribute to the development of scientific research and inspire new studies.

Prof. Dr. Hasan KÖTEN
Head of Mechanical Engineering Department
Istanbul Medeniyet University

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CHAPTER 0

BIOACTIVE GLASS-CERAMICS FOR BONE REGENERATION AND CANCER THERAPY: FROM FUNDAMENTALS TO MULTIFUNCTIONAL SYSTEMS

NESLİHAN TAMSÜ SELLİ[1], NESLİHAN BAŞARAN[2], SEDA CETINDERE[3]*, GÖNÜL YENİLMEZ ÇİFTÇİ[4]

1. Introduction

Glass and glass-ceramic materials constitute two closely related yet intrinsically different categories of inorganic solids. Conventional glasses are amorphous in nature, characterized by the absence of long-range atomic order, whereas glass-ceramics are obtained through the deliberate and controlled crystallization of precursor glasses. This process yields a heterogeneous microstructure composed of crystalline phases uniformly distributed

[1] Assoc. Prof. Dr., Gebze Technical University, Department of Materails Science and Engineering, Orcid: 0000-0002-1871-2925
[2] Dr., Gebze Technical University, Department of Materails Science and Engineering, Orcid: 0000-0001-7467-8613
[3] Assoc. Prof. Dr., Gebze Technical University, Department of Chemistry, Orcid: 0000-0001-7599-8491
[4] Prof. Dr., Gebze Technical University, Department of Chemistry, Orcid: 0000-0003-3187-7166

within a residual glassy matrix. Owing to this dual-phase architecture, glass-ceramics typically exhibit superior mechanical performance, improved thermal resistance, and adjustable functional characteristics compared to fully amorphous glass systems. These advantageous attributes have rendered glass-ceramics highly suitable for a wide range of advanced technological applications, particularly within the biomedical domain (Höland & Beall, 2019; Fu et al., 2020; Deubener et al., 2018; Schneider & Komatsu, 2013; Rahaman et al., 2011; Jones, 2013; She et al., 2023; Cao et al., 2025; He et al., 2026; Jiang et al., 2024). design (Pope, 1983; Müller & et al., 1998).

Over the past few decades, there has been an increasing emphasis on the development of biomaterials that actively interact with biological environments rather than remaining passive or inert. Conventional implant materials, including metals and dense ceramics, provide adequate mechanical strength; however, they generally lack the capacity to establish strong biological bonding with surrounding tissues (Chen & Thouas, 2021). In contrast, specific glass and glass-ceramic formulations have demonstrated the ability to chemically bond with bone tissue, a phenomenon defined as bioactivity (Hench, 2006; Hoppe et al., 2020; Baino et al., 2021). This distinctive feature has elevated glass-ceramics to a prominent position in applications such as bone repair, tissue regeneration, and implant surface modification (Zhang et al., 2022; Kaur et al., 2022; Ribas et al., 2019; Safaei et al., 2026; Gupta et al., 2026).

The notion of bioactive materials was first systematically proposed by Hench in the late 1960s, representing a transformative milestone in the field of biomaterials science (Hench, 2006). Unlike bioinert materials, which are engineered to minimize biological interactions, bioactive materials are designed to trigger controlled biological responses at the material-tissue interface (Dash et al., 2023; Pantulap et al., 2022). Upon exposure to physiological environments, bioactive glasses and glass-ceramics undergo a sequence of surface

reactions, including ionic exchange processes, partial dissolution of the glass network, and the formation of a silica-rich layer (Kaou et al., 2023; Mîrț et al., 2024). These processes ultimately lead to the nucleation and growth of a hydroxycarbonate apatite (HCA) layer. Due to its chemical and structural similarity to the mineral component of bone, this layer facilitates strong interfacial bonding and enhances tissue integration. Furthermore, the capacity to tailor ionic release profiles enables these materials to modulate cellular responses such as proliferation, differentiation, and extracellular matrix production (Gabriel et al., 2025; Pantulap et al., 2022).

Bone tissue is a complex, hierarchical, and continuously remodeling system, which imposes stringent requirements on biomaterials intended for its repair or replacement. Such materials must provide adequate mechanical support while simultaneously promoting biological functions including tissue regeneration, vascularization, and biochemical signaling (Aldhaher et al., 2023; Li et al., 2025). Consequently, an ideal bone substitute should integrate mechanical compatibility with controlled degradation and intrinsic bioactivity. Glass-ceramic materials are particularly well-suited to meet these criteria. Through careful control of composition and crystallization behavior, it is possible to fine-tune their mechanical properties, dissolution kinetics, and ion release characteristics. In addition, the incorporation of biologically active ions such as strontium, zinc, lithium, and fluoride has further expanded their functional capabilities, enabling enhanced osteogenic activity, improved angiogenesis, and antibacterial effects (Rajendran et al., 2024; Ranmuthu et al., 2021).

In addition to their well-established role in bone tissue regeneration, glass and glass-ceramic biomaterials have recently attracted considerable attention in the context of bone-related cancer applications. Primary bone tumors and metastatic bone diseases often result in severe bone defects that require simultaneous tumor treatment and tissue reconstruction. In this regard, glass-ceramic

systems offer a unique advantage by combining structural support with therapeutic functionality (Hussein et al., 2025; Vallet-Regí et al., 2020; Li et al., 2025). Through the incorporation of specific therapeutic ions (e.g., Cu^{2+}, Ag^{+}, Ga^{3+}, or rare earth elements), these materials can exhibit anticancer, antibacterial, and angiogenic properties (Wu et al., 2019). Furthermore, certain glass-ceramic compositions have been explored for localized drug delivery and photothermal therapy, enabling targeted cancer treatment while minimizing systemic side effects (Amani et al., 2024; Borges et al., 2022). Their tunable degradation behavior and ion release kinetics allow for controlled therapeutic action, which is particularly advantageous in post-tumor resection scenarios where both tumor suppression and bone regeneration are required (Mobeen et al., 2026). Consequently, multifunctional glass-ceramic biomaterials are emerging as promising platforms for integrated cancer therapy and bone tissue engineering applications (Moeni et al., 2022).

Nevertheless, the design and development of glass-ceramic biomaterials are governed by complex interdependencies among composition, processing conditions, microstructure, and biological performance (Vallet-Regí & Ruiz-Hernández, 2011; Wu & Chang, 2012). A comprehensive understanding of these relationships is essential for optimizing material functionality and broadening their range of applications. Moreover, recent advancements in the field, including multifunctional systems, controlled ion delivery platforms, and hybrid materials that combine glass-ceramics with polymers or electrically conductive phases, are redefining conventional approaches to biomaterial design.

This chapter provides a focused yet comprehensive overview of glass-ceramic materials in biomedical applications. Initially, the fundamental aspects related to their structure, crystallization mechanisms, and processing techniques are outlined. Subsequently, the mechanisms of bioactivity and the influence of ion release on biological responses are discussed. The interplay between

composition, microstructure, and functional properties is then analyzed to elucidate key design considerations. Following this, major application areas, particularly in bone tissue engineering and implant technologies, are presented. Finally, recent developments in functional and ion-modified glass-ceramic systems are highlighted, along with current challenges and future research directions in this evolving field.

2. Fundamentals of Glass and Glass-Ceramic Materials

Glass and glass-ceramic materials constitute a fundamental class of inorganic solids whose structural characteristics directly govern their physical and functional properties (Zachariasen, 1932; Varshneya and Mauro, 2019; Fraser and Girtan, 2023). Unlike crystalline materials, conventional glasses lack long-range atomic order and instead exhibit a disordered network structure formed through the rapid cooling of a melt (Greaves and Sen, 2007; Vinay et al., 2025). This amorphous arrangement results in unique features such as isotropy, optical transparency, and compositional flexibility, making glass systems highly versatile for both structural and functional applications (Doremus, 1994; Zanotto and Mauro, 2020).

At the atomic scale, the structure of glass is commonly interpreted through the random network model originally proposed by Zachariasen, which describes a continuous three-dimensional network formed by interconnected structural units without periodicity (Zachariasen, 1932; Greaves and Sen, 2007). Within this framework, oxide glasses are typically described in terms of network formers, intermediates, and network modifiers (Varshneya and Mauro, 2019; Zanotto and Mauro, 2020). Network formers such as SiO_2, B_2O_3, and P_2O_5 establish the backbone of the glass structure through strong covalent bonding, while modifiers like Na_2O or CaO disrupt the network by generating non-bridging oxygens. These structural disruptions significantly influence macroscopic properties including viscosity, glass transition temperature, chemical durability,

and dissolution kinetics (Varshneya and Mauro, 2019; Fraser and Girtan, 2023).

In addition to compositional effects, processing conditions play a critical role in defining glass structure and properties. Parameters such as cooling rate, melting temperature, and thermal history can significantly influence structural relaxation phenomena, which in turn affect the physical properties of glass-forming systems (Hodge, 1995; Málek, 2010). These relaxation processes govern the evolution of the glass structure toward equilibrium and are strongly dependent on the thermal path followed during processing (Hodge, 1995; Debenedetti and Stillinger, 2001). Consequently, even glasses with identical compositions may exhibit markedly different physical behaviors depending on their thermal history, highlighting the importance of processing-structure-property relationships in glass science (Debenedetti and Stillinger, 2001).

Glass-ceramics, on the other hand, are produced through the controlled crystallization of precursor glasses via carefully designed heat-treatment schedules. This process, commonly referred to as ceramming, involves two primary stages: nucleation and crystal growth (Zanotto, 1998; Höland and Beall, 2012). The use of nucleating agents promotes the formation of a high density of nuclei, enabling the development of fine and homogeneous microstructures (Höland and Beall, 2012). As a result, glass-ceramics consist of crystalline phases uniformly distributed within a residual glassy matrix, distinguishing them from both fully amorphous glasses and conventional polycrystalline ceramics (Zanotto, 1998; Höland and Beall, 2012).

One of the most significant advantages of glass-ceramics lies in their microstructural tunability. By adjusting parameters such as composition, nucleating agents, and thermal treatment conditions, it is possible to control crystal size, morphology, orientation, and volume fraction (Höland and Beall, 2012; Zanotto, 2010). These microstructural features directly influence key properties such as

mechanical strength, fracture toughness, thermal expansion, and resistance to thermal shock (Höland and Beall, 2012). In many cases, glass-ceramics exhibit superior mechanical performance compared to their parent glasses due to the reinforcing effect of finely dispersed crystalline phases (Zanotto, 2010).

Furthermore, the presence of both crystalline and amorphous phases enables glass-ceramics to combine desirable characteristics from each component. While the crystalline phases contribute to strength, stiffness, and thermal stability, the residual glassy phase facilitates processing and can play a crucial role in functional behavior, particularly in terms of ion mobility, chemical reactivity, and surface interactions (Hench and Jones, 2015; Höland and Beall, 2012). This dual-phase architecture is especially advantageous in applications where controlled degradation, surface activity, or interaction with biological environments is required (Hench and Jones, 2015).

Another important aspect of glass-ceramic systems is their ability to be engineered across multiple length scales. At the atomic level, compositional design governs bonding and network connectivity; at the nanoscale, phase separation and nucleation phenomena determine crystal formation; and at the microscale, grain size and distribution influence macroscopic properties (Micoulaut, 2016; Smedskjaer, 2014; James, 1974; Fokin et al., 2006; Höland and Beall, 2012). This hierarchical control provides a powerful platform for designing materials with highly tailored performance characteristics (Raghavan et al., 2010; Zanotto, 2017).

In summary, the fundamental distinction between glasses and glass-ceramics lies in their structural organization and degree of crystallinity. The ability to manipulate composition, processing conditions, and microstructure enables the development of materials with precisely controlled physical, chemical, and functional properties. This versatility forms the foundation for their widespread use in advanced technological applications, particularly in areas

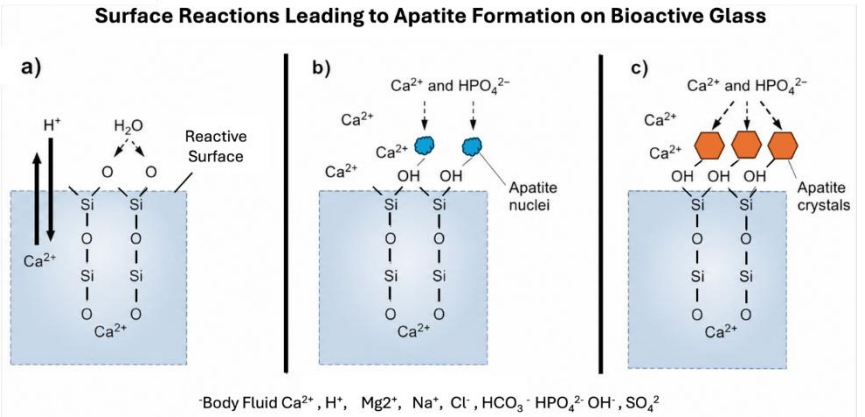
where a combination of structural integrity and functional performance is required.

3. Bioactivity Mechanisms of Glass Ceramics

Bioactive glass-ceramics represent a unique class of materials capable of eliciting specific biological responses when in contact with physiological environments. Unlike inert ceramics, these materials actively interact with surrounding tissues, leading to the formation of a stable bond with bone and, in some cases, soft tissues. The bioactivity of glass-ceramics is primarily governed by their surface reactions, ionic dissolution behavior, and the subsequent formation of biologically active layers (Piatti et al., 2024; Berbecaru et al., 2010). As shown in Figure 1, these reactions proceed through a sequence of stages including ion exchange between modifier cations and physiological fluids, the formation of a reactive silica-rich surface layer, apatite nucleation, and the subsequent growth of apatite crystals on the material surface. These processes occur through a series of well-defined physicochemical and biological mechanisms, including ion exchange, network dissolution, and hydroxycarbonate apatite (HCA) formation, which are strongly influenced by composition, crystallization behavior, and microstructure (Peitl Filho et al., 1996; Zhou et al., 2026). Specifically, Figure 1 illustrates the progressive development of a bioactive surface, beginning with Ca^{2+}/H^{+} exchange and hydroxylation of the glass surface (Figure 1a), followed by calcium-phosphate accumulation and apatite nuclei formation (Figure 1b), and culminating in the growth of apatite crystals that promote bonding with surrounding bone tissue (Figure 1c). In particular, recent studies have emphasized that compositional tuning and structural modification-such as the incorporation of network formers or modifiers like zirconium or variations in oxide ratios-can significantly alter dissolution kinetics and biological response both in vitro and in vivo (Piatti et al., 2024; Milewczyk et al., 2025). These

mechanisms span multiple length scales, from atomic-level ion exchange processes to macroscopic tissue integration, ultimately governing the performance of glass-ceramic biomaterials.

Figure 1. Surface reactions leading to hydroxycarbonate apatite formation on bioactive glass and glass-ceramic surfaces a) ion exchange and formation of a reactive silica-rich layer, b) nucleation of apatite, and c) growth of apatite crystals resulting in a bioactive surface.



Surface Reactions and Initial Ion Exchange: The bioactivity of glass-ceramics begins immediately upon exposure to body fluids. The first stage involves rapid ion exchange between modifier cations in the glass (such as Na^+, Ca^{2+}, or K^+) and hydrogen ions (H^+ or H_3O^+) from the surrounding physiological solution. This exchange leads to the formation of silanol (Si-OH) groups on the material surface and results in a localized increase in pH (Taye, 2022; Yadav et al., 2024).Figure 2. An example for POM-doped polymeric scaffolds (Zhao & et al., 2022). Simultaneously, the breakdown of the silicate network occurs through hydrolysis reactions, particularly affecting Si-O-Si bonds. This process leads to the release of soluble silica species (e.g., $Si(OH)_4$) into the surrounding medium. The dissolution

behavior is strongly influenced by the glass composition, network connectivity, and the presence of modifying oxides (Madival, 2026; Furko, 2025). Glass-ceramics with lower network connectivity generally exhibit higher dissolution rates, which can enhance bioactivity but may compromise long-term stability (Piatti et al., 2024; Milewczyk et al., 2025).

Formation of the Silica-Rich Layer: Following initial dissolution, a silica-rich layer begins to form on the material surface due to the condensation and repolymerization of silanol groups. This layer is typically amorphous and depleted in alkali and alkaline earth elements. It acts as a critical intermediate phase that facilitates further reactions leading to biological bonding (Omidian et al., 2022; Krishnamoorthy & Subramanian, 2026). The formation of this layer is essential because it provides a chemically active and structurally suitable surface for subsequent calcium phosphate nucleation. Its high surface area and abundance of silanol groups promote the adsorption of calcium and phosphate ions from the surrounding environment. This step represents a transition from purely chemical processes to biologically relevant mineralization mechanisms (Zăvoi et al., 2025; Taye, 2022).

Nucleation and Growth of Hydroxycarbonate Apatite (HCA): One of the defining features of bioactive glass-ceramics is their ability to form a hydroxycarbonate apatite (HCA) layer on their surface. This layer is chemically and structurally similar to the mineral phase of natural bone, enabling strong interfacial bonding (Larry L. Hench, 1998; Piatti et al., 2024). The formation of this biologically active apatite-like layer is widely recognized as the key mechanism underlying the bioactivity of these materials. The formation of HCA begins with the migration and accumulation of Ca^{2+} and PO_4^{3-} ions at the silica-rich surface. These ions initially form an amorphous calcium phosphate (ACP) phase, which subsequently crystallizes into HCA. The kinetics of this transformation depend on several factors, including ion release rates,

surface energy, and the presence of nucleation sites (Jones, 2013; De Micco et al., 2025). Recent studies further emphasize that surface reactions leading to silica gel formation play a critical intermediate role in enabling apatite nucleation. In glass-ceramics, the presence of crystalline phases can significantly influence apatite formation. Certain crystalline phases act as preferential nucleation sites, enhancing the rate and uniformity of HCA layer formation. This controlled crystallization is one of the key advantages of glass-ceramics over purely amorphous bioactive glasses (Piatti et al., 2024; Ellakwa et al., 2025). Moreover, recent findings suggest that compositional tuning and surface modification strategies can further optimize apatite-forming ability and biological performance.

Role of Ionic Dissolution Products in Biological Response: Beyond surface mineralization, the ions released from bioactive glass-ceramics play a crucial role in stimulating cellular responses. Dissolved species such as Si, Ca, P, and other therapeutic ions (e.g., Sr, Zn, Mg) can regulate gene expression and influence cellular activities including proliferation, differentiation, and extracellular matrix production (Julian R. Jones, 2013; Aldo R. Boccaccini et al., 2020). Silicon ions, for example, are known to enhance osteoblast activity and promote collagen synthesis, while calcium ions are involved in signaling pathways associated with bone mineralization. Phosphate ions, on the other hand, are essential for apatite formation. The synergistic and controlled release of these ions creates a favorable biochemical microenvironment that supports tissue regeneration (Larry L. Hench, 1998; Aldo R. Boccaccini et al., 2020). Importantly, the concentration and release kinetics of these ions must be carefully controlled. Excessive ion release can induce cytotoxic effects, whereas insufficient release may result in limited biological stimulation. Therefore, tailoring composition and microstructure remains critical for optimizing bioactivity and ensuring a balanced cellular response (Julian R. Jones, 2013; Hoppe et al., 2011; Zheng et al., 2021).

Influence of Microstructure on Bioactivity: The bioactivity of glass-ceramics is strongly dependent on their microstructural characteristics, including crystal size, distribution, and the volume fraction of crystalline phases. A fine and homogeneous microstructure generally enhances bioactivity by providing a larger surface area and more nucleation sites for apatite formation. Phase assemblage also plays a crucial role. For instance, certain crystalline phases may be bioactive, while others are relatively inert. The coexistence of crystalline and residual glassy phases allows for a balance between mechanical strength and bioactivity. The glassy phase typically governs ion release, whereas crystalline phases contribute to structural integrity. Additionally, porosity-particularly interconnected porosity-can significantly improve biological performance by facilitating fluid transport, nutrient diffusion, and tissue ingrowth. However, increased porosity often comes at the expense of mechanical strength, necessitating careful optimization depending on the intended application.

Biological Integration and Tissue Response: The final stage of bioactivity involves the interaction between the material surface and living tissue. Once the HCA layer forms, it serves as a biologically active interface that enables the adsorption of proteins and the attachment of osteogenic cells. This leads to the formation of a strong bond between the implant and bone tissue, often referred to as osseointegration. Cellular responses are influenced not only by chemical composition but also by surface topography and roughness. Micro- and nanoscale features can enhance cell adhesion and proliferation by providing favorable physical cues. Over time, the material may either remain stable or undergo controlled degradation, depending on its composition and structure. In applications such as bone regeneration, the ability of glass-ceramics to support new tissue formation while gradually integrating into the biological environment makes them highly valuable. Their multifunctionality-

combining mechanical support with biological activity-distinguishes them from traditional biomaterials

Summary of Bioactivity Mechanisms: In summary, the bioactivity of glass-ceramics is governed by a sequence of interconnected processes:

1. Ion exchange and network dissolution
2. Formation of a silica-rich surface layer
3. Nucleation and growth of hydroxycarbonate apatite
4. Release of biologically active ions
5. Cellular response and tissue integration

These mechanisms are highly sensitive to composition, processing conditions, and microstructure. The ability to control these parameters enables the design of advanced glass-ceramic materials with tailored biological performance, making them suitable for a wide range of biomedical applications, particularly in bone repair and regeneration.

4. Applications in Bone Tissue Engineering

Bone tissue engineering has emerged as a promising strategy to address the limitations of conventional treatments for bone defects, such as autografts and allografts, which are often associated with limited availability, donor site morbidity, and risk of immune rejection (Battafarano et al., 2021). In this context, bioactive glass-ceramics have gained significant attention due to their unique ability to combine structural support with biological functionality. Their capacity to bond directly to bone, stimulate cellular activity, and release biologically active ions makes them highly suitable for applications in bone regeneration and repair (Shearer et al., 2022; He, 2023). The broad range of biomedical applications of bioactive glass-ceramics in bone tissue engineering is summarized in Figure 2, including bone defect repair, spinal fusion, dental and maxillofacial reconstruction, drug delivery systems, osteochondral

repair, bone cancer reconstruction, and scaffold-based tissue regeneration.

Figure 2. Applications of bioactive glass-ceramics in bone tissue engineering.

Role of Bioactive Glass-Ceramics in Bone Regeneration: Bioactive glass-ceramics play a multifunctional role in bone tissue engineering by acting as both structural scaffolds and bioactive stimulators. Upon implantation, these materials undergo surface reactions that lead to the formation of a hydroxycarbonate apatite (HCA) layer, which closely resembles the mineral phase of natural bone. This layer serves as a biologically active interface that promotes osteoblast attachment, proliferation, and differentiation (Shearer et al., 2022; Fu et al., 2021). In addition to surface mineralization, the controlled release of ionic dissolution products (such as silicon, calcium, and phosphorus) plays a crucial role in regulating cellular responses. These ions can activate signaling pathways involved in osteogenesis, angiogenesis, and extracellular matrix formation. As a result, bioactive glass-ceramics not only

support bone growth but actively participate in the healing process by enhancing tissue regeneration at the molecular level (Baino et al., 2021; He, 2023).

Scaffold Design and Structural Requirements: A key requirement in bone tissue engineering is the development of scaffolds that mimic the hierarchical structure of natural bone. Bioactive glass-ceramics can be engineered into porous three-dimensional scaffolds with controlled architecture, enabling them to provide both mechanical support and biological functionality (Baino & Fiume, 2020). Porosity is one of the most critical design parameters. Interconnected macropores are essential for cell migration, vascularization, and nutrient transport, while micropores contribute to increased surface area and enhanced bioactivity. The ability to tailor pore size distribution and overall porosity allows for optimization of both mechanical strength and biological performance. Moreover, advances in fabrication techniques, such as sol–gel processing, foam replication, and additive manufacturing (3D printing), have enabled precise control over scaffold geometry and internal architecture. These technologies allow for the creation of patient-specific implants with optimized structural and functional properties (Cui et al., 2024; El-Rashidy et al., 2021).

Mechanical Performance and Load-Bearing Applications: While bioactive glass-ceramics exhibit excellent bioactivity, their relatively brittle nature poses challenges for load-bearing applications. To address this limitation, various strategies have been developed to enhance their mechanical properties without compromising bioactivity. One common approach involves the design of glass-ceramic composites, where reinforcing phases such as crystalline domains or secondary materials (e.g., polymers or ceramics) are introduced to improve toughness and strength. Controlled crystallization within the glass matrix can also enhance mechanical performance by creating a fine microstructure that resists crack propagation. Additionally, functionally graded materials (FGMs)

have been explored to achieve a balance between mechanical stability and biological activity. In such systems, the composition and structure vary gradually across the material, allowing for a strong core combined with a bioactive surface layer. This approach is particularly useful for implants that must withstand mechanical loads while maintaining bioactive functionality at the tissue interface.

Ion Doping and Functionalization: One of the most powerful advantages of bioactive glass-ceramics is their compositional flexibility, which allows for the incorporation of therapeutic ions to enhance biological performance. Ion doping has been widely used to tailor the properties of these materials for specific biomedical applications. For example, the incorporation of strontium (Sr) has been shown to stimulate osteoblast activity and reduce osteoclast-mediated bone resorption, making it particularly useful in the treatment of osteoporosis. Zinc (Zn) contributes to bone formation and exhibits antibacterial properties, while magnesium (Mg) plays a role in cellular metabolism and enhances mechanical performance. Copper (Cu) and cobalt (Co) ions have been investigated for their ability to promote angiogenesis by stimulating vascular endothelial growth factor (VEGF) expression. Beyond biological effects, ion doping can also influence the glass network structure, dissolution behavior, and crystallization kinetics. This provides an additional level of control over both material properties and biological responses, enabling the design of highly specialized biomaterials for targeted applications.

Drug Delivery and Controlled Release Systems: Bioactive glass-ceramics have also been extensively explored as platforms for drug delivery in bone tissue engineering. Their porous structure and surface chemistry enable the adsorption and controlled release of therapeutic agents, including antibiotics, growth factors, and anti-inflammatory drugs. This dual functionality—combining structural support with localized drug delivery—offers significant advantages

in clinical applications. For instance, the incorporation of antibiotics into bioactive scaffolds can help prevent post-surgical infections, while the delivery of growth factors such as bone morphogenetic proteins (BMPs) can accelerate bone regeneration. The release kinetics of these agents can be tailored by modifying the composition, porosity, and surface properties of the material. This allows for sustained and controlled delivery profiles that align with the different stages of the healing process.

Angiogenesis and Vascularization: Successful bone regeneration requires not only osteogenesis but also the formation of new blood vessels to supply nutrients and oxygen to the growing tissue. Bioactive glass-ceramics have demonstrated a strong ability to promote angiogenesis through the release of specific ions and the formation of bioactive surfaces. Ions such as silicon, copper, and cobalt have been shown to stimulate angiogenic signaling pathways, leading to increased expression of angiogenic factors and enhanced vascularization. The formation of a biologically active surface layer further supports endothelial cell attachment and proliferation, contributing to the development of functional vascular networks. The coupling of osteogenesis and angiogenesis is a critical factor in successful bone tissue engineering, and bioactive glass-ceramics offer a unique platform for achieving this synergy.

Clinical Applications and Future Perspectives: Bioactive glass-ceramics have already been applied in various clinical settings, including bone defect repair, spinal fusion, dental implants, and maxillofacial reconstruction. Their ability to bond with bone and support tissue regeneration has led to the development of several commercially available products. Looking forward, future research is focused on improving the performance of these materials through advanced design strategies, including nanostructuring, hybrid materials, and smart biomaterials capable of responding to environmental stimuli. The integration of bioactive glass-ceramics with emerging technologies such as bioprinting and tissue-

engineered constructs is expected to further expand their applications. Moreover, a deeper understanding of structure-property-biological response relationships will enable the development of next-generation materials with enhanced functionality and reliability. As a result, bioactive glass-ceramics are expected to play an increasingly important role in the advancement of regenerative medicine and bone tissue engineering.

5. Emerging Applications in Bone Cancer Therapy

Translating Bone cancer is a type of cancer in which tumors form, destroying bone tissue, due to the abnormal division and multiplication of cells in the bones. Cancers that originate in the bone itself are called primary bone cancers. Primary bone cancers are cancers that originate directly from the cells of the bone tissue itself. They are rarer and tend to occur especially during childhood, adolescence, or young adulthood [Hussein et al., 2025]. Three types of tumors are observed within the bone structure: osteosarcoma (OS), Ewing sarcoma, and chondrosarcoma. Osteosarcoma is the most common type of primary bone cancer. It most often occurs in children and young adults under the age of 20. It develops in the femur, tibia, and the ends of the humerus, particularly around the knee and shoulder. It can be aggressive and has the potential to metastasize even in the early stages. Despite making up less than 1 % of all malignancies diagnosed each year, these diseases have significant morbidity and fatality rates. Among adolescents and teen agers, osteosarcoma is the most frequent primary bone cancer, and the third most common type of cancer [Simpson and Brown, 2018]. Even after the development of adjuvant treatment in the 1970s, which increased the 10-year survival rate from 30 % to roughly 50 %, patients with osteosarcoma still face a weak prognosis. In the study conducted by Deliormanlı and his group, bioactive glass powders containing superparamagnetic maghemite (2%, 5%, 10%, 20% by weight) were prepared for the treatment of osteosarcoma.

For this purpose, maghemite nanoparticles were synthesized using the co-precipitation technique, and bioactive glass-ceramic composites containing maghemite were produced by the sol-gel process. The structural, morphological, thermal, and magnetic properties and in vitro bioactivity of the prepared bioactive glasses were investigated. In vitro cytotoxicity was examined using SaOS-2 and MC3T3-E1 cells. The fluorouracil (5-FU) release behavior of the studied bioactive glass powders was also monitored in phosphate-buffered saline as a function of time. The results revealed that the synthesized maghemite nanoparticles and bioactive glass-ceramic composites containing maghemite possess superparamagnetic properties. They have high bioactivity with up to 5% maghemite content. The prepared bioactive glass composites did not exhibit cytotoxicity against osteosarcoma and pre-osteoblast cells at low concentrations. The drug-loaded bioactive glass powder showed sustained release behavior. Overall results indicate that the prepared glass composites have high potential for use in magnetic hyperthermia and anticancer drug delivery [Deliormanlı et al., 2022]. Chondrosarcoma is a type of cancer that originates from cells that produce cartilage tissue. It most commonly occurs in the pelvis, shoulder, ribs, thigh, and upper arm bones. It is more common in adults, particularly those aged 40 and older, and some subtypes can be quite aggressive. While the overall 5-year survival rate is approximately 70–75 %, high-grade tumors and aggressive chondrosarcoma subtypes are associated with a particularly poor prognosis. Agulnik et al. Reported a rewiev about clinical behavior, molecular mechanisms, and emerging therapeutic strategies of chondrosarcoma. They explored chondrosarcoma subtypes, diagnostic approaches, prognostic factors, and molecular alterations, followed by a discussion of current and emerging treatment strategies [Agulnik et al., 2026]. Ewing sarcoma, commonly seen in children and young adults, is an aggressive tumor that can originate from bone or surrounding soft tissue. It is most frequently found in

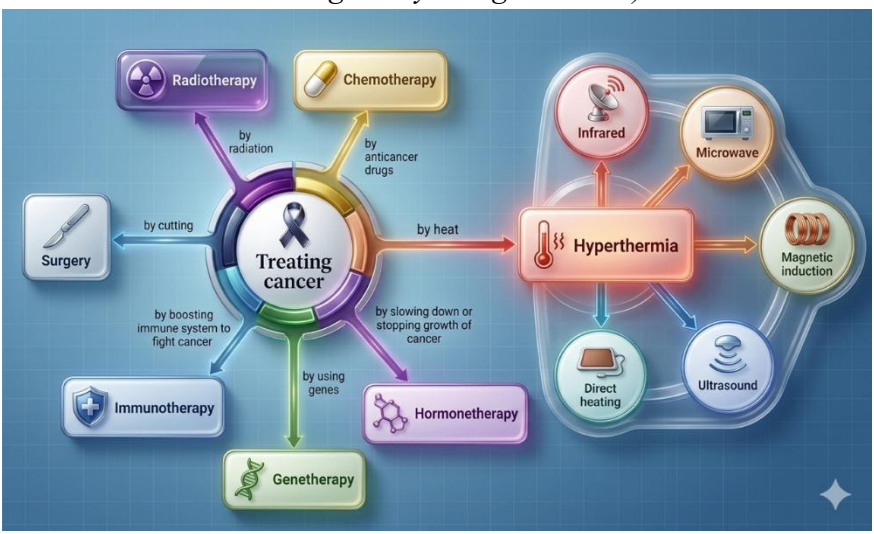
the ribs, pelvis, scapula, and hip bones. A recent review article published in 2026 reported that Ewing sarcoma is an aggressive bone and soft-tissue malignancy affecting adolescents and young adults, and that the development of in vitro and in vivo models has significantly contributed to a better understanding of the disease biology. These models have become essential tools for evaluating novel therapeutic approaches, particularly in metastatic or relapsed cases. Furthermore, the review summarized current preclinical modeling strategies, including cell lines, tumor organoids, and xenograft models, and discussed factors that may influence experimental outcomes [Bailey et al., 2026].

Bone cancer that starts in other tissues or parts of the body and spreads to the bones, known as metastasis, is considered a secondary type of cancer. Secondary bone cancers (bone metastases) occur when a cancer spreads to the bones via the bloodstream or lymphatic system. They develop when cancers from different organs of the body, such as breast, lung, prostate, kidney, and thyroid cancers, reach the bone and form new tumor metastases. Metastatic bone tumors, on the other hand, are much more common. Between 65 and 80 % of people with late-stage breast and prostate cancers have bone metastases, which is a common sign of advanced disease [Jakob et al., 2014], as do 35 to 42 % of people with advanced renal, lung, or thyroid cancers [Griffin et al., 2011; McCauley et al., 2011].

A single mechanism to fully cure cancer has not yet been developed. The most commonly used techniques include radiotherapy (treating cancer cells with radiation), chemotherapy (treating cancer cells with chemicals/drugs), and hyperthermia (treating cancer cells with heat) (Figure 3). Hyperthermia is considered one of the promising techniques because of its high potential for destroying cancer cells. For this purpose, interest in bioactive glass ceramics has increased due to their heat-generating capabilities. In addition to their heat-generating ability, these materials, when properly selected glass compositions react with

physiological fluids, can in some cases exhibit a bioactive response towards natural bone and even soft tissues. In this way, besides eliminating cancer cells, bioactive glass ceramics can also aid in the regeneration of affected bone portions [Danewalia and Singh, 2021; Zeisberger et al., 2006; Verne et al., 2015; Miola et al.,2017; Baino et al., 2018; Bruno et al., 2014; Gerhardt and Boccaccini, 2010; Fernandes et al., 2018].

Figure 3. Various techniques for treatment of cancer (This figüre was designed by Google Gemini).



6. Multifunctional and Hybrid Glass-Ceramic Systems and Biological Applications

In recent years, glass-ceramic systems have evolved from being purely structural biomaterials into multifunctional platforms capable of addressing complex biological requirements. This shift has been largely driven by the integration of organic and inorganic components, as well as the incorporation of functional additives that enable electrical, chemical, and biological responsiveness. Such

developments have positioned hybrid glass-ceramic systems at the forefront of advanced biomedical applications (Cui et al., 2024; Yang et al., 2025; Deubener et al., 2018; Baino et al., 2021; Jones, 2022; Kargozar et al., 2023).

Polymer-Glass-Ceramic Hybrids: Polymer-glass-ceramic hybrids are designed by combining organic polymer networks with inorganic glass-ceramic phases at the molecular or nanoscale level. This intimate integration allows the material to benefit simultaneously from the bioactivity of the inorganic phase and the flexibility of the polymeric component. Compared to conventional composites, these hybrids often exhibit improved interfacial compatibility and more uniform structural organization (Wu et al., 2021; Rizwan et al., 2022). From a biological standpoint, these materials are particularly attractive for tissue engineering applications. The inorganic phase can stimulate mineralization and support osteogenic activity, while the polymeric network provides mechanical compliance and reduces brittleness. Additionally, their degradation behavior can be tailored by adjusting composition and crosslinking density, allowing synchronization with tissue regeneration rates. This tunability is a key advantage in applications such as bone scaffolds, where both mechanical integrity and gradual resorption are required (Nommeots-Nomm et al., 2021; Sharifi et al., 2023; Li et al., 2022).

Electrically Conductive Systems (e.g., MXene-Based Composites): The incorporation of electrically conductive components into glass-ceramic matrices has opened new possibilities, especially in the context of neural tissue engineering and bioelectronic interfaces. Among emerging materials, MXenes have attracted considerable attention due to their unique combination of high electrical conductivity, hydrophilicity, and surface functionalization capability (Rasool et al., 2022; Szuplewska et al., 2023). When integrated into glass-ceramic systems, MXene nanosheets can form conductive networks that facilitate electrical signaling at the cell–material interface. This is particularly relevant

for electrically active tissues, such as nerve and muscle, where external or endogenous electrical cues influence cellular behavior. Preliminary studies suggest that such conductive hybrids can enhance cell proliferation, differentiation, and signal transmission, although their long-term biological stability and safety remain under investigation (Zha et al., 2022; Kang et al., 2023; Liu et al., 2024).

Stimuli-Responsive (Smart) Materials: Another important direction in this field involves the development of stimuli-responsive glass-ceramic systems. These materials are capable of altering their properties in response to environmental triggers such as pH, temperature, light, or magnetic fields. Rather than acting as passive scaffolds, they function as dynamic systems that interact with their surroundings in a controlled manner (Cui et al., 2024; Wei et al., 2022). For instance, pH-sensitive materials can exploit the acidic microenvironment of diseased tissues, enabling localized activation of therapeutic functions. Similarly, thermally or photo-responsive systems can be used for controlled drug release or combined therapies, such as photothermal treatment. The inherent stability of the glass-ceramic phase provides a robust framework, while the responsive component introduces adaptability, resulting in a synergistic effect that enhances overall performance (Liu et al., 2023; Zhang et al., 2021; Kargozar et al., 2022).

Controlled Ion Release Platforms: One of the defining features of bioactive glass-ceramics is their ability to release therapeutic ions in a controlled manner. Ions such as calcium, silicon, strontium, and zinc are known to play critical roles in cellular signaling pathways related to bone formation, angiogenesis, and antibacterial activity (Baino et al., 2021; Hoppe et al., 2022). In hybrid systems, the kinetics of ion release can be finely tuned through compositional design and structural modification. The presence of a polymeric phase, for example, can act as a diffusion barrier or degradation-controlled reservoir, allowing for more sustained and predictable release profiles. This level of control is particularly important in

regenerative medicine, where the timing and concentration of ionic cues can significantly influence treatment outcomes (Miguez-Pacheco et al., 2023; Jones et al., 2021; Zheng et al., 2024).

7. Challanges and Future Perspectives

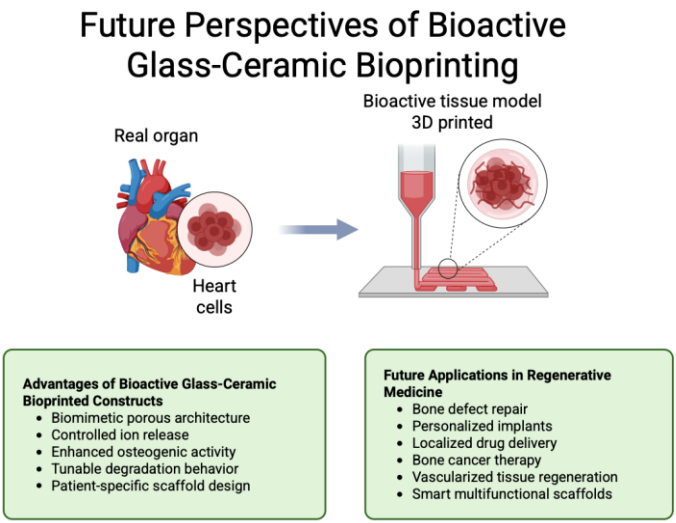
Despite the promising capabilities of multifunctional glass-ceramic systems, several challenges must be addressed before their full clinical potential can be realized. These challenges span material design, processing, and biological evaluation. Current challenges associated with hybrid bioactive glass-ceramic systems remain a major focus of ongoing research. One of the primary limitations lies in the complexity of fabrication processes. The synthesis of hybrid systems often requires precise control over multiple parameters, including composition, phase distribution, and microstructure. While such control is achievable at the laboratory scale, translating these methods to industrial production remains a significant hurdle (Fu et al., 2021). Another critical issue is the balance between mechanical properties and biological functionality. Enhancing bioactivity or introducing additional functionalities may compromise structural integrity, particularly in load-bearing applications. Achieving an optimal balance between these competing requirements continues to be a key research focus (Boccaccini et al., 2022; Deliormanlı & Rahaman, 2021). Long-term biocompatibility is also a concern, especially for systems incorporating novel nanomaterials. Although short-term studies often demonstrate promising results, the long-term effects of these materials within the human body are not yet fully understood. This uncertainty poses challenges for regulatory approval and clinical adoption (Gaharwar et al., 2022;). Furthermore, achieving precise control over ion or drug release profiles remains technically demanding. Small variations in material structure or environmental conditions can lead to significant changes in release behavior,

potentially affecting therapeutic efficacy (Mouriño & Boccaccini, 2021; Wu et al., 2022).

Future Perspectives, looking ahead, the development of personalized biomaterials is expected to play a central role in this field. Advances in additive manufacturing technologies, particularly 3D printing, are enabling the fabrication of patient-specific implants with tailored structural and functional properties (Bose et al., 2021; Tarafder et al., 2022). As illustrated in Figure 4, bioactive glass-ceramic bioprinting offers the potential to combine living cells with bioactive scaffold materials, enabling the fabrication of tissue-mimicking constructs that more closely replicate the architecture and biological function of native tissues. Furthermore, the biomimetic porous architecture and tunable ion-release characteristics of bioactive glass-ceramic systems make them particularly attractive for next-generation tissue engineering platforms. Combined with advances in stem cell technology, biofabrication, and artificial intelligence-assisted design, these materials may enable the production of highly customized regenerative therapies in the future. The integration of bioactive glass-ceramics with bioprinting technologies is expected to expand their application beyond conventional bone substitutes toward advanced regenerative medicine strategies. Future developments may include patient-specific implants, localized drug delivery systems, vascularized tissue constructs, smart multifunctional scaffolds, and novel approaches for bone cancer reconstruction, as summarized in Figure 4. These innovations aim to improve therapeutic outcomes while providing greater control over tissue regeneration and functional recovery. There is also a growing interest in designing truly multifunctional platforms that can simultaneously provide mechanical support, deliver therapeutic agents, and modulate biological responses. Such integrated systems could significantly improve treatment efficiency and reduce the need for multiple interventions (Zheng et al., 2026). The incorporation of

nanotechnology will likely continue to expand, offering new ways to control material behavior at the molecular level. Nanostructured additives can enhance surface interactions, improve mechanical performance, and enable more precise control over biological processes (Liu et al., 2022; Gao et al., 2021). In addition, the concept of autonomous or self-regulating materials is gaining attention. These systems would be capable of sensing changes in their environment and responding accordingly without external intervention, representing a significant step toward intelligent biomaterials (Zheng et al., 2026). Finally, efforts to standardize fabrication methods and establish comprehensive biological evaluation protocols will be essential for accelerating clinical translation. Bridging the gap between laboratory research and real-world application will require interdisciplinary collaboration and a strong focus on reproducibility and safety.

Figure 4: Future perspectives of bioactive glass-ceramic bioprinting, highlighting the transition from cell-based biofabrication toward personalized regenerative medicine applications.



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