JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S11

The Use of Graphene in Dental Implants: A Review of Current Applications

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Abstract
Titanium, the prevailing material in dental implantology, encounters challenges such as peri-implantitis and suboptimal osseointegration, potentially compromising long-term success. Graphene, a two-dimensional nanomaterial with exceptional properties, has emerged as a promising avenue for enhancing implant performance. This review comprehensively examines the current applications of graphene and its derivatives, graphene oxide (GO) and reduced graphene oxide (rGO), in dental implants. We explore graphene's multifaceted role in augmenting osseointegration, combating bacterial infections, serving as a platform for drug delivery and biosensing, and reinforcing dental materials. Different incorporation methods, including coatings, composites, and functionalized membranes, are discussed, alongside their respective advantages and limitations. Finally, we address the challenges and future perspectives of graphene in dental implantology, underscoring the need for rigorous research, particularly clinical trials, to fully translate its remarkable potential into clinical practice.

Introduction

Dental implants have profoundly transformed restorative dentistry, providing a robust solution for replacing missing teeth. Titanium and its alloys remain the preferred materials due to their biocompatibility, mechanical strength, and corrosion resistance (Elias et al., 2012; Shah et al., 2019). However, challenges persist, including peri-implantitis (inflammation of the tissues surrounding the implant) and insufficient osseointegration (direct bone-to-implant contact), which can jeopardize implant longevity (Albrektsson&Sennerby, 1991; Esposito et al., 1998; Xu et al., 2022). These complications arise from a confluence of factors, including bacterial colonization, inadequate bone formation, and corrosion of the implant material (Eliaz, 2019; Delgado-Ruiz &Romanos, 2018).

Nanomaterials present a promising approach to mitigate these limitations, and graphene, with its unique attributes, has garnered significant attention (Li et al., 2022; Tahriri et al., 2019). Graphene, a single layer of carbon atoms arranged in a hexagonal lattice, boasts exceptional mechanical strength, remarkable electrical conductivity, and inherent biocompatibility (Allen et al., 2010; Novoselov et al., 2012; Williams et al., 2023). Its derivatives, GO and rGO, offer further advantages such as enhanced hydrophilicity and the presence of functional groups that facilitate biomolecule attachment (Inchingolo et al., 2023; Li et al., 2022; Jiˇríˇckov´a et al., 2022).

This review meticulously explores the current applications of graphene in dental implants, focusing on its potential to: 1) enhance osseointegration, 2) combat bacterial infections, 3) act as a platform for drug delivery, 4) facilitate biosensing, and 5) reinforce dental materials. We examine the various methods employed to incorporate graphene into implant coatings and composites, analyzing their benefits and limitations. Finally, we discuss the challenges and future directions of graphene in dental implantology, emphasizing the critical need for further research, especially clinical trials, to fully realize its transformative clinical potential.

Synthesis and Properties of Graphene and Its Derivatives

Graphene, a single atomic layer of sp^2 hybridized carbon atoms arranged in a honeycomb lattice, has captivated the scientific community due to its extraordinary properties. Since its isolation in 2004 (Novoselov et al., 2004), extensive research has focused on developing scalable synthesis methods and exploring its potential in various fields, including dental implantology. The synthesis method employed significantly influences the characteristics of the resulting graphene, impacting its suitability for specific applications. Furthermore, chemical modifications of graphene have led to the development of derivatives like graphene oxide (GO) and reduced graphene oxide (rGO), each possessing unique properties that further broaden the scope of graphene's applications.

Several methods exist for synthesizing graphene, each with its own advantages and disadvantages regarding scalability, cost, and the quality of the resulting material. Mechanical exfoliation, the original method used to isolate graphene, involves peeling layers from highly ordered pyrolytic graphite using adhesive tape (Novoselov et al., 2004). While this method yields high-quality, single-layer graphene with minimal defects, it is not scalable for large-scale production. Liquid-phase exfoliation offers a more scalable approach, involving the sonication or shearing of graphite in solvents to separate individual graphene sheets (Ghuge et al., 2017). However, this method often results in small graphene flakes with varying numbers of layers and may require the use of toxic organic solvents.

Chemical vapor deposition (CVD) has emerged as a prominent method for producing large-area, high-quality graphene films (Saeed et al., 2020). In CVD, a hydrocarbon gas is decomposed on a metal substrate at high temperatures, leading to the formation of a graphene layer on the substrate surface. The quality and thickness of the graphene film can be controlled by adjusting the growth parameters, making CVD a versatile method for tailoring graphene for specific applications. Chemical exfoliation, typically employing modified Hummers' method, is widely used for producing GO (Chen et al., 2022; Hummers Jr &Offeman, 1958; Tienne et al., 2022). This method involves oxidizing graphite with strong oxidizing agents, introducing oxygen-containing functional groups that make GO highly dispersible in water. GO can then be further reduced to rGO using reducing agents, partially restoring the sp^2 carbon network and enhancing its electrical conductivity (Côté et al., 2009; Guo et al., 2009; Pei & Cheng, 2012).

Other synthesis methods include epitaxial growth on silicon carbide substrates and various solution-based methods. Epitaxial growth involves heating SiC under ultra-high vacuum, causing silicon atoms to sublimate and leaving a carbon-rich surface that rearranges to form graphene (Norimatsu& Kusunoki, 2014). Solution-based methods typically involve the reduction of GO or the exfoliation of graphite in specific solvents, offering potential for scalable and cost-effective production of graphene.

The properties of graphene and its derivatives are central to their applications in dental implantology. Graphene's exceptional mechanical strength, attributed to its strong covalent bonds within the hexagonal lattice, makes it a promising material for reinforcing dental composites and improving the wear resistance of implants (Allen et al., 2010; Lee et al., 2015a). Its high electrical conductivity, arising from the delocalized pi-electrons in the sp^2 carbon network, is advantageous for biosensing applications and may also play a role in cell stimulation (Novoselov et al., 2012; Tahriri et al., 2019).

The biocompatibility of graphene and its derivatives is a critical factor for their use in dental implants. While graphene is generally considered biocompatible, its interaction with biological systems is complex and influenced by factors like concentration, lateral size, surface functionalization, and synthesis method (Duch et al., 2011; Olteanu et al., 2015; Rosa et al., 2021). Studies have shown that graphene can stimulate cell differentiation, particularly osteogenic differentiation, which is essential for promoting osseointegration of implants (Kang et al., 2021; Li & Wang, 2020; Shin et al., 2018). This osteogenic potential is attributed to graphene's ability to enhance protein adsorption, promote cell adhesion and proliferation, and modulate cellular signaling pathways involved in bone formation (Li et al., 2015; Park et al., 2017; Zhou et al., 2016).

Furthermore, graphene and its derivatives exhibit antibacterial properties, inhibiting the growth of various oral pathogens (Dybowska-Sarapuk et al., 2017; He et al., 2015; Srimaneepong et al., 2022). The mechanisms of antibacterial action are still under investigation but are thought to involve membrane disruption, oxidative stress, and trapping of bacteria by graphene sheets (Akhavan& Ghaderi, 2010; Liu et al., 2011). The antibacterial properties of graphene make it a promising material for preventing peri-implantitis and improving the long-term success of dental implants.

The unique properties of GO and rGO, arising from their oxygen-containing functional groups, offer additional advantages for dental applications. GO's hydrophilicity and dispersibility in water make it easier to process and incorporate into various dental materials (Jiříčková et al., 2022). The functional groups on GO also provide sites for chemical modification and conjugation with biomolecules or drugs, enabling targeted drug delivery and enhanced bioactivity (Li & Wang, 2020; Ren et al., 2017). rGO, with its partially restored sp^2 carbon network, exhibits improved electrical conductivity compared to GO, making it suitable for biosensing applications (Wang et al., 2018). The tunable properties of GO and rGO further expand the possibilities for their application in dental implantology.

Applications of Graphene in Dental Implants

Graphene's unique physicochemical properties, combined with its biocompatibility and antibacterial activity, have positioned it as a promising material for various applications in dental implantology. Current research focuses on leveraging graphene and its derivatives to enhance osseointegration, combat bacterial infections, facilitate targeted drug delivery, enable biosensing, and reinforce dental materials.

Enhancing Osseointegration: Osseointegration, the direct structural and functional connection between living bone and the surface of a load-bearing implant (Albrektsson et al., 1981), is crucial for the long-term success of dental implants. Graphene's ability to promote osteogenic differentiation, the process by which mesenchymal stem cells differentiate into bone-forming osteoblasts, is a key advantage in enhancing osseointegration. Studies have demonstrated that graphene coatings and composites can significantly increase bone-to-implant contact (BIC) and bone volume fraction (BVF) around implants, leading to a stronger and more stable implant-bone interface (Folkman et al., 2020; Kwak et al., 2022; Park et al., 2017; Shin et al., 2022).

Several mechanisms contribute to graphene's osteogenic potential. Graphene's surface topography, even at the nanoscale, can influence cell behavior, promoting cell adhesion, spreading, and proliferation (Cervino et al., 2021; Zhu et al., 2021). Its electrical conductivity may also play a role in stimulating osteogenic differentiation by influencing cellular signaling pathways (Li et al., 2015; Tahriri et al., 2019). Furthermore, graphene can enhance protein adsorption, creating a more favorable environment for bone cell attachment and growth (Park et al., 2017; Zhou et al., 2016). In vivo studies using animal models have shown that graphene-coated implants exhibit enhanced bone formation and faster healing compared to uncoated titanium implants, further supporting its potential for improving osseointegration (Li & Wang, 2020; Shin et al., 2022).

Combating Bacterial Infections: Peri-implantitis, a common complication characterized by inflammation of the tissues surrounding a dental implant, is a major cause of implant failure (Jansåker et al., 2003; Kordbacheh et al., 2019). Bacterial biofilm formation on the implant surface plays a critical role in the development and progression of peri-implantitis (Manaf& Rahman, 2020). Graphene's inherent antibacterial properties offer a promising strategy for preventing and treating this debilitating condition.

Graphene coatings on implants can effectively inhibit bacterial adhesion and growth, reducing the risk of biofilm formation and subsequent infection (Jang et al., 2021; Rocha et al., 2023; Zafar et al., 2019). The antibacterial activity of graphene is attributed to several mechanisms, including physical disruption of bacterial membranes by graphene's sharp edges, oxidative stress induced by graphene's interaction with bacterial cells, and trapping of bacteria by graphene sheets (Akhavan& Ghaderi, 2010; Liu et al., 2011). Furthermore, graphene can be functionalized with antimicrobial agents like silver nanoparticles or antibiotics, creating synergistic antibacterial coatings that further enhance the implant's resistance to infection (Jin et al., 2017; Qian et al., 2018; Souza et al., 2019). These combined approaches offer a powerful tool for combating peri-implantitis and improving the long-term success of dental implants.

Drug Delivery: Graphene and its derivatives, particularly GO, can serve as versatile drug delivery platforms, enabling localized and sustained release of therapeutic agents at the implant site (Li et al., 2022; Malhotra et al., 2020). GO's abundant oxygen-containing functional groups provide sites for chemical conjugation with various drugs, allowing for controlled release and targeted delivery to the peri-implant tissues (Li & Wang, 2020; Ren et al., 2017). This localized drug delivery approach minimizes systemic side effects and maximizes therapeutic efficacy, offering significant advantages over conventional drug administration methods.

Graphene-based drug delivery systems can be used to deliver a wide range of therapeutic agents, including antibiotics, anti-inflammatory drugs, growth factors, and bone morphogenetic proteins (Bjeli´c&Finˇsgar, 2021; Chi et al., 2022). For instance, delivering antibiotics directly to the implant site can effectively treat peri-implantitis and prevent recurrent infections. Similarly, delivering growth factors or bone morphogenetic proteins can promote bone regeneration and accelerate osseointegration, particularly in patients with compromised bone quality (Delgado-Ruiz &Romanos, 2018; Safavi et al., 2022).

Biosensing: Graphene's exceptional electrical conductivity and large surface area make it an ideal material for biosensor applications in dental implantology (Goldoni et al., 2021; Tahriri et al., 2019). Graphene-based biosensors can be integrated into implants to monitor biomarkers in the surrounding tissues, providing valuable real-time information for diagnosis and treatment (Li et al., 2022; Wei et al., 2021). These sensors can detect a wide range of biomarkers, including inflammatory mediators, bacterial byproducts, and even specific pathogens, enabling early detection of peri-implantitis and other implant-related complications (Chekin et al., 2018; Verma et al., 2017).

The high sensitivity and selectivity of graphene-based biosensors allow for precise monitoring of the peri-implant environment, providing valuable insights into the healing process and enabling timely intervention in case of complications. For example, detecting elevated levels of inflammatory markers could indicate the onset of peri-implantitis, prompting early treatment and potentially preventing implant failure. Furthermore, graphene biosensors can be designed to detect specific bacterial species associated with peri-implantitis, enabling targeted antimicrobial therapy and personalized treatment strategies.

Methods of Incorporating Graphene into Dental Implants

Several methods have been developed to incorporate graphene and its derivatives into dental implants, each offering distinct advantages and posing specific challenges. The primary methods include creating graphene coatings on titanium surfaces, incorporating graphene into composite materials, and functionalizing collagen membranes with graphene.

Coatings: Applying graphene coatings directly onto titanium implant surfaces is a widely explored approach. These coatings aim to enhance the surface properties of the implant, promoting osseointegration and imparting antibacterial properties. Various techniques are employed for creating these coatings, including chemical vapor deposition (CVD), electrophoretic deposition, spin coating, and layer-by-layer assembly (Corado et al., 2022; Li et al., 2015; Park et al., 2017; Qian et al., 2019). CVD allows for the growth of high-quality graphene films directly on the titanium surface, while electrophoretic deposition enables controlled deposition of graphene or GO onto complex implant geometries. Spin coating offers a simple and cost-effective method for applying thin graphene coatings, and layer-by-layer assembly allows for the creation of multilayered coatings with tailored properties. A key challenge with graphene coatings lies in ensuring their long-term stability and adhesion to the titanium substrate, preventing delamination and potential release of graphene particles into the surrounding tissues.

Composites: Incorporating graphene into composite materials used for implant fabrication or as bone graft substitutes is another promising approach. Graphene can be added to polymer matrices like polymethyl methacrylate (PMMA) or calcium silicate cements, enhancing their mechanical properties, bioactivity, and antibacterial activity (Azadian et al., 2020; Dubey et al., 2017; Lorusso et al., 2021; Nileshkumar et al., 2017; Patil et al., 2020; Suo et al., 2018; Wu et al., 2019). The addition of graphene can improve the strength and toughness of PMMA, making it more resistant to fracture and wear. In bone graft composites, graphene can act as a scaffold for bone cell attachment and growth, promoting bone regeneration. The uniform dispersion of graphene within the composite matrix is crucial for achieving optimal performance and preventing agglomeration, which can compromise the material's properties.

Functionalized Membranes: Collagen membranes are frequently used in guided bone regeneration (GBR) and guided tissue regeneration (GTR) procedures to prevent soft tissue ingrowth and promote bone healing. Functionalizing these membranes with graphene can enhance their biocompatibility, mechanical properties, and ability to promote bone regeneration (Chu et al., 2017a; Chu et al., 2017b; Di Marco et al., 2017). Graphene can be incorporated into collagen membranes through various methods, including non-covalent functionalization via hydrogen bonding or covalent attachment using chemical crosslinkers. The presence of graphene can improve the membrane's stability, prevent premature degradation, and enhance its ability to promote cell adhesion and differentiation. Optimizing the interaction between graphene and collagen within the membrane is crucial for maximizing its beneficial effects on bone regeneration.

Challenges and Future Perspectives

Despite its immense potential, several challenges need to be addressed before graphene can be universally adopted in dental implantology:

- **Long-term Biocompatibility and Biodegradability *in vivo*:** While preliminary studies indicate good biocompatibility *in vitro*, the long-term effects of graphene *in vivo*, including its biodegradation pathways and potential accumulation in organs, warrant further investigation (Lotz et al., 2020; Malhotra et al., 2020; Vaidya et al., 2024). Understanding the long-term fate of graphene in the biological environment is crucial for ensuring its safety and efficacy in clinical applications.
- **Standardized Synthesis and Characterization:** Variations in graphene synthesis methods can result in inconsistencies in its properties, posing challenges for reproducible results in clinical settings (Mbayachi et al., 2021; Safian et al., 2021). Establishing standardized protocols for graphene synthesis and comprehensive characterization is essential for clinical translation and ensuring consistent performance of graphene-based dental materials.
- **Cost-Effectiveness:** The cost of graphene production remains a barrier to its widespread use in dental implants. Developing more cost-effective and scalable synthesis methods is crucial for making graphene-based implants economically viable and accessible to a broader patient population.
- **Clinical Trials:** While preclinical studies have yielded promising results, large-scale, well-designed clinical trials are indispensable to validate the safety and efficacy of graphene-based dental implants in humans (Aneksomboonpol et al., 2023; Velasco-Ortega et al., 2022). These trials should assess long-term outcomes, including osseointegration success, peri-implantitis rates, and any potential adverse effects.
- **Delamination of Graphene Coatings:** One concern with graphene coatings is the potential for delamination under mechanical stress, which could lead to particle release and inflammation (Rosa et al., 2021; Schupbach et al., 2019). Improving the adhesion and stability of graphene coatings on implant surfaces is crucial for ensuring their long-term performance and preventing complications.
- **Effects on Cell Cycle and DNA Synthesis:** Some studies suggest that graphene oxide may interfere with cell cycle progression and DNA synthesis, raising concerns about potential genotoxicity (Hashemi et al., 2020). Further research is needed to fully understand these effects and ensure the safety of graphene-based materials for dental applications.
- **Antibacterial Efficacy in Polymicrobial Biofilms:** While graphene has shown antibacterial activity against single bacterial species, its effectiveness against complex polymicrobial biofilms, which are

characteristic of peri-implantitis, needs further investigation. Developing graphene-based strategies that can effectively disrupt these complex biofilms is crucial for preventing and treating peri-implantitis.
The future of graphene in dental implantology holds immense promise. Addressing the current challenges through rigorous research can unlock its full clinical potential. Promising future directions include:

- **Developing novel graphene-based coatings with enhanced bioactivity, antibacterial properties, and improved adhesion to implant surfaces.**
- **Optimizing drug delivery systems using graphene and its derivatives for targeted therapy of peri-implantitis and bone regeneration.**
- **Creating advanced biosensors for real-time monitoring of implant health, surrounding tissue status, and early detection of complications.**
- **Exploring the synergistic use of graphene in combination with other nanomaterials, biomolecules (e.g., growth factors), or therapeutic modalities (e.g., photobiomodulation) (Dompe et al., 2020) for enhanced implant performance.**

Conclusion

Graphene and its derivatives possess transformative potential for revolutionizing dental implantology. Their unique properties offer innovative solutions to current challenges, including peri-implantitis and limitations in osseointegration. While challenges remain, ongoing research and development efforts are paving the way for the clinical translation of graphene-based dental implants. With continued advancements, graphene has the potential to significantly improve implant success rates, reduce complications, and ultimately enhance patient outcomes in restorative dentistry.

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