Review Article

Graphene in Implant: A Systematic Review

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Abstract

Background: The use of nanoparticles in dentistry has caused a new revolution in dental materials. Graphene is one of the carbon nanoallotrope that has the potential to enhance properties of materials used in dentistry due to which in the last few years, this biomaterial had evoked immense research interest. Although potential applications of graphene had been highly reviewed in other fields of medicine, especially for their antibacterial properties and tissue regenerative capacities, *in vivo* and *in vitro* studies related to Prosthodontics are very limited. **Materials and Methods:** An electronic search in PubMed was undertaken in JANUARY 2023 using the following combination of key words and MeSH terms without time periods: Graphene in Prosthodontics, graphene in implants, graphene as implant surface coating, graphene as implant biomaterial. The titles and abstracts from these results were read to identify studies within the selection criteria. **Results:** Implant surfaces functionalized with GO have shown to be biocompatible and less susceptible to biofilm formation and enhance the osteoblastic differentiation. These results encourage further *in vivo* investigation of the tested materials on infection prevention, in prevention and reduction of peri-implant mucositis and periimplantitis incidence. **Conclusion:** Graphene is a promising material for modifying the surface of dental implants due to its extraordinary features.

Keywords: Graphene in prosthodontics, Dental implants, Dental implant surface coating, Implant biomaterial, Osteogenic differentiation, Antimicrobial property.

Introduction

Prosthetic materials come into contact with water, periodontal fluid, and saliva when placed in the oral cavity. They are also susceptible to abrasion, occlusal and masticatory forces, temperature fluctuations, mechanical failures, and eventual replacement. Almost all materials come into contact with oral tissues, so they must be biocompatible and non-cytotoxic to function effectively.[1] Among various nanomaterials, graphene is a two-dimensional carbon material that is thin and strong. It was first discovered in 2004, and was later awarded the Nobel Prize in 2010.[2] This novel 2D material consists of a single atomic layer of carbon atoms in a hexagonal sp2 2D lattice (honeycomb layer of carbon atoms). Its extraordinary physical, electronic and mechanical properties derive from the 2D confinement of electrons within an atom-thick layer.[3] Graphene family nanomaterials include ultrathin graphite, few-layer graphene, graphene oxide (GO; from monolayer to few layers), reduced GO (rGO), and graphene nanosheets.[4] They differ from each other in terms of surface properties, number of layers, and size.[5] GO is one of the most important chemical derivative.

Search Strategy

A review was performed on PUBMED database to identify relevant studies regarding graphene in implants. The electronic search was performed using the following combination of key words and MeSH terms: "graphene in implants" OR graphene in Prosthodontics OR "graphene as implant coating" AND "graphene as implant biomaterial." The inclusion criteria used for this review involved clinical trials, *in vivo*, and *in vitro* studies written in English language up to January 2023. Selected studies was independently evaluated the titles and abstracts of potentially relevant previous studies. Selected studies were individually read and analyzed concerning the focus of the present review, which was to discuss and summarize important key publications regarding graphene in implants. Author names, journal, publication year, objectives, methods, and main outcomes were retrieved from the selected relevant articles.

Results and Discussion

A total of 287 articles were found and selected based on their titles after reading the abstracts, titles explaining graphene,

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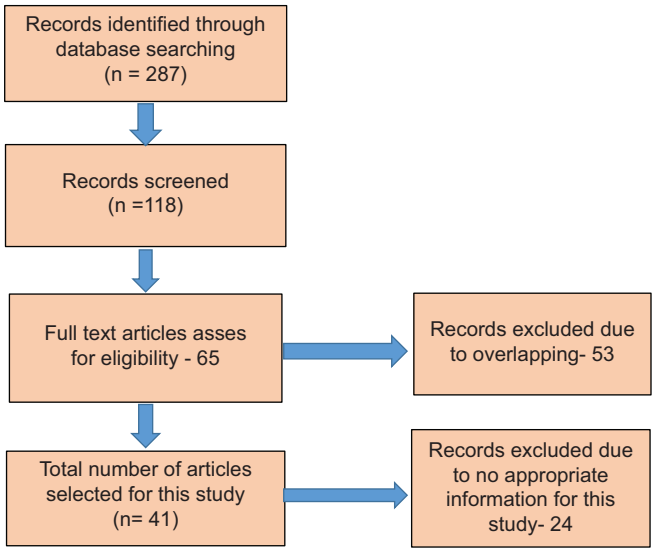
graphene as an implant material, and properties altered by graphene treatment were selected for reading the full text. Finally, articles were selected (*in vitro*, original research article, and review) and excluded because the author did not provide relevant information.



Osteoinduction Effects of Graphene (Table 1)

Graphene has been demonstrated in numerous studies to be a promising foundation for bone tissue regeneration. However, the mechanism of its osteogenic effects is still unknown. Some authors suggested that the pre-concentration of osteogenically related molecules might play a significant role in graphene's osteoinducing activities. Furthermore, increasing the mechanical strength of the connections using graphene components may better resemble the mechanical qualities of actual bone tissue, allowing scaffold integrity to be sustained during treatment. Its drug delivery and sustained release qualities allow for the distribution of osteogenic factors to the target location, resulting in faster tissue regeneration.[6]

Many researchers have found that graphene can cause mesenchymal stem cells (MSCs) to differentiate into osteoblasts. MSCs may be induced to differentiate into osteoblasts by GO and rGO. Furthermore, the ability to differentiate osteogenically may be strongly related to graphene family concentrations and species. Alkaline phosphatase (ALP) is recognized to be an early marker for osteogenic differentiation, and is critical to facilitate the differentiation of stem cells into osteoblasts on the implant site for osseointegration following implantation. The most common early marker for osteogenic differentiation is ALP expression. Wu *et al*. assessed osteogenic differentiation of rBMSCs on sample surfaces (G-PLGA), quantitative analyses were performed at 3, 7, and 14 days post-culture. After 3 days of culture, ALP expression was significantly higher on the 0.5 and 1.0 wt% G-PLGA films, and a similar trend was seen on day seven.[7] similarly Ti-GO loaded with aspirin has higher ALP activity than the other groups compared in the study.[8] No matter bicomponent or tricomponent composites scaffolds, the addition of graphene family materials to chitosan can favorably improve the mechanical properties and regulate the biological response of osteoblasts, promoting osteogenic differentiation.[9] Suo *et al*. produced a homogeneous GO/chitosan/hydroxyapatite (GO/CS/HA) coating using electrophoretic deposition on Ti. The GO/CS/HA coating's wettability and bonding strength were greater than the HA, GO/HA, and CS/HA coatings, it significantly enhanced the cell–material interactions *in vitro*

Table 1: Osteoinducing effects of graphene[7,16,34-37]

Method				Result	Reference
Solution Casting Method	Graphene nanoplates incorporated poly (lactic-co-glycolic acid	MSC'S, ALP	*In vivo*	Enhanced differentiation of rbmsc by graphene nanoplates might be modulated through activation of p13k/akt/gsk-b/b-catenin signaling circuit	Wu *et al*.
LBL technique	GO, Lys and TA into a Thin coating	hDPSCs, ALP, Run×2, OCN and ON	*In vitro*	Enhanced osteogenic differentiation of HDPSCS.	Li *et al*.
	Graphene doped Poly (methyl methacrylate)	BIC%, BAIT, BAOT, VOI	*In vivo*	GD-PMMA biocomplex used as a dental implant induces a better osseointegration when compared to the PMMA implant especially in the BAIT, BOAT and VOI.	Scarano *et al*.
	Graphene oxide wrapped porous CF/PEEK composites	ALP activity of BMSCs	*In vitro* *In vivo*	On Day 14 the ALP activity of BMSCs on GO modified materials were consistent with those on Day 7. Specifically, on Day 14, the ALP activity of BMSCs on GO-S-40CF was 4.186±0.083 nmol/min/g protein, which was more than 2 times higher than that of 0CF (1.701±0.075 nmol/min/mg protein). The animal experiments *in vivo* indicated that modified materials promoted new bone formation effectively.	Qin *et al*.
Cathodic Electrodeposition	Dual-functionalized GO (nGO-PEG-PEI	Bone-to-implant contact (BIC)	*In vivo*	The percent of bone-to-implant contact increased from PT about 36% to NT-GPP/siCkip-1 about 96%.	Zhang *et al*.
Electrophoretic technology	Graphene/hydroxyapatite coating deposit on titanium alloys	BMSCs Bone–implant contact rate	*In vitro* *In vivo*	The proliferation rates of BMSCs were significantly higher in HA-2wt%GO and HA-5wt%GO than those of the Ti, HA, and GO groups. The highest bone–implant contact rate was found in the HA-2wt%GO group, followed by HA-5wt%GO group	Baheti *et al*.

and osseointegration *in vivo*.[10] Graphene coating enhances cell adhesion and osteogenic differentiation. Gu *et al*. using chemical vapor deposition with heat treatment at 160°C for 2 h (Ti implants modified with graphene sheets). Growth and transfer of graphene sheets found that graphene coating on Ti, promoted cell adhesion and osteogenic differentiation and exhibited antimicrobial properties.[11] Similarly, another study yielded similar results, that is osteogenic differentiation of MSCs using graphene. Therefore, graphene can improve the surface properties of NiTi-based implants.[12] Ren *et al*. Functional Ti-GO was prepared using an alkaline hydrothermal reaction with loaded aspirin and his-MC3T3- on various surfaces on days 1, 3, and 7 by WST-8 assay. The results suggest that MC3T3-E1 cells grew well on these substrates without apparent toxicity.[8] Similarly H. Lee *et al*. observed that osteogenesis in MC3T3-E1 cells was spontaneously stimulated by rGO/HAp-NC without osteoinductive agents. Furthermore, incubation of cells in the presence of osteogenic agents stimulated when the cells were incubated in the presence of osteogenic agents.[13]

Jang *et al*. was performed WST-8 assay (GO deposition on zirconia surface) to assess osteoblast adhesion and proliferation, and cell differentiation was assessed using the ALP activity assay. In cell assessment, adhesion of MC3T3-1 cells in Zr and ZrGO groups was not significant, but cell proliferation and cell differentiation increased by 3.23% and 15.79%, respectively.[14] Shin *et al*. observed the rGO-coated Ti surface significantly promotes cell growth and osteogenic differentiation without any osteogenic factors and accelerates the osseointegration and dental tissue regeneration *in vivo*.[15] The sulfonated CF/PEEK composites were immersed in GO solution. The results revealed that GO functional wrinkle up-regulated surface hydrophilicity. *In vitro* cell experiments showed that porous nanostructures and GO wrinkles dramatically promoted initial cell behaviors. Significantly, GO modified composites exhibited enhanced bioactivity and osseointegration *in vivo*. Fortunately, the GO wrapped porous CF/PEEK composites displayed biosafety.[16] ZnO/GO-COOH nanocomposites synthesized by Chen *et al*. characterized by X-ray diffraction, X-ray photoelectron spectroscopy, Raman spectra, and transmission electron microscopy and concluded that ZnO/GO-COOH nanocomposites not only increased ALP and OCN production, promoted ECM mineralization and upregulated osteogenic-related genes in MG63 cells.[17] The bioactivity of PEEK has been significantly improved after G modification. Increased osteogenesis and osseointegration were observed on the G-PEEK implants with increasing G concentration, with 5% G-PEEK demonstrating the best tissue regeneration performance both *in vitro* and *in vivo* by Jiang *et al*.[18] Li *et al*. fabricated ultrathin GO/Lys coating using LBL assembly technique. ultrathin film. With lysozyme as the outmost layer, the (GO/Lys)n films possess stronger antibacterial ability and higher osteogenic efficiency, through combing the strong bacterial property of Lys and osteogenic profile of GO.[19] BMSCs on the graphene-coated titanium sheet were flattened and expressed more obvious osteogenic related genes and proteins compared to pure titanium, due to the fact that graphene coating mediated cytoskeletal deformation through the RhoA/ROCK1/ERK1/2 signaling pathway to accelerate the osteogenic differentiation of BMSCs.[20]

Di Carlo *et al*. experimental evidence shows that test + GO titanium discs have outstanding capabilities in promoting DPSCs differentiation into the osteoblastic cell lineage: the gene expression, particularly that TGFβ and BMP2 at early stage, leads to positive regulation of RUNX2 transcription factor at day three. Furthermore, the subsequent SP7 increase in test + GO following RUNX2 upregulation confirmed the osteoblastic differentiation progress only when DPSCs were cultured on test + GO surface. Moreover, the increased secretion of PGE2 also evidences a possible immunomodulatory role for GO. These results promote the GO-functionalization technique described herein for the production of novel dental implant materials, displaying an improved integration with the host tissue.[21] Kang *et al*. suggested that the rGO-Ti substrates can be exploited to craft a range of strategies for the development of novel dental and orthopedic bone implants to accelerate bone regeneration because these graphene-coated materials have potentials to enhanced cell adhesion, protein adsorption from serum, and cell-cell or cell-matrix signaling attributed to enhanced the proliferation of hMSCs and promoted osteogenic differentiation of hMSCs.[22] Li and Wang used the ultrasonic atomization spraying technique to develop a GO coating on a titanium surface treated with SLA, which endowed the SLA surface with the enhanced proliferation, adhesion and osteogenic differentiation of BMSCs *in vitro*. The SLA/GO implants showed excellent osseointegration performance *in vivo*. GO modification is a potential implant surface modification method that exerts a positive influence on the bone regeneration.[23] Graphene nanocoating has antiadhesive properties and enhances bone formation on titanium alloys. GN maintains very high structural integrity when challenged by different physicochemical stresses relevant to the oral environment. Furthermore, GN does not increase inflammatory responses by macrophages.[24]

Anti biofilm activity of graphene (Table 2)

At present implant systems are utilized extensively to replace missing teeth. Oral biofilms consisting mainly of Streptococcus spp. accumulate on implants (Nakazato *et al*. 1989). The formation of biofilm on these implants is one of the major causes of implant failure. Nanoparticle-based implant coatings may well offer useful antimicrobial and anti-biofilm functionalities to prevent dental implant failure.

Radunovic *et al*. evaluate the effect on biofilm formation when barrier membranes and titanium surfaces were coated with 2 or 10 μg/mL GO. Significantly higher values of CFU were obtained from control discs compared to discs coated with GO for all single species biofilms after both 24 h and 5 days of incubation.[25] Similarly another study indicates that GZNC may be an effective antibacterial and anti-biofilm

Table 2: Anti biofilm activity of graphene[17,38-41]

Titanium disks with sand-blasted and acid-etched surfaces were sprayed with 2 mL colloidal GNP suspensions.	Graphene nanoplatelets	*Staphylococcus aureus*	*In vitro*	GNPs have antibacterial effects and can help to prevent implant infection	Pranno *et al*.
Electrostatic powder Spraying method	Graphene oxide/ carbon fibers/ polyetherether Ketone (GO/CF/PEEK)	*S. aureus*, *E. coli* and *S. mutan*	*In vitro*	GO/CF/PEEK-TC4 exhibits excellent antibacterial ability toward S. aureus and the antibacterial ratio reaches 99.56±1.53%. antibacterial tests revealed that the GO/CF/PEEK - TC4 exhibited excellent suppression toward *S. aureus* while showing no cytotoxicity	Qin *et al*.
	Carboxylated graphene oxide (GO-COOH) sheets decorated with zinc oxide	Streptococcus	*In vitro*	The sharp edges of GO-COOH nanosheets and the surface abrasiveness of ZnO NPs resulted in physical damages to the bacterial membranes, and the relatively high local concentration of Zn2+could finally cause bacterial death.	Chen *et al*.
Electroplating and ultraviolet Method	GO-Ag-Ti multiphase nanocomposite	*S. mutans* and *P. gingivalis*	*In vitro*	The relative adhesion rate of the control group was the highest which was close to 100% (the control group was used as reference); and the four experimental groups were 10.05%, 11.00%, 5.25%, 4.55%, which corresponded to the G20, G50, 80, G100, respectively.	Jin *et al*.
Electrophoretic deposition	Graphene oxide/ silver nanoparticles (GO/AgNPs) coated nickel-titanium (NiTi) alloy	*Streptococcus mutans*	*In vitro*	Higher amounts of GO/AgNPs on the coated NiTi alloys generated an increased anti-bacterial efect. GO/AgNPs can be a promising anti-bacterial surface coating material on NiTi alloy for dental uses.	Pipattanachat *et al*.

MSC: Mesenchymal stem cells, ALP: Alkaline phosphatase activity, LBL: Layer by layer technique, GO: Graphene oxide, LYS: Lysozyme, TA: Tannic acid, hDPSC: Dental pulp stem cells, Run×2: Runt-related transcription factor 2, OCN; Osteocalcin, ON: Osteonectin, BIC%: Bone-to-implant contact percentage, BAIT: Bone area inner threads, BAOT: Bone area outer thread, VOI: Volume of interest, CF: Carbon fibers, BMSC: Bone marrow mesenchymal stem cells, PEG: Polyethylene glycol, PEI: Polyethylenimine, HA: Hydroxyapaptite, GNP: Graphene nanoplatelets, TC4: Ti-6Al-4V, ZnO: Zinc oxide, NP: Nanoparticles

agent against *Streptococcus mutans* (The minimum inhibitory concentration [MIC] of GZNC against *S. mutans* and its clinical isolates was found to be 125 μg mL^{-1} whereas the minimum bacteriocidal concentration (MBC) was found to be 250 μg mL^{-1}. The antibacterial effect of GZNC is much greater than that of ZnO nanoparticles alone where the MIC and the MBC are reported to be 500 ± 306.18 μg mL^{-1} and 500 μg mL^{-1}, respectively (Hernández-Sierra *et al*. 2008) indicating that graphene is enhancing the antibacterial property of ZnO nanoparticles).[26] 256 μg/mL of GO combined with brushing significantly removed polymicrobial biofilms when evaluated whether GO can remove polymicrobial biofilms which are established on titanium surfaces *in vitro* and treated with different methods removed only with brushing, treated with different GO concentrations (64, 128, 256, and 512 μg/mL), combined groups, and untreated titanium surface used as control.[27] Qian *et al*. study result indicated that Minocycline hydrochloride on GO-modified titanium surface (M@GO-Ti) showed a slow release behavior and exhibited excellent antibacterial activity with the synergistic effect of contact-killing and release-killing by GO and minocycline hydrochloride, respectively. In the coculture process with the presence of *S. aureus*, HGF cells on M@GO-Ti demonstrated the best of cell viability and cell surface coverage.[28] Alam *et al*. evaluated the carbon deposition on the surface of titanium (hydrophobic; superhydrophobic, hydrophilic, and bare Ti substrate) with various surface conditions. They found that carbon coating with hydrophilic feature proved to be a far better surface than other surface conditions *S. mutans* on the hydrophilic surface grows slowly rather than on the bare-Ti surface. Therefore, the GO deposition with hydrophilicity enhanced the antibacterial effect and the biocompatibility on the Ti implant.[29] When compared to the Cp-Ti, Ti-0.125G was stronger to suppress the viability of bacterial multispecies biofilms (including *S. mutans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*) and activate HGFs bioactivity.[30] Jin *et al*. suggests that proper concentration of Ti-GO-Ag composite material has a two-way function of antibacterial and high biological activity, stimulates bone formation, reduces peri-implantitis, and improves the success rate of implant surgery.[31]

Inhibiting Corrosion with Graphene Nanocoating

Malhotra *et al*. find that graphene has high impedance and R_{ct} confirmed passive behavior with high electrochemical stability in one study[32] and after 240 days of corrosion challenge, the corrosion rate and roughness increased by 2 and 12 times

for the control whereas remained unchanged for GN. The nanocoating presented remarkably high structural integrity and coverage area (>98%) at all time points in another study.[33]

Conclusion

Graphene is a promising material for various fields, including bone tissue engineering. Studies have shown that graphene has various effects on the adhesion, proliferation, and differentiation of MSCs, as well as its potential to promote osteodifferentiation and antimicrobial and corrosion resistant properties. However, much more research is needed to determine the full potential of graphene in this field.

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