coatings

Review

Can Graphene Oxide Help to Prevent Peri-Implantitis in the Case of Metallic Implants?

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Abstract: This paper is a review focused on the capability of graphene oxide (GO) coatings in preventing peri-implantitis. Firstly, the paper establishes GO's place in the frame of carbonic materials and its role as a composite material in dentistry in the prevention of bacterial infections and in sustaining osseointegration. Secondly, the most relevant articles on GO as implant coatings and their associated shortcomings are presented and emphasizing is placed on the areas where more data is needed. The main chapters are devoted to the relationship between GO and biofilm formation on the implants and the surrounding periodontal tissue and we also attempt to evaluate GO's efficacy in the case of peri-implantitis. Our findings strongly indicate that GO is a promising material for mitigating the problems mentioned, but some answers remain to be answered through rigorous research before declaring it a real success.

Keywords: graphene oxide; graphene oxide biofilm; implant biofilm formation; graphene oxide peri-implantitis

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1. Introduction

Due to its valency, carbon can be present in a great number of different allotropes with remarkable properties and thus it can be used in challenging industrial applications [1–5]. Based on traditionally known carbon allotropes structures [6–15] such as diamond, graphite and amorphous carbon, micro and nano forms have been elaborated and investigated as nanoparticles [16], fibers [17], films [18], complex heterostructures [19], coatings [20] and 3D structures [21], starting from the middle of the last century. This has also led to the elaboration of new complex materials and the identification of new correlations between structure, properties and applications [22–33] as it can be seen in Figure 1. Following the synthesis of molecular carbon in the form of C_{60} and other fullerenes [2], the preparation of a new type of structure consisting of needle-like tubes was a significant achievement in the material carbon world [3]. Although H.P. Boehm reduced graphite oxide with a thin film formation in the last century, the serious investigation of chemically modified graphene started much later, in 2004 [5]. In fact, the remarkable properties of the carbon family [22,23,26] with an accent on graphene [27], enlarged the application fields from electronics and energy to biomedicine [28]. With a positive answer to the question "Is it toxic or is it safe?" and the discovery of the antibacterial effect of carbonic materials [34,35], including graphene and its composites, graphene was accepted as a biomaterial for tissue engineering, bioimaging and drug delivery [28,36]. Moreover, coatings with graphene and graphene oxide (GO) are intensively studied as sustainable coatings in biomedical applications and especially in the dental industry [37].

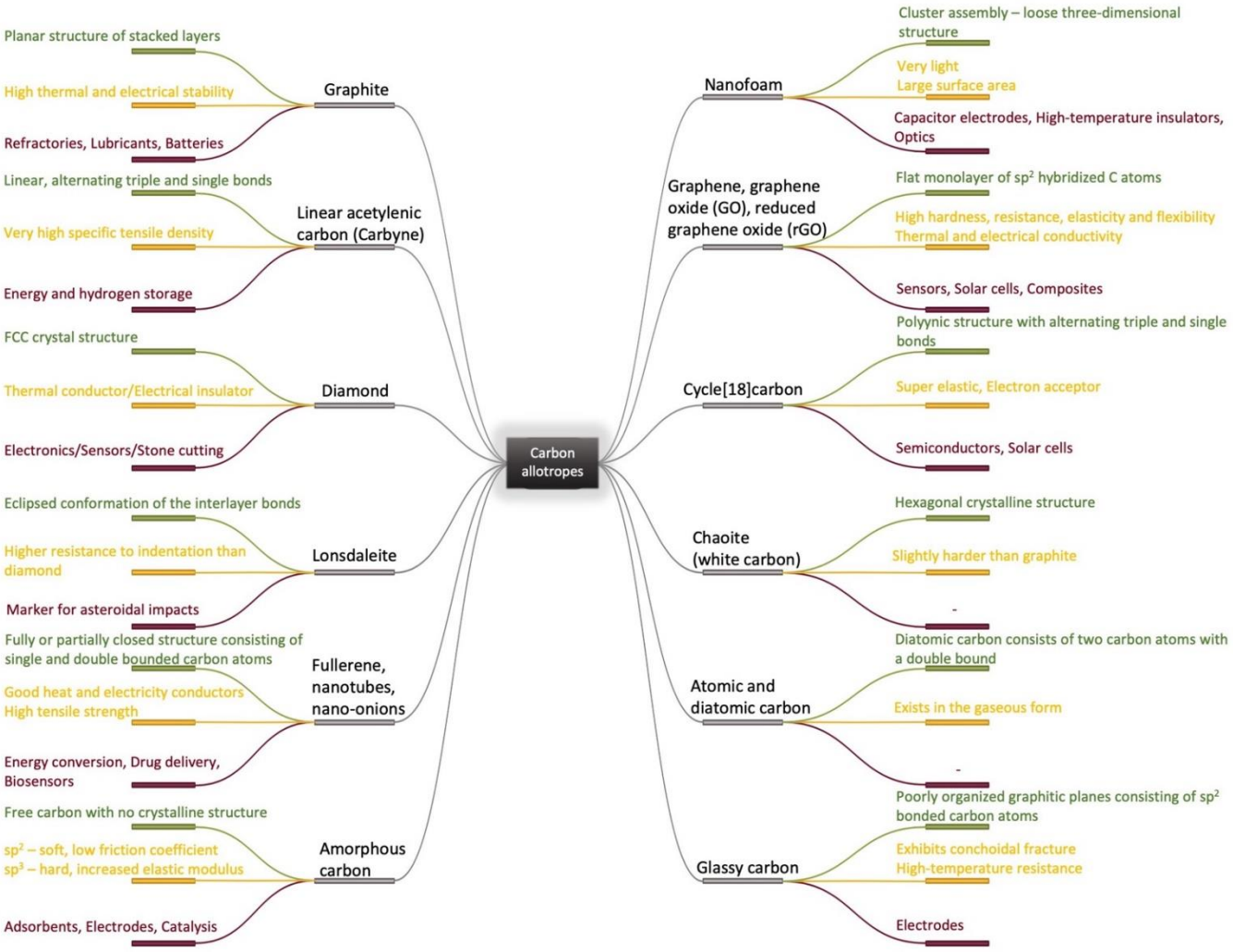

Figure 1. Carbon allotropes (—structure, —physicochemical properties, —applications) [2–9,11–15,24,25,29–33].

The dental implant industry was quantified at about USD 3.7 billion in 2015 and is estimated to almost double its value by 2023 [38]. To overcome the existing problems, multiple materials are being researched for use as implant coatings: proteins, peptides, microRNA, hydroxyapatite, calcium phosphate, antibiotics, silver nanoparticles, carbon-based nanomaterials, etc. or various combinations of these. From these, GO has already proved beneficial in multiple applications and the number of articles that study graphene and its derivatives as a reinforcing phase in composite coatings is exponentially increasing in recent years [39–46].

Dental materials used for reconstructing tooth defects can be improved with GO, dental implants can be coated using GO, it can be used in tissue engineering in order to repair bone defects and it can also be used to suppress cariogenic biofilm formation [47–52]. Additionally, GO has also been promoted as a good candidate for neural implants, not only because it provides outstanding resistance to corrosion, but also because it promotes the growth of neuronal cells and reduces ROS expression [53].

The implant failure rate is nowadays approximately 11% and considering that 100,000–300,000 dental implants are inserted yearly, an 11% implant failure rate indicates that there are between 11,000 and 33,000 patients affected per year. Moreover, even when the implant is successful, a full recovery is achieved in 3–6 months; until then, patients may experience masticatory difficulties [54,55].

There are various types of materials studied in dentistry regarding implant osseointegration [56], from which the use of GO in implant coatings seems promising for mitigating

the main problems. Firstly, one of the principal causes of implant failure is represented by the bacteria on peri-implant tissue and graphene oxide's antimicrobial activity, as well as its ability to promote osseointegration which has been proven in numerous studies. Secondly, due to its structure and physicochemical properties, GO can bind different substances which could speed up the recovery process [47,57–62].

2. Articles Selection

In order to answer our question, a thorough investigation was conducted, reviewing the specialized literature, starting from 10 years ago until the present. The chosen search phrases were used in order to search in the Scopus database, as it is the largest database of peer-reviewed literature, while the approach chosen consisted of multiple searches with specific, grouped keywords as opposed to more general terms. Both open access and subscription-based journals were considered. This helped us to find the relevant material while also functioning as a first selection. Additional studies were then selected in a second phase from the references of the articles read in the first phase and other individual searches were conducted, ensuring thus that most of the relevant studies were taken into account. The keywords used, as well as the results obtained, are shown in Table 1.

Table 1. Article selection process.

Terms Searched	Number of Initial Results	Number of Articles Selected Based on Title and Abstract	Number of Articles Selected after a Full Reading
graphene oxide metallic implants	22	12	10
graphene oxide dental implants	57	43	32
graphene oxide biofilm formation	144	70	41
graphene oxide peri-implantitis	7	7	7
peri-implantitis metallic implant	27	19	14
Total number	257	131 (after duplicate exclusion)	104
Number of additional articles selected	-	-	28
Total number of articles selected	-	-	132

3. Graphene Oxide as an Implant Coating

The industry concerning the products of graphene was estimated to reach USD 1.3 billion in 2023 [63]. Graphene, as well as GO and reduced graphene oxide (rGO), have multiple applications in the fields of science and engineering, due to its physicochemical properties such as their high surface area, biocompatibility, mechanical strength, etc. [64–66] Regarding the synthesis of GO, it is important to note that different starting materials, as well as different method parameters, could lead to a structure with different functional groups and properties. The same applies to rGO, when due to different reduction conditions the product obtained might display slightly different properties [67–70].

Additionally, due to the high surface area and multiple functional groups, such as hydroxyl, epoxy, carbonyl, carboxyl, phenol, quinone and lactone, GO forms a stable aqueous dispersion that is able to also bind polymers, biomolecules and active substances [47,71–76]. Although both forms present π-π stacking between the aromatic rings that promotes protein adsorption and implicit cell attachment and proliferation, rGO exhibits somewhat

different properties than GO. Compared with the traditional surface modifications such as grit-blasting, acid etching, micro arc oxidation, etc., both GO and rGO seem to naturally stimulate osteogenic differentiation, which is crucial for the success rate of dental implants [77].

In a study conducted by Yadav et al., the effect of two GO-coated surfaces created through two distinct methods was studied, further highlighting the influence of the preparation method. One method created a rougher surface, with a non-uniform thickness, where GO was carboxylic rich and displayed an increased inhibitory effect against *Staphylococcus aureus*, while the other method created a smoother surface, where GO presented more epoxy and hydroxyl groups and showed a more selective inhibiting effect against *Escherichia coli* [78].

When negatively charged, the carboxyl groups prevent anion adsorption, increasing the resistance to corrosion, while the aromatic ring enhances protein adsorption through a non-covalent interaction. Moreover, the hydroxyl and epoxy groups beside carboxyl groups, in combination with a large surface area, enable the possible multi-functionalization with various bioactive substances [79,80]. Such an example was provided by the coating of an Mg alloy by GO-chitosan (CS), that contained heparin and the bone morphogenetic protein 2 (BMP-2) incorporated within it and that was sustainably released over a period of14 days [79]. In another study on rats, rGO was used as a coating for CP Ti that showed an increased cell attachment and cell viability. Additionally, dexamethasone was loaded and the implant was placed on calvarial bone defects for bone tissue regeneration [81]. The dexamethasone-loaded rGO was also studied for dental applications and showed a significant increase in cell growth and differentiation. By comparing the bare substrate with the coated one, with and without dexamethasone, it became clear that rGO alone had a beneficial effect, which was further increased by the gene regulating drug [82]. The incorporation of BMP-2 in the GO coating was also studied on Ti substrates along with Substance P (SP), which was incorporated in order to help recruit stem cells. The study evaluated the bone formation, in vivo, and showed that the GO coated implants with BMP-2 and SP induced extensive bone formation [83].

The hydrophobic/hydrophilic character, in combination with the surface roughness, dictates the interaction with the proteins and subsequently with the cells, the goal being to promote cell growth, differentiation and anchorage for the implant. An interesting material that lacks these surface properties, but has a closer elastic modulus to the natural bone, is the polyether ether ketone (PEEK) [84]. Taking advantage of the GO structure, a functional modification was proposed on sulfonated PEEK, reinforced with carbon fibers, that showed promising results in vitro and in vivo regarding cell adhesion and proliferation, as well as promoting new bone formation [85].

Moreover, the rough surface that favors cell attachment, the π-π stacking, as well as the hydrogen bonds, allow the GO to absorb osteoinductive factors by non-covalent binding, thus accelerating the osteogenic differentiation of stem cells [86].

One of the substances with great biocompatibility that could be used in dental implant coatings is hydroxyapatite. However, hydroxyapatite alone is not suitable because of its low stability on long-term contact with tissue/biological fluids, even though it has great biocompatibility. Moreover, the acidic environment created through the fermentation of sugars that accumulate on teeth further accelerates the corrosion of hydroxyapatite. To deal with this issue, GO was researched as a reinforcement material and this showed the homogeneous dispersion and fluoride ions were also introduced by partially substituting the hydroxyl ions from hydroxyapatite. The resulting composite presents an increased biocompatibility, an increase in corrosion resistance and promotion of cell proliferation and differentiation [87].

A cathodic electrophoretic procedure was first mentioned for the fabrication of a GO/hydroxyapatite coating on a pure Ti substrate, in the employment of the GO at nanoscale in a bioactive coating [88]. Later, the GO was also used in combination with hydroxyapatite as a coating for 316L stainless steel. The functional groups of GO bind

the calcium ions from the hydroxyapatite, thereby improving the strength of the material and also acting as anchors for the metallic surface and increasing the adhesion of the coating [89]. To further improve the biocompatibility and other parameters, polymers can also be used in combination with the hydroxyapatite and the GO. It was shown on a Ti alloy that the hydroxyapatite, doped with Mg and Zn and topped with polycaprolactone-GO, can establish direct bonds with the bone tissue, while also having bactericidal properties [90]. Many other combinations of GO with bioactive materials have been recently investigated, introducing more applications using new technologies [91,92].

Furthermore, it was proved in a series of studies that graphene-based coatings can improve the corrosion resistance of different substrates, and this was further challenged by Malhotra R et al., who performed corrosion tests over a period of 240 days, with the use of a very acidic solution. The coated alloy, Ti-6Al-4V, showed negligible signs of corrosion after 240 days, thereby maintaining its structural integrity, while the uncoated alloy presented a high corrosion rate, resulting in a 12-fold increase in surface roughness [93]. Another study on the same alloy that used a bioglass/graphene oxide coating, showed improved antibacterial activity that increased along with the content of the GO [94].

Of course, other factors contributed to the outcome, such as the geometry of the implant. Different alterations regarding the helix angle, the thread pitch and the dimensions also produced different results, due to stress distribution [95].

4. Aspects of the Interface Processes between Graphene Oxide Containing Materials and Tissues

The materials used for tissue engineering should mimic the host tissue as much as possible, in terms of their physicochemical properties. Ideally, the structure should have interconnected pores in order to facilitate cell attachment and migration, as well as the diffusion of molecules through it. GO can improve the biocompatibility of different materials by providing binding sites for cells, triggering cell differentiation and improving the mechanical properties [96].

The interface processes between a material and tissue depend on many factors such as material composition, dimensions, surface chemistry and physical aspects, as presented in Figure 2. Of course, various nanostructures such as nanoparticles, nanotubes and nanochannels [97,98] of biomaterials which were already tested regarding the influence on biocompatibility are proof for nanotechnology in guiding tissue regeneration [56], but more specific research is needed in order to complete the fundamental aspects of the tissue material interface [99].

It has been shown that the interaction between the GO and stem cells can be tailored to guide the differentiation into specialized lineages. GO can act as a preconcentration platform for growth factors and other molecules that bind easily through π-π non-covalent binding [100]. Alternatively, through a covalent interaction, GO can form stable hybrid structures with multiple molecules [101–103]. Chitosan is one such molecule, which binds through its amino groups to the carboxylate groups from GO. This hybrid structure was successfully used as a scaffold for neuronal networks, owning to GO's capability to act as a barrier through the oxygen-containing functionalities that can bind enzymes and thus prevent chitosan degradation [102]. Scaffolds based on protein-GO bio-complexes display great biocompatibility, while also having good mechanical properties. They are currently being investigated for bone tissue, cardiac and nerve tissue, favoring cell attachment and differentiation [103].

Besides the advantages derived from the binding capability of GO, the existence of wrinkles and ripples in the structure increases the surface roughness which facilitates the adsorption of growth factors and proteins and subsequently influences cell attachment and differentiation [104].

Figure 2. Factors that dictate the outcome of biomaterial–tissue interaction.

In order to investigate the interaction between GO and tissue, as well as the influence of thickness [105] and lateral dimension [106], intravenous GO was administered to rodents. Regarding its thickness, it was observed that thicker GO sheets remained in the body for a prolonged period, mainly in the spleen and liver, while GO with a large lateral dimension was observed to accumulate in the lungs and excreted at slower rates.

Moreover, in a comprehensive review on the interaction of graphene-based materials in cancerous cells and non-cancerous cells, it was shown how the GO obtained through different synthesis routes, as well as how the GO-containing materials affect the expression of microRNAs, protein coding genes, sub-cellular structures and organelles in both types of cells [107].

5. The Relationship between Graphene Oxide and Bacterial Film Formation on the Implant and Surrounding Periodontal Tissues

The biofilm is a three-dimensional structure, formed by bacterial communities embedded in self-produced extracellular polymeric substances (EPS), that protects the cells from harmful substances, such as antibiotics [108]. The process of biofilm formation can be described in four stages, as shown in Figure 3 [109].

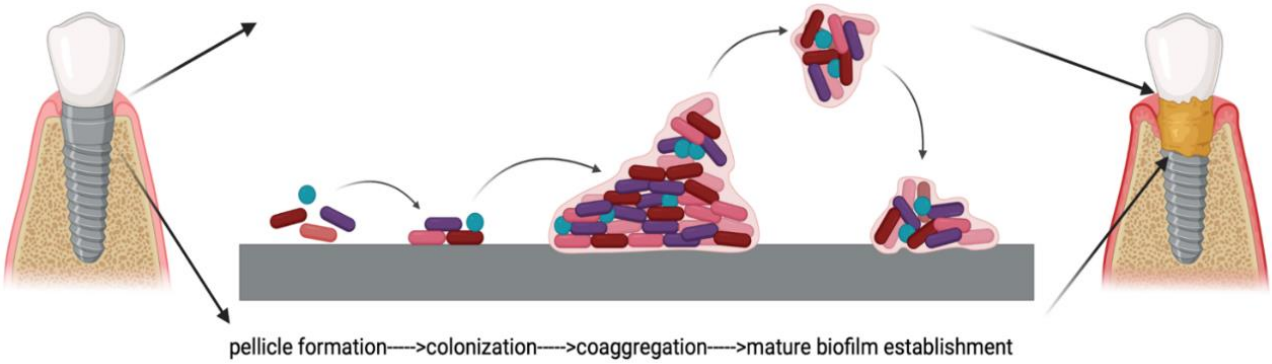

Figure 3. Biofilm formation process. Adapted from "Polymicrobial Biofilm 2", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates (accessed on 25 June 2022).

In the human mouth, there are up to 700 different types of pathogens present that are colonizing different sites, according to the specific environment of the site (temperature, oxygen availability, pH, etc.). The peri-implant biofilm seems to be mostly formed by anaerobic bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia* and *Treponema denticola* [110] and in a study conducted on the effect of GO against dental pathogens, it was shown that GO efficiently decreased the proliferation of *F. nucleatum* and *P. gingivalis*, thereby making it a great candidate for implant coatings [111].

In multiple studies that researched GO alone as a coating or GO incorporated/deposited as a second step, it was shown that GO can improve biocompatibility while displaying antibacterial activity [54,112–115]. In order to evaluate the efficiency of GO against microbial biofilms, an in vitro study was conducted using contaminated titanium implants. The methods used for comparison were brushing, treatment with different concentrations of GO and a combination of these. Compared with the control, neither brushing nor GO treatment alone were successful in removing the biofilm, but brushing followed by the GO treatment removed the biofilm and inhibited its reformation. An increased osteogenic differentiation was also observed when using this combination [116]. Using a commercial orthodontic composite, it was also shown that GO could enhance its biocompatibility. Compared with the control group, the GO coated composite could significantly decrease the metabolic activity of *Streptococcus mutans*, which is one of the primary cariogenic agents [117]. Another composite coating on a Ti substrate and composed of GO-CS-HA showed a decreased attachment of *S. aureus*, in addition to providing good corrosion protection and displaying no cell toxicity [118]. The same coating also showed promising results in vivo, by manifesting improved osseointegration [119].

The GO was also deposed after nitriding and anodic oxidation on the CP TI by using an atmospheric plasma-based method, an alternative to the conventional methods. It was observed that the GO created a rougher and sharper surface with increased bacterial inhibition properties, thereby supporting the hypothesis that states that the sharp edges of the GO destroy the bacterial membrane [120]. Possibly through the same mechanism, it was shown that the GO coated Zr reduced the adhesion of *S. mutans* by 59%, while it increased the cell proliferation by 3% and increased the cell differentiation by 16% [121].

The need for alternative antibacterial substances is continuously increasing in the context of multidrug-resistant bacteria and the main focus nowadays is on nanocomposite materials [122–127]. Such a material, Ag_2O/GO, was studied by Khan et al., showing antibacterial and antibiofilm properties against *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *S. aureus* [128]. Another composite, GO/Zn(Cu)O, showed good results when tested against *S. aureus*, *Enterococcus faecium*, *E. coli*, *Salmonella typhi*, *Shigella flexneri* and *P. aeruginosa* [129] and a study that combined both Ag and Cu, along with GO, highlighted the antibacterial properties against *Methylobacterium* spp., *Sphingomonas* spp., and *P. aeruginosa* at a concentration that was non-toxic to human cells [123]. Besides Cu and Ag, Zn can also be used in nanocomposite coatings. Graphene/zinc oxide nanocomposites showed

an anti-biofilm behavior against *S. mutans* [130]. A more complex coating used methacryloyl and phenylboronic acid, along with GO, as a Zn ions reservoir, thereby observing a sustained release throughout a 3 week testing period. The coating showed improved antibacterial activity against *P. aeruginosa* and *S. aureus* [131].

The antibacterial mechanism was also investigated in a study conducted on Ti-GO-Ag. Having both Ag and GO, the antibacterial performance was seen at exceptionally low concentrations, 14 μg/mL for *S. aureus* and 4 μg/mL for *E. coli*. Interestingly, the mechanism observed was different in the case of *S. aureus*, where it inhibited the bacterial division, while in the case of *E. coli*, it destroyed the integrity of the bacterial membrane [132]. The bacterial membrane has an outside negative charge, and it is believed that the nanoparticles with negatively charged surfaces display lower antibacterial features than positively charged particles of comparable size. This hypothesis was confirmed in an investigation, where hydrogenated nanodiamonds were positively charged and these displayed more bactericidal activity than negatively oxygenated charged nanodiamonds [133]. An alternative research conducted on GO/AgNPs/Collagen showed that the combination of GO with Ag would also be suitable to use with visible light irradiation in order to achieve rapid disinfection [134]. Another protein, lactoferrin, with antibacterial properties was used in combination with AgNPs to coat Ti. The results showed an impressive 98% reduction of *S. aureus* colonization, while also promoting preosteoblastic adhesion, proliferation and differentiation [135].

GO was also paired with curcumin and polyethylene glycol and tested against *Candida albicans*, a fungus that is responsible for many hospital acquired infections [136,137]. While GO alone showed poor efficacy in preventing *C. albicans* adhesion, it stabilized the curcumin, which has poor solubility in aqueous solvents, but is a potent fungicide [137]. However, another study that researched the effect of GO against *S. aureus*, *P. aeruginosa* and *C. albicans,* showed that the effect on *C. albicans* was tardive, after 24 h of incubation [138]. Curcumin was also paired with graphene quantum dots and researched as a photosensitizing agent for antimicrobial photodynamic therapy, which can be used as a treatment for peri-implantitis. The results indicated a high efficacy in inhibiting biofilm formation [139].

Considering the concerning increase of antibiotic resistant bacteria after prolonged exposure, it is advisable to research what may happen after a new promising agent with antimicrobial properties is frequently used. Q. Zhang and C. Zhang have repeatedly exposed 200 subcultures of *E. coli* over 400 days to 5 mg/L GO. It was observed that the continuous exposure to GO transformed *E. coli* by activating the envelope stress response and increasing the membrane permeability and fluidity. The resulting *E. coli* cells manifested a higher pathogenicity and survived better in an acidic and oxidative environment [140].

One special attention must be taken regarding the potential adverse effects of graphene and its derivates upon entering the bloodstream. It was previously reported that they can trigger mitochondria apoptosis, platelet aggregation and pulmonary thromboembolism [141]. When testing graphene oxide containing coatings, it was shown that the effect on cells was generally non-toxic. However, if detached from the substrate it could show some toxicity. Therefore, an important aspect is to ensure the coating's stability [142]. It is clear that the concentration of the GO used in these coatings needs to be carefully selected, after rigorous research, not only to avoid possible adverse effects but also to avoid a possible enhancing effect in the case of very low concentrations, a phenomenon that could be explained by the fact that the partially dead cells can serve both as a barrier and as nutrients for the living cells [143].

Concluding, there are several mechanisms proposed in order to explain the antimicrobial activity of GO such as as a physical impediment for bacteria growth by wrapping nanosheets around them; the breaking of the bacterial cell membrane due to the sharp edges of the graphene sheets; and the overproduction of reactive oxygen species (ROS) that break down the cell membrane [66]. These mechanisms are illustrated in Figure 4, created using BioRender.com. Due to the nonspecific mechanism, other cells could also be affected, but it has been found that below 20 μg/mL, the GO has no significant biotoxicity [38]. It

was also observed that pairing GO with hydrophobic macromolecules such as chitosan, polyethylene glycol or proteins, can significantly decrease the associated cytotoxicity [144]. In addition to concentration and functionalization, the lateral size can influence the cellular uptake and the distribution to organs, with the nanometric size GO bearing more risks than the micrometric GO [145].

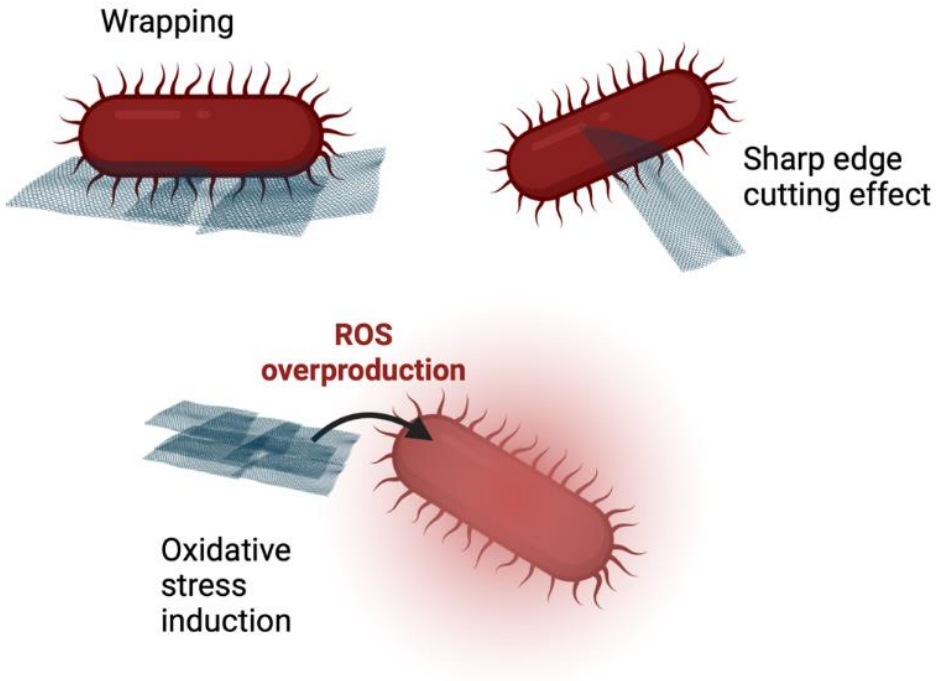

Figure 4. Graphene oxide antimicrobial mechanisms. Retrieved from https://biorender.com (accessed on 25 June 2022).

6. Peri-Implantitis as Related to Metallic Implant Biomaterials

The pathological conditions that characterize peri-implant diseases are mucositis and peri-implantitis, which consist of a reversible inflammatory condition without bone loss and an irreversible inflammatory condition, respectively, with marginal bone loss. Both pathological conditions are considered as plaque-associated pathologies that can ultimately lead to progressive bone loss [146,147].

Similarly to periodontitis, which represents a chronic inflammatory bacterial condition that affects the tooth's soft and hard supporting tissues (cementum, periodontal ligament, alveolar bone and gingiva), and that leads to their gradual destruction [148], peri-implantitis represents a chronic inflammatory process associated with a microbial challenge and an immune-mediated biological complication, that leads to the gradual destruction of the implant's soft (gingival tissue) and hard (alveolar bone) supporting apparatus, thereby leading to implant instability and its eventual failure [149–151].

In addition to the biofilm, the exogenous elements released by the metallic implants in the peri-implant milieu, might also contribute to the chronic inflammatory response [152,153]. It was suspected that metallic ions could be generated before the corrosion of the metallic implant, starting from the surgical insertion, due to abrasion of the implant. An investigation on simulated bone materials, consisting of polyurethane foam with different densities found that no particles were released during insertion [154], while another investigation that used bovine bone blocks detected Ti after insertion [155]. Regardless, metallic debris can be released over time into the surrounding tissue and it appears that these particles are contributing to the inflammatory response [156–158].

Osseointegration is a crucial factor in reducing the risk of implant failure. Although many implants have promising mechanical properties and are corrosive resistant, they do not bind to the bone nor are they inefficient in stimulating bone formation, therefore their

surface needs to be modified in order to induce these properties [20]. Besides osseointegration, another important aspect in preventing implant failure is the soft tissue sealing capacity. The tissue should function as a barrier, preventing the access of bacteria to the alveolar bone. In a study conducted on human gingival fibroblasts, it was shown that the number of defects from the structure, along with the sp_2 domains, influenced the cells adhesion and proliferation [159].

The risk of peri-implant mucositis is about 80%, while that of peri-implantitis is about 28%–56%, depending on several factors. Graphene, graphene oxide and reduced graphene oxide are studied in order to increase the success rate of dental implants [59].

Some options are available in case of peri-implant infections in order to avoid implant removals, such as the mechanical removal of the formed biofilm, antibiotic therapy or regenerative surgery. However, prevention remains the best "treatment". Following an in vitro study on GO loaded with minocycline hydrochloride (MH), that showed strong antibacterial properties against several bacterial strains [160], the authors conducted an in vivo study on beagle dogs. The study showed very promising results for the group that received the implant coated with MH/GO when compared to the group that received the uncoated implant [146].

The physicochemical characteristics of the surface, especially the roughness and hydrophilicity, also influence directly the cell interaction, but molding these is insufficient in preventing peri-implantitis [161].

Zirconia implants are increasingly used, due to their good biocompatibility and mechanical properties. However, the antibacterial efficacy needs to be improved in order to prevent peri-implantitis. Therefore, GO plasma coated zirconia implants were studied regarding osteoblastic activity. The results showed an increase in cell proliferation and differentiation by 3% and 16%, respectively [121].

The rGO was successfully used in the design of a polylactic acid (PLA) based scaffold for bone engineering. Paired with polydopamine, it manifested the multifunctionality desired. In addition to the osteoinductive potential, it prevented any biofilm formation, while also having antioxidant properties [162]. Another type of scaffold researched was based on poly(e-caprolactone) loaded with GO. The research showed a directly proportional relationship between the concentration of GO and the antimicrobial proprieties against both gram-positive and gram-negative bacteria, without altering the adhesion and proliferation of human fibroblasts [163]. In another study, GO, rGO and amine functionalized GO (aGO) were studied comparatively as part of a composite surface formed with poly(e-caprolactone). The comprehensive research investigated the influence on stem cell response, biofilm formation and mechanical properties. It was found that aGO was the most effective, both in promoting human mesenchymal stem cell (hMSC) proliferation and osteogenesis and in inhibiting biofilm formation, followed by GO, while rGO displayed no significant differences regarding cell proliferation and osteogenesis and it had the lowest biofilm formation activity [164].

Starting from the already promising titania nanotubes, which have an increased biocompatibility and have been proven versatile in numerous studies [165–167], Rahnamaee et al. investigated the properties of such materials after introducing chitosan nanofibers and rGO. The multi layered surface displayed some antibiofilm formation properties, as well as enhanced bone cell viability. Moreover, the structure formed could be further incorporated with active substances, acting also as a reservoir for prolonged release [168].

The human mesenchymal stem cells show enormous potential for bone tissue regeneration. The challenging part is triggering their differentiation into osteoblasts. The studies conducted on graphene and its derivatives show promising results in this direction [169]. One such study performed on rGO-hydroxyapatite found that this composite has a potent osteoinductive effect [170]. Another in vitro study conducted on the influence of titanium coated with GO on the dental pulp stem cells showed an increased proliferation in the early stages and successful differentiation into osteoblasts [171].

In a comparative study, GO and rGO were used in order to incorporate dexamethasone on a titanium substrate. Both coatings were able to adsorb dexamethasone and assure a sustained release of it. However, the proliferation rate was considerably higher in the case of GO compared to rGO, possibly due to the multiple sites available on GO for protein binding [141].

The relation between the concentration of GO and the cellular behavior of marrow-derived mesenchymal stem cells shows that at a concentration of 0.1 μg/mL, it facilitated the cell proliferation for up to seven days and that it might promote osteogenic differentiation. However, improved alkaline phosphatase activity and mineralization were not observed [172].

7. Conclusions and Future Perspectives

The use of GO in implant coatings seems promising for solving some main problems. Firstly, one of the principal causes of implant failure is represented by the bacteria on peri-implant tissue and the graphene oxide's antimicrobial activity. Additionally, GO's ability to promote osseointegration has been proven in numerous studies. Secondly, due to the high surface area and multiple functional groups such as hydroxyl, epoxy, carbonyl, carboxyl, phenol, quinone and lactone, GO forms a stable aqueous dispersion as it is able to also bind polymers, biomolecules and active substances that could further help to promote osseointegration and speed up the recovery process. It is important to note here that when synthesizing GO, different starting materials, as well as different method parameters, could lead to different functional groups and structures, therefore this aspect should always be factored in when analyzing the properties of GO based coatings.

Moreover, as the need for alternative antibacterial substances is continuously increasing in the context of multidrug-resistant bacteria, the main focus nowadays is on nanocomposite materials. One special attention must be taken regarding the potential adverse effects of graphene and its derivates upon entering the bloodstream, while another important aspect to be researched, considering the concerning increase of antibiotic resistant bacteria after abusive use, is the influence on the bacterial pathogenicity after prolonged exposure.

Based on the existing literature, we can conclude that GO coatings are very promising in keeping a good balance between the ability of a coated dental implant in order to inhibit the biofilm formation and the ability to stimulate a favorable cell response. It is especially difficult nowadays, in a time with aggressive dynamic changes regarding the development of bacteria and viruses, to foresee the trends for longer periods. In this context, we must be extra cautious and pursue more complex in vitro studies on bacterial pathogenicity and multiple cell lines, as well as in vivo studies, both on animal and human models.

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