

Carbon nanotubes for dental implants

5

Swe Jyan Teh^{*,†}, Chin Wei Lai^{*,†}

^{*}Nanotechnology and Catalysis Research Centre (NANOCAT), Institute of Graduate Studies Building, University of Malaya, Kuala Lumpur, Malaysia, [†]Centre for Innovation in Medical Engineering (CIME), Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur, Malaysia

5.1 Introduction

Dental implants are defined as an artificial prosthesis inserted into the gumline of a patient as a replacement for damaged or infected teeth. Successful tooth replacement can improve and restore the quality of life of the patient through improved bite and a better eating experience, and can serve the patient for a long time. Metallic and ceramic materials, for example, titanium, glassy carbon, and zirconia have been commonly used in commercial dental implants; but each material has its limitations related to osseointegration and differences in mechanical properties between natural bone and the implant, thus limiting its long-term survival and stability. The cost of replacing a tooth using dental implant technology is also very high, limiting the access of this treatment option to the public. In recent years, the development of new implant materials has been an active area of research, with opportunity to discover new materials that are able to better adapt to the oral environment. Since achieving fame in 1991, carbon nanotubes (CNTs) have been considered a unique material with remarkable properties, due to the simple structure of sp^2 -hybridized carbon atoms [1]. Hence, nanocomposite materials incorporating CNTs into the composite matrix are believed to produce a new generation of durable and affordable dental implant materials.

This chapter reviews the advances of CNT-based nanocomposite materials for dental implants. Beginning with a brief overview of CNT properties and how these properties may be of use in the oral environment/dental implant applications, the subsequent section evaluates the effect of incorporating CNTs toward the properties of existing dental implant material. The chapter continues with a general view of the limitations and challenges faced in the application of CNTs in nanocomposite materials for dental implants. Finally, the chapter concludes with an outlook on research opportunities.

5.2 Properties of CNTs

5.2.1 Mechanical properties of CNTs

Dental implants are subjected to high stress and forces within the oral environment, and the implant must be able to withstand high stress and forces applied as a result of

eating or oral disorders. For example, the force generated during routine mastication (chewing) of food such as carrots or meat is about 70–150 N. Bruxism is also a common condition that causes high stress to the teeth. The maximum masticatory force may reach up to 500–700 N [2]. The management of the biomechanical load imposed on dental implants needs to take into account the compression, tension, and shear forces applied on the implant, and the functional surface area involved in dissipating the biomechanical load [3].

CNTs are composed of graphene sheets rolled-up into a tube-like structure. CNTs may be formed using either one (single-walled) or a few sheets of graphene (multi-walled) [4]. The carbon atoms in CNTs are sp^2 hybridized and arranged in a hexagonal lattice. Due to their unique structure, CNTs exhibit properties such as high mechanical strength, low water resistance, and high adsorption properties. CNTs are durable materials—the C–C bond as well as sp^2 hybridization results in their notable mechanical strength. Using atomic force microscopy to perform tensile loading experiments, Yu and coworkers reported a mean Young's modulus of 1 TPa [5]. The observed Young's modulus of CNTs was in agreement with its predicted value of 0.969 TPa for CNTs with 14 nm diameter [6], and also demonstrated that CNTs possess similar tensile strength to that of diamonds (1.063 TPa). CNTs demonstrate high shear modulus as carbon-carbon bonds have a higher spring constant (k) compared with metals and ionic solids. Hence, the application of CNTs into new dental implant materials, for example, as a coating, or into the bulk material, incorporate the outstanding mechanical properties of CNTs to enhance the shear, compression, and tensile strain resistance of dental implants.

The incorporation of an optimum loading of CNTs into the composite matrix is often done with the goal of maximizing the efficiency of stress transfer at the CNT-matrix interface. Effective reinforcement of a bulk material using CNT is dependent on the aspect ratio, dispersion, alignment, and interfacial stress transfer at the CNT-matrix interface. The high surface area of CNT structures causes CNTs to form an intimate interaction with the composite matrix. It follows that the lack of a well-dispersed CNT across the matrix network limits the toughening action. Well-dispersed, randomly aligned CNTs are the preferred material structure, as aligned composites have very anisotropic mechanical properties, in contrast to randomly oriented CNTs [7]. CNTs possess high fracture toughness due to their ability to transfer loads efficiently across an interconnected network, and this property is able to prevent or delay the initiation and propagation of cracks in the CNT composite.

5.2.2 Biocompatibility properties of CNTs

In a typical implant procedure, the damaged tooth is removed and the gumline is disinfected before inserting the dental implant. After allowing the implant to heal and adapt to the new oral environment, the tooth replacement procedure is completed by attaching a prosthetic tooth to the top of the implant. The healing process, also known as osseointegration, involves the growth of osteoblasts (bone cells) on the implant's surface, resulting in the integration of the dental implant into the natural bone. When an implant biomaterial is inserted into the living body, proteins first adsorb on the

implant surface, and subsequently act as mediators between bone cells and the implant surface, for processes such as platelet adhesion and hemostasis, the activation of the complement system, inflammation, and differentiation of osteogenic cells [8–11]. These reactions take place on the surface of the dental implant, leading to cell adhesion for successful osseointegration [12, 13].

In some cases, the patient's body may identify the implant as a foreign object that does not belong, and thereby reject the implant [14]. Failed osseointegration may be caused by one of four possible situations: (1) bone loss, (2) failures due to improper positioning, (3) defects in soft tissue formation, and (4) failures caused by a defective implant [15]. Bacterial infections such as peri-implantitis also cause damage to the bone and gum regions surrounding the implant. The removal of failed implants incur additional cost and safety issues for the patient [16], hence motivating the research and development of improved implants and implant procedures. The properties of CNTs to support osseointegration and prevent bacterial infection have been explored and summarized in the following sections.

5.2.2.1 Bone growth activity

CNTs have been explored as a bone-substitute material both as pure and composite material, by investigating osteoblast growth and bone formation on the CNT surface. A study reported neutrally charged CNTs as a suitable surface for bone growth, as the results from the study showed the highest cell growth and production of plate-shaped crystals on CNTs with neutral surface charge [17]. Dramatic changes were also reported on the morphology of osteoblasts grown on neutral-charged single-walled CNTs versus multi-walled CNTs, which correlated with changes in plasma membrane functions. CNTs have been applied as a reinforcement component in hydroxyapatite composites with compressive strength up to 29.57 MPa [18, 19]. The increased toughness in CNT nanocomposites has been attributed to increased resistance to the growth of cracks, as CNTs are able to decrease the stress intensity at the microcrack region, thus preventing further crack growth [20].

The modulation of CNTs with appropriate functional groups has been found to dramatically change their physical, chemical, and biological properties with respect to bone growth. Examples of chemical functional groups that support or enhance the growth of osteoblasts on the surface of CNTs are amino [21], phosphate [22], and carboxylic groups [23]. CNTs functionalized with sodium hyaluronate also demonstrated enhanced bone mineralization [24]. Sodium hyaluronate is a glycosaminoglycan [25] that binds to cell surface receptors, such as CD44 [26] and the receptor for hyaluronic acid-mediated motility [27, 28]. This binding event stimulates the osteogenic cell response (migration, proliferation, and differentiation) [27, 29]. The presence of CNTs functionalized with sodium hyaluronate was proposed to enhance the mRNA expression of types I and III collagen, osteocalcin, and bone morphogenetic proteins 2 and 4, which enhanced the bone mineralization process.

In another study, the authors studied the adsorption of albumin on the surface of COOH-functionalized multi-walled CNTs-coated titanium implants as an initial indicator of cell adhesion on the implant surface. Using UV-Vis and Raman spectroscopy

to assess the changes of multi-walled CNTs conformation during interaction with albumin, the results from this study suggested that peptide bonds are formed between albumin and the COOH-functionalized multi-walled CNTs-coating, resulting in the formation of an albumin nano-layer coating the implant [30].

The interactions between CNT and the surrounding biomolecules may be modulated by tailoring the surface functional groups, which in turn determines the material's surface-charge density and net polarity. For example, a surface with net positive or negative charge may be more hydrophilic, in contrast to an electrically neutral surface [31]. Pristine CNTs are hydrophobic due to their aromatic, nonpolar nature. As such, CNTs interact with organic and charged molecules primarily via π - π and electrostatic interactions, respectively. In general, there are four types of locations where biomolecules may adsorb on the CNT [32]: on the surface of the CNT (external surface), at the grooves between two nanotubes at the periphery of a CNT bundle (external grooves), at the channels between nanotubes in a bundle of CNTs (interstitial channels), and within the hollow channel of the nanotubes (internal surface). The narrow diameter of the CNTs restricts the adsorption of organic molecules larger than the CNT diameter on the internal surface of the CNTs. Therefore, organic molecules predominantly adsorb at the interstitial pore spaces between the tube bundles, or at the external surface of the outermost CNTs. The modification of the CNT surface charge can induce electrical attraction or repulsion between the implant's surface and the chemical species of interest based on their polarity. As such, surface-charge modification of CNTs offers a promising new direction for improving osseointegration at the natural bone-implant interface.

The application of CNTs as a coating, or in a coating matrix (such as hydroxyapatite), has also enhanced the adhesion of osteoblasts on the implant surface due to an increase in surface roughness. The implant's surface texture is an important parameter influencing successful osseointegration, and implants with a rough, instead of a smooth, surface integrated better with the bone [33, 34]. Alongside a variety of fabrication methods to increase the surface roughness of the implant, for example, laser treatment, sandblasting, acid etching, polishing, and anodic oxidation [35], coating the implant with hydroxyapatite or via titanium plasma spraying are also able to add surface texture. The incorporation of CNTs into the coating matrix acts as a reinforcement material and increases the coating's toughness.

5.2.2.2 *Antifouling and bactericidal activity*

Bacterial infection at the gum and bone region surrounding the dental implant may pose serious risk to the implant's structural integrity, and necessary preventive precautions need to be taken in order to prevent medical complications. Peri-implantitis is a commonly occurring disease and is caused by bacterial infection leading to the gradual loss of the jaw bone supporting the implant [36]. The bacterial infection triggers an inflammatory response from the soft tissue surrounding the dental implant, and if left untreated, may eventually develop into the degeneration of connective tissue, and destruction of the mucosal seal surrounding the implant. At this point, the subgingival implant surface becomes exposed, and opportunistic pathogenic bacteria may proliferate here. Bone loss is the eventual outcome as a result of triggering an inflammatory response from the surrounding alveolar bone [37]. Strategies to minimize or prevent

bacterial infection include the development of antifouling surfaces, or developing materials with bactericidal properties.

The interaction between CNTs and pathogenic bacteria has been investigated and classified into two modes of operation: as an antifouling agent, or as a bactericidal agent. Pristine CNTs are inherently cytotoxic in nature [34], and prohibit the growth of pathogens on their surface, which serves as a useful antifouling layer on dental implants.

CNTs also exhibit bactericidal activity, whereby microorganisms exposed to CNT concentrations above the cytotoxic dosage induce cell cycle arrest [38]. In an experiment whereby human fibroblast cells were exposed to CNTs, a strong immune and inflammatory response was induced from the skin fibroblasts due to the activation of genes involved in cellular transport, metabolism, cell cycle regulation, and stress response [38]. In another experiment, it was observed that incubating bacteria in suspensions of single-walled CNTs and multi-walled CNTs caused the physiology of the bacteria to be heavily compromised, whereby a cytotoxic dosage of 200 $\mu\text{g/mL}$ of SWCNTs was able to inactivate concentrated solutions of *Salmonella* (10^7 CFU/mL) within 15 min [39], with no significant difference in antimicrobial activity between gram-positive and gram-negative microorganisms. The penetration of the sharp and narrow structure of CNTs onto the surface of pathogenic cells may have caused the compromise in cell wall integrity, causing death via cell lysis. The cytotoxic effect was also found to be dependent on the type of buffer solution [38].

CNTs may also serve as drug delivery carriers, supplying antibiotics whenever the gum barrier is breached, or releasing drugs to facilitate the healing process. Local delivery of antibiotics at the implant site offers several advantages: (1) the drugs can be delivered with high efficacy at the local site, and (2) localized drug delivery ensures that antibiotics are targeting specific peri-implantitis pathogens, and it prevents the development of antibiotic resistance. A group of researchers proposed a CNT-coated titanium alloy surface that was able to successfully de-colonize a *Staphylococcus epidermidis* biofilm through long-term release of antibiotics stored in the CNTs [40]. However, it must be taken into consideration that the amount of drug is finite, and that the antibacterial effect will diminish over time. Moreover, the effect of CNT toxicity on the surrounding tissues needs to be fully investigated.

5.3 CNT nanocomposites for dental implant applications

The incorporation of pristine or surface-functionalized CNTs into existing implant materials, for example, titanium, zirconia, and glassy carbon, has been able to modify the surface charge and texture. The effects of incorporating CNT into each matrix material, and its specific challenges, will be discussed in the following sections.

5.3.1 CNT-titanium nanocomposites

Titanium is a metal that has found widespread application as a bioimplant material, due to its biocompatibility and nonallergic properties. Titanium implants are used for many medical procedures such as hips, bone screws, and heart valves. However, the

cost of titanium implants is high, which limits wide access to using this material. The long-term effects of titanium implants are debatable due to issues of corrosion. When the implant is in the oral environment, it is exposed to organic fluids, for example, saliva, which acts as a solvent to dissolve titanium, forming ions that may be distributed into the blood circulation stream and bind to other body proteins. At the local level, metal leaching into the surrounding implant region results in an inflammatory response all around the implant [41]. On a systemic level, ionic Ti may alter the genetic makeup of cells in tissue culture (mutagenic effect). Metal ions, including Ti, may also impose a destructive effect on cell DNA (genotoxic effect), which is thought to be mediated by free radical attack on DNA, or by an indirect effect inhibiting the repair of DNA [42].

CNTs have been applied as a surface charge modification in Ti implants, and tested for strength as an indicator of bone growth. In a study investigating the effects of bone tissue growth on CNT-Ti composites [43], cell proliferations on the CNT-Ti composite were similar to that of pure titanium. In fact, the initial cell distribution was more rapid on the pure titanium surface, compared with the CNT-Ti composite, due to its rough surface. Nevertheless, cell differentiation was better on the CNT-Ti composite, as indicated by higher calcium deposition on the CNT-Ti composite material than on pure titanium. Additionally, the high production of alkaline phosphatase (ALP) activity observed on the CNT-Ti composite suggested that the cells started to differentiate earlier on this surface. The authors reported that the CNT-Ti composite was nontoxic, as no inflammatory response during the experiment was observed [43].

The results from one study indicated that an increase in the hydrophilicity of CNTs (by introducing COOH groups on the surface) in CNT-coated titanium surfaces has a positive influence on osteoblast proliferation, differentiation, and matrix mineralization [23]. The hydrophilic properties were responsible for superior cytocompatibility over MWCNTs [21].

5.3.2 *CNT-zirconia nanocomposites*

Zirconia implants were introduced as an alternative to titanium implants, with advantageous properties such as aesthetic appearance, mechanical properties, biocompatibility, and low plaque affinity [44, 45]. Additionally, zirconia is a ceramic, and does not pose issues of corrosion or metal leaching. Zirconium can also be used in patients with metal allergies who may have problems with titanium. However, similar to other metal implant materials, zirconia suffers from poor fracture toughness. Failure analysis of fractured dental zirconia implants revealed that fractures are often caused by mechanical overloading. Notches and scratches on the surface of zirconia implants due to sandblasting of the surface result in the concentration of stress at localized areas, leading to mechanical overloading [46].

Zirconia is also prone to aging, which is a slow surface transformation of the zirconia from its tetragonal structure into the thermodynamically stable monoclinic phase in the presence of moisture. Aging is accelerated under humid conditions, and induces microcracking, which in the most severe cases causes failure and loss of functionality [47].

A balance between aging and crack resistance was achieved as a result of formation of zirconia crystals with small grain size, and the addition of a small amount of CNT into the matrix as a reinforcement agent. The effect of aging was reduced when 3 wt% CNTs were incorporated into the zirconia matrix, and the authors proposed two toughening mechanisms: CNT pull-outs were observed on the fracture surfaces, as observed using atomic force microscopy (AFM), and zirconia coated MWCNT bridges were observed using scanning electron microscopy (SEM) [48].

Another study reported marginally delayed aging transformation from the tetragonal phase to the monoclinic phase under humid conditions, as a result of incorporating MWCNTs [49]. Alumina-toughened zirconia/CNT nanocomposites showed a marginal increase in the aging resistance, which the authors attributed to the hydrophobic character of the MWCNTs. Although the MWCNTs did not contribute significantly to delay implant aging, nevertheless it remained as a reinforcement agent. It may be termed as a reinforcement agent with mild aging resistance properties.

When CNT was applied as a coating on zirconia implants, better cell attachment was seen on the multi-wall CNT-coated zirconia sample than on the uncoated zirconia discs, most likely due to surface roughening effects [50]. A uniform and optimum loading of CNTs in the implant matrix is essential for implant toughness. It has been reported that the higher amounts of CNT added to the CNT-zirconia composite did not show any improvement to the implant toughness, which was attributed to the lack of a well-dispersed CNT net, which prevented its toughening action [48].

5.3.3 CNT-glassy carbon nanocomposite

Glassy carbon, also known as vitreous carbon implants, is an established technology using chemically inert and biologically compatible carbon materials. Compared with the metallic implants, carbon elicits a very minimal response from host tissues, and is more inert under physiological conditions. Vitreous carbon has the modulus of elasticity similar to that of dentine and bone. Vitreous carbon is a 99.99% pure form of carbon, with a compressive strength of 50,000–100,000 pounds per square inch, a transverse strength of 10,000–30,000 psi, and a modulus of elasticity between 3 and 4×10^6 psi. This modulus is similar to that of dentin; this is a significant factor in reducing shearing forces at the implant bone interface. Thus, carbon deforms at a rate similar to the tissues, enhancing the transmission of biomechanical forces. Nevertheless, glassy carbon is susceptible to fracture under tensile and stress conditions because of its brittleness, and susceptibility to fracture under tensile stress in the presence of surface flaws, which is usually generated as a component of flexural loading [51]. For this reason, attention has been shifted from pure vitreous carbon to silicon, zirconia, and titanium, as well as variants in the composite material.

5.3.4 CNT-hydroxyapatite nanocomposite

Hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] is a calcium phosphate ceramic [52], and has been a common choice as a bone-substitute material due to its similar chemical composition to bone (calcium-rich) and excellent biocompatibility. Dental implants are commonly

coated with hydroxyapatite to provide a microretention surface and improve osseointegration at the surface of the dental implant during the healing process. Hydroxyapatite offers several advantages over titanium plasma spray coating, including faster bone healing at the bone-implant interface, increased gap healing between bone and hydroxyapatite, and corrosion inhibition. Nevertheless, hydroxyapatite is a brittle material, and its low strength and toughness limit its application as a coating, rather than as a major load bearing implant material [53]. The formation of cracks in hydroxyapatite coating expose the underlying dental implant body to bacterial infection. Other practical disadvantages of applying a coating over dental implants include increased risk of infection, plaque retention when exposed above the bone, complication of treatment of failing implants, and flaking, cracking, or scaling upon insertion.

Strategies to enhance the mechanical properties of the brittle hydroxyapatite matrix involve the formation of nanocomposites with a variety of materials such as zirconia, alumina, titania, carbon fibers, and carbon nanotubes as reinforcing materials [54]. CNT-hydroxyapatite composites have been prepared using various synthesis techniques, including electrophoretic deposition [55], sol-gel [56], and plasma spraying [57, 58]. CNTs were also grown in situ to enhance the dispersion of CNTs in the hydroxyapatite interface [59]. CNTs enhance the mechanical properties of hydroxyapatite by increasing the fracture toughness of hydroxyapatite coatings. When coated over dental implants, the high surface area of CNTs may complement structural modifications to enhance the functional surface area, which participates by actively dissipating mechanical loadings at the implant-to-bone interface.

The high aspect ratio of CNTs results in its superb performance as a reinforcing agent [60]. The incorporation of CNT into hydroxyapatite coatings increased the elastic modulus and hardness of the composite coatings [61]. The incorporation of CNT into brittle hydroxyapatite was also able to improve the fracture toughness by 56% ($0.61 \pm \text{MPa m}^{-2}$) [57].

Brittle ceramics (e.g., hydroxyapatite) suffer from low strength under tensile conditions, and even the slightest flaw will amplify the applied stress. Thus, the CNTs serve to impede crack growth, by suppressing the initiation and propagation of microcracks during abrasion [53, 58]. The wear behavior of CNT-hydroxyapatite nanocomposites has been found to be superior compared with pure hydroxyapatite nanocomposites, whereby a 4 wt% CNT composition in hydroxyapatite coating reduced the volume of wear debris generation by 80% [62]. The reduction of wear debris was attributed to the improved elastic modulus and fracture toughness in the CNT-hydroxyapatite nanocomposite. CNTs were also reported to enhance abrasion resistance in hydroxyapatite coatings via stretching and splat-bridging mechanisms [58].

CNTs and hydroxyapatite were proposed to interact through physical cross-linking, in a study reporting the fabrication of a CNT-hydroxyapatite nanocomposite with a relatively high modulus strength (~ 131.1 GPa) and hardness (~ 6.86 GPa) achieved at the sintering temperature of 1100°C [63]. Alternatively, the functionalization of single-wall CNTs with phosphonates and poly(aminobenzene sulfonic acid) may result in intimate contact between hydroxyapatite and CNTs, as the study demonstrated nucleation and crystallization of hydroxyapatite by self-assembly on the CNT surface [22].

5.4 Challenges

CNTs are generally perceived to contribute positively when incorporated into the composite matrix, demonstrating enhanced bone integration, antifouling, and bactericidal properties. Nevertheless, challenges relating to composite fabrication and long-term biological effects of the CNTs will remain.

Ensuring the uniform dispersion of CNTs in the composite matrix remains a challenge as CNTs tend to agglomerate in solution. This issue is applicable to the preparation of any CNT-based composite materials in general, as the agglomeration of CNTs reduces the elastic stiffness of the matrix [64]. Pristine CNTs are chemically inert and do not disperse in any common solvents, due to their strong interchain van der Waals interactions. Hence, to enhance their dispersability and reactivity, carboxylation of the nanotube chains are often carried out using strong acids.

There is also limited understanding of the cytocompatibility of carbon nanofibers. Some studies report cytotoxic properties, while some indicate the opposite. For example, unrefined single-walled CNTs cause various adverse side effects, for example, accelerated oxidative stress, decreased cell viability, and altered cell morphology [65, 66]. Single-walled CNTs also induce apoptosis and decrease of cellular adhesion [67], whereas nonfunctionalized multi-walled CNTs induce the release of pro-inflammatory cytokine [68]. It was proposed that the toxicity of the CNTs may be reduced by chemical functionalization and tuning of the surface charge. On the other hand, CNT fibers with larger diameters and lower surface energies demonstrated positive effects on cell attachment and proliferation [69].

5.5 Conclusion

CNT nanocomposite materials have been fabricated with the goal of addressing the weakness of current commercial dental implant materials. CNTs have unique mechanical properties and biocompatibility that enhance the desirable properties of the nanocomposite material (mechanical stability, bone growth, preventing bacterial infection). Advances in research investigating the effects of CNT functionalization on nanocomposite fabrication and biological response have fostered greater understanding on the types of functional groups that may support osteoblast growth and antifouling properties, and enhance integration with a composite matrix. Challenges will remain in the application of CNTs in dental implants as a nanocomposite material due to limited control over the fabrication of CNT nanocomposites (to produce uniformly distributed CNTs in the matrix), as well as limited understanding on the cytocompatibility of CNTs in the human body. As such, the research trends are focused on better control of surface properties of CNTs to achieve the desired effect on nanocomposite materials (enhanced dispersion and/or antibacterial properties), as well as continuing robust and long-term investigations on the cytotoxic properties of CNTs.

Acknowledgments

This research work was financially supported by the University Malaya Research Grant (No. RP045B-17AET), University Malaya Research Fund Assistance (BKP) Grant (No. BK096-2016), and Global Collaborative Programme—SATU Joint Research Scheme (No. ST008-2017).

References

- [1] S. Iijima, Helical microtubules of graphitic carbon, *Nature* 354 (6348) (1991) 56–58.
- [2] C. Scully, A. Kalantzis, *Oxford Handbook of Dental Patient Care*, Oxford University Press, 2005. New York.
- [3] C.E. Misch, Implant body size: a biomechanical and esthetic rationale, in: *Contemporary Implant Dentistry*, Mosby, St. Louis, 2008, pp. 160–177.
- [4] R. Das, et al., Carbon nanotube membranes for water purification: a bright future in water desalination, *Desalination* 336 (2014) 97–109.
- [5] M.-F. Yu, et al., Tensile loading of ropes of single wall carbon nanotubes and their mechanical properties, *Phys. Rev. Lett.* 84 (24) (2000) 5552–5555.
- [6] J.P. Lu, Elastic properties of carbon nanotubes and nanoropes, *Phys. Rev. Lett.* 79 (7) (1997) 1297–1300.
- [7] J.N. Coleman, U. Khan, Y.K. Gun'ko, Mechanical reinforcement of polymers using carbon nanotubes, *Adv. Mater.* 18 (6) (2006) 689–706.
- [8] C. Larsson, et al., The titanium-bone interface in vivo, in: *Titanium in Medicine: Material Science, Surface Science, Engineering, Biological Responses and Medical Applications*, Springer Berlin Heidelberg, Berlin, Heidelberg, 2001, pp. 587–648.
- [9] H. Nygren, P. Tengvall, I. Lundström, The initial reactions of TiO₂ with blood, *J. Biomed. Mater. Res. A* 34 (4) (1997) 487–492.
- [10] P. Linderback, et al., The effect of heat- or ultra violet ozone-treatment of titanium on complement deposition from human blood plasma, *Biomaterials* 31 (18) (2010) 4795–4801.
- [11] C. Masaki, et al., Effects of implant surface microtopography on osteoblast gene expression, *Clin. Oral Implants Res.* 16 (6) (2005) 650–656.
- [12] C.Y. Guo, J.P. Matinlinna, A.T.H. Tang, Effects of surface charges on dental implants: past, present, and future, *Int. J. Biomater.* 2012 (2012) (2012) 1–5.
- [13] T.A. Horbett, J.L. Brash, Proteins at interfaces: current issues and future prospects, in: *Proteins at Interfaces*, American Chemical Society, Washington, DC, 1987, pp. 1–33.
- [14] J.M. Anderson, A. Rodriguez, D.T. Chang, Foreign body reaction to biomaterials, *Semin. Immunol.* 20 (2) (2008) 86–100.
- [15] W. Chee, S. Jivraj, Failures in implant dentistry, *Br. Dent. J.* 202 (3) (2007) 123–129.
- [16] A. Bowkett, et al., Removal techniques for failed implants, *Br. Dent. J.* 220 (3) (2016) 109–114.
- [17] L.P. Zanella, et al., Bone cell proliferation on carbon nanotubes, *Nano Lett.* 6 (3) (2006) 562–567.
- [18] F. Gholami, S. Ismail, A.F.M. Noor, Development of carboxylated multi-walled carbon nanotubes and bovine serum albumin reinforced hydroxyapatite for bone substitute applications, *J. Aust. Ceram. Soc.* 53 (1) (2017) 117–127.
- [19] F. Gholami, et al., Hydroxyapatite reinforced with multi-walled carbon nanotubes and bovine serum albumin for bone substitute applications, *AIP Conf. Proc.* 1791 (1) (2016) 020015.

- [20] K. PourAkbar Saffar, L.J. Sudak, S. Federico, A biomechanical evaluation of CNT-grown bone, *J. Biomed. Mater. Res. A* 104 (2) (2016) 465–475.
- [21] A. Bianco, K. Kostarelos, M. Prato, Making carbon nanotubes biocompatible and biodegradable, *Chem. Commun.* 47 (37) (2011) 10182–10188.
- [22] B. Zhao, et al., A bone mimic based on the self-assembly of hydroxyapatite on chemically functionalized single-walled carbon nanotubes, *Chem. Mater.* 17 (12) (2005) 3235–3241.
- [23] K. Subramani, et al., In vitro evaluation of osteoblast responses to carbon nanotube-coated titanium surfaces, *Prog. Orthod.* 17 (1) (2016) 23.
- [24] M.A. Sá, et al., Single-walled carbon nanotubes functionalized with sodium hyaluronate enhance bone mineralization, *Braz. J. Med. Biol. Res.* 49 (2) (2016) 1–10.
- [25] M.N. Collins, C. Birkinshaw, Hyaluronic acid based scaffolds for tissue engineering—a review, *Carbohydr. Polym.* 92 (2) (2013) 1262–1279.
- [26] P. Heldin, et al., Importance of hyaluronan-CD44 interactions in inflammation and tumorigenesis, *Connect. Tissue Res.* 49 (3) (2008) 215–218.
- [27] M. David-Raoudi, et al., Differential effects of hyaluronan and its fragments on fibroblasts: relation to wound healing, *Wound Repair Regen.* 16 (2) (2008) 274–287.
- [28] E.A. Turley, P.W. Noble, L.Y. Bourguignon, Signaling properties of hyaluronan receptors, *J. Biol. Chem.* 277 (7) (2002) 4589–4592.
- [29] G. Pasquini, et al., Mesenchymal stem cell interaction with a non-woven hyaluronan-based scaffold suitable for tissue repair, *J. Anat.* 213 (5) (2008) 520–530.
- [30] A. Weselucha-Birczyńska, et al., A model of adsorption of albumin on the implant surface titanium and titanium modified carbon coatings (MWCNT-EPD). 2D correlation analysis, *J. Mol. Struct.* 1124 (2016) 61–70.
- [31] B.D. Boyan, et al., Role of material surfaces in regulating bone and cartilage cell response, *Biomaterials* 17 (2) (1996) 137–146.
- [32] F.J.A.L. Cruz, I.A.A.C. Esteves, J.P.B. Mota, Adsorption of light alkanes and alkenes onto single-walled carbon nanotube bundles: Langmuirian analysis and molecular simulations, *Colloids Surf. A Physicochem. Eng. Asp.* 357 (1–3) (2010) 43–52.
- [33] E. Ajami, et al., Bone healing and the effect of implant surface topography on osteoconduction in hyperglycemia, *Acta Biomater.* 10 (1) (2014) 394–405.
- [34] C.P. Firme 3rd, P.R. Bandaru, Toxicity issues in the application of carbon nanotubes to biological systems, *Nanomedicine* 6 (2) (2010) 245–256.
- [35] G. Soon, et al., Review of zirconia-based bioceramic: surface modification and cellular response, *Ceram. Int.* 42 (11) (2016) 12543–12555.
- [36] A. Han, et al., Bacterial adhesion mechanisms on dental implant surfaces and the influencing factors, *Int. J. Adhes. Adhes.* 69 (2016) 58–71.
- [37] J.-P. Albouy, et al., Spontaneous progression of ligature induced peri-implantitis at implants with different surface characteristics. An experimental study in dogs II: histological observations, *Clin. Oral Implants Res.* 20 (4) (2009) 366–371.
- [38] L. Ding, et al., Molecular characterization of the cytotoxic mechanism of multiwall carbon nanotubes and nano-onions on human skin fibroblast, *Nano Lett.* 5 (12) (2005) 2448–2464.
- [39] L.R. Arias, L. Yang, Inactivation of bacterial pathogens by carbon nanotubes in suspensions, *Langmuir* 25 (5) (2009) 3003–3012.
- [40] J. Hirschfeld, et al., Long-term release of antibiotics by carbon nanotube-coated titanium alloy surfaces diminish biofilm formation by *Staphylococcus epidermidis*, *Nanomedicine* 13 (4) (2017) 1587–1593.
- [41] V. Sansone, D. Pagani, M. Melato, The effects on bone cells of metal ions released from orthopaedic implants. A review, *Clin. Cases Miner Bone Metab.* 10 (1) (2013) 34–40.

- [42] B. Daley, et al., Wear debris from hip or knee replacements causes chromosomal damage in human cells in tissue culture, *J. Bone Joint Surg. Br. Vol.* 86 (4) (2004) 598–606.
- [43] M. Bhattacharya, et al., Bone formation on carbon nanotube composite, *J. Biomed. Mater. Res. A* 96A (1) (2011) 75–82.
- [44] Z. Özkurt, E. Kazazoglu, Zirconia dental implants: a literature review, *J. Oral Implantol.* 37 (3) (2011) 367–376.
- [45] A. Scarano, et al., Bacterial adhesion on commercially pure titanium and zirconium oxide disks: an in vivo human study, *J. Periodontol.* 75 (2) (2004) 292–296.
- [46] M. Gahlert, et al., Failure analysis of fractured dental zirconia implants, *Clin. Oral Implants Res.* 23 (3) (2012) 287–293.
- [47] J. Chevalier, What future for zirconia as a biomaterial? *Biomaterials* 27 (4) (2006) 535–543.
- [48] N. Garmendia, et al., Zirconia-multiwall carbon nanotubes dense nano-composites with an unusual balance between crack and ageing resistance, *J. Eur. Ceram. Soc.* 31 (6) (2011) 1009–1014.
- [49] M. Estili, et al., Sintering in a graphite powder bed of alumina-toughened zirconia/carbon nanotube composites: a novel way to delay hydrothermal degradation, *Ceram. Int.* 41 (3) (2015) 4569–4580.
- [50] W. Kou, et al., An in vitro evaluation of the biological effects of carbon nanotube-coated dental zirconia, *ISRN Dent* 2013 (2013) (2013) 1–6.
- [51] H. Ananth, et al., A review on biomaterials in dental implantology, *Int. J. Biomed. Sci.* 11 (3) (2015) 113–120.
- [52] M.I. Kay, R.A. Young, A.S. Posner, Crystal structure of hydroxyapatite, *Nature* 204 (4963) (1964) 1050–1052.
- [53] A.A. White, S.M. Best, I.A. Kinloch, Hydroxyapatite-carbon nanotube composites for biomedical applications: a review, *Int. J. Appl. Ceram. Technol.* 4 (1) (2007) 1–13.
- [54] S. Mukherjee, et al., Enhanced bone regeneration with carbon nanotube reinforced hydroxyapatite in animal model, *J. Mech. Behav. Biomed. Mater.* 60 (2016) 243–255.
- [55] A.R. Boccaccini, et al., Electrophoretic deposition of carbon nanotube-ceramic nanocomposites, *J. Eur. Ceram. Soc.* 30 (5) (2010) 1115–1129.
- [56] A. Abrishamchian, et al., Preparation and characterization of multi-walled carbon nanotube/hydroxyapatite nanocomposite film dip coated on Ti-6Al-4V by sol-gel method for biomedical applications: an in vitro study, *Mater. Sci. Eng. C* 33 (4) (2013) 2002–2010.
- [57] K. Balani, et al., Plasma-sprayed carbon nanotube reinforced hydroxyapatite coatings and their interaction with human osteoblasts in vitro, *Biomaterials* 28 (4) (2007) 618–624.
- [58] K. Balani, et al., Tribological behavior of plasma-sprayed carbon nanotube-reinforced hydroxyapatite coating in physiological solution, *Acta Biomater.* 3 (6) (2007) 944–951.
- [59] S. Liu, et al., Preparation and properties of in-situ growth of carbon nanotubes reinforced hydroxyapatite coating for carbon/carbon composites, *Mater. Sci. Eng. C* 70 (Pt 1) (2017) 805–811.
- [60] M. Dresselhaus, G. Dresselhaus, A. Jorio, Unusual properties and structure of carbon nanotubes, *Annu. Rev. Mater. Res.* 34 (2004) 247–278.
- [61] Y. Chen, et al., Carbon nanotube reinforced hydroxyapatite composite coatings produced through laser surface alloying, *Carbon* 44 (1) (2006) 37–45.
- [62] D. Lahiri, et al., Wear behavior and in vitro cytotoxicity of wear debris generated from hydroxyapatite-carbon nanotube composite coating, *J. Biomed. Mater. Res. A* 96A (1) (2011) 1–12.

- [63] J.L. Xu, et al., Preparation and characterization of a novel hydroxyapatite/carbon nanotubes composite and its interaction with osteoblast-like cells, *Mater. Sci. Eng. C* 29 (1) (2009) 44–49.
- [64] J. Pan, L. Bian, Influence of agglomeration parameters on carbon nanotube composites, *Acta Mech.* 228 (6) (2017) 2207–2217.
- [65] A.A. Shvedova, et al., Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells, *J. Toxicol. Environ. Health A* 66 (20) (2003) 1909–1926.
- [66] A. Nimmagadda, et al., Chemical modification of SWNT alters in vitro cell-SWNT interactions, *J. Biomed. Mater. Res. A* 76 (3) (2006) 614–625.
- [67] D. Cui, et al., Effect of single wall carbon nanotubes on human HEK293 cells, *Toxicol. Lett.* 155 (1) (2005) 73–85.
- [68] N.A. Monteiro-Riviere, et al., Multi-walled carbon nanotube interactions with human epidermal keratinocytes, *Toxicol. Lett.* 155 (3) (2005) 377–384.
- [69] J.L. McKenzie, et al., Decreased functions of astrocytes on carbon nanofiber materials, *Biomaterials* 25 (7–8) (2004) 1309–1317.