Cold Plasma Treated Titanium Surfaces Coated with Polydopamine/Copper Resist Endotoxin-Induced Surface Oxidation and Promote Tissue Healing

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BDS

Submitted in fulfilment of the requirements for the degree of

Master of Philosophy

Centre of Biomedical Technologies

School of Mechanical, Medical and Process Engineering

Faculty of Engineering

Queensland University of Technology

2023

Keywords

Surface modification, dental implants, peri-implantitis, cold plasma technique, atmospheric plasma treatment, polydopamine coatings, cell attachment, human gingival fibroblasts, antimicrobial coatings, antibiofilm coatings, multifunctional coating, copper coating, titanium oxide.

Abstract

Titanium metals are biocompatible and commonly utilised in the dentistry sector to create dental implants though are prone to deterioration, due to the increased risk of periimplant infection and the acidic nature of saliva, resulting in implant failure. Several approaches including multifunctional coating can be used to change the material, where two or more components are integrated simultaneously to modify the surface. In this research the surface of titanium (Ti) sheet was modified using cold atmospheric plasma (CAP), polydopamine (PDAM), and copper (Cu). Three distinct plasma gases, argon (Ar), nitrogen (N), and atmosphere (Atm), were used in the investigation, which was reduced down to atmosphere Atm. Atm-modified titanium samples showed increased surface modification, hydrophilicity, and changes in polydopamine particle size and distribution. It was possible to deduce the study from the results of Xray diffraction (XRD) and inductively coupled plasma optical emission spectrometry (ICP-OES) data that Ti treated with Atm plasma, PDAM, and Cu demonstrated reduced Ti surface degradation and increased cell survival. This study will have great significance in dentistry by decreasing the degradation of dental implants thereby increasing longevity.

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List of Abbreviations

CAP - cold atmospheric plasm

Ar - argon plasma

N - nitrogen plasma

Atm - atmospheric plasma

Cu - Copper

PDAM - polydopamine

TiO_2 - titanium dioxide

MIC - microbiologically induced corrosion

TiAlV - titanium alloy

LPS - lipopolysaccharide

RGD - arginine–glycine–aspartic acid

PDAM@Cu - polydopamine and copper coated

DBD - dielectric barrier discharge

ROS - reactive oxygen species

RNS - reactive nitrogen species

PHAs - antibiotic-loaded polyhydroxyalkanoates

(TNF- α) - Tumour necrosis factor

VB - breakdown voltage

MRSA - methicillin-resistant *Staphylococcus aureus*

AFM - atomic force microscopy

XPS - X-ray photoelectron spectroscopy

ICP-OES - inductively coupled plasma-optical emission spectroscopy

SEM - scanning electron microscope

Acknowledgements

I would like to express my admiration and heartfelt gratitude to the people listed below, without whom my thesis would not be possible.

First and foremost, I thank my Principal Supervisor, Dr Yinghong Zhou, for her guidance and continuous support throughout my journey. Thank you for encouraging me to do more than I ever thought possible. I am grateful to my Associate Supervisors, Professors Yin Xiao, Jennifer MacLeod, and Kostya (Ken) Ostrikov, for their guidance and expertise. I feel tremendously lucky to have had the opportunity to work with all of them.

I would like to thank all the sources of funding, including Queensland University of Technology, Dr Yinghong Zhou, for my Supervisor's Scholarship and Professor Yin Xiao, for supporting the publication of my first paper.

I would like to thank former and current Bone Group members, especially Dr Jayanti Mendhi, Dr Wai Fun Patrick Lau, and Ms Yunxia Wan, for helping me with my lab work in their busy schedule, guiding me in learning interesting new things throughout my studies. Dr Jayanti Mendhi helped me to tackle many difficult situations through this entire phase. I would like to thank Ms Shital Wakale for helping and supporting me as I was going through a challenging period of my life and to help me overcome to some extent, my introverted nature.

I thank all of the CBT support personnel who maintained the smooth and efficient functioning of our lab. I would like to express my gratitude to the CARF staff, especially Dr Yanan Xu, Dr Osama Yousef Ali Ghidan (Sam), Mitchell de Bruyn and Dr Tony Wang, for helping me with various scientific and technical assistance. Moreover, I thank the School of Mechanical, Medical and Process Engineering and the Faculty of Engineering for allowing me to explore the beautiful world of research and for their support.

I would like to thank my dear family, my husband, my two beautiful kids and my parents, without whom I wouldn't have achieved this goal. My husband and kids were going through the same phase as me throughout this journey. They were adjusting and caring for me through all my ups and downs.

Chapter 1 Introduction

1.1 Background

Titanium has excellent osseointegration properties and strong biocompatibility[1-3] for orthopaedic and dental implants and with a reasonable success rate, failures are still being reported.[4] One contributing factor for dental implant failure is the degradation or corrosion of titanium,[5] which in implants can result in mechanical and biological consequences.[6] It is the confluence of the three factors of infections, rusting or corrosion, and mechanical forces that can cause peri-implantitis, the damaging inflammatory condition occurring around the dental implants, leading to implant failure.[7, 8] (**Figure 1.1**). The microenvironment in infectious implants may be further conducive to the wear of titanium surfaces.

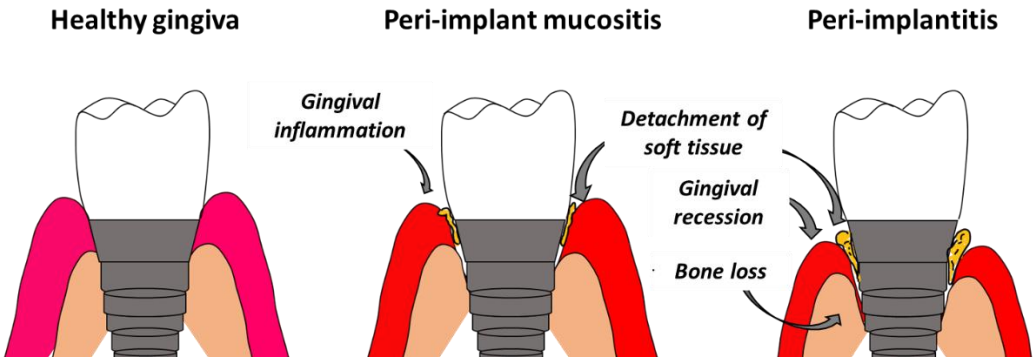


Figure 1.1 Progression of peri-implantitis.[8] This work is licensed under a Creative Commons Attribution-Non-commercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Bacterial endotoxin and stimuli to inflammatory cells surrounding the implants results in dental implant diseases involving bone resorption, such as osseointegration failure and peri-implantitis.[9] When a foreign material enters or is introduced into the human body because of corrosion, the tissue around it responds in several ways, often undesired and cause persistent inflammation and, or hypersensitivity. On the titanium samples, gram-negative bacteria like *Streptococcus sanguinis* and *Porphyromonas gingivalis* can generate stable biofilms.[10] Bacterial corrosion by endotoxin lipopolysaccharide (LPS) triggers titanium ion release[11, 12] from these titanium plates, which was significantly greater on pure titanium under aerobic circumstances. Corrosion, in general, is the slow degradation of metals that occurs as a result of air, humidity, or a chemical reaction such as an acid on their surface.[13] Corrosion processes cause alterations in the structure of the implanted material, reducing its integrity and resulting

in material discontinuities and the release of ions that destroy the protective titanium dioxide (TiO_2) layer.[14]

Titanium and titanium alloys are very reactive, and when exposed to air or liquid fluid media, immediately form a coating of TiO_2.[15, 16] This layer of oxide establishes a barrier between the biological medium and the metal structure. An improvement in properties of titanium may also be noticed in the case of thick oxide coatings.[14] The top sublayer of the titanium oxide layer suppresses any metal ion release and promotes osseointegration and bone attachment. The titanium oxide layer dissolves as a result of ion diffusion into the layer from the saliva, extracellular body fluid and blood. Protein and amino acids also accelerate the corrosion process.[16]

Tribocorrosion and microbiologically induced corrosion (MIC) have been identified as the key degradation processes causing dental implant failure.[17] Material deterioration occurring from the combination of wear and corrosion is called tribocorrosion[18] whereas, MIC is degradation caused by the action of microorganisms.[19] In the presence of metal particles and ions, pro-inflammatory cytokines, inflammatory cell infiltration, and osteoclast activation are all promoted in peri-implant tissues. Degenerative alterations have also been observed in macrophages and neutrophils that phagocytose titanium microparticles, leading to an increased release of the tumour necrosis factor (TNF-α), a proinflammatory cytokine in human peri-implant tissues (**Figure 1.2**).[5, 20] Dental implant debris has the potential to be cytotoxic and genotoxic to the tissues around the implants which means the extent of the adverse effect on peri-implant tissues is determined by the number and physicochemical qualities of the degradation products. As a result of these effects it is critical to increase the service life of dental implants by minimising the tribocorrosion effects and MIC by developing new dental implant materials containing hybrid or composite metals and altering the surface of the implants.[21]

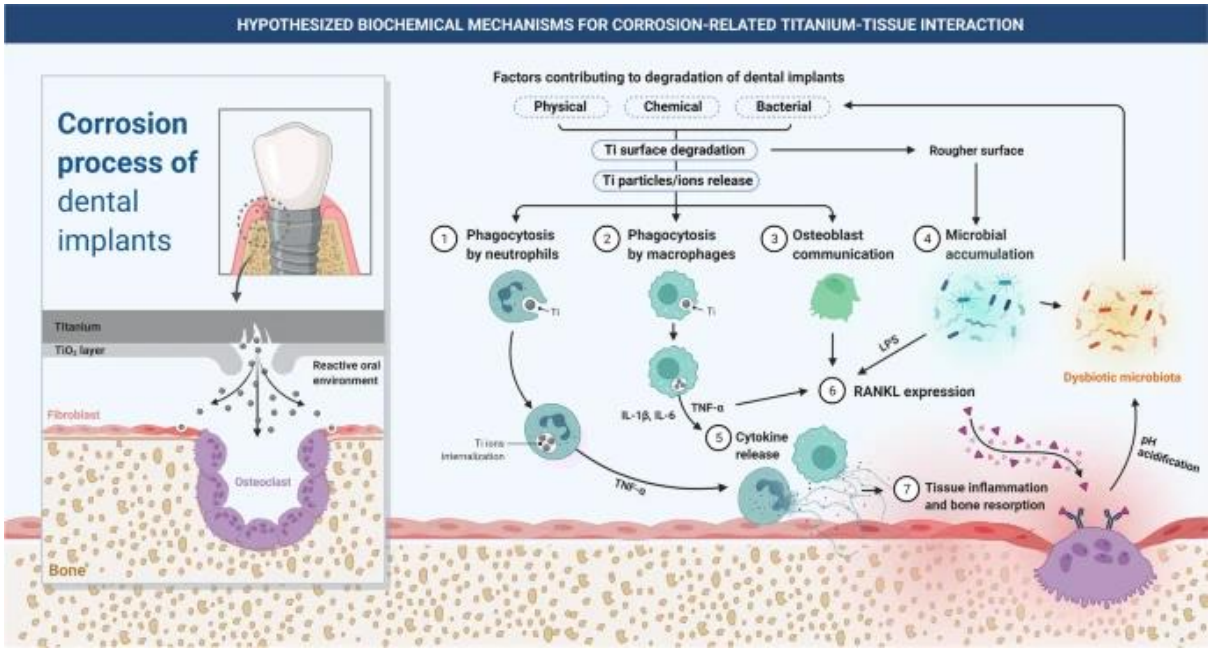


Figure 1.2 Corrosion process of dental implants. Permission to reuse received from Springer Nature Switzerland AG[5].

Since the surface of the titanium implants are initially effected by tribocorrosion and MIC the primary aim of this research was to modify the titanium surface to improve its property to resist degradation by these factors. Surface modification helps increase the osseointegration of titanium implants[22, 23] and with a combination of diverse materials[24] currently utilised as a multifunctional coating material, aids in improving titanium characteristics. However, these techniques have several challenges, including rapid release, toxic to cell, a short half-life, and low stability.[24]

Many studies are underway to solve these issues by coating with controlled release qualities and a synergetic impact between the surface. Similarly, this project endeavours to modify the titanium surfaces with CAP, a non-thermal plasma technique followed by coating with PDAM and Cu. CAP therapy increases the hydrophilicity of dental implants while also removing contaminants,[25] in an environmentally friendly way of material modification that has no negative side effects. CAP treatment is a beneficial procedure for priming surfaces for improved secondary modification, which can create carbonyl, hydroxyl, and other groups to improve surface adhesion.[26] Since CAP helps reduce the initial contamination of the titanium surface the chance of MIC-induced degradation also decreases. The CAP treatment helps to improve the dispersion and stability of nanoparticles and helps to modify the particle size.[27-30]

PDAM is a nature-inspired biopolymer that increases the wettability of the titanium surface, helps in cell growth, and has corrosion resistance ability,[31] and has a universal adhesion property.[32] Along with these advantages, it does have some key limitations which should be considered. For example, the increased concentration results in toxicity, agglomeration, non-uniform particle size and above all, PDAM is not mechanically stable although it is adhesive. Since CAP treatment helps in uniform dispersion of the biopolymers and enhancing their properties, it is postulated that CAP application can overcome these main drawbacks.

A study to optimise the PDAM coating recommended that to produce a better surface modification using the PDAM layer, a second layer of Cu or silver (Ag) could be applied.[33] Incorporating certain metals, such as Cu or Ag, into the polymer structure may be beneficial for a variety of biological applications. To avoid nosocomial infections, materials that resist or impede bacterial adhesion, establishment, and multiplication must be developed. Polydopamine's flexible chemical characteristics facilitate the modification of titanium implants with both passive and active agents that inhibit the development of microbiological biofilms. Polydopamine films exhibit reductive properties, enabling direct metal film deposition when exposed to a noble metal salt solution and therefore serving as a foundation layer for Ag or Cu. Adding extra metals to the surface helps resist corrosion and abrasion with a lower coefficient of friction.[34] It is feasible to produce a hybrid coating with antibacterial characteristics and corrosion protection by mixing PDA and copper coatings.

The PDA coating can serve as a priming layer, enhancing the copper coating's adherence to the titanium substrate. The copper covering can therefore operate as a sacrificial anode, corroding before the titanium and thus shielding the titanium from corrosion. This simple and low-cost technique of surface modification may be applied to a wide range of instruments, including medical equipment. In this case, the antibacterial characteristic of the Cu aids in reducing the deterioration caused by MIC.[33]

1.2 **Purposes and Aims**

Protecting the TiO_2 layer from the degradation process and maintaining the biocompatibility of the titanium implants will reduce the chance of implant failure and increase the longevity of titanium implants. The metallic implant corrosion can have three effects on the surrounding tissues: 1) electrical current can impact cell behaviour; 2) the corrosion process can modify

the chemical environment; and 3) metal ions can effect cellular metabolism. Reduction of corrosion by modifying the implant will help achieve optimal tissue healing. Therefore this research aims to develop a cost-effective approach to modify the titanium surfaces with a less corrosive effect for better osseointegration.[35]

The aims of this research therefore are to:

- characterise the titanium surface treated with different plasma treatment.
- characterise plasma modified titanium coated with polydopamine and copper.
- investigate the impact of modified titanium substrates on the cell viability.
- investigate the degradation of the titanium substrates modified with plasma, polydopamine and copper.

Chapter 2 Literature Review

2.1 The notable accomplishments and failures in implant applications

Studies have reported[36-38] that microorganism covered implant surfaces corrode more quickly due to the acidic surroundings created by bacterial cellular metabolism and the by-products.[21] The MIC accelerates surface deterioration, resulting in many changes like staining, splitting, cracking, abrasion, and increases surface roughness. As a result of microbial deterioration, metallic ions or nanoparticles are released from the titanium surface, causing inflammation and bone resorption surrounding the peri-implant area.[21] Ex vivo investigations have shown that the presence of degraded Ti particles in the peri-implant regions is highly linked to the failure of implants,[39, 40] with microbial corrosion identified as a critical indicator of whether or not the implant will survive.

Similarly, a study on the impact of LPS on the tribocorrosive behaviour of titanium demonstrated that LPS negatively effected the titanium surfaces and increased corrosion[41] That study looked at two distinct titanium substrates, pure titanium, and titanium alloy (TiAlV), and found the presence of LPS increased the roughness of the worn surfaces of both titanium substrates. The clinical findings of this study suggested that patients with oral infections (e.g., with the presence of LPS) were more likely to have their dental implants deteriorate with increased bacterial biofilm development, which might have a negative influence on implant prognosis.[42] In an another study, the pure titanium surface was coated with titanium nitride and silicon carbide, less corrosion was observed on the coated titanium discs compared to uncoated

ones, emphasising the fact that surface modification of titanium surfaces with other materials helps in corrosion prevention. However, this alteration was only effective against *Porphyromonas gingivalis* in vitro.[10]

Research was carried out using silicon carbide (SiC) as the coating to evaluate the coating's stability to decrease corrosion and its influence on titanium durability under stimulated settings, using plasma-enhanced chemical vapour deposition to coat the titanium surface using SiC. The coated titanium implants were placed in a polymethyl methacrylate (PMMA) block to replicate clinical implant insertion and assessed the coating's integrity using energy dispersive spectroscopy. Even after the stimuli, the coating remained intact. Despite these promising findings more research is needed before SiC can be applied as a suitable covering for implant placement in the clinic.[43,10]

Scientists have attempted to leverage the deterioration of implant coating in a better way for drug delivery using antibiotic-loaded polyhydroxyalkanoates (PHAs) coatings on titanium implants, and the Dip-coating process for surface modification[33]. Dip-coating is the process of immersing substrate material in conformal coating, then removing it and allowing it to drip dry.[44] The use of coatings with varying medication concentrations per layer can result in more regulated and uniform drug release.

2.2 **Plasma and its application in material modifications**

Plasma, along with solid, liquid, and gas is commonly referred to as the "fourth state of matter"[45-47] which occurs naturally and can also be artificially made. In nature 99% of matter is made of plasma[48, 49] where for instance, energetic electromagnetic radiation from the sun and stars are made of plasma, and artificially formed plasmas are plasma TV, fluorescent lighting, and plasma-assisted coating[50, 51] Plasma, like gases, does not have a fixed shape or volume and is less dense than solid and liquid.[52] Unlike gases, plasma can conduct electricity and respond to the magnetic field.[52, 53] The neutral gas is ionized when heat or energy is added to it and this process of conversion of gas to plasma by ionization is called the breakdown process.[54, 55] During the ionization of gas, it starts to lose its electrons and become positively charged ions. The plasma breakdown depends on how strong the energy or electrical field is given between the two electrodes. Friedrich Paschen in 1889 established a law that indicates that the gas breakdown voltage (VB) relies on the product of the gas pressure (p) and the gap length (d)

between the electrodes (VB= f(pd)).[55-57] Paschen created graphs for the different gases, called a Paschen curve (**Figure 2.1**). As pd grows, a minimum breakdown voltage is attained, which is typically in the region of 100-500 V for pd values of around 1 Pa m. This pd value indicates that under atmospheric pressure, the electrode gap at which the lowest breakdown voltage occurs is around 10 µm. The Paschen curve helps predict the very high breakdown voltage for the low pd values.[58]

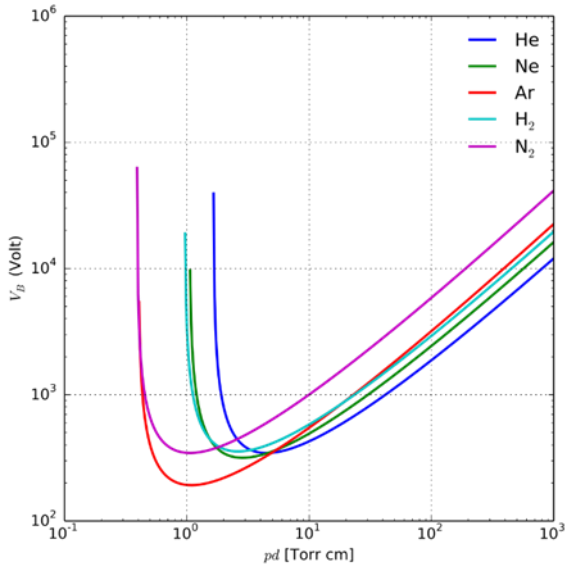


Figure 2.1 Paschen curves produced for helium, neon, argon, hydrogen, and nitrogen using the breakdown voltage equation.[59] Reproduced with permission from creative commons.

The three main types of artificial plasma are cold or non-thermal , hot or thermal, and warm plasma.[60] There are several types of cold plasma generating systems utilised in industries for diverse applications[61] including corona discharges, microwave plasma, inductively coupled plasma, electron cyclotron resonance plasma, and dielectric barrier discharge plasma.[62, 63] The most common are dielectric barrier discharge (DBD) and jet plasma[63, 64,65] due to their straightforward design and adaptability to a wide range of targets and treatment requirements.[65]

DBD plasma treatment is a modification technology known as 'silent discharge'[49] since the current limiting dielectric controls the gas ionisation rate. DBD plasma is excellent for producing enormous volumes of non-equilibrium air pressure diffuse plasma.[66] DBDs cover at least one electrode with a dielectric substance such as glass or alumina.[67] The electrodes are powered by high alternating current voltages in the kV range and frequencies in the kHz range.[68] DBD plasmas have been applied in the creation of ozone, the alteration of material surfaces, flow control actuators, and other applications. The capacity of cold atmospheric

plasma to inactivate bacteria is been the focus of recent interest[69, 70] to address modern society's multiple serious healthcare difficulties, such as multidrug-resistant infections and biofilms.[71, 72] Plasma can be applied in either direct or indirect exposures[73] with "direct" exposure referring to the plasma directly touching the biological target; all plasma-produced chemicals that act on the cells/tissues directly.[68] The "indirect" exposure refers to the plasma applied to activate a liquid medium before being applied to cells/tissues.[68, 74]

Cold plasma is used in various fields such as agriculture and packaging, and[75] in the medical field, atmospheric plasma is widely used for purposes such as promoting wound healing[68, 76, 77], inducing haemostasis, and curing cancer[76-78]. Antibiotic-resistant bacteria, including *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA), are common causes of nosocomial pathogens, which can be lethal in patients with impaired immune systems. Similarly, diabetic ulcers are chronic sores that may not heal quickly or at all and may be harmed by an increased risk of bacterial infection. Cold atmospheric plasma has been demonstrated to successfully restrain the growth of bacteria such as MRSA while also dramatically reducing the microbial load in infected chronic wounds and providing long-lasting antiseptic efficacy.[68, 79] These favourable CAP wound healing benefits were demonstrated in randomised clinical trials to treat diabetic foot ulcers, where plasma therapy was able to minimise wound area and time required for wound healing.[80-82]

Plasma may cause reactive nitrogen species (RNS) and oxygen species (ROS)[63] in cells, both of which have major effects on cellular function, and many illnesses have been linked to elevated levels of oxidative stress.[83] This oxidative stress is beneficial in treating cancer-causing cells since the excessive release of ROS damages the cancer cells and can lead to subsequent cell death.

CAP is used to modify many materials, allowing them to change their surface morphology, wettability and other properties. Plasma treatment helps modify the medical and dental implants which enhances the material properties. Surface modification can help improve the dental implant osseointegration allowing for better cell attachment to the implant surface,[84] resulting in a stable fixation.[14] Titanium dental implants may be surface-modified using cold plasma.[85] Titanium surfaces treated with plasma showed increased wettability, enhanced mesenchymal stem cells-to-osteoblast differentiation, decreased pro-inflammatory cytokine production and increased osteoblast activity.[85] Increasing the hydrophilicity of an implant's surface can improve the interaction between the implant and the surrounding environment[86-88]. Plasma treatment also aids the adhesion of cells and proteins, which facilitates both soft and

hard tissue attachment to implant surfaces.[89] Cell attachment is very important for the osseointegration and longevity of the dental implants. Despite having adequate mechanical and biocompatible qualities, titanium-based implants may fail to achieve adequate osseointegration due to their intrinsic surface bio-inertness and inadequate surface osteoconductivity.[90] So many researchers have tried to modify the titanium by adding one or more organic or inorganic components (hybrid or composite) into titanium. Integrating CAP and materials with different properties has become a promising tool for many medical and dental applications[91] including CAP treatment along with arginine–glycine–aspartic acid (RGD) peptide coating to enhance cell attachment and proliferation over Ti surfaces, and significantly enhancing cell adhesion and proliferation compared to the untreated ones.[92] Similarly, cell adhesion and proliferation are all closely connected to biomaterial surface qualities including roughness and wettability.[93,90]. In contrast, extensive research claims that surface roughness results in increased deterioration of titanium surfaces[94-97] since the TiO_2 layer formed on the higher surface can be easily damaged.[94] Plasma treatment is used for TiO_2 deposition in many electrical devices and also as a photocatalytic agent.[98, 99] However, there has been very limited research to investigate the impact of CAP on implant surface deterioration.

CAP is also used to modify organic materials such as polysaccharides, proteins as well as polysaccharide/protein composite-based films, which help change the structure and properties of these materials.[100] For example, CAP has been used to improve the adhesion property of polylactic acid to increase surface wettability, surface energy and surface roughness.[101] Similarly in another study, poly (L-lactide acid) (PLLA) and poly-4-methyl-1-pentene (PMP) were treated with CAP to increase surface wettability, alter the morphology, chemical structure of the surface and electrokinetic (zeta) potential of the materials, which in turn helped improve cell adhesion and proliferation.[102] CAP treatment can also help reduce the agglomeration of nanoparticles and improve material properties. For instance, it has been demonstrated that an increased concentration of polydopamine particles resulted in the agglomeration of nanoparticles, thereby leading to decreased tensile strength and visible defect in the matrix and subsequent breakage,[103] CAP helps convert these agglomerates into coatings that are less thick[104-106] and helps achieve excellent cell adhesion.[107] Research has shown that cold plasma may reduce agglomeration and uniformly disperse nanoparticles, as in an experiment for the deposition of silver nanoparticles on titanium nanotubes utilising the plasma approach. By the experiment they were determined to accomplish correctly distributed and non-agglomerative nanoparticle distribution on the surface of titanium nanotubes. The use of cold plasma

treatment assisted achieving the desired result of optimum dispersion and size of silver nanoparticles.[106]

2.3 **The application of polydopamine in dental implants**

Polydopamine, a mussel-inspired biopolymer with exceptional properties, is frequently employed in biomedical applications as a possible chemical for attachment or as a sticky layer of various biological and synthetic molecules.[108, 109] Mussels have a high adhesive characteristic that enables them to endure severe shear stress caused by water movement. In the many mussel foot proteins secreted during the sticky growth of the mussel byssus adhesive plaque The presence of 3,4-dihydroxy-L-phenylalanine (DOPA) and lysine amino acids in these foot proteins raises the possibility that the combination of catechol (DOPA) and amine (lysine) groups is essential for robust interaction. Polydopamine (PDA) (**Figure 2.2**),[109-111] which contains both catechol and amine groups is used to modify various implant surfaces.

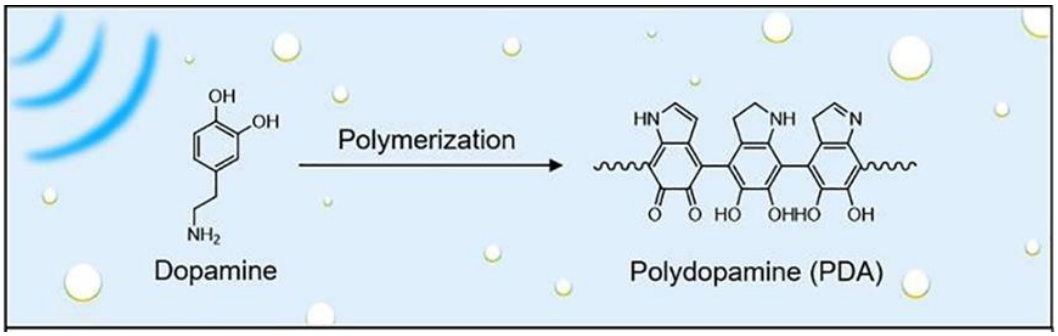


Figure 2.2 Chemical structure of polydopamine formed from dopamine after polymerisation.[110] Reproduced with permission from creative commons.

PDAM coatings are widely used in many studies to increase the properties of dental implants making them capable of fighting off bacteria,[112, 113] acting as drug carriers,[114] resisting corrosion,[115] promoting osseointegration,[116, 117] and being ecofriendly.[118] While PDAM has a number of key advantages, it must be utilised correctly particularly when increasing the concentrations and sizes of PDAM particles can cause cytotoxicity.[119] The agglomerative character of PDAM effects the material characteristics such as weaken the antibacterial

effect.[120] A recent study on the antibacterial and biological effect of PDAM-coated titanium substrate subjected with metal ions like Sr^{2+} Cu^{2+}, Ag^{+}, or Zn^{2+}, demonstrated that while Cu and Ag showed a significant antibacterial effect by inhibiting the adhesion of Escherichia coli and *Staphylococcus aureus* strains, they decreased the cell function, as evidenced by suboptimal cell viability and differentiation.[113] It would therefore be of value to know if the plasma treatment can improve the biological characteristics of a Cu-PDAM composite materials.

2.4 **The antimicrobial action of copper**

Cu is a well-known alloying element in metals and an essential trace element in the human body,[121] where it is involved in glucose and lipid metabolism as well as the creation of several enzymes *in vivo*. The unique structure, large surface area, exceptional mechanical and thermal durability, and optimal optical, magnetic, and catalytic capabilities[122] of these copper nanoparticles have contributed to their broad applications. These nanoparticles can be made at a reasonable cost, easily at room temperature, utilising environmentally friendly technologies with no or little synthetic ingredients. The applications of Cu nanoparticles are increasing substantially in numerous science and technology domains, including health, biotechnology, electronics, energy, and the environment. For example, Cu nanoparticles are widely used in the medical field to treat ailments such as diabetes, cancer, osteoporosis, and osteoarthritis.[122] Similarly, Cu nanoparticles have been used in the dentistry profession to improve the physical and chemical characteristics of numerous restorative dentistry such as dental amalgam, corrective cements, obturation materials, dental implants, as well as orthodontic arch wires and brackets.[123] Apart from having good mechanical and chemical properties, Cu nanoparticles are effective antibacterial, antiviral, anti-inflammatory and antifouling agents. The antibacterial effect of Cu against microbes has been studied extensively to show the aggregation of Cu nanoparticles alters the permeability of bacterial cell membranes which eliminates LPS, membrane proteins, and proteins in the bacterial cell membrane, and results in the dispersion of proton-motive energy on the membrane. The post-oxidative damage to cell structure occurs as a result of the activity of oxygen species such as nanoparticles or ions. The absorption of ions created by nanoparticles in the cell reduces the formation of intracellular adenosine triphosphate and deoxyribonucleic acid (DNA) replication.[124, 125] (**Figure 2.3**).[126]

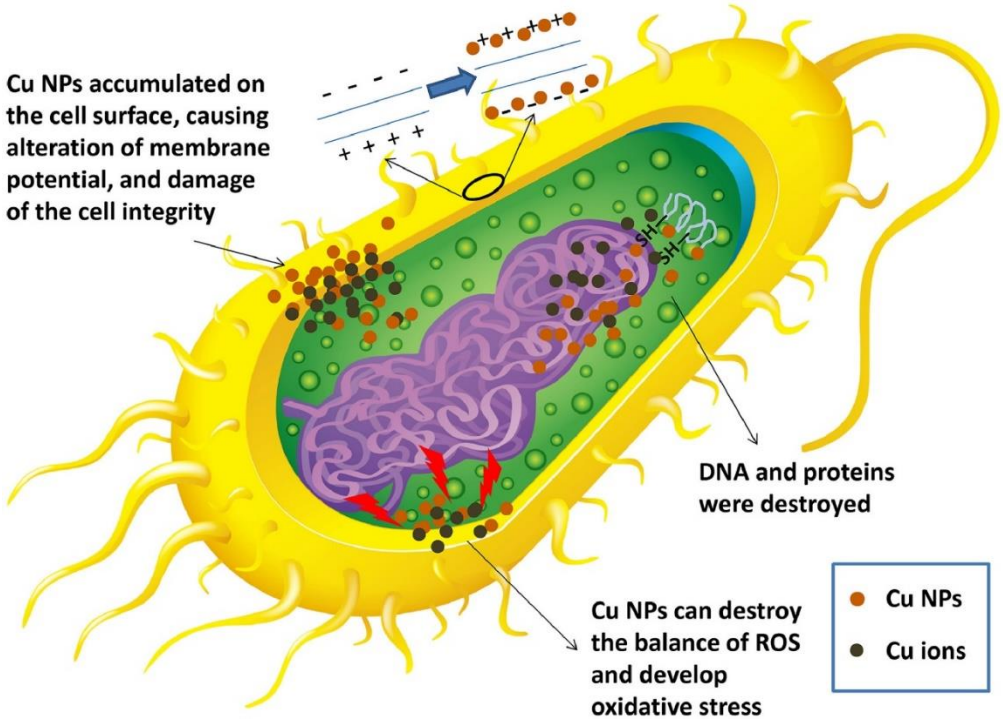


Figure 2.3 The antibacterial mechanism of copper nanoparticles.[126] Reproduced with permission from Elsevier and Copyright Clearance Centre.

Many studies have examined the antibacterial properties of Cu nanoparticles (**Table 1**). Zhuang. Y et al., for example created a copper-containing titanium alloy that released Cu^{2+} in a continuous and steady manner. Ti6Al4V-Cu was shown to efficiently destroy MRSA and limit biofilm formation *in vitro*.[127] Similarly, another study examined the osteoconductive and antibacterial characteristics of a titanium-copper-nitride (TiCuN) film and demonstrated the TiCuN film could prevent bacterial biofilm development on orthopaedic implants and increase osteoblast activity,[128] identifying that copper helps in protecting the surface from microbial action.[35]

Table 1 Studies using Cu as an antibacterial agent

Type of copper used	**Bacteria**	**Method**	**Outcome**
[Cu(bitpy)(dmp)] $(NO_3)2$ - Complex 1 $[Cu(bitpy)_2]$ $(ClO_4)_2$ - Complex 2	*Staphylococcus aureus*		Both Complex 1 and Complex 2 have inhibitory effect on *Staphylococcus aureus*, whereas complex 2 has higher *anti-staphylococcus* activity.[129]
Different copper (Cu) sources, e.g., copper acetate (CuAc), copper sulfate (CuS), and copper oxide (CuO)	*Streptococcus sanguinis*	Using bioactive components (calcium and phosphorus) and various copper, plasma electrolytic oxidation creates antibacterial coatings on titanium	Coating with CuAc displayed ideal hydrophilicity, pore density, and minimal surface roughness among the different copper complexes, resulting in the most potent antibacterial activity paired with suitable responses of human primary stem cells and angiogenic cells.[130]
Copper-containing titanium alloy (Ti6Al4V-Cu)	*methicillin-resistant Staphylococcus aureus*	Released Cu^{2+} to break the cell membrane of bacteria	Limited biofilm formation.[127]

Cu nanoparticles can also target the viral genome, specifically the genes that cause viral infections. Viruses are particularly prone to Cu nanoparticle-induced damage because, unlike bacteria and fungi, they lack a repair mechanism, resulting in immediate cell death, often known as "contact killing." Several investigations revealed a similar reactive oxygen species mechanism in the viral envelope or capsid, which is comparable to antibacterial action. Many researchers are attempting to create materials coupled with Cu to increase antiviral properties

for various viral illnesses such as dengue virus,[131] influenza virus,[132] and the most recent SARS-CoV-2.[133-135]

Copper, in addition to antibacterial and antiviral activity, is a good source for promoting wound healing, found to induce new blood vessel creation and improve wound healing. A recent study conducted by Li et al found that copper-containing alloys Ti6Al4V-1.5Cu promote angiogenesis in both normal and irradiated macrophages,[136] with many other studies conducted to demonstrate the effectiveness of copper in wound healing.[137-139]

As listed above, many studies use different techniques to reduce the deterioration and increase the osseointegration of dental implants. But limited studies showed the application of CAP to mitigate the degradation of titanium along with Cu and PDAM. Despite the usefulness of PDAM and CU being established several years ago, they do have many limitations. To overcome these limitations and to increase the life span of dental implants, the modification of titanium was used as a strategy in this study using CAP, PDAM, and Cu.

Chapter 3 Project Design

3.1 Plasma treatment

Commercially pure titanium plates 1 cm ×1 cm (Ti, 0.1mm thickness, Grade Ⅱ) is used in this study. A plasma reactor made from quartz was used for a non-thermal atmospheric dielectric barrier discharge plasma (DBD) treatment, powered by a high-frequency AC power supply (CTP-2000K/L plasma generator Nanjing Suman electronic Co., Ltd., China) with input voltage of about 35 kV and frequency of the power supply ranging from 1-3 kHz.[140] Pure titanium sheets were treated in the reactor chamber placed between the electrode connected to the DBD plasma device with discharge gas air introduced into the quartz reactor at the flow rate of 1 L min^{-1}. Initially three different gases, including argon (Ar), nitrogen (N), and atmospheric (Atm) were used to observe the effect of the plasma.

3.2 Preparation of PDAM and Cu coating

Plasma-treated titanium plates were coated with PDAM and PDAM with Cu solution which was created by combining 1 mg/mL dopamine hydrochloride (DA, Sigma-Aldrich, USA) with copper in Tris buffer (1.2 mg/mL, pH 8.5). $CuCl_2$ at a concentration of 50 μg/mL was used for preparing PDAM@Cu coating.[8] Titanium plates were submerged in various solutions to facilitate polymerisation. The samples were taken from the solution after 24 hours, rinsed three times with distilled water, and air dried. All the plasma treated titanium samples were sterilized with 80% ethanol and subjected to ultraviolet light for 20 minutes before the cell viability assay.

3.3 Surface characterisation

3.3.1 Particle analysis

A TESCAN MIRA scanning electron microscope (SEM) was used to examine the surface morphology of samples before and after coating. The SEM images were collected at 5.0 kV voltage with a beam intensity of 12.0 and a view field of 100 μ *100 μ. Image J software was used to measure the particles before and after coating. The particle size was compared using

GraphPad, and outliers were removed using the prism programme ROUT technique with Q=0.1%.

3.3.2 Hydrophilicity measurement

The hydrophilicity was measured after the atmospheric plasma treatment and prior to coating using a Biolin Theta Flex drop shape analyser. Three different samples were used to take the average value of the water contact angle and ImageJ software was used to measure the angles of the different samples.

3.3.3 X-ray photoelectron spectroscopy

The chemical contents of the samples before and after coating were determined using X-ray photoelectron spectroscopy (XPS, Kratos Axis Supra, UK). The XPS device used a monochromatic Al Kα (1486.6 eV) X-ray source that ran at 12 kV×15 mA at a pressure of 2×10^{-7} Pa with charge compensation.[141]

3.3.4 Atomic force microscopy

Surface roughness was assessed in contact mode using Bruker Dimension Icon Atomic Force Microscopy (AFM). The AFM images were generated by scanning three 5 μm × 5μm regions in the sample and analysing them after adjusting for plane tilt to determine Ra values for average roughness before and after coating.

3.4 Cell proliferation

Human gingival fibroblasts (HGFs) cell line was routinely passaged, and passage number 7 was used for the experiments as follows.[8] The MTT test was used to examine the coating's direct effects on HGFs. The cells were seeded on the titanium surface at a density of 2×10^4/mL. On days 1, 3, and 5, following cell seeding, a 1:9 solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added and incubated at 37 ºC for 4 hours before adding DMSO and measuring absorbance at 490 nm.

3.5 Coating degradation

3.5.1 Inductively coupled plasma optical emission spectrometry

Samples were exposed to various CAP gases (Ar, N, and ATM) and submerged in saline and LPS solutions during 5 and 10 days, respectively. 1mL of solution was collected after 5 and 10

days and utilised for further testing. After overnight evaporation at 80 ˚C, the solution was diluted to 2% and analysed using PerkinElmer Optima 8300 ICPOES. The quantity of copper in 4 cm^2 was estimated using the copper removed from the coating.

3.5.2 **X-ray diffraction**

Samples for XRD were prepared using Ti of 2 cm × 2 cm size. After plasma treatment and coating with PDAM@Cu, the Ti plates were immersed in saline and LPS for 10 days. A Rigaku SmartLab XRD was used to detect the different crystalline materials in the surface coating.

3.6 **Statistical analysis**

The results were reported as the ± mean standard deviation. P values were computed for statistical assessment using one-way analysis of variance (ANOVA). $p<0.05$ is regarded as statistically significant.

Chapter 4 Results

4.1 Surface characterisation of cold plasma modified titanium

XPS measures the elemental composition as well as the chemical and electronic state of atoms within the titanium. The XPS data revealed that Ti, oxygen (O), carbon (C) and nitrogen (N) exist in the coatings treated with the different plasmas (**Figure 4.1** a). Binding energy shifts in the samples treated with atmospheric plasma are seen in the Ti core level (**Figure 4.1** b) which indicates changes in the surface chemistry. Peak shifts in XP spectra are associated with chemical states of elements with differing formal oxidation states.[106] The Ti 2p 3/2 peak for Atm plasma was seen at approximately 457.8 eV which indicates that it originates from the Ti^{4+} oxidation state.[142] Of the different oxidation states of titanium, Ti^{4+} is the most stable state.[143] The titanium oxidation state in titanium dioxide, which helps in corrosion resistance, is +4. Supporting the data it is evident that there is a peak shift for the O1s (**Figure 4.1** c)after ATM treatment which is in the range of 530.4 eV which indicated the presence of metal oxide layer of TiO2.[144]

An increase of surface roughness of the titanium samples after different plasma treatments is visible in the AFM images (**Figure 4.1** d) and substantiated by quantitative root mean square average (R_q)values (**Figure 4.1** h) for the roughness. Of the four different cold plasma treatments used, the titanium surface modified with atmospheric plasma exhibits the greatest surface roughness with R_q values ranging from 40.4 nm to 79.3 nm. The R_q values of samples with nitrogen range from 44.9 nm to 59.2 nm, with argon from 32.9 nm to 41.8 nm, and untreated titanium ranging from 25.7 nm to 31 nm. Based on the hydrophilicity measurement using water contact angle, this study revealed the increase in surface roughness correlates with an increase of the wettability of material. Specifically, the atmospheric plasma and nitrogen-treated samples have increased wettability compared to the other two cold plasma treatments evidenced by a decrease in the water contact angle (**Figure 4.1** e f) from 105.95—111.84 (Ti) to 63.45˚ - 71.38˚ (Atm), and 65.43˚ - 69.26˚ (N). Surface wettability increases with decreasing contact angle, and a surface is considered hydrophilic with the angle less than 90.[145] The argon-treated surfaces exhibited water contact angles ranging from 74.47˚ to 78.82˚ which, compared to the control titanium, showed an increased wettability. This result establishes that different

plasma exhibited different values in surface wettability, and that they all help in increasing surface wettability.

The sample morphologies were detected by SEM (**Figure 4.1** g). Representative SEM images of the samples treated with atmospheric plasma reveal the most prominent changes in the surface morphology.

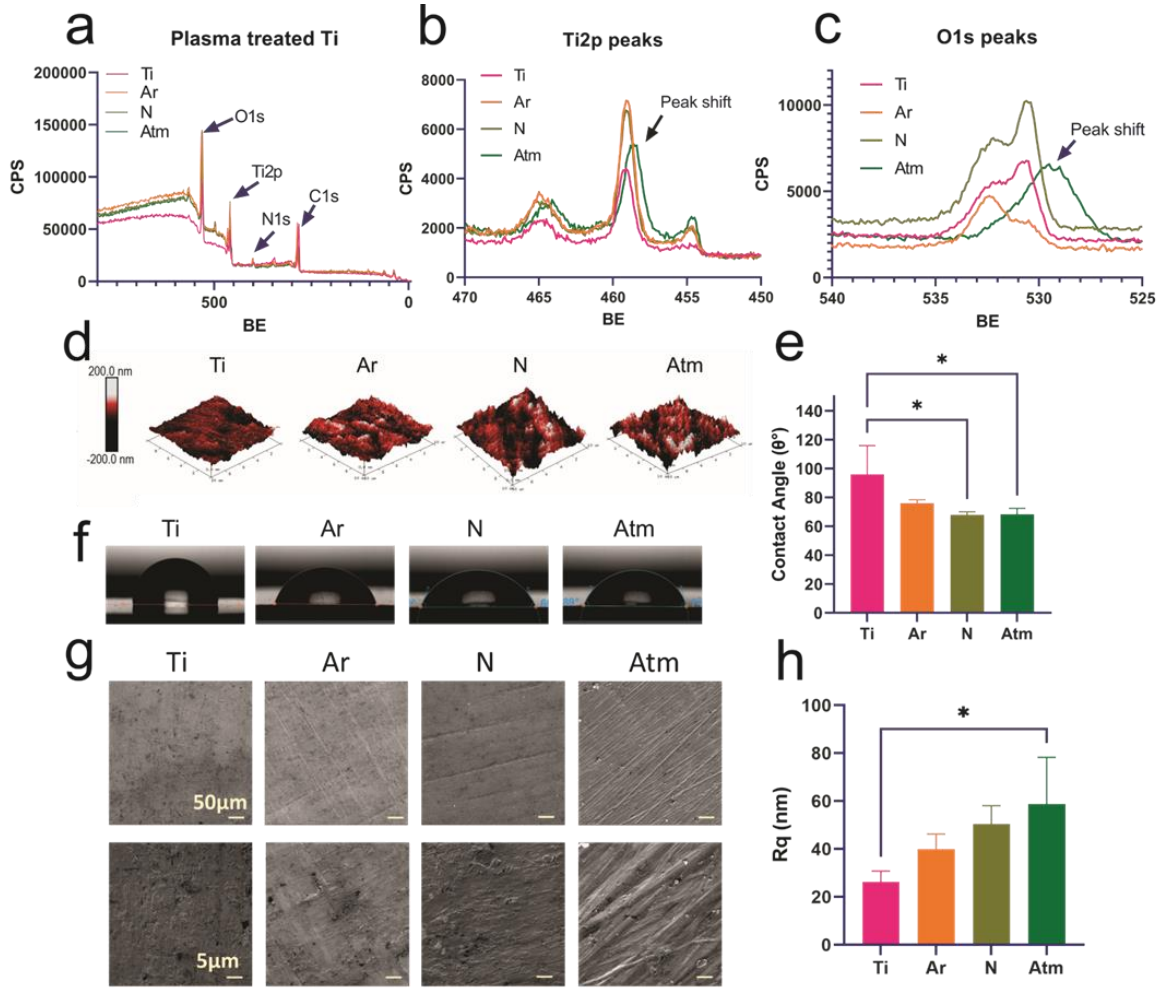


Figure 4.1 Surface characterisation of titanium surfaces after different plasma treatments showed changes in surface chemistry with atmospheric plasma treatment. (a) XPS wide spectra with relevant peaks of Ti, O, C and N annotated, (b) magnified peaks of Ti, and (c) O1s peaks revealed peak shift in sample treated with atmospheric plasma indicating changes in surface chemistry. (d) AFM images and (h) quantification with R_q values for surface roughness showed an increase in surface roughness on samples treated with atmospheric plasma. (f) Images and,

(e) quantitative measurements of water contact angle showed significantly increased hydrophilicity in samples treated with nitrogen and atmospheric plasma. (g) SEM images showing changes in surface morphology. *p<0.05, **p<0.01, ***p<0.005, ****p<0.001.

4.2 **Surface characterisation of cold plasma modified titanium after coating with PDAM and Cu.**

The morphology of samples treated with different plasmas and followed by PDAM and PDAM@Cu coating was characterised with SEM (**Figure 4.2** a b). The images revealed changes in the coatings after plasma treatment. The The particle size difference can be seen in samples treated with different plasma before and after coating with copper in **Figure 4.2** c and **Figure 4.2** d. The atmospheric plasma treated surfaces had larger particles occupying larger areas of surfaces in both **Figure 4.2** e and **Figure 4.2** f which show the PDAM and PDAM@Cu coated surfaces, respectively. The surface roughness of different samples after coating with PDAM was identified using the AFM (**Figure 4.2** g). Changes are noted on the sample surface after coating, as evidenced by higher roughness compared with the non-coated ones (**Figure 4.2** h). The surface roughness is more visible on titanium surfaces treated with nitrogen and PDAM followed by those treated with argon and Atm. These results signify that different plasma treatments have different effects on the particle size of PDAM. **Supplementary Figure 1** shows the EDS data and XPS of samples after the coating. Atm treatment has changed the particle size and the particles were able to cover the roughened surface of the samples, making the surface less roughened.[146]

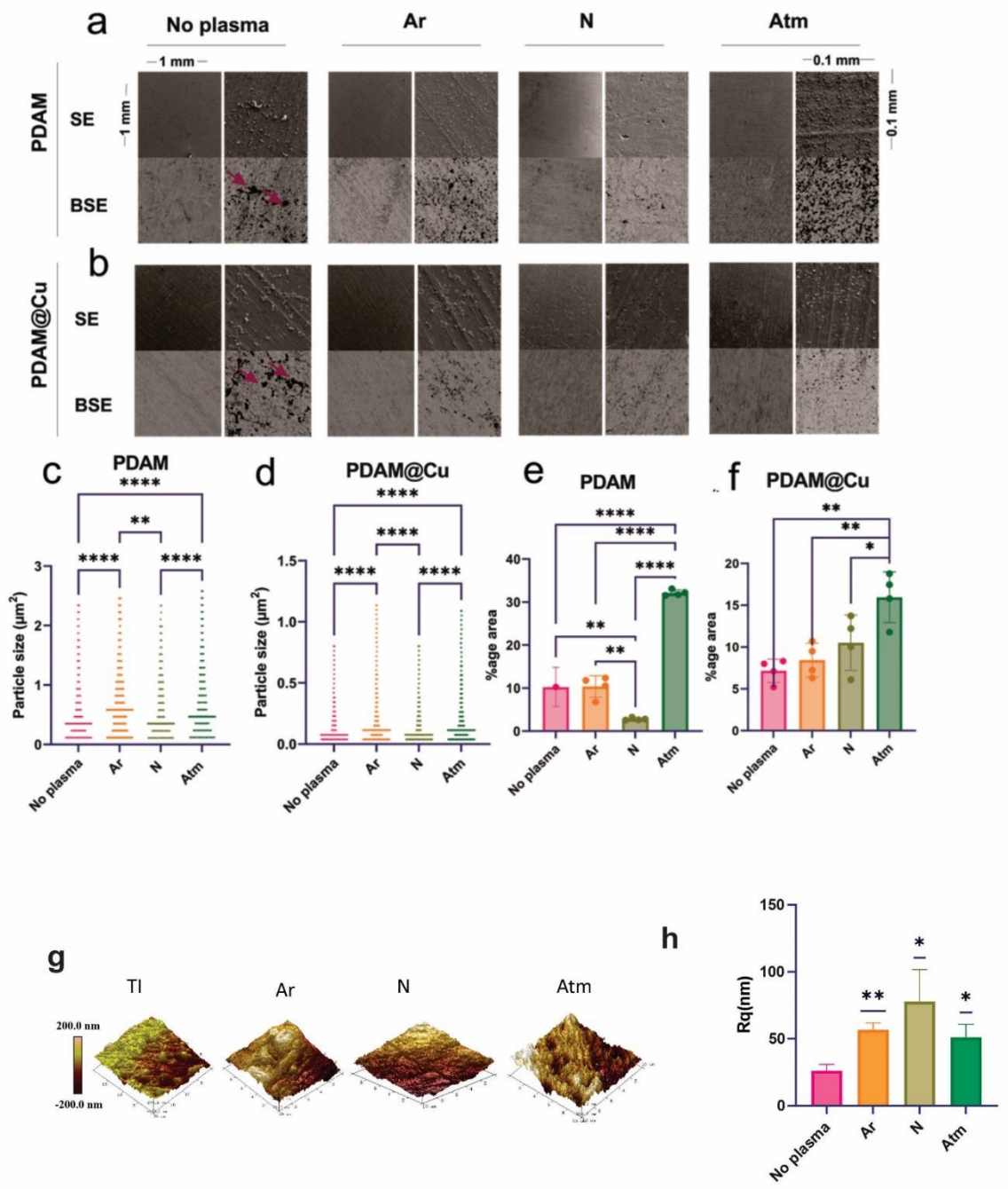
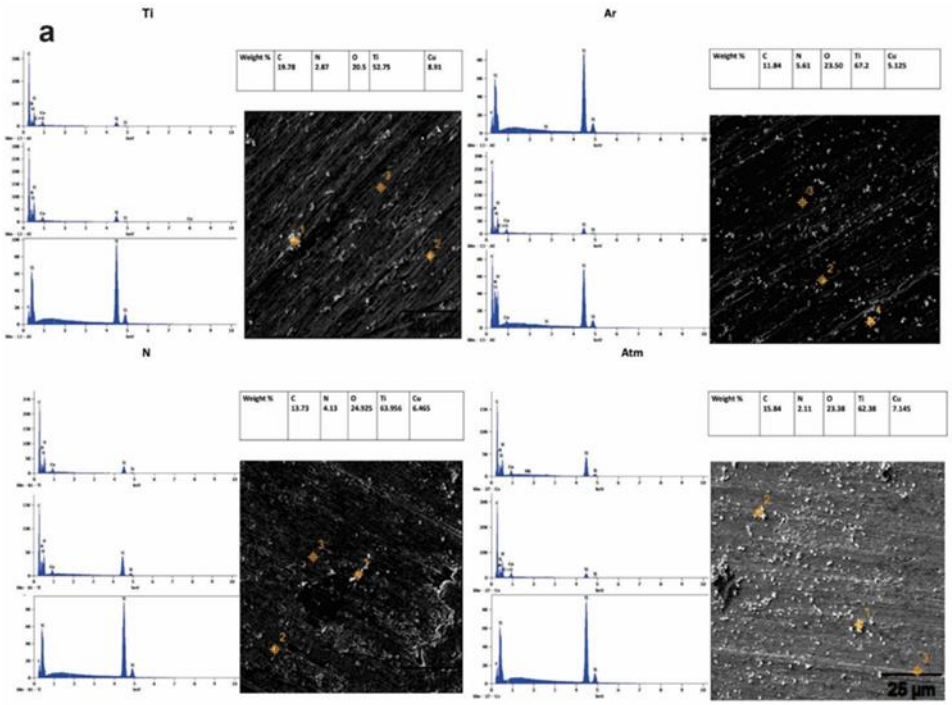
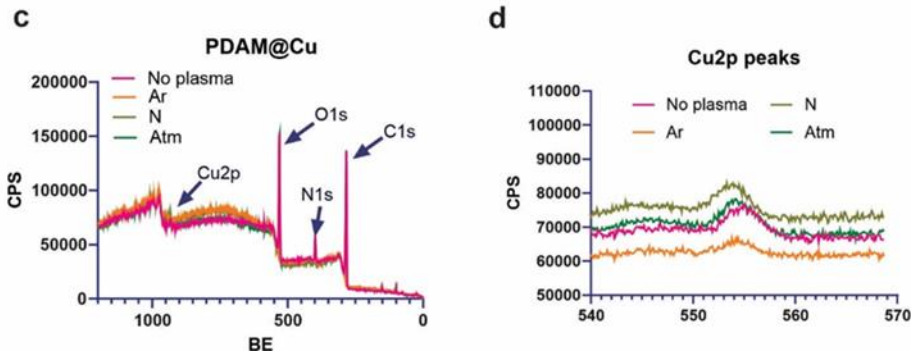


Figure 4.2 Surface characterisation of plasma modified titanium after coating with PDAM and Cu. SEM and backscatter images of (a) PDAM and, (b) PDAM@Cu coatings deposited on various plasma treated surfaces. 1 mm^2 (left) and 0.1 mm^2 (right) area scans revealed changes in coating deposition after plasma treatment. Arrows point to aggregated particles seen on surfaces that were not treated with plasma before coating. Particle size analysis in (c) PDAM coatings and, (d) PDAM@Cu coatings revealed that atmospheric plasma treated surfaces had larger particles occupying larger areas of surfaces in both (e) PDAM and, (f) PDAM@Cu coated surfaces. In (c) and, (d) each scatter dot represents area of particles analysed from at least 3 different images with outliers removed (q=0.1). In (e) and (f), values are mean percentages from 4 areas of 500 μm^2 analysed. AFM images (g), and the R_q roughness value (h) indicating reduced surface roughness in Atm plasma treated samples. *p<0.05, **p<0.01, ***p<0.005, ****p<0.001.



b

	C	N	O	Cu
No plasma	76.02 ± 1.63	5.12 ± 0.53	18.68 ± 1.13	0.17 ± 0.04
Ar	78.02 ± 3.19	4.11 ± 0.92	17.75 ± 2.43	0.13 ± 0.03
N	74.58 ± 0.32	5.58 ± 0.38	19.73 ± 0.41	0.17 ± 0.01
Atm	74.61 ± 0.73	5.54 ± 0.42	19.76 ± 0.76	0.14 ± 0.03



Supplementary Figure 1 Supplementary data of (a) EDS spectra, (b) at%, (c) XPS wide spectra and, (d) magnified Cu peaks of PDAM@Cu coatings.

4.3 **Cell proliferation on coating**

Ti samples treated with Atm and coated with the PDMA, and copper (PDAM@Cu+Atm) showed a small increase in cell proliferation and cell attachment relative to the control (Ti) samples. This pattern was visible from day 1 to day 5 (**Figure 4.3**). Followed by PDAM@ Cu+Atm, samples treated with PDAM Atm showed more cell viability than the control group Ti. This result confirms the fact that plasma modification helps to increase cell viability of the samples.[147, 148] Therefore, the surface modification with CAP and PDAM@ Cu did not negatively effect the viability of HGFs.

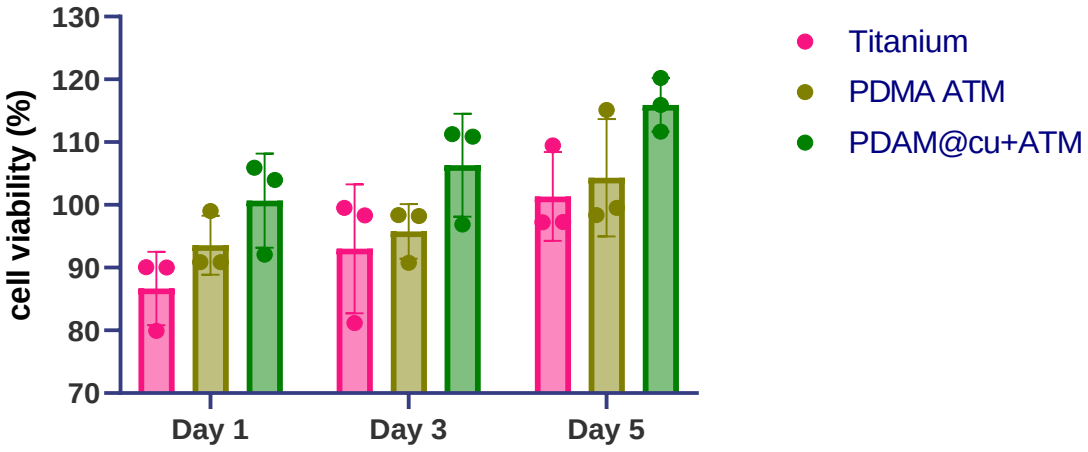


Figure 4.3 Results from the MTT assay showing Atm+PDAM @ Cu samples promoted cell proliferation in a time-dependant manner.

4.4 **Coating degradation**

4.4.1 ICP-OES

ICP-OES is an analytical method used to determine the atomic composition of a material and effectively detects the type and relative amount of each element within a compound by using

the unique photophysical signals of each element. This project focused on the presence of Ti and Cu.

The presence of Ti and Cu were analysed after immersion of samples in saline and LPS for 5 days and 10 days using the ICP-OES (**Figure 4.4**). The concentration of Ti in the degraded solution was below the detection limit in the samples coated with copper whereas Cu concentration was seen in different samples coated with Cu. On day 5, the PDAM@Cu coated samples immersed in saline showed the highest release of Cu whereas the lowest release value was seen in the samples pre-treated with Atm. Similar findings were shown when the samples were immersed in an inflammatory microenvironment. Similarly, it is visible that Ti peaks are reduced in the coated samples compared with the control, indicating that copper helps less to expose the titanium surface for corrosion (**Supplementary Figure 2**). All these results suggests that Atm plasma may help to reduce the degradation of the titanium samples. These results guided this study to focus only on the atmospheric plasma.

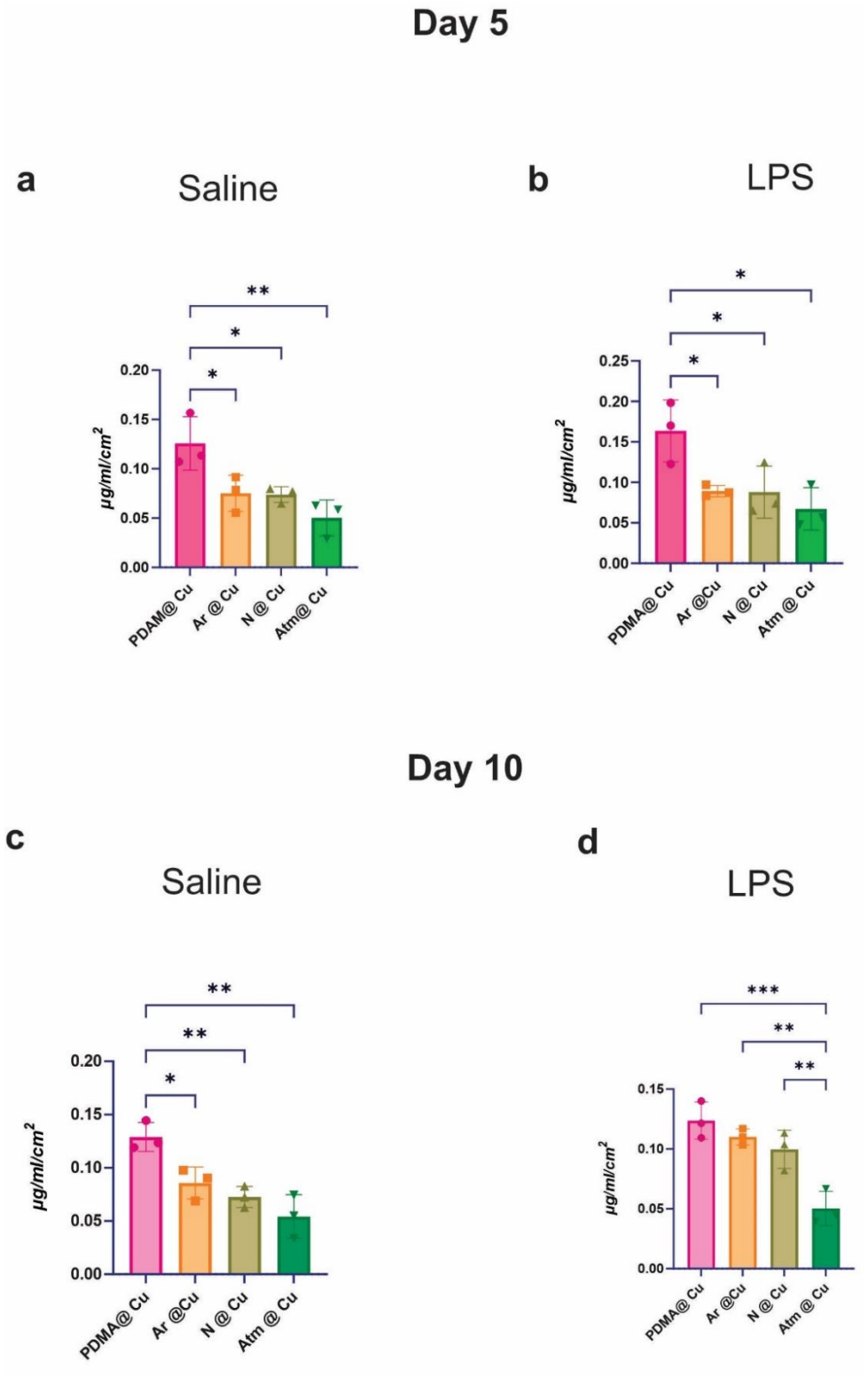
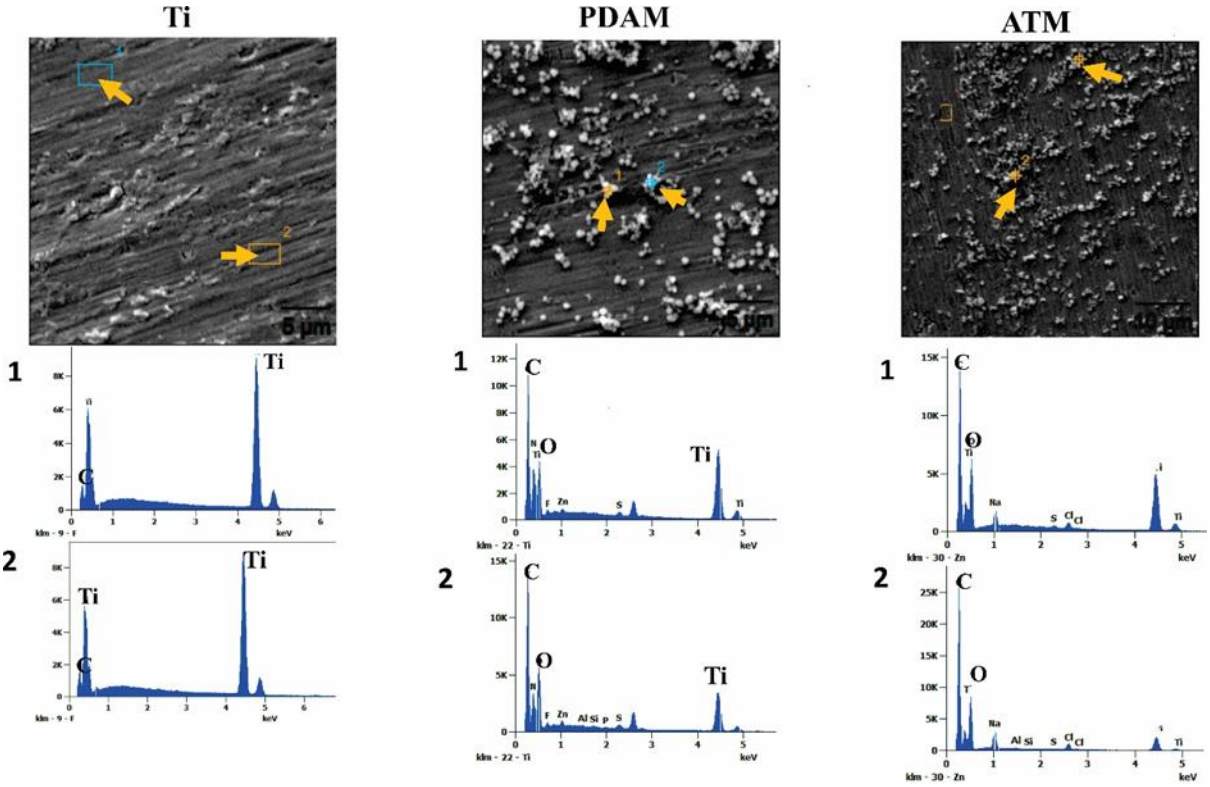


Figure 4.4 Quantitative measurement of ICP-OES data for samples immersed in saline (a, c) and LPS (b, d) for 5 and 10 days showing reduced copper release from atmospheric plasma-coated samples.



Supplementary Figure 2 EDS data and SEM images after degradation

4.4.2 XRD data

Figure 4.5 shows XRD patterns collected from the Ti samples after degradation for 10 days. The Ti and TiO_2 phases are the major phases evident in the four different samples. Peaks that are sharp in the XRD pattern indicate the crystalline materials, whereas short and broad-bumped peaks indicate amorphous material. The results suggest that apart from the crystal phases, the amorphous phase of polydopamine coating was present in all samples.

In both uncoated PDAM samples treated with ATM plasma, immersed in saline (**Figure 4.5** a) and (**Figure 4.5** c**)** immersed in LPS solution showed the Ti peak (101) with maximum intensity at a 2θ angle of 40˚, although there is a decrease in the peak of the copper coated PDAM samples (**Figure 4.5** b d) compared with the non-coated ones. In these samples there is a stronger Ti signal in untreated samples because the Ti signal is not attenuated by the coating. Similarly, the change is visible in the peaks of TiO_2. The formation of the TiO_2 peak indicates the surface has entered a passive condition of titanium. Passivation thickens the TiO_2 layer, increasing the material's resistance to corrosion.[149] The presence of this thin passive layer converts modified Ti into a physiologically inert metal. Overall, the coated and uncoated

samples show a change in the broadening peaks of the XRD patterns. The degraded coated samples show a decrease in peak intensity and sharpness in both the Ti peaks (100, 002, 101, 110, and 103) and the TiO_2 peaks (111, 200, 220 and 311). The coated samples have visible Cu peaks corresponding to 111, 200, 220, 222, 400, 420 and 422, showing the cubic nature of Cu particles. These results suggest that modified Ti samples have a greater degradation resistance in both physical (saline) and inflammatory microenvironment (LPS).

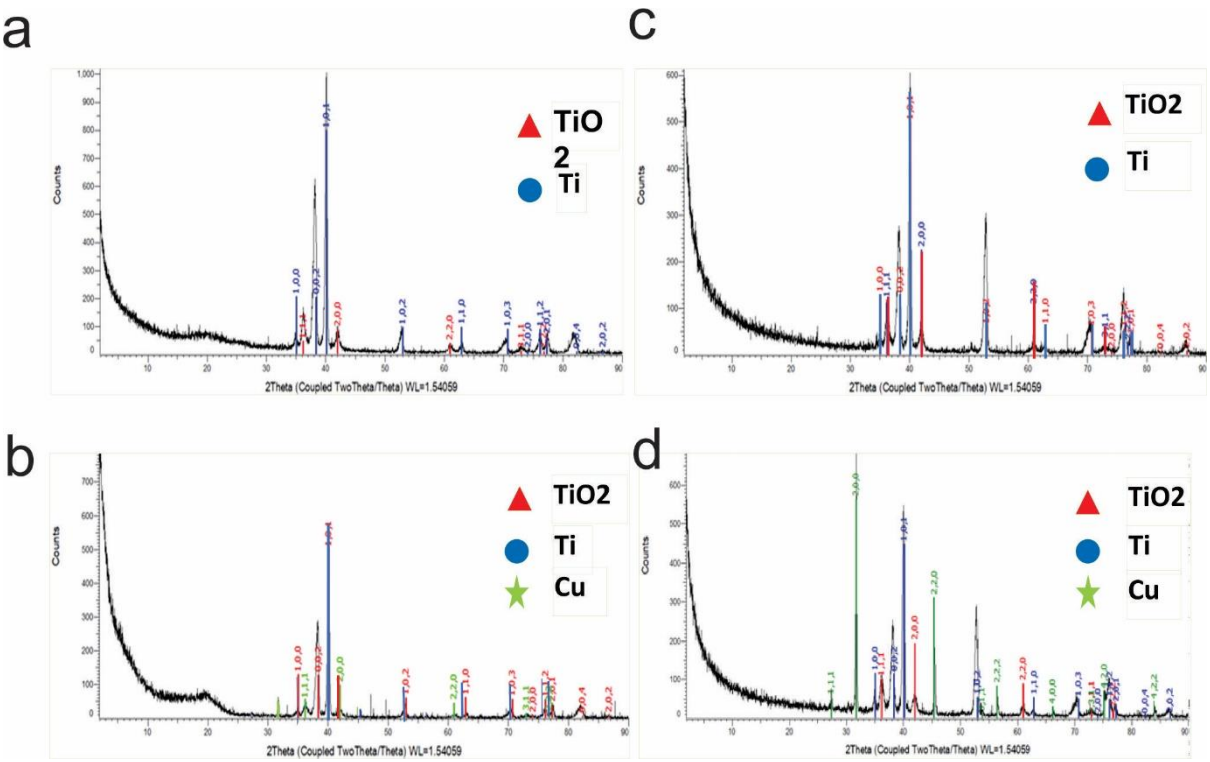


Figure 4.5 shows the XRD patterns formed on the samples after degradation. (a) Uncoated Ti immersed in saline, (b) coated samples immersed in saline, (c) uncoated sample immersed in LPS and, (d) coated samples immersed in LPS.

Chapter 5 Discussion

Titanium is a popular material for medical and dental implants because to its biocompatibility, strength, and longevity.[150]Although titanium is recognised for its remarkable corrosion resistance, it is not totally impervious to deterioration over time.[151] When a titanium implant is implanted in the body, LPS can be generated by any bacteria present in the surrounding tissues, causing an inflammatory reaction that can compromise the device's integration and success[152, 153] by accelerating the degradation process.[20] Several research are being conducted to decrease titanium deterioration, one of which is surface modification.[5, 154] This study found that modifying titanium surfaces using CAP, PDAM and Cu helped reduce titanium degradation under the action of LPS *in vitro*, and increased cell viability was also visible. Similar to prior investigations,[8, 155-157] the results show that this multifunctional surface modification strategy improves the performance of titanium surfaces.

The multifunctional technique of modifying the titanium surfaces helped to elevate the hydrophilicity and surface roughness and reduce the particle agglomeration to achieve a uniform dispersion of the PDAM particles. Improving implant surface roughness and hydrophilicity can increase biocompatibility and osseointegration[158] while also improving antibacterial characteristics.[159] Surface roughness in the range of 10-100 nm has been proven in studies to increase cell adhesion and proliferation.[160, 161] It was evident throughout this study that different gases used in CAP treatment showed better outcomes when compared with the untreated titanium surface. Of the three different gases Ar, N and Atm, the Atm treatment showed a better result. Titanium coated with Atm showed increased surface roughness, which is within the limits of 100nm, increased surface wettability and a more stable TiO_2 layer, with all these properties being essential for better osseointegration and implant success.

Cold plasma treatment helped to modify the PDAM which is a universal adhesive material. This modification using plasma reduced the agglomerative character of PDAM. Polydopamine particle agglomeration can have a substantial impact on their adhesion capabilities and capacity to enhance adhesion between diverse materials. Agglomerated particles can result in uneven and non-uniform coatings, which reduce adherence and performance.[162] Additionally, the modified PDAM, with the aid of CAP, helped increased the binding of the copper ions to the titanium surface. The controlled and optimised coating of copper can assist in striking a balance between the favourable and harmful effects of copper coatings on titanium surfaces.[163] The

higher concentration of copper ions can result in toxicity. Following earlier research, the lower concertation of copper was chosen in this investigation.[8] Thus, the cell viability on the modified samples showed significant differences compared with other studies where increased copper concentrations lead to reduced cell viability. With the help of the plasma treatment and use of an ideal Cu concentration, there was an increase in cell viability of HGFs on the PDAM@Cu+Atm sample. The addition of Cu helped reduce the corrosion of the titanium surface. However, the antibacterial efficiency of this modified surface is yet to be studied along with the copper ion release.

Finally, the TiO_2 layer formed on the surface helped to build greater corrosion resistance to the titanium surface even with the presence of LPS. The existence of a stable and well-formed titanium oxide layer is vital for the prevention of corrosion of titanium.[164] The plasma treatment helped reduce the copper release from the surface, which highlights the potential wider applications of the coating in the manufacturing of highly corrosion-resistant implants. Ions released by the coatings into the surrounding tissues can have therapeutic effects such as encouraging bone formation and lowering inflammation.[165] The surface degradation study can be extended for a longer period to evaluate the maximum duration of coating protection along with the action on lowering inflammation and bone formation as well. It is an *in vivo* study that is also required to investigate the osseointegration and function of the modified titanium implants.

Chapter 6 Conclusion

This research demonstrated that a Ti surface modified with CAP, PDAM-Cu helped to successfully control the degradation of the Ti surface with no negative impact on cell viability. The cold plasma treatment on titanium surface has the potential to significantly improve the characteristics and performance of polydopamine and copper coatings. The adherence, surface characteristics, degradation, and release of the coating may be adjusted to individual applications and demands by modifying the plasma treatment settings. This approach can be translated to prevent the dental implant failure followed by the degradation by the bacterial action which remains a significant problem in clinical dentistry. This novel method can be developed further to incorporate biofilm dispersion and decontaminating from bacteria in a multifunctional coating. This strategy can be applied to prevent peri-implantitis and increase the successful rate and longevity of dental implants. The CAP treatment helped to reduce PDAM particle agglomeration, and its use can be expanded to new fields where it has not previously been employed owing to this drawback. As previously indicated, the antibacterial, osseointegration and long-term copper release properties of this modified material should be investigated.

Appendices

1.1 Publication

1. Vijay, R., Mendhi, J., Prasad, K., Xiao, Y., MacLeod, J., Ostrikov, K., & Zhou, Y. (2021). Carbon nanomaterials modified biomimetic dental implants for diabetic patients. *Nanomaterials*, *11*(11), 2977.

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