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# Applications of Chitosan in Dental Implantology - A Literature Review

Review Article

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## Abstract

Dental implants are commonly resorted treatment options for prosthetic rehabilitation of the missing tooth albeit being successful, the titanium implant surface exhibits poor bioactivity and antimicrobial properties, which could lead to primary and secondary early, implant failure. The unique properties of chitosan, a natural bioactive material, could be used as a coating for stabilization of the implant and the integration at the bone–biomaterial interface. It has received significant attention in the medical/dental field to explore its potential to enhance osseointegration function and clinical performance of the implant. This review aims to shed light on chitosan and their performance as a bioactive coating on implant surfaces.

**Keywords:** Titanium Implant; Chitosan; Coating Surface; Functionalization; Osseointegration.

**Abbreviations:** kDa – Kilodalton; IL – Interleukin; Ti – Titanium; DDA – Degree Of Deacetylation; BMP – Bone Morphogenic Protein; PMN - Polymorphonuclear Leukocytes; CaP – Calcium Phosphate Coating; MDA – Malondialdehyde; HPX - Hydroxyproline; TNF α – Tumor Necrosis Factor – Alpha; PDGF- Platelet Derived Growth Factor; PGE2 – Prostaglandin E2; MBC - Minimum Bactericidal Concentration; MAPLE - Matrix Assisted Pulsed Laser Evaporation; PBMT - Photobiomodulation Therapy; HA - Hyaluronic Acid; CMCS - Carboxymethyl Chitosan; SBCS - Sulfated Benzaldehyde Chitosan; GChi - Glycol-Chitosan; CAF - Cancer-Associated Fibroblast.

## Introduction

Dental implants have revolutionized the prosthetic rehabilitation of the tooth, overcoming the limitations of the fixed and removable prosthesis [1]. Osseointegration is the principle behind the longevity and clinical performance of the dental implant. The concept of osseointegration was first put forth by Branemark [2]. The implant substrate gets integrated and has new bone formation surrounding its surface. Over the course of months, about 60–70% of the implant surface is covered by bone. The amount of bone-implant surface contact has been designated as %BIC. This defines the amount of osseointegration percentage and relies on macro and micro topography of the implant material, type of alloy, design, size, surface texture and surgical implantation technique, quality/quantity of the alveolar bone and occlusal loading[3, 4]. Inspite of overly high success rates seen in implant dentistry, commonly used material for implants are titanium (Ti), due to their biocompatibility. However, they do have an effect on their on the implant surface and are not resistant to bacterial attacks which may over a duration of time leads to primary and secondary implant failure such as poor osseointegration, mechanical problems, immobilization, poor oral hygiene, systemic complications, and infection [5]. In order to overcome the limitations, various efforts have been undertaken, including coating the implant surface to enhance their clinical performance is long been thought to enhance osseointegration by mediating the direct interaction to host osteoblasts in bone formation.

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Materials used in dentistry are at a constant phase of evolution, overcoming their existing limitations. Naturally derived biomaterials have excellent properties such as biodegradability, biocompatibility and non-toxic profile, which makes them an ideal substances. Such materials should resemble extra cellular matrix in order to emulate their osteogenic and physiological function. Some of the bioactive materials that have been investigated include starch, collagen, gelatin, alginate, cellulose, elastin and chitosan [6, 7]. Incorporating chitosan represents an ideal choice to enhance their performance. The osteoconductive and osteoinductive property, anti-inflammatory, anti-bacterial and wound repairing mechanism have rendered them to be an ideal coating to enhance bone formation and to prolong the longevity of orthopedic and dental implant devices [8]. In this review, we discuss the latest application of chitosan coating on dental implants.

## Chitosan

Chitosan was first reported by Rougat in 1859 is a cationic polysaccharide is made up of β-(1-4)-linked d-glucosamine and N-acetyl-d-glucosamine in repeated units [9]. It was first detected in the exoskeleton of sea creatures such as shrimp, crabs. Chitosan is the most widely present polysaccharide after cellulose. Apart from marine sources, chitosan can also be extracted from fungi namely, *Aspergillus spp., Rhizopus. Gongronella spp., Absidia spp.*, as they are known to harbor chitosan as their primary cell wall component [10].

Chitin is the raw form of chitosan, is treated to demineralization, deproteinization and decolourization using chemical reagents. Chitin is deacetylated to chitosan. The raw material is a translucent, resilient, highly organized crystalline structure with poor reactivity and low solubility in the aqueous medium. To make them suitable for various applications, the reactive hydroxyl group is chemically modified through carboxymethylation, etherification, Quaternization and precipitation or flocculation. These modifications impart more stability, solubility, lower toxicity and less inflammatory properties [12]. The method of extraction of chitosan determines the degree of deactelyation, and is given by the ratio of GlcNAc to GlcN structural units is an important criterion influencing the physical property such as solubility, viscosity and absorption. The degree of deacetylation confers the molecular weight of the chitosan biomaterials. They could range from low molecular weight (50–190 kDa), medium molecular weight (190–300 kDa) and high molecular weight (310–375 kDa).

Chitosan has been employed as a carrier for drugs, proteins, vaccines through nanoparticles in the biomedical field due to their excellent biocompatibility, non-toxicity, hemostatic, mucoadhesive, antitumor, antioxidant, and antimicrobial properties. The common usage of chitosan in the field of dentistry is given in Table 1.

The coated material on the implant surface should have the potential to withstand heavy masticatory forces. As, the when exceeding the threshold limit, the stress results in delamination and disintegration of the coating along the implant-bone surfaces [46]. Chitosan does not adhere to the implant surface due to its lack of surface reactivity, so they are applied to the implant surfaces in combination with different polymer compounds to amplify the surface conductivity. The optimization of bioactive chitosan coatings requires the intricate knowledge of the mechanisms influencing bioactivity, surface properties, and bonding strength to titanium implants.

## Coating of Chitosan

### Silanization

Silanes are chemical compounds that oxidize the implant surface leaving it rich in hydroxyl groups, this enables the chitosan to chemically bond with implant surfaces to increase coating– substrate fracture resistance. Commonly employed silane chemicals include 3-Aminopropyltriethoxysilane (APTES), isocyantopropyltriethoxysilane (ICPTES) and triethoxysylilbutyraldehyde (TESBA) [47]. The compound reacts with glutaraldheyde groups of the chitosan molecule forming a covalent bond strength of 1.5–1.8 MPa [48]. Ethanol and water due to relatively harmless profile have been examined in deposition of APTES/Chitosan on implant surfaces. It was found that bond strength had significantly increased from mean 0.5 MPa for chitosan simply absorbed to the titanium to 1.5 MPa [49].

Greene et al. used the APTES–glutaraldehyde to coat chitosan onto a 316L stainless steel screw via a dip-coating process. They screwed chitosan-coated screws into solid rigid polyurethane

**FIGURE 1 . Schematic representation of chitin and chitosan [11].**

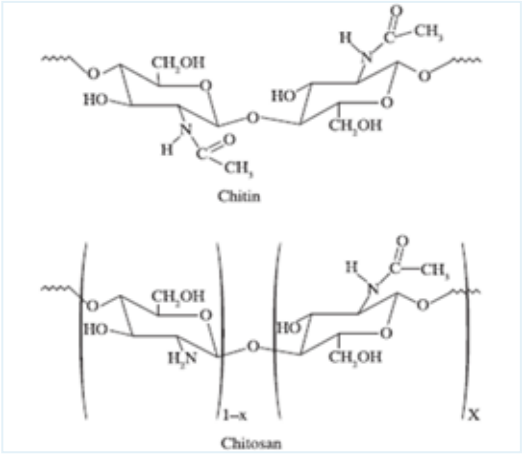

**Table 1. Uses of Chitosan in Dentistry**

| Specialty | Author name | Method of Chitosan Use |
|---|---|---|
| Periodontics | Rahmani F et al. [13] | Chitosan dentifrice |
| | Bae K et al. [14] | Chitosan Mouthwash |
| | Qasim B et al. [15] | Periodontitis |
| | Costa EM et al. [16] | Inhibition of biofilm formation |
| | Akncbay H et al. [17] | delivery of metronidazole |
| | Yeo J et al. [18], Park JS et al. [19] and Ji QX et al. [20] | Bioresorbable membrane in GTR |
| Oral Surgery | Kale et al. [21], Gupta A et al. [22] | Extraction wound healing |
| | Pippi et al. [23] | Surgical bleeding hemostasis |
| | Singh et al. [24] | Bone healing |
| | Değim Z[25] | Increasing tensile strength of wound |
| | Wu Y[26] | TMJ Arthritis |
| | Bousnaki M27[27] | TMJ Disc Regeneration |
| Conservative Dentistry & Endodontics | Tarsi R et al. [28], Fujiwara M et al. [29] | Anti-Cariogenic Agent |
| | Samprasit W et al. [30] , Uysal T [31] | |
| | Arnaud et al. [32] | Tooth Remineralization |
| | Dragland IS et al (Dragland et al. 2019) | Incorporated in zinc oxide eugenol |
| | Schlueter N et al. [33] | Toothpaste for Abrasive enamel wear |
| | Camacho-Alonso F et al. [34] | Removal of smear layers |
| | Kishen A [35] | Root canal irrigant |
| | Surboyo MD et al. [36] | Pulpal Regeneration |
| | Senthil Kumar R et al. [37], Soygun K et al. [38], Mishra A et al. [39] | Incorporation with Glass ionomer cements |
| Orthodontics | Uysal T. [31] | Enamel demineralization surrounding brackets, |
| Prosthodontics | Chander NG et al. [40] | Incorporation in heat cured denture base resin |
| | Namangkalakul W et al. [41], Stenhagen ISR et al. [42] | Antifungal denture adhesive |
| Oral Pathology/Medicine | Adhikari HS et al. [43] | Targeted delivery of the chemotherauptic compound |
| | Mazzarino L et al. [44] | Initation of apoptosis and cell cycle arrest |
| | Potdar PD et al. [45] | Inhibition of tumor progression and metastasis |

foam simulating the density of bone and showed that approximately 90% of the chitosan coating was retained even in hydrated conditions, based on change in mass [50].

Ethylene oxide gas sterilization, DDA of the chitosan, 2% gentamicin in the chitosan solution on titanium or stainless steel surfaces have been explored to increase the bond strength47. Due to the crystalline structure of the chitosan, Nano-indentation methods have been used by Wang SF et al and Majd S et al to investigate the bond strength of chitosan films, however it did not have a significant effect [51, 52]. Martin et al investigated toluene added to APTES onto titanium samples, to increase the bond strength of the chitosan coating to titanium, they observed that the bond strength more than tenfold as compared to the ethanol/water-deposited APTES. This increase in bond strength was attributed to increased silane deposition with toluene solvent as compared to ethanol/water solvent, as measured by X-ray photoelectron spectroscopy [53]. Renoud P et al demonstrated that chitosan coated surfaces were scratch resistant with strong adhesive properties. When tested for bacterial resistance, they showed strong inhibition of *Actinomyces naeslundii* growth and good biocompatibility to fibroblasts [54].

**Electrodeposition**

In this method, an electrical current is utilized to deposit charged material from a conductive solution onto a target surface (the implant surface). Electrodeposition of chitosan particle is relatively inexpensive and allows control of the thickness of the coating on the implant surface [55]. Coatings produced from electrodeposition are dependent on electrolytic medium, the electrical nature of electrodes, particle charge, particle size, and viscosity of the suspension along with the applied electric field [56]. The pH of the suspension affects the particle charge distribution and ionic conductivity of the suspension, which in turn affects the electrophoretic mobility of the particles.

Sputter coated chitosan-calcium phosphate and uncoated titanium pins in a 12-week rabbit model when examined histologically, showed new bone formation and accelerated healing of implant wounds which were identical to the results obtained from controls samples which were uncoated [57]. Electrodeposited CaP/chitosan coatings were found to favour osteoblast differentiation and proliferation from MC3T3-E1 cells, which may endow them with great potential for future application [58].

Panda S et al in 2019, studied the osseointegrative properties of pure Ti-6Al-4V substrates with three different surface roughness

(1.1, 1.9 and 3.1 μm) coated with chitosan and bovine serum albumin successfully by using sol-gel dip coating and electrophoretic deposition (EPD) methods. The coating produced a better coating stability over the Ti substrate than sol-gel dip coating and Chi-BSA conjugate coating demonstrated higher stability and surface texture than only Chitosan coating [59].

Degree of deacetylation was modified and a 91.2% de-acetylated chitosan did not affect the bond strength (1.5-1.8 MPa) when they were sterilized using gas. There was a mild dissolution in the coatings surfaces that were sterilized with gas and the growth of the osteoblast cells was greater on the chitosan-coated samples than on the uncoated titanium. These results indicated that chitosan promotes osteoblast proliferation more than the controls [48].

The latest innovative technique that used for chitosan deposition is the physical vapor deposition method, where a dilute frozen solution of the coating material is vaporized using a pulsed laser. The vapor from the solvent material absorbs the energy of the laser, and is volatilized along with the coating material. The larger vapour molecules are deposited rapidly on the substrate surface. The process provides excellent control over several film coating parameters, including thickness, roughness, and homogeneity. Patz et al. used this technique, matrix assisted pulsed laser evaporation (MAPLE) to coat chitosan onto a titanium wire mesh. The MAPLE chitosan coating showed high coating uniformity on the mesh (demonstrating the ability to coat complex shapes and internal surfaces) and compatibility with cultured bone cells [60].

Layer-by-layer self-assembly techniques have also been used to make chitosan coatings. This technique forms multilayers on the titanium surfaces. A layer of positively charged material (chitosan) is first induced followed by alternate deposition of negatively charged Gel and positively charged material utilizing electrostatic interactions [61]. The technique is a relatively low cost, simple technique that can be performed with minimal equipment at room temperature. The method takes advantage of the static or hydrogen-bond interactions between different kinds of macromolecules. The process results in very thin membranes and coatings that retain the original and desirable properties of the component polymers such as heparin, hyaluronic acid, oxy-chitin, gelatin, and bioglass particles [62].

## Thickness and Concentration of Chitosan Coating

The thickness of the biomaterial coating also plays a significant role in osseointegration. A adequate thickness of the coating is around 30-40 μm, which degraded only after 52 weeks and it exhibited better early bone apposition without any inflammation signs [71]. The smooth surfaces of chitosan microspheres does not show any features for cell attachment. Therefore it was combined with β-TCP to form a β-TCP/chitosan composite microspheres. It was then seeded with murine MC3T3-E1 osteoblasts for evaluating the attachment interaction between cells and materials. It was observed that the adherence and proliferation of osteoblastic cells were significantly better than on chitosan microsphere alone [72].

Chitosan combined with strontium ranelate was evaluated for their bone regenerating capacity on titanium surface in different concentrations of strontium ranelate (SR) (0, 2, 20, 40, and 80 mmol/L of the strontium ion [Sr2+]). SR-loaded chitosan film on a titanium surface promoted significant osteoblast proliferation and differentiation in a dose-dependent manner, this could potentially a new treatment for cases where the quality/quantity of the alveolar bone is in question [73].

A complex of a chitosan/collagen coating was hypothesized to promote gingival epithelial cell adhesion to titanium implants conditioned with plasmid pLAMA3-CM. Ne epithelial attachment was seen at the end of the study which were confirmed through immunofluorescence studies. The authors concluded that modification of titanium implants by plasmid-mediated pLAMA3-CM diffusion is an optimistic method to create a biological seal around the transmucosal sites of implants. A novel implant substrate was developed containing graphene–chitosan has been demonstrated to show increased surface wettability and roughness, thereby upregulating osteoblast proliferation [74].

## Chitosan Degradation

The degradation rate describes the reduction of chitosan layers/films caused by enzymes, lysozymes and free radicals. The amount of lysozyme can be used to determination of chitosan degradation rates. To gain long term mechanical stability, coating material should exhibit optimal degradation behavior and match the speed of the new tissue formation [75] Ma K et al observed that chitosan-gelatin coating degraded completely after 28 weeks through which it was found to be more stable [76]. However, since Chitosan is sensitive to mild changes in the pH of the solution, alkaline buffer solutions such as phosphate-buffered saline (PBS) tends to degrade chitosan faster than usual [77]. The in vivo study of Wang J et al. also demonstrated the stability of chitosan from degradation after 26 weeks and 12 weeks [71].

## Bioactivity Of Chitosan Coating

Cellular behavior is influenced by the surface characteristics and DD, with distinct effects depending on the cell type. Osteoblastic cell attachment and proliferation are favored on high DD chitosan membranes, which aid in the differentiation process and stimulate the secretion of extracellular matrix proteins. Chitosan coated implant surface are positively charged which attracts the negatively charges red blood corpuscles, cytokines, hormones and a plethora of growth factors to the site of implantation and orchestrates tissue repair and remodeling [63]. Absorption of chitosan coating onto the surface of the implant paved the way for the coating to be used for drug delivery, incorporation of growth factors [64]. Chitosan films and coatings sustain osteoblastic cell growth and act as a vehicle for growth factors, bone morphogenetic protein (BMP), release of BMP with as much as 80–85% of the BMP being retained in the films after 7 days [65].

Greene et al. employed a double trypsinization method to collect normal human fibroblasts and cells from a human osteoblastic precursor cell line from chitosan coatings bonded to stainless steel as compared to uncoated stainless steel coupons. Their results showed that both the fibroblasts and osteoprecursor cells grew equally well on the chitosan coatings as on the uncoated controls [50].

The osteogenic potential of chitosan coating was studied by Zujur D et al in 2015, who chemically modified the chitosan through lactobionic and 4-azidebenzoic acid to convert it to a hydrogel and photocrosslinkable. It was then treated to the pure Ti alloys sandblasted with alumina particles. The coating had sustained able to support cell proliferation of osteoblasts and could be used for further studies in the encapsulation of bioactive molecules to improve osteogenic potential at the tissue-implant interface [66].

Norowski et al in 2011 incorporated tetracycline at 20 wt% or the antimicrobial chlorhexidine at 0.02 wt% of coatings made with an 81% DDA chitosan bonded to titanium. They found that chitosan coatings released 89% of the tetracycline in 7 days and 100% chlorhexidine in 2 days in vitro. Released tetracycline inhibited the growth (95–99.9%) of *Actinobacillus actinomycetemcomitans* and *Staphylococcus epidermidis* for up to 7 days with no cytotoxicity to human fiboroblastic or osteoblastic cells [67].

Leedy et al in 2009 loaded vascular endothelial growth factor in chitosan coatings bonded to titanium via to assess the osseointegration via local stimulation of angiogenesis, in patients on bisphosphonate therapies for osteoporosis or myeloid cancer. The growth factor had rapidly released over 3 days from coatings with an initial peak of ~44 ng/mL/cm2 at day 1 and 0.15 ng/mL/cm2 at day 3. The growth-factor-loaded coatings enhanced the viability of endothelial cells and significantly stimulated the proliferation of osteoblastic cells in *vitro* [68].

Wang et al. used a chitosan-plasmid DNA coated titanium screws to which type-IV collagen was applied in order to mimic extra cellular matrix environment. The authors observed significant new tissue attachment surrounding the dental implants [69]. Electrodeposited calcium hydroxide particles and chitosan coatings in Ti6Al4V plates to stimulate osteoblast function and osteogenesis. They found an increase in alkaline phosphatase activity, collagen expression and both bone sialoprotein and osteocalcin genes were up-regulated on cells that were cultured on the electrodeposited CaP/chitosan coatings [58].

Chen et al assessed the antioxidant and osteogenic capacity of a multilayer surface on Ti substrates (Chitosan was combined with catechol and compared against coatings of gelatin, and hydroxyapatite on their capacity to form multilayer bioactive coatings, it was found that chitosan coating along with catechol displayed multilayered coating on the implant surface which in turns promoted Ti implants were able to promote osteogenesis through upregulation of osteoblast-related gene expression.[70] Klokkevold et al. reported that chitosan films facilitated the differentiation of osteoprogenitor cells, and inhibited fibroblast proliferation [78]. More recently, Lahiji et al. demonstrated that osteoblasts maintained phenotypic morphology and expression of extracellular matrix proteins for seven days when cultured on 90% de-acetylated chitosan films as compared to plastic coverslips [79].

A conglomeration of chitosan- hydroxyapatite hydrogels were produced by a thermal cross-linking reaction using glycerol phosphate disodium salt coated on 316L SS implants were found to increase osseointegration biocompatibility and protection against corrosion. Recently, CS has been utilized in 3D printing for various tissue engineering applications [80].

Immediate loading implants after tooth extraction is an attractive alternative that presents several advantages such as reduction of post-extraction resorption, optimal positioning of the implant and reduction of the time required for prosthetic rehabilitation. On, which requires a prerequisite of adequate bone volume. Several regenerative treatment modalities, such as guided tissue regeneration (GTR) and autogenous bone grafting (autografts), have already been introduced into clinics, and been unequivocally accepted as the standard of care.

An *in-vitro* study by Alnufaiy BM et al in 2020 investigating the osteogenic potential of chitosan coated implant surface by altering the degree of deacetylation to 80 or 95 DDA% in hMSC-TERT 20 cells It was observed that all cells exhibited significant attachement although it was higher in 95% along with a significant increase in the expression of osteogenic markers compared to the 80% chitosan and control groups. The biomineralization and enhanced osseointegrative function of high DDA of was justified and is thought to enhance future dental implant healing processes and osseointegration [81]. Zhang Y et al in 2017 constructed chitosan/ collagen composites combined with virus encoding BMP7 gene by freeze-drying methods demonstrated the osteogenesis induced by chitosan/collagen combined with BMP7 [82].

Murine mandibles were implanted with chitosan/GNP/GFBP-3 coating for 4 weeks. Histopathology revealed enhanced bone remodeling and increase in bone density around the implant. The authors suggested that the coating had down-regulating osteoclastogenesis and up-regulating osteogenesis [83]. The same author also examined the role of chitosan/ Peroxisome proliferator activated receptor gamma around implants and observed a significant reduction of pro-inflammatory mediators and upregulation of osteoblastic gene expression which reinforced the bone–implant integration [84]. Lactose-modified chitosan coating for implants in minipig femur model by Marsich et al reported evidence of anti-inflammatory and antioxidant effects of chitosan and lactose scaffold on chondrocytes [85].

Although favorable results were obtained from animal models, *in-vitro* conditions. These results cannot be extrapolated to the environment of human oral cavity, where dynamic factors might influence the chitosan coating pertaining to implantology since cortical remodeling is absent and they stop growing later than other mammals. Future research should be aimed to assess if such coatings would sustain and facilitate osseointegration within the harsh environment of human beings.

## Conclusion

Chitosan has attracted considerable attention in dentistry due to its strong favours. This novel bioactive coating of chitosan can produce robust titanium surfaces with greater osseointegration capacity than uncoated titanium alloys. The quality and quantity of bone formation surrounding the implant surfaces can be increased by using chitosan along with other polymer compounds of mineralization substantially increased with an increased number of bi-layers.

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