REVIEW ARTICLE

# POTENTIAL OF DENTAL IMPLANTS AS DRUG CARRIERS

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**ABSTRACT**

*Dental implants are continuously gaining popularity in dental practice as a treatment modality for the missing teeth. It has led to extensive research on every aspect of dental implants. The objective of this systemic review was to establish the degree of success of dental implants as drug carriers. A customized electronic search for published literature of last fifty years was done and all the articles on dental implants as drug carriers were carefully analyzed. It was concluded that dental implants could be utilized effectively as drug carriers. So far bone morphogenetic proteins (BMPs) delivery via dental implants have been investigated more than any other therapeutic agent.*

**Key Words:** *Dental Implants, Drug carriers, Bone Morphogenetic Proteins (BMPs).*

## INTRODUCTION

Dentistry has seen a massive paradigm shift in replacing the lost oral tissues via implants. They are being used to replace lost teeth or to repair orofacial defects caused by congenital defects, neoplasms or trauma. According to PubMed the term "Dental Implant" was introduced in 1990 and it refers to biocompatible materials placed into the jawbone to support prosthesis or to stabilize an infected tooth. The most common type of dental implants being used is screw shaped which are drilled into the alveolar bone, known as endosseous implants. The implants available in the market are made up of titanium, titanium alloys, ceramics or polymers, but biocompatibility and durability of titanium and its alloys have made them the materials of choice for manufacturing dental implants.[1,2]

Many commercially available implants have surface modifications and some implants are coated with a layer of hydroxyapatite or plasma sprayed to promote early osseointegration.[3] The coatings of implants have led to the concept of implants as drug carriers. Despite a wide variety of therapeutic options, the use of prophylactic antibiotics during implant placement remains controversial. A review article found inadequate evidence rejecting or advocating their use.[4] Therefore peri-implant delivery of antibiotics, using implants as drug carriers may play a significant role in the success of implants. According to PubMed the term "Drug Carriers" was introduced in 1988 and it refers to forms to which substances are incorporated to increase the delivery and the effectiveness of drugs. Drug carriers are a component of drug-delivery systems which may increase the targeted drug delivery, efficiency as well as decrease the systemic effects and metabolism of the drug.

The objective of this systematic review is to evaluate the success of dental implants as drug carriers and the methods and therapeutic agents which have been successfully delivered using dental implants.

## METHODOLOGY

A customized electronic search from 1st April.1965 to 1st April. 2015 from PubMed was done. Mesh terminologies were used to search the database. The articles available on dental implants from last 50 years were found to be 26558 and for drug carriers were found to be 74517. When "Dental Implants"[Mesh] AND "Drug Carriers"[Mesh] were searched, the number of articles narrowed down to 47. All articles on dental implants as drug carriers of last 50 years were retrieved. The trend of research on dental implants as drug carriers has been increasing over last few decades as demonstrated in the graph below. The graph was plotted with number of articles published per five years.

After a careful evaluation, 17 articles which strictly adhered to the topic of this systemic review and fulfilled the inclusion criteria were included. The inclusion and exclusion criteria is shown in the Table 1.

The screening process is illustrated in the form of a flowchart in Fig 2. The results from all the selected articles were organized in the Table 2 & 3 and later discussed.

## RESULTS

Findings of all studies were compiled and organized in the form of a table. More studies were based on

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TABLE 1: ELIGIBILITY CRITERIA FOR THE SELECTION OF LITERATURE TO BE ADDED IN THIS REVIEW

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Articles which discussed dental implants as drug carriers | Review articles |
| Drugs such as antimicrobial agents, growth factors and hormones | Articles in which therapeutic agents or autogenous bone grafts were placed before implant placement |
| Publications from 1965 to 2015 | Publications before and after 1965 and 2015 respectively |
| Full text articles and abstracts | Abstracts with insufficient data |

TABLE 2: OVERVIEW OF STUDIES OF IMPLANTS CARRYING GROWTH FACTORS

| Citation | Year of publication | Type of study & sample size | Therapeutic agent used | Mechanism of action | Reason for including the article |
|---|---|---|---|---|---|
| 5 | 2013 | In vitro | Bone morphogenetic protein-7 (BMP-7) | Adenovirus encoding BMP-7 immobilized on titanium surface | Growth factor delivery |
| 6 | 2012 | In vivo | bFGF | local delivery of bFGF from PLGA microspheres | Growth factor delivery |
| 7 | 2004 | In vivo (pilot study) | Bone morphogenetic protein-2 DNA | Surface activation of implants by liposomal vector system for BMP-2 DNA transfer | Growth factor delivery. This vector system may be investigated for therapeutic options |
| 8 | 2013 | Unclear | Bone morphogenetic protein-2 | Immobilization of BMP-2 on nano-hydroxyapatite-coated titanium surface using a chitosan calcium chelating agent | Growth factor delivery |
| 9 | 2013 | In vivo + in vitro | BMP-2 gene | BMP-2 gene delivery from plasmid multilayers formed on sandblasted titanium | Growth factor gene delivery |
| 10 | 2011 | In vivo | BMP-2 | Local delivery via scaffolds with miniature dental implants | Growth factor delivery |
| 11 | 2010 | In vivo | insulin like growth factor-1 | Sustained release of growth factor from poly(lactide-co-glycolide) microspheres | Growth factor delivery |
| 12 | 2009 | In vivo | RhBMP-2 | Purpose designed titanium porous oxide implant surface to deliver growth factor for alveolar augmentation | Growth factor delivery |
| 13 | 2008 | In vivo | rhBMP-2 | Purpose designed titanium porous-oxide implant surface combined with rhBMP-2 | Growth factor delivery |
| 14 | 2003 | In vivo | bFGF | Local delivery of growth factor from PLGA microspheres around implants | Growth factor delivery |
| 15 | 2006 | In vivo | rhBMP-2 | De novo bone growth on exposed implant surfaces using photodynamic therapy & rhBMP-2 | Growth factor delivery |
| 16 | 2004 | In vivo | rhBMP-2 | Hollow cylinder implants filled with absorbable collagen sponge soaked with growth factor | Growth factor delivery |

TABLE 3: OVERVIEW OF STUDIES INVESTIGATING IMPLANTS AS CARRIERS OF OTHERTHERAPETIC AGENTS

| Citation | Year of publication | Type of study | Therapeutic agent | Mechanism of action | Reason for inclusion |
|---|---|---|---|---|---|
| 17 | 2014 | In vitro | Hydroxyapatite (HA)-heparin composites | electrodeposition of nanostructured bioactive composite coatings onto titanium substrates | Local delivery via titanium implant |
| 18 | 2011 | In vivo | 20% tetracycline or 0.02% chlorhexidine digluconate | Chitosan coatings deliver antimicrobials for prevention of acute implant infection | Local drug delivery |
| 19 | 2012 | In vivo | insulin | Topical delivery from fibrin gel loaded with poly(lactic-co-glycolic Acid) Microspheres | Drug delivery via titanium implants in type 1 diabetic rats |
| 20 | 2011 | In vivo | 1alpha,25-dihydroxyvitamin D3 | Submicron particle coating on an implant surface | Drug delivery |
| 21 | 2000 | In vivo | bisphosphonate/hydroxyapatite and plain hydroxy apatite | Porous hydroxyapatite implants were pre-incubated in 10(-2)M bisphosphonate solutions at pH 3.49 which led to adsorption of 115 micro G bisphosphonate | Local drug delivery |

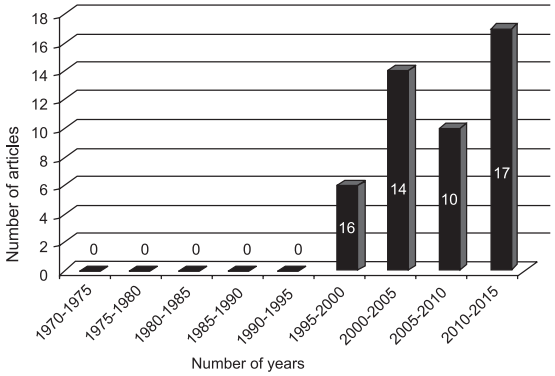


Fig 1: Trend of research on dental implants as drug carriers over last 50 years in literature.

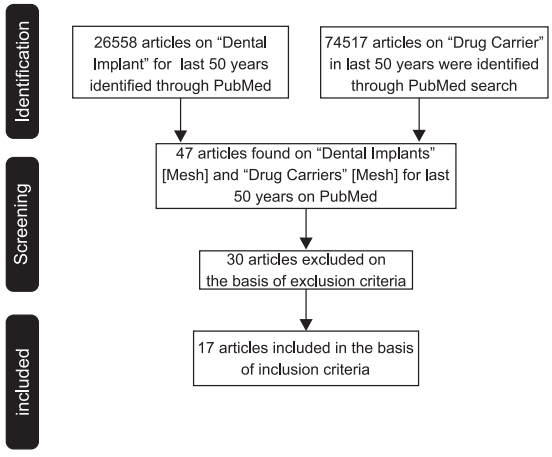


Fig 2: Flowchart showing the screening of the selected articles.

investigating implants as carriers of growth factors. Therefore, all such studies were grouped together and rest of the studies were grouped in another table. Overview of all included article studies can be see in the Table 1 and 2 below.

## DISCUSSION

The first article on dental implants as a carrier was published in 1997 and since then a significant number of articles have been published, with the highest number of publications between the year 2010 to 2015. There is a lot of research potential in this field as it has been less explored and a lot of new developments can take place. This literature review found that mostly the investigation on the effectiveness of dental implants as drug carriers were in vivo studies.

### Bone Morphogenetic Proteins

Most of the articles discussed dental implants as carriers for bone morphogenetic proteins to increase osseointegration. Osseointegration is a widely investigated topic and is crucial to the success of dental implants. Both clinicians and researchers have tried to find more viable ways to ensure good osseointegration of dental implants. Surface modifications and use of microspheres to deliver bone morphogenetic proteins at peri-implant sites have mostly shown positive results. However, it is found that the bone formation observed via radiographs appear to be enhanced compared to

when observed histologically 22. A study investigated liposomal vector system 7 to transfer Bone morphogenetic protein-2 DNA to the animal model, this technique can be further investigated for therapeutically relevant options for treatment of peri-implant defects using dental implants.

**Antimicrobial Agents**

Only two articles were found on dental implants as carriers of antimicrobial agents[18,23], among which one was a review article which didn't meet the inclusion criteria. A gap in research on implants as antimicrobial agent carriers has been identified. Targeted antimicrobial release may solve the issue of peri-implantitis. Another critical need is to investigate ways for controlled drug release over longer periods of time. Most of the studies have established methods for drug delivery over a period of days or weeks, but the release of drugs for durations longer than that still needs to be investigated. It might play a vital role in extending the durability of an implant in function.

**Modifications enabling implants to carry drugs effectively**

According to literature various methods were used to modify dental implants into drug carriers. Among the various methods used, surface treatment or surface modification of implants was the most common.[5,7-9,12,13,17-19,21] Followed by the microsphere loading method.[6,11,14,19] Both these methods provided good results. Other methods used, included scaffolds with miniature dental implants[10], filling of hollow cylindrical implants with growth factors[16] and photodynamic therapy.[15] The most effective methodology of drug delivery via dental implants cannot be concluded so far.

## CONCLUSIONS

Dental implants can be used successfully as drug carriers.

Most successfully delivered and tested therapeutic agents via dental implants are bone morphogenetic proteins (BMPs).

The most common method used for drug delivery via dental implants is surface coatings or surface modifications of dental implants.

A gap in research on implants as antimicrobial agent carriers has been identified.

## RECOMMENDATIONS

A comparative study may be done to evaluate the effectiveness of each method employed using dental implants as drug carriers, which may help to determine the most effective methodology.

More search engines and databases may be used to broaden the data for review.

The methods used for delivery of growth factors may be utilized for the provision of antibiotics or other antimicrobial agents which may help to prevent peri-implantitis.

Methods for controlled drug release over years using implants need to be investigated.

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## CONTRIBUTIONS BY AUTHORS

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|---|---|
| **1 Hudia Rizwan:** | Conception of topic, literature search and writing. |
| **2 Shahreen Zahid:** | Corrected methodology and made systematic analysis. |
| **3 M Kaleem:** | Supervisor. |
| **4 Samira Rizwan:** | Correction of final proof. |
| **3 Maleeha Nayyer:** | Formatting carried out at Army Medical College, NUMS. |