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RESEARCH ARTICLE

EFFECT OF BONE MORPHOGENETIC PROTEIN COATING OF DENTAL IMPLANT: A SYSTEMATIC REVIEW.

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Abstract

Dental implants had become an integral treatment modality in prosthetic dentistry. Implant prostheses have shown dramatic improvements in masticatory performance, esthetics, and patient satisfaction.Recently, theapplications of molecular and nanoscale-based biological substances as bone morphogenetic proteins, peptides, and stem cells in association with calcium phosphate coatings always play an essential role in enhancing the osseointegration of dental implants and shortening the time period for implant integration.Hypothetically, oral implants' surfacescovered with a bone inductive agent such as a BMP may stimulateregional bone development and osseointegration in sites of poor bone quality or in need of augmentation. Objectives were to evaluate the effects of bone morphogenetic protein surface coating of dental implant in improving the oosseointegration in human. The search was done at Cochrane Central Register ofControlledTrials (CENTRAL), PubMed. Only English papers were to be included. Most recent search: october2016. The Selection criteria were Randomized controlled clinical trials(RCTs) including patients with dental implant coated withbone morphogenetic protein (BMP) surface coating against dental implants without bone morphogenetic protein (BMP) of surface coating. The outcome measures considered were: osseointegration, implant stability, and implant failure. Chiefresults: We found that there was no randomized controlled or controlled clinical trials. Conclusions: in this research area, there is utmost need for RCTs toevaluated therole of bone morphogenetic protein surface coating of dental implant in enhancing the osseointegration in human (clinical studies).

Background: -

Dental implants had become an integral treatment modality in prosthetic dentistry. Implant prostheses have shown dramatic improvements in masticatory performance, esthetics, and patient satisfaction. The placement of dental implants and the insertion of implant-supported prostheses have been found to substantially reduce bone loss in the edentulous jaw, as well as promote bone deposition distal to implants. (1)

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Because the time frame to achieve full osseointegration, in addition the physiology and composition at the bone implant connection, is mainly related to the implant surface, there is a necessity to establish surfaces modifications that will lead to a predictive improvement of implant-to-bone response.(2)

Such modifications, whether surface topographical or surface chemical, have been successful in accelerate osseointegration at early implantation times which may shorten the total treatment period.

Recently, the applications of molecular and nanoscale-based biological substances as bone morphogenetic proteins, peptides, and stem cells in association with calcium phosphate coatings always play an essential role in enhancing the osseointegration of dental implants and shortening the time period for implant integration.(3)

The BMPs are dissoluble, small molecular weight transmembrane glycoproteins that found as dimers linked by a disulfide bond within natural bone.Due to there is only a little quantity of active protein/kg bone, extraction of adequate amounts would demand a large quantity of bone, making this process very difficult and expensive. (4)
BMPs are growth factors that naturally found within the bone matrix and act as pleiotropic organizer of chemotaxis mitosis, differentiation, excitation of extracellular matrix formation, bound to matrix components, conservation of phenotype and apoptosis. In addition, they play a role in regulation of bone volume, skeletal organogenesis and the Regeneration of bone after a fracture.(5)

Hypothetically oral implants' surfaces covered with a bone inductive agent such as a BMP may stimulate regional bone development and osseointegration in sites of poor bone quality or in need of augmentation. (6)
The consequences of BMP-2 and its applicationon dental implants' osteoconductivity had been evaluated by ***(Liu et al, 2007)***[(7)]by using a bared titanium surface or with a calcium-phosphate covered implant. They found that the method of application bone morphogenetic protein (BMP-2)was greatly affects the osteoconductivity of dental implant surfaces.

(Kim et al, 2015)[(8)] used recombinant human bone morphogenetic protein-2 (rhBMP-2)-loaded pedicle screws to formulate a new hypothesis of bone-to-bone biologicallock .

(Yoo et al, 2014)[(9)] had examined if plasma-sprayed hydroxyapatite implant surfaces dipped in protein solution prior to dental implant installation in order to cover the implant surface with rhBMP-2 onto by immersion in protein solution before implant placement may lead to greatly enhance the process of bone formation . ***They concluded*** that the mixture of plasma-sprayed calcium-phosphate implant surface and rhBMP-2 coating remarkably improve the osseointegration, which certified the postulated hypothesis.

Biological Function of BMP: -

- BMPs are growth factors that naturally found within the bone matrix and act as pleiotropic organizer of chemotaxis mitosis, differentiation, excitation of extracellular matrix formation, bound to matrix components, conservation of phenotype and apoptosis.
- In addition, they play a role in regulation of bone volume, skeletal organogenesis and the Regeneration of bone after a fracture. (5)
- BMP-2 has been the most inclusively studied of any of the BMPs.
- The jobs of the protein have been resolved in fracture healing, bone defects and different spinal fusion models.(5)
- Expression is regenerative with the differentiation of chondroblasts and osteoblasts from mesenchymal stem cells, proposing that it might be an inducer of bone formation and chondrogenesis.(5)
- Meantime, more than 40 agents of the mutated growth factor beta 1 (TGF-β) family were known that they have a great part in differentiation and growth of matters.(10)
- In addition, BMP-2 is considered as one of the growth factors that have osteoinductive properties; others include BMP-4, BMP-6 and BMP-7.(10)
- From all of these advantages, it could be important for implant's patients, clinical researchers, and society to investigate the effectiveness of bone morphogenetic protein surface coating of dental implant in improving the oosseointegration in human, asthe recombinant human bone morphogenic protein (rhBMP-2) dental implant coating was approved to be used safely in human

Objectives: -

The main objective of this review isto estimate whether the bone morphogenetic protein coating of dental implant's surface can enhance the osseointegration in human.

Moreover, to investigate if the bone morphogenetic protein coating of dental implant can improve the osseontegration better than non-bone morphogenetic protein surface coating of dental implant in human studies.

PICO: -

- **Population:** edentulous patients (partial or complete)
- **Intervention:** bone morphogenetic protein surface coating of dental implant
- **Control:** non-bone morphogenetic protein surface coating of dental implant
- **Outcome*:*** - osseointegration
  - Implant stability
  - Implant failure
- **Study design:** randomized clinical trial (RCTs)

Methods: -

Inclusion Criteria for selecting studies: -

Included studies:

- The studies were Randomized controlled clinical trials (RCTs) which may be parallel studied or split mouth design without time limiting frameof these studies.

Types of participants: -

- The patients could be male or female with no age limit.
- The Patients could be partially or completely edentulous.
- The dentulous areas can be found at maxilla or mandible
- The edentulous spaced could be anteriorly or posteriorly.
- The super structure could be fixed or removable prosthesis.
- The loading may be immediate or delayed.

Types of interventions: -

Dental implants with or absence of the growth factor (bone morphogenetic protein (BMP)) surface coating

Types of outcome measures: -

- Assessment of the osseointegration through calculating the bone height around the dental implant at each follow up period in each group
- Evaluation ofstability of dental implant, where primary or secondary implant stability are pre-requisite for successful osseointegration and subsequent success of implant treatment
- Implant failures which could be identified through detecting the mobility of dental implant that may be caused by marginal bone loss around the installed implant.

Search procedure for the included studies: -

For identification of included studies, there were some databases used in search process.

Databases used in searching: -

- The latest electronic search was performed on 14 October 2016 by using PubMed- NCBI data base, and Cochrane Library for the Controlled Trials.

Language selected: -

The articles with English language only selected during the search strategy.

Hand searching: -

hand searching was made through electronic search in different journals and screening the references of relevant papers and reviews.

Search strategy: -
PubMed index term: -

#1 (bone morphogenetic protein[MeSH] OR bone morphogenetic proteins[MeSH] OR bone morphogenetic protein 2[MeSH] OR bone morphogenetic protein-2[MeSH] OR bone morphogenetic protein 4[MeSH] OR bone morphogenetic protein receptor[MeSH] OR bone morphogenetic protein 7[MeSH] OR bone morphogenetic protein signaling[MeSH] OR bone morphogenetic protein 6[MeSH] OR bone morphogenetic protein-7[MeSH] OR bone morphogenetic protein 9[MeSH] OR bone morphogenetic protein 15[MeSH] OR bone morphogenetic protein receptor 2[MeSH]OR recombinant human bone morphogenetic protein-2[MeSH] OR bone morphogenetic protein 1[MeSH] OR rhbmp-2 dental[MeSH] OR rhbmp-2 bone[MeSH] OR rhBMP-2[MeSH] OR BMP-2[MeSH] OR Recombinant Human Bone Morphogenetic Protein-2[MeSH]) (22129)

#2 (bone morphogenetic protein[T W] OR bone morphogenetic proteins[T W] OR bone morphogenetic protein 2[TW]OR bone morphogenetic protein-2[TW] OR bone morphogenetic protein 4[TW]OR bone morphogenetic protein receptor[TW] OR bone morphogenetic protein 7[TW]OR bone morphogenetic protein signaling[TW]OR bone morphogenetic protein 6[T W] OR bone morphogenetic protein-7[T W] OR bone morphogenetic protein 9[TW] OR bone morphogenetic protein 15[TW] OR bone morphogenetic protein receptor 2[TW] OR recombinant human bone morphogenetic protein-2[TW] OR bone morphogenetic protein 1[TW] OR rhbmp-2 dental[TW]OR rhbmp-2 bone[TW] OR rhBMP-2[TW] OR BMP-2[T W]OR Recombinant Human Bone Morphogenetic Protein-2[TW] (17608)

#3 dental implant surface [MeSH] OR dental implant surfaces [MeSH] OR dental implant surface treatment[MeSH] OR titanium dental implant surface[MeSH] OR dental implant surface roughness[MeSH] OR dental implant surface modification [MeSH] OR dental implant surface design[MeSH] OR dental implant surface modifications[MeSH] OR endosseous dental implant surfaces[MeSH](412)

#4 dental implant surface[TW]OR dental implant surfaces[TW] OR dental implant surface treatment[TW] OR titanium dental implant surface[TW] OR dental implant surface roughness[TW] OR dental implant surface modification[TW] OR dental implant surface design[TW] OR dental implant surface modifications[TW] OR endosseous dental implant surfaces [Text Word] (234)

#5 (**humans [MeSH Terms]) OR human [MeSHTerms] (**
16047664**)**
#6 **(human[Text Word]) OR humans[Text Word] (**16535072**)**
#7 #1 OR #2 (**22187)**
#8 #3 OR #4 (**636**)
#9 #5 OR #6 **(**16535072)
10 #7 AND #8 AND #9 **(37)**

Cochrane literary index terms: -

#1 (bone morphogenetic protein OR bone morphogenetic proteins OR bone morphogenetic protein 2 OR bone morphogenetic protein-2OR bone morphogenetic protein 4 OR bone morphogenetic protein receptor OR bone morphogenetic protein 7 OR bone morphogenetic protein signaling OR bone morphogenetic protein 6 OR bone morphogenetic protein-7 OR bone morphogenetic protein 9 OR bone morphogenetic protein 15 OR bone morphogenetic protein receptor 2 OR recombinant human bone morphogenetic protein-2 OR bone morphogenetic protein 1 OR rhbmp-2 dental OR rhbmp-2 bone OR rhBMP-2 OR BMP-2 OR Recombinant Human Bone Morphogenetic Protein-2) (317)

 # 2 dental implant surface OR dental implant surfaces OR dental implant surface treatment OR titanium dental implant surface OR dental implant surface roughness OR dental implant surface modification OR dental implant surface design OR dental implant surface modifications OR endosseous dental implant surfaces. (348)

 # 3 humans OR human (741994)

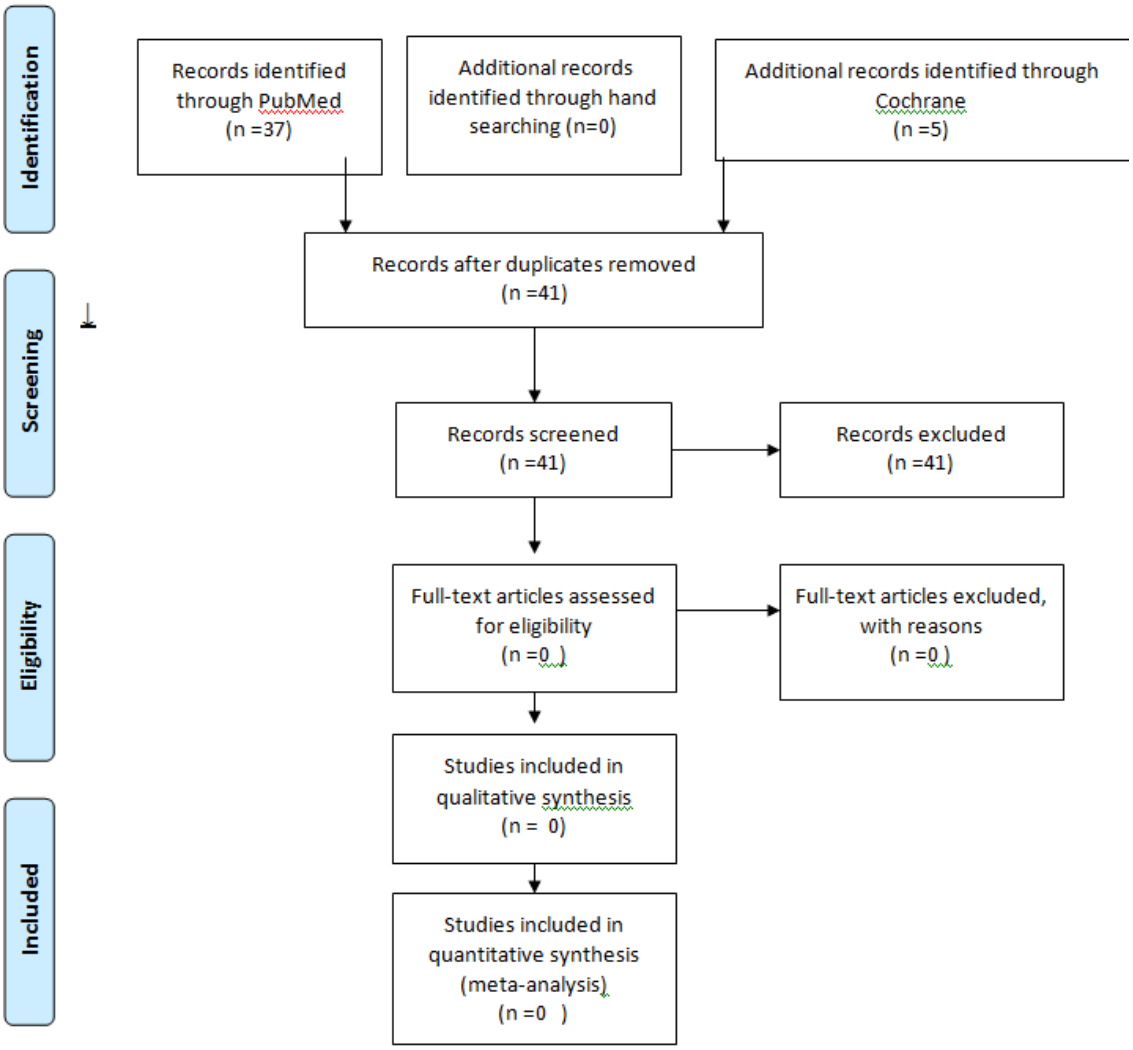
#1 and # 2 and #3 (5)
Data extraction

- Literature search resulted in 37 studies in PubMed and 5 studies on Cochrane data base. the first step of filtrating studies was performed through title and /or abstract with the resultant of zero studies retrieved from PubMed and Cochrane data base

Thesubsequent data should be registered for each clinical study:

- ❖ publication year, originatingcountry, environment and origin of studyfunding.
- ❖ participants' information including demographic data and inclusion criteria.
- ❖ the type of intervention's details and information.
- ❖ Detailed information of the outcomes measured, incorporating methodof evaluation and time interval

PRISMA 2009 Flow Diagram: -



Gathering and analysis of data: -

All the studies selected according to the criteria of search strategy were screened by titles and abstracts independently by two authors to decide whether these selected studies followed up the inclusion criteria. In addition, in case of in sufficient available information about the studies in title and abstract, a report was made about the status of each study to be checked by the two authors independently to make a clear decision about them. In case of the disagreements, the discussion was the appropriate solution in this condition but if this way is not worked, athird author was invited to give the final decision. After that, the quality of each selected study was evaluated, then tableof exclusion studies was made with clarifying the cause of this exclusion.

Quality assessment of the included studies: -

- The evaluation was done according to standard criteria:
- The first one was the Allocation concealment which may be: adequate concealment or un clear or inadequate one.
- After that, evaluation of follow up period, if all patients complete the whole study period or there was a drop out. In this case, a clear explanation for this drop out should be given, as it was evaluated as follow:
- The answer was yes, in case of the presence of clear explanation for drop out.
- The answer was no, in case of absence of explanation.
- The studies were to be gathered in groups after analyzing the data of each one in to these categories:
- If all evaluation criteria were present, this study was considered as low risk of bias.
- If one or more of the evaluation criteria were not completely explained, this study was considered as moderate risk of bias
- If one or more of the evaluation criteria were absent, this study was considered as high risk of bias

Data composition: -

For the estimation of the influence of an intervention, the risk ratios were used with 95% confidence interval for all selected studies. The mean difference with 95% confidence interval were used to continuous out comes. After screening the types of participants, outcomes and interventions, the clinical heterogeneity was assessed. A planned subgroup analysis for methods of applying bone morphogenetic protein (BMP) coating on the implant surface and sub group analysis for various types of bone morphogenetic protein (BMP). For only studies which had the same outcome measures, assessmentmethods, and comparisons, the meta analyses were made. The random effect model was used to collect the risk ratio for dichotomous data. In addition, it was used to collect the mean differences for continuous data present. The I^2 test was used to test and quantify the amount of heterogeneity between the studies.The influence of randomization may be evaluated by using sensitivity analysis.

Results: -

Regarding the studies' description, assessment of risk of bias in the included studies,and the influence of the intervention, it was found that there was no published randomized controlled clinical trials (RCT) or controlled clinical trialsafter searching in to different data bases.

Discussion: -

It was so dis appointed not to find a randomized controlled clinical trial or even controlled clinical trials to compare and evaluate the effect of bone morphogenetic protein surface coating of dental implant in improving the osseointegration in human. Several published animal studies have become available.We are also ongoing to publish randomized clinical trial (RCT) including 10 patients, they are divided into two groups **Group (I)**: Five patients had received two conventional titanium implant coated with `Bone morphogenetic protein (BMP) installed in the inter-foraminal area. **Group (II)**: Five patients had received two conventional titanium implant surface installed in the inter-foraminal area. with a 1-year follow up from Egypt, CairoUniversity, Faculty of Dentistry.

In this section, we introduce a summary about some of the animal studies performed by using bone morophogenetic protein coating of dental implant's surface with different techniques and types to guide the clinical researchers in this field, and the evidence extracted from this review was limited as there was no randomized clinical trials in this research field.

(Liu et al, 2005)[(11)]hadtested kinetics and histomorphometry of bone development in combination with BMP-2 coating of dental implant by using a rat model. The models were divided into one experimental and three control groups. They concluded that the incorporation of BMP-2 with calcium phosphate coatings could enhance the bone development in vivo with excellent degree strength and even with low concentration of the given dose. In addition, the ability to withstand this action was high as its activity may last for large period of time.

The consequences of BMP-2 and its application on dental implants' osteoconductivity had been evaluated by ***(Liu et al, 2007)***[(7)] by using a bared titanium surface or with a calcium-phosphate covered implant. They found that the method of application bone morphogenetic protein (BMP-2) was greatly affects the osteoconductivity of dental implant surfaces.

(Ramazanoglu et al, 2011)[12]had tested the influence of recombinant human bone morphogenetic protein-2 in single ,and double delivery techniques and recombinant human vascular endothelial growth factor (rhVEGF165) from dental implants coated with biomimetically octa-calcium phosphate on osseointegration. These Implants were installed into frontal skulls of nine domestic pigs. ***They concluded*** that the combination of coating implants with BMP-2 and VEGFcould enhance the bone volume density in the area surrounding the implants, although there was not Bone implant contact observed in this condition.

(Kim et al, 2015)[8] used recombinant human bone morphogenetic protein-2 (rhBMP-2)-loaded pedicle screws to formulate a new hypothesis of bone-to-bone biological lock .

(Yoo et al, 2014)[9] had examined if plasma-sprayed hydroxyapatite implant surfaces dipped in protein solution prior to dental implant installation in order to cover the implant surface with rhBMP-2 onto by immersion in protein solution before implant placement may lead to greatly enhance the process of bone formation . ***They concluded*** that the mixture of plasma-sprayed calcium-phosphate implant surface and rhBMP-2 coating remarkably improve the osseointegration, which certified the postulated hypothesis.

The effects of bone morphogenetic proteins (BMPs) in cellular functions in adult and postnatal animals have been investigated in recent years. Most of these animal studies recommend to use the BMP as surface coating for dental implant. Moreover, bone morphogenetic protein as surface coating for dental implant is considered to be a new surface coating technique for dental implant. For these reasons, it is important to plan good standard randomized clinical trials (RCTs) to evaluate the influence of bone morphogenetic protein coating for dental implant, this is a very important step to produce trustable evidence about its effectiveness in improving the bone formation. In addition, Different techniques for BMP application and mode of coating delivery should be properly tried and tested in vivo studies.

Conclusions: -

Clinical suggestions:

There were no published randomized controlled clinical trialsor controlled clinical trials, thus the good evidence is difficult in this case to recommend the clinician to use thebone morphogenetic protein surface coating of dental implant in improving the osseointegration in human. It seems that bone morphogenetic protein surface coating might improve the oseointegration depends on the technique used for application of coating on to the implant surface,however, these results depend on animal studies. Thus, we don't recommend to use bone morphogenetic protein as surface coating for dental implant till a strong and reliable evidence developed.

Research suggestions:

Although, thebone morphogenetic protein surface coating for dental implant is relatively anew coatingtechnique, the absence of randomized clinical trial on this point is so depressed, as its effect in improving the osseointegration in human stilldoubtful. For this reason, we advise the researchers to pay attention to this research point to help in generating reliableand strong evidence base decision.In addition, Different techniques for BMP application & release should be tried.

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