Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/8135
DOI URL: http://dx.doi.org/10.21474/IJAR01/8135

RESEARCH ARTICLE

BONE SUBSTITUTE VERSUSSTEM CELLS IN REGENERATION OF ALVEOLAR BONE DEFECTS IN HUMANS: SYSTEMATIC REVIEW.

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Manuscript Info

Manuscript History
Received: 01 October 2018
Final Accepted: 03 November 2018
Published: December 2018

Keywords:-
bone regeneration, alveolar bone defect, bone substitute**,** stem cells.

Abstract

Background: Healing of alveolar bone defect in humans is considered a major problem in oral and maxillofacial area. Stem cells being a new technique that evolved in past years was used to close defective areas. This review was conducted to evaluate and compare bone substitute materials versus stem cells in the regeneration of alveolar bone defect in humans.

Materials and Methods: A comprehensive electronic research in PubMed, Booksc.org,LILACS, and Google scholar as well as manual search from January 1990 up to April 2017 with language restriction to English only.

Result: initial screening and manual searching resulted in **153** articles from which only 4 articles were compatible with our inclusion criteria. The analysis of the results showed that the evaluated studies are too limited in number moreover exhibiting small sample sizes. They are not include all bone substitute materials nor do all stem cells types. They are clinically heterogeneous so that a no solid evidence based conclusion can be reached.

Conclusion: No strong and solid evidence to support the difference between two interventions in regeneration of alveolar bone defects in humans.

Introduction:-

The repair and regeneration of alveolar bone defect is a major problem encountered oral and maxillofacial field**.**Bone loss is mainly producedby different causes and diseases includingcongenital anddegenerative diseases, traumas as well as surgical procedures. This diseases might led to functional, social, and esthetics problems especially in old.Critical conditions of the alveolar bone due to periodontitis, extraction, or trauma provoke decrease in the alveolar ridge volume due to bone atrophy. Bone atrophy might produce changing in interarch relationship in vertical, transverse, and sagittal planes[1, 2].The defective alveolar bone could be augmented by different techniques including: onlay and inlay grafting [3], ridge expansion [4]**,** distraction osteogenesis [5]and guided bone regeneration (GBR) [6].

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Stem cells are primitive cells foundin all multicellular organisms characterized by self-renewal and have the capability of differentiation into any mature cell type. Stem cells have the potential for regeneration and repair ofdamaged cells. According to the origin and differentiation potential of the stem cells, there are two main types, embryonic stem cells derived fromfetal tissue and adult stem cellsthat can be harvested from bone marrow and other sources such as liver, umbilical cord, placenta, adipose tissue, synovial membrane, amniotic fluid and teeth. Stem cellshave multipotency to differentiate and develop into various types of tissues as adipose, cartilage, and bone[7-11].

Dental pulp (DPSCs) is a niche housing neural-crest-derived stem cells. It is easily available with limited morbidity after collection. DPSCs are capable of differentiating into osteoblasts that secrete abundant extracellular matrix that can build a woven bone *in vitro.* It is also capable of forming acomplete and well-vascularized lamellar bone after grafting. Dental pulp could be considered an interesting and possibly an important source of autologous stem/progenitor cells that are ready for use for therapeutic purposes, as the repair/regeneration of craniofacial bones [12-17].

The ideal graft material should not only be a bone substitute but a bone regeneration material that is completely resorbed simultaneously with the formation of new bone. Its decomposition products should be reused for building new bone [18]. It should serve as space keeper preventing invasion of soft and connective tissue and should not carry any immunological risk. Autogenous bone grafts which are still regarded as a gold standard appear to be ideal but their availability and storability is limited and secondary surgical sites with all related risks are still founded[19-21]. Allogenic or xenogenic grafting materials do not require secondary surgery.They are readily available and can be stored but the risk of immunological reaction due to foreign protein and transmission of viral or other infections cannot completely be prevented, making their use doubtful. The resorption of xenogenic materials has been the subject of controversy and may be identified histologically after many years[22-25]. Synthetic calcium phosphate as hydroxyapatite, alpha and beta tri-calcium phosphate are artificial, sterializable, free from any risk of material induced infections and easily available. The gradual dissolution and resorption of the synthetic bone substitute in physiologic environment occurs predominantly through physiochemical means without osteoclast activity. This procedure leads to interlocking porosity, allowing an invasion of fluids, migration of cells and ingrowth of vessels and newly formed bone, thus being osteoconductive [26, 27].

Human dental stem cells that have been isolated and characterizedderived from different sources include,dental pulp stem cells (DPSCs), human exfoliated deciduous teeth, stem cells from apical papilla (SCAP) and periodontal ligament stem cells (PDLSCs)(28). In the last ten yearsstem cells have gained more interest because of their high differentiation potential and their availability. Different types of stem cells represent a potential key component in autologous graft for bone regeneration.In contrast, bone substitute materials that were commonly used for reconstruction of alveolar bone defect including autogenous bone graft, allograft, xenograftand synthetic bone materials. The aim of the present investigation was to systematically review and assess all relevant literature concerning the regeneration of alveolar bone defect using bone substitute versus stem cell in humans

Materials and Methods:-

Search Strategy:

Identification of studies to be considered for inclusion was based on a search strategy for each electronic database PubMed, Booksc.org, LILACS, and Google scholar. In,accordance with guidelines of the preferred reporting items for systematic reviews and meta-analysis (prisma) statement and Cochrane handbook from January 1990 up to April 2017. LILACSsearch lead toarticles in different language so it was excluded. The search used the following keywords: (bone regeneration OR alveolar bone defect ORbone substitute OR dental pulpstem cell OR adipose derived stem cell OR autograft OR allograft OR alloplast OR xenograft)that was combined with manual search.

The search was limited to randomized clinical trials involving human subjects with restrictions to English.

All original research and review articles bibliographies were identified to be relevant to the scanned subject for any possible additional studies. Title and abstract of identified studies were screened bytwo reviewers for eligibility (AK and WA).Consensus was obtained by discussion or consultation with the third reviewer (MD).
The detailed search sequence presented in table (1).

Selection criteria:
Allrandomized controlled clinical trial (RCT) assessing stem cells and bone substitute in regeneration of alveolar bone defects were included. No limitation was positionedin regard the number of patients treated. Studies published between January 1990 and April 2017 were included.

Inclusion criteria:
1. Human studies.
2. Bone substitute studies.
3. Stem cells studies.
4. Treatment outcomes that was clearly reported by the authors.

Exclusion criteria:
1. Articles in language rather than English.
2. Animals study
3. Case report.
4. Reviewpapers.
5. Paper including periodontal or intra-bony defect.
6. Paper with unclear patient grouping
7. Technical reporting.

Table 1:-Detailed search sequence of the 4 articles used in this review

Paper name	Author (year)	Study design Duration	Subjects Gender Age in years (mean / range)	Funding	Groups		Original authors' conclusions
					Test group	Control group	
Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial.	Kaigler,et al 2013 USA	Tissue repair cells isolated from bone marrow were investigated to reconstruct localized craniofacial bone defects Oral implants were installed, subsequently restored, and functionally loaded with tooth restorations. 1 year	24 Both ages 20–70	No	TRC was placed onto gelatin sponge 12 a bone marrow aspiration of the posterior ilium under conscious sedation and local anesthetic	sponge, soaked in 1 ml sterile saline GBR 12	-Clinical, radiographic, tomographic, and histological measures demonstrated that TRC therapy accelerated alveolar bone regeneration compared to GBR therapy. - TRC treatment significantly reduced the need for secondary bone grafting at the time of oral implant placement with decrease in implant bony dehiscence exposure (residual bone defects) as

							compared to GBR-treated sites. - Transplantation of TRCs for treatment of alveolar bone defects appears safe and accelerates bone regeneration, enabling jawbone reconstruction with oral implants. -The results from this trial support expanded studies of TRC therapy in the treatment of craniofacial deformities.
Human Mandible Bone Defect Repair the Grafting of Dental Pulp Stem/Progenitor Cells and Collagen Sponge Biocomplexes	Aquino et al 2009 Italy	Biocomplex (DPCs) and a collagen sponge scaffold used for (OMF) bone tissue repair in patients requiring extraction of their third molars. 3 months	17 Both No	Yes	(DPCs)and collagen spongescaffold was used to fill extraction site.	Collagen sponge used to fill the extraction site.	(i) DPCs can be used for OMFbone repair; (ii) The use of DPCs on appropriate scaffold produces an efficient biocomplex; (iii) Collagen sponges can be considered an optimal supportfor DPCs.
Role of platelet-rich plasma in combination with alloplastic bone substitute in regeneration of osseous defects	Singhet al 2011 India	Evaluate the alloplastic bone substitute for its osteogenic potential with or without PRP 180 days	23 Both No	No	Group B had 13 (56.5%) patients whose osseous defects were filled with ABS with PRP	Group A had 10 (43.5%) patients whose osseous defects were filled with ABS mixed in normal	PRP accelerates vascularization of the graft, improves soft tissue healing, reduces postoperative morbidity and enhances bone regeneration. Advantages of

						saline (NS)	using an autologous PRP include no risk of cross-reactivity, immune reaction or disease transmission. In addition, the use of PRP improves handling characteristics of particulate graft material and affords easier packing into a grafting site thus, facilitating space maintenance and potential for bone regeneration.
Three Years after Transplants in Human Mandibles, Histological and In-Line Holotomography Revealed That Stem Cells Regenerated a Compact Rather Than a Spongy Bone: Biological and Clinical Implications	Giuliani et al 2013 Italy	DPCs capable of producing bone when seeded on collagen scaffolds and can be used for repair of human mandible defects. 3 years	7 Both No	Yes	DPCs seeded in collagen sponge scaffold treated mandible at extraction site	Collagen sponge inserted at extraction site	(a) DPCs seeded on a collagen scaffold repair bone. (b) Three years after grafting in mandibles, revealed that regenerated bone is uniformly vascularized and qualitatively a compact type, rather than a cancellous type that is physiological for the area. (c) Regeneration of compact bone occurs because DPCs do not follow the local signals of the surrounding

							spongy bone. (d) Clinical advantages afforded by the grafting of autologous DPSCs more significant than the disadvantages arising from regeneration of a bone type that is not normally present in the area treated.

Risk of bias within studies:-For RCT studies, according to Cochrane Risk of Bias Tool, all studies were judged as low risk of bias for, selective reporting and intention to treat . Regarding random sequence generation and Allocation concealment, 2 studies: Kaigler et al 2013 and, Singh et al 2011) (table 1) were judged as low risk of bias while it was judged as unclear for,Aquino et al 2009 and Giuliani et al 2013 study(table 1)as it did not mention type of randomization used. Regarding Blinding of outcome assessment, 3 studies (Aquino et al 2009 , Singh et al 2011 and: Giuliani et al 2013) were judged as unclear as there was no any mention about blinding of the assessor or statistician while it was low risk of bias for Kaigler et al 2013 study. Singh et al 2011 consider as high risk of bais for incomplete result and other 3 studies were considered overall low risk of bias. Figure (1) represents risk of bias summary: review authors' judgments about each risk of bias item for each included RCT study while Figure (2) represents risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included RCT study.

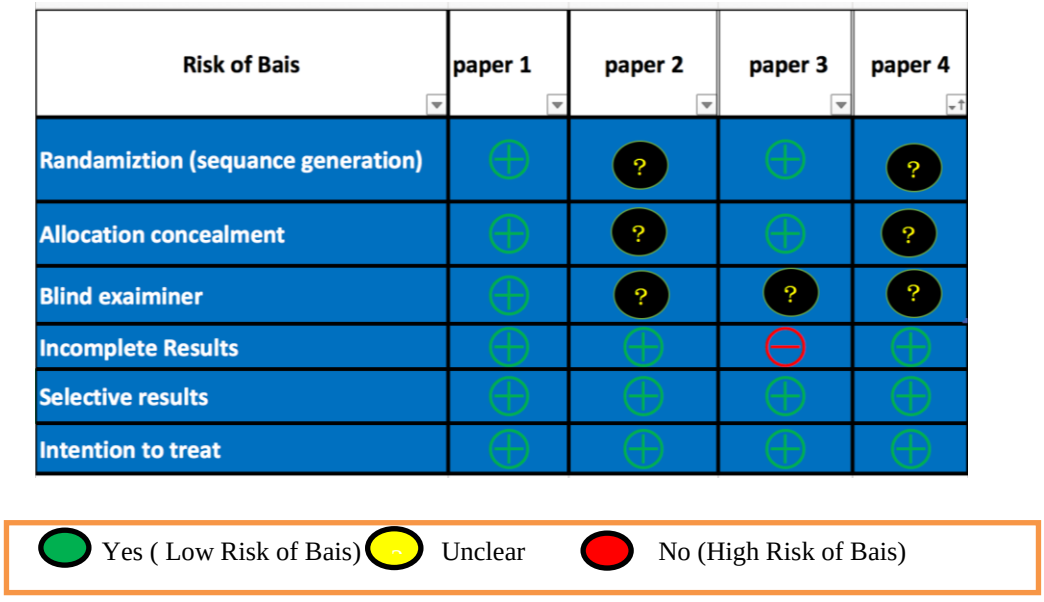

Figure 1:- Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT study

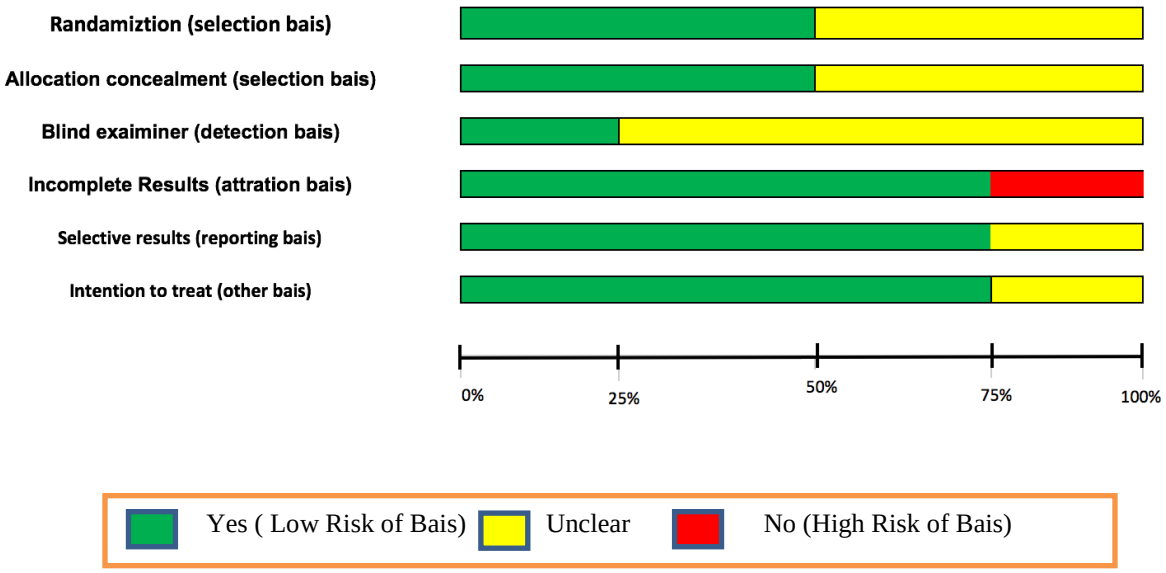

Figure 2:- Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included RCT studies

Paper 1: Kaigler et al 2013
paper2: Aquino et al 2009
paper3: Singh et al 2011
paper4: Giuliani et al 2013

Results:-

Out of the initial search that yielded 153 studies, 20 were considered potentially relevant for the present study, out of which 4 were, finally, selected. Figure (3) represents the flow chart for the study. The excluded studies before final inclusion was summarized in table (2) for reasons.

The final included studies were four (Kaigler et al 2013, Aquino et al 2009, Singh et al 2011 and Guliani et al 2013). The heterogeneity between trials prevented meta-analysis. Rather, a descriptive analysis of the reported studies was performed. Table (3, 4, 5, 6) represents summary of findings.

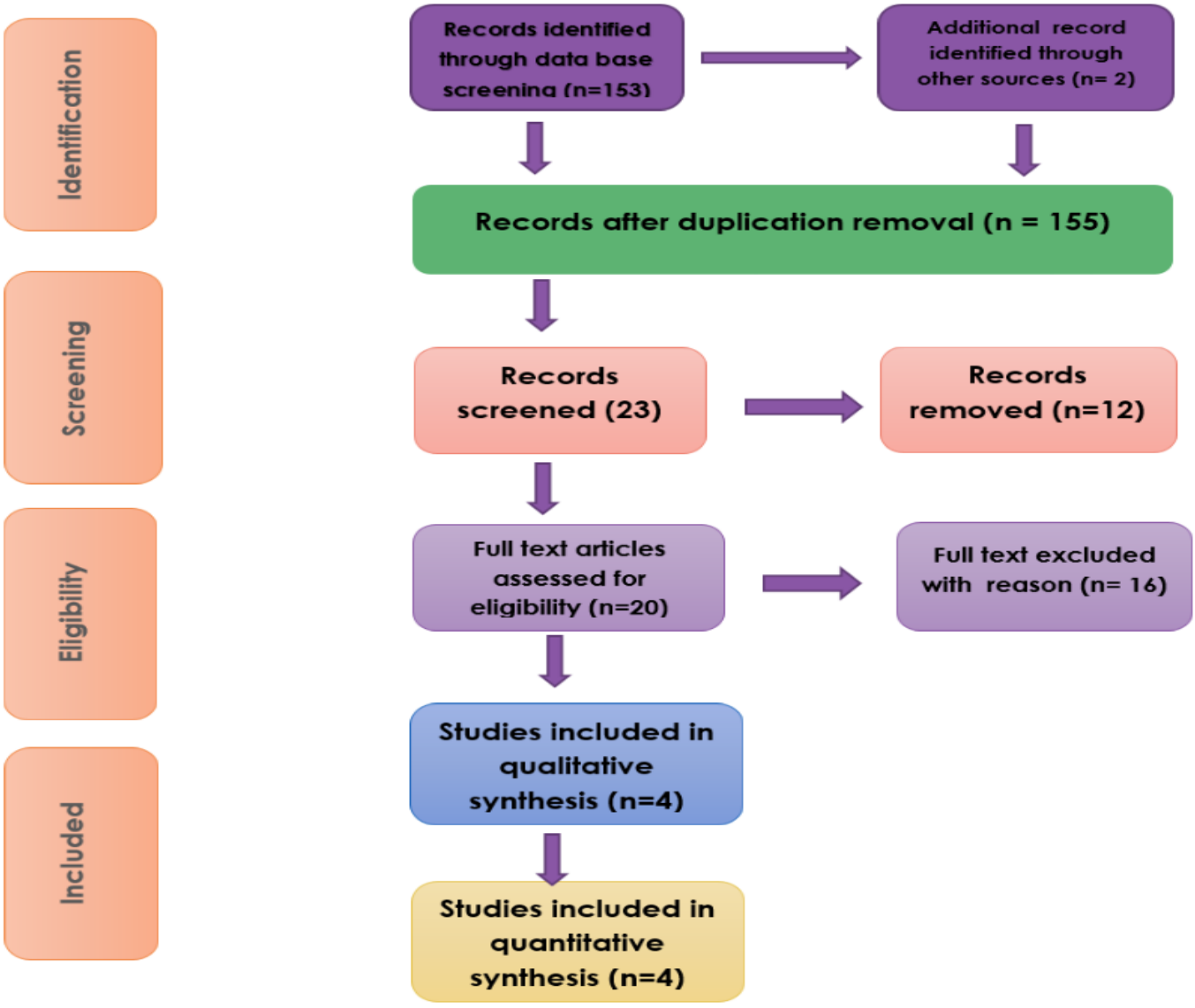

Figure 3:- Prisma flow chart for the study.

Table 2:-Summary of the excluded studies and the reason for their exclusion:

	References	Reasons for exclusion
1	Grunder et al 2011	Periodontal defect
2	Snyder et al 2012	Case report
3	Friedmann et al 2002	Problem in patient grouping

4	Walters et al 2003	Periodontal defect
5	Rodrigues et al 2011	Periodontal defect
6	kasaj et al 2008	Periodontal defect
7	Lekovic et al 2002	Periodontal defect
8	Yukna et al 2000	Periodontal defect
9	Cetinkaya et al 2006	Periodontal defect
10	Camargo et al 2005	Periodontal defect
11	Lekovic et al 2012	Periodontal defect
12	Camargo et al 2002	Periodontal defect
13	Gupta et al 2011	Periodontal defect
14	Matos et al 2007	Periodontal defect
15	Yamamiya et al 2008	Periodontal defect
16	Grimm et al 2014	Case report

Table 3:-Summary of findings for Paper 1: Kaigler et al 2013: Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial.

Parameters	Test group	Control group
Bone Density and Residual Bone Defects	80.1 + 2.0% (p = 0.01).	74.6 +3.3%
photographic images	Bone-like appearance clinically, was denser, and demonstrated high vascularity during biopsy harvest.	Highly vascular and fibrous, and most specimens were notably soft during biopsy harvest
Biopsy Analyses: micro-CT analysis (μCT) and Histomorphometry	Bone volume fraction (BVF) 28 ± 8% (p = 0.08). Bone mineral density (BMD) (195.0 ± 63.3 mg/cc) p = 0.1	13 + 6%, (85 ± 46.3 mg/ cc).
% bone area/tissue area (BA/TA)	At 6 weeks 28.8 ± 9.1% (p = 0.10) At 12-week 35.2 ± 8.9%,	19.6 ± 4.2% 35.1 ± 3.2% and

Table 4:-Summary of findings for paper2: Aquino et al 2009. Human mandible bone defect repair the grafting of dental pulp stem/progenitor cells and collagen sponge bio- complexes

Parameters	Test group	Control group
Clinical	7 Day: both group same- slight edema- no postoperative pain-normal healing with no scar	
Bone level Probing depth	30 Day: Cortical bone reach to level of CEJ of 2nd molar	Not seen

	3 Month: cortical bone level higher 6.2+2.3 mm	4.4+ 1.2 mm
Radiological	30 Day: High rate of mineralization	
Histology	Well organized and well vascularized bone with a lamellar architecture surrounding the Haversian channels	Immature, with fibrous bone entrapped among new lamellae, incomplete and large Haversian channels and evidence of bone reabsorption
Immune florescence analyses	Significant differences were observed for BMP-2 and VEGF expression: they were expressed at much higher levels ($p<0.001$) in the T group with respect to the C group	
One year Bone regeneration	Higher in T group with $p<0.01$, vs C group for all patients except N. 7.	

Table 5:-Summary of findings for paper3: Singh et al 2011: Role of platelet-rich plasma in combination with alloplastic bone substitute in regeneration of osseous defects

Parameters	Test group	Control group
Clinical	Healing was significantly higher T group (ABS + PRP) as compared with C (ABS + NS) Pain: no significant difference between two groups at any time interval ($P >0.05$) Postoperative swelling: no significant difference between two groups at any time interval ($P >0.05$) Infection and graft rejection: no significant difference between two groups at any time interval ($P >0.05$)	
The scintigraphic	3 patients with bilateral defects showed increased tracer uptake in region of osseous defect filled with ABS with PRP. The tracer uptake was 1.36 times higher in 1 patient, 1.30 times in second and 1.79 times in third patient in region of osseous defect filled with ABS with PRP	

Table 6:-Summary of findings for paper4: Giuliani et al 2013: Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerated a compact rather than a spongy bone: biological and clinical implications

Parameters	Test group	Control group
Clinical	Both group same normal	
Bone regeneration	Harder than C Drilling force 36N-cm	Less hard Drilling force 21N-cm
Bone level Probing depth	6.3 + 2.1 mm	4.5+ 1.4 mm
Radiological	High rate of mineralization	
Histology	compact bone architecture Haversian channels surrounded by lamellae (more than 20 in most cases), osteocyte containing lacunae, and a high density of ECM	Cancellous (spongy) bone type interrupted lamellae surrounding numerous large marrow-filled spaces arranged in a more or less regular pattern
Histomorphometric analysis	BV: 1.10 + 0.3 ($x10^8$)μm^3 $\leq .001$ BS/TV (%): 79.8+ 10.3 $\leq .01$	0.53 + 0.31 ($x10^8$) μm^3 47.6 +7.6
Synchrotron Radiation-Based Holotomography	more compact bone	

Discussion:-

Bone substituteand stem cells can be used as alternatives for regenerationand restoration of damaged and lost alveolarbone defects in humans in oral and maxillofacial field.Clinical analyses of the bone defect after replacement and augmentation demonstrated that there was bone regenerative response determined radiographically, and

histologically. Stem cells is easily accessible with limited morbidity, capable ofdifferentiating into osteoblasts and producing well-vascularized lamellar bone. Thus,it could be used for bone regeneration forcraniofacial bones[29-32]. Bone substitute can restore and maintain facial boneand help soft tissue support with reasonableesthetics, easy to use and handling, with favorable cost and time advantages and adaptability to a variousoral and maxillofacial areas[33-36].Review of literature revealed that both bone substitute and stem cellshave several advantages and disadvantagesand,hence,the research hypothesis was established,to comparebone Substitute versus stem cell in regeneration of alveolar bone defects in humans.

Alveolar bone defects is an esthetic and functional problem for many patients. Bony defects can be resulted fromoncologic surgery, traumatology, and implant surgery. Reconstruction of such a defect represent clinical challenges. Different modalities have been proven its effectiveness in restoring the bony defects. These modalities included bone substitute and stem cells with its different sources, advantages, and disadvantages. However, up to date, no evidencebasedapproval for either to replace the bony defectswith conventionalmodalities including bone substitute or replace it with the recent technique including stem cells and its variety. The trials presented in this review agreed that both modalities are efficiently used for reconstruction of alveolar bone defects but further discussion is recommended to advocate one over the other.

Frequency of bone grafting is the second most frequent tissue for transplantation, worldwide[33-36]. Bone substitutes with different types and forms considered the best method for replacement the different types and sizes of alveolar bone defects being biocompatible, easily molded into the bone defect.Also bone substitute is consideredosteoconductive,osteoinductive, thermally nonconductive, sterilizable, as well as readily available at a reasonable cost. This concept in agreement with Mironet al [37] and Pryor et al [38].

Several studies [39-42]proved that autografts are the gold standard method in bone substitution for several reconstruction procedures. The autografts possess an osteoconductive and osteoinductive properties, contain many growth factors and osteogenic cells for bone formation as well as slowly replaced by newly formed bone. The disadvantages of autografts was the second surgical donor site with possibility of post-operative pain and complications; infection, fracture, or neurovascular injury, as well as cosmetic deformity, and longer operative time.Tomford[43]and Lomas et al[44]recommended the use of allograft asa suitable alternative to autogenous bone graft. But, the disadvantages are costs, difficult procedure (tissue processing, harvesting), and its mechanical resistance limited the process of osteoinduction as well as it has risk of infectiontransmission[43,44].

Xenograftsa can be used for reconstruction of alveolar bone defects being osteoconductive with good mechanical properties, low costs and easy available[45-49].Alloplastic material in form of hydroxyapatitemost commonly dueto its osteoconduction, hardness, and acceptability by bone. However, calcium carbonate was completely resorbed in short time that lead to bone fracture.Tricalcium phosphate in combination with hydroxyapatite giving the effect of both, resorbable and steoconduction[50].

Despite that bone substitute has been the brillianttechnique for reconstruction of defective alveolar bone, stem cells start to gain importance in that fieldbecause itpossess superior osteogenic ability. Using of stem cells for reconstruction provides benefits not only to oral and maxillofacial surgeon but also for the patients. Patient-centered outcomes are the main target for researches in the last decade.

Concerning prevention of facial deformity as one of the complication resulted from defective alveolar bone theosteoinductive stem cells based therapies can be used to improve and accelerate the clinical outcomes. One of the advantages of using stem cellsis more predictable regenerative outcomesand improved esthetics. Local immune responses by the host cells against the stem cell are highly relevantin regenerative medicine. Mesenchymal stem cells may be applicable to suppress the local immune response during transplantation to attain ideal tissue regeneration. Stem cells and tissue engineering therapies are expected to provide a novel capability to regenerate large defects in periodontal tissues [51] and alveolar bone [52–54], and to ultimately replace the lost tooth itself [55, 56].

The present review ascertained that stem cells hold several advantage over bone substitute in reconstruction procedures. This idea was supported by the opinion of Watt[10]and Graziano[12]. Beingautologous and harvested form a natural source, easy and faster method to repair and regenerate damaged tissues with low-risk and effective therapeutic strategy,exhibits minor morbidity of the collection site, free from diseases experienced by disease transmission, and no need for secondary bone grafting procedures in small defect.However, on grafting a defective

area with stem cells, it must be taken into consideration their behavior as it might be relatively variable on the differentiation process. It may be affected by their origin rather than by the local signals arise from the treated area. The clinical advantages afforded by the grafting of autologous stem cells may be more significant than the disadvantages arising from the tissue that regenerated.

A doubt remains regarding the use of stem cells to find adverse effects. Stem cells are usually introduced to find common and intended outcomes, whereas adverse effects tend to be less frequent and unintended. Trials upon which this review is based might be useful to detect systematic adverse effects as the type of regenerated tissuesbut might be less advantageous as mentioned above.In contrast, in the 4 human clinical trials that met the eligibility criteria for this systematic review (Tables 1)and encompassed 71 adult subjectsin various clinical settings between January 1990 and April 2017, all the 4publications concluded thatthe use in stem cells or bone substitute for reconstruction of alveolar bone defect produced uncounted safety outcomes.[17, 57-59]

The finding could be categorized in one or more ways: stem cells and bone substitute can be used for alveolar ridge reconstruction; dental pulp stem cells seeded on an appropriate scaffold as collagen can repair bone and produces an efficient biocomplex, tissue repair cells isolated from bone marrowaccelerated alveolar bone regeneration and reduced the need for secondary bone grafting at the time of dental implant placement and finallythe use of platelet rich plasma with autogenous or alloplastic bone substitute can accelerate vascularization of the graft, improves soft tissue healing, reduces postoperative morbidity and enhances bone regeneration. Besides, it improves handling of graft material particles and help to manage and packing it easily into the proposed graft site therefore, assisting maintenance of the space with rapidly bone regeneration.

Conclusion:-

Clinical studies that encountered in this research are too limited in number and so it displays small sample sizes. It is clinically heterogeneous with nosolid conclusion can be reached. Investigators should pay their attention to this remarkable subjectand investigate it deeply. Each kind of stem cells should pull attention of researchers in oral and maxillofacial field to close obvious, yet important, research gaps of lack of enough randomized clinical trials that can be more trustedand get a standard evidence based clinical practice. Within the limitations of this review, it can be concluded that stem cells can be used as a safer and effective treatment modality to provide reconstruction of small maxillofacial bone defects. However, bone substitute ishigher cost-effective procedure reconstruction of such defects. The easily availability and less disease transmission with less morbidity of the donor site and cost of surgical approach to harvest stem cellsmake this technique superior to higher cost alloplastic bone graft. Further studies with a larger study samples and a longer follow-up period would be desirable with special concern on technique is recommended for larger bone defect site.

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