Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/12808
DOI URL: http://dx.doi.org/10.21474/IJAR01/12808

RESEARCH ARTICLE

COMPARISON BETWEEN STRONTIUM RANELATE AND METAL SUBSTITUTED HYDROXYAPATITE AS GRAFTING MATERIALS IN TREATMENT OF PERI-IMPLANT BONY DEFECTS WITH IMMEDIATE IMPLANTS (CLINICAL AND EXPERIMENTAL STUDY)

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Manuscript Info

Manuscript History
Received: 05 March 2021
Final Accepted: 09 April 2021
Published: May 2021

Abstract

Objective: The aim of this study is to compare between both of strontium ranelate and metallic substitute of hydroxyapatite as grafting materials in the treatment of peri-implant bony defects with immediate placement of dental implant in type I extraction sites within maxillary esthetic zone among clinical and experimental levels. This assessment was based on clinical, radiographic and histological studies.

Subjects and Methods: The present study was carried on two types of population among both experimental levels on experimental white albinus rabbits and on clinical level among human patients for replacement of non-restorable maxillaryanterior and/or premolar teeth within esthetic zone by immediate implant. A written informed consent was obtained from all patients before their participation in this study.Patients were classified into two groups: the first one was with five patients with non-restorable maxillary anterior or premolar tooth that was treated by an immediately placed implant in conjunction with metallic substituted hydroxyapatite while the second one was treated by an immediately placed implant in conjunction with strontium ranelate as grafting material.The second sample population of study was carried out among ten male white (newzland) experimental rabbits with average body weight between 2.5 and 3 KG and within suitable environmental conditions in Medical Experimental Research Center (MERC) in faculty of medicine, Mansoura University. All rabbits sample was also divided equally and randomly in two groups with five rabbits within each one by the same criteria as mentioned where the first group was composed of five rabbits that received dental implant within intentionally made defect in tibia by trephine bur in conjunction with metallic substituted hydroxyl apatite as grafting material within gap between implant and defect and the second group was with the same criteria and procedures with strontium ranelategafting material within the defect. Pre-oparative photographs and cone beam computed topography (CBCT) were taken for study sample population. Within clinical patients, immediately paced dental implant have been placed in anterior esthetic zone with bone grafting around dental implant

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according to each group, Immediate CBCT and implant stability measurements has been taken after surgery followed by six months follow-up period to evaluate marginal bone loss, bone density, papillary esthetic score, implant stability and probing depth around dental implants. While within experimental animals trephine bur was used to intentionally create the bony defect that will simulate defect around immediate dental implant with grafting material around according to each group with six months follow-up to evaluate marginal bone loss, implant stability,bone density and for histological examination around implant within grafted area. All data were collected and statistically analyzed.

Results: Generally among both clinical and experimental levels within both of clinical patients and experimental rabbits, metal substituted hydroxyl apatite (MSHAP) showed better results with significant difference than that presented in other group that has received Strontium ranelate (Sr) as a grafting material to fill the bony marginal gap around immediate dental implant during six months follow-up study period. Results presented high difference of significance between two groups in experimental and clinical levels in concern with both implant stability, marginal bone loss and even in bone quality and denisty when measured after six months follow-up. On the other hand there was no significant difference in concern with soft tissue response after six months in relation with peri-implant probing depth and MSHAP showed slight better results than that of Sr in records of papillary esthetic scores among clinical patients. Histological results showed better response of surrounding bony tissues towards MSHAP than that of Sr with more affinity of osteoblasts and osteocytes to the site of the grafted area.

Conclusions: Metallic substituted hydroxyl-apatite (MSHAP) with its additive magnetic molecules within hydroxyapatite structure has better bony response from surrounding bony tissues than that provided by Strontium Ranelate (Sr) according to bone filling and preservation with less marginal loss, more affinity of new osteoblasts and mature osteocytes, long term implant stability after grafting and better bone density and quality at the grafted area around immediate dental implants in anterior maxillary area.

Introduction:-

Tooth replacement by dental impant is form of an evolution after years of research and fundamental studies depending on concept of osseointegration which is well documented [1]. Due to the wide advantages and versatilities of dental implant like improved esthetics, function, and osseous preservation, so lost tooth replacement by dental implant is more viable choice nowadays than fixed bridges which involves preparation of adjacent sound teeth. Classical traditional Branemark implant surgical protocol involved flap elevation, drilling within alveolar ridge, and implant placement then primary closure, where extraction of hopeless teeth is the first procedure which is followed by socket healing for about three to six months before drilling and implant placement, But there was a problem that alveolar ridge resorption after extraction may make bone unsuitable for implant placement within many cases. [2]Resorption of the Alveolar ridge that occurs according to this classical protocol after tooth extraction is mandatory phenomenon. After tooth extraction bone loss is accelerated within first 6 months with loss of about 40% of height and 60% of the width of the alveolar bone [3] which limits the use of dental implants according to Branemark classical protocol and search for new ways to preserve alveolar ridge after extraction [4, 5], so immediate implant placement after extraction has been recommended to reduce bone loss[6,7]. After that, dental implant was classified according to placement time into immediate, recent, delayed and mature by Wilson and Weber [8] then there were many descriptive classifications for dental implant placement till International team for implantology (ITI) classification system that was presented in 2008 [9]. Immediate implant placement is defined to be placement of dental implant immediately after tooth extraction within the same visit [10] which requires combining of grafting bone in many cases to treat peri-implant socket defects [11].This gives to immediate implant placement technique many advantages over the classical Branemark protocol, such as: reducing bone and soft tissue loss in healing period after extraction, shortening of the ovelall treatment time, reducing the number of surgical interventions and more patient satisfaction [12].Although all these advantages of immediate placement protocol but immediate implant has many challenges as difficulty in control of implant position and angulation, bony defects of the osteotomy site during drilling , difficulty in achieving primary stability and finally the major challenge which is represented in the difference between size of the extraction socket and size of the implant which in most cases require bone substitution grafting materials to fulfill these gaps [13, 14] so, implantation into fresh sockets is often associated with gaps between implant and residual bony wall because the fresh extraction socket is wider than the implant diameter and this gap between socket walls and dental implant is called jumping distance or peri-implant gap which influences the primary stability of dental impant and osseointegration.[15, 16] where these gaps may cause cell migration from adjacent tissues into the gap which may affect osseointegration[17, 18].Bone grafting in these gaps between the implant surface and socket wall is important especially at the buccal aspect which is of great importance in aesthetic zone as it is usually thin [19, 20] and its resorption may result in gingival recession [21]. Regenerative management of this bony gap is mandatory to achieve best results with optimal bone fill with optimal bone-to implant contact (BIC), and least amount of bone loss. Many techniques and materials have been used to fulfill these requirements of an ideal immediate implant placement including wide versatility of barrier membranes and grafting materials bone substitutes that have been used as bone substitutes in guided tissue regeneration such as: autogenous, allografts, xenografts and alloplastic materials for the management of these defects according their ability for osseoinduction and/or osseoconduction[22].Among these materials that has been developed recently in the field of guided tissue regeneration and has been used for bone replacement as abone substitute material is strontium ranelate (SR). Strontium ranelate was used firstly in treatment of osteoporosis. Its chemical composition is formed from two atoms of stable strontium (Sr) which is combined with ranelic acid acting as carrier, unlike other drugs which were used in the treatment of osteoporosis as bisphisphonates, strontium ranelate (SR) has a dual effect on remodeling of bone as it is able to stimulate bone formation by activation of osteoblasts which is a property that shared with bone-forming materials, and to inhibit bone resorption by inhibition of osteoclasts, as anti-resorptive agents [23, 24].In vitro studies have showed that strontium ranelate enhances the differentiation and proliferation of early progenitor cells of pre-osteoblastic cells to mature osteoblasts and also increases their production of collagen type I [25, 26, 27]so, there is growing evidence that strontium affects the process of bone remodeling by affecting both bone formation and bone resorption. In vivo, administration of low doses of strontium at low concentrations also inhibits bone resorption as detected by bone histomorphometry in osteoporotic patients [28, 29, 30].Strontium ranelate (SR) also improves bone mass in an experimental model of osteopenia in rats and these histomorphometric data in estrogen-deficient rats suggest that (SR) has dual effect between bone resorption and bone formation with stimulation of collagen production within bony matrix [31]. All These findings raise the possibility that strontium ranelate may have beneficial effects on bone remodeling and within the field of guided tissue regeneration as a bone substitute grafting material in large mammals by decreasing bone resorption while maintaining bone formation so it may has a beneficial role as a grafting material with immediate implants [32].Development of new materials is one of the most important aims of biomaterials science especially in bone substitution. Hydroxyapatite (HAp) {Ca10(PO4)6(OH)2} is one of the most important bio-minerals in calcium phosphate based bioceramics which is considered to be the main inorganic constituent of bone so it is used as bone grafting material and reported to be fully non-resorbable[33, 34, 35].The major advantage of hydroxyapatite materials is that the nano size (10–100 nm) crystalline pattern between collagen fibers within bone is bonding directly with bone and providing perfect lattice between bone surfaces. HAp shows osteoconductive property which is stable to bioresorption, and has no side effects on the human.Its structure is similar to natural bone which consists of 72 wt% apatitic materials and Calcium to phosphate ratio in structure of HAp is 1.67 which is very close to that of natural bone [36, 37]. The most important characteristic properties of HAps are good bioactivity and biocompatibility which comes from the non-toxic effects on human tissues [38, 39]. Implants coated with HAps promote a direct physiochemical bond with bone, which leads to more rapid osseointegration but the main disadvantage of HAp is low mechanical properties in wet environments and can be dissolved during setting in living tissues. [40] These problems of HAp can be solved by addition of some types of reinforced agent as iron oxide and Mn oxides to produce what is called metallic substitute of hydroxyapatite. These agents can play role in enhancing magnetic properties of the product [41]. Magnetic-nanoparticles are made from biocompatible materials such as magnetite (Fe3O4) for which susceptibility is large. These particles have to be integrated into structure of HAp. [42]Insertion of the spinel ferrite MnFe2O4 resulted in nanoparticles having a core–shell structure in which the core was made up of the ferrite and the shell of Hap which has been used in regenerative bony surgery as it is able to undergo bonding osteogenesis .This metallic substitute of Hap mediate cellular interactions with extracellular matrix and cell surface ligands that improve bone grafting solubility and improves cellular reactions in relation to bony resorption so it may has beneficial effects in the field of immediate implant placement [43].From previous mentioned properties of both of strontium ranelate and metallic substitute of hydroxyapatite, less is still known about their effect with peri-implant defects with immediate implant so, recent study aims to compare each other on clinical and experimental levels.

Patients and Methods:-

The present study was carried on two types of population among both experimental level on experimental rabbits firstly then on clinical level among human patients where;Ten patients selected from the department of Oral Medicine, Periodontology, Oral Diagnosis and Radiology, Faculty of Dentistry, Mansoura University for replacement of non- restorable maxillaryanterior and/or premolar teeth within esthetic zone by immediate implant.A written informed consent was obtained from all patients before their participation in this study. Included patients within the study arepatients who are medically free from systemic diseases, good oral hygeine, no acute infection is present and patients with sufficient quality and quantity of bone. Patients were classified into two groups: first one included five patients with non-restorable maxillary anterior or premolar tooth treated by an immediately placed implant in conjunction with metallic substitute of hydroxyapatite (MSHAP)as grafting material and the second one treated by an immediately placed implant in conjunction with Strontium Ranelate (SR). Experimental rabbits groups were divided equally and randomly to avoid bias with five rabbits in each group for both MSHAP and SR. Pre-operative measurements; photographs for all items under research, preoperative Radiographs: CBCT was taken for clinical patients before treatment and premedication with antibiotic administration for both patients and rabbits before implant placement. Among clinical sample (patients):Surgical procedures included full thickness flap reflection with atraumatic removal of remaining root or tooth.Implant(J Dental Evolution System, J Dental care, Modena, Italy)was placed in fresh socket using implant motor with saline coolant after curettage and its size is determined according to pre-operative CBCT within both groups.Patients were divided into 2 equal groups:The 1st group was grafted with MSHAP to fill the jumping space around immediate dental implant and the 2nd group was grafted with Sr.Post-operative care has been done for all patients.Prosthetic procedures began at six months from surgical intervention.Among experimental sample (rabbits): After experimental rabbits have beenanesthesized, small incision about 3 cm was made upon proximal side of tibia.Trephine bur with adequate size was used to remove the cortical bone and intentionally create the bony defect that simulated defect around immediate implant.Implant drilling and insertion with adequate irrigation and coolant and the bony defect around the implant was filled with grafts from both comparative groups where;the 1st group was grafted with MSHAP while the 2nd group have grafted with Sr. This is followed by surgucal closure and post-operative care.All patients and rabbits will be seen at regular time interval for evaluation at the visit of surgical intervention and six months postoperative.Soft tissue evaluation: This wasdone among clinical sample (patients) in all groups where, soft tissue evaluation will be done by measuring peri-implant probing depth and pink esthetic score (PES).Implant stability: Using Osstell implant stability was assessed in all groups soon after implant placement to assess primary implant stability and six months after surgery to assess secondary implant stability within each group.Radiographic assessment was held pre-operatively among clinical patients by CBCT then six months post-operatively after implant placement that is to detect marginal bone loss and bone denisty after graft material application.Among laboratory samples (Rabbits): Rabbits were sacrificed and selected tibia was selected and fixed on CBCT machine for CBCT radiographic evaluation to assess peri-implant crestal bone loss 6 months postoperatively. Further histological examinations to tibia of rabbits have been done under light microscope by H&E stains to detect number of osteocytes around implant within the grafted area.

Results:-

Table (1):- Mean values of implant stability (IS) by ostell among the two study groups at insertion of implant and 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
At insertion	69.60±1.14	68.40±1.67	1.325^{ns} 0.222

6 months	74.80±0.83	69.60±0.89	9.494*** 0.000
P	0.000***	0.070 [ns]	
Paired samples t-test			

Table (2):-Mean values of marginal bone loss (MBL) between the two treated groups at 6 months post insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
6 months	0.52±0.24	0.88±0.21	2.438* 0.041

Table (3):- Type of bone density (BD) between the two treated groups at 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Personan Chi-Square P value
6 months	5D2	4D3/1D2	6.667[a] 0.024*

Table (4):- Mean values of peri-implant probing depth (PD) between the two treated groups at 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
6 months	1.90±0.41	2.10±0.41	0.756[ns] 0.471

Table (5):- Mean values of pink esthetic score (PES) between the two treated groups after final restoration.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
After final restoration	11.40±0.89	10.00±0.70	2.746* 0.0.025

Table (6):- Mean values of implant stability (IS) by ostell among the two experimental rabbits groups at insertion of implant and 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
At insertion	69.00±1.00	68.40±1.14	0.885[ns] 0.402
6 months	72.80±0.83	69.00±0.70	7.757***

			0.000
P	0.001**	0.070 [ns]	
Paired samples t-test			

Table (7):- Mean values of marginal bone loss (MBL) between the two experimental rabbits groups at 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
6 months	0.72±0.21	1.34±0.38	3.139* 0.014

Table (8):- Type of bone density (BD) between the two experimental rabbits groups at 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Personan Chi-Square P value
6 months	4D2/1D3	3D3/2D4	7.000[a] 0.03*

Table (9):- Mean values of the number of mature osteocytes (MOC) per-field X4 between the two experimental rabbits groups at 6 months post-insertion.

Time of assessment	Group I (n=5)	Group II (n=5)	Independent samples t-test P value
	Mean± SD	Mean± SD	
6 months	37.60±2.07	28.60±3.36	5.095** 0.001

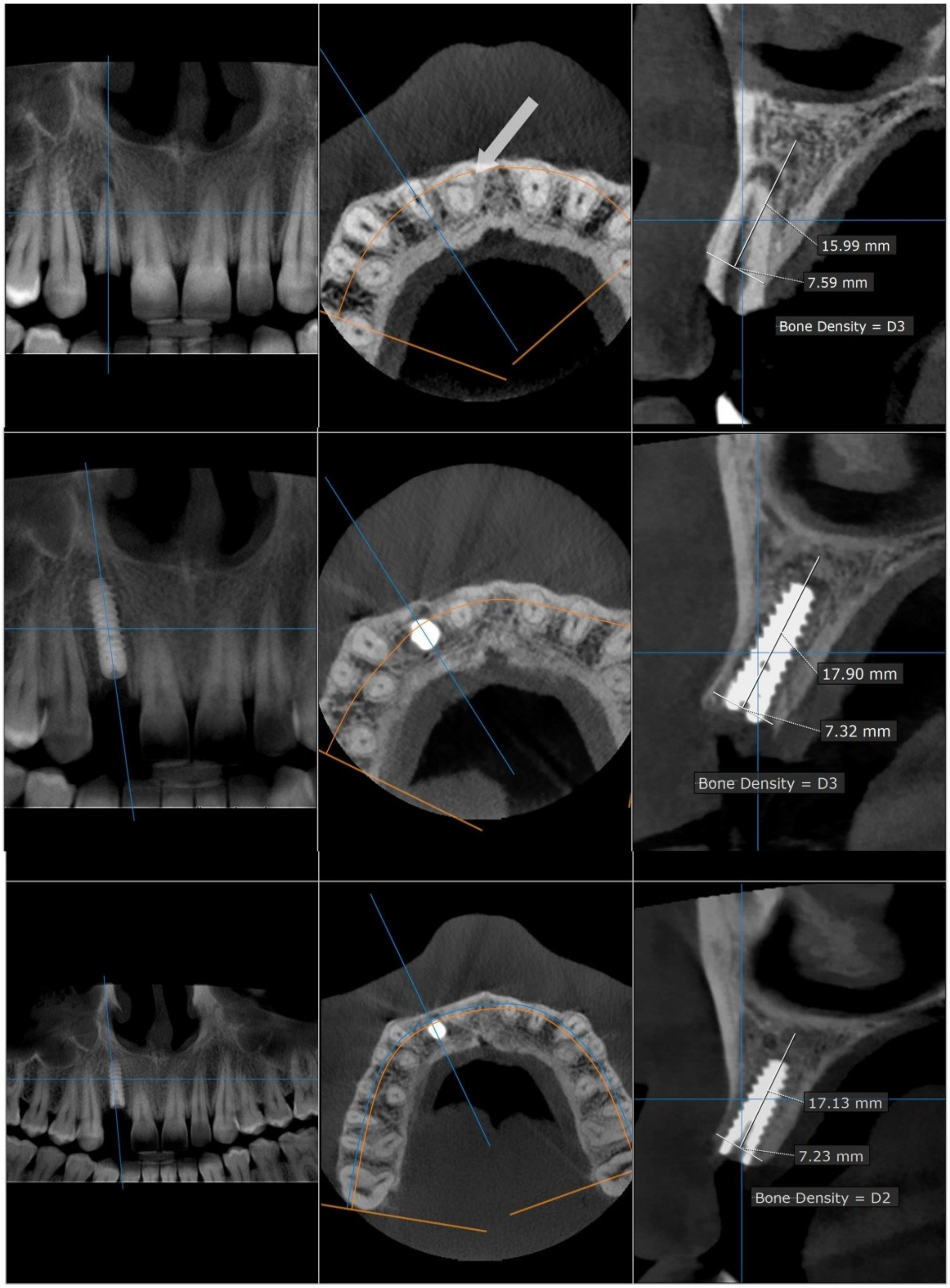

Figure (1):- Showing CBCT before, just after and after six months follow-up within MSHAP clinical group.

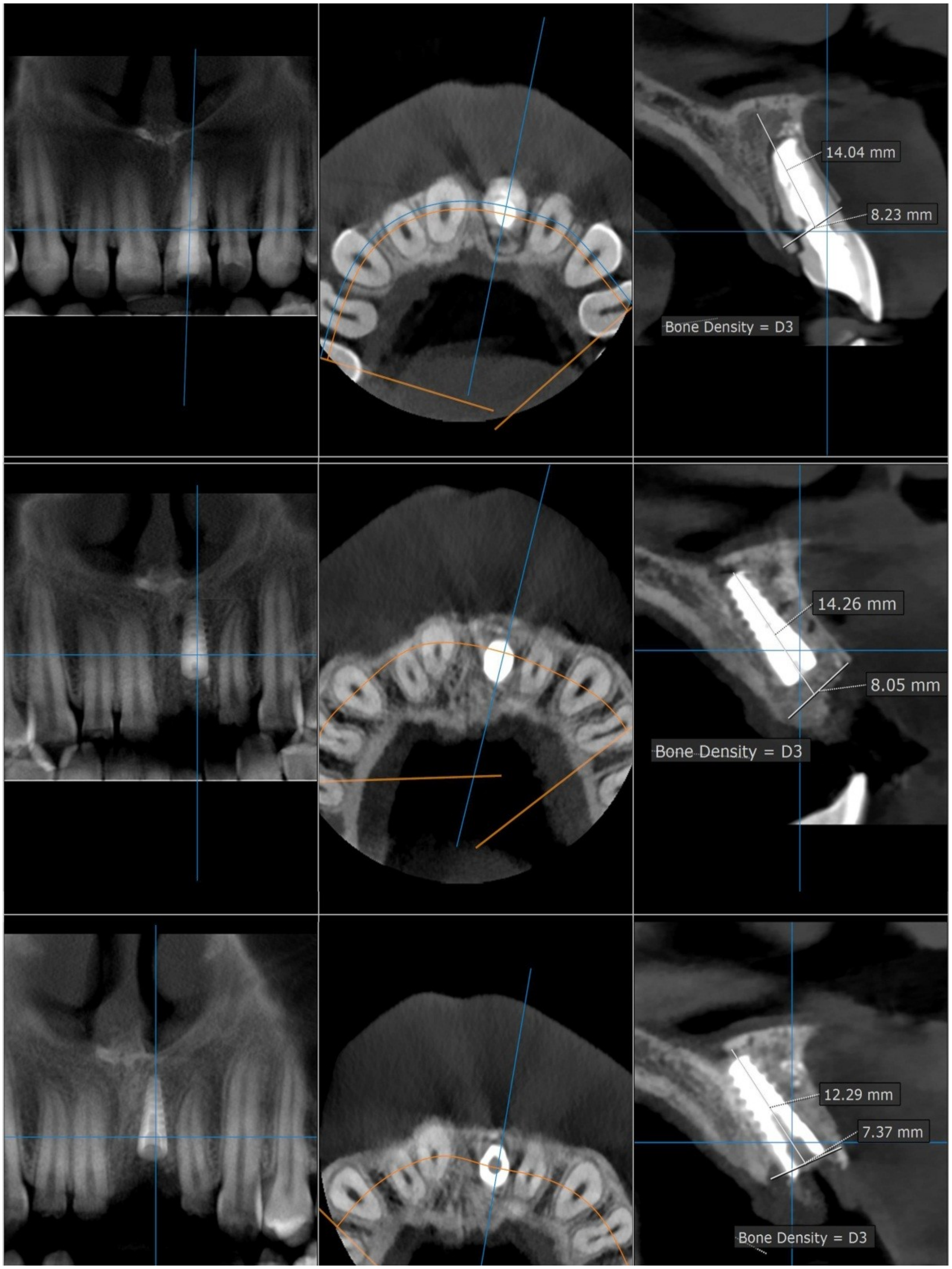

Figure (2):- Showing CBCT before, just after and after six months follow-up within Srclinical group.

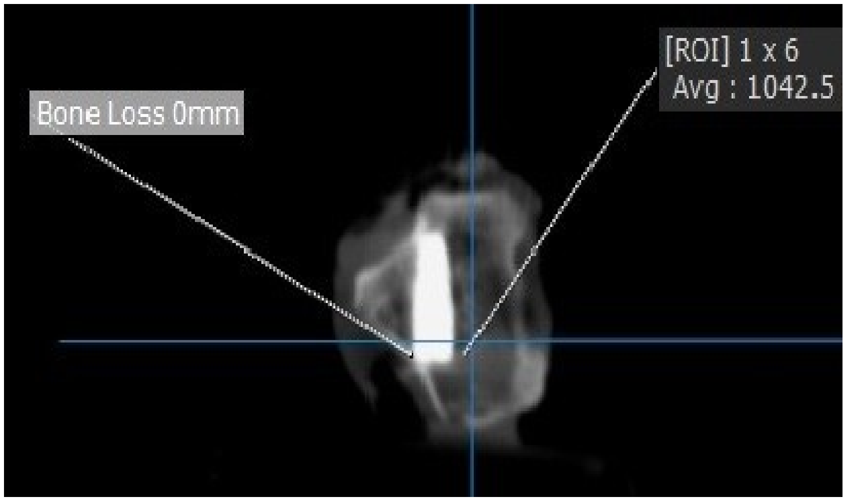

Figure (3):- Showing marginal bone loss (MBL) within MSHA experimental group.

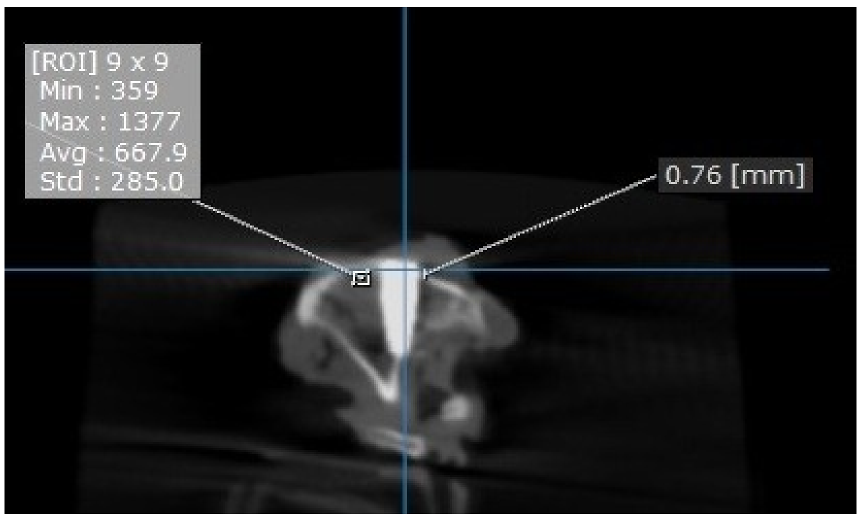

Figure (4):- Showing marginal bone loss (MBL) within Srexperimentalgroup.

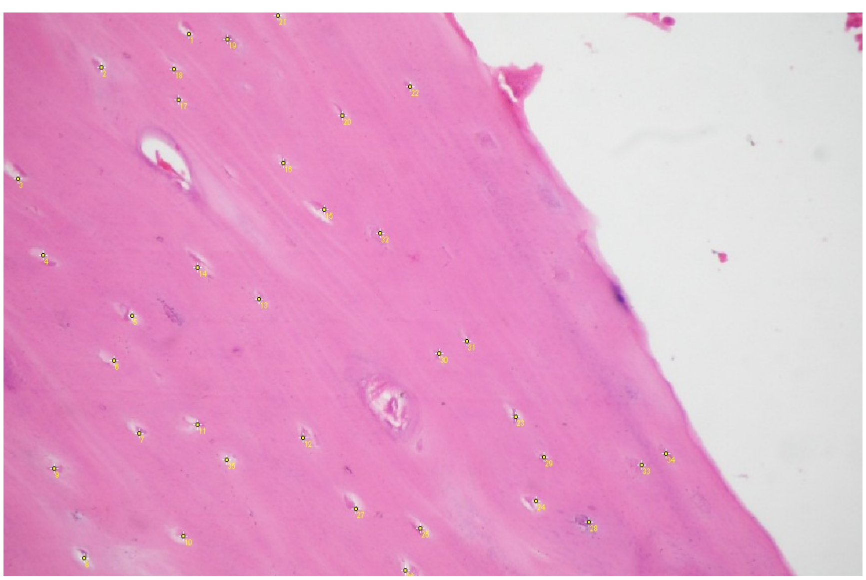

Figure (5):- Showing histological osteocyte number and distribution within MSHAP group.

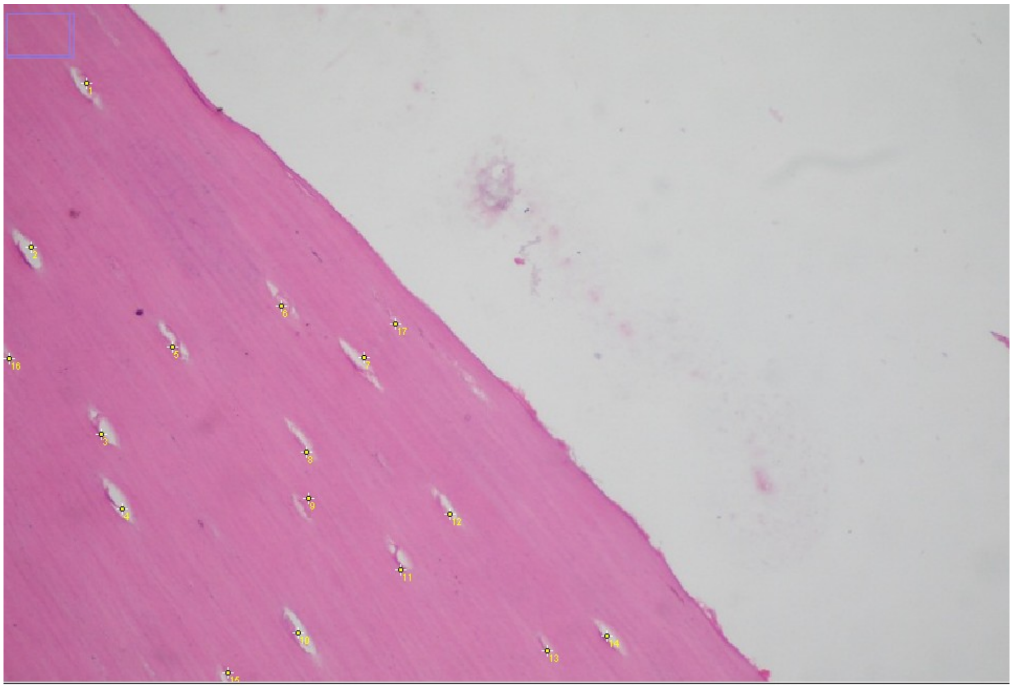

Figure (6):- Showing histological osteocytenumber and distribution within Sr group.

Discussion:-

While implant insertion at the time of tooth extraction is desirable for a number of reasons previously discussed, thereare a number of challenges, such as unfavorable extraction socket morphology, inadequate soft tissue for implant coverage, and bonedefectswhichmaypresentuniquechallengestotheclinician for ideal implantposition. The immediate placement of implants provides significant advantages, including fewer surgical procedures, shorter treatment time, and improved esthetics. There are significant areas of information that need to beclarifiedregardingtheuseofbonegraftswithorwith- out barriers around immediate implants that is to fill jumping spaces. Thekeyto immediate implantsuccessistoachieveprimarystabilitywithadequatecontactoftheimplant. [(44)]The extraction socket is usually wider than the implant diameter, which results in a gap between the cervical region of the implant and the bone tissue. The use of grafting biomaterials is indicated to preserve alveolar ridge. [(45)] Bone replacement grafts, including autografts, allografts, xenografts, and alloplasts are the most widely used as a treatment for the regeneration of peri-implant defects. [(46)]The administration of strontium at low concentrations inhibits bone resorption and stimulates bone formation, as evaluated by bone histomorphometry in osteoporotic patients.[(47)] Studies on healthy animals confirm that Sr improves bone microarchitecture at both trabecular and cortical levels and preserves the structure of bone matrix crystals without affecting the mineralization process. These changes can possibly be attributed to the improvement in the biomechanical properties of bone and it has anti-inflammatory effect on the soft tissues. [(48)]Magnetic HAP nanoparticles which present the metallic substitute of hydroxyapatite (MSHAP) enable their use in numerous applications in the field oftherapeutics and guided bone regeneration. MSHAP has been used for replacement of bone loss as biological grafting material with modification of previously mentioned disadvantages of conventional non-modified HAP materials. Metal substituted hydreoxy apatite is composed of 70% pure hydroxyapatite (HAP) nanoparticles doped with 30% Mn^{2+} and Fe^{3+} ions were manufactured using wet chemical method (WCM). [(49)]Synthetic HAP has been successfully used in hard tissue surgery, as it is capable of undergoing bonding osteogenesis and is relatively insoluble in vivo to overcome any previous drawbacks within conventional HAP.[(50)]

According to obtained clinical, radiographic results among clinical and experimental levels in concern with newly formed bone by both of MSHAP and Sr between groups of the study; implant stability, marginal bone loss and bone denisty were measured at six months follow-up study .According to ISQ scale of ostell both of MSHAP and Sr have achieved acceptable values of secondary implant stability over a period of six months follow-up.These results have been achieved among clinical and experimental subjects. At time of implant insertion as a baseline record there was no difference of significance between both groups as there was no any treatment yet, but after six months MSHAP groups have showed very highly difference of significance in implant stability than achieved through Sr groups of study where (P < 0.001). On the other hand intra-group comparison within each group separately, MSHAP groups showed high difference of significance between baseline and six months follow-up records (P < 0.001) while there was no difference of significance between baseline records and 6 months follow-up among the Sr group although these reading of Sr group is still acceptable.Implant stability records have supported the results obtained from radiographic examinations in concern with marginal bone loss within both groups where both groups have achieved acceptable marginal loss but there was significant difference of results for MSHAP over Sr groups (P<0.05) which reflect efficient bone fill ability of MSHAP. Also bone quality and density results showed significant difference between both groups along Hounsfield digital calculations.

Strontium ranelate has been used widely to improve osseointegration either by coating of dental implant, grafting material or either by systemic administration of the drug where, **Li *et al*.** found that systemic administration of Sr increased implant osseointegration process, improved peri-implant bony trabecular microstructure, produced anabolic effects and enhanced implant stability with significantly increased bone volume and that refers to dual action of Sr by direct action on bone progenitor osteoblasts and inhibitory effect on the osteoclastic activity. [51]**Ammann*et al.*** found that rats treated with Sr show increased trabecular and cortical bone volumes and trabecular number and thickness and further more bone trabeculation. These findings were contributed to increase bony growth factors which reflect the bone quality to achieve adequate and acceptable implant stability. Theyshowed by CT measurements that Sr treatment could positively influence intrinsic bone tissue quality. [52]

Results of this study comes also in consistent with **Xuan J *etal***[53] They have attributed their results as Sr has shown to stimulatebone collagen synthesis in vitro, as a result of a modification of the bone matrix mainly constituting type I collagen. It has also consistently shown in rat calvaria to stimulate DNA synthesis and bone collagen synthesis.Sr has demonstrated to stimulate bone formation, which may be beneficial for Osseointegration, and it has also been reported to stimulate preosteoblastic and osteoblastic cell replication and synthesis of collagenous matrix. These results were not in consistent with **Junyu Shi *etal***[54] who found no addidtive effect of strontium on process of osseointegration around titanium dental implants in animal rabbit mode.According to metal substituted hydroxyapatite group and its results over Sr this leads to that MSHAP has succeded to provide more stability, marginal bone preservation and better bone quality at the grafted area.DuringassessmentofMarginalbonelevel(MBL),asuccessfulimplant should present less than 1.5 mm of bone loss during the first year of service and less than 0.2 mm annually thereafter, **Kasaj*et al.***[55] have evaluated the clinical efficacy of MSHAP as a generative material in the treatment of periodontal defects and reported adequate values of bone gain.**Bhardwaj*et al.*** evaluated the efficacy of zinc incorporated nano-hydroxyapatite bone graft in treatment of periodontal defects.A split-mouth study with 45 sites were randomly treated with MSHAP or with HAP alone. Statistically significant improvements in all clinical parameters were seen with MSHAP at 12 months. They concluded that MSHAP bone graft can be considered as a prospective bone regenerative material. [56]**Li et al.** have concluded that MSHAP exhibited a remarkably beneficial effect on bone cells and they proved that a relatively high Mn2+ concentration induce the osteocalcin production. Also, Mn-substituted hydroxyapatites were able to support human osteoblast differentiation, proliferation and metabolism activation. [57] Hence, the adhesion of osteoblast to HAP coating is a crucial step for subsequent osteoblast functions. Mn2+ ions increase ligand binding affinity of integrate and activate cell adhesion.[58] Results of this study came in consistent with **JinxiangPan,**SelvakaniPrabakaran **and** MariappanRajan who have concluded that the anti-microbial activity of grafting HAP was increased by the presence of minerals such as Zn and Ce in the composition. This was further enhancing the bio-compatibility of the material along with the **in-vitro** osteoblast proliferation and act as a scaffold for osteoblast differentiation. They concluded that the drawbacks of pure HAP like inefficient osteogenic and anti-microbial potential which was overcome by adding multi-minerals. [59]Results are showing acceptable soft tissue response towards the grafting materials where that mean± SD with MSHAP was 1.90±0.41 mm while it was 2.10±0.41 mm among Sr group. These results is showing no significant difference between both of two groups in concern with peri-implant probing depth with (P>0.05). Also, results were comparable in concern with PES in both groups with slight significant difference between two groups in favor of MSHAP (P<0.05). In the strontium ranelate group the soft tissue response was in agreement with that reported by **Nunes& Pelletier,** who found that Sr has anti-inflammatory effect by reduction in the release of cytokines tumor necrosis factor alpha (TNF-α) and interleukin 1 beta(IL-1β). [60,61].Number of osteocytes was measured after six months follow-up period of dental implant and grafting procedures using Image J software of images captured from light microscope under 400 X magnification power.Results were acceptable among both groups of the study but it showed difference of significance between two groups in favor of MSHAP (p<0.01).These results was in consistent with our clinical and radiographic results within this study. **JE Fonseca** alsohas seen that strontium ranelate is able to increase pre-osteoblast replication, osteoblast differentiation, collagen type I synthesis and bone matrix mineralization probably through a CaR-dependent mechanism. Paralleling these anabolic effects, there is inhibition of osteoclast differentiation and activity and enhanced osteoclast apoptosis apparently mediated by an increase in OPG/RANKL ratio and by a CaR-mediated mechanism.[(62)]**Ghasak H. Jani, Shatha S. Al-Ameer and Salam N. Jawad**[(63)] have compared between both Sr and non-metallic substituted HAP and concluded that Sr has better histological results with more number of mature osteocytes and more bone formation area when used as titanium implant coating than that achieved with conventional non-metallic substituted HAP. The antibiosis of results with ours of recent study proved that the additive value of metallic ions within HAP structure to form MSHAP provide more affinity to osteoblasts and enhance maturation of osteocytes with more bony matrix formation and mineralization within the grafted area.

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