ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
Volume 3, Issue 11, May 2014

Zinc-doped glass role in filling of loss of diaphyseal bone substance in NZW rabbits

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Abstract*— Biomaterials utilized into bone sites have much interest, both scientifically and industrially. In this context, our work concerns the study of bone callus after filling a diaphyseal loss of bone by a bioactive glass doped by Zinc. For this study we created loss of bone of 1 cm3 by a surgical operation at the level of diaphysis of a New Zealand white rabbit. The vacuum creates has been subsequently filled by a bioactive glass doped with Zinc. The experiments were carried on groups of five rabbits for each duration of implantation of 1, 2, 4 and 6 months. The purpose of our work is to assess the osseointegration bone resorption and bioactivity of Zn-BG, after experimentation'' in vivo''. We have studied the behavior of implanted glass and of bone callus well as the bioconsolidation by means of the exploration of bone / implant interface. For this, we carried out analyzes physico-chemical in order to understand the evolutionary phenomena over time .The scanning electron microscopy (SEM), to follow the morphological evolution of the implant over time. The SEM photos show the morphological changes of callus, which from the 4th month, reveals a similar morphology to that of osseous tissues to the interface of the bone and the Zn-BG. The X-ray diffraction shows that the Zn-BG gradually degrades over time up to the 4th month after implantation. The diagrams obtained are characteristic of a biological apatite which crystallizes in a hexagonal system similar to other of the bone matrix. The clinical studies were carried out by medical imagery preliminary radiological and by scanner. Indeed, using radiology, we note that during the first month ago juxtaposition between Zn-BG and bone, while toward the 3rd, 4th and 6th month several phenomena was observed among which, we quote the corticalization of the implant, the absence of border between glass and the bone and the resorption of the implant.

***Index Terms*— diaphysis bone callus, physic-chemical Characterization, radiology, Zinc-doped bioactive glass**

I. INTRODUCTION

To test the efficiency of biomaterial, we should implanted it “in vivo” to seen it’s important role in bone regeneration, for this, we must created a diaphyseal bone loss [1]. In previous work, we have created a diaphyseal bone loss and we filled it by hydroxiapatite [2], also we created a bone defect in femoral condyle and we filled it by bioglass doped with strontium [3] and chitosane [4], we conclude that those bioglass have a good effect for osteogenesis, these were approved by biological and physicochemical analysis [2].

Several categories of bone graft and graft substitutes exist and encompass a variety of materials, material sources, and origins. The available graft substitutes formed from composites of one or more types of material. These composites are generally built on a base material. Laurencin *et* al [5] classification of grafts and graft substitutes could be modified as follows: Harvested bone grafts and graft substitutes; bone grafts, endogenous or exogenous, are often essential to provide support, fill voids, and enhance biologic repair of skeletal defects due to traumatic or non-traumatic origin. Limitations of use of endogenous bone substance involve additional surgery; often resulting donor site morbidity and limited availability [6], [7] where as allograft have been encountered with risk of disease transmission, immunogenicity [8]. And ceramic-based bone graft substitutes; include calcium phosphate, calcium sulfate, and bioglass used alone or in combination with other elements such us Zinc, Strontium, Bioactive glass ceramics (Bioglass) were first developed by Hench *et al* [9]. This glass is biocompatible, osteoconductive and bonds to bone without an intervening fibrous connective tissue interface [10], [11]. This material has been widely used for filling bone defects [12]-[14] alone and in combination with autogenous and allogenic cancellous bone graft [15]. Bioglass is composed mainly of silica, sodium oxide, calcium oxide and phosphates.

Zinc is an essential trace element that is required for growth, bone development, feathering, enzyme structure and function and appetite for all avian species, Zinc is commonly added as a supplement to all formulated, poultry diets due to natural feed ingredients are marginally , poultry diets due to natural feed ingredients are marginally deficient in Zn.

II. MATERIELS ET METHODES

A. Bioactive glass synthesis

We used a method similar to that already used in previous works in the doping of our Zn-BG with strontium Sr. Now we just changed Sr by Zinc (Zn). The first material studied was pure 46S6 possessing a composition closes to that of Hench’s 45S5 [16] which were used as a reference to validate our experimental procedure. Then, Zn was introduced into the 46S6 bioglass; a similar content of Zn to

ISSN: 2277-3754
ISO 9001:2008 Certified
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that of bone. Appropriate amounts of calcium metasilicate, sodium metasilicate, sodium metaphosphate, and magnesium oxide were weighed and mixed for 45 min using a planetary mixer. The powdered mixture was heated in a platinum crucible at 1300 °C for 3 h. The molten material was then poured into preheated brass molds to form cylinders of 13 mm in diameter and 10 mm in height. The prepared samples were annealed for 4 h at the appropriate temperature, corresponding to the phase transition temperature of the glass composition (about 560 °C), in a regulated muffle furnace, which was left to cool to room temperature at a rate of 1°C min–1. After elaboration, the powder particles, sized between 40–63 µm, were compressed in a perfectly isostatic manner. The prepared implants were sterilized by γ-irradiation from a 60Co source gamma irradiation at a dose of 25 Gy (Equinox, UK) using standard procedures for medical devices.

B. Animal model

New Zealand White Male rabbits weighing 1.5-2 kg and bred in the Central Animal House were used in this study. The animals were fed on a pellet diet (Sico, Sfax, Tunisia) and water *ad libitum*. The animals were maintained in a controlled environment under standard conditions of temperature (22±2˚C) and humidity (55±5%) with an alternating light-and-dark (12/12 hours) cycle. All rabbits were acclimatized for one week prior to the start of the experimentation. They were divided into 3 groups, each one containing 5 rabbits: control rabbits (T), intact tibias without the surgical creation of bone defects; operated rabbits with implant (IP), bone defects filled with (Zn-BG) to be tested; operated rabbits without implant (NIP), bone defects without any filler.

C. Surgical and postoperative protocol

Zn-BG powder (particle≤20 µm), was sterilized by γ-irradiation from a 60Co Source gamma irradiation at a dose of 25 Gy (Theratron external beam teletherapy, Equinox, Ottawa, ON, Canada), and then implanted and stabilized by mini external fixator (Fig.1). Anesthesia was induced with 10 mg/kg of ketamine (KetaminoL, Intervet International GmbH, Unterschleibheim, Germany) and 0.1 mg/kg of Xylazine (Rompun, Bayer Healthcare, Puteaux, France). Supplemented local anesthesia was applied after 15 to 20 minutes using 4 mg/kg carprofen (Rimadyl, Pfizer, and Paris, France). Cutaneous and under cutaneous incisions on the inner face of the tibia followed by an opening of the muscular aponeurose were carried out. A gap (1 cm of diameter) in the mid-diaphyseal level of the tibia was created aseptically. Zn-BG filled the loss of osseous substance only for the first group (IP). On the other hand, no filling was made for the second group (NIP). During a period which varies between 1 month and 6 months, the subjects were checked daily for clinical lameness or other complications. The handling of the animals was approved by the Tunisian Ethical Committee for the care and use of laboratory animals.

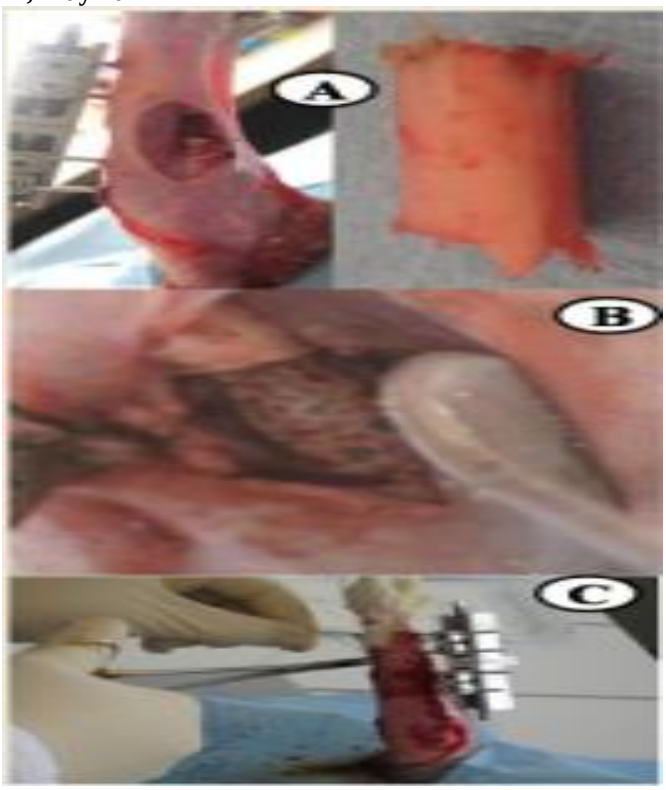

Fig 1: step of surgical operation: resection of an segment of bone (A), filling of bone loss by the Zn-BG (B) and Zn-BG fixing of by an external mini-fixator (C).

D. Radiographic analysis

To assess bone and Zn-BG density, conventional X-ray radiographs (Polymobil III, Siemens AG Wittelsbacherplatz 2 D- 80333, Muenchen, Germany) were taken following craniocaudal views. Radiography evaluated the quality of Zn-BG osteointegration and the levels of resorption.

E. Scanning electron microscopy coupled with EDS

The morphology of surfaces slumps was studied by using scanning electron microscopy (SEM) (JeolJSM6301). It is a technique of morphological analysis based on the principle of electron- matter interaction. To allow surface condition, bone was metalized by gold-palladium layer (a few µm of thickness) before being introduced into the analysis room. Semi quantitative chemical analysis on implanted bones surfaces, covered by gold–palladium layer to allow surface conduction, was performed by energy dispersive spectroscopy (EDS) inJeolJSM6400.

F. Phase analysis by X-ray diffraction (XRD)

X-ray diffraction (XRD) technique (Philips X'Pert-MPD system with a CuKa wavelength of1.5418Å) was used to analyze the structure of implanted bones .The diffractmeter was operated at 40kV and 30mA at a 2θ range of10–701 employing a step size of 0.058/s.

G. Statistical analysis

The statistical analysis of the data was made using the Student's t-test. All values are expressed as means±standard

ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
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error. Differences are considered significant at the 95% confidence level ($p<0.05$).

III. RESULTS

A. Animal condition after surgery

The animals were allowed to move freely in their cages after surgical operation. All surgical interventions were performed without complications. The postoperative healing was uneventful in all rabbits. The rabbits walked without a limp after 5 days. The operated rabbits remained healthy and showed no signs of discomfort or lameness. Any infection surrounding the fixator or the osseous-substitute was detected. No problems occurred in the bone defects during surgeries and healing, i.e., no failure of any implantation site was observed during the whole study period. All the implants appeared to be fixed securely in the tibias.

B. Macroscopic and radiographic evaluation

The radiological study shows that groups operated and not implanted (PIN) showed no consolidation over time (Fig 2),

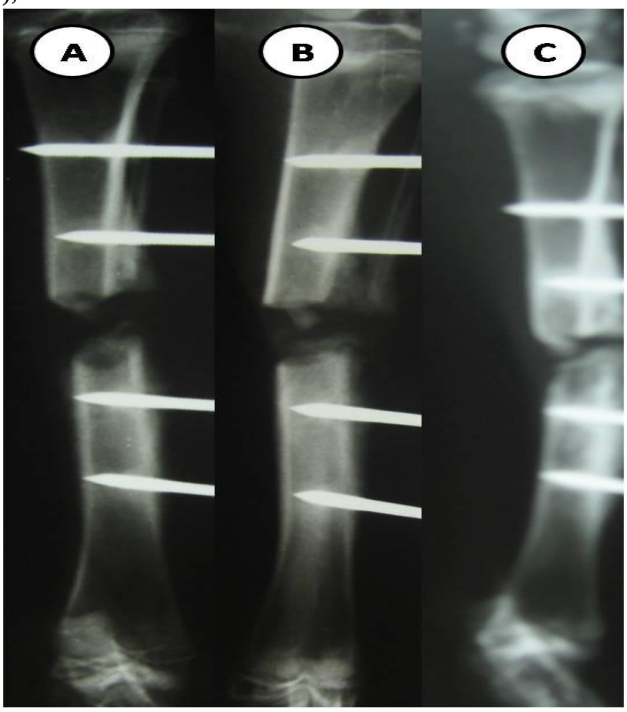

Fig 2: radiological follow for 3 months in group not implanted: 1 month (A), 2 months (B) and 3 months (C).

Whereas in implanted groups we showed that more we advance in time more than the phenomenons of consolidation have evolved. In one month we noted just only a juxtaposing between bone and Zn-BG (Fig 3 A), in the 3rd and the 4th month we note the phenomena of integration and corticalization (Fig 3 B, C), but as from of the 6th and the 9th month we note the presence of the phenomena of degradation and resorption of the Zn-BGs and it shall be replaced by bone cells (Fig 3 D, E).

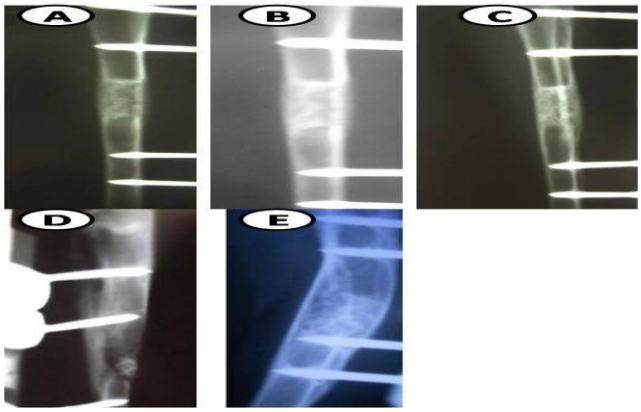

Fig 3: radiological follow for 9 months in group implanted with Zn-BG: 1 month (A), 3 months (B), 4 months (C), 6 months (D) and 9 months (E).

The scanner TDM 2D and 3D has confirmed radiological data such as the corticalization, osseointegration and resorption of bioglass (Fig 4).

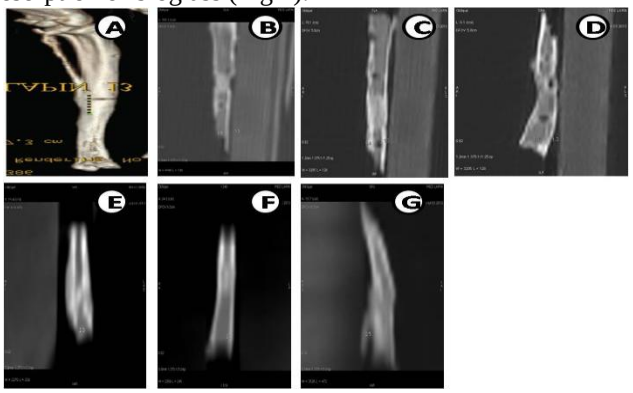

Fig 4: scanner follow for 6 month: group operated not implanted (A), operated and implanted with Zn-BG: 1 month (B), 2 months (C), 3 months (D), 4 months (E), 5 months (F) and 5 months (G).

C. Scanning electron microscopy coupled with EDS

SEM results showed that in the control group we have an appetite structure (Fig 5).

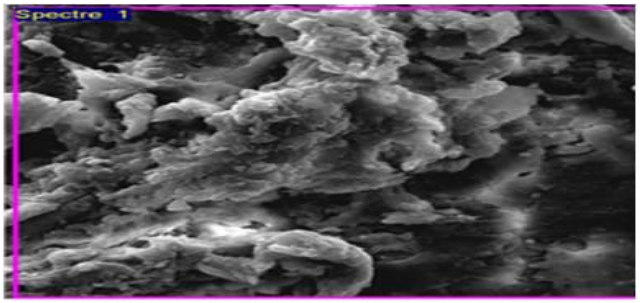

Fig 5: SEM of control group.

Also in the group of one month the SEM results have shown that in the bone-Zn-BG interface we have only juxtaposition between Zn-BG and the bone, but in the bone portion we have an appetite structure and in the Zn-BG portion we have only the Zn-BG (Fig 6).

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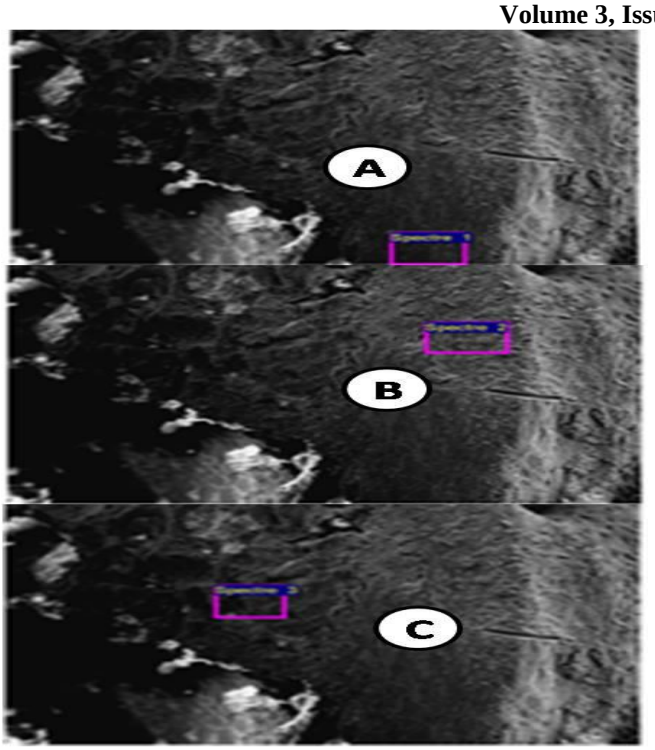

Fig 6: SEM of the group implanted of one month: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

Whereas in the group of 2 months we have a good interface link between bone and the bioglass and onset of exchange between bone and the Zn-BG (Fig 7).

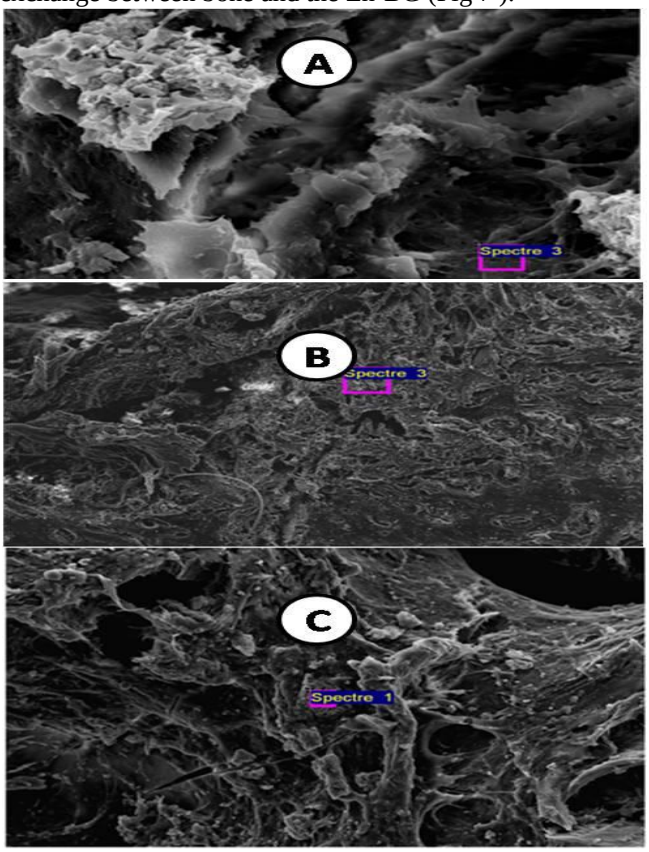

Fig 7: SEM of the group implanted of 2 month: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

The SEM has shown that from 4th month we have in the interface of Zn-BG and bone morphology similar to that of the bone tissue, we also note the presence of bone cells in the portion of the Zn-BG this clearly shows osseointegration of bone cells in the Zn-BG (Fig 8).

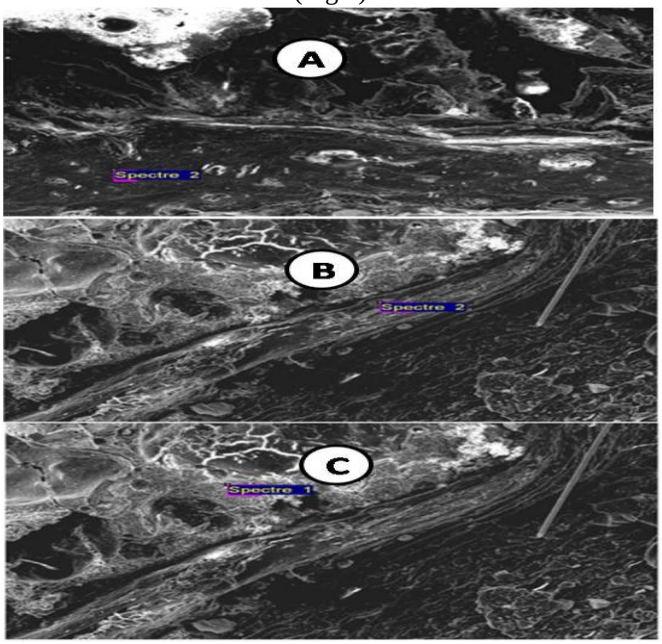

Fig 8: SEM of the group implanted of 4 month: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

Toward the 9th month the material is almost completely degraded and replaced by bone cells, and remains few crystals of Zn-BG, this explains well the degradation and resorption of Zn-BG and their replacement by bone cells (Fig 9).

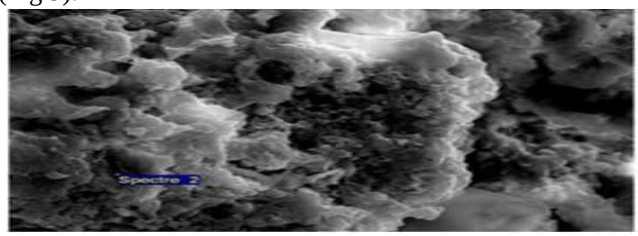

Fig 9: SEM of the group implanted of 9 month

EDS analysis showed that in the control group we noted only Ca and P (Fig 10),

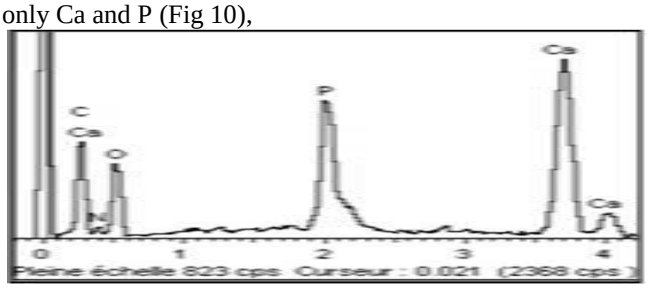

Fig 10: EDS of control group

But in the group of 1 month we noted in the portion of bone only Ca and P (Fig11 A), in the portion of bone- Zn-BG we have only Ca and P (Fig 11B). Also, in the Zn-BG we showed that in addition to the Ca and P a height rate of Zn and of silicone (Si) (Fig 11 C).

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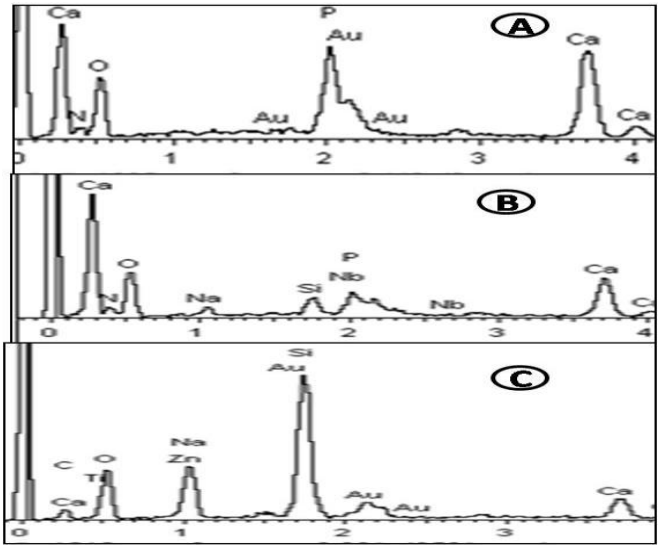


Fig 11: EDS of the group implanted of one month: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

After 2 month we don't seen a grand difference to other of 1 month (Fig 12).

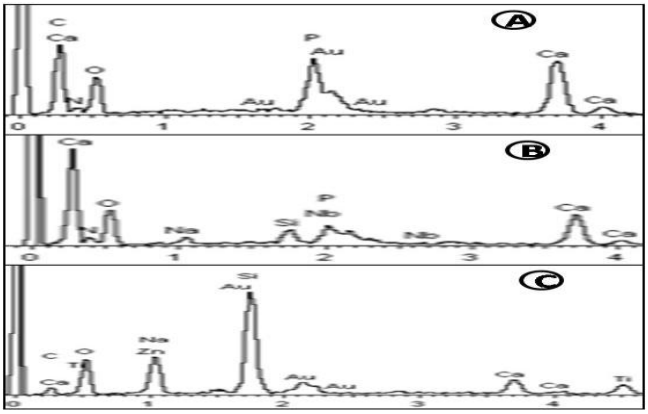


Fig 12: EDS of the group implanted of 2 months: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

Moreover, after 4 month we note that in the bone-bioglass interface we have in addition of Ca and P the Zn and the Titane (Ti) (Fig 13 A), but the most level is for Ca and P, also we noted a height level of Ca and P in the portion of Zn-BG (Fig 13 B).

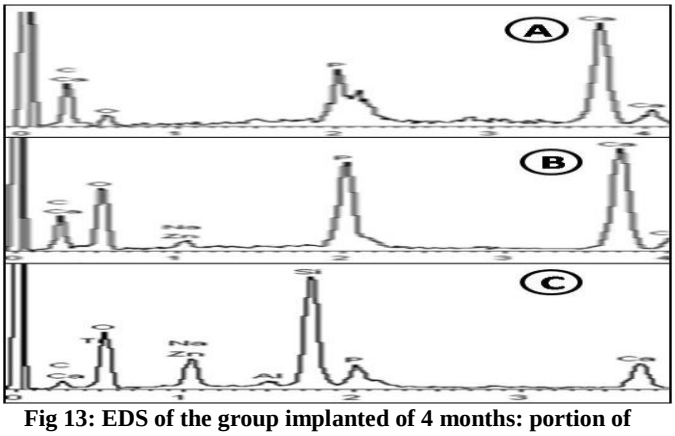


Fig 13: EDS of the group implanted of 4 months: portion of bone (A), bone –Zn-BG interface (B) and Zn-BG portion (C).

After 9 month we don't distinct between portion of biomaterial and bone, this indicates the osseointegration, bone reception and degradability of bioglass (Fig 14).

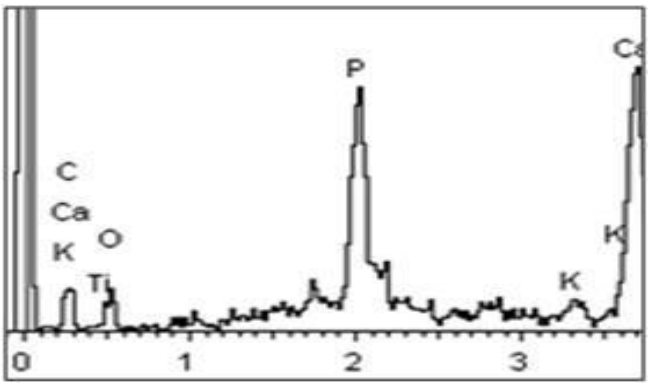
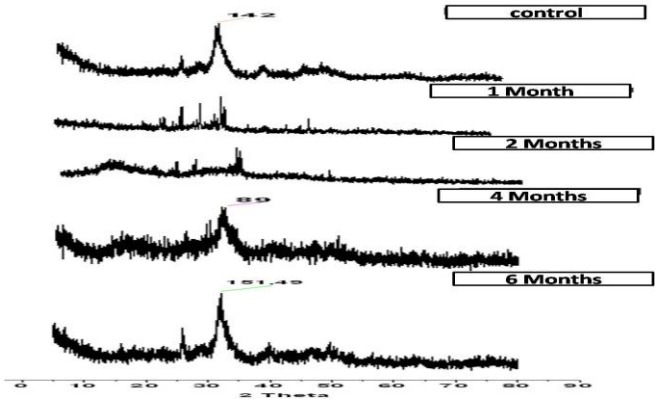


Fig 14: EDS of the group implanted of 9 month

D. Phase analysis by X-ray diffraction (XRD)

In the control group we observe that we have a hydroxyapatite which crystallized in a hexagonal system. Moreover, in the 1st we have an amorphous structure, XRD diffractogram does not correspond to apatite structure indeed the stingrays do not index in the amorphous system like in the other hexagonal which corresponds to the biological apatite, and we conclude that the Zn-BG persists. In the 2 moth, the results are quite similar to that of 1 month. After 4 month we noted that the apatite structure begins to appear this is testified by the presence of the most intense stingrays with index of Muller equal to 89 and with a position of 2 theta equal to 32.87°. Finally after 6 months, we notice that the index of stingrays equal to 151.49 is accentuated. These results are in agreement with others results SEM, EDS, scanner and radiology which show that from of the 4th months the Zn-BG is degraded and gave place for bone cells that are newly formed (Fig15).



. Fig 15: X-ray diffraction from bones implanted by bioglass-Zinc (BG-Zn) after 1, 2, 4 and 6 months compared with control spectrum.

IV. DISCUSSION

Developmental pathology, accidents, and tumor resection frequently cause bone loss, [17], [18] which is still a problem in orthopedic and reconstructive surgery. To resolve these problems, autografts and allografts have long

ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
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been used to fill bone defects caused by surgery, trauma or disease [19]. For solving problems of large bone losses we have recourse to the use of biomaterials. In previous work we used hydroxyapatite as a bone graft [1] but in the present study, we investigate the osseointegration of Zn-BG with the assistance of mini external fixor in a rabbit model over an observation period of 9 month. Macroscopic and radiographic evaluations have shown the phenomenon of corticalization, resorption, degradation and neoformation of bone cells, this explain the bioactivity and the biocompatibility of biomaterials [3]. Also scanner TDM 1D and 2D has confirmed the results of the radiology, this expresses osseointegration, compatibility, biodegradability and resorption of the biomaterial. Bioactive glasses have been clinically used for tympanoplasty reconstruction [20], as filling material in benign tumour surgery[21], for reconstruction of defects in facial bones[21], [22] , for treatment of periodontal bone defects [23], [24], in obliteration of frontal sinuses[25],[26], in repairing orbital floor fractures [27], [28], in lumbar fusion[29], and for reconstruction of the iliac crest defect after bone graft harvesting[30]. Also the SEM observation has shown that there is an evolution of exchanges over time of minerals between the Zn-BG and the bone, in one month we have juxtaposition between Zn-BG and bone, but after 2 month we noted an exchange, this explain well the biodegradability and biocompatibility of bioglass, The bone-bonding reaction results from a sequence of reactions in the glass and its surface [31]. After 4 moth and 9 month we noted in interface between bioglass and bone morphology similar to the bone this explain that the Zn-BG is degraded and replaced by bone cells, This is also due to the incorporation of Zn in the bioglass, After long-term implantation, this biological apatite layer is partially replaced by bone[32]. The behavior of bioactive glasses is dependent on the composition of the glass [33], [34], the surrounding pH, the temperature, and the surface layers on the glass [35], [36]. Zinc is an essential element for bone because it encourages the synthesis of osteoblasts and inhibits the synthesis of osteoclasts, Zinc increases the number of osteoblasts by inhibitingosteoclast-like cell formation in mouse marrow culture in vitro [37], [38]. Many factors are involved in regulating the activity of osteoblasts and osteoclasts. Of particular interest here is zinc's role as a local regulator of osteoblastic/osteoclastic function. **[39]-[43]** Zinc has a stimulatory effect on the production of TGF-β in osteoblasts in vitro[44],[45].TGF-β plays a role as a coupling factor in bone formation and bone resorption,[46] and is now believed to have a regulatory effect on osteoclast formation.
In addition, Recent literature now shows that TGF-β has a stimulatory effect and an inhibitory effect on osteoclast-like cell formation,[47], [48] and that zinc compounds can inhibit the stimulatory effects of TGF-β[40], [41], [43],[49]. Enzyme activity induced by another growth factor, IGF-1, is significantly enhanced by zinc. Also EDS has shown increased rates of Ca and P at the interface Zn-BG and bone and in the portion of the biomaterial and an increasing of rate Zn, Si, Ti, Na, which explains the mineralization of the biomaterial, their resorption, their degradation and their biocompatibility with bone, Bioglass was found to trigger new bone formation by allogenic demineralized bone matrix, and the biocompatibility of the glass was verified by the absence of adverse cellular reactions [50], [51]. Bone-bonding response significantly enhanced with the micro roughening of the bioactive glass surface, but the glass composition affected the intensity of the response [52]. Zinc is known to play a key role in regulating cellular activity by acting as a cofactor, stimulating protein synthesis needed for organic matrix formation (eg, the production of collagen) [53]-[56]. In addition Zinc also functions as a metal component of alkaline phosphatase, a metalloenzyme that plays a key role in the formation of new bone. Alkaline phosphatase structure incorporates 4 zinc atoms per molecule, 2 of which are essential for enzyme activity. [57], [58] Also we don't noted an inflammatory reaction after implantation, this explain the role by enabling better healing, In another study, the microroughening of the bioglass surface accelerated temporal changes in the expression of specific genes involved in the bone healing process [59]. X-ray diffraction pattern showed that, after 4 month we have an X-ray diffraction pattern similar to the biological hydroxyapatite this explains well that the Zn-BG has been almost degraded and replaced by bone cells. The results that are provided by the radio, scanner, SEM, EDS are consistent with the results that are provided by the XRD. All this explains well the mineralization of bioactive glass and the important role of Zn in the osteogenesis process. The bone-bonding reaction results from a sequence of reactions in the glass and its surface [32].

VI. Conclusion

Bioactive glasses, doped with zinc (Zn) were synthesized by fusion method. Zn presents interesting functions for the biological metabolism through their antibacterial, anti-inflammatory and antifungal properties. By biological and physico- chemical analysis we note that the layer of hydroxyapatite trained in surface of Zn-BG increases with time. We note also a good link of interface between bone and Zn-BG during the first speeds; in addition during the last speeds we note a osseoingration, resorption and degradation of bioactive glass and their replacement by bone cells, this explain the role of Zinc in the ossification process. Moreover, the introduction of zinc in the vitreous matrix has the effect of greatly modifying the kinetics of formation and crystallization (morphology and crystal size) of the hydroxyapatite layer. In the other hand, Zn has enhanced osteoblast proliferation well as bone growth over the implant site, by allowing better healing. Finally, all those results give the possibility to be a medical support for bioactive glass; consequently Zn-BG may solve several problems of orthopidie as being a bioimplant.

Acknowledgment

I think university of rennes1, France and university of sfax, Tunisia.

ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
Volume 3, Issue 11, May 2014

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ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
Volume 3, Issue 11, May 2014

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