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### REVIEW ARTICLE

#### SIMVASTATIN AS A SOLE OSTEOPROMOTIVE MATERIAL IN CRITICALLY SIZED BONE DEFECTS: SYSTEMATIC REVIEW.

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#### Abstract

**Objective:** The aim of this study is to evaluate the effect of simvastatin as a sole osteoinductive material on bone formation by eliminating the role that may be attributed to the various bone grafts that have been used with simvastatin as drug carriers. **Material and methods:** The search terms (Simvastatin) AND (Bone Defect) were used to search the PUBMED electronic database. In addition to this online search, a hand search of the relevant major international journals was also performed. **Results:** The search results showed total of 46 articles, only 3 articles were found to fulfill the inclusion criteria. Two out of these 3 articles used the same simvastatin concentration (0.2ml simvastatin solution on either collagen or gelatin sponge) while in the third article, collagen graft of swine origin was used with two different simvastatin dose (2.2 mg and 0.5 mg). Simvastatin seems to have osteoinductive potentials when applied locally in bone defects when used in proper dose and with proper carrier. **Conclusion:** The safety and osteoinductive properties of simvastatin are directly affected by the used dose and carrier, thus further studies are needed in order to determine the ideal dose/carrier complex that maximize the osteoinductive capabilities and eliminate or minimize the associated inflammatory reaction.

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#### Introduction:-

Although considered as the gold standard for bone regeneration, yet , autogenous bone is far away from being the (ideal) graft material because of its disadvantages such as donor site morbidity , limited availability [1,2]and unpredictable resorption.[3]

This has led to the use of other graft material such as allografts, xenografts and alloplastic materials in order to avoid these drawbacks especially in elective surgeries in which limiting patient discomfort should be considered as a main priority. [4] However, the use of these bone substitutes is also associated with some disadvantages such as the lack of osteoinduction, antigenicity & risk of disease transmission. [5, 6]

In the past years, researchers investigated the visibility of combining the osteoconductive properties of alloplasts with the osteoinductive properties of the recombinant bone morphogenic proteins (BMP). [7, 8] Which in spite of

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showing promising results, yet it did not have its way to the common daily clinical practice due to the difficulties facing its application such as the high cost and the inability to deliver the accurate dose of BMP.[9,10]

These aforementioned drawbacks of the current reconstructive options led to the rise of a new concept **THE IN SITU TISSUE REGENERATION APPROACH** [11]"this is authors quoted text" which involves the use of an external stimuli that up-regulate the patient own cells. This can be achieved via the addition of certain pharmacological compounds to an osteoconductive bone substitute.[12]

The bone anabolic action of statins was first reported by Mundy et al in 1999 after he screened more than 30,000 pharmacological compounds. He found statins to be the only compounds that have the ability to up-regulate BMP-2 and stimulate osteoprogenitor cells proliferation .[13]In addition to their osteogenic properties , statins were found to have anti-inflammatory , anti-oxidant and angiogenic effects.[14,15]

However, on addressing the anti-inflammatory effect of simvastatin, it should be kept in mind that, simvastatin in high doses can actually induce inflammation around the site of local application, [16] that is to say, while a low dose can be inefficient in bone formation, high doses may stimulate an excessive inflammatory response [17] which is well recognized as a major contributing factor to delay healing in both animal and human models. [18, 19]

The effect of locally applied simvastatin on bone formation received the main attention of researchers in the last few years as it was used in combination with various carriers such as collagen sponge,[17,20] Alpha tricalcium phosphate ( $\alpha$ - TCP),[12,21]Beta tricalcium phosphate( $\beta$ -TCP),[21]hydroxyapatite (HA),[21] gelatin sponge[22]and bioglass.[23] The results of these studies showed that the local effect of Simvastatin on bone depends on 2 main factors which are the used carrier and the simvastatin dose.[11]

The aim of this study is to evaluate the effect of simvastatin as a sole osteoinductive material on bone formation by eliminating the role that may be attributed to the various bone grafts that have been used with simvastatin as drug carriers.

## **Materials and methods:-**

### **Search strategy:-**

The search terms (Simvastatin) AND (Bone Defect) were used to search the PUBMED electronic database. In addition to this online search, a hand search of the major international journals that covers the field of dental implants was performed to detect any overlooked articles (Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, Implant Dentistry, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Journal of oral implantology). Search was carried out on the 20<sup>th</sup> of November 2016

### **Inclusion criteria:-**

1. Simvastatin applied in surgically created critical sized bone defects.
2. Simvastatin used as sole effective osteoinductive material.
3. Studies provide histomorphometric results.
4. In vivo studies only

### **Exclusion criteria:-**

1. Studies in language other than English
2. Simvastatin applied in periodontal defects or on surface of intact bone.
3. Systemically administrated simvastatin.
4. Simvastatin used with specially designed carriers, bone substitutes or mixed with any other material than may induce new osteogenesis.
5. Presence of any systemic condition that may affect the osteogenesis process.

### **Study selection and data collection:-**

The search results showed total of 46 articles which were subjected to a 3 staged filtering process in order to detect the articles that comply with the aforementioned inclusion criteria. In the first stage, 31 articles were excluded after screening their titles. In the second stage another 8 articles were excluded after screening their abstract. In the last stage the full text of the remaining 7 articles were screened which result in eliminating another 4 articles. In the end

of the filtering process, only 3 articles were found to fulfill the inclusion criteria {Table 1}. The screening process was accomplished by 2 reviewers. No additional articles were found through hand searching.

### Results:-

The 3 selected papers were all animal studies which may reflect that simvastatin did not find its way to human application due to the diversity in the results which varies from success in some studies to failure in others.

Collagen sponges were used in 2 out of these 3 studies [17, 20] yet, they were of different origin and the simvastatin dose used in both studies was also different. In the third study gelatin sponge was used as a carrier for simvastatin. [22].

In the study performed by Wong et al in 2003, [20] the collagen graft used was of bovine origin. In this study 15 critical sized bone defects (10x5 mm) were created in the parietal bone of 9 New Zealand rabbits. The defects were divided into 3 equal groups, passive control group (received no graft), active control (grafted with 0.2 mg collagen graft) and experiential group (grafted with 0.2 mg collagen graft mixed with 0.2 ml simvastatin solution). All animals showed normal recovery without any complication. The histomorphometric results of the biopsies obtained after killing the animals in the 14<sup>th</sup> day showed that the amount of newly formed bone was 308 % more in the experiential group { mean  $1.63 \text{ mm}^2 \pm 0.48 \text{ mm}^2$  } compared to the active group {  $0.4 \text{ mm}^2 \pm 0.28 \text{ mm}^2$  }. The difference between the 2 groups was considered statistically significant.

The second study that used collagen sponge was performed by Calixto et al in 2011 [17] in which it was of swine origin due to the outbreak of bovine spongiform at this time. A bilateral critical sized bone defects were created in the parietal bones of 64 Wistar rats using a 5- mm diameter trephine. Animals were divided into 4 equal groups, Control group (received no treatment), carrier group (received 0.2 mg collagen sponge), Simvastatin -1 group (received collagen sponge mixed with 2.2 mg/50 $\mu$ l Simvastatin solution), Simvastatin-2 group (received collagen sponge mixed with 0.5mg/50 $\mu$ l Simvastatin solution).

During the recovery period, all animals of Simvastatin -1 group showed necrosis and crust formation which persisted until the 45<sup>th</sup> day after surgery. On the other hand, only 4 animals of the simvastatin -2 group showed such complication which lasts only for 30 days. The histomorphometric results of the biopsies obtained after killing the animals in the 60<sup>th</sup> day showed that the highest amount of newly formed bone was detected in the control group (mean  $0.98 \text{ mm}^2 \pm 0.1 \text{ mm}^2$  ) followed by the simvastatin-1 group ( $0.75 \text{ mm}^2 \pm 0.2 \text{ mm}^2$  ) while the least amount was in the simvastatin-2 group ( $0.5 \text{ mm}^2 \pm 0.15 \text{ mm}^2$  ). The differences between these groups were considered statistically significant.

Unlike the previous studies, gelatin sponge was selected as a drug carrier by Özeç et al in 2007 [22] to perform his study in which he used a 3-mm round bur to create a 23 critically sized defects in the mandible of 23 Wistar rats. Animals were divided into 3 unequal groups, experimental group (include 9 animals that received 0.2mg gelatin sponge mixed with 0.2 ml simvastatin solution), active control group (include 8 animals that received gelatin sponge) and passive control group (include 6 animals that did not receive any graft).

All animals showed normal and complication free recovery. The histomorphometric results of the biopsies obtained after killing the animals in the 14<sup>th</sup> day showed that the amount of newly formed bone was 190 % more in the experiential group compared to the active group and 240 % more than the passive group { mean values were not available }. These results were both considered to be statistically significant.

### Discussion:-

The direct effect of statins on bone was discovered for the first time by Mundy et al [13] in 1999. Their study, along with others, suggest that statins, administered either locally or systemically, act as potent stimulators of bone formation and regeneration [13,24,25] Simvastatin was found to up regulate BMP-2, [26] vascular endothelial growth factor (VEGF) gene expression and alkaline phosphatase expression in osteoblasts, [27] it was also found to inhibit osteoclastogenesis. [28]

On comparing the effect of locally applied versus systemically administered statin on stimulating bone healing, locally applied statin was found to be 50-80 times more potent than systemically administered statin. [29] The

minimal effect of systemically administered statin on bone is expected as statins are known for targeting liver to treat hyperlipidemia with only small amount that reach and accumulate in bone. [30]

The aim of this study was to highlight the anabolic potentials of Simvastatin on bone when used as a sole osteoinductive material; any study that used simvastatin with a carrier that may affect either osteogenesis or the rate of simvastatin release was excluded from this study.

As it was mentioned earlier, whether the locally applied statin will play a positive or negative effect on osteogenesis is mainly determined by the used carrier and the statin dose. The 3 papers selected in this research showed that 3 different carriers were used as well as 3 different doses of Simvastatin.

In two out of the three papers, the dose of simvastatin was the same (0.2 ml simvastatin solution); yet 2 different carriers were used. In the study conducted by Wong et al,[20] collagen graft of bovine origin was used while in the study conducted by Özeç et al,[22] gelatin sponge was used. The results of these two studies showed that collagen sponge may be preferred over gelatin sponge as a drug carrier for simvastatin. This was based on the fact that although in Wong's study the size of defect was larger than the size of defect in Özeç's study (10x15 mm vs. 3x3mm), yet when the experimental group in each study was compared to its relevant active control group, the amount of newly formed bone was higher in Wong's study than in Özeç's study (308 % vs. 190 %).

It is worth to be mentioned that in both studies, animals were killed at the 14<sup>th</sup> day after the surgical procedure which will eliminate the time factor in the process of bone formation. However, the limited number of the studies does not enable the author to reach a definite decision regarding the superiority of collagen sponge over gelatin sponge.

In the 3<sup>rd</sup> study conducted by Calixto et al, [17] two different doses of simvastatin were used (2.2 mg and 0.5 mg). The carrier used in this study was collagen sponge of swine origin. Unlike the previous studies, the passive control group showed the highest amount of bone formation when compared to the other 3 groups.

This was attributed to the higher inflammatory levels that were found in the carrier group compared to the control group. The inflammatory reaction was even higher in the simvastatin groups especially within the group that received higher simvastatin dose. The synergetic inflammatory reaction of both a high simvastatin dose and an antigenic carrier was found to have deleterious effect on bone formation.

Regarding the safety of using simvastatin, animals in studies conducted by Wong [20] and Özeç [22] showed normal and complication free recovery, whereas all animals in Calixto[17] study that received simvastatin showed necrosis and crust formation which was more evident in the animals that received 2.2mg simvastatin. In addition to this local complication 6 animals of the simvastatin groups died (4 animals from the 2.2mg group and 2 animals from the 0.5mg group). These results comply with the findings of Nyan [16] and Calixto[17] that statins may have a dual effect on osteogenesis based on the degree of inflammatory reaction which is affected by the used dose.

### **Conclusion:-**

The safety and osteoinductive properties of simvastatin are directly affected by the used dose and carrier, thus further studies are needed in order to determine the ideal dose/carrier complex that maximize the osteoinductive capabilities and eliminate or minimize the associated inflammatory reaction.

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### **Disclosure statement:-**

The authors report no conflict of interest. The Final version of this manuscript was revised and approved by all authors.

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