Gingival Crevicular Fluid BMP-2 Levels Following Application of Atorvastatin or Enamel Matrix Derivative as an Adjunct to Open Flap Debridement in the Treatment of Periodontal Intrabony Defects

Proposal submitted in partial Fulfillment of the Requirements of Master Degree in Oral Medicine, Periodontology and Oral Diagnosis

BY

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بسم الله الرحمن الرحيم

وَيَسْـَٔلُونَكَ عَنِ ٱلرُّوحِ ۖ قُلِ
ٱلرُّوحُ مِنْ أَمْرِ رَبِّى وَمَآ أُوتِيتُم
مِّنَ ٱلْعِلْمِ إِلَّا قَلِيلًا ﴿٨٥﴾

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Dedication

To my beautiful and supportive family,

My life (husband & my sons), Mother , Father , Brothers especially Mohammed for encourage me , Sisters , my uncle and my aunt thanks for everything .

To my encouraging and sincere friend (Khawla)

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Acronym	Definition
CAL	Clinical Attachment Level
PD	Probing Depth
DFDB	Demineralized Freeze- Dried Bone
BMP	Bone Morphogenic Proteins
HA	Hydroxyapatite
TCP	Tricalcium Phosphate
β-TCP	Beta- Tricalcium Phosphate
NHA	Nano-crystalline Hydroxyapatite
EMD	Enamel Matrix Derivative
EMPs	Enamel Matrix Proteins
GCF	Gingival Crevicular Fluid
CBCT	Cone Beam Computed Tomography
GI	Gingival Index
ELIZA	Enzyme Linked Immunosorbent Assay
ATV	Atorvastatin
VEGF	Vascular endothelial growth factor
PPD	Prpbing pocket depth
OFD	Open flap depridement
ORS	Osseous respective surgery
PDL	Periodontal ligament
EDTA	Ethylene diamine tetra acetic acid
GTR	Guided tissue regeneration
d-PTFE	Dense polytetrafluoroethylne
FDDMA	Freeze dried duramater
IGF-1	Insulin-like growth factor-1
PDGF	Platelet derived growth factor
FGF	Fibroblast growth factor
TGF- β	Transforming growth factor beta
ALK	Activin receptor-like kinase
RANK	Receptor activator of nuclear factor kappa-B
RANK-L	Receptor activator of nuclear factor Kappa-B ligand
M-CSF	Macrophage- colony stimulating factor
PRP	Platelet-rich plasma
PRF	Platelet-rich fibrin

WBCs	White blood cells
LPL	Low-density lipoproteins
CRP	C-reactive protein
TNF	Tumor necrosis factor
SRP	Scaling and root planning
TMB	Tetramethyle benzidine
HRP	Horseradish peroxidase enzyme
OD	Optical density

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INTRODUCTION

Periodontal diseases are multifactorial chronic inflammatory diseases characterized by destruction of tooth-supporting tissues, in which progression of periodontal destruction involves complex interaction between periodontal bacteria and cells of immune system ***(Bascones, et al. 2005).***

Several treatment procedures have been introduced in attempts to regenerate lost periodontal tissues through mimicking the events that took place during the development of periodontal tissues ***(Saito, et al. 2010).*** Amelogenins are involved in the formation of enamel and periodontal attachment formation during tooth development and seems to control and promote periodontal regeneration through stimulating the early stages of osteoblast maturation by increasing cell proliferation ***(Schwarz, et al. 2000).***

Enamel matrix derivatives **(EMDs)** showed also angiogenic properties and can promote fibroblasts proliferation on the root surface and found to have anti-inflammatory properties ***(Lyngstadaas, et al. 2001, Wennstrom & Lindhe. 2002),*** while the differentiation of

progenitor cells to cell types of mineralized tissue found to be mainly due to Bone morphogenic proteins **(BMP)** signaling ***(Kémoun , et al. 2011).***

Randomized clinical trials verified the use of EMDs not only with intrabony and furcation defects but also in sites with horizontal bone loss and reported beneficial influence on periodontal regeneration ***(Esposito, et al. 2009 , Graziani , et al. 2014).***

Statins are 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, prescribed to prevent cardiovascular and cerebrovascular diseases by reducing serum cholesterol levels. Furthermore, statins have been reported to stimulate the expression of bone anabolic factors ***(Staal, et al. 2003***). **Statins** induce BMP-2 expression which stimulates VEGF gene expression and its production in osteoblasts thus promotes osteoblast differentiation and mineralization and can also directly affect osteoclasts ***(Deckers, et al.2002 , Maeda, et al.2004).***

Statins can modify the inflammatory cascades through pleiotropic actions at multiple levels, such as changing inflammatory mediators, altering leukocyte–endothelial cell interaction, and reducing expression of

major histocompatibility complex-II ***(Terblanche, et al. 2007).***

Atorvastatin **(ATV)** has been demonstrated to exhibit favorable effects in the treatment of bone remodeling disorders and bone fractures through the promotion of osteogenesis and the reduction of bone resorption ***(Bauer. 2003 , Wang, et al.2007).*** The anti-inflammatory and bone stimulating properties are among the actions of Atrovastatin that could positively affect periodontitis, and its use has been associated with decreased tooth loss in patients with chronic periodontitis ***(Sakoda, et al. 2006, Cunha-Cruz, et al.2006, Pradeep, et al. 2013).***

Current techniques to treat bone defects associated with periodontitis consist of surgically placing bone particles or substitutes into the defects to stimulate host bone formation. However, the use of inexpensive pharmacologic compounds to stimulate the host to produce autogenous bone growth factors, such as bone morphogenic protein-2 **(BMP-2)**, could be a cost-effective alternative in the management of osseous defects ***(Reynolds, et al.2003).***

Thus this randomized clinical trial was conducted to compare the clinical effect and estimate **(BMP-2)** in gingival crevicular fluid **(GCF)** after local application of either Atorvastatin gel or Enamel matrix derivatives in infrabony defects.

REVIEW OF LITERATURE

Periodontal diseases are group of chronic inflammatory diseases characterized by destruction of periodontal tissues in which periodontal pathogens activate host cells to produce pro-inflammatory mediators and enzymes which in turn promote periodontal tissues destruction ***(Offenbacher, et al. 1996, Bascones, et al.2005).*** Furthermore, periodontal diseases may be associated with modifying factors such as systemic diseases, cigarette smoking and local factors ***(Löe, et al. 1978, Baelum, et al. 1986, Okamoto, et al. 1988, Papapanou, et al. 1988, Hugoson, et al. 1998)***

The American Academy of periodontology in **1999** issued a new classification for periodontal disease that includes several major categories which are gingival diseases that is divided into plaque induced gingivitis, non plaque induced gingivitis, chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic diseases necrotizing periodontal diseases, abscesses of the periodontium, periodontitis associated with endodontic lesions and developmental or acquired deformities and conditions ***(Armitage, et al. 1999).***