



Cairo University

Comparative Histopathological Study on The Effect of Oral and Intraperitoneal Bisphosphonates on the Jaw Bones of Rats (In vitro study)

A thesis Submitted to Faculty of Oral and dental medicine
Cairo University,
in Partial Fulfillment for the Degree of Master in Basic Dental Sciences
(Oral and Maxillofacial Pathology)

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ACKNOWLEDGMENT

I would like to express my deepest gratitude to my supervisors,
Prof. Dr. Heba Mahmoud Dahmouh, *Professor of Oral and Maxillofacial Pathology, Faculty of Oral and Dental Medicine, Cairo University* for her constant encouragement and motivation to always do better.

Ass. Prof. Dr. Safa Fathy , *Associate Professor of Oral and Maxillofacial Pathology, Faculty of Oral and Dental Medicine, Cairo University* for her guidance, care and efforts to help me write this thesis. One simply could not wish for better or friendlier supervisors.

My sincere thanks also goes to Prof. Dr. Dalia El-Roubi, *Professor Doctor and theformer Head of Oral and Maxillofacial Pathology Department* who is always willing to help and give her best suggestions.

I would like to thank my family specially my brother khaled darwish for his help and support.

Special thanks to my beloved husband for his endless support
I couldn't have done it without you, you simply mean the world to me.

specially Sarah Badawy for helping me survive all the stress and not letting me
I would like to thank my friends and colleagues for their support and patience

give up.

DECLARATION

I declare that this thesis and the work presented in it are my own and that I have consulted all the references cited. This work has been carried out in the Faculty of Oral and Dental Medicine, Cairo University . under the guidance of Prof. Dr. Heba Dhmoush and Associate Professor Dr. Safa Fathy.

SIGNATURE

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JULY, 2016

List of abbreviations

ATP	Adenosine tri phosphate
BMD	Bone mineral density
BPs	Bisphosphonates
BRONJ	Bisphosphonate related osteonecrosis jaw
E	Extraction
FDA	Food and drug administration
FPPS	Farnesyl diphosphate synthase
GIT	Gastro intestinal
H&E	Haematoxylin and eosin
IPG	Intra-peritoneal group
IV	Intra...venous
NC	Normal control
NE	Non-extraction
OG	Oral group
ONJ	Osteonecrosis jaw
PAI-1	Plasminogen activator inhibitor-I
P03	Phosphate group
RVJ	Radiovisiography

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INTRODUCTION

[CHAPTER 1]

The skeletal system supports and protects the different organs of the body. It functions and is maintained on the basis of the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Bone fragility leading to fracture and disability is implicated in the pathogenesis of various bone resorption diseases. Preservation of bone strength, mainly determined by the amount of minerals, is a key to the management of these conditions (Bellido & Plotkin, 2011 and Matsurru et al., 2014).

Bisphosphonates (BPs) are drugs that have a high affinity for bone minerals. After the discovery of their pharmacological activity in the late 1960s, BPs have been employed as the treatment of choice for various skeletal pathologies of excessive bone resorption, such as osteoporosis, Paget's disease, hypercalcaemia, multiple myeloma and osteolysis associated with bone metastases of malignant tumors. They are available in two formulations oral and intravenous (IV) (Licata, 2005; Siddiqi et al., 2009 and Tardast et al., 2015)..

However, an extremely serious complication of BPs known as bisphosphonate related osteonecrosis of the jaw (BRONJ) was first reported in 2003, and has become an acknowledged complication of BPs (Oryan et al., 2009). BRONJ was considered as a new clinical entity associated with BPs treatment. It has been defined as a condition in which exposed, necrotic bone of the jaw has presented in a patient who was treated by BPs for at least 8 weeks but not exposed to radiation therapy (Woo et al., 2006 and King & Umland , 2008).

Since the emergence of the term BRONJ, it attracted the attention of many researchers due to its exclusive localization to the maxillary and mandibular jaw bones. However, its etiology and pathogenesis has not been fully elucidated (Pacheco et al., 2015). Many reports have shown that the effect of BPs on jaw bones

varied with the mode of administration, where IV BPs has been proven to be more potent than oral ones. Moreover, the incidence of BRONJ for patients was significantly greater in association with IV BPs. Although administration of oral BPs was involved in development of BRONJ as well, it was believed that most of these patients had other risk factors or their duration of treatment exceeded three years (Taylor et al., 2013).

Unfortunately, BRONJ lesions have been resistant to standard therapies for osteomyelitis. Furthermore, radical resection of the jaw has been a frequent consequence for BRONJ patients (Abu-ID et al., 2008). Another concern is the association of BRONJ with different risk factors. One of the most common risk factors is dental extraction which is a common dental procedure in elderly who are frequently taking BPs for treatment of osteoporosis (Khan et al., 2008).

Therefore, further studies would be beneficial for better understanding of the effect of BPs on jaw bones, different risk factors in addition to the pathologic basis of BRONJ lesions, which will ultimately improve diagnosis and patient outcome. Accordingly, it seems interesting to study the effect of oral and IV BPs on the jaw bones and to detect the histopathological changes associated with both modes of administration, in addition to evaluation of this effect by histochemical and histomorphometrical approaches.

Due to the limited and misleading public information regarding BRONJ, many patients have discontinued BPs treatment, resulting in inadequate care of the underlying skeletal condition so, medical and dental practitioners have requested guidelines regarding diagnosis, prevention and treatment of BRONJ (Khan et al., 2008).