بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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قسم

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MONA MAGHRABY

Possible Role of Deferoxamine in Autophagy Regulation Via Divalent Metal Transporter-1 (DMT1) in a Rat Model of Liver Cirrhosis-Induced Osteoporosis

Thesis submitted for partial fulfilment of
M.D. in clinical pharmacology

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2021

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LIST OF ABBREVIAITONS

Abbreviation	Full Name
AGA	American Gastroenterological Association
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
bFGF	Basic Fibroblast Growth Factor
BMD	Bone Mineral Density
BMI	Body Mass Index
CCl4	Carbon Tetrachloride
CLD	Chronic Liver Disease
DFO	Deferoxamine
DMT1	Divalent Metal Transporter-1
DFX	Deferasirox
ECM	Extracellular Matrix
H&E	Hematoxylin and Eosin
HCC	Hepatocellular Carcinoma
HOD	Hepatic Osteodystrophy
HSCs	Hepatic Stellate Cells
HYP	Hydroxyproline
ICH	Intracerebral Hemorrhage
IGF-1	Insulin-Like Growth Factor-1
IL	Interleukin
IM	Intramuscular
INF-γ	Interferon-γ
IP	Intra-Peritoneal
IV	Intravenous
LC3	Light Chain 3
LDs	Lipid Droplets
LSD	Least Significant Difference
MCP-1	Monocyte Chemoattractant Protein-1
NAFLD	Non-Alcoholic Fatty Liver Disease
Nramp	Natural Resistance-Associated Macrophage Protein

NTBI	Non-Transferrin-Bound Iron
OC	Osteocalcin
OLT	Orthotopic Liver Transplantation
OVX	ovariectomized
PBC	Primary Biliary Cholangitis
PBS	Phosphate Buffer Solution
PDGF	Platelet-Derived growth Factor
PTH	Parathormone
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell
ROS	Reactive Oxygen Species
SC	Subcutaneous
SEM	Standard Error of Mean
TAA	Thioacetamide
TGF-β1	Transforming Growth Factor-β1
TNF	Tumour Necrosis Factor
Vit D	Vitamin D
WHO	World Health Organization

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ABSTRACT

BACKGROUND: The liver plays a major role in iron homeostasis. Thus, in patients with chronic liver disease, iron regulation may be disturbed. Iron deposits responsible for further damage to hepatic and extrahepatic tissues by inflicting autophagy. ***AIM:*** The present study was designed to assess the effect of deferoxamine (DFO) on a rat model of thioacetamide (TAA) induced liver cirrhosis associated with osteoporotic changes. Further, to examine the possible role of DMT1 and autophagy. METHODS: Rats were divided into 4 groups Naïve control , DFO group, TAA untreated group received TAA ip (200 mg/kg/rat) twice weekly for 12 weeks, and TAA DFO treated group received TAA intra-peritoneal in addition to DFO intraperitoneal injections (300 mg/kg/ 3 times/week, for the last 4 weeks of TAA injections. ***RESULTS:*** DFO showed improvement in liver functions together with reduction in liver cirrhosis-associated iron overload, as evidenced by decrease in serum ferritin and decreased DMT1 expression. Moreover it had a beneficial effect in bone changes in rat model of liver cirrhosis indiced by TAA as evidenced by increased cortical thickness, trabecular volume, increased osteocalcin , and reduced hydroxyproline. These effects might be related to DFO effect

on autophagic process as evidenced by decrease in LC3 expression. ***CONCLUSION:*** Autophagy induced by iron overload is a suspected mechanism that mediates the toxic effects on bone in thioacetamide induced model of liver cirrhosis. Iron chelation, in particular with deferoxamine, has the potential to alleviate bone changes and the suspected mechanism. Further work is still needed to be translated to a clinical trial for hepatic osteodystrophy.

KEYWORDS: liver cirrhosis, osteoporotic changes, iron, thioacetamide, Deferoxamine, Autophagy.

INTRODUCTION

Liver cirrhosis, end-stage of chronic liver disease (CLD), is the leading cause of liver-related death globally regardless the etiology (***Roth et al.***, ***2018***). Almost all patients with CLD show altered bone metabolism and severe osteoporosis in up to 75% of the affected patients. Due to high prevalence, the generic term hepatic osteodystrophy (HOD) evolved, describing altered bone metabolism, decreased bone mineral density, and deterioration of bone structure. Once developed, HOD is difficult to be treated and increases the risk of fragility fractures. Existing fractures affect the quality of life and, more importantly, long-term prognosis of these patients, which presents with increased mortality (***Ehnert et al.***, ***2019***).

Pathogenesis of HOD is due to imbalance of factors responsible for bone matrix synthesis, leading to bone mass loss, bone fragility and recurrent pathological fractures. Many risk factors share in the pathogenic mechanisms of osteoporosis, including disturbed interaction between bone osteoblasts and osteoclasts, reduction of Insulin-like Growth Factor-1 (IGF-1) levels, low vitamin D levels, hypogonadism, poor nutrition, and iron overload (***Högler, Baumann and***