Procollagen III Amino Terminal Propeptide (PIIINP): A Non Invasive Marker of Methotrexate Induced Liver Fibrosis in Rheumatoid Arthritis Patients

Thesis

Submitted For Partial Fulfillment of Master Degree in Clinical Pathology

By

Amany Mohamed Mansour Mohamed
M.B.B.Ch., Ain Shams University

Under Supervision of

Professor. Hanaa Ahmed Amer
Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

Professor. Hala Ghareeb Mohamed
Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

Doctor. Neama Lotfy Mohamed Hassan
Assistant Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2019

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **Allah**, *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to ***Professor. Hanaa Ahmed Amer,*** *Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Professor. Hala Ghareeb Mohamed,*** *Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Doctor. Neama Lotfy Mohamed Hassan,*** *Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all ***my family*** *for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Amany Mohamed

List of Contents

List of Tables

List of Tables (Cont...)

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term

ALT .....*Alanine Aminotransferase*
ANA .....*Antinuclear Antibodies*
Anti-CCP .....*Anti Cyclic Citrullinated Peptide*
Anti-ds .....*Anti-Double-Stranded*
AST .....*Aspartate Aminotransferase*
CBC .....*Complete Blood Count*
CRP .....*C-Reactive Protein*
DMARDs .....*Disease-Modifying Anti-Rheumatic Drugs*
ELF .....*Enhanced Liver Fibrosis*
ELFTM .....*Enhanced Liver Fibrosis Test*
ELISA .....*Enzyme-Linked Immunosorbent Assay*
ESR .....*Erythrocyte Sedimentation Rate*
GCs .....*Glucocorticoids*
HA .....*Hyaluronic Acid*
HSCs .....*Hepatic Stellate Cells*
ICAM-1 .....*Intracellular Adhesion Molecule1*
IL6.....*Interleukin*
IVC .....*IV Collage*
LN .....*Laminin*
MI .....*Myocardial Infarction*
MIF .....*Migration Inhibitory Factor*
MMP .....*Matrix Metalloproteinases*
MTX .....*Methotrexate*
NAFLD .....*Non Alcoholic Fatty Liver Disease*
NPV .....*Negative Predictive Value*
NSAIDs .....*Non-Steroidal Anti-Inflammatory Drugs*
PADs .....*Peptidylarginine Deaminase Enzymes*
PAF .....*Platelet Activating Factor*
PGs .....*Prostaglandins*

List of Abbreviations (Cont...)

Abb.	Full term
PIIIP	*Procollagen III Aminoterminal Peptide*
PPV	*Positive Predictive Value*
RA	*Rheumatoid Arthritis*
RF	*Rheumatoid Factor*
rhGH	*Recombinant Human Growth Hormone*
SD	*Standard Deviation*
SJC	*Swollen Joint Count*
SPSS	*Statistical Program for Social Science*
TGF-β	*Tumor Growth Factor-Beta*
TIMP	*Tissue Inhibitor Metalloproteinases*
TJC	*Tender Joint Count*
VCAM-1	*Vascular Cell Adhesion Molecule1*
VEGF	*Vascular Endothelial Growth Factor*

Abstract

In the present study, the serum level of PIIINP was significantly higher in patients on MTX therapy (group I) compared to patients on other medications (group II).

Data from the present study confirmed the presence of positive correlation between Fib-4 score, AST/ALT ratio and PIIINP in patients on MTX therapy (group I).

Data from the present study also found that there was a statistically significant difference among the groups as regard MTX dose and duration and PIIINP levels.

Data from the present study confirmed the presence of statistical significant difference and negative correlation between PIIINP and Folic acid intake in group I where PIIINP levels were lower in patients on folic acid.

Keywords: *Recombinant Human Growth Hormone - Tender Joint Count - Vascular Endothelial Growth Factor*

INTRODUCTION

Rheumatoid arthritis is a systemic autoimmune disease characterized by inflammatory synovitis and progressive joint destruction, which are associated with severe disability and increased mortality ***(Taylor et al., 2017).***

In the new criteria set, classification as "definite RA" is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0–5), serologic abnormality (score range 0–3), elevated acute-phase response (score range 0–1), and symptom duration (2 levels; range 0–1) ***(Aletaha et al., 2010).***

The management of rheumatoid arthritis (RA) rests on several principles. Drug treatment, which comprises disease-modifying antirheumatic drugs (DMARDs), also non-steroidal anti-inflammatory drugs and glucocorticoids (GCs), as well as non-pharmacological measures, such as physical, occupational and psychological therapeutic approaches, together may lead to therapeutic success. However, the mainstay of RA treatment is the application of DMARDs ***(Smolen et al., 2011).***

Methotrexate is an antifolate and antimetabolite; thereby inhibiting synthesis of purines and pyrimidines and decreasing DNA and RNA synthesis that is used extensively in the therapy

of leukemia, lymphoma and several solid organ tumors. It also has potent activity against psoriasis and has immunomodulatory activity against inflammatory bowel disease and the inflammatory arthritis ***(Singh et al., 2012)***.

Long term therapy with methotrexate has been associated with development of fatty liver and hepatic fibrosis and, in rare instances, portal hypertension and symptomatic cirrhosis. Symptoms are usually absent until cirrhosis is present, and liver tests are typically normal or minimally and transiently elevated. Routine monitoring of patients with regular liver biopsies done at 1 to 2 year intervals or with cumulative methotrexate doses of 1 to 10 grams demonstrates that approximately 30% of patients develop mild-to-moderate histological abnormalities and 2 to 20% of patients develop some degree of hepatic fibrosis ***(Wong et al., 2013).***

Liver biopsy is the standard for diagnosing liver fibrosis, but it may be associated with significant morbidity and mortality of up to 0.33%, thereby limiting its use. So the noninvasive markers of hepatic fibrosis such as serial platelet counts, serum procollagen III aminoterminal peptide (PIIIP), serum bile acids, hepatic ultrasound and advanced imaging techniques may be more efficient in screening for fibrosis in patients on long term methotrexate ***(Singh et al., 2012***).

AIM OF THE WORK

The aim of the present work is to evaluate the reliability of Procollagen III amino terminal propeptide (PIIINP) in screening for hepatic fibrosis induced by long term methotrexate therapy in rheumatoid arthritis patients compared with FIB 4 score and ALT/AST ratio.