

**Impact of Normalization of Uric Acid Level
on the Clinical Outcome of Non-Alcoholic
Fatty Liver Patients: A Pilot Study**

Thesis

**Submitted for fulfillment of Master's degree in Pharmaceutical
Sciences (Clinical Pharmacy)**

By

Sylvia Samir Fouad

B. Pharm. Sci.

**Assistant Researcher at Pharmacology Department
National Research Centre, Cairo, Egypt**

Under Supervision of:

Dr. Osama Ahmed Badary

**Professor of Clinical Pharmacy
Faculty of Pharmacy
Ain Shams University**

Dr. Salwa Henry Salama

**Professor of Pharmacology
National Research Centre**

Dr. Mohamad Ali Mikhles

**Professor of Hepatology & Gastroenterology
National Research Centre**

**Faculty of Pharmacy
Ain Shams University**

2016

Acknowledgment

First and foremost, praise is to God, by whose abundant grace, this work has come to completion.

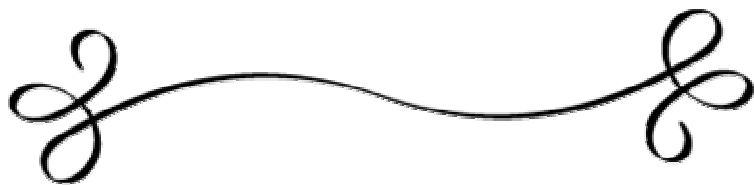
*I owe my deepest gratitude and appreciation to **Dr. Osama Badary**, Professor of Clinical Pharmacy – Faculty of Pharmacy - Ain Shams University, for sacrificing his precious time, sincere help, valuable guidance, and continuous support in completing this work.*

*I am very grateful to **Dr. Safwa Salama**, Professor of Pharmacology - National Research Centre, for her great assistance, precious advice, continuous encouragement and support throughout all stages of this work.*

*I am deeply thankful to **Dr. Mohamed Mokhles**, Professor of Hepatology and Gastroenterology - National Research Centre, for his close supervision and precious effort. If it wasn't for his patience, help, continuous encouragement and support, this work would have never been as it is.*

I would like to thank all members of the Pharmacology Department, National Research Centre, for their consideration, help and support, also thanks is extended to all the members of Clinical Pharmacy Department, Faculty of Pharmacy- Ain Shams University, for their support, patience and continuous help.

Last but not the least, I would like to dedicate this work and express my deep appreciation to my parents, family and friends, to whom I am greatly indebted for their love and spiritual support throughout my life. Saving my deepest gratitude for my very supportive husband, for it is only with his help and tremendous effort through every step that this work is finally done.



Abstract



Abstract

Background: Non Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver injury. Elevated Uric acid (UA) is an important factor in the development of NAFLD.

Objective: Evaluating the effect of treating hyperuricemia by allopurinol on NAFLD patients by blood markers as CK 18, adiponectin, liver enzymes (GOT, GPT), Cholesterol (Chol) and Triglycerides (TGs) and measuring fatty liver (FL) by ultrasound (US) .

Methods: Thirty-one hyperuricemic patients with NAFLD diagnosed by US were enrolled in the study and divided into two groups; Group A (14 patients): Placebo group who received starch based tablets for 3 months and Group B (17 patients): Treatment group who received allopurinol (100-300 mg) for 3 months. UA, CK 18, adiponectin, GPT, GOT, Chol, TGs and FL size and grade by US were measured before and after treatment.

Results: The study showed a significant decline in CK18 levels after treatment with allopurinol ($P=0.006$), improvement in GPT and GOT levels after treatment ($P<0.001$ and $P=0.013$, respectively). Also there was an improvement in Chol and TGs levels after treatment ($P=0.01$ and 0.038 , respectively). US parameters showed no significant difference in the FL size and grade before and after treatment ($P=0.208$ and 0.325 , respectively) and also no significant improvement in adiponectin level is observed ($P=0.058$)

Conclusion: Allopurinol succeeded in decreasing Chol , TGs and liver transaminases levels in the treatment group more than that of the placebo group and CK18 may be used as a good marker in assessing the improvement in patients with NAFLD associated with hyperuricemia.

Keywords: UA, NAFLD, allopurinol ,CK -18, adiponectin, GPT, GOT, US, FL size and grade

List of Contents

Title	Page No.
List of Abbreviations.....	i
List of Tables	ii
List of Figures	iv
Review of Literature	
▪ Non-alcoholic fatty liver	1
▪ Uric Acid	24
▪ Blood markers as a non-invasive tool in NAFLD	44
Aim of the work	64
Patients and Methods	65
Results	83
Discussion.....	108
Conclusion	117
Limitations of the study.....	118
Recommendations	119
Summary	120
References	125
Arabic Summary	

List of Abbreviations

Abb.	Full term
ALP	Alkaline phosphates
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Chol	Total Cholesterol
CK-18	Cytokeratin 18
CRP	C-reactive protein
GGT	Gamma glutamyl transpeptidase
HDL-C	High density lipoprotein cholesterol
IL-1	Interleukin-1
IL-18	Interleukin-18
IL-6	Interleukin-6
LDL-C	Low density lipoprotein cholesterol
MetS	Metabolic Syndrome
MRS	Magnetic resonance spectroscopy
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NO	Nitric oxide
RAS	Renin angiotensin system
T2DM	Type 2 diabetes mellitus
TGs	Triglycerides
TNF-a	Tumor necrosis factor-a
UA	Uric acid
UDCA	Ursodeoxycholic acid
US	Ultrasonography
XO	Xanthine oxidase

List of Tables

Table No.	Title	Page No.
Table (1):	Age, Sex and BMI Distribution of Study Groups.....	85
Table (2):	Baseline Biochemical Parameters of the Study Groups.	87
Table (3):	Baseline liver transaminases level in both study groups.....	89
Table (4):	Baseline blood markers in both study groups.....	91
Table (5):	Baseline ultra sonographic data in both study groups.....	92
Table (6):	Uric acid level at baseline and after 3 month of treatment in both study groups	94
Table (7):	Differences in lipid profile parameters in the study groups at baseline and after 3 months of treatment.....	97
Table (8):	Liver transaminases at baseline and after 3 months of treatment in the study groups.....	101
Table (9):	Percentage Change in Liver transaminases in the 2 Study Groups	103
Table (10):	Differences in Blood markers in both study groups before and after treatment	105
Table (11):	Differences in ultrasonographic data in both study groups before and after treatment.....	121

List of Figures

Fig. No.	Title	Page No.
Figure (1):	The “two hits” hypothesis of NAFLD.....	11
Figure (2):	Structural formula of uric acid.	24
Figure (3):	Hypouricemic drugs (FDA allopurinol drug insert)	37
Figure (4):	Mechanism of Action of Allopurinol and Oxipurinol (FDA allopurinol drug insert)	39
Figure (5):	The study flow chart.....	67
Figure (6):	Standard curve of CK-18 concentration against optical density.	76
Figure (7):	Standard curve of adiponectin concentration against optical density.....	81
Figure (8):	Mean Baseline Serum Uric Acid Level in placebo and treatment groups.	88
Figure (9):	Mean baseline lipid profile parameters level in both study groups.....	88
Figure (10):	Mean Baseline liver transaminases in placebo and treatment groups.	90
Figure (11):	Fatty liver grades among placebo group patients.....	93
Figure (12):	Fatty liver grades among treatment group patients.....	93
Figure (13):	Uric acid level percent change in placebo and treatment groups.....	95
Figure (14):	Serum cholesterol level percent change in placebo and treatment groups.	98
Figure (15):	Serum triglycerides level percent change in placebo and treatment groups.....	98