شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
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HANAA ALY

The Effect of Metformin on the Clinical Outcome of Patients with Rheumatoid Arthritis

A Thesis

Submitted for fulfillment of the requirements for the

Master's degree
In Pharmaceutical Sciences
(Clinical Pharmacy)

By

Mahmoud Mustafa Mahmoud Gharib

Bachelor of Pharmaceutical Sciences, 2013
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2022

Ain Shams University
Faculty of Pharmacy
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2022

Acknowledgement

I am deeply thankful to **"Allah"** by the grace of whom, this work was possible.

I would like to express my deep appreciation to **Prof. Dr. Nagwa Ali Sabri**, Professor of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, for her valuable guidance, patience, motivation, and continuous support in completing this work.

I am very grateful to **Prof. Dr. Ebtissam Abdel Ghaffar Darweesh**, Professor of Pharmacology, Faculty of Pharmacy, Future University in Egypt, for her great assistance, precious advice and valuable guidance in completing this work.

I would like to thank **Dr. Walaa Fahmy Al-baz**, Professor of Internal Medicine, Rheumatology, and Immunology, Faculty of Medicine, Al-azhar University, for her great and valuable help in the clinical aspects of the study.

I would like to thank **Dr. May Ahmed Shawki** for her continuous support, endless help, and valuable guidance throughout all steps involved in this work.

I would like to thank **my colleagues** and **all members of Pharmacy Practice and Clinical Pharmacy Department**, Faculty of Pharmacy, Future University of Egypt, for their support as well as all **staff members of Al-Zahraa University Hospital** especially Ahmed Salem for their help in collection of data, samples, and their valuable guidance.

Many special thanks and deep gratitude for **my family** and best **friends** for their kind and sincere help, love, and support.

Finally, my thanks go to **all people** who have supported me to complete my research work directly or indirectly.

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List of Abbreviations

28SJC	28 swollen joint count
28TJC	28 tender joint count
A	Absorbance
ACPAs	Anti-citrullinated protein antibodies
ACR	American college of Rheumatology
AGEs	Advanced glycation end products
ALT	Alanine transaminase
AMPK	Adenosine monophosphate-activated protein kinase,
Anti-CCP	Anti-cyclic citrullinated peptide
APCs	Antigen-presenting cells
AST	Aspartate transaminase
bDMARDs	Biologic disease modifying anti-rheumatic drugs
BMI	Body mass index
CAIA	Collagen antibody-induced arthritis
CBC	Complete blood count
CDAI	Clinical disease activity index
CRP	C- reactive protein
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
CV	Cardiovascular
DAS-28-CRP	Disease activity score based on C-reactive protein
DMARDs	Disease modifying anti-rheumatic drugs
DPP	Diabetes Prevention Program
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FBG	Fasting blood glucose
FC	Fragment crystallizable
FDA	Food and Drug Administration
FLS	Fibroblast-like synoviocytes
GI	Gastrointestinal
HAQ-DI	Health assessment questionnaire-disability index
HDA	High disease activity
HDL-C	High density lipoprotein cholesterol
HLA	Human leukocyte antigen
IgG	Immunoglobulin G
IL	Interleukin
JAK	Janus kinase
JAKIs	Janus kinase inhibitors
LDA	Low disease activity

LDL-C	Low density lipoprotein cholesterol
MATE	Multidrug and toxin extrusion transporter
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony-stimulating factor
MDA	Moderate disease activity
MDHAQ	Multi-dimensional health assessment questionnaire
MMPs	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NFκB	Nuclear factor kappa B
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OCTs	Organic cation transporters
OD	Optical density
OPG	Osteoprotegerin
PARP-1	Poly ADP ribose polymerase 1 pathway
PAS-II	Patient activity score-II
QOL	Quality of life
RA	Rheumatoid Arthritis
RANKL	Receptor activator of nuclear factor kappa B ligand
RAPID-3	Routine assessment of patient index data-3
RBG	Random blood glucose
RF	Rheumatoid factor
ROS	Reactive oxygen species
Scr	Serum creatinine
SDAI	Simplified disease activity index
SNPs	Single nucleotide polymorphisms
STAT3	Signal transducer and activator of transcription 3
Tfh	Follicular T helper
Th	T helper
TNF-α	Tumor necrosis factor-α
Treg	T regulatory
tsDMARDs	Targeted synthetic disease modifying anti-rheumatic drugs
VEGF	Vascular endothelial growth factor

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Abstract

Abstract

Background

Rheumatoid Arthritis (RA) is a chronic, inflammatory autoimmune disorder, primarily affects small joints of hands, wrists, and feet in early stages and larger joints in advanced stages as well as many systemic manifestations and comorbidities. The estimated global prevalence of RA ranges from 0.4 to 1.1%. Inappropriately managed RA can lead to bone erosions, cartilage destruction, irreversible disability, loss of productivity, impairment of quality of life (QOL), and high mortality rates. Pathogenesis of RA is complex and generally involves activation of elements of both innate and adaptive immunity under influence of several cytokines and inflammatory mediators. Despite of sticking to guidelines treatments, many RA patients have many unmet needs in many disease areas including fatigue, pain, and stiffness suggesting the need for additional therapeutic options for RA management. Numerous preclinical and clinical studies reported metformin's anti-inflammatory and immunomodulatory actions with its potential benefits for ameliorating RA activity.

Aim of the study

The aim of the study was to evaluate efficacy and safety of adjunctive metformin use to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) in patients with RA.

Patients and methods

This was a prospective, randomized, placebo-controlled study carried on patients with established RA presented to Rheumatology and Immunology Unit, Al-Zahraa University Hospital, Cairo, Egypt. The study protocol was revised, approved by Research Ethics Committee of Experimental and Clinical Studies of Faculty of Pharmacy, Ain Shams University. Adult RA patients (18 years or older) with moderate or high disease activity identified as disease activity score of 28 joints based on C-reactive protein levels (DAS-٢8-CRP) >3.2 and received stable regimen of csDMARDs for at least three months before the study were enrolled. Exclusion criteria were known metformin hypersensitivity, diabetes mellitus, heart failure, history of alcohol abuse,

severe anemia, impairment of kidney function, elevated liver transaminases, pregnancy or lactation, and the use of biologic disease modifying anti-rheumatic drugs (bDMARDs). Using sequence generator software, patients were simply randomized to receive either metformin 850 mg twice daily (n=33) or placebo twice daily (n=33) in addition to their stable anti-rheumatic regimen and were followed-up for the following six months. Serum C-reactive protein (CRP) and DAS-28-CRP were the primary efficacy outcomes of metformin use that were evaluated at baseline and then every three months. Secondary outcomes included serum adiponectin level which was assessed at baseline and after six months as well as QOL of RA patients which was evaluated at baseline and then every three months. Patients were instructed to report any adverse effects occurred during the study.

Results

From October 2018 to March 2020, 97 patients were screened for eligibility and 66 patients were enrolled. The mean age of enrolled RA patients (±S.D.) was 51.1 (±8.5) years with disease duration ranged from 4 to 20 years. Females represented the majority of study population (96.5%). Around 49 (81.6%) patients were receiving prednisolone. Only 60 patients completed the study where dropouts were due to intolerance to metformin gastrointestinal (GI) side effects (n=3) and non-compliance to the study protocol (n=3) in the control group. Metformin significantly decreased CRP levels and DAS-28-CRP after six months compared to the control group (P-value<0.001). Metformin also significantly improved QOL of patients of the metformin group after three (p-value=0.006) and six months (p-value<0.001) compared to the control group. Evaluation of serum adiponectin levels between the study groups revealed significant difference at baseline where metformin group had higher levels compared to the control group (p-value <0.001). The median percent change of serum adiponectin levels from baseline was -63.49% in the metformin group compared to 92.40% in the control group (p-value<0.001). There were no serious adverse events associated with metformin use during the entire study duration. Most of reported side effects were GI related mainly nausea, abdominal pain, and diarrhea that were mild to moderate in the majority of metformin users and required no specific intervention.

Conclusion

The findings of this study support the anti-inflammatory roles of metformin in RA patients in the form of reducing CRP, disease activity, and serum levels of adiponectin. These actions were accompanied by improved QOL along with high safety profile associated with metformin use. Therefore, metformin is suggested to be used as an add-on therapeutic option to csDMARDs in RA patients who need further disease control.