بسم الله الرحمن الرحيم

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Relationship between Clinical, Serological and Ultrasound assessment of rheumatoid arthritis activity

Thesis

*Submitted in Partial Fulfillment of the M.D. Degree in **Internal Medicine***

By

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Mostafa Adel Mohammed Mohammed

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List of Abbreviations

Abb.	Full term
MTP	*metatarsophalangeal*
micro-CT	*Microfocal computed tomography*
HRpQCT	*high resolution peripheral quantitative computed tomography*
NSAIDs	*Non-steroidal anti-inflammatory drugs*
GCs	*Glucocorticoids*
MR-pred	*modified-release prednisone*
MTX	*Methotrexate*
sc	*subcutaneous*
COX	*cyclooxygenase*
PG	*prostaglandins*
SSZ	*Sulphasalazine*
HRQoL	*health-related quality of life*
FDA	*Food and Drug Administration*
IL1RN	*interleukin 1 receptor antagonist*
CPK	*creatine phosphokinase*
mAb	*monoclonal antibody*
MTX-IR	*methotrexate inadequate response*
AEs	*adverse effects*
TNFi-IR	*TNFi inadequate response*
GM-CSF	*Granulocyte– macrophage colony- stimulating factor*
EMA	*European Medicines Agency*
csDMARD	*conventional synthetic DMARD*
GS	*grayscale*
PD	*power Doppler*
US	*ultrasonography*

List of Abbreviations (Cont…)

Abb.	Full term

MRI ..... magnetic resonance imaging
SH ..... synovial hypertrophy
UA ..... undifferentiated arthritis
IA ..... inflammatory arthritis
GS ..... greyscale
MTP ..... metatarsophalangeal
ACR ..... American College of Rheumatology
SDAI ..... Simple Disease Activity Index
CDAI ..... Clinical Disease Activity Index
Anti-CCP..... Anti-cyclic citrullinated peptide
ALT ..... Alanine transaminase
AST..... Aspartate aminotransferase

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of synovial tissue that leads to damage of cartilage and bone, resulting in irreversible joint destruction ***(Smigielska-Czepiel et al., 2014).***

Joint damage and functional impairment are highly important adverse outcomes of rheumatoid arthritis (RA). They have been repeatedly shown to be associated with clinical disease activity, in particular with swollen joint counts and acute-phase reactant levels, as well as composite measures of disease activity in which these variables are included as components. Moreover, in states of very low disease activity, progression of joint damage is related to residual joint swelling rather than acute-phase reactant levels, and the association between radiographic progression and joint swelling has been observed at the level of individual joints ***(Gärtner et al., 2013).***

It has been suggested that some patients may experience radiographic progression of joint disease despite being in clinical remission, although this presumably is a carry-over effect of past disease activity. Nevertheless, if clinical assessment of joint swelling is not a sufficiently reliable method to assess patients with RA in a state of remission, more sensitive methods for assessment of disease activity might be needed ***(Gärtner et al., 2013).***

Ultrasound (US) is a bedside tool increasingly used to help in diagnosis and monitoring different rheumatic diseases. It is readily available, radiation free, relatively inexpensive and provides a real-time complementary tool for clinical evaluation, although its long learning curve and operator dependence may be considered as potential disadvantages ***(Cerqueira et al., 2017).***

Musculoskeletal ultrasound is primarily used by rheumatologists for detecting and assessing inflammation of joints and joint damage in rheumatoid arthritis. Specifically, ultrasound is capable of evaluating the two elementary findings associated with synovitis: synovial hypertrophy (SH) and synovial fluid/effusion (SF). Both SF and SH are evaluated primarily on gray-scale (GS) ultrasound, while Color Doppler (CD) and Power Doppler (PD) are utilized to demonstrate activity related to SH ***(Mandl et al., 2011).***

The relevance of US for monitoring RA is well reflected in European League Against Rheumatism (EULAR) recommendations for the use of imaging on clinical management of RA. On those recommendations, it is recognized that US is superior to clinical examination in the detection of joint inflammation and that the inflammation observed on US predicts response to treatment and future damage ***(Cerqueira et al., 2017).***

AIM OF THE WORK

The purpose of this study is to assess the relationship between systematic ultrasound (US) evaluation using 7-joint and 12-joint scores and both clinical and serological evaluations in the determination of disease activity in rheumatoid arthritis patients.

Chapter 1

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a common systemic inflammatory autoimmune disease characterized by painful, swollen joints that can severely impair physical function and quality of life. The presenting symptoms of musculoskeletal pain, swelling, and stiffness are common in clinical practice, so familiarity with diagnosing and managing RA is crucial. Patients with RA are at greater risk for serious infection, respiratory disease, osteoporosis, cardiovascular disease, cancer, and mortality than the general population. In recent years, early diagnosis, aggressive treatment, and expanded therapeutic options of disease-modifying antirheumatic drugs have markedly improved both the management and long-term prognosis of RA ***(Sparks, 2019).***

Epidemiology:

Many studies have estimated the prevalence of RA around the globe. A systematic effort, undertaken in the first decade of the century, on the global burden of RA, estimated the global prevalence of RA as 0.24%, with no discernible change from 1990 to 2010. Slight variations exist, from higher estimates in polar countries to lower in tropical countries, also lower estimates (or underreporting) in some African and Asian settings.

In African countries, a prevalence of 0.13 was reported in Algeria, 0.9 in Congo, 0.2 in Egypt, 0.9 in South Africa, and less than 0.5 in Nigeria. RA occurs more commonly in women than men, in a 1:2 to a 1:3 ratio. This female preponderance is thought to be related to differing sex hormones, their effect on the immune system, and perhaps to epigenetics or microbiome ***(Otón and Carmona, 2019).***

Etiology and risk factors:

Multiple hormonal, genetic and environmental factors have been associated with increased (or decreased) risk for RA.

Gender and hormonal influence:

Women have higher prevalence than men with about 2.5 times as men. The disease can manifest at any age mostly between thirties and sixties in females, but it can start later in males. United States statistics show that lifetime risk of RA in females is about 3.6% while risk in males is 1.7% only ***(Bullock et al., 2018).***

The effect of sex hormones on immune system and the interaction with environmental and genetic factors could explain the higher prevalence of RA in women. It was apparent that female patients receiving oral contraceptive pills have much lower incidence of RA (0.3/1000 women years) in comparison to those who never receive oral contraceptive pills (0.65/1000 women years). Both female subfertility and the early postpartum