INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis. The hallmark of RA is symmetric synovial proliferation and tenderness of multiple joints, particularly the small joints of the hands and feet. It has an annual incidence of approximately 0.4 per 1000 in females and 0.2 per 1000 in males, A prevalence of 0.4% to 1% is reported in diverse populations worldwide ***(Liao and Karlson, 2012).***

Prolactin receptors (PRL-Rs) are members of the cytokine receptor super-family. Several isoforms of PRL-Rs have been described based on the differences in the amino acid sequence and size of the cytoplasmic domain , PRL-Rs are expressed on monocytes, macrophages, T and mainly B lymphocytes, natural killer (NK) cells, granulocytes and thymus epithelial cells ***(Shelly et al., 2012).***

In addition to its unique roles in reproduction and lactation, PRL acts as a potent immunomodulator. The immune capability of PRL is generally stimulatory, while oestrogens and cortisol support the anti-inflammatory Th2 immune response. PRL maintains immune homeostasis, and its receptors have been detected on several immune cells, synovial fibroblasts and chondrocytes, In immune cells, PRL up regulates transcription of the interferon regulatory factor IRF-1 gene and modulates expression of pro-inflammatory cytokines

interleukin (IL)-12, interferon (IFN)α and tumour necrosis factor (TNF) ∞,. Moreover, PRL exhibits anti-apoptotic activities, leading to increased survival of both autoreactive T cells and B-cells ***(Fojtíková et al., 2010).***

In some clinical trials the level of PRL in serum was significantly higher in patients with RA, implicating that PRL may play a role in disease severity and the process of joint damage in RA and contributes to the development of the disease, In some studies PLR level was higher with longer disease evolution and worse functional condition ***(Shelly et al., 2012).***

Moreover, it was found that the risk for developing RA is increased postpartum and it seems that breast-feeding is associated with an increased risk of rheumatoid arthritis, particularly after the first pregnancy ***(Shelly et al., 2012).***

Aim of the Work

The aim of this study is to determine the level of serum prolactin in patients with rheumatoid arthritis and its association with disease activity and structural damage.

Chapter (1)

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis. The hallmark of RA is symmetric synovial proliferation and tenderness of multiple joints, particularly the small joints of the hands and feet ***(Liao and karlson, 2012).***

In addition to articular manifestations, systemic involvement may cause constitutional symptoms (such as weight loss, low-grade fever, and malaise), rheumatoid nodules, serositis and vasculitis ***(Khurana and Berney, 2005).***

Epidemiololgy:

The prevalence and incidence of RA vary across ethnic groups. The incidence of RA varies across populations. In Southern Europe, lower incidences of 9 to 24 cases per 100,000 populations have been reported. Studies done in North America and Northern Europe have shown prevalence of 0.5% to 1.1%. In Southern Europe, lower prevalence of 0.3% to 0.7% has been found. The few prevalence studies performed in developing countries based on the 1987 American College of Rheumatology (ACR) criteria suggest significantly lower prevalence than in Northern Europe and North America, of about 0.1% to 0.5% cases per 100,000 populations have been reported ***(Tobón et al., 2009).***

RA has a predisposition for women, with a female-to-male ratio of 3:1. However, the trends in RA incidence vary with age within each sex. Among women, the incidence increases from the age of menarche and peaks around menopause; RA is rare in men under the age of 45 years, but the incidence increases with age, approaching the incidence in women ***(Jawaheer et al., 2006).***

Etiology and risk factors of RA:

1-Genetic factors:

The genetic component is emphasized by a 3-4 fold higher concordance rate in monozygotic compared to dizygotic twins ***(Miterski et al., 2004).***

Genetic factors contribute 50% to 60% of the risk of developing RA. The gene most strongly associated with RA is the human leucocytic antigen-determining region B1 (HLA-DRB1) gene in the major histocompatibility complex, where specific alleles within the DRB1 04 and 01 clusters encode the "shared-epitope" sequences within the expressed DRB1 molecule ***(Tobón et al., 2009).***

2-Hormonal factors:

The predominance of RA in females suggests a role for hormonal factors. In addition, estrogens stimulate the immune system. Low testosterone levels have been reported in men with RA ***(Tobón et al., 2009).***

A history of child-bearing may protect against RA. In patients with RA, pregnancy often leads to a remission, followed by a flare-up after delivery ***(Salliot et al., 2009).***

3-Socioeconomic factors:

Socioeconomic factors appear to influence the course and the outcome of RA rather than the risk of developing RA. Occupational, educational level, marital status, and social group have been studied as possible risk factors for disease susceptibility, or predictors for disease severity and outcome ***(MacGregor and Silman, 2003).***

4- Smoking:

Smoking has by far the strongest association with RA. Smoking increases susceptibility to RA and adversely affects the clinical course of the disease ***(Costenbader et al., 2008).***

5-Infectious agents:

Several microorganisms have been implicated in the development of RA based on higher titres of the relevant antibodies in patients with RA. Evidence supporting a role for parvovirus B19 includes the presence of viral double stranded nuclear acid (DNA) in the synovial fluid, synovial cells, and/or synovial tissue of RA patients. Sera from RA patients contain high titres of Epstein–Barr virus (EBV) antigens and of antibodies to latent and replicative EBV antigens. In addition, EBV RNA has been identified in B cells in synovial tissue from RA patients ***(Meron et al., 2010).***

6-Dietary factors:

A diet rich in fish, olive oil, and cooked vegetables has been shown to protect against RA, an effect ascribed to the high content in these foods of omega 3 fatty acids. A high vitamin D intake has been associated with a lower risk of RA ***(Tobón et al., 2009).***

Pathogenesis of RA:

The articular manifestations of RA can be divided into two categories:

(i) Reversible signs and symptoms related to aseptic inflammatory synovitis and

(ii) Irreversible structural damage caused by synovitis. This concept is useful for disease staging, determining prognosis and medical or surgical treatment selection ***(Wick et al., 2007).***

After disease onset the normally hypocellular synovial membrane becomes hyperplasic, comprising a superficial lining layer of synovial fibroblasts and macrophages. The lining layer overlies an interstitial zone with marked cellular infiltrates containing fibroblasts, macrophages, dentritic cells, mast cells, T cells and B cells ***(McInnes and Schett, 2007).***

The interaction between activated lymphocytes and monocytes, leading to production of pro-inflammatory cytokines, immunoglobulins and rheumatoid factors (RF) is central to this immunological reaction. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are suspected to stimulate synoviocytes and

osteoclasts, events that lead to the irreversible destruction of bone and cartilage. These cytokines are also involved in the expression of cell-adhesion-molecules necessary for cell migration and inflammation on endothelial cells, which promote local accumulation of leukocytes. Rheumatoid factor (RF) and other auto-antibodies accumulate in the synovial tissue and fluid, where they maintain inflammation by activating complement in the adjacent cartilage and tissue. In addition to the cellular basis of synovial inflammation, newly formed blood vessels also infiltrate the synovial membrane. All these events lead to the development of a non- suppurative proliferating synovitis, also known as synovialitis pannus. The pannus extends over and sometimes through adjacent articular cartilage, leading to complete destruction of the cartilage, observed radiologically as joint space narrowing and bone erosion. Pannus growth can be compared with the progression of a benign tumor (tumor-like progression) ***(Wick et al., 2007).***

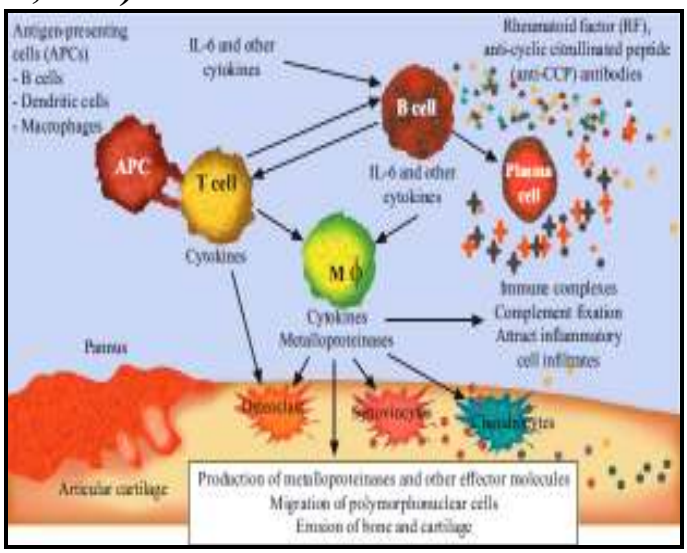

Figure (1): The integrated immune response and pathogenesis of rheumatoid arthritis ***(From Fan and Leong, 2007)***.

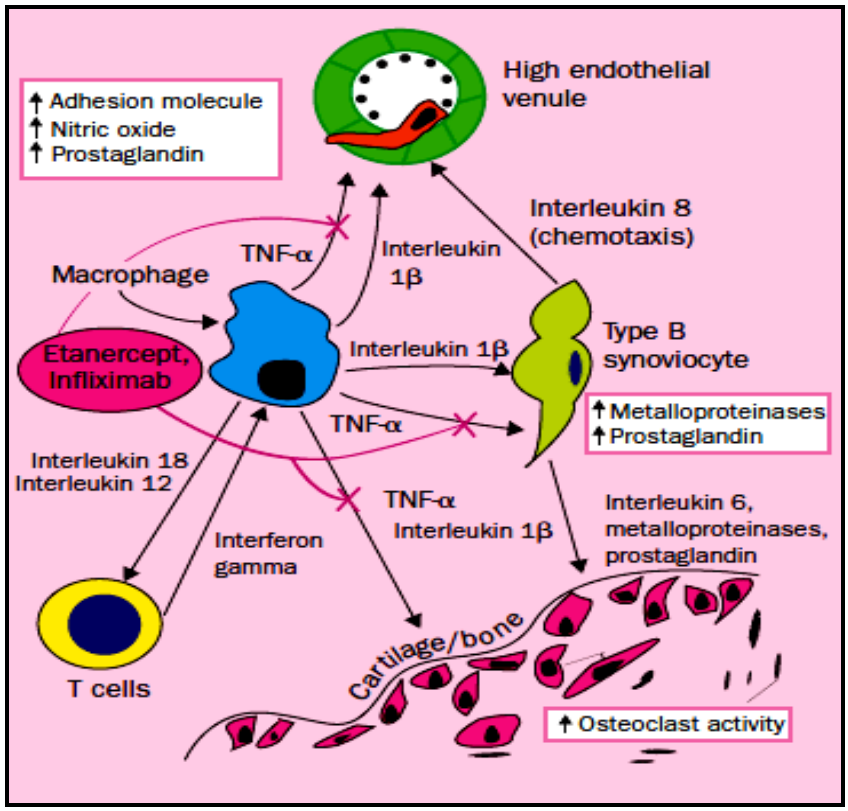

Figure (2): Simplified schematic representation of cytokine network in rheumatoid arthritis. (TNF=tumour necrosis factor. Black arrows indicate upregulatory effects, red arrows indicate downregulatory effects. Red crosses represent pathways blocked by anti-TNF drugs) ***(From Lee and Weinblatt, 2001).***

Mechanisms of focal bone loss in RA:

Several studies have provided evidence that osteoclasts are the principle cell type for focal bone loss in RA ***(Teitelbaum, 2006).***

Most data are derived from experimental knock-out animal studies, in which osteoclast activity and differentiation are impaired by specific deletion of genes which are known to

be important for osteoclast formation, or by targeting the cytokine receptor activator of nuclear factor- κB ligand (RANKL), also known as osteoprotrgerin ligand (OPGL) ***(Wick et al., 2007).***

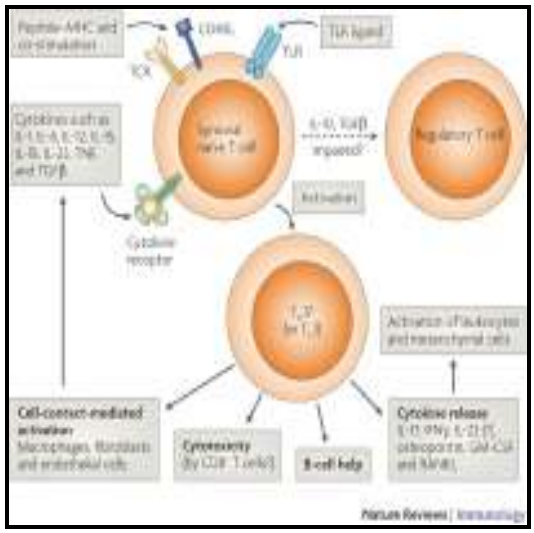

Figure (3): Pathways leading to activation of synovial T cells in RA and their key effector pathways: (CD40L, CD40 ligand; GM-CSF, granulocyte/macrophage colony-stimulating factor; RANKL, receptor activator of nuclear factor-κB (RANK) ligand; IFNγ, interferon-γ; TNF, tumour-necrosis factor) ***(From McInnes and Schett, 2007).***

Mechanism of cartilage loss in RA:

Cartilage degradation is regulated through different mechanisms. Chondrocytes switch from an anabolic matrix-synthesizing state which is characterized by the formation of matrix metalloproteinases (MMPs) that cleave cartilage components such as proteoglycan and collagen fibres. The chondrocytes themselves synthesize or respond to local cytokines released by the synovial membrane such as IL-1β and

TNF. This has a synergistic effect in cartilage destruction, although the effect of IL-1β seems more potent than that of TNF. In addition, synovial fibroblasts, neutrophils, and mast cells situated in the synovial membrane further release (MMPs), in turn contributing to cartilage degredation ***(McInnes and Schett, 2007).***

Clinical features of RA:

I-General:

Low- grade fever, fatigue, malaise, and other systemic complaints may arise, especially in an acute presentation ***(Rindfleisch and Muller, 2005).***

II-Articular manifestations:

The initial symptoms of RA (frequently articular) typically can present one of two ways, with a slow insidious onset or an explosive sudden onset. The 55-65% of cases begin insidiously, over weeks to months. The 8-15% of patients have an acute onset of symptoms that peak within a few days. Asymmetrical presentations (with symmetry developing later in the course of disease) are not unusual ***(Khurana and Berney, 2005).***

Joints most commonly affected are those with the highest ratio of synovium to articular cartilage. Rheumatoid joints typically are boggy, tender to the touch, and warm, but they usually are not erythematous. Morning stiffness lasting at least 45 minutes after initiating movement is common. Patients often

hold joints in flexion to minimize painful extension of joint capsules ***(Rindfleisch and Muller, 2005).***

The joints most commonly involved first in RA are the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal joints, and wrist (see Table 1). Larger joints generally become symptomatic after small joints. Synovitis in large joints is likely to remain asymptomatic for a longer time than in smaller ones, and a biopsy specimen of an asymptomatic knee often shows histologic evidence of synovitis ***(Harris and Firestein, 2009).***

Table (1): Distribution of Joints Involved in Attacks Based Upon a Cumulative Experience ***(From Harris and Firestein, 2009)***.

Joint involvement	Mean % of patients	Range % of patients
MCP, PIP	91	74-100
Wrist Joints	78	54-82
Elbow Joints	38	13-60
Shoulder Joints	65	33-75
Spines	4	0-11
Hip Joints	17	0-40
Knee Joints	64	41-94
Ankle Joints	50	10-67
Feet	43	15-73
Tempromandibular Joints	8	0-28
Sternoclavicular Joints	2	0-6
Para-articular sites	27	20-29

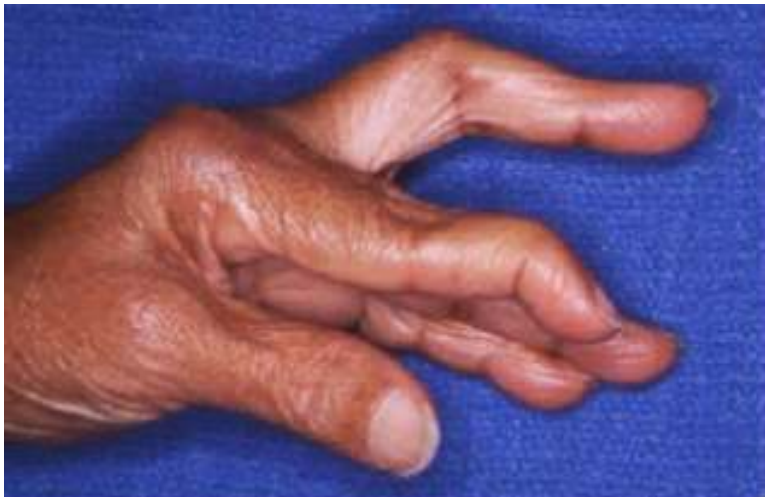

Figure (4): Swan neck and Boutonniere deformities of fingers ***(From Khurana and Berney, 2005).***

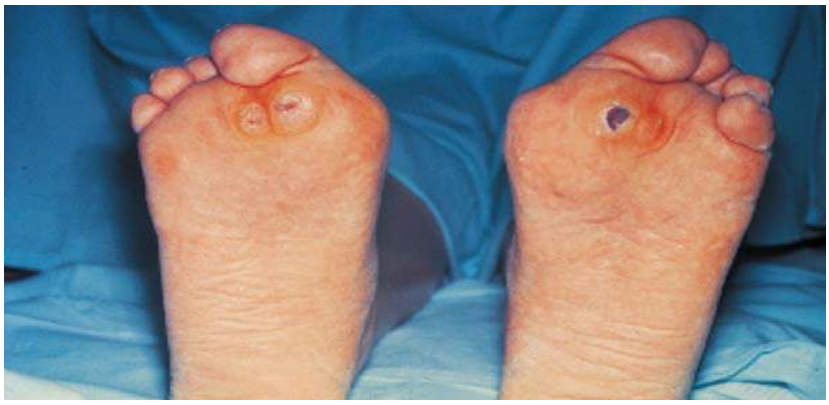

Figure (5): Plantar view of the feet in a patient with RA who has protruding metatarsal heads ***(From Khurana and Berney, 2005).***

III-Extra- articular manifestations:

The number and severity of extra-articular features vary with the duration and severity of the disease. Extra- articular manifestations of RA are associated with the observed excessive mortality ***(Turesson et al., 2002).***

1-Rheumatoid Nodules:

Palpable nodules in the subcutaneous tissues have been reportd in 7% at initial presentation of RA patients and are found at same time during the disease course in 30 to 40 % of patients, the vast majority of nodules formers have positive tests for rheumatoid factor, nodules are found in 75 % of patients with RA-associated Felty's syndrome, RA patients with nodules are also more likely to develop vasculities ***(Davis et al., 2014).***

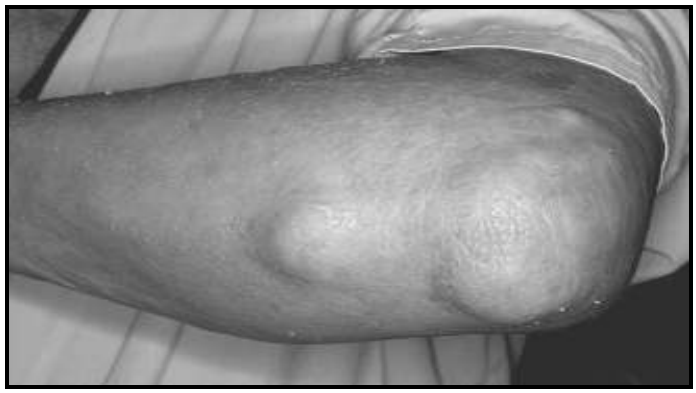

Figure (6): Rheumatoid nodule of elbow ***(García-Patos, 2007).***

2-Lung manifestations:

The majority of lung disease occurs within the first 5 years after the initial diagnosis, and may be a presenting manifestation in 10 to 20% of patients. RA affects all of the anatomic compartments of the lung ***(Brown, 2007).***

Autopsy studies reported pleural involvement in 50% of patients, with only 10% clinically detected, pleural effusion are usually exudates with mixed cell counts and high protein

concentration, parenchymal pulmonary nodules generally are asymptomatic and found in RF positive patients with nodules, diffuse interstitial pulmonary fibrosis in RA tends to occur more often in RF positive male patients with longstanding nodular diseases ***(Cojocaru et al., 2010).***

3-Renal manifestations:

The reported prevalence of chronic kidney disease in patients with RA patients had varied between 5 and 50% ***(Farman et al., 2012).***

Systematic estimation of glomerular filtration rate (GFR) with Cockcroft-Gault (CG) or abbreviated Modification of Diet in Renal Disease (aMDRD) formula even at levels of serum creatinin (S.Cr) usually considered as 'normal' and assessment of urine dipstick is necessary in RA patients ***(Karie et al., 2008).***

4-Cardiac manifestations:

The reported incidence and prevalence of coronary artery disease in patients with RA was 59% higher than in general population ***(Katherine et al., 2014).***

Premature death in RA patients is often caused by cardiovascular disease, especially ischemic heart disease and congestive heart failure ***(Baltic, 2009).***

Most importantly, RA patients are less likely to report symptoms of angina and are more likely to experience