INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation leading to cartilage and local bone erosion **(Walsh et al., 2005).**

Three forms of bone loss have been described in rheumatoid arthritis**.** include: focal bone loss affecting the immediate subchondral bone and bone at the joint margins, periarticular osteopenia adjacent to inflamed joints and generalized osteoporosis involving the axial and appendicular skeleton. As, osteoclasts are the principal cell type responsible for bone loss in RA. Focal and systemic bone loss contribute to the morbidity associated with RA. Generalised osteoporosis is more associated with long-standing, destructive and disabling RA, whereas early RA is associated with periarticular osteoporosis **(Goldring and Gravallese, 2000).**

Joint erosions are the hallmark of RA. They are caused by an increased bone resorption. However there in no increased bone formation to prevent or heal these erosions (**Walsh and Gravallese, 2004)**.

Periarticular osteopenia is a characteristic feature of early RA and occurs before marginal erosions are evident (**Güler-Yüksel et. al., 2009)**.

Generalized osteoporosis is an extra-articular complication of rheumatoid arthritis that results in increased risk of fractures and associated morbidity, mortality, and healthcare costs**.** Osteoporosis, specially in patients with RA, is a multifactorial condition. risk factors for osteoporosis include older age, female sex, menopause, glucocorticoids use, lower body mass index, high RA disease activity, long RA disease duration, and decreased physical activity, Some studies have suggested the association between osteoporosis and proinflammatory cytokines such as TNF-α, IL-1 and IL-6, as these cytokines play an important role in bone resorption **(Oelzner et al., 2008).**

The Wnt family of glycoproteins is involved in the regulation of multiple cellular activities, including bone formation and remodeling **(Johnson and Kamel, 2007).**

The Wnt/b-catenin pathway involves the binding of Wnt proteins to a coreceptor complex, comprising low-density lipoprotein receptor-related protein LRP5 or LRP6 and a member of the frizzled (Fz) family of proteins. This interaction eventually leads to an increase of the intracellular b-catenin levels through inhibition of the b-catenin degradation complex. Wnt/b-catenin pathway play an important role in bone mass regulation and osteoclastogenesis in RA and osteoarthritis (OA) **(Daoussis et at., 2010).**

Sclerostin is protein encoded by SOST gene, and belongs to Dan (differential screening-selected gene aberrant in neuroblastoma) family secreted proteoglycans, a specific subfamily cystine knob containing proteins, which function as antagonists of bone morphogenetic protein (BMP) activity (**David et al., 2008).**

Nowadays, sclerostin has been identified as binding to LRP5/6 receptors and inhibiting the Wnt signaling pathway which leads to decreased bone formation. Sclerostin is expressed in osteocytes and some chondrocytes and inhibits bone formation by osteoblasts **(Burgers and Williams, 2013).** Sclerostin may have a catabolic action through promotion of osteoclast formation and activity by osteocytes, in a RANKL-dependent manner **(Wijenayaka *et al*., 2011).**

In RA,antagonists of the canonical Wnt/b-catenin signaling pathway, including Dkk1 and sclerostin, and subsequently inhibit osteoblast proliferation, maturation and progenitor differentiation **(Wang et al., 2011).**

AIM OF THE WORK

The aim of the present study is to measurement:

Clinical, Laboratory, and radiology study in patients with RA to assess Serum sclerostin level in order to:

- Assess its relation to bone mineral density.
- Assess its effect on disease activity.

Chapter (1)

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is the most common autoimmune disease that affects the joints. Worldwide, approximately 1% of the population is affected, with higher prevalence in persons of European or Asian origin (**Helmick et al., 2008).** Rheumatoid arthritis can develop in persons of any age, with the typical age at onset of about 55 years. The prevalence of rheumatoid arthritis increases considerably with age, affecting approximately 6% of the white population older than 65 years. In the United States, the lifetime risk of developing rheumatoid arthritis is 3.6% in women and 1.7% in men. **(Crowson et al., 2011)**

Clinical features of rheumatoid arthritis include symmetric polyarthritis with joint swelling, especially of the hands and feet, although any of the appendicular joints may become involved. Patients with rheumatoid arthritis experience morning stiffness that lasts one hour or longer. Characteristic subcutaneous nodules and other extra-articular disease manifestations including interstitial lung disease, vasculitis, and various forms of inflammatory eye disease are markers of severe disease **(David and matteson., 2012).**

Bone loss in Rheumatoid Arthritis

The inflammatory process that occurs in RA increases the risk of bone loss and fractures. Normally, the body maintains healthy bone by a process of repair (called remodeling) occur by two types of bone cells, osteoclasts, which are responsible for removing (resorption) of old existing bone, and osteoblasts, which are responsible for forming new bone. A balance between the activities of osteoclasts and osteoblasts keeps the overall mass of bone in the body constant. In RA this balance is upset. Bone loss is common and is associated with the severity of inflammation and the duration of the disease (**Schett et al., 2009)**

The skeleton is composed of trabecular bone, the fine bony network hosting the bone marrow, and cortical bone, the dense bony shell that provides structural support in weight-bearing regions. Both types of bone are targeted for erosion in RA. Moreover, RA is considered as an independent risk factor for generalized osteopenia and osteoporosis, involving trabecular and cortical bone in the axial and appendicular skeleton **(Karsenty et al., 2009).**

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periarticular osteopenia adjacent to inflamed joints and generalized osteoporosis involving the axial and appendicular skeleton. As, osteoclasts are the principal cell type responsible for bone loss in RA. Focal and systemic bone loss contribute to the morbidity associated with RA. Generalised osteoporosis is more associated with long-standing, destructive and disabling RA, whereas early RA is associated with periarticular osteoporosis **(Goldring and Gravallese, 2000)**

Focal bone loss in Rheumatoid Arthritis

Definition of bone erosion:

Bone erosion is a radiological term that refers to a break in cortical bone with destruction of the natural barrier between the extra skeletal tissue and the bone marrow compartments, particularly at the bare area of the joints, at the mineralized cartilage, or adjacent to the insertion sites of periarticular ligaments and at sites of overlying tenosynovitis **(Schett and Gravallese., 2012).**

Erosions are apparent on plain radiographs as breaks in the cortical bone surface, and are often accompanied by loss of the adjacent trabecular bone. By contrast, bone cysts are areas of osteolysis inside the trabecular bone compartment, without any signs of cortical bone destruction. Owing to the severity and typical distribution pattern along multiple peripheral skeletal

sites, as well as absence of concomitant new bone formation, the appearance of bone erosions is unique in RA and is substantially different from other types of arthritis (**Aletaha et al., 2010).**

Bone erosions comprise a key outcome measure in RA and are predictive of a more severe course of disease with a higher degree of disability and increased mortality (**Ødegård et al., 2006).**

All major anti-rheumatic agents approved for disease-modification of RA have been proved for their ability to retard, or even arrest, structural damage, which is a composite of bone erosion and cartilage degradation. Radiography is widely used to assess structural damage in clinical practice and to monitor the efficacy of therapy in retarding structural damage. Thus, at present, detection and quantification of bone erosion constitutes a major instrument for disease diagnosis, as well as for monitoring and measurement of efficacy of drug therapy in patients with RA **(McInnes and Schett., 2007).**

Anatomic factors and microstructure involved in bone erosions of RA

Stach and his Colleagues observed that bone erosions do not emerge at random locations, but show a predilection for certain anatomical sites. Detailed analysis of the distribution of bone erosions has been conducted by high-resolution CT, high-

resolution ultrasonography and Magnetic resonance imaging (MRI). The radial aspects of the finger joints were revealed to be 'hot spots' for bone erosions, whereas the ulnar aspects were less frequently affected, and the palmar and volar surfaces of the joints were virtually spared from such lesions **(Stach et al., 2010).**

Distinct localization pattern of bone erosion in RA could be linked with certain anatomical features, bone erosions typically emerge at the site at which the synovium comes into direct contact with bone (known as bare areas), suggesting that anatomical factors render these areas of juxta-articular bone susceptible to erosion (**McGonagle et al.,2009).** Anatomical factors that predispose skeletal sites for erosions include: the presence of mineralized cartilage, a tissue particularly prone to destruction by bone-resorbing cells; the insertion sites of ligaments to the bone surface, which transduce mechanical forces to the bone and could induce microdamage; and inflamed tendon sheaths (termed tenosynovitis), which pass by the bone surface, and enable the spread of inflammation from the tendon to the articular synovium **(Tan et al., 2003).**

The small bone channels that penetrate cortical bone carry microvessels and bridge the outer synovial membrane and the inner bone marrow space; these channels are also prone to erosive change early in the course of RA. The microvessels

located within these channels facilitate homing of osteoclast precursor cells to the bone, which, upon contact with bone and receipt of the appropriate molecular signals, differentiate into osteoclasts **(Schett et al., 2005).**

Detection of bone erosions

Detection of bone erosions has improved by marked technological advances in musculoskeletal imaging. Computed tamography, high-resolution ultrasonography and MRI can reliably detect even small bone erosions in patients with RA. Imaging has also highlighted and substantiated the role of inflammation in triggering bone erosions, showing that not only synovitis, but also inflammation of the adjacent intertrabecular space (osteitis), correlates with the development of radiographic bone erosions **(Haavardsholm et al., 2008).**

Plain radiographs of the hands show periarticular trabecular bone loss results in diffuse or spotty demineralization and blurred or glassy bone and cortical bone loss in tunneling, lamellation, or striation of cortical bone. Cortical bone loss occurs early in the disease, preferentially around affected joints and before generalized osteoporosis can be detected (**Alenfeld et al., 2000).**

Magnetic resonance imaging (MRI) can image areas previously hidden, including the bone marrow compartment.

Normal bone marrow is rich in fat and has a characteristic signal on MRI imaging, appearing bright on T1- weighted images and dark on T2-weighted images. Inflamed RA joints show signal changes that involve the bone marrow cavity and are linked to cortical bone destruction (MRI bone erosion) or changes in the marrow space (bone marrow edema, or "osteitis"), **(Schett, 2009-a).**

Digital X-ray radiogrammetry (DXR) is an effective and sensitive modality for monitoring periarticular osteoporosis, which is among the earliest features of rheumatoid arthritis, preceding bone erosions. Digital X-ray radiogrammetry is a promising technique, which can provide quantitative data that allow early diagnosis. During the course of rheumatoid arthritis it can be deployed in combination with established X-ray scoring methods. Whole-hand bone mineral density, determined using DXA, indicated demineralization only during the first 3 years of RA. The disease activity independently predicted decline in DXR-BMD, but the loss of hand DXA-BMD was similar in patients with high disease activity and in those with low disease activity. These findings indicate that DXR surpassed DXA as an outcome measure in both early and late stages of RA **(Böttcher & Pfeil, 2008).**

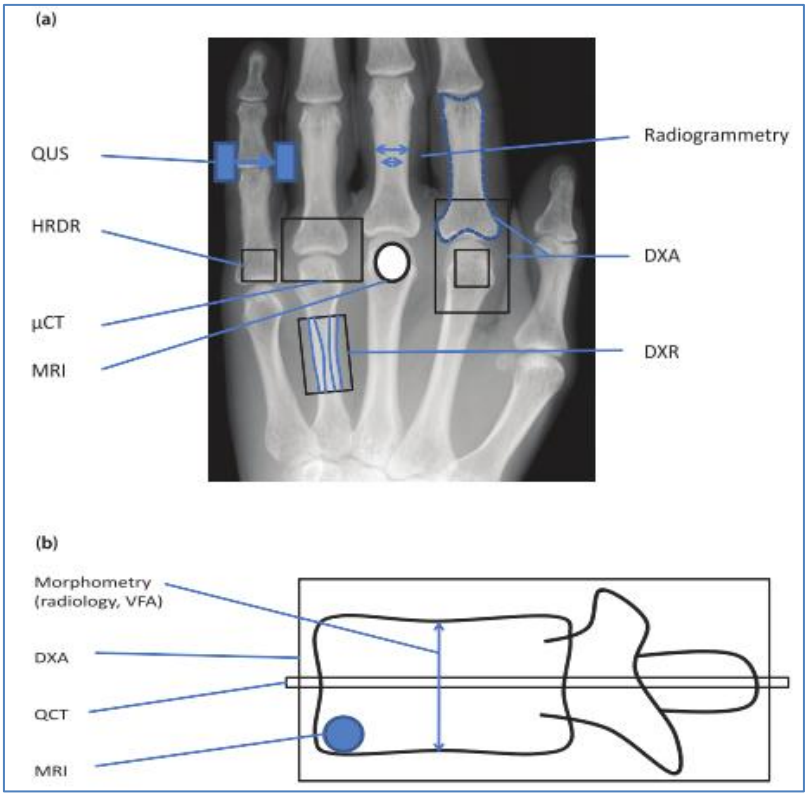

Fig. (1): Methods to quantify bone changes in the hands and vertebrae. (a) Methods to quantify periarticular bone changes. (b) Methods to quantify vertebral bone changes. µCT, micro-computed tomography; DXA, dual-energy x-ray absorptiometry; DXR, digitalized radiogrammetry; HRDR, high-resolution digital radiology; MRI, magnetic resonance imaging; QCT, quantitative computed tomography; QUS, quantitative ultrasound; VFA, vertebral fracture assessment. Adapted from **(Geusens & Lems, 2011).**

Periarticular osteopenia

Periarticular osteopenia in proximity to inflamed joints, which is a typical phenomenon in early and prolonged rheumatoid disease, and generalized osteoporosis, which affects the axial and appendicular bones. Inflammation has the effect of

provoking more severe and accelerated bone loss in the hand as compared with hip and spine **(Hoff et al., 2007).**

The mechanisms underlying periarticular bone loss include: release of bone resorbing cytokines from the inflamed synovium, increased vascularity, and immobility of affected joints (**Joffe and Epstein., 1991).**

Periarticular osteoporosis is an ideal radiographic finding in RA and may occur before the erosions are visible, It is considered as a hallmark of RA and may distinguish RA from other rheumatic diseases (**Haugeberg et al., 2006).**

Pathogensis of bone destruction in RA

In patients with RA the skeletal homeostasis is altered. Localized bone loss in RA results from the activation of an inflammatory immune response, which increases both the number and the activity of osteoclasts. The unique propensity of the inflamed synovium in RA to induce bone resorption is likely related to its capacity to produce a variety of factors with potent osteoclast differentiation and activation, including receptor activator of nuclear factor-κB ligand RANKL, interleukin-1, interleukin-6, interleukin-11, interleukin-15, interleukin-17, monocyte colony stimulating factor, tumor necrosis factor-α and parathyroid hormone related peptide. Particular attention has focused on RANKL because of its potent osteoclastogenic activity (**Romas et al., 2000)**.

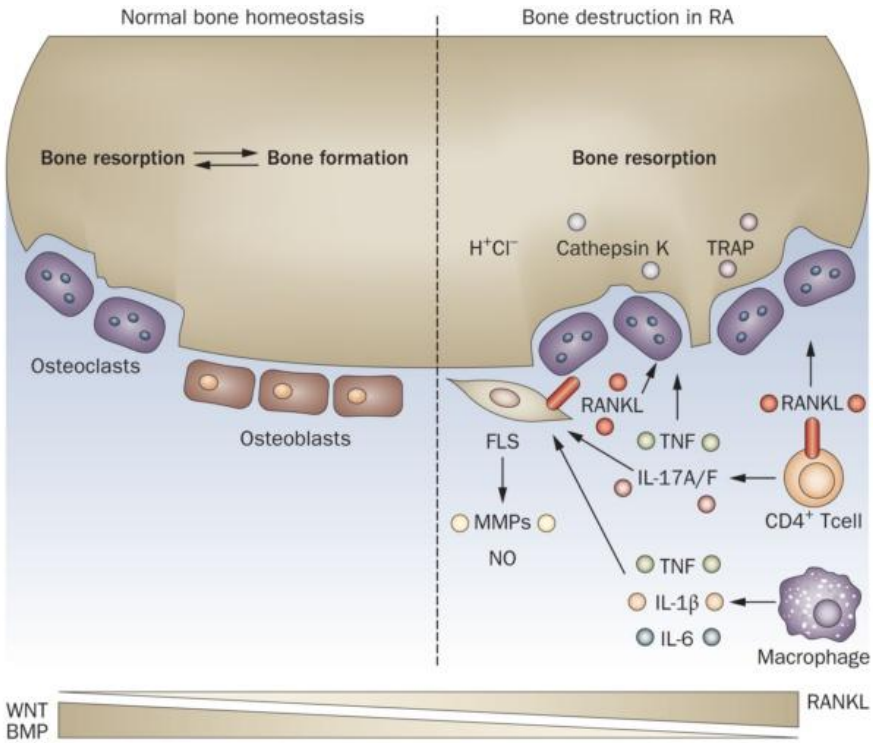

Fig. (2): Bone homeostasis in healthy and RA joints. In normal joints, bone formation and bone resorption are maintained by the balanced function of osteoblasts and osteoclasts. The molecular basis of this homeostasis is controlled in part by the opposing actions of Wnt on osteoblasts and the RANKL pathway on osteoclasts. In RA, activity of infiltrating macrophages and CD4+ T cells results in expression of proinflammatory cytokines such as TNF that drive osteoclast formation via induction of RANKL in the synovium. In addition, RANKL is expressed on synovial fibroblasts and infiltrating T cells resulting in increased bone resorption and joint destruction. **(Choi et al. 2009).**

Focal erosions in the joint, occur at two principal sites: at the joint margins and in subchondral bone. The inflammatory synovial tissue (pannus) is directly responsible for the development of marginal bone erosions that are clearly evident on radiographic evaluation. However, the pannus has access to

the bone marrow as well, where inflammatory changes can enhance osteoclastic resorption at the subchondral bone surface. As a result, articular cartilage is subject to inflammatory attack from below through subchondral bone, as well as from above, as the pannus moves across the articular surface. Standard radiographs do not accurately identify the extent of subchondral bone erosion and subsequent cartilage destruction from below, but recent evidence provided by magnetic resonance imaging (MRI) indicates the importance of this site of attack. It follows that agents capable of protecting against subchondral bone resorption should also have chrondroprotective properties. **(Goldring, 2003).**

The invasion of inflammatory tissue in to subchondral bone involves many cell type including fibroblast, lymphocyte and monocyte. Monocyte are precursors of osteoclast that resorb bone through acidic dissolution of bone mineral and enzymatic destruction of bone matrix **(Schett, 2007).**

There are many other factors that indirectly cause osteoclast differentiation have been identified in rheumatoid synovium, including interleukin-1α (IL-1α), IL-1ß, tumor necrosis factor-α(TNF-α), interleukin-6 (IL-6), Macrophage colony-stimulating factor(M-CSF), interleukin-15(IL-15), interleukin-17(IL-17), and parathyroid hormon related peptide. For example, IL-1 and TNF-a can synergize with low levels of